Treatment Options for Glioblastoma and other Gliomas

Prepared by Ben A. Williams (in collaboration with Stephen Western)
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Introduction

Since my own diagnosis of glioblastoma (GBM) in 1995 at age 50, I have spent considerable time researching treatment options, and the following discussion summarizes what I have learned. Most of the information is from medical journals and the proceedings of major cancer conferences. Some information has been contributed by others to various online brain tumor patient support groups, which I have followed up on, and some is from direct communications with various physicians conducting the treatments that are described. References are presented at the end for those who would like their physicians to take this information seriously. Although this discussion is intended to be primarily descriptive of the recent development of new treatment options, it is motivated by my belief that single-agent treatment protocols are unlikely to be successful, and patients are best served if they utilize multiple treatment modalities, and go beyond the "certified" treatments that too often are the only treatment options offered.

A more extensive account of my philosophy of treatment, and the reasons for it, are provided in my (2002) book, ***Surviving "Terminal" Cancer: Clinical Trials, Drug Cocktails, and Other Treatments Your Doctor Won't Tell You About***. Currently, it is available only at Amazon.com, where reviews of the book also are available.

When I began my search for effective treatments, the available options offered little chance for surviving my diagnosis. The standard treatment included surgery, radiation, and nitrosourea-based chemotherapy, either BCNU alone or CCNU combined with procarbazine and vincristine (known as the PCV combination). While this treatment has helped a small minority of people, its 5-year survival rate has been only 2-5%. Median survival has been about a year, which is 2-3 months longer than for patients receiving radiation alone without chemotherapy. Fortunately, as will be discussed in the next section, the past ten years has produced a new "gold standard" of treatment for newly diagnosed patients: the combination of radiation with a new chemotherapy agent, temozolomide (trade name Temodar in the USA and Temodal elsewhere in the world). While this new standard appears to produce a notable improvement over previous treatments, it still falls far short of being effective for the great majority of patients.

Also available now are three other treatments that have FDA approval for tumors that have recurred or have progressed after initial treatment: Avastin, Gliadel, and an electrical field therapy named Optune (formerly known as NovoTTF). All of these are considered standard of care for recurrent tumors (which is important for insurance reasons), and can legally also be used for newly diagnosed patients as well. Each will be discussed later in this article.

There are three general premises to the approach to treatment that will be described. The first is borrowed from the treatment approach that has evolved in the treatment of AIDS. Both viruses and cancer cells have unstable genetic structures susceptible to mutations. This implies that the dynamics of evolution will create new forms that are resistant to whatever the treatment may be. However, if several different treatments are used simultaneously (instead of sequentially, which is typically the case), any given mutation has a smaller chance of being successful. A mathematical model instantiating these assumptions has recently been developed and has been shown to describe the pattern of tumor growth for melanoma (1).

The second premise is that cancer treatments of all sorts are probabilistic in their effects. None work for everyone, in part because any given cancer diagnosis is an amalgam of different genetic defects that respond in different ways to any given treatment agent. This is especially true for glioblastomas, which have a multiplicity of genetic aberrations that vary widely across individuals and sometimes even within the same tumor of a given individual. As a result it is common that any given "effective" treatment agent will benefit only a minority of patients, often in the range of 10-35%, but do little if anything for the majority. The result is that the chances of finding an effective treatment increase the more different treatment agents that are utilized. Probabilistic effects can and do summate.

An important implication of the genetic diversity of GBM tumors is that tests of treatment agents presented individually will often fail, not because they lack effectiveness, but because they target only one or sometimes two growth pathways, leaving other growth pathways to be upregulated to maintain the growth of the tumor. Thus, even at the level of clinical trials, tests of individual treatment agents in isolation may be a misguided strategy. A drug that fails in isolation might in fact be effective when combined with other drugs that target the additional alternative growth pathways.

A third general principle is that any successful treatment needs to be systemic in nature because it is impossible to identify all of the extensions of the tumor into normal tissue. Moreover, cancer cells are typically evident in locations in the brain distant from the main tumor, indicating that metastases within the brain can occur, although the great majority of tumor recurrences are within or proximal to the original tumor site. Localized treatments such as radiosurgery may be beneficial in terms of buying time, but they are unlikely to provide a cure, except in cases when the tumor is detected early and is very small. Even if the localized treatment eradicates 99% of the tumor, the small amount of residual tumor will expand geometrically, eventually causing significant clinical problems.

Until the development of immunological treatments in just the last few years, which will be discussed in a later section, the only systemic treatment available has been cytotoxic chemotherapy, which historically has been ineffective except for a small percentage of patients. An important issue, therefore, is whether chemotherapy can be made to work substantially better than it typically does. Agents that facilitate or augment its effects are critically important. As will be seen, a number of older drugs developed for other purposes have been shown in laboratory studies to be effective against cancer, often with minimal toxicity. The availability of these treatments raises the possibility that some combination of these new agents can be packaged that provide effective treatment based on several different independent principles. Thus, the AIDS-type of combination approach is now a genuine possibility whereas it would not have been fifteen years ago. Because many of these relatively nontoxic new agents were developed for purposes other than cancer, or for different kinds of cancer, their utilization in the treatment of glioblastomas is "off-label", with the result that many oncologists have been hesitant to prescribe them. Thus, patients themselves need to become familiar with these new agents and the evidence available regarding their clinical effectiveness. It is possible, although by no means proven, that some combination of these newly repurposed agents offers the best possibility for survival.

Patients may or may not learn about the treatments that will be described from their physicians. To appreciate why, it is important to understand how American medicine has been institutionalized. For most medical problems there is an accepted standard of what is the best available treatment. Ideally, such treatments are based on phase III clinical trials in which patients are randomly assigned to receive the new treatment or some type of control condition. Treatments that have been studied only in nonrandomized phase II trials will rarely be offered as a treatment option, even if the accepted "best available treatment" is generally ineffective. What happens instead is that patients are encouraged to participate in clinical trials. The problem with this approach is that most medical centers offer few options for an individual patient. Thus, even though a given trial for a new treatment may seem very promising, patients can participate only if that trial is offered by their medical facility. Yet more problematic is that clinical trials with new treatment agents almost always initially study that agent in isolation, usually with patients with recurrent tumors who have the worst prognoses. For newly diagnosed patients this is at best a last resort. What is needed instead is access to the most promising new treatments, in the optimum combinations, at the time of initial diagnosis.

In the discussion to follow, it is important to distinguish between treatment options at the time of initial diagnosis versus those when the tumor either did not respond to the initial treatment or responded for a period of time and then recurred. Different measures of treatment efficacy are often used for the two situations, which sometimes makes treatment information obtained in one setting difficult to apply to the other. The recurrent tumor situation is also complicated by the fact that resistance to the initial treatment may or may not generalize to new treatments given at recurrence.

The Importance of Brain Tumor Centers

When someone is diagnosed with a brain tumor they are faced with a situation about which they know very little, but nevertheless must develop a treatment plan very quickly, because GBMs grow very rapidly if left untreated. The first step, if possible, is to have as much of the tumor removed as possible, because various data show substantially increased survival times for those with complete resections, relative to those who have incomplete resections or only biopsies. Accordingly, it is best that patients seek treatment at a major brain tumor center because neurosurgeons there will have performed many more tumor removals than general neurosurgeons that typically work in the community setting. This is especially important in recent times, as surgical techniques have become increasingly more sophisticated and utilize procedures that community treatment centers do not have the resources to perform. I know of numerous cases in which a local neurosurgeon has told the patient the tumor is inoperable, only to have the same tumor completely removed at a major brain tumor center.

An additional advantage of utilizing a major brain tumor center is that they are better equipped to do genetic analyses of tumor tissue, which are increasingly important in guiding treatment decisions. Moreover, they provide a gateway into clinical trials.

1. The “Gold Standard” for Initial Treatment

Although chemotherapy has a long history of being ineffective as a treatment for glioblastoma, a large randomized European-Canadian clinical trial (EORTC trial 26981/22981) has shown clear benefits of adding the new chemotherapy agent, temozolomide (trade name Temodar in the USA, Temodal elsewhere in the world) to the standard radiation treatment (2). This treatment, followed by 6 or more monthly cycles of temozolomide, has become known as the “Stupp protocol” after Roger Stupp, the Swiss oncologist who led the trial. In this trial, one group of patients received radiation alone; the other group received radiation plus temodar, first at low daily dosages during the six weeks of radiation, followed by the standard schedule of higher-dose temodar for days 1-5 out of every 28-day cycle. Median survival was 14.6 months, compared to a median survival of 12 months for patients receiving radiation only, a difference that was statistically significant. More impressive was the difference in two-year survival rate, which was 27% for the patients receiving temodar but 10% for those receiving only radiation. Longer-term follow-up has indicated that the benefit of temozolomide (TMZ) persists at least up to five years: The difference in survival rates between the two treatment conditions was 16.4% vs. 4.4% after three years, 12.1% vs. 3.0% after four years, and 9.8% vs.1.9% after five years (3). As a result of these new findings, the protocol of TMZ presented during radiation is now recognized as the "gold standard" of treatment. Note, however, that all of these numbers are somewhat inflated because patients over the age of 70 were excluded from the trial.

A two-year survival rate of less than 30% obviously cannot be considered an effective treatment, as the great majority of patients receiving the treatment obtain at best a minor benefit, accompanied with significant side effects (although temodar is much better tolerated than previous chemotherapy treatments, especially with respect to the cumulative toxicity to the bone marrow). This raises the issues of how to determine who will benefit from the treatment, and, most importantly, how to improve the treatment outcomes.

One approach to determining whether an individual patient will benefit from chemotherapy is simply to try 1-2 rounds to see if there is any tumor regression. The debilitating effects of chemotherapy typically occur in later rounds, at which point there is a cumulative decline in blood counts. The extreme nausea and vomiting associated with chemotherapy in the mind of the lay public is now almost completely preventable by anti-nausea agents, including Zofran (ondansetron), Kytril (granisetron) and Emend (aprepitant). Marijuana also can be very effective in controlling such effects, and recent research has suggested that it has anti-cancer properties in its own right. Thus, for those patients who are relatively robust after surgery and radiation, some amount of chemotherapy experimentation should be possible without major difficulties.

An alternative way to ascertain the value of chemotherapy for an individual patient is the use of chemosensitivity testing for the various drugs that are possible treatments. Such testing typically requires a live sample of the tumor and thus must be planned in advance of surgery. Culturing the live cells is often problematic, but a number of private companies across the country offer this service. Costs range from $1000-$2500, depending on the scope of drugs that are tested. Such testing is controversial, in part because the cell population evolves during the process of culturing, which results in cells possibly different in important ways from the original tumor sample. Nevertheless, recent evidence has shown that chemosensitivity testing can enhance treatment effectiveness for a variety of different types of cancer, including a recent Japanese study using chemosensitivity testing with glioblastoma patients (4). However, this study did not involve cell culturing but direct tests of chemosensitivity for cells harvested at the time of surgery. In general, when chemosensitivity testing indicates an agent has no effect on a patient's tumor the drug is unlikely to have any clinical benefit. On the other hand, tests indicating that a tumor culture is sensitive to a particular agent do not guarantee clinical effectiveness, but increase the likelihood that the agent will be beneficial.

The role of MGMT

A significant advance in determining which patients will benefit from temodar was reported by the same research group that reported the definitive trial combining low-dosage temodar with radiation. Tumor specimens from the patients in that trial were tested for the level of activation of a specific gene that determines resistance to alkylating chemotherapy (which includes temozolomide and the nitrosoureas, BCNU, CCNU, and ACNU). More specifically, there is an enzyme produced by the MGMT gene that allows the damaged tumor cells to repair themselves, with the result that chemotherapy is less effective. Patients whose MGMT gene is inactivated through gene promoter methylation (which occurs in 35-45% of patients) have a significantly greater chance of responding to temodar than those for whom the gene is still functional (5). Comparing patients who received only radiation, those with an inactive gene had two-year survival rate of 23%, compared to only 2% for those with an active gene. For patients receiving both radiation and temozolomide, those with an inactive gene had a two-year survival rate of 46%, compared to 14% for those with an active gene. This implies that patients should have tumor tissue taken at the time of surgery tested for the methylation status of the MGMT gene.

The use of genetic markers to predict treatment outcome is an important advance, but so far it has not been routinely incorporated into clinical practice. Considerable controversy exists about the predictive validity of the MGMT marker, as several studies have failed to show a relationship between that marker and clinical outcome. This appears to due primarily to different measurement procedures. A recent paper (6) compared the degree of MGMT protein expression by using commercial anti-MGMT antibody and an assessment of the methylation status of the promoter region of the MGMT gene. The two measures correlated only weakly, and only the measure of gene promoter methylation correlated strongly with survival time. New methods for assessing methylation have recently been introduced (7) which may resolve the controversy.

The predictive validity of the methylation status of the MGMT gene promoter is an important issue to resolve because temozolomide appears to produce little survival improvement for those whose MGMT gene is activated (ie. gene promoter is unmethylated). Thus, patients with the activated gene might be better served by use of a different chemotherapy agent. This strategy has been used in a recent Japanese study in which patients with an activated MGMT gene received treatment with the platinum-based drugs cisplatin or carboplatin in combination with etoposide while those with the inactive gene received ACNU (a cousin of BCNU and CCNU). Maintenance therapy with interferon was also given. The median survival time for the 30 GBM patients whose chemotherapy protocol was individualized was 21.7 months, while their two-year survival rate was 71% (8). While these results (especially the two-year survival rate), are seemingly a notable improvement over the results obtained when the gold standard treatment has been administered to all patients regardless of MGMT treatment, the comparison is confounded due to the addition of interferon to the treatment protocol. As will be described in a later section, the combination of temodar and interferon has produced results better than the use of temodar alone.

A similar strategy was used in a German clinical trial (9) restricted to patients with MGMT unmethylated (MGMT active) tumors. Patients (N=170) were randomly assigned to receive either the standard Stupp protocol or a protocol consisting of avastin during radiation followed by a combination of avastin and irinotecan, a chemotherapy agent commonly used for colon cancer. The measure was the percentage of patients progression-free after six months (PFS-6). PFS-6 was substantially greater in the avastin group (71%) than in the standard treatment (26%). It is important to note, however that PFS-6 and overall survival often are weakly related when avastin has been used for recurrent tumors.

In addition to changing the chemotherapy agent, there are other possible strategies for patients with an active (unmethylated) MGMT gene. One involves the schedule of temodar. An alternative to the standard 5 days/month is a daily low-dose schedule. Previous studies using metronomic schedules have detected no effect of MGMT status on clinical outcome. The issue of the best schedule for temodar will be discussed in a later section. The second strategy is to utilize drugs that inhibit MGMT expression. Two such drugs are antabuse (disulfiram) and Keppra (levetiracetam) (10, 206).

2. Strategies for improving the "Gold Standard"

Combatting chemoresistance

There are several ways that cancer cells evade being killed by cytotoxic chemotherapy. Already mentioned is that the damage inflicted by the chemotherapy is quickly repaired before actually killing the cell (due to the activity of the MGMT repair enzyme). A second source of resistance is that the chemo agent is extruded from the cancer before the next cell division (chemotherapy typically affects only those cells in the process of dividing). A third way is that the chemo agent doesn't penetrate the blood-brain barrier. While temodar is generally believed to cross the blood-brain-barrier effectively, empirical studies of its concentration within the tumor tissue have shown that its penetration is incomplete.

A major source of chemo-resistance for many types of cancer comes from glycoprotein transport systems (technically called ABC transporters) that extrude the chemotherapy agent before it has the chance to kill the cell. This is important because chemotherapy is effective only when cells are dividing, and only a fraction of the cell population is dividing at any given time. The longer the chemotherapy remains in the cell, the more likely it will be there at the time of cell division. If extrusion of the chemotherapy drug could be inhibited, chemotherapy should in principle become more effective. Calcium channel blockers, which include commonly used medications for hypertension such as **verapamil**, have thus been studied for that purpose (11).

Unfortunately, these agents have potent effects on the cardiovascular system, so that dosages sufficiently high to produce clinical benefits usually have not been achievable. However, a recent study (12) did report a substantial clinical benefit for patients with breast cancer with a relatively low dosage (240 mg/day). An earlier randomized trial with advanced lung cancer (13) also demonstrated a significant benefit of verapamil, using a dose of 480 mg/day, both in terms of frequency of tumor regression and survival time. In addition, the combination of verapamil with tamoxifen (which itself blocks the extrusion by a somewhat different mechanism) may possibly increase the clinical benefit (14). In laboratory studies, the calcium channel blockers nicardipine and nimodipine (15, 16) have also been shown to effectively increase chemotherapy effectiveness, and may have direct effects on tumor growth themselves. Quinine derivatives such as quinidine and chloroquine also inhibit the extrusion pump. Among the strongest inhibitors of the extrusion pump is a common drug used in the treatment of alcoholism, Antabuse (also known as disulfiram), although as yet this has not been studied clinically (17,18). Yet another class of drugs that keep the chemo inside for longer time periods are proton pump inhibitors used for acid reflux (e.g., Prilosec) (19). One approach to blocking the glycoprotein pump without the high toxic doses is to combine several agents together, using lower doses of each individual agent, as combining different agents has been shown to be synergistic in laboratory studies (20).

A variety of other existing drugs have also been shown to increase the effectiveness of chemotherapy, often by unknown mechanisms. The statin drugs used for the treatment of high cholesterol levels, such as simvastatin, have been shown to augment the effects of BCNU in laboratory studies (21), but have not yet been combined with chemotherapy in any reported clinical study.

Yet another common drug with promising anti-cancer properties is metformin, developed for the treatment of type II diabetes. In a small study conducted in Romania (22), available only in abstract, eight newly diagnosed high-grade glioma patients had their tumor tissue tested for sensitivity to temozolomide with or without metformin, and in seven cases sensitivity to temozolomide was substantially greater with metformin.

The most promising clinical results for combating chemo-resistance has come from the addition of **chloroquine**, an old anti-malaria drug, to the traditional chemotherapy agent, BCNU. In a series of studies conducted in Mexico City (23, 24, 25) patients received the traditional chemotherapy agent BCNU, with or without a 150-mg daily dose of chloroquine (the equivalent of 250 mg chloroquine phosphate). The results were that patients receiving chloroquine had a median survival time of 25-33 months, while those receiving BCNU alone had a median survival time of 11 months. Chloroquine at the dose used had no detectable toxicity. Because the cytotoxic mechanism of BCNU is similar to that of temodar, it seems likely that chloroquine should increase the efficacy of temodar, although this has yet to be demonstrated. One of several mechanisms by which chloroquine makes chemotherapy more effective is that it inhibits autophagy, an intracellular process that involves the cell digesting some of its internal parts to allow repair of the damage caused by the chemotherapy.

Disappointingly, a multi-center phase I/II trial testing the addition of hydroxychloroquine (which differs from chloroquine only by a single hydroxyl group) to standard radiochemotherapy for newly diagnosed glioblastoma failed to show any improvement in survival over historical averages. In the phase I safety and toxicity study, all 3 subjects given 800 mg/d hydroxychloroquine along with chemoradiation experienced grade 3 or 4 neutropenia or thrombocytopenia, and 600 mg/d was determined to be the maximum tolerated dose. 76 patients were then treated at this dose in the phase 2 cohort. Autophagy inhibition (the proposed mechanism of action) was not consistently achieved at that dose, and patient survival (median OS 15.6 months, 2-year survival of 25%) was not improved relative to historical control groups. The study concluded that hydroxychloroquine was ineffective in this context at the maximum tolerated dose (304).

Recent preclinical work (305) has shown increased reliance on autophagy and sensitivity to chloroquine treatment in EGFR-overexpressing glioma cells, and any future trials with chloroquine for high-grade gliomas may benefit from a subgroup analysis based on EGFR status.

Disruption of the blood-brain-barrier (BBB) is also potentially very important and has been extensively investigated. The issue is complicated by the fact that tumor tissue already has a substantially disrupted BBB (which is the basis of using contrast agents to identify the tumor). However, this disruption is incomplete, so any chemotherapy agent that does not cross the intact BBB will not contact all portions of the tumor. Various ways of disrupting the BBB have been studied, but none has been generally successful, primarily because of their systemic side effects. Recently, however, the common erectile dysfunction drugs (Viagra, Levitra, Cialis) have been discovered to disrupt the BBB in laboratory animals. In a rat brain tumor model, the addition of Viagra or Levitra to a common chemotherapy agent, Adriamycin, substantially improved survival time (26). However, it has been several years since these laboratory studies, and no human clinical results have yet been reported; often such delays portend that the approach failed to be effective.

A second agent that opens the BBB is methamphetamine (27). Notably, selegiline, a drug commonly used to treat Parkinson's disease, is catabolized into methamphetamine, and could provide a more convenient way to obtain the drug without the government restrictions on its use.

Optimizing the Schedule of Chemotherapy

The standard schedule for using full-dose temodar is days 1-5 out of every 28-day cycle. The large EORTC-NCIC study (2005) described above also added daily temodar during radiation at a lower dosage, followed by the standard five-day schedule after radiation was completed. But there has never been a persuasive rationale for why this standard schedule should be preferred over various alternatives, and it has become increasingly questionable whether the standard schedule is in fact optimal. One of the earliest small clinical studies with temodar used a daily schedule with lower doses (28), which produced clinical outcomes seemingly better than those obtained with the standard schedule, although based on a small number of patients.

In addition to the standard schedule, three other schedules have been studied: (1) a "metronomic" low-dose daily schedule; (2) an alternating week schedule; (3) a "dose-intense" schedule in which temodar is used on days 1-21 of every 28-day cycle. While it is possible to compare the outcomes of these different studies across different clinical trials, only a few studies have compared the different schedules within the same clinical trial.

In one randomized trial with newly diagnosed patients, the alternating week schedule was compared with the metronomic schedule. (29). One-year survival rates were 80% vs., 69%, and two-year survival rates 35% vs. 28%, both favoring the alternating week schedule. However, neither difference was statistically significant. (The corresponding numbers for the landmark Stupp trial, for comparison, were 61% and 27%). Median survival times for the alternating week and metronomic schedules were 17.1 vs. 15.1 months, compared to the Stupp et al. results of 14.6 months.

A second very large randomized trial compared the standard 5-day schedule with a dose-intense schedule (21 of 28 days). The rationale of the dose-intense schedule was that it would better deplete the MGMT enzyme (30). Median PFS favored the dose-dense arm (6.7 months vs. 5.5 months from the time of study randomization, p=0.06), while median overall survival favored the standard schedule (16.6 vs. 14.9 months from randomization). While neither difference was statistically significant, the dose-intense schedule had substantially more toxicity and hence cannot be recommended. Very similar results were obtained in an earlier trial as well (31).

Additional information is provided by a nonrandomized trial (32) in which temodar was used as the initial treatment after surgery and radiation (and not concomitant with radiation). Patients received the standard schedule, the alternating week schedule described above, or a daily schedule in which the dose was 75 mg/ square meter of body surface. The corresponding median survivals were 11.9 months for the standard schedule, 15.7 months for the alternating week schedule, and 29.5 months for the daily schedule. There were corresponding differences in two-year survival rates: 21%, 30%, and 51%, for the standard, alternating week, and daily schedules, respectively. This study was published in the form of an abstract for the 2006 annual ASCO meeting.

The above study was expanded upon and published in the Journal of the National Cancer Institute (online March 2015, May 2015 print edition). In this new study (313), 40 patients undergoing the standard 5-day temozolomide schedule and 30 patients undergoing the daily schedule (75 mg/m2) were included in the final analysis. The metronomic temozolomide schedule led to highly statistically significant increases in both progression-free survival and overall survival, and in both univariate and multivariate analysis. Even more importantly, this study found that the benefit of the metronomic schedule mainly occurs for those patients with EGFR overexpression (EGFR protein expression in over 30% of tumor cells), or EGFR gene amplification. This advantage of the metronomic temozolomide schedule for patients with EGFR overexpression/ amplification was independent of MGMT status. Median overall survival for patients with EGFR overexpression treated with metronomic temozolomide was 34 months, compared to 12 months with standard schedule. EGFR overexpressing patients treated with metronomic temozolomide had highly statistically significantly improved progression-free survival and overall survival compared to all other groups (the other groups being EGFR overexpressing treated with standard schedule, and EGFR non-overexpressing treated with either schedule).

The investigators of the above study went further than survival analysis, and analysed tumor tissue samples from patients who underwent repeat resection at the time of recurrence. Interestingly, they found that samples from EGFR overexpressing tumors treated with metronomic temozolomide had significantly fewer cells positive for NF-kB/p65 (a promoter of cell proliferation and survival) compared with untreated tumors from the same patients at the time of diagnosis. No such change was observed between the primary and recurrent EGFR overexpressing tumors from patients treated with the standard schedule. Recurrent EGFR amplified tumors treated with the metronomic schedule showed fewer EGFR amplified cells and weaker EGFR staining at the time of recurrence compared with the primary tumor. No such difference was observed in EGFR amplified tumors treated with the standard schedule. The authors draw the conclusion that this metronomic schedule impairs survival of EGFR expressing GBM cells more effectively than the standard schedule. These findings will hopefully lead to testing in prospective clinical trials.

The most frequent setting in which different temodar schedules have been studied are nonrandomized phase II trials using a single temodar schedule, involving tumors that have recurred after initial treatment. Any comparisons of different temodar schedules are thus between different clinical trials, with all of the potential confounds that involves. The most common measure used for this comparison has been the percentage of patients who are progression-free six months after treatment initiation (known as PFS-6). A compilation of statistics from prior phase II studies involving patients with recurrent tumors treated with various different chemotherapy agents produced a PFS-6 value of 15%. The use of temodar with a comparable set of patients produced a PFS-6 value of 21%, when using the standard 5-day schedule of temodar administration. In contrast, the alternating week schedule (i.e., days 1-7 and 15-21 of a 28 day cycle) seems to produce substantially better results (33). Here, with an initial 21 patients, the PFS-6 was 48%. A follow-up report (34) after the number of patients had expanded to 64 yielded a PFS-6 value of 44%, approximately double the 21% value produced by the standard 5-day schedule. The dosage of temodar used in this study was 150 mg/ square meter of body surface. It should be noted that the majority of patients in these trials had not received temodar as initial treatment, unlike the present situation in which the great majority of patients receive the gold standard protocol involving temodar. However, even patients who have failed the standard temozolomide protocol seem to benefit from the alternating week schedule. In a study done in Germany (35), patients with high-grade gliomas who had failed the standard protocol were given 150 mg/sq. meter on days 1-7 and 15-21 of a 28-day cycle. The PFS-6 value was 43% and the median time to progression was 18 weeks.

Somewhat less positive results with the alternating week schedule were obtained in a Dutch study of 24 GBM patients (36), where the PFS-6 value was only 29%. Given the small number of patients, however, it is difficult to know whether the variation was due to random variability.

There are also several clinical trials in which patients who have failed the standard protocol are presented temozolomide again but on a metronomic schedule. Part of the rationale for this approach is that continuous chemotherapy, even at low doses, will inhibit the growth of new blood vessels feeding the tumor (37, 38). Moreover, in comparison to the bolus dosage, continuous low dosages (so-called metronomic chemotherapy) have less toxicity. Early clinical results (39) for patients with glioblastoma whose tumors had progressed during the standard temodar protocol have supported the generality of the results from experimental animal models. After tumor progression, a daily schedule of temodar at a dosage of 40 mg/square meter was used, which resulted in an additional median survival time of 11 months and a PFS-6 value of 50%, although it should be noted that only 12 patients were included in the study. A larger study (35 patients) also presented continuous daily temodar after the standard schedule had failed, but here at a dose of 50-mg/square meter of body surface (40). Patients were also subdivided according to when their tumors had recurred: (a) while on the standard TMZ protocol (N=21), or (b) after the TMZ protocol had been completed (N=14). The corresponding PFS-6 values were 17%, and 57%.

At the 2008 meeting of the Society for Neuro-oncology, two additional studies were reported in which daily low-dose temodar has been presented after the standard monthly schedule failed. The first with 13 GBM patients (41) used a daily dose of 50 mg/meter-squared, and reported a PFS-6 value of 23%. The second study (42), done in South Korea, included 38 patients with either the 50 mg/meter-squared, or 40 mg/meter-squared, and reported a PFS-6 value of 33%.

A more recent report of the use of metronomic schedules for recurrent tumors, from the Sloan-Kettering Cancer Center (42), presented 37 GBM patients a daily dose of 50 mg/meter-sq. and reported a PFS-6 value of 19% and a median survival after metronomic treatment initiation of 7 months. However, most of the patients were heavily pretreated after multiple recurrences, and 50% of them had failed avastin as a salvage therapy. This history is important because those who had failed avastin had much worse outcomes: those with prior avastin had a median survival of 4.3 months and a PFS-6 value of 11%, while those who were avastin naïve had a median survival of 13 months and a PFS-6 value of 26%. It should be noted that the median survival of 13 months was likely impacted by the fact that 50% of the avastin-naïve patients received avastin when the metronomic schedule had failed.

The optimal dosage for this metronomic schedule of chemotherapy remains to be established because dividing blood vessel cells are more sensitive to chemotherapy than are dividing tumor cells, but they are also much quicker to recover when chemotherapy is removed, which implies that any recess from using chemotherapy will allow the blood vessels feeding the tumor to quickly regrow.

The lowest temodar dose in metronomic chemotherapy reported to date was presented to newly diagnosed glioblastoma patients (44). After completion of standard radiation treatment, continuous daily doses of temozolomide approximately 1/10 of the typically used full dose were used in combination with vioxx (celebrex is now used instead). Median survival for 13 patients was 16 months, with minimal toxicity. A second study (45) from the same medical group compared the very low-dose schedule (20 mg/meter-squared) with a more typical metronomic dosage (50 mg/meter-squared), although only six patients were included in the later group. Also included were patients who received only radiation. Median survival was 17 months and 21 months, respectively, for the two metronomic chemotherapy groups vs. 9 months for the radiation-only patients.

The same German medical group (46) also administered very low-dose metronomic schedules of temodar to 28 patients with recurrent tumors after initial treatment with the standard temodar protocol (four had prior treatment with CCNU or PCV instead). A twice-daily dose of 10 mg/square meter was presented in combination with 200 mg of celebrex. Median survival from the start of metronomic chemotherapy was 16.8 months, which compares very favorably to the 7.3 months when the standard schedule of temodar has been used for tumors that recurred after prior treatment with nitrosoureas. The PFS-6 value was 43% vs. 21% for standard-schedule temodar, while the median time to progression was 4.2 months compared to 2.9 months for temodar on the standard schedule. Unlike the standard temodar protocol, toxicity was virtually absent except for one patient who developed lymphopenia. An important feature of the metronomic schedule was that even after tumor progression was detected, patients could continue on the schedule for several months before the progression produced significant clinical problems. But it also should be noted that a high percentage of patients (68%) had surgery for their recurrent tumors prior to starting the metronomic schedule of temozolomide. How much this contributed to the positive outcome is impossible to assess.

The positive results of the just-described clinical trials appear to be in conflict with a prior study that also used a metronomic schedule for 28 GBM patients with recurrent tumors after nitrosourea prior treatment; here the PFS-6 value was only 19%, and the median survival was 8.7 months (47). However, there were several important differences between the two studies. Most obvious was the use of celebrex in combination with metronomic temodar in the German study, and its use of a much lower dose of temodar. In the second study, the daily dose was 75 mg/meter-squared, almost twice that of the German study. Patients in the second study were also given a hiatus from chemotherapy after 7 weeks of treatment. A critical feature of the metronomic schedule approach is that the chemotherapy agent be constantly present until the tumor finally regresses from starvation, as regrowth of the blood vessels feeding the tumor can occur very rapidly. Also important is that patients in the second study had different treatment histories.

Further evidence supporting the use of a metronomic chemotherapy schedules comes from an Italian study (314) in which 43 recurrent GBM patients received a daily dose of 50 mg/m-sq. Median KPS was 65, unusually low, reflecting an overall lower level of functioning and presumably poorer prognosis. PFS-6 was 54%, and 22/43 patients were still alive at one-year after diagnosis of recurrence and ten patients were still alive at 18 months. For patients with unmethylated MGMT, median PFS was 9.6 months; for those with methylated MGMT, median PFS was 12 months, so there was some effect of MGMT status even with the metronomic schedule.

Given the complexity of the results described in this section, which temodar protocol is best? For newly diagnosed patients the alternating week schedule can be recommended, although the protocol used in the German study with extremely low metronomic doses seems comparable in terms of overall survival statistics. For patients with recurrent tumors after prior use of standard-schedule temodar, the metronomic protocol used in the German study had the best survival outcomes, but it should be recognized that survival statistics can be seriously confounded by which salvage therapies are given after tumor progression.

Various other temodar schedules have also been investigated. One surprising result is a variation of the Stupp standard protocol in which TMZ is presented only during the first and last weeks of the six-week radiation treatment (48), a procedure that results in substantially less toxicity. Here the median survival (for GBM patients only) was 18 months and the two-year survival was 35%. However, only 25 patients were included in the clinical trial.

An important question is how long the use of TMZ should be continued. The Stupp clinical trial continued it for only six cycles after radiation, but many patients have continued that protocol for longer period of times. In a clinical trial in England with 32 patients (49), the Stupp protocol was continued until evidence of progression, or unacceptable toxicity. The average number of cycles was 18, with a range of 7-31. The average survival rates, based on Kaplan-Meier estimates, were 88% for one year, 69% for two years, and 69% for three years. The two-year and three-year survival rates were notably greater than those from the standard Stupp protocol.

Two additional studies have confirmed the benefits of more extended periods of temozolomide use. In an Indian study (50), 36 GBM patients were randomly assigned either to 6 or 12 cycles of temozolomide, which produced median PFS of 10 months versus 18.4 months. A retrospective study done in Canada (51) compared patients who received the standard six cycles of temozolomide with those who had more than six cycles (up to 12) Patients receiving six cycles had a median survival of 16.5 months, while those receiving more than six cycles had a median survival of 24.6 months.

Combining the Standard Treatment with Additional Agents

Few oncologists believe that single-agent treatments are likely to be curative. The issue is finding the optimal combinations, based on toxicities and differences in the mechanisms of actions. Prior to the introduction of temozolomide, the PCV combination of procarbazine, CCNU, and vincristine, had been the most widely used combination treatment for glioblastomas, but its use has never been shown to produce a better outcome than treatment with BCNU as a single agent. Nevertheless, there is now a large amount of research studying the effects of combining temozolomide with other therapies, most of which supports the view that such combinations improve treatment outcome, sometimes substantially. A variety of additional therapies are discussed in the following chapters.

3. Optune (formerly NovoTTF-100A) by Novocure

In the spring of 2011, the FDA approved the fourth treatment ever for glioblastoma. Unlike the previous three (gliadel, temozolomide, and avastin), the new treatment involves no drugs or surgery, but instead uses a “helmet” of electrodes that generates a low level of alternating electrical current. A small biotech company in Israel (Novocure) has developed the device, called Novo-TTF, based on experimental findings that electromagnetic fields disrupt tumor growth by interfering with the mitosis stage of cell division, causing the cancer cells to die instead of proliferating (138). Healthy brain cells rarely divide and thus are unaffected. The treatment involves wearing a collection of electrodes for 18 or more hours/day, which allows the patient to live otherwise normally. In a large clinical trial (N=230) with heavily pretreated recurrent glioblastomas, patients randomly received either the Novo-TTF device or whichever chemotherapy was chosen by their oncologists (139). PFS-6 was 21% in the Novocure group versus 15% in the chemotherapy group. Tumor responses occurred in 15% of Novocure patients and 5% of the controls, which was significantly different. Neither result is very impressive, but it should be noted that patients who have failed multiple prior treatments have a generally poor prognosis. When a subgroup analysis was performed for patients with a higher level of functioning, the difference was substantially greater. The benefit of the device was also significant for patients who previously failed avastin. Also to be noted is that quality of life measures were much higher for patients using the device (140).

In an earlier pilot study involving ten newly diagnosed patients, the Novocure device was used in combination with the standard Stupp protocol and produced a median survival of 39+ months (141). Currently underway is a larger randomized clinical trial comparing this combination with the Stupp protocol alone. The final results of this phase 3 trial were presented at conferences in 2014 and 2015 and are described on page 18, below.

In a long-term follow-up (142) of the initial 20 patients treated with TTF fields in pilot studies (10 using TTF as a single agent, 10 using it in combination with temodar), four were found to be tumor-free 5-7 years after treatment. Notably, some of these required considerable treatment time to obtain tumor regressions, some even after some initial tumor growth while in the early stages of treatment.

Patient Registry Dataset (PRiDe)

A Supplement to the journal Seminars in Oncology appeared in October 2014, featuring several new studies of the NovoTTF-100A system, renamed Optune in November. One of these studies (308) describes patient outcomes obtained from the Patient Registry Dataset (PRiDe for short), which includes the records of all recurrent glioblastoma patients treated with Tumor Treating Fields from October 2011 through to November 2013, a total of 457 patients.

The median overall survival from the start of NovoTTF therapy for the entire cohort was 9.7 months. While this is longer than the 6.6 months median obtained in the pivotal phase 3 trial that led to approval of the device in 2011, there are significant differences in the two patient populations. In the PRiDe group, 33.3% were at first recurrence, 26.9% were at second recurrence, and 27.4% were at third to fifth recurrence. In contrast, the NovoTTF-treated group from the phase 3 EF-11 trial had 9% at first recurrence, 48% at second recurrence, and 43% at third to fifth recurrence. With far more patients at first recurrence in the PRiDe group, it's not surprising that median OS was longer.

When looking only at the patients at first recurrence (33.3% of the PRiDe group, or about 152 patients) we find a strikingly positive overall survival of 20 months from start of NovoTTF therapy. No other large glioblastoma study has reported such a long median survival from the time of first recurrence.

In addition to number or prior recurrences, additional prognostic factors which were statistically significantly linked to longer overall survival included compliance (the percentage of time that the device is in operation each day) and prior Avastin therapy. Patients were divided into those with equal to or more than 75% compliance (wearing the device for 18 hours or more each day), and those with less than 75% compliance (wearing the device for fewer than 18 hours per day on average). Median survival was 13.5 months for those with >75% compliance, and only 4 months in the group with <75% compliance. When patient outcomes were stratified by prior Avastin use, median survival was 13.4 months for patients who had not received prior Avastin, and 7.2 months for those who had received prior Avastin. Overall 55.1% of patients in the PRiDe dataset had prior Avastin treatment.

This study is limited by the lack of reporting of progression-free survival data or details about concomitant therapies undertaken along with or just prior to NovoTTF (for example, how many patients had repeat surgery prior to NovoTTF treatment?). Nevertheless, 20 months median survival with NovoTTF therapy from first recurrence of glioblastoma is a figure few, if any, studies have matched to date.

Optune plus chemoradiation, the next standard of care?

EF-14 is a phase 3 randomized clinical trial for newly diagnosed glioblastoma which compares standard of care chemoradiation followed by **Optune (NovoTTF)** and monthly cycles of temodar, versus chemoradiation followed by monthly cycles of temodar alone.

In November 2014, at the annual SNO meeting in Miami Beach, Roger Stupp made a "late-breaking" presentation before a packed audience, describing interim survival outcomes from the EF-14 trial, essentially ushering in what may become the new standard of care for newly diagnosed glioblastoma, pending FDA approval. *This trial is the first major phase 3 trial since the "Stupp protocol" was established in 2005 to report a positive, statistically significant survival benefit for newly diagnosed glioblastoma*. In fact, the trial was so successful that it was terminated early and on December 2, Novocure announced that the FDA had approved an investigational device exemption (IDE) supplement allowing all the control patients in the EF-14 trial to begin receiving therapy with Optune tumor treating fields.

The interim results presented in Miami were based on the first 315 patients enrolled in the trial, who had at least 18 months of follow-up. Of these, 105 were randomized into the control arm and 210 were randomized to receive tumor treating fields. Survival and progression-free survival were measured from the time of randomization, which was a median of 3.8 months after diagnosis. Median progression-free survival was 7.1 months in the Optune arm versus 4 months in the control arm (hazard ratio 0.63, with a high degree of statistical significance, p=0.001). Median overall survival from randomization was 19.6 months in the Optune arm versus 16.6 months in the control arm (hazard ratio 0.75, statistically significant, p=0.034). 2-year survival was 43% in the Optune arm versus 29% in the control arm. It must be kept in mind that all these statistics are measured from randomization, roughly 4 months from diagnosis, meaning that median overall survival in the Optune arm approaches 24 months from diagnosis.

While the establishment of Optune tumor treating fields as a new standard of care still awaits FDA approval for newly diagnosed glioblastoma and the addition of the therapy to the NCCN guidelines, the historic success of the EF-14 trial essentially ushers in a new era in brain tumor treatment.

4. Other Chemotherapy

CCNU (lomustine)

A report from Germany combined TMZ with CCNU (lomustine), the nitrosourea component of the PCV combination (52). Patients (N=39) received CCNU on day 1 of each 6-week cycle, and TMZ on days 2-6. Eight patients received intensified doses of both drugs, with somewhat better survival results (but with substantially increased toxicity). For present purposes, the results of all patients are aggregated. Median survival time was 23 months, and survival rates were 47%, 26%, 18%, and 16% at 2, 3, 4, and 5 years, respectively. Four of the 39 patients had no recurrence at the 5-year mark. Only 23 of the 39 patients were assessable for the status of the MGMT gene. Those with an inactive gene (methylated MGMT promoter) had a median survival of 34 months, while those with an active gene (unmethylated MGMT promoter) had a median survival of only 12.5 months.

These results, including a 5-year survival rate of 16%, are among the best yet reported, albeit with a relatively small number of patients. But it also should be appreciated that patients who suffered a recurrence received extensive salvage therapy of various types, which may have contributed substantially to survival time. The addition of CCNU to standard therapy for newly diagnosed glioblastoma is currently being tested in a phase 3 trial in Germany.

BCNU (carmustine) and Gliadel (carmustine wafers)

The combination of temodar with BCNU, the traditional chemotherapy for glioblastomas, has also been studied, but has been complicated by issues of toxicity and the optimal schedule of dose administration for the two drugs. However, a recent published report involving patients with tumors recurring after radiation but no prior chemotherapy failed to show any benefit of combining BCNU with temodar, compared to temodar alone, as the PFS-6 for the combination was only 21%, accompanied by considerable toxicity (53).

An important variation in the use of BCNU has been the development of polymer wafers known as gliadel. A number of such wafers are implanted throughout the tumor site at the time of surgery. BCNU then gradually diffuses from the wafers into the surrounding brain. A possible problem with the treatment is that the drug will diffuse only a small distance from the implant sites, and thus fail to contact significant portions of the tumor. However, a phase III clinical trial has demonstrated that survival time for recurrent high-grade gliomas is significantly increased by the gliadel wafers relative to control subjects receiving wafers without BCNU, although the increase in survival time, while statistically significant, was relatively modest (54). Probably the best estimate of the benefit of gliadel as an initial treatment comes from a randomized clinical trial, conducted in Europe (55), which reported a median survival of 13.9 months for patients receiving gliadel compared to a median survival of 11.6 months for patients implanted with placebo wafers. As with other forms of chemotherapy, larger differences were evident for long-term survival. After a follow-up period of 56 months, 9 of 120 patients who received gliadel were alive, compared to only 2 of 120 of those receiving the placebo. However, the results were not reported separately for glioblastomas vs. other high-grade gliomas, suggesting that the outcome results would have been more modest for the glioblastoma patients alone.

When gliadel has been combined with the standard TMZ + radiation protocol, survival time seems to be significantly improved, as assessed in three different retrospective clinical trials. In the first, from the Moffitt Cancer Center in Florida (56), the combination produced a median overall survival of 17 months, and a 2-year survival rate of 39%. In a second clinical trial reported by Johns Hopkins, where gliadel was developed (57), 35 patients receiving the combination had a median survival time of 20.7 months and a 2-year survival of 36%. In a third trial conducted at Duke University (58), 36 patients receiving gliadel in addition to the standard TMZ protocol had a median survival of 20.7 months and a 2-year survival of 47%. The Duke cohort also received rotational chemotherapy (which included TMZ) subsequent to radiation. It is important to keep in mind that patients eligible to receive gliadel must have operable tumors, which excludes patients who have received a biopsy only and have a generally poorer prognosis as a result. The effect of this selection bias is difficult to evaluate but it is likely to account for a significant fraction of the improvement in survival time when gliadel +TMZ is compared to TMZ alone.

A major advantage of gliadel is that it avoids the systemic side effects of intravenous BCNU, which can be considerable, not only in terms of low blood counts but also in terms of a significant risk of major pulmonary problems. But gliadel produces its own side effects, including an elevated risk of intracranial infections and seizures. However, the lack of systemic toxicity makes gliadel a candidate for various drug combinations. Especially noteworthy is a recent phase II trial with 50 patients with recurrent tumors that combined gliadel with 06-BG, a drug that depletes the MGMT enzyme involved in repair of chemotherapy-induced damage, but also causes unacceptable bone marrow toxicity when chemotherapy is given systemically. Survival rates at six months, one year and two years were 82%, 47%, and 10%, respectively (59) which seems notably better than the earlier clinical trial with recurrent tumors using gliadel without the 06-BG, in which the corresponding survival rates were 56%, 20%, and 10%. Median survivals were also notably improved by the addition of 06-BG (50.3 weeks versus 28 weeks).

Similarly promising results come from a recent small trial (16 newly diagnosed patients) combining gliadel with carboplatin. A single dose of carboplatin was given 3-4 days after surgery during which gliadel wafers were implanted, and carboplatin was resumed after radiation was completed. Median survival was 22 months (60).

Platinum compounds

An improvement in results relative to those obtained with temodar alone has also been reported when temodar has been combined with cisplatin. In a pair of clinical studies performed in Italy (61, 62) with patients with recurrent tumors, the PFS-6 was 34% and 35%. A treatment protocol with newly diagnosed patients that also seems to have produced better results than temodar as a single agent combined temodar with both cisplatin and etoposide (VP-16), given through the carotid artery (63). Cisplatin and etoposide were given after surgery and continued for three cycles spaced every 3 weeks apart, followed by the standard protocol of radiation plus low-dose temodar, then high-dose temodar on the schedule of days 1-5 of every month. For 15 patients studied, median survival was 25 months.

Procarbazine

Temodar has also been combined with procarbazine (64). While the report of that study did not include the PFS-6 statistic, it did report an unusually high percentage of tumor regressions, suggesting that this combination might be effective.

Interferons

The standard temodar protocol has also been combined with the immunological agent, interferon-beta. In a Japanese study with 68 patients, the standard protocol was presented alone or in combination with interferon-beta for newly diagnosed glioblastomas (65). The temodar-alone group had a median survival time of 12.7 months, while those with the added interferon had a median survival of 19.9 months. The addition of interferon seemed especially efficacious for patients with an active MGMT gene; median survival was 17.2 months for those receiving interferon vs. 12.5 months for those receiving temodar without interferon.

A follow-up report involving 122 patients had a median survival of 20 months for those receiving the standard Stupp protocol and a median survival of 24 months for those with the added interferon (315).

Temozolomide has also been combined with interferon alfa-2b, which produced a PFS-6 value of 38% for recurrent glioblastoma patients (66), notably better than the 21% when temozolomide has been used as a single agent.

Avastin (bevacizumab)

The most notable development in drug combinations has been the addition of the anti-angiogenic drug, avastin (also known as bevacizumab), to the standard Stupp protocol. As will be discussed later, avastin has FDA approval for the treatment of glioblastomas that have recurred or progressed after initial treatment. Several clinical trials have now investigated its combination with the gold standard temodar protocol. In a trial conducted at Duke University (N=70), low-dose temodar and avastin were used during radiation,followed by chemotherapy with avastin, temodar and an additional chemotherapy agent, CPT-11 (67). The median progression-free survival was 14.2 months and the overall survival was 21 months. In the original Stupp et al. clinical trial using temodar without avastin, the corresponding figures were 6.9 months and 14.6 months. Thus, the addition of avastin seems to have produced a notable improvement in survival.

Further support for this benefit comes from a similar study conducted in New York (68). The addition of avastin to the Stupp protocol produced a median overall survival of 23 months (N-51), with a one-year survival of 85% and two-year survival of 43%.

However, a different perspective is provided by a clinical trial conducted at UCLA (69), which also used both temodar and avastin during radiation and afterwards. Here the progression free survival was 13.6 months and median overall survival was 19.6 months, results similar to that of the Duke study and also seemingly better than those from the Stupp protocol. However, UCLA's own control cohort, who had received the standard Stupp protocol followed by avastin therapy as salvage therapy when temodar alone had failed, provided a second comparison group. For this control cohort the median progression-free survival was 7.6 months and the median overall survival was 21.1 months. By the latter comparison, there appears to be no increase in survival time using avastin as part of initial treatment, although the increase in progression-free survival does imply a better quality of life for a longer time period.

Most recently, there have been two large randomized phase III clinical trials comparing the Stupp protocol and the Stupp protocol + avastin, for newly diagnosed patients. In the first of these (70), known as the AVAglio trial, median PFS was 10.6 months for those receiving avastin versus 6.2 months for those receiving only the Stupp protocol, a statistically significant difference. However, median overall survival was not different (16.8 months vs. 16.7 months). It should be noted that patients in the control group typically received avastin after tumor progression occurred, so that the comparison was really between avastin given early versus avastin give only after recurrence. Additional results were that 72 % of the avastin group was alive at one year, compared to 66% of the control group, while two year survival was 34% vs. 30%.

In the second of these large trials (71), conducted by the RTOG consortium, the design was essentially similar to the AVAglio trial, as were the results. Median PFS was 10 months for those receiving avastin vs. 7.3 months for the control group (again statistically significant), while median overall survival was 15.7 months for the avastin group compared to 16.1 months for the control, a nonsignificant difference.

The best interpretation of these results is that patients have a longer time without tumor progression, and presumably a better quality of life, when avastin is used as part of the initial treatment. However, there is no benefit for overall survival, when compared to withholding avastin until recurrence is detected. An additional feature of the results, not emphasized by the authors of the reports, is that the overall survival times were not notably better, and in many cases worse, than those obtained when the Stupp protocol is combined with various other treatment agents.

EGFR inhibitors: Iressa, Tarceva, and Erbitux (gefitinib, erlotinib, and cetuximab)

These three drugs, which have FDA approval for several different types of cancer, have the common feature that they target a growth-signaling channel known as the epidermal growth factor. Overexpression or mutation of EGF receptors is involved in the growth many different kinds of cancer, including more than half of glioblastomas. In general, use of these drugs as single agents has produced disappointing results, although occasional long-term survivors have occurred. More promising results have occurred when EGFR inhibitors have been used in combination with the Stupp protocol.

When tarceva has been added to the standard temodar protocol for newly diagnosed patients, median survival was 15.3 months (N=97) in one study (72) and 19.3 months (N=65) in a second study (73). The results of the second study were compared to two previous phase II trials involving a similar patient population, in which temodar was combined with either thalidomide or accutane. Median survival for those trials was 14.1 months.

The moderately positive results of the just described trial are in conflict with a very similar trial (N=27) conducted at the Cleveland Clinic (74). In that trial median survival was only 8.6 months, notably worse than the outcomes obtained when temodar has been used without tarceva. How the conflicting results can be reconciled is unclear.

Erbitux (also known as cetuximab) is a monoclonal antibody, which differs from Iressa and Tarceva, which are small molecules, Because monoclonal antibodies are not believed to cross the blood-brain barrier, the natural expectation is that Erbitux would be ineffective against brain tumors. As a single agent, this seems to be true, as PFS-6 was only 10% for patients with recurrent high-grade gliomas (75). But when Erbitux was added during the radiation phase of the standard temozolomide protocol for 17 newly diagnosed patients (76), 87% of patients were alive at the end of one year and 37% were progression free. The median survival time had not been reached at the time of the report (an abstract at a meeting). It is possibly important to note that some investigators believe that radiation temporarily disrupts the blood-brain-barrier, which would allow a monoclonal antibody such as erbitux to reach the tumor.

An important development for identifying patients likely to respond to tarceva has come from a study (77) of glioma patients whose tumor pathologies were also assessed for their levels of a second protein called PKB/AKT. This is a signaling channel that results from inactivation of the PTEN gene, a tumor suppressor gene commonly mutated in glioblastomas. None of the tumors with high levels of PKB/AKT responded to treatment with Tarceva, whereas 8 of 18 tumors with low levels did respond to the treatment. A refinement of this approach tested for three different proteins: expression of PTEN, expression of EGFR, and of a mutation of the EGFR protein known as EGFR variant III

(78). The level of EGFR was not related to clinical outcome, whereas the co-expression of EGFR variant III and PTEN strongly predicted clinical outcome.

Because the inhibition of PKB/AKT should plausibly increase the effectiveness of EGFR inhibitors, a treatment strategy now being tested is the combination of EGFR inhibitors with rapamycin (trade name rapamune, generic name sirolimus), an existing drug used for organ transplants to suppress the immune system and prevent organ rejection, but which also inhibits mTOR complex 1, a tumor growth promoter downstream of AKT. A phase I trial (79) combined Iressa with rapamycin for 34 patients (25 GBM) with recurrent tumors; two patients had a partial tumor regression and 13 patients achieved stable disease. PFS-6 was 24%. A second clinical trial (80) with 28 heavily pretreated patients with low performance status (median Karnofsky score of 60) received either Iressa or Tarceva in combination with rapamycin, with the result that 19% of patients had tumor regression while 50% had stable disease, with a PFS-6 value of 25%. Yet a third clinical trial (81) that combined tarceva and sirolimus for recurrent GBM had much worse results, with PFS-6 value of only 3%.

An alternative method of suppressing the PKB/AKT signaling channel has been suggested by a recent *in vitro* study (82) in which Iressa and Tarceva were tested for efficacy against glioblastoma cells in the presence of the common anti-cholesterol drug, lovastatin. The effectiveness of the drugs was greatly enhanced by the combination, with the enhancing effect of lovastatin being independent of both level of EGFR variant III and PTEN status.

The foregoing results of the use of EGFR inhibitors for GBM treatment range from moderately positive to minimal efficacy. The reasons for this variability are not obvious, although treatment efficacy is likely dependent on numerous genetic markers. Thus, without a genetic analysis of individual tumors, it is hard to see a basis for recommending their use.

One recent paper (83) of potential major importance has noted that tumors may not respond to anti-EGFR drugs because of activation of the gene for a second growth factor known as the insulin-like growth factor receptor I (IGF1R). IGF1R has also been implicated as a source of resistance to tamoxifen and various other treatment agents. It is noteworthy, therefore, that two of the supplements to be discussed, silibinin and lycopene, are known to inhibit IGF-I. This suggests that silibinin and lycopene might substantially increase the effectiveness of any treatment that relies on EGFR inhibition. Metformin, a widely used diabetes drug, is also known to reduce the level of IGF-1, currently is under investigation as a treatment for several different kinds of cancer.

An important issue is how the effectiveness of EGFR inhibitors are related to the findings discussed earlier that metronomic schedules of temodar produce a large survival improvement for GBMs that have EGFR overexpression. All of the clinical trials discussed in this section used the standard temodar schedule, so it is unclear whether a metronomic schedule might produce different outcomes.

Gleevec (imatinib)

Gleevec (also known as imatinib), a small molecule which targets a specific gene involved in the growth of a form of leukemia, received a great deal of publicity because of its unprecedented effectiveness. As will be discussed later, this general strategy of identifying the growth signals for tumor growth and then targeting those signals, or their receptors, is one of the major new areas in cancer research. Such growth signaling channels often are involved in several different types of cancer. Although Gleevec was developed specifically for chronic myelogenous leukemia, it also has been shown to inhibit a more general type of growth signal, platelet-derived growth factor (PDGF), which is also involved in the growth of gliomas and other forms of cancer (e.g., small-cell lung cancer). Laboratory research has supported the importance of this similarity in that gleevec has been shown to strongly inhibit glioma growth, with the result that there now have been a number of studies reporting its use with high-grade gliomas. When used as a single agent for recurrent tumors, it appears to have minimal activity, as one study reported a PFS-6 value of only 11%, accompanied by an increased risk of intracranial hemorrhaging (84), although another study, using different dosage levels, did report a number of tumor regressions, which occurred very gradually over time (85). More promising results have been reported when gleevec is combined with hydroxyurea, an older drug that at one time was believed to be a radiation sensitizer among other functions. In the initial trial (86) with this combination, performed in Germany, 5 of 14 patients with recurrent glioblastomas had tumor regressions, another 5 had stable disease and 4 had disease progression. A subsequent study (87) confirmed this activity and reported a PFS-6 value of 32%, with 4 of 30 patients alive without evidence of tumor progression over two years after the initiation of treatment. Yet another study, done in the USA, (88) produced a PFS-6 value of 27%. However, in a much larger (N=220) multi-center clinical trial (89), results were much less positive, as PFS-6 was only 10% and median survival was 26 weeks.

These generally disappointing results using gleevec for brain tumors may have occurred for several different reasons. It may not readily cross the blood-brain-barrier, and it may engender different mechanisms of resistance than other treatment agents. In the study of gleevec for leukemia, for example, high levels of autophagy have been observed, which can be inhibited by the concurrent use of chloroquine or other autophagy inhibitors.

An important variation in the use of gleevec was to restrict its usage to patients with recurrent tumors who tested positive for overexpression of the platelet-derived growth factor receptor (90). PDGFR is overexpressed in 50-65% of tumors, especially tumors labeled secondary glioblastomas, which are believed to have evolved from lower-grade tumors (in contrast to de novo glioblastomas that occur without such evolution). For this restricted patient population, the PFS-6 value was 53%.

Vorinostat (Zolinza) and a role for epigenetics

A major new topic in oncology is epigenetics, the modification of gene expression by other aspects of the cell's biology. One source of gene-deactivation is an enzyme named histone deacetylase (HDAC). HDACs produce tight coiling of the chromatin, thus disrupting the uncoiling necessary for proper function of several critical genes, including those that produce cell-cycle regulatory proteins. By inhibiting HDAC, drugs such as vorinostat re-activates the genes that have been silenced, resulting in apoptosis for the mutated cells.

Vorinostat, sometimes known as SAHA, is FDA-approved for the treatment of cutaneous T-cell lymphoma, is a histone deacetylase (HDAC) inhibitor. To date one small clinical trial has tested vorinostat with patients with recurrent GBM (129). While PFS-6 was only 15%, several patients had extended progression-free intervals. More promising results were obtained when Vorinostat was combined with avastin and metronomic temodar (50 mg/meter-sq.) for 46 recurrent GBM patients. PFS-6 was 52%, with 2 complete responses, 17 partial responses and 20 stable disease (130). Vorinostat is known to be synergistic with various other agents, including gleevec and chloroquine, among others. For example, a case report of a patient with a pineoblastoma (131) used a combination of accutane and vorinostat, with the result that a complete regression was obtained, which persisted for at least three years (the last follow-up).

A potentially important sidelight on histone deacetylation is that a critical component of broccoli, and especially broccoli sprouts, sulforaphane, has been shown to be a powerful inhibitor of histone de-acetylation activity as measured by its level in circulating blood. This effect was shown with a single ingestion of 68 g of broccoli sprouts (207). The same article also noted that garlic compounds and butyrate had a similar effect.

5. Drugs Initially Developed For Other Purposes

There are a large number of drugs that were developed initially for various different purposes that subsequent laboratory research demonstrated to have significant anti-cancer properties. Given these old drugs have been used for years, have well-defined toxicity profiles, and are generally cheaper due to being off-patent, they offer the possibility of augmenting the benefits of the current standard treatment without significant additional toxicity. However, because their FDA approval is for different purposes, many if not most neuro-oncologists have been reluctant to take advantage of their possible benefits as components of a treatment cocktail. Some of these drugs have been investigated as single agents for brain cancer treatment and some have also been combined with the now standard Stupp protocol.

Accutane (isotretinoin, 13-cis retinoic acid)

When temodar has been combined with accutane, a retinoid used for acne treatment (also known as 13-cis-retinoic acid, or isotretinoin), the PFS-6 (for recurrent tumors improved from the 21% historical value of temodar alone, to 32% (96).

In contrast to the improvement in clinical outcome when accutane was combined with temodar for recurrent tumors, a clinical trial with newly diagnosed patients that combined temodar with accutane produced less impressive results (97). Fifty-five evaluable patients used both accutane and low-dosage temodar during radiation, followed by full-dose temodar + accutane, and produced a median survival time of only 57 weeks and a two-year survival of 20%, both below the survival rates from the large clinical trial with the same protocol that used temodar without accutane. A second, retrospective clinical trial in Canada (98) that combined accutane with temodar with newly diagnosed patients produced a median survival of 15.1 months and a two-year survival of 26.7%, both comparable to when temodar has been used alone.

Although accutane appears not to improve outcome when added to the standard temodar protocol, it does seem to have activity as a single agent. A phase II clinical trial evaluating accutane for recurrent gliomas was conducted at the M. D. Anderson Brain Tumor Center (99). The median survival time was 58 weeks for glioblastoma patients and 34 weeks for grade III gliomas. Aggregated over both tumor types (43 evaluable patients) 3 achieved a partial tumor regression, 7 had minor regressions, and 13 had tumor stabilization. A more complete report, using accutane with 86 glioblastoma patients with recurrent tumors was less impressive (100). Median survival time from the onset of treatment was 25 weeks and PFS-6 was 19%. Accutane now is used at M. D. Anderson as a "maintenance therapy" for patients after initial treatment with radiation or traditional chemotherapy. It also has been used in Germany for patients who have had a complete response to other treatment modalities as a maintenance therapy (101). The major side effects have been dry skin, cracked lips, and headaches, although occasional liver toxicity has also occurred. Increases in blood lipid levels frequently occur, often requiring anti-cholesterol medication such as Lipitor. Accutane also may produce severe birth defects if taken during pregnancy.

Although various data now suggest that accutane should not be combined with chemotherapy (for example, see the discussion on page 39 called *A trial of 3 repurposed drugs plus temodar*), a series of studies with various types of cancer, including pancreatic, ovarian, colorectal, and melanoma (although not yet with brain tumors), suggest it can be very effective for patients who get a good response from their initial treatment protocol. This is especially relevant to GBM patients who have clean MRIs either after surgery or after treatment with radiation and chemotherapy. An example of the protocol with ovarian cancer involved 65 patients who received the standard treatment of a taxane and a platinum drug (316). After one year of the standard treatment those receiving a benefit were moved to a maintenance treatment using subcutaneous low-dose IL-2 plus oral 13 cRA at a dose of 0.5 mg/kg. This plan was continued for one year after which frequency of dosing was gradually reduced. Patients receiving this treatment plan had a median PFS of 23 months and a median survival of 53 months. Concomitantly, various measures of immune function (lymphocyte count, NK cell count) were substantially improved and there was a substantial reduction in the level of VEGF, reflecting a reduction in angiogenesis.

Celebrex (and other NSAIDs)

Carcinogenesis of several types involves an inflammatory process. When anti-inflammatory drugs such as aspirin or ibuprofen are taken on a regular basis the incidence of colon cancer is reduced as much as 50%. This substantial effectiveness has motivated investigation of the mechanisms of these benefits. One component of the inflammatory process is angiogenesis, which is now believed to be a critical component of cancer growth. COX-2 enzymes play an important role in inflammation, so that COX-2 inhibitors should reduce angiogenesis and inhibit tumor growth. Many nonsteroidal anti-inflammatory drugs (NSAIDs) are known to be COX-2 inhibitors, but most (e.g., ibuprofen) also inhibit COX-1 enzymes, which are necessary for healthy maintenance of the stomach lining, which is why many users of NSAIDs eventually develop intolerance to them. Thus, much recent attention has been given to the new COX-2 inhibitors such as Celebrex that were developed to avoid COX-1 inhibition for the purposes of arthritis treatment. Because inhibition of angiogenesis is one of the major new approaches to the treatment of cancer, some oncologists have begun adding Celebrex to their regular treatment protocols, based on laboratory findings that COX-2 inhibitors inhibit tumor growth. In recent meetings of American Society for Clinical Oncology (ASCO), there have been various clinical trials reported that combined one or another COX-2 inhibitor with conventional radiation, chemotherapy, and new targeted treatments. The great majority of these were phase 2 clinical trials which had only historical controls with the conventional treatment alone to assess the value of the added COX-2 inhibitors, but most concluded there appeared to be a significant benefit, Some larger randomized clinical trials (115, 116) have shown substantial outcome improvements when celebrex has been added to standard chemotherapy protocols, but others have failed to find a benefit.

Two clinical trials have been reported that have used celebrex in the treatment of gliomas In a clinical trial conducted jointly by several hospitals in New York, temodar was combined with celebrex (117). For the 46 patients in the study (37 with GBM), the PFS-6 was 35%. However, an unusual schedule of temodar was also used, so whether the results were due to the new schedule or the celebrex is uncertain. Celebrex has also been combined with CPT-11 (118), a chemotherapy agent used widely for colon cancer, with patients with recurrent tumors, and produced a PFS-6 value of 25%.

Because of the mild toxicity of NSAIDS, considerable recent research has investigated the mechanisms of their clinical benefit. Whereas initial research focused on the anti-angiogenic properties of this class of drugs, several other mechanisms have been identified, including the enhancement of various aspects of the immune system, and inhibition of the genes that prevent damaged cells from undergoing apoptosis (119). It is critical to note that many of the mechanisms by which NSAIDS work are strongly involved in the growth of high-grade gliomas, and that the expression of the cyclooxygenase enzyme that is the target of COX-2 inhibitors correlates strongly with the proliferation rate of glioblastoma tumors and correlates inversely with survival time (120, 121).

Chloroquine

See page 10 for a discussion of chloroquine and hydroxychloroquine as additions to standard treatments.

Cimetidine (Tagamet)

A strong candidate for a nontoxic addition to standard therapy is the old stomach acid drug, cimetidine (trade name Tagamet). While no clinical studies have yet been reported using it with brain cancer, very impressive results have been reported from its use with colon cancer (132), the rationale being that it decreases cell migration (and hence the spread of the tumor beyond the original site) by affecting the critical genes controlling cellular adhesion. Support for its use comes from a recent experimental study using mice with implanted glioblastoma tumors that received either temozolomide or temozolomide + cimetidine (133). Survival was substantially longer in the latter group. One important caveat about cimetidine is that it has the potential to interact with numerous other drugs in terms of their metabolism in the liver, thus affecting their effective concentration.

Clomipramine (chlorimipramine)

This old FDA-approved drug was first used for the treatment of depression, and now also for treatment of obsessive-compulsive neuroses. Its rationale as a treatment for gliomas is that it selectively depresses mitochondrial function in glioma cells while leaving normal cells unaffected, causing the glioma cells to undergo apoptosis (programmed cell death). Reported at the 2005 ASCO meeting (122) was a clinical trial evaluating the outcome of its use with 27 patients with high-grade gliomas (the distribution of GBMs vs. grade 3 tumors was not reported in the abstract, nor was the clinical history of the patients). Chlorimipramine was added to their conventional treatment with doses from 25 mg daily escalated to 150 mg daily. Median survival was 27 months; 20 of the 27 patients showed partial tumor regressions. This appears to be a promising new treatment, although additional testing with more detailed reporting of the results is clearly needed. An interesting sidelight on chlorimipramine is that laboratory research has shown that it strongly potentiates the toxicity of gleevec for glioma cells (123).

Dichloroacetate (DCA)

This simple chemical compound has been used for the treatment of childhood lactic acidosis, a disorder of the mitochondria that control a cell's energy production. Its use as a cancer treatment is based on the Warburg Effect, the finding that cancer cells are much more likely to utilize anaerobic metabolism, a very inefficient process, even in the presence of sufficient oxygen. DCA affects the membrane of the mitochondria, thus inhibiting the anaerobic metabolism, which results in changes in the cell's microenvironment that can cause the cancer cells to die.

Because DCA is a simple chemical, it can be easily manufactured, which caused early experimental reports of its effectiveness against cancer to motivate many cancer patients to take it on their own. Only recently has there been a report from a clinical trial that seems to corroborate the earlier laboratory results (124). A group in Alberta, Canada reported the results for five GBM patients, three with recurrent tumors even after multiple forms of therapy, and two who were newly diagnosed, who received DCA in combination with the standard temozolomide protocol. One of the three recurrent tumor patients died after three months, due to massive edema from his very large tumor present prior to DCA treatment. All of the others were alive as of the follow-up period of 18 months from the start of therapy. Patients were treated with an oral starting dose of 12.5 mg/kg twice per day, escalated to 25 mg/kg twice per day. The only apparent significant toxicity was peripheral neuropathy, which was reversible. Doses of 6.25 mg/kg twice per day produced no neuropathy. The authors noted that the serum concentration required 2-3 months to reach therapeutic concentrations. A notable recent laboratory finding using implanted GBM cells in a mouse xenograft model showed a dramatic synergy between DCA and avastin with a coherent rationale for why such synergy should occur (125).

Disulfiram (Antabuse)

This old drug has been used for decades for the purpose of preventing alcohol consumption. A great deal of research in Germany has shown it also has several anti-cancer properties. With regard to GBM treatment, one of its mechanisms is to block the glycoprotein pumps that extrude the chemotherapy agents from the cell body before they have had a chance to be effective. It also inhibits the MGMT enzyme that allows the cell to repair treatment damage before the cell undergoes apoptosis (programmed cell death), and metalloproteinase activity, which is a primary mechanism by which GBM cells invade adjacent tissue. Perhaps most important it also inhibits the growth of stem cells, which are now believed to be the major source of treatment failures. When alcohol is not consumed, it has minimal toxicity. There is also evidence that its anti-cancer effects are potentiated by the concurrent use of copper gluconate, a common nutritional supplement.

Keppra (levetiracetam)

Keppra (levetiracetam) was approved by the FDA in 1999 as an anti-seizure medication, and the drug has since become perhaps the most commonly prescribed agent for seizure prevention in brain tumor patients. Laboratory studies have shown that Keppra can inhibit the activity of the DNA-repair enzyme MGMT and sensitize glioblastoma cells to temozolomide chemotherapy (206). Furthermore, retrospective studies in newly diagnosed glioblastoma patients show that the use of Keppra during chemotherapy can lead to significantly increased progression-free and overall survival. In one such study by Korean investigators (323), 58 glioblastoma patients who received Keppra for at least three months during temozolomide chemotherapy were compared with 45 patients who received standard treatments without extended Keppra use. Patients receiving Keppra during chemotherapy had a median progression-free survival of 9.4 months versus 6.7 months in the group not taking Keppra, a highly significant difference (HR=0.42, p=0.004 in multivariate analysis). Likewise, overall survival was also extended in the patients receiving Keppra: median OS was 25.7 months versus 16.7 months in the patients not taking Keppra (HR=0.31, p=<0.001). Whether the apparent survival advantage for patients taking Keppra during standard chemotherapy is restricted to patients with unmethylated MGMT status remains to be determined.

Proton Pump Inhibitors

Cancer cells of all varieties thrive in an acidic environment. They also produce large amounts of lactic acid due to their reliance on anaerobic metabolism. Proton pumps are critically involved in extruding the intracellular acid to the extracellular microenvironment. Proton pump inhibitors, which were developed for heartburn due to excess stomach acid, can disrupt this extrusion, and hence suppress tumor growth. A variety of recent evidence indicates that pretreatment of cancer cells with PPIs causes the cells to become much more sensitive to cytotoxic drugs (19), and also to DCA (126). Importantly, the effect occurs only when the PPI is begun prior to treatment, because it takes 1-3 days to fully suppress the proton pump. Evidence for the clinical benefit of PPIs (in vivo) comes from a study of pet dogs and cats with various kinds of cancer. Thirty-four cats and dogs given lansoprazole (Prevacid) prior to their normal chemotherapy were compared to 17 dogs and cats receiving only the chemotherapy (127). Twenty-three of the patients receiving the PPI had a complete or partial response, and the remainder had stable disease and improved quality of life. Of patients that received only the chemotherapy, only 3 (17%) had a partial response (of short duration) and the remainder died of progressive disease within two months.

The clinical efficacy of proton pump inhibitors for human patients is supported by a Chinese study of metastatic breast cancer (128) that compared conventional chemotherapy alone with chemotherapy in combination with 100 mg of nexium twice per day, or in combination with 80 mg of nexium twice per day. The median PFS values were 7.5 months for those receiving only chemotherapy, 9.5 months for those with the 100 mg dose and 10.9 months for the 80 mg dose. The greater PFS value with the lower nexium dose suggests that even lower doses might also be efficacious.

Tamoxifen

This drug is well known for its usage in the treatment of breast cancer. Its mode of action is to compete with estrogen for attachment to the estrogen receptors of breast cells, thus reducing estrogen's ability to serve as a growth factor for carcinogenesis. This mode of action has little to do with tamoxifen's ability to serve as a therapeutic agent for gliomas. Effects on glioma are instead due to tamoxifen being an inhibitor of protein kinase C activity - an intracellular enzyme that is involved in glioma cell proliferation. Protein kinase C is now also known to play a significant role in stimulating angiogenesis. To obtain inhibition of PKC activity, and thus slow or stop the growth of the cancer cells, very high doses of tamoxifen are used, in contrast to its usage for breast cancer. The typical dosage for breast cancer is 10-20 mg daily, while for gliomas the dosage used has ranged from 160-240 mg per day. This high dosage is potentially problematic and does indeed have side effects. The most important is an increased risk of blood clots. For women, there is also an increase in the risk for uterine cancer, and for men, impotence and loss of libido are frequent problems. Weight gain is another significant side effect. Overall, however, such side effects are mild in comparison to traditional chemotherapy.

A phase II clinical trial (102) evaluating the effects of tamoxifen for patients with recurrent gliomas produced tumor regression in 25% of patients and stabilization of tumor growth for an additional 20% of patients. The percentage of patients with responses to treatment was greater with Grade III Astrocytomas than for patients with GBMs. The median survival time from the initiation of tamoxifen treatment was 16 months for Grade III tumors and 7.2 months for glioblastomas. This perhaps seems to be a minimal benefit (survival time for recurrent glioblastomas typically ranges from 3-7 months when second-line chemotherapy is used) but it should also be noted that a percentage of those who had either regression or stabilization had survival times greater than two years. Thus, for those "responders" tamoxifen produced a major benefit.

Tamoxifen has been studied as a single agent, in combination with radiation, in a clinical trial with 77 newly diagnosed GBM at a dose of 80 mg/m-sq. (103). Median survival was 11.3 months, not notably better than studies with radiation alone. Here long–term survival was not evident, as only 9% of patients lived longer than two years.

Tamoxifen has also been used in combination with traditional chemotherapy, because it should in principle reduce the level of chemo-resistance in addition to having its own direct effects on tumor growth. A European clinical trial combined tamoxifen with carboplatin as the initial treatment after radiation (104). Dosages of tamoxifen ranged from 40 to 120 mg/day, all of which were smaller than that used when tamoxifen has been used alone (160-240 mg/day). Combined over all dosages, the 12-month and 24-month survival rates were 52 and 32 %, respectively. For the patients receiving the highest dosage of tamoxifen, 12-month survival rate was 78%. In comparison, a matched set of subjects who received carboplatin alone after radiation had 12- and 24-month survival rates of 30% and 0%. However, a second similar study combining tamoxifen with carboplatin (105) reported a median survival time of only 55 weeks, which was only slightly superior to historical controls using carboplatin alone (48 weeks). However, the latter study noted that a minority of patients did have unusually long survival times, which was not reflected in the median survival times. The combination of carboplatin and tamoxifen has also been studied with patients with recurrent tumors. Here the median survival time was 14 months, but only 6 months for the subset of 16 patients with GBM (106).

Tamoxifen with a dosage of 240 mg/day has also been studied in combination with BCNU as the initial treatment after radiation (107). Median survival time was 69 weeks, while the 1-year, 2-year, and 3-year survival rates 65%, 45% and 24%, respectively. It should be noted that while the 1-year survival rate and median survival time are only marginally greater than those obtained with BCNU alone, the 2-year and 3-year survival times are substantially greater. Note, however, that these numbers are based on a small number of patients (N=23). This benefit in terms of the number of longer-term survivors again reflects the fact that tamoxifen is effective only for a minority of patients, but for those its benefits can be very substantial. That only a minority of patients benefit from tamoxifen is relevant to the negative results of a phase III trial conducted in France (108). Patients received BCNU alone or BCNU in combination with 40-100 mg/day of tamoxifen (note that these dosages are substantially below that used in the other studies).

No increase in median survival time was found, whereas the addition of tamoxifen did significantly increase the frequency of serious blood clots.

Several clinical trials have studied tamoxifen in combination with temodar. In one preliminary report with sketchy details (109), the combination treatment, presented as the initial treatment after standard radiation, resulted in all of the patients being alive at 12 months after diagnosis. More details are clearly needed, but the results as described are unusually promising. However, a second published trial combining temodar and tamoxifen (110) produced especially negative results and was in fact terminated early because of the low response rate and frequency of toxicity. However, this toxicity most likely resulted from the daily schedule of TMZ used, which involved a dose apparently too high for patients that were heavily pretreated. One important feature of tamoxifen is that its toxicity to glioma cells is due primarily to its first metabolite, which takes 2-8 weeks to reach asymptotic levels. Thus, short-term usage, even with high dosages, is not likely to be effective.

A third study (111) combining tamoxifen with the standard Stupp protocol (N=17) used a dose of 100 mg/m-sq., and reported a median survival of 17 months and a 2-year survival of 35%, slightly better than the Stupp protocol alone.

The most recent report (112) of using the combination of tamoxifen with temozolomide was with recurrent tumors (N=32) and used an alternating week schedule of temozolomide. Patients had previously received temozolomide according to the usual schedule. After start of the new schedule combined with tamoxifen, median time to tumor progression was 7 months and median survival time was 17.5 months, unusually high for recurrent tumors. The tamoxifen dose was 80 mg/sq. meter. In addition, the authors reported no difference in outcome as a function of the MGMT status of the tumors.

An important development with respect to tamoxifen has been the report (113) that it may be possible to predict which patients will be among the minority that benefits from tamoxifen. This Canadian study compared patients who responded to tamoxifen with those who did not and reported that there was a systematic difference in the metabolites from tamoxifen. This potentially allows a decision very early in treatment about whether tamoxifen is worth continuing.

Tamoxifen's efficacy can be increased by suppressing thyroid function (114). Thyroid hormones maintain the level of the insulin-like growth factor (IGF), which is now known to play an important role in causing resistance to several different kinds of cancer treatments. Eleven of 22 patients with recurrent tumors became hypothyroid as a result of a drug treatment. Their median survival time was 10.1 months, versus 3.1 months for patients whose thyroid function was not effectively suppressed. However, no information is available for how thyroid suppression affects survival time, independently of whether tamoxifen is used.

Thalidomide

This drug became infamous during the 1950s and 1960s because it produced a large number of birth defects involving abnormal or completely missing limbs. It is now believed that this was due to its effects on inhibiting new blood vessels because limb buds are especially dependent on the growth of new blood vessels for normal development. Thalidomide was initially approved by the FDA for the treatment of leprosy, but now also is approved for multiple myeloma. It also has several common off-label uses, including melanoma, Kaposi's sarcoma, and prostate cancer. Unfortunately, a considerable amount of paperwork is necessary, both by the pharmacist and the prescribing physician, so obtaining it for off-label uses is not as simple as having your physician write a prescription. These bureaucratic restrictions have been imposed despite the fact that the majority of potential users of the drug, males, and females past the age of menopause, are unaffected by the drug's teratological potential.

Thalidomide's utility as a cancer treatment comes from it being the first anti-angiogenic drug that has been FDA approved, although it is now believed to have other mechanisms of action as well. The major side effects are somnolence (thalidomide was originally introduced for its sedative purposes), constipation, and neuropathy with long-term use.

The best results using thalidomide as a single agent comes from a small study performed in Switzerland (91). Nineteen glioblastoma patients received 200 mg/day of thalidomide, starting after radiation, escalating to 600 mg/day if tolerated. The actual median dose used was 200 mg/day. Median survival time was 63 weeks. Median progression-free survival was 17 weeks. Some patients had surgery for recurrent tumors so it is difficult to know how much of the survival time was due to the additional surgery. The same study also reported the results of 25 patients who received the same regimen of thalidomide but in combination with temozolomide. Here the median survival time was 103 weeks and the median progression-free survival was 36 weeks.

A subsequent study produced a more conservative estimate of the benefits of the temodar + thalidomide combination. In contrast to the median survival time of 103 weeks from the clinical trial just described, this second trial using the combination of temodar + thalidomide with newly diagnosed patients produced a median survival time of 73 weeks, marginally better than the 61 weeks from the now standard treatment of temodar alone (92). Two differences in their protocols are evident: first, the latter study used temodar and thalidomide during radiation which was then continued after radiation was finished; the earlier study began the temodar and thalidomide only after the standard radiation treatment was completed. Secondly, the dosage of thalidomide was considerably less in the earlier study. This latter difference is interesting because clinical trials using thalidomide as a single agent seem to have better results with lower dosages of the drug. It is possible, but not proven, that the dose-effect curve for thalidomide is non-monotonic just as it appears to be for some other agents that have angiogenesis as their target.

However, the most likely difference in the results for the two studies is that the earlier study included many patients who had re-operations for their tumors when they recurred, while there is no mention of re-operations in the latter study. When the number of patients who were progression-free at one year is considered (a measure that is not affected by any role of re-operation), the two studies have essentially identical results (28-29%). In any event, both studies show an improvement over the results with the standard treatment protocol. However, a subsequent study failed to find an improvement in outcome from adding thalidomide. (92). When the combination of temodar + thalidomide has been used with patients with recurrent GBM (93), PFS-6 was 24%.

Other trials have combined thalidomide with chemotherapy agents other than temozolomide. A clinical trial involving the combination of thalidomide with carboplatin for recurrent glioblastomas was reported at the 1999 meeting of the American Society for Clinical Oncology (94). Of 46 patients assessable for efficacy, 5 had a partial regression, 28 had stable disease and 13 had progressive disease. Estimated median survival for all patients was 40 weeks. When thalidomide was combined with BCNU (95) for recurrent GBM (N=38). PFS-6 was 27% (with 9 of 38 patients having some degree of tumor regression), a significant improvement over the 15% PFS-6 value from the historical database. Thus, while the reports of thalidomide's efficacy have been inconsistent, the weight of the evidence suggests it adds to treatment efficacy, although probably not a large amount.

A major exception to the generalization that thalidomide has limited benefit comes from an Austrian study (317) in which apparent survival benefits were restricted to patients with "secondary" GBM, i.e. those that evolved from initially lower-grade tumors. Twenty-three patients whose tumors had advanced after both radiation and chemotherapy received 100 mg of thalidomide nightly, in part to help with their sleep. The median survival time after the start of thalidomide was 18 months, substantially longer than typically obtained with recurrent GBM. It should be noted that the 100 mg dosage is much lower than the studies in which thalidomide had limited benefits.

Valganciclovir (Valcyte)

Since 2002, Charles Cobbs and others have demonstrated a role of human cytomegalovirus in promoting the progression of glioblastoma tumors, the majority of which are positive for CMV proteins. This has led to the conjecture that treatment of brain tumors with anti-CMV drugs such as valganciclovir (Valcyte) could have therapeutic benefit. A small clinical trial using this approach has been conducted at the Karolinska Institute in Sweden. Forty-two patients were randomly assigned to the standard Stupp protocol versus the Stupp protocol combined with valcyte (173). Although there were some differences in tumor volume, these did not reach statistical significance, nor did the median survival time (17.9 vs. 17.4 months). However the design of the study allowed patients to receive valcyte when their tumors progressed or after six months, thus confounding the determinants of the outcome.

Accordingly, the authors did a post-hoc analysis of patients who had at least six months use of valcyte. For those patients, median survival was 24 months and 4-year survival of 27%. A subsequent report analyzed the trial patients with at six months exposure to valcyte, along with others receiving the treatment outside of the trial (174). For these patients, 2-year survival was 70% and median survival was 30 months.

The benefits of valcyte seem partly dependent on the degree of CMV infection (175). For patients with low-grade infection, median survival was 33 months, while those with high-grade infection had a median survival of 14 months.

The retrospective analysis described above has generated a great deal of controversy, mostly centred around the built-in bias inherent in such a time-dependent analysis (technically termed "immortal time bias"). Properly designed trials will be necessary to prove the efficacy of Valcyte for glioblastoma. In the meantime, many patients impressed with the results of the retrospective analysis have included Valcyte in their treatment regimens, with or without their oncologist's blessing.

Valproic acid/sodium valproate (Depakote)

A common anti-epileptic drug, valproic acid (trade name Depakote), is an inhibitor of histone deacetylase (discussed in the section on epigenetics). It also has the advantage of not inducing liver enzymes that reduce the concentration of chemotherapy agents in the serum, which does occur when using many other anti-epileptic drugs (in fact valproic acid may increase concentration of chemotherapy, so that the standard dosages need to be monitored for toxicity. That its use rather than other anti-epileptic drugs might improve clinical outcome is supported by a retrospective clinical trial comparing enzyme-inducing anti-convulsants with valproic acid. Median survival for the former was 11 months, while median survival for those receiving valproic acid was 14 months (203). Similar results were obtained in a post-hoc analysis of the Stupp trial that definitively showed the effectiveness of temozolomide (204). For patients receiving the combined temozolomide + radiation protocol, median survival was 14 months for those not using any anti-convulsant drugs, 14.4 months for those using a drug other than valproic acid, and 17. 4 months for those using valproic acid. A similar pattern occurred for the rate of 2-year survival: 25%, 26% and 30.6%.

A similar retrospective study from the Sloan-Kettering dataset produced a similar result. Patients using valproic acid had a median survival of 16.9 months versus 13.6 months for those using other antiseizure medications. When the analysis was restricted to patients receiving valproic acid during radiation, the corresponding median survivals were 23.9 months vs. 15.2 months (318).

The most impressive results with valproic acid were reported by the brain tumor center at the National Cancer Institute at the 2014 SNO meeting. In a prospective study of 37 newly diagnosed patients, valproic acid was used during combined chemoradiation only. Median survival was a very impressive 29.6 months and median PFS was 10.5 months. The study was published in full in July 2015 (319).

Although the foregoing results support the use of valproic acid because of its ability to inhibit HDAC, a recent Korean study directly compared 38 patients prospectively enrolled to receive Keppra with 42 patients taking valproic acid as a control group. Median progression free interval was 9.3 months for Keppra vs. 6.5 month for valproic acid. Overall survival was 26 months vs. 16 months (205). This abstract does not include full details of drug dosing or scheduling, and it is possible that valproic acid is more effective as an adjuvant during the radiation phase of treatment, while Keppra may be more effective during monthly temozolomide cycles, especially for those tumors with unmethylated MGMT. *See page 32, above, for a discussion of Keppra as a chemosensitizer in glioblastoma therapy.*

A trial of 3 repurposed drugs plus temodar

The above list of drugs do not exhaust the list of older drugs that have the potential to improve treatment outcome when added to standard treatment. The critical issue is whether using combinations of these drugs actually does improve outcome in the clinic.

The most disappointing outcome has been for a treatment combination involving temodar, thalidomide, and celebrex for newly diagnosed patients (134). Fifty GBM patients received the standard radiation therapy followed by the standard monthly schedule of high-dose temodar in combination with celebrex and thalidomide. Median survival from the time of diagnosis was 16.1 months and 2–year survival was 21%, seemingly not an improvement over the current gold standard of treatment.

More positive results were obtained in a study (135) of different combinations of temodar, thalidomide, accutane, and celebrex. Although the goal of the study was a factorial design of different 2 –and 3-way combinations, not enough patients were recruited into the various arms of the study to conduct the planned comparisons at the time of the initial report. Forty-two patients were assigned to receive temodar alone (with an alternating week schedule), or temodar in combination with one or more additional drugs. For unclear reasons 19 of the 42 patients received temodar alone and 23 patients received some combination. Unfortunately, results were reported in aggregate without any distinction between patients receiving the different combinations, nor any distinction between those receiving only temodar versus temodar + additional therapy. Nevertheless, median survival was 20 months and two-year survival rate was 40%, despite the inclusion of 12 patients who never received any of the combinations due to early progression. The authors also noted that ten patients were alive 4.8 to 6.9 years from entry into the study.

A follow-up report after the number of patients was expanded to 155 was presented at the 2012 ASCO meeting (136), and published in full in Neuro-Oncology in September 2014 (advance online access) (307). Patients were randomized into one of eight arms, with approximately 20 patients in each arm:

- temodar alone
- temodar+isotretinoin (Accutane)
- temodar+celecoxib
- temodar+thalidomide
- temodar+isotretinoin+celecoxib
- temodar+isotretinoin+thalidomide
- temodar+celecoxib+thalidomide
- temodar+isotretinoin+celecoxib+thalidomide

Thus, for each of the three additional drugs, there were four arms that included that drug, and four arms not including that drug. The primary objective of the study was to judge the efficacy of the three additional drugs by comparing the four arms including a drug versus the four arms not including that drug, in terms of progression-free survival measured from the time of randomization. The four arms including celecoxib showed a trend toward improved progression-free survival compared to the four arms not including celecoxib (hazard ratio=0.8), though the effect did not reach formal statistical significance. The four arms including isotretinoin and the four arms including thalidomide had worse outcomes than the arms not including these agents (hazard ratios of 1.3 and 1.2 respectively), though again the differences did not reach formal statistical significance.

When each of the 8 treatment arms were compared individually, temodar plus isotretinoin led to significantly worse outcomes than temodar alone (hazard ratios of 2 and 2.2 for progression-free survival and overall survival compared with temodar alone). The combination of temodar+celecoxib had an outcome equivalent to temodar alone (hazard ratio=1). All other combinations had inferior outcomes to temodar alone, though as only approximately 20 patients were included in each arm, only the temodar+isotretinoin combination reached statistical significance (worse survival compared with temodar alone). Thus, with the dosages and schedules used in this study, both isotretinoin and thalidomide appeared to be antagonistic when combined with temodar, with the antagonistic effect of isotretinoin on temodar efficacy appearing especially significant. Other results with thalidomide cited above (91-95, 317) argue that at least with some usage parameters thalidomide can be effective, with some indication that lower dosages are more effective.

CUSP9 (Co-ordinated Undermining of Survival Paths) with 9 repurposed drugs

A paper appearing in April 2013 introduced a “conceptually new” approach for recurrent glioblastoma (10). In this paper, various repurposed drugs in addition to metronomic temozolomide are proposed as part of an extensive treatment cocktail, including aprepitant (an anti-nausea drug), artesunate (a malaria drug), disulfiram (discussed above), sertraline (an anti-depressant), captopril (an ACE inhibitor used for hypertension), auranofin (a gold compound used for arthritis), nelfinavir (an HIV drug), and ketoconazole (an anti-fungal drug). In the updated version of this combination, called CUSP9* (306), ritonavir has been substituted for nelfinavir, itraconazole replaced ketoconazole, copper gluconate was removed, and celecoxib was added. All of these have extensive in vitro evidence for inhibiting various biochemical processes underlying glioblastoma growth, but none as yet has traditional evidence from human clinical trials. However, the main argument of the authors of the article is that tests of individual treatment agents in isolation are doomed to failure, because there are multiple growth pathways that must be inhibited simultaneously.

6. Over-the-Counter Drugs and Supplements

The treatments discussed above generally require a physician’s cooperation in prescribing them. However, there are a number of agents available over-the-counter that have promising anti-cancer properties, and it is reasonable to believe that these can increase the chances of surviving. Some of these with supporting clinical evidence (e.g., proton-pump inhibitors such as Prilosec) have been discussed above. A frequent conflict between patients and their oncologists is that patients, often desperate to find treatment agents that will improve their chances of survival, are eager to use such adjunctive treatment while their oncologists generally oppose using such supplementary agents, on the ground that they might interfere with the standard treatment. While negative interactions are possible, to date there have been very few if any documented cases. Given the bleak prognosis of a glioblastoma diagnosis, my belief is that concerns about negative interference are misplaced and get in the way of potentially useful treatment adjuncts. However, it is important to attend to the evidence supporting the use of any specific agent under consideration, as there are many products on the market that are hyped, supported only by testimonials of dubious validity, and some have the potential for harm.

Melatonin

This is a naturally occurring hormone secreted by the pineal gland that regulates the body's diurnal rhythm. It is commonly used for the treatment of jet lag and for insomnia. It is readily available in any health food store and most drug stores. Its role in cancer treatment has been based on the assumption that it boosts the immune system, with the current hypothesis being that it augments the activity of T-helper cells. It recently also has been shown to inhibit angiogenesis (225). It may also have direct cytotoxic effects on some types of cancer cells, notably melanoma cells. It has no known toxic side effects.

Clinical research on the use of melatonin for cancer treatment has been done primarily in Italy, where it has been used either as a single agent after radiation treatments, or in combination with various chemotherapy or immunotherapy regimens, most frequently interleukin-2. Part of the rationale for such combinations is that it decreases the side effects of the chemotherapy, especially with respect to blood counts. One of the clinical studies (226) randomly assigned GBM patients either to radiation-alone or to radiation concomitant with 20 mg/day of melatonin. Melatonin was continued after completion of the radiation. Survival was significantly greater for subjects receiving the melatonin. In terms of one-year survival rates, 6/14 patients receiving melatonin were alive, while only 1/16 patients without melatonin was alive.

This GBM study involved a relatively small number of patients, so that the effects should be considered tentative until a larger study is conducted. However, comparable effects have been reported in a similar design for the use of melatonin with advanced lung cancer (227). Like the GBM study, a substantial increase in survival rate occurred for the patients receiving melatonin.

To date there have been at least a dozen phase-2 clinical trials using melatonin either alone or in combination with other agents and five phase-3 trials involving random assignment of subjects to melatonin versus some type of control group. The majority of these has been relatively small and has involved patients in the terminal stages of their disease, which is perhaps why American oncologists have largely ignored them. However, some trials have been much larger and seem to leave little doubt that melatonin significantly increases the efficacy of chemotherapy. One of the most extensive randomized clinical trials involved 250 patients with advanced metastatic cancer of various types (228). Patients were randomly assigned to chemotherapy alone (using different chemotherapies for different types of cancer) or chemotherapy plus 20 mg of melatonin per day. Objective tumor regression occurred in 42 (including 6 complete regressions) of 124 patients receiving melatonin but in only 19/126 (with zero complete regressions) of the control patients. A comparable difference occurred for survival rate: 63/124 of those receiving melatonin were alive after one year while only 29/126 were alive of those receiving chemotherapy alone. A different trial, involving 100 patients with metastatic non small-cell lung cancer (229), compared chemotherapy alone with chemotherapy in combination with melatonin. With chemotherapy alone, 9 of 51 patients had a partial tumor regression, while 17 of 49 chemo + melatonin patients had either a complete (n=2) or partial (n=15) regression. Twenty percent of the chemo-alone patients survived for one year and zero for two years, while the corresponding numbers for chemo + melatonin were 40% and 30%. Melatonin not only increased the efficacy of chemotherapy, but also significantly reduced its toxicity.

The most extensive report included 370 patients, subdivided into three different types of cancer: lung cancer (non-small cell), colorectal cancer, and gastric cancer (230). Aggregated over all three types, the response rate (percentage of patients with tumor regression) was 36% for those treated with chemotherapy and melatonin, versus 20% for those treated with chemotherapy alone. The corresponding two-year survival rates were 25% vs. 13%. Melatonin's benefits occurred for all three cancer types that were included. Moreover, patients receiving melatonin had fewer side effects.

These trials leave little doubt that the effects of melatonin are of clinical significance. Moreover, a recent study has shown that using multiple components of the pineal gland secretions instead of melatonin alone enhances clinical effectiveness still further (231). One caveat about the use of melatonin is that a recent randomized trial compared radiation treatment for metastatic brain cancer with and without melatonin and found no benefit of the melatonin (232). Given that almost all of the supporting evidence for the use of melatonin has come from its addition to chemotherapy, it is possible that it offers no benefit when added to radiation, perhaps because of its strong antioxidant properties.

PSK and other polysaccharides

PSK is the abbreviation for polysaccharide krestin (sometimes known simply as krestin), which is an extract from the mushroom, Coriolus versicolor. It has become a standard component of cancer treatment protocols in Japan (a Chinese version of the same extract is known as PSP) for many different kinds of cancer, predicated on the assumption that it is an immune-system enhancer. Among the effects on the immune system that have been identified are gamma-interferon production, interleukin-2 production, and in increase in T-cell activity. Other effects include inhibition of matrix-degrading enzymes that underlie tumor invasion of adjacent tissue, and the inhibition of angiogenesis. Numerous clinical trials have been conducted in Japan comparing chemotherapy regimens with the same regimens with PSK added, for a variety of different cancers, most frequently stomach and colon cancer.

In one representative study, with non-small cell lung cancer (233), stage I patients receiving PSK (3 g/day) had a five-year survival rate of 39% compared to 22% for patients not receiving PSK. For stage III patients, the 5-year survival rate with PSK was 16% versus only 5% for those not receiving PSK. Both differences were statistically significant. A meta-analysis of several different clinical trials with colorectal cancer (over 1000 patients) who were randomized to receive either the standard chemotherapy or the standard chemotherapy in combination with 3.0 g/day of PSK showed that the addition of PSK increased both the survival rate and the duration of disease-free survival, with relative risks of .71, and .72, respectively (234). The three-year disease-free survival rate was 81% for patients receiving PSK, compared to 69% for those receiving only chemotherapy. I have found only one study that used PSK in the treatment of glioma, in combination with ACNU (a chemical cousin of BCNU) and vincristine (235). The survival rate for 25 GBM patients after one, two, and three years was 56%, 37%, and 12%, respectively. No control condition was studied that did not receive PSK, so exactly what its effect was is unclear. Note, however, that the two-year and three-year survival rates are substantially greater than that typically seen for GBM following traditional treatment with chemotherapy alone.

The source for PSK that I have used is JHS Natural Products in Eugene, Oregon (phone # 541-344-1396 or 888-330-4691; website:www.jhsnp.com). Other sources undoubtedly can be found through a web search. Other mushroom extracts that also have the long-chain polysaccharides (beta-glucans) that appear to be the active ingredient in PSK are more readily available. These include maitake, reishi, and shiitake mushrooms. However, none of these has the same level of scientific evidence for treatment efficacy in human clinical trials. Maitake D-fraction seems an especially promising mushroom extract based on a laboratory study of chemically induced tumors in mice (236). Tumor growth was inhibited 90% when the mushroom extract was combined with chemotherapy versus an inhibition of only 50% when chemotherapy was used alone for control subjects.

Gamma-Linolenic Acid (GLA) and Fish Oil

GLA is an essential fatty acid found in evening primrose oil, borage seed oil, and black currant seed oil. Numerous laboratory studies have shown it to be highly cytotoxic to many different kinds of cancer cells, with the presumed mechanism that metabolism of GLA by the cancer cells creates high levels of free radicals that are lethal to the cells. Iron and zinc potentiate this cytotoxic effect; Vitamin E (and perhaps other anti-oxidants) counteracts it. GLA is harmless to normal cells and has been shown to have clinical utility for a variety of disorders, notably rheumatoid arthritis and as a topical treatment for superficial bladder cancer. It also has been shown to lower LDL cholesterol and increase insulin sensitivity. GLA is also known to change the structure of cell membranes, which is believed to underlie the finding that it increases the effectiveness of both chemotherapy and radiation. At the same time GLA has been shown to protect normal cells from radiation damage.

Evidence that GLA is effective against gliomas comes from a study conducted in India (237, 238) in which GLA was infused directly into the tumor bed. Of the 15 patients treated, most had major tumor regressions, and 12 of the 15 were alive at the time of the report's publication (1-2 years later). The three who died were all quite elderly and probably would not have received any conventional treatment beyond radiation in this country. A subsequent study (239) involving patients with very advanced disease had notably less success but here too there were notable tumor regressions attributable to the treatment.

A critical question is whether oral ingestion of GLA has any clinical effects. A clinical trial using it for breast cancer substantiates that it does (240). Advanced breast cancer patients received the standard treatment of tamoxifen alone or tamoxifen in combination with 2.8 g of GLA/day. The source of GLA was borage seed oil, which is approximately 20-25% GLA, which meant that the patients were taking 12-15 g of borage seed oil per day. Borage seed oil is available in most health food stores, usually in the form of 1000 mg capsules, although it can also be obtained in liquid oil form and makes tasty salad dressings. The measure of treatment effectiveness in the breast cancer clinical trial was the status of patients three months after the initiation of treatment. With tamoxifen alone, none of the patients had a complete response to treatment, and 13% had partial regression of their tumors. For tamoxifen + GLA the corresponding percentages were 5, and 37%, a significant improvement.

The use of GLA as a cancer treatment is controversial because it is an N-6 (omega 6) fatty acid, which metabolizes into arachidonic acid, a precursor to both the lipoxygenase and cyclooxygenase inflammatory pathways. These inflammatory pathways are believed to stimulate the growth of cancer cells, which seems to contraindicate using GLA. However, it should be noted that GLA has been used successfully as a treatment for rheumatoid arthritis because of its anti-inflammatory effects, so obviously the story is more complicated. One potential problem with GLA is that there have been isolated reports of it increasing the likelihood of seizures.

The major fatty acids found in fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have also been demonstrated to have potent cytotoxic effects on cancer cells in various laboratory experiments. Part of their mechanism of action is similar to that of GLA, in that the metabolism of these fatty acids creates high levels of free radicals. In addition, a recent laboratory study has shown that EPA-treated tumors showed a significant arrest of cell division due to inhibition of cyclins at the G1 phase of cell division, which resulted in an increased rate of programmed cell death known as apoptosis (241).

A clinical trial comparing fish-oil supplements versus a placebo has also been reported, involving patients with several different types of advanced cancer (242). Thirty malnourished patients suffering from cachexia were randomly assigned to receive 18 g of fish oil per day or a placebo sugar pill. An additional thirty subjects, adequately nourished, received a similar random assignment. For both groups the fish oil significantly increased survival. For the malnourished patients the median survival times, as estimated from their survivor functions, were 110 days for the patients receiving placebo and 210 days for patients in the fish oil group. For the adequately nourished patients, the corresponding numbers were 350 versus 500 days.

In laboratory studies (243) fish oil has also been shown to increase the effectiveness of chemotherapy and radiation. A phase II trial involving 25 heavily pretreated metastatic breast cancer patients, used 1.8 g/day of DHA, one of the two major fatty acids in fish oil, in combination with standard anthracycline-based chemotherapy (244). Patients previously had failed both chemotherapy and hormone treatments and many had multiple metastases, including many liver metastases. Because this was a phase II trial, there was no control group that received chemotherapy alone, but patients were subdivided according to their level of plasma DHA. The two groups were approximately equal with respect to all major prognostic variables. Median survival for the high DHA patients was 34 months, vs. 18 months for the low-DHA patients.

A second clinical trial presented 2200 mg of EPA plus 240 mg of DHA to patients with advanced non small cell lung cancer (245). Patients either received only the standard of care of chemotherapy, or the same treatment in combination with daily fish oil. Response rate (tumor regressions) was 60% in the fish oil group and 26% in those receiving only the standard of care. One-year survival was 60% in the fish oil group versus 39% in those receiving only chemotherapy. Chemotherapy toxicity was also decreased in those using fish oil.

Vitamin D

Numerous laboratory studies have shown that Vitamin D is highly cytotoxic to cancer cells, due to several different mechanisms (although labeled as a vitamin it more properly should be considered a hormone). While most research has focused on its ability to activate genes that cause cancer cells to differentiate into mature cells, other effects have also been identified, including cell cycle regulation, inhibition of the insulin-like growth factor, and the inhibition of angiogenesis (246). However, the calcitriol form of Vitamin

D is not readily usable for cancer treatments because the dosages producing anti-cancer effects also cause hypercalcemia, which can be life threatening (the major function of Vitamin D is to regulate calcium absorption and resorption from the bones and teeth). But like many vitamins/hormones, the generic designation refers not to a specific chemical structure but to a family of related molecules that may have different properties of various sorts. For Vitamin D several of these variants (commonly referred to as analogues) have been shown to effectively inhibit cancer cell growth but without the same degree of toxic hypercalcemia. In a 2002 paper in the Journal of Neuro-oncology (247), 10 patients with glioblastoma and one with a grade III AA tumor received a form of Vitamin D called alfacalcidol in a dosage of .04 micrograms/kg each day, a dosage that produced no significant hypercalcemia. The median survival was 21 months, and three of the eleven were long-term survivors (greater than 5 years). Although the percentage of patients who responded to the treatment was not high, the fact that any relatively non-toxic treatment can produce any number of long-term survivors is remarkable. There is also strong reason to believe that Vitamin D is synergistic with retinoids such as accutane (248). Its effectiveness is also increased in the presence of dexamethasone (249) and a variety of anti-oxidants, notably carnosic acid, but also lycopene, curcumin, silibinin, and selenium (250).

Alfacalcidol is not available in the USA, but is available in Europe and Canada. For those in the USA it is possible obtain it from various online marketers. It also should be noted that several other Vitamin D analogues are available, which also have much reduced hypercalcemic effects. One of these, paricalcitol, was developed for treatment of a disorder of the parathyroid gland, and recently has been the subject of several experimental studies (251, 252, 253) that have shown it to be highly cytotoxic to many different types of cancer. Given that other forms of Vitamin D have been shown to be highly cytotoxic to for glioblastoma cells, and that glioma cells are known to have receptors for Vitamin D, it seems likely that paricalcitol should have efficacy for glioblastoma as well. Unfortunately, its routine use is complicated by the fact it is available only in a form that requires intravenous injection.

The most common version of Vitamin D3 found in health food stores is cholecalciferol, which is the precursor of calcitriol, the form of Vitamin D utilized by the body. A recent study of cholecalciferol with prostate cancer patients who had progressed after standard therapy (254) suggests that this common form of Vitamin D3 may be clinically beneficial. Fifteen patients who had failed standard treatments were given 2000 I.U. daily. PSA levels were reduced or stayed the same for nine patients, and there was a reliable decrease in the rate of PSA increase for the remainder. No side effects of the treatment were reported by any of the patients.

Because serum Vitamin D levels have recently been shown to be inversely related to cancer incidence, there recently has been considerable discussion about the dosage that is toxic. Doses as high as 5000-10,000 I.U. per day appear to be safe. Recently, it has become common for women suffering from osteoporosis with low Vitamin D levels to be given as much as 50,000, I.U./day for short time periods. Nevertheless, it is important to note that all forms of Vitamin D can occasionally produce dangerous serum calcium levels, in part because there is a great deal of variability in their effects across individuals. It is thus important that blood calcium levels be monitored, especially while a nontoxic dosage is being established.

Perillyl Alcohol/ Limonene

These closely related chemical compounds are derived from citrus oils, and have been extensively investigated as anti-cancer agents, including several early-stage clinical trials. Unfortunately, the gastro-intestinal side effects of these compounds have retarded their clinical development. A recent clinical trial with recurrent glioma patients, conducted in Brazil, circumvented this problem by administering perillyl alcohol intranasally four times daily. In the initial report, of 29 GBM patients with recurrent tumors receiving the treatment, one had a partial response and 13 had stable disease, for a PFS-6 value of 48% (255). In a later study of 89 GBM patients, who had failed a minimum of three prior treatments (and thus had especially poor prognoses), patients were separated into those that had primary GBM vs. secondary GBM (tumors that evolved from lower-grade tumors), median survival for primary GBM was 5.9 months, while that for secondary GBM was 11.2 months. Median survival for a set of matched control patients who received only supportive care was 2.3 months (256). It was also noted that patients with tumors in their midbrain area benefited more from the treatment than did patients with tumors in their cerebral lobes.

Nutraceuticals

Oncologists routinely warn their patients not to use supplements, usually based on the belief that supplements that are anti-oxidants will interfere with both radiation and chemotherapy. While this issue is extremely complex, my own evaluation of the relevant evidence strongly disagrees with this opinion. Accordingly, I have posted my own analysis of the clinical evidence as an accompanying article on this website. Here I list the supplements that seem most likely to be efficacious, based on extensive laboratory data. Unfortunately, few clinical results are available to corroborate the experimental data, primary because the supplements cannot be patented; hence there is no financial incentive to develop their clinical usage. The result is that little information is available about the best dosage and about bioavailability, which is often a problem. However, a great deal is known about the mechanisms of action of the various supplements, which often overlap those of conventional drug therapy. A detailed consideration of such mechanisms is not possible here, as it would require a great deal of molecular biology. A special issue (2009, Vol. 269, Issue #2) of the journal, Cancer Letters, was devoted to the molecular targets of many of the individual agents to be considered. A more general review is provided in Reference # 257.

The list of supplements to be considered is necessarily selective. Undoubtedly, there are numerous other agents that could be useful that are omitted.

Genistein

This is an isoflavone derived from soy products (it is also found in red clover extract) that has been shown in the laboratory to inhibit the growth of many different types of cancer, including glioma cells. In addition to the laboratory evidence, there is substantial epidemiological evidence that high dietary intakes of soy products decrease cancer mortality by at approximately 50%. There is also evidence from scattered clinical trials, mainly for prostate cancer. One example (258) involved patients with localized prostate cancer scheduled for a prostatectomy. One group received 30 mg/day of synthetic genistein, the remainder received a placebo. Genistein decreased PSA, a surrogate measure for tumor growth, by 8%, while that of the placebo group increased by 4%, a statistically significant difference.

Genistein has also been studied in combination with other supplements for the treatment of prostate cancer (259). In one such study, patients who had rising PSA after initial treatment received a combination of soy isoflavones, lycopene, silymarin, and anti-oxidants or a placebo for 10 weeks, then a wash-out period, followed by the reverse assignment of patients to treatment. This experimental design is much more powerful than a randomized group design because it allows an assessment of the treatment for each individual patient. The measure was the slope of the increase in PSA value. A significant decrease in the slope occurred during the supplement periods, as the PSA doubling time increased from 445 days to 1150 days.

Diets rich in soy have also been compared to normal diets for prostate cancer patients. For one group, bread incorporating 50 mg of soy was compared to bread incorporating an equal amount of wheat (260). Four slices of each type were eaten daily. PSA decreased 13% in the soy group, but increased 40% in the wheat group, a significant difference.

Soy extracts containing genistein are available in most health-food stores. The concentration of genistein is often not well specified. Most importantly, the listed amounts of genistein are so low that they are unlikely to provide much clinical benefit.

The highest concentration (about 10 times greater than the others that I have found) is marketed by the Life Extension Foundation (phone: 800-841-5433). It may also be possible to purchase it wholesale in the form of a product named NovaSoy, manufactured by the Archer-Daniels-Midland Corporation.

Recent experimental studies have examined the mechanisms whereby genistein produces its anti-cancer effects (261). The consensus is that this results from its ability to inhibit tyrosine kinase activity. This is a general class of intra-cellular signals that strongly stimulate cell division. Genistein also appears to produce inhibition of protein kinase C (discussed earlier with respect to the mechanisms of tamoxifen). This in turn suggests that a combination of genistein and tamoxifen might be especially effective. Finally there is increasing evidence that genistein is an inhibitor of angiogenesis.

Of special interest to brain cancer patients is a laboratory study in which glioblastoma cells were treated with a combination of genistein and BCNU (262). The result was a highly synergistic suppression of the rate of growth. It has also been shown to increase the effectiveness of other chemotherapy agents (e.g., carboplatin, tamoxifen) and other supplements (263).

Green Tea

Green tea has been consumed in both China and Japan for 5000 years based on its medicinal properties A recent review has summarized its anti-cancer effects in several different animal models using both mice and rats (including major inhibition of glioblastoma cell lines), both when human tumors have been implanted and when they have been induced by various chemical carcinogens (264). In a representative study of chemically induced tumors in mice (265), green tea was provided as the sole source of fluid, at a concentration of 6% (6 g of tea per liter of water), the incidence of lung tumors was reduced by 30%. The same study identified several different mechanisms of action, the most prominent of which was the inhibition of angiogenesis.

The major active ingredient in green tea is epigallocatechin gallate (EGCG), one of a family of molecules known as catechins. Not only has this molecule been shown to be cytotoxic to glioma cells in vitro, it also substantially increases the effectiveness of both cisplatin and tamoxifen (266).

Of special interest is a recent in vivo study in which glioblastoma cells were implanted into mouse brains, after which the mouse were treated with either temozolomide alone, EGCG alone, or their combination. EGCG alone did not increase survival time, but its combination with temozolomide greatly increased its efficacy, relative to temozolomide alone (267).

A recent review by the new Division of Alternative Medicine of the National Institutes of Health identified green tea as the most promising of treatments advocated by proponents of alternative medicine. Accordingly, several clinical trials investigating its efficacy are ongoing. The only one reported to date used green tea in the treatment of patients with androgen independent metastatic prostate cancer (268). Dosage was 6 g of green tea per day. Only limited clinical benefit was reported. It is important to recognize that anti-angiogenic agents generally take a long time to produce clinical regressions, work better with less advanced stages of disease, and also work better in combination with other treatment agents.

A second clinical trial used a green tea extract at a dose of 2000 mg twice daily with patients diagnosed with chronic lymphocytic leukemia (269). Significant reductions in the absolute lymphocyte count were observed along with substantial reductions in the size of the lymph nodes reflecting the extent of disease. However no survival data were reported.

Green tea also has been used with patients who have had polyps excised from their colons, or who had tumors previously removed, known high-risk factors for the development of colon cancer (270). Patients received a combination of apigenin (20 mg), a flavonoid most commonly found in celery, and 20 mg of EGCG; the remaining patients received no supplements. Both groups had surveillance colonoscopies. In the supplemented group (n=-31), only one patient developed an adenoma (7%), while in the matched controls (n=56), 47% of the patients had cancer recurrence or the development of adenomas.

One counter-indication for the use of green tea is in combination with Velcade (Bortezomib). Green tea combines with the boron component of the drug, thus inactivating it (271). However, this interference effect appears to be unique to Velcade due to its chemical structure.

Curcumin

This is an ingredient in the Indian cooking spice, turmeric. It has been shown to inhibit the growth of cancer cells of various types in laboratory studies via numerous different mechanisms (272). Like genistein, it inhibits the tyrosine kinase signaling and also inhibits angiogenesis. Perhaps most importantly, it inhibits proteins that prevent damaged cells from undergoing apoptosis, a family of genes known as nuclear factor kappa B. Of all of the supplements on this list it is the most potent anti-cancer agent in laboratory studies. However, it also should be noted that its bioavailability from oral intake is limited, although bioavailability supposedly is increased when curcumin is combined with piperine (the main ingredient in black pepper). The Life Extension Foundation sells a version of curcumin that they claim has much greater bioavailability than anything else on the market. Despite the limited bioavailability, there is some evidence of clinical effectiveness. In a study of dermatitis induced by radiotherapy for breast cancer, a double-blind placebo controlled trial compared a placebo with curcumin (2 grams three times/day), both of which were taken throughout radiation treatment. Significantly less dermatitis occurred in patients receiving curcumin (273).

Curcumin has also been used in combination with a second supplement, quercetin, (see below) for the treatment of an inherited disorder of the colon in which hundreds of adenomas develop and eventually colon cancer (274). Five patients with the disorder received 480 mg of curcumin and 20 mg of Quercetin three times daily. Polyp number and size were assessed at baseline and then six months after starting the supplements. For all patients there was a decrease in polyp size and number, which was statistically significant.

Silibinin (an ingredient of Milk Thistle)

Silymarin is an extract from the milk thistle plant that has been used extensively in Europe as an antidote for liver toxicity, due to mushroom poisoning and overdoses of tylenol. Its active ingredient is a molecule called silibinin. Recently a great deal of laboratory research has shown it to have anti-cancer effects, which recently have been reviewed (275). Like genistein and quercetin it is a tyrosine kinase inhibitor, but it appears to have multiple other effects, including the inhibition of the insulin-like growth factor (IGF) that contributes to the development of chemoresistance (276) (see the section on tamoxifen), and the inhibition of angiogenesis (277). It also inhibits the 5-lipoxygenase inflammatory pathway and suppresses nuclear factor kappa B, which is a primary antagonist to apoptosis (278). It also appears to protect against common chemotherapy toxicities (279), while at the same time increasing the effectiveness of chemotherapy (280).

Lycopene

This is a carotenoid that is found most abundantly in tomatoes but occurs in various other red-colored vegetables as well (including watermelon). Unlike the most well known carotenoid, beta-carotene, it is not transformed into Vitamin A, and thus has no hepatic toxicity. In a small clinical trial involving prostate cancer patients about to undergo surgery (281), those who consumed lycopene for several weeks before surgery had a reduction in both the size and malignancy of their tumors relative to control patients not receiving lycopene. In a study of 54 patients with advanced prostate cancer (282), patients were randomized to receive castration or castration plus 2 mg of lycopene daily. At two years after treatment inception both groups had reductions in PSA level with 40% of the castration-only group having a complete PSA response, while 78% had a complete

PSA response for those also receiving lycopene. Bone scans also showed a greater clinical benefit for those receiving lycopene.

In an experimental study involving both cell cultures and implanted glioma tumors in rats (283) lycopene (and beta-carotene) were found to substantially inhibit tumor growth in both experimental preparations, and in fact had a greater inhibitory effect than did a collection of retinoids commonly used clinically. Of further relevance to gliomas is that one of lycopene's mechanisms of action is to inhibit the insulin-like growth factor, which as noted above is involved in the development of resistance to a variety of different treatment agents (284). Also of interest is evidence that it synergizes with Vitamin D (285).

The only report of lycopene's clinical use with gliomas is from a meeting abstract of a randomized clinical trial conducted in India with 50 high-grade (32 GBM) glioma patients receiving a treatment protocol of radiation + taxol. Patients also received lycopene (8 mg/day) or a placebo (286). Eighty percent of patients receiving lycopene had either complete or partial tumor regressions, while this was true for only 44% of those receiving a placebo. Progression-free survival was also greater for those receiving lycopene (40.8 weeks vs. 26.7 weeks). However, neither difference was statistically significant using the p <. 05 probability criterion.

Sulforaphane

Brassica vegetables, which include broccoli, cauliflower, brussel sprouts, and cabbage, have long been believed to have anti-cancer properties. A major source of these effects is a substance known as sulforaphane. Recently it has been discovered that the 3-4 day-old broccoli sprouts contain 10-100 times the concentration of sulforaphane as that of the full-grown vegetables. To test whether the oral ingestion of sprouts has anti-cancer effects, dried broccoli sprouts were included in the diet of rats with chemically induced cancers, with the result that considerable regression of the tumors were observed (287). Broccoli sprouts are also very tasty additions to salads. Subsequent research has shown that sulforaphane is a powerful inhibitor of histone de-acetylation, the target of several new drugs, including vorinostat (discussed in a previous section)

Ellagic Acid

This is a family of phenolic compounds present in fruits and nuts, including raspberries, blueberries, strawberries, pomegranate juice, and walnuts. In laboratory experiments it has been shown to potently inhibit the growth of various chemical-induced cancers, with the basis of the effect being an arrest of cell division in the G stage of cell division, thus inducing the programmed cell death known as apoptosis. While there have been no trials to assess its clinical effects with brain cancer, a recent clinical trial, performed at UCLA with prostate cancer demonstrate its potential (288). Patients with prostate cancer, whose PSA levels were rising after initial treatment with either surgery or radiation, drank pomegranate juice (8 oz/ daily), which contains high levels of eligitannnins (precursors to ellagic acid). The dependent measure was the rate of increase in the PSA level, which typically rises at a steady rate for this category of patients. Pomegranate juice produced an increase in PSA doubling time, from 15 months at baseline to 54 months after consuming the juice. Of the 46 patients in the trial, 85% exhibited a notable increase in the doubling time, and 16% had decreases in their PSA.

Berberine

This is an alkaloid extract from *Coptides rhizoma* commonly used in China as an herbal medicine. It is also found in high concentration in the widely used supplement, goldenseal. In one laboratory study of using various kinds of glioma cell cultures and implanted tumors in rodents (289), the cytotoxic effects of berberine were compared to those of BCNU and to the combination of berberine and BCNU. Berberine alone produced a 91% kill rate in cell cultures, compared to 43% for BCNU. The combination produced a kill rate of 97%. Comparable results were obtained with the in vivo implanted tumors. Such results suggest that berberine is among the most promising treatment agents, but to date very little research using it has been reported. Part of the reason may be that berberine is poorly absorbed from the GI tract. It appears that the structure of berberine is closely related to Ukrain, a drug that combines an alkaloid from a plant named celandine with an old chemotherapy agent named thiotepa. After years of Ukrain's use only in alternative medicine, it recently has been licensed for commercial development. A recent clinical trial using it for pancreatic cancer has produced impressive results. (290).

Resveratrol

This is a naturally occurring polyphenol found most abundantly in grapes and mulberries. Red wine is among the sources. Numerous experimental studies have shown that it inhibits proliferation of various kinds of cancer, including glioma, leukemia, prostate, breast, and colon cancer. It has also been shown to be synergistic with temozolomide in in vivo rodent models (291). Among its mechanisms of action are activation of the P53 gene, inhibition of protein kinase C, and the inhibition of new blood vessel growth. In the one recent study of its use with implanted glioma tumors (292), rats received either sub-cutaneous injections or intra-cerebral injections of tumor cells, which in control animals rapidly grew and became fatal. With sub-cutaneous tumors a dose of resveratrol of 40mg/kg produced major growth inhibition with 70% of the rats becoming long-term survivors. A higher dosage (100 mg/kg) was necessary to inhibit the growth of the intracranial tumors, and even then it was only marginally effective. The difference in outcome for the two preparations suggests that resveratrol may be impeded by the blood-brain barrier. However, the authors note that it had significant anti-angiogenic effects, which may be independent of the blood-brain barrier. Whether resveratrol has clinical utility for brain cancer is unclear, although it is known that anti-angiogenic agents of various sorts synergize with various kinds of conventional treatment.

Quercetin

This is a member of the class of flavonoids found in fruits and related plant products. Its most abundant sources are onions, shallots, and apples. Like genistein it appears to be an inhibitor of tyrosine kinase activity, and appears to be synergistic with genistein when the two have been combined in laboratory studies involving both ovarian and breast cancer cell lines. As a single agent it has been shown to inhibit the in vitro growth of several glioma cell lines. It currently is being investigated in phase-1 clinical trials.

Garlic

Garlic, like green tea, has been used hundreds of years for its medicinal purposes. A recent cell culture study with glioblastoma cell lines demonstrated its potent cytotoxic effects that were mediated by its ability to induce apoptosis (293). It is also a potent inhibitor of histone de-acetylase (HDAC).

Cannabis

After years of governmental discouragement of research on Cannabis (the plant from which marijuana is derived), the last few years has seen a proliferation of research on its mechanisms of action. One result of this research has been that cannabis inhibits the growth of various kinds of cancer cells, including gliomas (294). In one recent paper (295), cannabinoids were shown to significantly inhibit angiogenesis in gliomas implanted in mice, which was accompanied by significant inhibition of glioma growth. A subsequent paper with a mouse model combined cannabis with temozolomide and reported a strong synergy between them (296).

A small phase I trial infused pure THC (one of the active ingredients in cannabis) into the tumors of nine patients with recurrent tumors after surgery and radiation (and in some cases chemotherapy), and produced a median survival time after treatment initiation of 24 weeks (297). While this number is not impressive, it should be noted that this outcome is similar to that reported when temozolomide is used as a single agent for recurrent tumors. It should also be noted that the intracranial infusion of THC was probably not the ideal mode of drug delivery because of the limitations of all localized treatment procedures. Moreover, THC itself is only one of several active components of cannabis. Systemic delivery of the whole set of molecules contained in cannabis may produce an improved outcome.

The direct anti-cancer effect of cannabis is noteworthy because it is also one of the most effective anti-nausea agents, without many of the side effects of those drugs routinely used (Zofran and Kytril). Moreover, a liquid form of cannabis (Sativex) has been government approved in both Canada and Great Britain (for neuropathic pain), and can be used as an aerosol much like an asthma inhaler. Unfortunately, the United States is unlikely to follow suit, given the recent pronouncement by the current drug czar that marijuana has no useful medical purpose. Apparently he was unaware of the contrary opinion in other countries.

Boswellic Acids

This is a collection of aromatic acids related to the biblical spice, frankincense. Its relevance to cancer treatment is that is a potent inhibitor of the lipoxygenase inflammatory pathway, one of the two major sources of inflammation associated with cancer progression. Cyclooxgenenase is the other pathway, which can be inhibited by celebrex. Both pathways should be suppressed to maximally inhibit inflammation. Of more immediate interest to glioma patients is that Boswellic acid is a powerful inhibitor of the edema caused by tumor growth, which is the major reason many brain tumor patients require steroids to suppress the swelling. In a randomized, double-blind study conducted in Germany, 44 brain tumor patients received either boswellia serrata (one of the several forms of boswellia) or a placebo (298). Both groups also received radiation. Compared to baseline, patients receiving boswellia had a 75% reduction in edema, while placebo patients had a reduction of 26%. There were no significant side effects of the boswellia. Given the many side effects of steroids, boswellia offers the promise of substantially improving the quality of life. However, the dose of boswellia used in this study was 4200 mg/day, far greater than can be readily obtained by the usual sources of boswellia that can be obtained from health food stores.

The Importance of Synergy

There is also evidence that supplements may be synergistic when combined.
An experimental demonstration of synergy between supplements with glioma cells studied the combination of resveratrol and sulforaphane (299). Low doses of either in

isolation produced moderate inhibition of cell growth but the combination of the same low doses produced major growth inhibition by a variety of different mechanisms.

The most systematic analysis of synergy between various supplements targeted two different pancreatic cancer cell lines, known to be highly resistant to treatment. In the first set of experiments, dose-effect functions were established independently for curcumin and soy isoflavones (containing a high level of genistein). As expected, the tumor cells were highly resistant to treatment. Then the combination of agents was tested, using dosages that were ineffective in isolation. The combination produced strong inhibition of cell growth (300). In the second set of experiments the same strategy was used, but now with four different agents: curcumin, soy isoflavones, resveratrol, and EGCG (the active ingredient in green tea). Once again the combination produced inhibition of cell growth at even lower dosages than used with the two-way combinations. The interpretation of the synergy was that the use of several supplements caused the suppression of multiple different growth pathways, which seems necessary given the multiplicity of the signals controlling tumor growth.

Skeptics of supplements/dietary components such as those discussed above have argued that the laboratory studies providing evidence for their anti-cancer effects have used dosages that can never be achieved in human patients, and therefore the supplements are unlikely to be useful clinically. Without a study of the dose-effect relations in clinical settings there is no easy way to evaluate this concern. However, in several cases investigators of the various substances have noted that their effects in the laboratory were obtained with dosages comparable to what easily can be realized by dietary supplementation, and in several cases there is direct clinical evidence supporting its use. In any event, for most of what has been discussed there is little if any risk to using the supplements, with the only cost being financial in nature. Contrary to the concern expressed by many oncologists, the addition of supplements to standard treatment protocols generally do not interfere with the standard treatment, but make the treatment more effective (301).

Promising New Treatments

The above discussion focuses on ways to improve the efficacy of the Stupp protocol, the gold standard of treatment for newly diagnosed glioblastoma patients. While a variety of changes and/or additions to the protocol seem promising, none has obtained general acceptance. An alternative strategy for newly diagnosed patients is to enroll in clinical trials. While new treatment agents studied for the first time in clinical trials are unknown quantities, some have preliminary outcome data that can help the patient’s decision. Many of the clinical trials also test the new treatment in combination with the gold standard rather than as single agents alone. When I was diagnosed 20 years ago, few clinical trials seemed promising. Now, however, many more seem likely to be an improvement over the current gold standard.

7. Immunological Approaches

Because cancer cells have a genetic structure different from normal cells they generate foreign proteins that in principle should be detected by the immune system and evoke the same type of immune reaction as any foreign virus or bacteria. This basic fact suggests that augmenting one's immune system might be an effective approach to cancer treatment. Such an approach has an immediate appeal because it is surely preferable to reinforce the immune system than to poison the entire body in the hope the cancer cells will be killed before the body is depleted of vital resources. However attractive this philosophy may be, translating it into an effective cancer treatment has proven to be extraordinarily difficult. Contrary to general belief, immunological treatments are not benign to implement. Interferon treatment has very definite debilitating effects, as do cytokines such as interleukin-2 and tumor necrosis factor, because their modus operandi are essentially to create an inflammatory immune reaction not unlike a severe allergic reaction. When this inflammatory process is too severe, it can in fact be fatal.

Cytokines

One of the early examples of the use of cytokine-based immunological treatment was reported in *Cancer* in 1995 (143). Mixing the white blood cells of individual patients with those of unrelated donors, then incubating for several days, created lymphocyte killer cells. The mixture of unrelated blood cells creates "angry white cells" that generate a wide array of different inflammatory cytokines. These cells were then infused through an intracranial catheter into the tumor bed in combination with additional doses of IL-2. Patients received this regimen for multiple cycles until disease progression. The results were a median survival time of 53 weeks for patients with recurrent glioblastoma, which compares favorably with the 4-7 month survival times when recurrent tumors are treated with additional chemotherapy. Moreover, 6 of 28 patients survived longer than two years.

A clinical trial using a similar protocol with patients who had not progressed after initial radiation (and some with chemotherapy) was conducted at the Hoag Cancer Center in Newport Beach, California (144). Of 33 GBM patients, median survival from the time of immunological therapy was 14.5 months, and 20.5 months from the time of initial diagnosis. Two-year survival rate was 35%.

Poly-ICLC

A generalized immunostimulant with minimal toxicity is Poly-ICLC, a double-stranded RNA, which initially was developed to induce the body to produce its own interferon, but is now believed to have a variety of immune-system enhancement effects, including de-activating an as yet unknown tumor suppressor mechanism of the immune system. These latter effects apparently only occur at low doses and are suppressed by high doses of Poly-ICLC. Its initial results for AA-III tumors were exceptional: the initial clinical trial with Poly-ICLC (in combination with CCNU for about 1/2 of the patients) reported that all but one patient with AA-III tumors were alive with a median follow-up time of 54 months (145). It was less effective for glioblastomas, with a median survival time of 19 months (but note that this too is greater than the standard treatment). There were minimal side effects except for a mild fever early in treatment (145). However, a more recent multi-center clinical trial with recurrent AA-III tumors produced less impressive results (146), as the initial cohort of patients had a PFS-6 value of only 23%. Note, however, that the latter study involved patients with recurrent tumors while that of the earlier study involved patients after initial diagnosis.

Two trials using Poly-ICLC with newly diagnosed glioblastoma patients recently have been reported. In the first, Poly-ICLC was given in combination with standard radiation, followed by its use as a single agent (147). No chemotherapy was given. One-year survival was 69% and median survival was 65 weeks (about 15 months). Both values are superior to historical studies using only radiation without chemotherapy. In the second study with 83 newly diagnosed glioblastoma patients (148), Poly-ICLC was combined with the standard temozolomide + radiation protocol. For 97 patients median survival was 18.3 months with a 2-year survival rate of 32%. Thus, the addition of Poly-ICLC increases survival by several months, relative to the standard protocol, notably with minimal additional toxicity.

The fact that immunological treatments have produced at least some degree of success is encouraging, and highlights the need to strengthen the patient's immune function as much as possible. The effects of melatonin and mushroom extracts such as PSK presumably are due at least partly to such strengthening, and therefore should be generally useful.

Vaccines

The holy grail of immunological approaches to cancer treatment is the development of effective vaccines. In principle this should be possible because of the differences in the protein structure of cancer cells and normal cells. But, two general problems must be overcome. The first is that different individuals have tumors with different collections of antigens (proteins), so that generic vaccines are unlikely to be effective; thus patient-specific vaccines are required. The second problem is that the immune system is not an efficient detector of the tumor's foreign antigens. In part this is due to the tumor secreting enzymes that in effect provide a protective cloak preventing such detection. The larger the tumor the stronger is its defense mechanisms to counteract immune-system detection. This is one reason that most vaccines work best when there is a minimum of tumor burden.

Personalized vaccines

DCVax and other lysate-pulsed dendritic cell vaccines

Methods to enhance the detection of tumor antigens are now the subject of intensive research, for various types of cancer. The most successful approach to date involves the use of dendritic cells, which have been characterized as "professional antigen-presenting cells". Dendritic cells are extracted from the blood, then co-cultured with a lysate prepared from cells from the patient's tumor, and stimulated with granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin-4 (GM-CSF is the growth factor used to counteract the decrease in white-cell blood counts due to chemotherapy). This growth factor causes the mixture of tumor and dendritic cells to be expanded as well. This mixture is then injected into the patient, evoking an increased reaction from the immune system.

This use of dendritic cells has been applied to several different types of cancers. Its use with brain cancer was pioneered by Dr. Keith Black and his team at UCLA, then continued at Cedars Sinai when Dr. Black’s team moved to that institution. A separate program at UCLA was continued by Dr. Linda Liau. Other centers using this approach are in Belgium, China, and Japan. In one of the first small clinical trials (149) nine newly diagnosed high-grade glioma patients received three separate vaccinations spaced two weeks apart. Robust infiltration of T cells was detected in tumor specimens, and median survival was 455 days (compared to 257 days for a control population). A subsequent report (150) involving 8 GBM patients produced a median survival time of 133 weeks, compared to a median survival of 30 weeks of a comparable set of patients receiving other treatment protocols. At two years 44% of patients were progression free, compared to only 11% of patients treated with the gold standard of temodar during radiation and thereafter. An excellent review of the clinical outcomes and technical issues associated with the vaccine trials is provided by Wheeler and Black (151).

In the largest of the initial clinical trials (152), 34 GBM patients (23 with recurrent tumors, 11 newly diagnosed) were assessed for their immunological response to the vaccine using interferon production as the measure, with the result that only 50% of patients exhibited a response. The degree of response was moderately correlated with survival time: 642 days for responders, 430 days for nonresponders. Five of the 34 patients were alive at the time of the report, with survival times ranging from 910 to 1216 days, all of whom were classified as immunological responders. It should be noted that the average age of patients in this trial was 52 years, only slightly lower than the typical GBM population, whereas many of the other vaccine trials have included mainly younger patients.

Among the most promising results using lysate-pulsed dendritic cell vaccines has come from the UCLA research program led by Dr. Liau. In the most detailed report of the results (153) 15 newly diagnosed GBM patients and 8 patients with recurrent tumors (average age =51), received the initial dendritic vaccine (followed by three booster vaccines in combination with either POLY ICLC or imiquimod (applied locally to the injection site). For all patients, median time to progression was 15.9 months. Median survival time for newly diagnosed patients was 35.9 months, and 2- and 3-year survival rates were 77% and 58%. For recurrent patients, mean survival from the time of initial enrollment in the trial was 17.9 months. Subsequent reports have come from press releases from Northwest Biotherapeutics, the biotech company sponsoring the DCVax trials. Survival at four years has been 33 %, and 27% have exceeded six years (154). Currently underway is a large multi-center phase III trial.

As of July 2015, no outcomes from the phase 3 DCVax-L trial have yet been made public, though patient outcomes from an “informational arm” receiving DCVax-L were published by Northwest Biotherapeutics in March (see press release here). This informational arm consisted of 51 patients who had enrolled into the phase 3 trial, but were excluded from the trial due to early disease progression prior to the first vaccination. The patients received the DCVax injections and were followed up on a Compassionate Use basis. Survival outcomes in this group are summarized on a youtube video featuring Marnix Bosch, the company’s Chief Technical Officer. Within this group of 51 patients was a subgroup of 25 patients considered to be “indeterminate”, meaning that they had evidence of disease progression at the baseline visit (rendering them ineligible for the trial), but subsequently had either stable disease, modest progression, or modest regression. This group of patients is reported to have a median survival of 21.5 months (the report does not make clear whether this is from surgery or from randomization post-radiation). As of March 2015, nine of these patients were still alive after 24 months of follow-up, six of these nine were alive after 30 months of follow-up, and four of these nine are alive at 35 to over 40 months. Therefore we can expect that median survival in the phase 3 trial (patients without disease progression at the baseline visit) will be at least greater than 21.5 months. The estimated primary completion date of the phase 3 trial is September 2015.

Less impressive results were obtained in a DC-Vax trial that implanted gliadel wafers at the time of surgery, followed by the vaccine protocol (155). For eight newly diagnosed GBM patients median survival was 25.5 months, while for the 15 recurrent tumor patients , median survival was 16 months. Trials with small numbers of patients are of course less reliable than larger trials, but the trial does suggest that the vaccine is certainly no guarantee of long-term survival.

The importance of patient selection to the outcome of immunological trials is emphasized by the results of a relatively large clinical trial conducted in Belgium (156). Seventy-seven newly diagnosed GBM patients received the standard Stupp protocol. After the radiation phase was finished, four induction DC vaccinations were administered, followed by four additional vaccinations during the maintenance chemotherapy. Over all patients, the median survival was 18.3 months. When patients were divided according to their RPA classification, the survival times differed widely, from 39.7, 18.3, and 10.7 months, for classes III, IV, and V, respectively. The RPA classification system rates patients in terms of prognosis based on Karnofsky score and age, among other variables. For the patients in this study, the average ages were 40, 58, and 62, for classes III, IV, and V, respectively.

But patient selection alone cannot account for all of the apparent benefits of the vaccination treatment. In a randomized clinical trial conducted in China (157), 18 newly diagnosed patients received the conventional Stupp protocol with the additional vaccine treatment, while 16 control patients received only the Stupp protocol. For the vaccine group, 2-year and 3-year survival rates were 44% and 17%, while the corresponding values for the control patients were 19% and 0%, differences that were statistically significant. Median survival for the vaccine group was 31.9 months, and 15 months for the control group. Also, nine of the vaccine patients were still alive at the end of the follow-up period, four of whom were still progression-free, while only one control patient was alive and zero was progression-free.

Agenus Prophage (heat-shock protein peptide complex-96) vaccine

A variation in the use of dendritic cells first subjected tumor tissue to a heat-shock treatment to elevate the expression of heat-shock proteins, which were extracted from the blood and incubated with dendritic cells from individual patients. In a clinical trial (163) conducted at UCSF and Columbia with patients with recurrent heavily pretreated tumors, the vaccine produced a median survival of 42.6 weeks (about 9.8 months), which compares favorably to the 6-month survival time for historical controls, and is comparable to the 9-11 months when avastin is used with patients with recurrent tumors.

A subsequent news release from Agenus, Inc, a biotech company sponsoring the research, reported the results of phase II clinical trial in which the heat-shock dendritic vaccine was combined with the standard Stupp protocol (164). Median progression-free survival was 17.8 months and median survival was 23.8 months. ***This median progression-free survival of 17.8 months is perhaps the longest PFS yet seen in any substantially sized phase 2 trial for newly diagnosed glioblastoma.***

A similar protocol was used in a small clinical trial conducted in China using the heat-shock vaccine with newly diagnosed GBM patients. Patients were randomly assigned to the standard Stupp protocol or to the standard protocol in combination with the vaccine (165). Of the 13 patients receiving the vaccine, 9 had a CR or PR when assessed at 9 months, while for the patients receiving only the standard treatment 3 of 12 patients had a CR or PR. Median survival was 17 months and 11 months for the vaccine and control patients, respectively. Corresponding 2-year survival was 40% and 0%.

Tumor-associated antigen vaccines

ICT-107

One disadvantage of the DCVax approach is that it requires that brain tissue be extracted from individual patients in order to make the vaccine. An alternative approach has been used by Dr. Black’s team at Cedars Sinai. Dendritic cells are still drawn from the peripheral blood of individual patients, but instead of tumor tissue lysate being mixed with those cells, a collection of six proteins typical of of GBMs is mixed with the dendritic cells, creating an immune response to those antigens, with the mixture then returned to the patient via vaccinations. In a phase I trial (158), 20 GBM patients (17 newly diagnosed, 3 with recurrent tumors) received three vaccinations two weeks apart. Median PFS was 16.9 months, and median overall survival was 38 months. At the time of the clinical trial report, six of the patients had shown no sign of tumor recurrence. A later follow-up was reported in a Press release from ImmunoCellular Therapeutics (159), the biotech company sponsoring the vaccine (now called ICT-107). Survival rate at three years was 55%, with 38% of patients showing no evidence of recurrence, The most recent update of the clinical trial (160), presented at the 2013 meeting of the World Federation of Neuro-oncology, reported that 7 of the original 16 patients in the trial were still alive, with survivals ranging from 60 to 83 months. One additional patient who was still tumor free after five years died from leukemia.

Currently ongoing is a randomized phase II trial, the interim results of which have recently reported by ImmunoCellular Therapeutics (161). Despite the impressive results described above, there was no statistically significant difference in median survival between the vaccine group and those treated with a placebo, although there was a numerical 2-3 month advantage for the vaccine group. However there was a similar difference in progression-free survival, which was statistically significant. The company emphasized that the results were preliminary and that they expected the difference in progression-free survival to translate into differences in overall survival with longer follow-up. However, the results also suggest that median survival and percentage of long-term survivors may be only weakly correlated due to the possibility that only a minority of patients benefit from the treatment, but those who do benefit a great deal.

Updated data from the phase II ICT-107 trial were presented on June 1, 2014 at the annual ASCO meeting (309). An important conclusion to be drawn from the new data is that mainly patients positive for HLA-A2 (a variant of the Human Leukocyte Antigen-A gene) seem to derive significant benefit from the vaccine. HLA are antigen-presenting proteins found at the cell surface. HLA-A2 is the most common variant in North America and Europe according to the press release and this group comprised 62% of patients randomized in this trial. The updated results are presented only for HLA-A2 positive patients, with results further subgrouped according to MGMT methylation status. Survival results in this trial are measured from the time of randomization after chemoradiation, and average time from initial surgery to randomization was 83 days (2.7 months).

For HLA-A2 positive patients with *unmethylated MGMT*, the ICT-107-vaccinated group had a median 4-month survival advantage compared with the placebo-vaccinated group. The ICT-107 group also had a median 4.5 month advantage in progression-free survival. These advantages in the vaccine-treated group did not reach statistical significance, though that is perhaps due to the small numbers of patients within these subgroups. 21% of ICT-107 treated patients were still alive at the time of the analysis, compared with only 7% of the placebo-treated patients.

Median survival has not yet been reached in the HLA-A2 positive, *MGMT methylated* group, though in this subgroup, ICT-107 treatment led to a dramatic and statistically significant increase in median progression-free survival: 24.1 months versus 8.5 months in the placebo-treated group. It is likely that this huge improvement in median progression-free survival in this subgroup will translate into significant median overall survival improvement.

SL-701

A similar approach has been used by Dr. Hideho Okada and colleagues at the University of Pittsburgh. In a pilot study using this approach with patients with recurrent tumors (162) several major tumor responses were observed. Median survival for the 13 GBM patients in the trial was 12 months, with several of the patients still progression-free at the time of the report. A later version of this therapy, called SL-701, consists of three shortened peptides corresponding to glioma-associated antigens and is now being tested in a phase I/II trial for HLA-A2 positive recurrent glioblastoma.
NCT02078648

Dendritic cell vaccine targeting Cytomegalovirus (CMV)

This approach relies on the finding that most GBM tumors are infected with the cytomegalovirus, a common herpes virus. GBMs have a high incidence of the virus being present (by some estimates over 90%) whereas normal brain cells do not. The new treatment approach involves targeting a specific protein component of the CMV virus, which then kills the virus and the cell harboring it. Newly diagnosed GBM patients received this vaccine in combination with the standard temodar treatment protocol (172). Median survival time was not reached by the time of the report (a convention abstract) but was greater than 20 months.

Results of a small trial for Duke's anti-CMV dendritic cell vaccine with or without preconditioning with an injection of tetanus/diptheria toxoid was published in Nature in March 2015 (320). There were 6 newly diagnosed glioblastoma patients in each arm. In the 6 patients treated with the vaccine but without tetanus/diptheria preconditioning, median progression-free and overall survival was 10.8 and 18.5, not significantly better than historical controls. In the group of patients receiving preconditioning of the injection site with tetanus/diptheria, three of the patients were alive without disease progression at 44-47 months from diagnosis. A Wall Street Journal article published at the same time as the Nature study gave more up-to-date information, revealing that two of these longer-term survivors had died at nearly 5 and 6 years from diagnosis, while the remaining patient was still alive over 8 years from diagnosis. The purpose of the tetanus/diptheria booster is to improve migration of the dendritic cells to lymph nodes. Despite the striking success of the anti-CMV dendritic cell vaccine combined with a tetanus/diptheria booster injection, a *randomized* phase 2 trial is scheduled to open in 2015 with one arm randomized to receive the tetanus/diptheria toxoid preconditioning, and the other arm randomized to receive saline (essentially placebo). Both arms receive the anti-CMV dendritic cell vaccine (trial NCT02366728).

Rindopepimut: anti-EGFR variant III (EGFRvIII) vaccine

A very different approach to developing a treatment vaccine, which has the virtue of being usable "off-the-shelf", without modification for individual patients, targets a mutation of the epidermal growth factor receptor, known as variant III, which occurs in 25-40% of GBMs. One reason that EGFR inhibitors such as Iressa have not been more effective is that they target the normal EGFR receptor, not this mutated receptor. EGFR variant III is also rarely seen in anything other than GBM tumors. To be eligible for the trial, patients must first be tested whether they possess the mutation.

In the initial clinical trial using the vaccine as a single treatment agent after surgery and radiation, median PFS was 7 months and median survival time from diagnosis was 23 months (166).

The sponsor of the vaccine (now called rindopepimut or Rintega) is Celldex Therapeutics, which recently provided an update of the outcome data for patients treated to date. Patients who received the vaccine as a single agent after the standard temozolomide + radiation initial treatment (N=18) had a median PFS of 14 months, and an overall survival of 26 months. Three patients were progression-free more than four years post-treatment. Patients receiving the vaccine in combination with maintenance temozolomide after the initial treatment (N=22) had a median PFS of 15.2 months and an overall survival of 24 months (167).

In January of 2015, final results of the phase 2 ACT III study were published online in the journal Neuro-Oncology (321). Median time from diagnosis to randomization was 3 months. Median PFS was 9.2 months from randomization (or about 12.3 months from diagnosis). Median overall survival was 21.8 months from randomization (or about 24.8 months from diagnosis). These results are quite impressive, especially considering that EGFRvIII positive patients are normally expected to have a reduced prognosis on account of this mutation.

Immune checkpoint inhibitors (drugs targeting CTLA-4 and PD-1)

Another immunotherapy approach involves the combination of two new immunological agents, ipilimubab (Yervoy) and nivolumab (Opdivo, FDA approved in 2014), which have produced unprecedented clinical efficacy in the treatment of metastatic melanoma, one of the most intractable of all malignancies. For patients using the combination at the highest dose, 53% had tumor regression, all with a reduction of 80% or more (176). This treatment protocol is now being tested with multiple different forms of cancer, including glioblastoma.

At the 2015 annual meeting of ASCO, outcomes of 20 recurrent GBM patients treated with either nivolumab (3 mg/kg) or nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) were reported (download poster here). In the nivolumab arm, no patients discontinued treatment due to toxicity, while in the combination arm, 3 out of 10 patients discontinued treatment due to drug toxicity. In the nivolumab monotherapy arm, one patient had a partial response and four patients had stable disease. In the combined treatment arm, there were no responses, and four patients had stable disease. 9-month survival rate was 60% in both arms. This trial has continued to phase 3, in which nivolumab alone is compared with Avastin alone for recurrent GBM.

8. Oncolytic virotherapy

Genetically modified Poliovirus (PVS-RIPO)

In 2015, this phase I trial for recurrent glioblastoma at Duke University received a boost in public interest when an episode of the television show 60 minutes was devoted to it. Most exceptionally, the first two patients treated in this study were complete responders. As of March 2015 (when the 60 minutes special aired) these two complete responders were still alive and progression-free at 33 and 34 months from treatment. 11 of 22 patients in the trial were still alive, though six of these patients were less than 6 months from treatment. Importantly, dose escalation of PVS-RIPO failed to improve efficacy, and the more recent patients in the trial are being treated with a smaller dose than the trial originally started with. Read an interview with Darrel Bigner discussing this trial here.

DNX-2401 adenovirus

Another viral therapy in phase 1 has had impressive results, comparable to the PVS-RIPO trial. DNX-2401 is a modified adenovirus that is directly injected into the tumor. Preliminary results of a phase 1 trial at MD Anderson in Houston, Texas were presented at the November 2014 SNO conference in Miami. 37 recurrent high-grade glioma patients had been treated, with no adverse events attributable to the virus being reported. 3 of 25 patients responded to the treatment with complete, durable responses of 42, 32, and 29 months so far. These three complete responders had vigorous immune responses, with 10-1000 fold increased levels of interleukin-12p70, a cytokine with great importance for type-1 anti-tumor immune responses.
Abstract from the 2014 SNO conference.

Newcastle Disease Virus

An alternative approach to vaccine treatment utilizes viruses. Newcastle disease is a lethal chicken disease, which is caused by a virus that is innocuous to humans, causing only transitory mild flu-like symptoms. It was developed as a cancer treatment in Hungary but has largely been ignored in this country until only recently. A paper in the Journal of Clinical Oncology reported the first use of a modified Newcastle virus in a phase I trial with various types of advanced tumors (168). Some tumor regressions were observed, along with clear responses of the immune system to the tumor tissue. A clinical trial (169) using a vaccine based on the Newcastle virus with newly diagnosed GBM patients was conducted in Heidelberg, Germany. Patients (N=23) receiving the vaccine after standard radiation had a median PFS of 40 weeks, a median overall survival of 100 weeks, and a 2-year survival rate of 39%. Matched control patients (N=87) who received only radiation had a median PFS of 26 week, a median survival of 49 weeks, and a 2-year survival rate of 11%. Unfortunately, these promising results seem not to have been pursued further.

Herpes Virus

Another virus used in cancer therapy is a modified form of the herpes virus. Initial trials used a retrovirus version, which infects only those cells dividing when the virus was infused. Subsequent trials have used an adenovirus version, which infects both dividing and non-dividing cells. Because the herpes virus can be lethal to the brain if allowed to proliferate, soon after the virus infusion patients receive ganciclovir, an effective anti-herpes agent. In one study using this technique performed at Mt. Sinai Hospital in New York (170), median survival of 12 patients with recurrent GBM tumors was 59 weeks from the point of treatment, with 50% of the patients alive 12 months after the treatment. The authors also reported the absence of toxicity from the treatment, which was a major concern due to significant brain damage when the procedure was tested with monkeys. Why the difference from the monkey study's results is unclear.

More recent research with the herpes virus has been focused on forms of the virus that have been engineered to retain the anti-cancer effects of the virus but without its property of producing neurological inflammation. The first use of this modified virus in a clinical trial was in Glasgow, Scotland. Nine patients with recurrent glioblastomas received the virus injected directly into the tumor. Four were alive at the time of the report of the study, 14-24 months after the treatment (171).

9. Gene therapy

Toca 511 is an engineered form of murine leukemia virus which delivers a specific gene to tumor cells, which then induces the tumor cells to make an enzyme named cytosine deaminase (CD). After the vector spreads throughout the tumor, patients receive a course of oral 5-FC, a prodrug of the common chemotherapy agent, 5-FU. The CD gene converts the 5-FC to 5-FU, thus killing the cancer cell. Rodent model data with this approach have been extremely impressive. The first human trials of the drug have begun enrolling patients in multiple treatment centers. Data from two phase 1 ongoing clinical trials have been published by the company (view press release here). Several partial responses have been seen, though the dramatic efficacy seen in the rodent studies has not scaled up to human patients thus far. A randomized phase II/III trial of this therapy for recurrent GBM or anaplastic astrocytoma is expected to begin in September 2015 (NCT02414165).

10. Photodynamic Therapy

When brain tumor cells absorb a molecule named hematoporphyrin (and other photo-sensitizers), exposure to high-intensity laser light will kill the cells. A treatment based on this rationale has been developed in Australia, used there and in some places in Europe, but not to my knowledge in the United States. Early results with this approach were not impressive but the most recent report of clinical trial results with patients with newly diagnosed high-grade gliomas indicates greater success. For patients with AA- III tumors median survival was 77 months while that for glioblastoma patients was 14 months (222). More impressive were long-term survival rates, as 73% of grade III patients survived longer than 3 years, as did 25% of glioblastoma patients. Also impressive were the results for patients with recurrent tumors. Median survival was 67 months for AA-III patients and 14.9 months for GBM. Forty-one percent of patients with recurrent GBM survived beyond 24 months, and 37% beyond 36 month. However, a review (223) of six different clinical trials using the procedure indicated wide variability in outcomes, with an aggregate median survival for newly diagnosed GBM of 14.3 months and for recurrent GBM tumors of 10 months. The treatment was reported to have minimal toxicity.

More positive results have come from a Japanese study using a new photo-sensitizer named talaporfin sodium (224), followed by the standard Stupp protocol. For 13 patients with newly diagnosed GBM, the median PFS was 12 months and the median overall survival was 25 months, a substantial improvement over the result obtained with the Stupp protocol used alone.

A phase II clinical trial of photodynamic therapy for recurrent high-grade glioma using Photofrin as photosensitizer has opened at the Medical College of Wisconsin in June 2015 (NCT01966809).

11. Treatments for Recurrent Glioblastoma

The unfortunate nature of glioblastoma tumors is that they typically recur. When the gold standard Stupp protocol is used as the initial treatment, the median progression-free interval before recurrence is detected is 6.9 months. This means that the median patient will need to seek additional treatment sometime in the first year after his/her diagnosis.

As noted above, there are three treatments that have FDA approval for the treatment of recurrent GBM: avastin, gliadel, and the Novocure TTF device. However these do not exhaust the possibilities, as additional chemotherapy, including a rechallenge using temodar itself, are also used. Indeed, all of the treatments discussed above for newly diagnosed patients can be used in the recurrent setting as well. The question for the patient is which to choose to optimize the chances of survival.

Avastin (bevacizumab)

Currently, the most frequently used treatment for recurrent GBM is avastin, the anti-angiogenic drug that is widely used in many different forms of cancer. In the earlier section on additions to the Stupp protocol for initial treatment, avastin was considered as one possible addition, but two different clinical trials failed to show any improvement in survival outcome relative to the Stupp protocol alone followed by avastin used only after recurrence has been detected. In this section we discuss the results of avastin as a treatment for recurrent tumors. Its first use with brain tumors was reported at a 2005 European Neuro-oncology conference (177). Avastin at a dose of 5 mg/kg was given every two weeks to 29 patients with recurrent tumors (apparently including both glioblastomas and grade III tumors), followed by weekly infusions thereafter. Patients also received CPT-11 (irinotecan) concurrently with Avastin. Tumor regressions occurred for a high percentage of patients, with 19 patients having either complete or partial regressions, some of which were evident after the first course of treatment. Long-term survival data were not mature at the time of the report. Avastin does increase the risk of intracranial bleeding, but in the aforementioned clinical trial, this occurred for only 1 of the 29 patients.

Since the initial study just described, additional studies has been reported. The largest of these, performed at Duke University (178), involved 68 patients with recurrent tumors, 35 of whom had glioblastomas. For those, the PFS-6 was 46% and median survival was 40 weeks. The latter number is disappointing given that a high percentage of patients had tumor regressions early in treatment, although the 10-month survival for GBM patients after recurrence compares favorably to the typical value of 5-7 months, as shown by a retrospective analysis (179). From the other reports a similar pattern emerged: a high response rates in terms of tumor regression, but then often a rapid regrowth of the tumor thereafter. A longer-term follow-up of the Duke study reported a two-year survival rate of 17 % (180), not impressive in absolute terms but much better than the 0-5% 2-year survival typical for recurrent tumors.

Except for the initial study by Dr. Stark-Vance, which used a dosage of 5 mg/kg, almost all other studies have used a dosage of 10 mg/kg every two weeks. A paper presented at the 2013 meeting of the Society of Neuro-oncology (181) suggests that the lower dosage may have better outcomes. Forty-eight patients who had received the 5 mg/kg dose were compared retrospectively to all of the remaining patients receiving the standard dose at the same institution. Median survival for the standard dose was 8.6 months, similar to the typical outcome. Median survival for the 5 mg/kg patients was 14 months, a notable improvement.

One concern about the use of avastin is that several investigators have observed that its use results in a higher likelihood of the tumor spreading to brain locations distant from the original tumor site. This issue remains controversial, in part because distant tumor spread may occur for many different treatments, not just those that rely upon the inhibition of angiogenesis.

Avastin, like other drugs, typically is given until tumor progression. However, a report at the 2012 meeting of ASCO suggests this may not be optimal (182). Patients receiving avastin for recurrent tumors until treatment failure (N=72) were compared to those who began avastin but stopped for reasons other than tumor progression (N=18), either because they had completed a planned schedule, or due to toxicity. In the latter group, progression--free survival at 1 year was 83%, and the median progression-free interval was 27.6 months, much better than patients receiving avastin until treatment failure (PFS-12 = 25% and Median PFS 9.7 months. Moreover, the former group was less likely to show an infiltrative pattern of recurrence.

An important issue is the efficacy of avastin as a single agent without concomitant chemotherapy. In a large (N=167) randomized trial (183), avastin alone was compared with avastin + CPT-11 in patients with recurrent glioblastoma. PFS-6 values were 43% for avastin alone and 50% for avastin + CPT-11; corresponding numbers for the percentage of tumor regressions were 28% and 38%. However, this outcome advantage for the combination group was offset by its higher rate of adverse events (46% vs. 66%). Moreover, median survival times were slightly in favor of avastin as a single agent (9.3 vs. 8.9 months). A longer-term follow-up was reported at the 2010 ASCO meeting (184).

Two-year survival rates were 16% and 17%, respectively. Overall, therefore, adding CPT-11 to avastin appears to provide a marginal improvement in survival outcome, a benefit that must be weighed against the added toxicity.

One initially promising protocol combined avastin with daily low-dose temodar (50 mg/square meter) for patients whose tumors had progressed on the standard temodar schedule of days 1-5 each month (185). While the results were still preliminary, a high rate of tumor regression and disease stabilization was noted, although the duration of these was not reported. However, a subsequent study (N=32) by the same investigators (186) reported much less positive results, as the PFS-6 value was only 19%, substantially below the 35-50% range obtained with avastin+CPT-11, or avastin alone. However, patients in this study had a more extensive history of prior treatments that had failed.

The best results yet reported when avastin has been used for recurrent tumors has come from its combination with hypofractionated stereotactic irradiation, based on the idea that avastin prevents the re-vascularization that is required to repair the damage caused by radiation. Twenty patients with recurrent GBM received the standard bi-weekly avastin infusions in combination with radiation during the first five cycles (187). Fifty percent of patients had tumor regressions, including five with a complete response. The PFS-6 value was 65% and median survival time was 12.5 months. Positive results were obtained in a second study (188) combining avastin and stereotactic radiosurgery with heavily pretreated patients. The median PFS was 5.2 months for those receiving the combination versus 2.1 months for those receiving stereotactic radiosurgery alone. The corresponding results for overall survival were 11.2 months vs. 3.9 months.

Avastin has also been combined with tarceva, a drug targeting the epidermal growth factor signaling channel. Although a high percentage of recurrent GBM patients had tumor regressions, the PFS-6 value was 29% and median survival was 44 weeks, not notably better than when avastin has been used alone (189).

The important question of whether to administer Avastin at first or later recurrences was addressed in a large retrospective study (310) published in the June 2014 edition of Neuro-Oncology (corresponding author Albert Lai, Department of Neurology, UCLA). A large cohort of 468 glioblastoma patients treated with Avastin was examined retrospectively, which included 80 patients treated with Avastin at diagnosis, 264 at first recurrence, 88 at second recurrence, and 36 at third or higher recurrence. Between all three recurrence groups (first, second, or third and higher), no significant difference was found in progression free survival on Avastin, overall survival from the start of Avastin treatment, or post-Avastin survival. In other words, treatment with Avastin led to “fixed” median progression-free and overall survival times from the start of Avastin, regardless of whether Avastin was started at early or later recurrences. The implication of this finding is that delayed use of Avastin may be preferable and lead to longer overall survival (from diagnosis) when administered at later rather than earlier recurrences. This idea remains to be tested in a prospective clinical trial.

This study also identified risk factors for the inability to receive further treatments at recurrence, thereby identifying patients who may benefit from earlier therapy with Avastin. The risk factors for inability to receive further treatment at first recurrence were: age over 60, and biopsy only. The one risk factor for inability to receive further treatment at second recurrence was age over 60. The conclusion of this study is that delayed use of Avastin is not associated with diminished efficacy and may even be preferable for those patients who can afford to delay such treatment until later progressions. On the other hand, older patients and patients with inoperable tumors, at risk of being unable to receive treatment at later recurrences, may benefit from earlier use of Avastin.

A study done at the MD Anderson Cancer Center reaching similar conclusions was published in the August 2014 edition of the Journal of Neuro-Oncology (311). This was a retrospective study including recurrent glioblastoma patients treated with Avastin between 2005 and 2011. 298 patient records were included in total, and divided into 112 patients treated with Avastin at first recurrence, and 133 patients treated with Avastin at second or higher recurrence. There was no significant difference in progression-free survival on Avastin between the two groups (PFS, 5.2 vs 4.3 months, p=0.2). In contrast, median overall survival from diagnosis was significantly shorter in the group treated with Avastin at first recurrence (OS, 20.8 vs 25.9 months, p=0.005). There was no significant difference in the time from diagnosis to first recurrence between the two groups. The authors conclude that delayed use of Avastin is not inferior to use of Avastin at first recurrence. The apparent improval in overall survival in the patients receiving delayed, rather than early, Avastin requires testing in a prospective clinical trial.

There now are two other anti-angiogenic drugs that have received FDA approval, and several others undergoing clinical trials. The two already available are Sutent (also known as sunitinib) and Nexaver (also known as sorafenib). Both target several different signaling pathways whereas avastin targets only VEGF, the most potent signal produced by the tumor to recruit new blood vessel growth. Both of these new drugs are now in early-stage clinical trials with glioma patients, but limited reports have failed to show significant clinical efficacy.

One important effect of avastin, and of other drugs that target VEGF, is that they reduce the edema common to brain tumors that is a major cause of the need for steroids. VEGF causes a large number of tiny leaky capillaries, which are pruned away when VEGF effects are blocked. Some have argued that the initial stage of blocking VEGF increases blood flow to the tumor, and hence makes it easier for chemotherapy agents to reach the tumor and be effective.

Avastin combined with CCNU (lomustine)

A 3-arm randomized phase 2 trial called BELOB, conducted at 14 centers in the Netherlands, tested Avastin alone, or CCNU (lomustine) alone, or Avastin + lomustine combined for glioblastoma at first recurrence or progression following standard radiochemotherapy (312). Overall, the patient group receiving combined Avastin and lomustine had better median PFS, 6-month PFS rate, median overall survival and 12-month survival rate than either of the single-agent groups. When the data was separated out on the basis of MGMT methylation status, the patient group with methylated MGMT receiving combination therapy had a 6-month progression free survival rate that was about twice as high (62%) as the MGMT methylated groups given Avastin alone (33%) or lomustine alone (26%). Predictably, patients with unmethylated MGMT did poorly on lomustine alone (0% were progression-free at 6 months), and also did better with combined therapy (6-month PFS rate of 23% versus 8% with Avastin alone). The methylated group had an equal 9-month overall survival rate with combined therapy or Avastin alone (67%), while the unmethylated group had a better 9-month overall survival rate with combination therapy (58%). The combination treatment was well tolerated after an early dose reduction from 110 mg/m2 to 90 mg/m2. This study concluded with the interpretation that combined treatment with Avastin and lomustine was superior to single agent therapy and the combination is now being studied in a phase 3 EORTC trial (NCT01290939).

Rechallenging with Temodar

When a treatment drug fails to be effective, or becomes ineffective with continued use, standard practice in oncology is to stop using the drug for that specific patient. However, a major exception to this general rule is to continue to use the drug but with a different schedule of presentation, usually with lower doses but given on a daily or more frequent basis. The most successful use of this approach when temodar has initially failed was a German study in which temodar was given at a very low dose (10 mg/sq.m.) twice per day, in combination with 200 mg/day of celebrex (45). PFS-6 was 43%, which is comparable to the results discussed above with avastin. Median survival was 16.8 months, which is superior to those with avastin, although this possibly was due to salvage treatment that could have included avastin.

An important study done at Sloan-Kettering suggests that the use of a metronomic daily low-dose schedule of temodar should be used prior to avastin to get the full benefit of using both treatments sequentially (42). Patients with tumor progression after undergoing the standard Stupp protocol were given the metronomic schedule using a daily dose of 50 mg/sq.m. Patients who had also previously received avastin had a much shorter survival time (4.3 months) than patients who received the metronomic temodar without prior use of avastin (13 months).

Optune (formerly NovoTTF) by Novocure

Like avastin, this treatment has FDA approval as a treatment for recurrent GBMs, and currently is in a clinical trial in which it is combined with the Stupp protocol for newly diagnosed GBMs. The basis of the FDA approval for recurrent tumor was a large clinical trial (139) that was discussed in the earlier section on agents that could be combined with temodar. The trial compared the Novocure device alone vs. whatever chemotherapy was chosen by the clinician. The results were a small survival advantage for the Novocure device, with much less toxicity. Also, a higher rate of tumor regression occurred. Overall the outcome results weren't impressive, but it is critical to appreciate that the patient population were patients who often had many prior treatments (there were no restrictions on how many), including a number who previously had failed avastin. Also, as discussed in a previous section, there is good reason to believe that the device is more effective when used in combination with chemotherapy.

Other chemotherapy agents at recurrence

While temodar is now the drug of choice for the initial treatment of glioblastoma, the majority of patients will receive minimal benefit. Patients who have failed the standard treatment protocol often proceed to other chemotherapy drugs. These include the nitrosoureas, BCNU and CCNU (and ACNU in Europe and Japan), and also the platinum drugs, and irinotecan, a drug developed for colon cancer known also known as CPT-11.

While BCNU was the standard chemotherapy treatment for glioblastomas for decades, there never was definitive evidence of its efficacy. A recent study of patients with tumors recurring after radiation treatment is typical of the evidence (190). Of forty patients receiving BCNU at the time of tumor recurrence after radiation, the PFS-6 value was 17%, accompanied by considerable hepatic and pulmonary toxicity. Even less promising results were produced in a small Australian study in which BCNU was given to patients who had progressed when using temozolomide. Here 23 of 24 patients failed during the first six months (191).

Given that BCNU and PCV (which contains CCNU, an oral cousin of BCNU) have never been shown to be differentially effective, a somewhat surprising result has been reported using PCV for tumors recurrent after radiation (and for some patients after radiation and prior chemotherapy). In a relatively large study of 86 patients (192), PFS-6 was 38%, a value superior to that obtained for temodar in a comparable setting, although with considerable toxicity. However, another study (193) that used PCV for patients with recurrent tumors after temodar had failed had a PFS-6 value of only 13%. One plausible explanation for the discrepancy between the two studies is the nature of the prior treatment that had failed.

A new member of the nitrosourea family is fotemustine, now available in Europe. In a recent review of its use with a variety of different schedules for patients with recurrent tumors after the standard Stupp protocol treatment, the PFS-6 value ranged from 26 to 44% (194). The best results have been obtained when fotemustine was given every two weeks for five consecutive treatments at a dose of 80 mg/sq.-meter followed by maintenance therapy every four weeks. The PFS-6 value was 61% with a median time to progression of 6.7 months (195). In an Italian study reported at the 2014 SNO meeting, patients who had failed the initial standard protocol received either avastin or fotemustine at the time of recurrence. Survival six months after recurrence was the primary measure, which was slightly higher for patients receiving fotemustine (322).

The platinum drugs cisplatin and carboplatin have also been used as single agents. Carboplatin has increasingly become the preferred drug because it has significantly less toxicity for eyes, ears and kidneys. In a representative study of carboplatin (196), 4 of 29 patients with recurrent glioma had a partial regression and 10 achieved stable disease. However, other treatment studies using the platinum drugs have produced highly variable results, with the source of the variability not clearly identifiable.

One of the newer chemotherapy agents is CPT-11 (also known as irinotecan), which has been FDA-approved for the treatment of colon cancer. Its application to gliomas has been pioneered by Dr. Henry Friedman at Duke University and is now undergoing clinical trials at a number of other medical centers as well. The initial results from the early trial were that 9 of 60 patients with recurrent gliomas had a confirmed partial response, while an additional 33 patients had stable disease lasting more than 12 weeks (197). However, results from other reported studies have been less positive (198, 199).

Like temodar, CPT-11 is now being studied in various combinations with other chemotherapy regimens, notably gliadel, intravenous BCNU, and temodar. Some results are available for the combination of CPT-11 with BCNU, which produced a PFS-6 value of 30% for patients who had failed temozolomide-based initial chemotherapy (200). One interesting sidelight about CPT-11 is that the gastro-intestinal toxicity that it produces, which can be severe, is substantially attenuated by low doses of thalidomide (see pages 36-37 for further discussion of thalidomide as a treatment agent in its own right). A recent study combining CPT-11 and thalidomide with patients who had failed both temodar and nitrosourea chemotherapy produced a PFS-6 value of 28% (201). Finally, CPT-11 has been combined with celebrex, with patients with recurrent tumors, and produced a PFS-6 value of 25% (202).

12. The Role of Radiation

For many years the only treatment (other than surgery) offered to patients with glioblastomas was radiation, due to radiation being the only treatment found to improve survival time in randomized clinical trials. This continued to be the case in Europe until the last decade, but in this country chemotherapy (usually BCNU) gradually came to be accepted as a useful additional treatment component despite the absence of definitive evidence from clinical trials. Part of the reason for this acceptance of chemotherapy has been that very few patients receiving only radiation survive longer than two years (3-10%), compared to 15-25% of patients also receiving chemotherapy.

The initial approach to using radiation to treat gliomas was whole-head radiation, but this was abandoned because of the substantial neurological deficits that resulted, sometimes appearing a considerable time after treatment. Current clinical practice uses a more focused radiation field that includes only 2-3 cm beyond the periphery of the tumor site. Because of the potential for radiation necrosis, the current level of radiation that is considered safe is limited to 55-60 Gy. Even at this level, significant deficits may occur, often appearing several years after treatment. The most common causes of these deficits are damage to the myelin of the large white fibers, which are the main transmitters of information between different centers of the brain, and damage to the small blood vessels, which results in an inadequate blood supply to the brain and also increases the likelihood of strokes. An additional risk, not yet proven clinically because of the typical short survival times of glioblastoma patients, is the growth of secondary tumors due to the radiation damage to the DNA. However, experimental work with animal models has supported the reality of this risk (208). Three-year-old normal rhesus monkeys were given whole brain radiation using a protocol similar to the common human radiation protocol and then followed for 2-9 years thereafter. A startling 82% of the monkeys developed glioblastoma tumors during that follow-up period. It is currently unclear to what degree a similar risk occurs for human patients who are long-term survivors.

The major additional use of radiation in the treatment of gliomas has been localized radiation to the tumor field, after the external-beam radiation treatment is finished (or sometimes concurrently), either by use of implanted radiation seeds (typically radioactive iodine), a procedure known as brachytherapy, the use of radiosurgery (including gamma knife), or by the insertion into the tumor cavity of an inflatable balloon containing radioactive fluid (gliasite). Previous editions of this treatment summary devoted considerable discussion to these treatments. However, these treatments now are used much less frequently. Two different randomized trials of brachytherapy failed to show a statistically significant survival benefit even though the procedure causes considerable toxicity in terms of radiation necrosis (209). A recent randomized study of radiosurgery (210) similarly failed to show a benefit. Gliasite has yet to be studied in a randomized trial.

The usual interpretation of the failure to find a benefit in the randomized trials is that the initial studies indicating a survival benefit (usually increasing survival time about a year) involved a highly selected patient population, who otherwise had a good prognosis regardless of whether they received the procedure. However, selection bias seems not to account for all of the benefits of the procedure. For example, the use of gliasite for recurrent GBM tumors produced a median survival time of 36 weeks (211), which compares favorably with a median survival time of only 28 weeks when gliadel wafers were implanted for recurrent tumors, even though eligibility criteria were similar for the two procedures. Moreover, when patients receiving gliasite as part of the initial treatment (212) were partitioned according to according to established prognostic variables, and each partition was compared to its appropriate historical control, survival time was greater for patients receiving gliasite in each of the separate partitions.

Perhaps the best results reported involving radiation boosts comes from the combination of permanent radioactive iodine seeds with gliadel (212). Median survival for patients with recurrent glioblastomas was 69 weeks, although accompanied by considerable brain necrosis. The use of gliadel alone in the same treatment center, by comparison, produced a median survival time of 28 weeks, while the use of the radiation seeds alone produced a median survival of 47 weeks.

Impressive results have also been obtained with the addition of fractionated radiosurgery to the standard Stupp protocol for newly diagnosed patients (213). For 36 GBM patients median survival (from diagnosis) was 28 months and two-year survival was 57%. Median progression-free survival (from study entry) for the GBM patients was 10 months.

The foregoing results suggest that supplementary radiation procedures do provide some benefit, but it is important to appreciate that all only a portion of patients will be eligible for such treatment. Radiation necrosis caused by the treatment must be considered as well.

Hyberbaric oxygen and other radiosensitizers

A potentially important modification of the standard radiation protocols involves the use of hyperbaric oxygen prior to each radiation session. In a study conducted in Japan (214), 57 high-grade glioma patients received the standard radiation protocol with the addition of hyperbaric oxygen 15 minutes prior to each radiation session. Four rounds of chemotherapy were also administered, the first during the radiation period of treatment. For the 39-glioblastoma patients, the median survival time was 17 months, with a very high rate of tumor regression. For the 18 patients with anaplastic astrocytoma, median survival was 113 months. Two-year survival was reported separately for recursive portioning categories I-IV and V-VI, the latter including only glioblastoma patients. For categories I- IV, two-year survival was 50%; for categories V and VI, two-year survival was 38%.

A long-standing goal of radiation oncology has been to find a radiation sensitizer that does not increase toxicity to normal tissue. One of the most promising advances toward this goal was reported at the 2011 ASCO meeting (215). A new drug derived from the taxane family, with the name OPAXIO, was combined with the standard temodar + radiation protocol during the radiation phase of the treatment. The response rate for 25 patients (17 GBM) was 45% with 27% having a complete response. With a median follow-up of 22 months, median progression-free survival was 14.9 month (13.5 months for GBM patients). Median overall survival had not been reached at the time of the report. Note that the median PFS for the standard treatment without OPAXIO is 6.9 months.

Proton radiation therapy

An alternative to the standard X-ray radiation is the use of proton beams, although only a few treatment centers have the required equipment. To date, there has been no meaningful comparison of the efficacy of proton-beam radiation and the normal procedure. However, one recent study in Japan did report unusually positive results when the two forms of radiation were combined, the standard procedure in the morning, and the proton-beam radiation in the afternoon (216). Also used was ACNU, a chemical cousin of BCNU and CCNU. Median survival for 20 patients was 21.6 month, with -1-year and 2-year progression-free rates of 45% and 16%. However, there were six cases of radiation necrosis that required surgery, indicating a considerably higher toxicity than normally occurs with the standard radiation procedure.

Radiation via Monoclonal Antibodies

An alternative for providing a radiation boost beyond the standard external field radiation involves attaching radioactive iodine-131 to a monoclonal antibody that targets a specific antigen, tenascin, which occurs on almost all high-grade glioma tumors and not on normal brain cells. The monoclonal antibodies are infused directly into the tumor cavity over a period of several days, and reportedly produces much less radiation necrosis than either brachytherapy or radiosurgery. The median survival time from a phase 2 clinical trial of this treatment for recurrent GBM tumors was 56 weeks (217). In the first study that reported using this approach as initial treatment (218) patients received the monoclonal antibodies, followed by the standard external-beam radiation and then a year of chemotherapy. Of 33 patients, only one required re-operation for necrotic tissue caused by the radiation. Median survival time was 79 weeks for the patients with glioblastoma (27 of 33 of total patients) and 87 weeks for all patients. Estimated two-year survival rate for GBM patients was 35%. A subsequent report of the results for an expanded number of patients indicated a mean progression-free survival of 17.2 months, compared to 4-10 months for other treatment procedures (219). Median overall survival measured from the time of diagnosis was 24.9 months. At the present time, however, only one treatment center (Duke University) has used this procedure. A multi-center clinical trial was planned, but the company sponsoring the trial apparently has shelved those plans for the indefinite future.

A second type of monoclonal antibody treatment, developed at Hahneman University Medical School in Philadelphia, targets the epidermal growth factor receptor, which is overexpressed in the majority of GBM tumors (220) For patients who received the MAB treatment in combination with standard radiation, median survival time was 14.5 months; For patients who received the same protocol but with the addition of temodar, median survival was 20.4 months.

A third type of monoclonal antibody, named Cotara, is designed to bind with proteins that are exposed only when cells are dying, with the result that adjacent living tumor cells are radiated by the radiation load carried by the monoclonal antibody. This rationale is based on the fact that that centers of GBM tumors have a large amount of necrosis. This approach has been under development by Peregrine Pharmaceuticals, a small biotech with limited funding. Recently they reported the long-term results from 28 recurrent GBM patients studied over a nine-year period (221). Seven of the 28 patients survived more than one year, while 3 of the 28 survived longer than five years (2 more than 9 years). Median survival was 38 weeks.

13. Recommendations

With each passing year the information about treatment options has expanded, making it increasingly difficult for the newly diagnosed patient, or their families, to discern which is the best treatment plan to follow. So here I offer my own opinions about the relative merits of the various options, based on what I would do today if I were a newly diagnosed patient. Keep in mind that I am not a physician with direct contact with patients and the valuable information that provides. On the other hand, my opinions are not constrained by the conventions of the medical system, which often hamstring oncologists in considering the possible options.

My first piece of advice is to seek treatment at a major brain tumor center. Their surgical techniques are more likely to be state-of-the-art, which in turn means the patient will be more likely to receive a complete resection, now known to be a strong contributor to longer survival. Also important is that major centers will be better equipped to retain tumor samples that will allow various tests of genetic markers that have important implications for which treatments are most likely to be successful for the individual patient. Patients should request prior to surgery that their tumor tissue be frozen and preserved for later use.

Several tests for genetic markers seem worthwhile at the present time, although others undoubtedly will emerge in the near future. The most important is for the methylation status of the MGMT gene (encoding the MGMT DNA repair enzyme), which predicts whether the standard treatment protocol involving temodar will be successful. If a high level of activity is detected (the MGMT promoter is unmethylated), the standard protocol seems not to work any better than radiation, so a different treatment protocol is advisable, such as a metronomic schedule of temozolomide as discussed in another section.

A second test is for the amplification of the epidermal growth factor receptor (EGFR) and for the variant III (EGFRvIII) mutation. Amplification of EGFR combined with an unmethylated MGMT promoter indicates that a metronomic schedule of temodar should be used instead of the standard monthly schedule (Reference 313; see discussion on page 11, above), while the variant III mutation indicates that the new vaccine targeting this mutation (rindopepimut) should be an effective treatment. Note that combining the vaccine with chemotherapy actually seems to improve outcome, contrary to the typical expectation that immunotherapy and chemotherapy treatments are incompatible. The presence of the EGFR variant III is also important for predicting the likely outcome of EGFR inhibitors like Tarceva but such prediction is more accurate when combined with a test for an intact PTEN gene.

Yet a third test is for the presence of overexpressed platelet-derived growth factor (PDGFR), which is a target of gleevec (imatinib). Gleevec has been generally ineffective when applied to the entire patient population, but can be effective if the PDGFR overexpression is present.

Unlike even five years ago, there now are meaningful choices for effective treatment protocols, although several of the most promising are still in clinical trials and not generally available. On the basis of current evidence, the best treatment protocols after initial diagnosis are now four vaccines: the **DCVax-L** vaccine developed at UCLA, the **ICT-107** vaccine developed at Cedars Sinai, the vaccine for the EGFR variant III (**rindopepimut**, now also known as Rintega) developed at M. D. Anderson and Duke, and the **vaccine targeting cytomegalovirus** (in combination with preconditioning with a tetanus shot), also developed at Duke. Note that all three of these are used concomitantly with the standard temodar protocol, based on the surprising finding that vaccines and chemotherapy are synergistic rather than antagonistic. But it is important to appreciate that these vaccines are likely to be available only for a minority of patients, partly because of the limited number of treatment centers using them, and partly because of various eligibility restrictions.

The standard temodar protocol is also used in combination with the Novocure electrical field therapy (**Optune**), which is also compatible with almost any other treatment modality. The most recent results with **photodynamic therapy** (224) are also very encouraging.

Also promising, although now with the results of only five patients having received the protocol, is DCA, which like the vaccines can easily be combined with chemotherapy. It also may be combined with other treatments that target the mitochondria, (e.g., chlorimipramine).

For those whose options are restricted to chemotherapy, the best results have come from a phase 2 trial combining **temodar and CCNU**. Median survival from that combination was 23 months and 3-year survival rate was 26%. However, the combination did produce considerable toxicity. This combination is currently being tested in a phase 3 trial in Germany (NCT01149109).

Given that temodar is part of all of the above new treatment protocols, it is important to maximize its effectiveness. As reviewed earlier there are two very important changes to the standard protocol that should improve its effects. The most potent appears to be the addition of chloroquine, which doubled survival time when added to the old chemotherapy standard, BCNU. While it is not certain that a similar benefit will occur with temodar, it seems likely given that both drugs are alkylating agents. More recent evidence (discussed on page 10 above), indicates that hydroxychloroquine added to conventional radiation and temozolomide did not improve survival beyond historical controls (304). There is some evidence for a link between overexpression of EGFR or the presence of the EGFR variant III mutation and increased benefit from chloroquine (305). The second change is to substitute a daily (metronomic) schedule of temodar for the standard (5/23) schedule for tumors with unmethylated MGMT status, especially if the tumor has overexpression or amplification of EGFR (313).

There are numerous other relatively benign treatment agents that should also improve outcome, as reviewed in the earlier section. As a strong believer in the cocktail approach to treatment, my general rule is that any treatment that does not add significantly to toxicity should be considered as an additional facet of treatment. These include accutane (but not during radiation and preferably not simultaneously with chemotherapy), celebrex (which should be used during radiation), low doses of thalidomide, and high-dose tamoxifen. Also worthwhile is the calcium blocker verapamil, metformin, the diabetes drug, and disulfiram (antabuse), the drug used by alcoholics. Especially in combination with chemotherapy, the proton pump inhibitors (e.g., nexium) used for acid reflux, should be useful as well. In reality, such combinations will be very difficult to obtain, as few neuro-oncologists will cooperate with this approach.

The above suggestions apply to the initial treatment protocol. It is unclear whether these same approaches will work for patients with tumor recurrence. The situation at recurrence is more complex, because the previous treatments used by a patient affect the success or failure of subsequent treatments. Avastin is now the most commonly used treatment for recurrent tumors. An alternative to avastin for recurrent tumors is the use of extremely low-dose temodar in combination with celebrex. Patients received temodar at a dose of 10 mg per meter-squared body surface twice per day, along with 200 mg of celebrex. For patients receiving this protocol, PFS-6 = 43% and median survival was 16.8 months. Treatment toxicity was minimal. Use of this relatively benign treatment would allow avastin to be held until needed for a later recurrence. A second alternative would be a metronomic schedule with a somewhat higher dose (50 mg/day/sq.m.), which while more toxic had somewhat better outcomes.

An alternative chemotherapy protocol for recurrent GBM tumors, which may also apply when avastin fails, is the chemotherapy drug, fotemustine. A recent Italian clinical trial (N=40) studied this as a single agent and produced a PFS-6 value of 61% and a median survival of 11 months, both better than the results obtained when avastin has been used for recurrent tumors (195).

Two additional recommendations may also add to the changes of treatment success. For patients using anti-seizure medicine, the use of valproic acid (Depakote) is advisable as there are meaningful data that its property of being an inhibitor of histone deacetylase (HDAC) improves clinical outcome (319). This assumes, of course, that Depakote is as effective as the alternative medicines in controlling seizures and has acceptable side effects. Keppra (levetiracetam) is another possibility, as it now appears to inhibit MGMT expression and thus increase chemotherapy effectiveness (323). In a similar vein, for patients needing anti-emetic medication, medical marijuana is advisable. Not only does it avoid the constipation problem caused by the standard drugs (Zofran and Kytril), but it appears to have anti-tumor properties in its own right. A new anti-nausea drug, Emend (aprepitant) also has been shown to have anti-cancer properties of its own (in vitro).

Finally, it is clear that the immune system is important, and that agents which activate the immune system should be helpful. Both melatonin and PSK fall into this category. Poly-ICLC should also be helpful (with little toxicity), assuming it becomes generally available.

Epilogue

Over the years I have received many valuable suggestions about additional agents that should be included in my review. Some of these are nutriceuticals; most are drugs developed for other purposes used off-label. My criteria for inclusion of a treatment option are impressionistic at best, and an argument can be made for additional agents. One example is noscapine, a nontoxic ingredient of cough syrup (apparently now sold only in Europe) and derived from opium (without the psychotropic effects). Substantial tumor regression has been demonstrating using it in a GBM mouse model, and its mechanism of action has been identified (302). Also of significant interest is low-dose naltrexone, which has produced positive clinical results with pancreatic cancer (303).

Appendix A: Summary of major revisions for 2015 edition

Page 10 - discussion of clinical trial of hydroxychloroquine added to standard of care for newly diagnosed glioblastoma. Evidence for sensitivity of EGFR-overexpressing GBM cells to chloroquine.

Page 12 - discussion of retrospective study showing benefit of metronomic temozolomide schedule for EGFR-overexpressing or EGFR-amplified glioblastoma.

Page 17-19 - discussion of Optune (Novocure tumor treating fields) including the PRiDe dataset and results from the recent phase 3 trial for newly diagnosed glioblastoma.

Page 29 - evidence for low dose Accutane plus interleukin-2 in other cancers

Page 32 - Keppra (levetiracetam) extends survival when added to standard of care chemotherapy for newly diagnosed glioblastoma

Page 37 - thalidomide for advanced secondary GBM

Page 39 - valproic acid combined with chemoradiation for newly diagnosed glioblastoma

Page 40 - updated results for a trial of 3 repurposed drugs (Accutane, Celebrex, thalidomide) plus temodar

Page 62 - new results for “informational arm” of DCVax-L trial (ie. outcomes for patients who were disqualified from the phase 3 trial due to early disease progression, but who received the vaccine on compassionate use basis)

Page 64-65 - updated results of randomized phase 2 trial of ICT-107 vaccine in newly diagnosed glioblastoma

Page 65-66 - results of trial testing CMV-targeted vaccine with or without preconditioning with tetanus/diptheria toxoid

Page 66-67 - updated results of the phase 2 ACTIII trial of rindopepimut (anti-EGFRvIII vaccine) for newly diagnosed glioblastoma

Page 67 - preliminary results of nivolumab combined with ipilimumab for recurrent glioblastoma

Page 67 - genetically modified poliovirus (PVS-RIPO) for recurrent glioblastoma

Page 68 - modified adenovirus (DNX-2401) for recurrent glioblastoma

Page 69 - preliminary results of Toca 511/TocaFC therapy for recurrent high-grade glioma

Page 73 - discussion of optimal timing of Avastin treatment (upfront versus delayed)

Page 74 - Avastin plus CCNU for recurrent glioblastoma

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