Treatment Options for Glioblastoma and other Gliomas

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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 is from information that 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 by phone or e-mail 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'. It can be ordered elsewhere on this website, from Amazon.com, from your local bookstore, or directly from the publisher:

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When I began my own 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 worked for 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 five 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 in outcome from previous treatments, it still falls far short of being effective for the great majority of patients. What is needed, therefore, is a new philosophy of treatment that goes beyond rigidly defined protocols to include a variety of different agents used in combination.

 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 very susceptible to mutations. This implies that unless a treatment is immediately effective 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 much smaller chance of being successful.

The second premise is that cancer treatments of all sorts are probabilistic in their effects. None of them 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 15-40%, 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.

The third general principle is that any successful treatment will need 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. 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 recently, 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. Such agents are available but not widely used. Also becoming available are new systemic treatments that are much less toxic than traditional chemotherapy. The

availability of these treatments raises the possibility that some combination of these new agents can be packaged that is substantially less toxic, yet 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 new 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 this may be, 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. An even more serious problem 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 "Gold Standard" for Initial Treatment

Although chemotherapy has a long history of being ineffective as a treatment for glioblastoma, a large randomized European clinical trial 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 (1). One group of patients received radiation alone; the other group received radiation plus temodar, first at low 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 (2). As a result of these new findings, the protocol of TMZ presented during radiation is now recognized as the "gold standard" of treatment and is one of the few treatments for glioblastoma that is FDA approved. 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 the new anti-nausea agents, Zofran and Kytril. Marijuana also can be very effective in controlling such effects, and recent research has suggested that is 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 chemo-sensitivity 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 at least a half-dozen 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 significantly enhance treatment effectiveness for a variety of different types of cancer, including a recent Japanese study using chemosensitivity testing with glioblastoma patients (3). 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 substantially increase the likelihood that the agent will be beneficial.

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 both radiation and chemotherapy are less effective. Patients whose MGMT gene is inactivated (which occurs in 45% of patients) have a significantly greater chance of responding to temodar than those for whom the gene is still functional (4). For patients with an inactive gene, two-year survival was 23% for those receiving radiation only, compared to 46% for those who received radiation and temodar together. For those with an active MGMT gene the corresponding numbers were 2% and 14%. This implies that patients should have tumor tissue taken at the time of surgery tested for the 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. The reason is that there remains considerable controversy 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 (5) compared the degree of MGMT protein expression by using commercial anti-MGMT antibody and an assessment of the methylation status of the promoter gene for MGMT expression. The two measures correlated only weakly, and only the measure of promoter gene methylation correlated strongly with survival time. New methods for assessing methylation have recently been introduced (6) which may resolve the controversy.

 The predictive validity of the methylation status of the MGMT promoter gene is an important issue to resolve because temozolomide appears to produce little survival improvement for those whose MGMT gene is activated. Thus, patients with the activated

gene might be better served by use of a different chemotherapy agent. Just such a 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%. (7)

A second genetic marker that predicts the effectiveness of temodar (and other chemotherapy agents) is the status of the gene (known as the MDR-1) that controls multi-drug resistance resulting from a glycoprotein pump, which actively extrudes the chemotherapy agent from the cell before it has a chance to kill the cell. In a recent study conducted in Germany (8), an analysis of genotypes for the MDR-1 gene for patients receiving temodar showed that those with one of three possible variations of the gene had substantially greater 2-year survival times than those with the remaining two versions of the gene. For the former patients, 2-year survival was 37%; for the latter, two-year survival was 9%. The predictive value of the MDR gene was independent of that of the MGMT promoter gene just discussed.

Strategies for improving the "Gold Standard"

<u>Combating chemoresistance</u>

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 an active MGMT gene). Also mentioned 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, usually because its molecular weight is too large. 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.

One approach to making temodar more effective is to directly target the mechanisms underlying temodar resistance. The importance of the MGMT enzyme noted above has inspired the use of a drug known as 06-benzylguanine (06BG), which depletes the enzyme, thus preventing the repair of the temodar-induced damage to the DNA of the glioblastoma cells. Unfortunately, 06BG also increases the sensitivity of the bone marrow cells to temodar's toxic effects, which implies that using 06BG in combination with temodar is functionally similar to using higher dose of temodar. It may be that careful titration of dosage levels will allow this to be a viable strategy, but at present this protocol, which is still experimental, is problematic.

A second source of chemoresistance comes from glycoprotein transport systems, noted above as one basis of multi-drug resistance. One of these pump-like mechanisms utilizes calcium channels; so that calcium channel blockers can interfere with its action, thus allowing the chemotherapy agent longer time to be effective. 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 the 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 (9).

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 (10) 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 (11) 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 (12). In laboratory studies other calcium channel blockers, especially, nicardipine and nimodipine

(13, 14) 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 block the extrusion pump.

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 simvastin, have been shown to augment the effects of BCNU in laboratory studies (15), but have not yet been combined with chemotherapy in any reported clinical study. Most recently, a common drug used in the treatment of alcoholism, Antabuse (also known as disulfuram), has been shown in laboratory studies to be a powerful inhibitor of the extrusion pump mechanism, although as yet this has not been studied clinically. (16)

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 (17, 18, 19) patients received the traditional chemotherapy agent BCNU, with or without a 150-mg daily dose of chloroquine. 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, and possibly other chemotherapy agents as well.

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 incomplete, which means portions of the tumor will not be contacted by any chemotherapy agent that does not cross the intact BBB. Various ways of disrupting the BBB have been studied, but none has been generally successful, primarily because of the systemic side effects of the BBB

disruptors. Recently, however, the common erectile dysfunction drugs (Viagra, Levitra, Cialis) have been discovered to disrupt the BBB at the dosages commonly used for erectile dysfunction. Moreover, in a rat brain tumor model, the addition of Viagra or Levitra to a common chemotherapy agent, Adriamycin, substantially improved survival time (20).

Optimizing the Schedule of Chemotherapy

The standard schedule for using full-dose temodar is days 1-5 out of every 28-day cycle. The recent large Swiss study described above also added daily temodar during radiation but 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 (21), and produced clinical outcomes seemingly better than those obtained with the standard schedule.

In addition to the standard schedule, three other schedules have been studied: (1) a "metronomic" daily schedule; (2) and alternating week schedule; (30) a "dose-intense" schedule in which temodar is used on days 1-21 of every 28-day cycle. A number of clinical trials comparing these different schedules are currently in progress.

To date, only two randomized trials directly comparing different temodar schedules have been reported, one comparing the alternating week schedule with the metronomic schedule, and one comparing the alternating week schedule with the normal monthly schedule The comparison (22) of the alternating week and metronomic schedules was conducted with newly diagnosed patients. One-year survival rates were 80% vs., 69%, and two-year survival rates 35% vs. 28%, both favoring the alternating week schedule. The corresponding numbers for the landmark Stupp et al. 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.

The randomized trial (23) comparing the alternating week schedule with the standard monthly schedule involved patients with tumors recurrent after radiation treatment (but apparently no prior chemotherapy). Median survival for the standard schedule was 14 months, while that for the alternating week schedule was 21 months. Two-year survival rate for the standard 5-day/month schedule was 10%, while 2-year survival with the alternating week schedule was 40%. The alternating week schedule was also reported to have considerably less hematological toxicity.

The two clinical trials just described suggest that the alternating week schedule is superior to both the standard monthly schedule and the metronomic schedule. However, a different outcome was obtained in a nonrandomized trial (24) in which temodar was used as the initial treatment after surgery and 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.

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 to make 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%. In contrast, the use of temodar with a comparable set of patients has 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 (25). Here, with an initial 21 patients, the

PFS-6 was 48%. A follow-up report (26) 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. By comparison, the dosage of temodar during the five days of the standard schedule is 200-300 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. This is important because a general principle of oncology is that after a given chemotherapy agent has failed, it should no longer be used.

An important exception to this generalization is the use of the metronomic schedule. Several prominent oncologists have reported experimental studies showing that rodents that have become resistant to chemotherapy administered with the usual bolus injections will nevertheless show a clinical response when the same chemotherapy is administered continuously at low dosages (27, 28). Moreover, in comparison to the bolus dosage, continuous low dosages (so-called metronomic chemotherapy) have less toxicity. Early clinical results (29) 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 (120 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 (30). Patients were also subdivided according to when their tumors had recurred, (a) while on the standard TMZ protocol, or (b) after the TMZ protocol had been completed. 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 has failed. The first with 13 GBM patients (31) used a daily dose of 50 mg/meter-squared, and reported a PFS-6 value of 23%. The second study (32), 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%.

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 (33). After completion of standard radiation treatment, continuous daily dosages 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 (34) 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 (35) has used very low-dose metronomic schedules of temodar given 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 20 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 7.1 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 lymphophenia. 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.

The positive results of the just-described clinical trial 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%, the median survival was 8.7 months and the PFS -6 value was 19% (36). 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 (35), and its use of a much lower dose of temodar. In the second study (36), 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, some of which included several different kinds of salvage therapy.

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 (37), a procedure that results in

substantially less toxicity. Here the median survival was 21 months and the two-year survival was 42%. However, only 29 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 (38), 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.

Combining the Standard Treatment with Additional Agents

Few oncologists believe that single treatment agents are likely to be curative. The issue is the optimal combinations, based on toxicities and differences in the mechanisms of actions. The PCV combination of procarbazine, CCNU, and vincristine has 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 drugs, most of which supports the view that such combinations improve treatment outcome, sometimes substantially.

Temozolomide with other Chemotherapy

A recent report from Germany in combined TMZ with CCNU (lomustine), the nitrosourea component of the PCV combination (39). 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, and somewhat better results as a result (with a 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 had a median survival of 34 months, while those with an active gene 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 also contributed substantially to survival time.

The combination of temodar with BCNU, the traditional chemotherapy for glioblastomas has also being 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 recurrent tumors 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 (40).

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 GBM 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 (41). Probably the best estimate of the benefit of gliadel as an initial treatment comes from a. randomized clinical trial, conducted in Europe (42), 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, in both of the just cited trials 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 (43), 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 (44), 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 (45), 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, the drug discussed above 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 (46) 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 (47).

An improvement in results relative 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 (48, 49) with patients with recurrent tumors, the PFS-6 was 34% and 35%. A treatment protocol (50) with more impressive results combined temodar with both cisplatin and etoposide (VP-16), given through the carotid artery. Cisplatin and VP-16 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 so far median survival was 25 months.

Temodar has also been combined with procarbazine (51). 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.

Other Chemotherapy Agents

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 recurrent after radiation treatment is typical of the evidence (52). 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 (53).

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 (54), PFS-6 was 38%, a value superior to that obtained for temodar in a comparable setting, although with considerable toxicity. However, another study (55) 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.

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 (56), 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 (57) However, results from other reported studies have been less positive (58, 59).

 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 (60) One interesting sidelight about CPT-11 is that the gastro-intestinal toxicity that it produces, which can be severe, is substantially attenuated by low dosages of thalidomide (see below 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 nitrosurea chemotherapy produced a PFS-6 value of 28% (61). Finally, CPT-11 has been combined with celebrex, with patients with recurrent tumors, and produced a PFS-6 value of 25% (62).

Temozolomide with Drugs Not Normally Used for Cancer

There are now a substantial number of clinical trials in which TMZ has been combined with treatment agents that were developed for other medical conditions, which subsequently were shown to have efficacy against glioblastomas as well. One example comes from a small phase II clinical trial that combined temodar with thalidomide, a known anti-angiogenic agent. Starting after the standard radiation treatment (63), patients received either thalidomide alone or thalidomide + temodar. Median survival time for the thalidomide-alone group was 63 weeks, while that for the group with thalidomide + temodar was 103 weeks. But the latter group involved only 25 patients.

 A more recent 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 (64). 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 produced 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. In fact 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. (65) Newly diagnosed glioblastoma patients received temodar alone on the standard schedule or the combination of temodar and thalidomide. Median survival was 12 months for temodar alone and 13 months for the combination. When the combination of temodar + thalidomide has been used with patients with recurrent GBM (66), PFS-6 was 24%.

When temodar has been combined with accutane, a retinoid used for acne treatment (also known as 13-cis-retinoic acid, to be discussed later), the PFS-6 improved from the 21% historical value of temodar alone, to 32% (67) Temozolomide has also been combined with interferon alfa-2b, which produced a PFS-6 value of 38% for glioblastoma patients (68). Temozolomide has also been studied in combination with interferon-Beta for newly diagnosed GBM (69). Fifty-four patients were randomized to receive the standard Stupp protocol or the standard protocol in combination with interferon –Beta. Median survival was significantly longer in the interferon-beta group (22.3 months) than the standard protocol (12.7 months). The benefits of adding interferon were particularly increased for patients with an active MGMT gene.

There are also several clinical trials underway combining temodar with a variety of biological agents that hold promise of improving outcomes without significantly increasing treatment toxicity. These include drugs that target the signaling pathways involved in cell division, and agents that inhibit the growth of new blood vessels. In the latter category is a trial conducted jointly by several hospitals in New York, which combined temodar with celebrex, the anti-inflammatory drug that is now widely used for arthritis (70). 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.

It is important to recognize the limitations of the PFS-6 measure of treatment efficacy. While it provides a rough means of comparing different treatments, it says little about whether the various treatment protocols improve overall survival. It is possible that treatments with low PFS-6 values produce a greater percentage of long-term survivors than those with higher PFS-6 values. Nevertheless, one major conclusion allowed by the above comparisons is that combinations of treatments are often superior to single-agent treatments, and that the combinations can include agents of relatively mild toxicity (e.g., accutane, celebrex). It is feasible that the use of such lower-toxicity agents will allow combinations involving 3 and 4 different agents, which presumably should improve treatment outcome still further.

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 (71), 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 (72). Survival was substantially longer in the latter group.

A later section will discuss several other nonprescription items that appear likely to add to treatment success. These include melatonin, PSK (a mushroom extract used widely in Japan), fish oil, and the seed oil, gamma linolenic acid.

Because of the improved results described above when additional agents have been added to temodar for patients with recurrent tumors, there now have been several recent clinical trials in which additional agents have been added to the initial treatment of patients just after diagnosis. Unfortunately, these trials have produced more confusion than clarification about the utility of combination treatments because the outcomes of different clinical trials have varied considerably.

In contrast to the improvement in clinical outcome when accutane was combined with temodar for recurrent tumors (67), a clinical trial with newly diagnosed patients that combined temodar with accutane produced less impressive results. . One study (73) with 55 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. However, a second smaller (33 patients, 29 of whom had a GBM diagnosis) retrospective clinical trial (74) produced a median survival of 102 weeks, and a 2-year survival rate of 75%. The major difference between the two studies is that the latter did not begin the use of accutane until after the radiation phase of treatment was completed.

The most disappointing outcome has recently been reported for a treatment combination involving temodar, thalidomide and celebrex for newly diagnosed patients (75). Fifty GBM patients received the standard radiation therapy followed by the standard days 1-5 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.

The somewhat conflicting data from the clinical trials just reviewed prevents any clear recommendations about which are the optimal treatment cocktails. More information about these additional agents, and the results from clinical trials in which they have been studied, will be presented in later sections.

Among the better results for combinations involving the Stupp protocol for newly diagnosed patients comes for an Italian study (N=37) that added fractionated stereotactic radiosurgery (76). Median survival was 22 months and two-year survival was 51%, although it should be noted that eligibility requirements excluded patients with large tumors.

New Treatment Agents Currently Available

In this next section, all of agents described are FDA-approved and thus can be obtained by prescription, despite the fact that their approvals have been for diseases other than brain tumors. This unfortunately causes some oncologists to be unwilling to prescribe them, although off-label prescriptions are entirely legal. The drugs that will be described differ from conventional chemotherapy in that they do not kill all dividing cells, and as a result have little of the traditional toxicity for the bone marrow that causes weakening of the immune system and anemia. This makes them ideal candidates for drug cocktails, including combinations with chemotherapy. Several of these combinations appear sufficiently promising that they might be a better choice as the initial treatment after surgery than the temodar "gold standard". For example, patients whose MGMT gene is active are known to respond poorly to temodar, so that an alternative protocol could provide a better chance of treatment success.

Avastin (and related drugs)

Avastin (also known as Bevacizumab) is a monoclonal antibody that is the first drug to receive FDA approval explicitly designed to inhibit the growth of new blood vessels. It now is used for several different kinds of cancer, almost always in combination with one or another form of chemotherapy. Only recently it received FDA approval for the

treatment of glioblastoma. As a result, it has now become the most frequently used treatment after temodar has failed. Its first use with brain tumors was reported at a 2005 European neuro-oncology conference. (77). 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), following 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 numerous other studies has been reported. The largest of these, performed at Duke University (78), 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. (79) 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 15 % (80), not impressive in absolute terms but much better than the 0-5% 2-year survival typical for recurrent tumors.

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. However, reviews of larger patient populations have failed to confirm these observations. It should be noted that distant tumor spread may occur for many different treatments, not just those that rely upon the inhibition of angiogenesis.

An important issue is the contribution of the chemotherapy combined with avastin. In

addition to CPT-11 and temodar, carboplatin and etoposide have also been used, and have produced PFS-6 values comparable to that with the more common avastin + CPT-11 combination (approximately 40-45%). Sorely needed is further exploration of other agents that might be combined with avastin that would result in tumor responses of longer duration.

Also at issue is the efficacy of avastin as a single agent without concomitant chemotherapy. In a large (N=167) randomized trial (81), 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 slight 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 (82). Two-year survival rates were 16 and 17%, respectively. Overall, therefore, there appears little advantage to adding CPT-11, especially given its added toxicity.

One 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 (83). While the results were still preliminary, a high rate of tumor regression and disease stabilization were noted, although the duration of these has yet to be reported. The possible role of daily low-dose temodar is further indicated by its use with 35 heavily pretreated patients who had failed avastin + CPT-11. When 20 mg/day of temodar was added while the avastin + CPT protocol was continued, a PR occurred for 4/35 patients and stable disease for at least 2 months occurred for 14/35 patients (84).

Daily low-dose temodar as a single agent has also been studied in heavily pretreated GBM patients who either did or did not have prior exposure to avastin. (85) Those without prior avastin exposure had a PFS-6 of 36%; those who previously had failed avastin had a PFS-6 of 14%.

The just-described studies, along with the impressive results from the use of metronomic temodar in combination with celebrex described in a previous section, suggest that daily low-dose temodar has substantial potential for increasing treatment efficacy. However a recently published Dutch study (86) failed to find any benefit of adding it to avastin for recurrent tumors. Instead, the combination of avastin and low-dose temodar produced a PFS-6 value of only 17%, substantially below the 40% value that is typical when avastin has been used in combination with CPT-11.

The best results yet reported when avastin has been used for recurrent tumors has come from its combination with hypofractionated sterotactic 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 (87). 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.

Avastin has also been combined with tarceva, a new drug targeting the epidermal growth factor signaling channel (see below). 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 (88).

Because of its success with recurrent tumors, avastin has also been added to the standard temodar + radiation protocol as initial treatment. Three separate small clinical trials combining avastin with the standard treatment protocol have now been reported. The first study involved only ten patients (89) and focused mainly on toxicity. Toxicity did seem higher than that standard protocol with respect to platelet counts, fatigue, and wound healing, although the small number of patients leaves unclear whether the increased toxicity was beyond the range typical of the standard protocol. In terms of clinical outcome, only one of the ten patients had died, and seven of the nine remaining patients had no evidence of progressive disease over 40 weeks post-diagnosis. A second similar

clinical trial was also just reported, here with 15 patients (90). The one-year progression-free survival was 59%, and the one-year overall survival rate was 87%. Like the preceding study, considerable toxicity was noted, which caused two patients to withdraw from treatment. A subsequent report of this trial (91), after 20 patients had been enrolled, had a 1-year survival of 83% and a 2-year survival of 57%, which compares favorably with the outcomes of patients with the same protocol without the avastin: 72% 1-year survival and 26.5% 2-year survival.

A third clinical trial combined the standard TMZ protocol with avastin but with the variation that CPT-11 was added after the radiation was completed. (92). From the initial report of the results presented at the 2009 ASCO meeting, 81% of patients were progression free at 9 months post-diagnosis. The most recent follow-up of this study (93) had outcome data available for 75 patients: median PFS was 14 months, and median survival was not yet reached at the time of the report, although 56% of patients were alive at a minimum follow-up of 18 months.

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. (For further discussion of this issue see the later section on angiogenesis.) Both of these new drugs are now in early-stage clinical trials with glioma patients, but limited reports have yet to indicate significant clinical efficacy. Several other new anti-angiogenic drugs, still involved in clinical trials and currently without FDA approval, do have clinical results with glioblastoma, which will be discussed in the later section.

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 small leaky capillaries, which are pruned away when VEGF effects are blocked. Some have argued that the initial stage of blocking VEGF actually

increases blood flow to the tumor, and hence makes it easier for chemotherapy agents to reach the tumor and be effective. This may be one reason that avastin produces such a high rate of early tumor regression.

STI-571 (Gleevec)

This small-molecule (also known as imatanib), 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 (94), although another study, using different dosage levels, did report a number of tumor regressions, which they reported occurred very gradually over time (95). 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 (96) 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 (97) 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, (98) produced a PFS-6 value of 27%. However, in a much larger (N=220) multi-center clinical trial (99), results were much less positive, as PFS-6 was only 10% and median survival was 26 weeks.

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. (100) 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%.

Given that avastin targets VEGF and gleevec targets PDGFR, the two most potent signals for angiogenesis, their combination might be expected to be synergistic or at least additive. Such combination has not occurred to my knowledge, in part because both drugs have some risk of internal bleeding. However, a combination of gleevec with a different anti-VEGF drug (PTK 787/ZK22584, trade name vatalanib) is now being studied in clinical trials (101). Although phase I trials are primarily concerned with establishing dosage levels, some efficacy was apparent with this combination as several patients with recurrent glioblastomas had tumor regression and a number of others have shown stable disease. However, the PFS-6 value was only 27%, and it is unclear to what the results would have been if vatalanib had been used alone. Median overall survival time was 48 weeks, which is comparable to the 10-month median survival times obtained with the standard avastin protocol.

Iressa, Tarceva, and Erbitux

These three recently FDA-approved drugs have the common feature that they target a growth-signaling channel known as the epidermal growth factor. Overexpression of EGF receptors is involved in the growth many different kinds of cancer, including more than half of glioblastomas. Iressa, (also called ZD 1839 and gefitinib) was the first of these drugs to be used with GBM (102); 53 patients with recurrent tumors received Iressa as a single agent, none of whom showed tumor regression. The 6-month PFS was only 13% and the median survival time was 39 weeks. There was no association between the degree of EGFR expression and clinical outcome. In a second study (103), 98 newly diagnosed

GBM patients received Iressa as a single agent during and after radiation therapy. Here the median one-year survival rate was 54%, not notably better than historical controls receiving radiation only. Again there was no relation between clinical outcome and the degree of EGFR expression.

A related drug, Tarceva (OSI-774, also known as erlotinib) has also being studied in clinical trials. A phase I trial (104) using it as a single agent for recurrent GBM patients failed to produce tumor regression for any patients and the PFS-6 value was zero. But two subsequent studies have produced substantially better results. A phase II study (105) with 48 patients with recurrent tumors produced complete or partial tumor regressions in four patients and 6-month PFS of 17%. A third study (106) produced tumor regressions of 50% or more in 6 of 30 patients and a PFS-6 of 27%.

 When tarceva has been added to the standard temodar protocol for newly diagnosed patients, median survival was 15.3 months in one study (107) and 19.3 months in a second study (108). 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 conducted at the Cleveland Clinic (109). 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 (110). But when Erbitux was added to the standard temozolomide protocol for 17 newly diagnosed patients (111) 87%

of patients were alive at the end of one year and 37% were progression free. The median survival time had not reached at the time of the report (an abstract at a meeting).

In contrast to these positive results, the addition of erbitux to the standard protocol for recurrent GBM of avastin + CPT-11 did not produce an improvement in outcome, as PFS-6 was 30% and the median survival was 29 weeks (112)

An important development for identifying patients likely respond to tarceva has come from a study (113) 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 (114). 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 the PKB/AKT signaling channel. A phase I trial (115) 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 (116) 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 (117) 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 (118) 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.

It should be noted that several of the supplements to be discussed in a subsequent section have been shown to disrupt the epidermal growth factor signaling channel in various ways, as does accutane. Probably the most important is genistein, but quercetin and curcumin have this property as well.

One recent paper (119) 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 I (IGF-I). IGF-I has also been implicated in the effect of tamoxifen. It is noteworthy, therefore, that one of the supplements to be discussed, silibinin, is known to inhibit IGF-I (120), as does lycopene. This suggests that silibinin and lycopene might substantially increase the effectiveness of any treatment that relies on EGFR inhibition.

Tamoxifen.

This drug is well known for its usage in the treatment of breast cancer. Its mode of action there 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 stage II clinical trial (121) evaluating the effects of tamoxifen for patients with recurrent gliomas has reported that it 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 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 (122). 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 (123) 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 temoxifen 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 (124).

 Tamoxifen with a dosage of 240 mg/day has also been studied in combination with BCNU as the initial treatment after radiation (125). Median survival time was 66.1 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. 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 (126). 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.

Most recent has been a trial combining tamoxifen with temodar (127). While details of this preliminary report are sketchy, its notable feature is that 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 (128) 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 asymptototic levels. Thus, short-term usage, even with high dosages, is not likely to be effective.

 An important recent development with respect to tamoxifen has been the report (129) 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 (130). 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 (to be discussed further in a later section). 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.

Accutane (Isotretinoin)

 This drug, which is FDA-approved for the treatment of severe acne, is an acid form of vitamin A chemically known as 13-cis-retinoic acid (also known as isotretinoin). Acid forms of Vitamin A are not stored in the liver; so unlike regular Vitamin A, high dosages may be used with less risk of liver toxicity. Its presumed mechanisms of action include the activation of genes that cause cancer cells to differentiate into normal cells and the blocking of the receptor for the epidermal growth factor (EGFR). High levels of

expression of that receptor cause cell division to occur at a rapid rate. A variety of other anti-proliferative effects have been identified as well.

 A phase II clinical trial evaluating accutane for recurrent gliomas was conducted at the M. D. Anderson Brain Tumor Center (131). 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, for a total response rate of approximately 50%. A more complete report, using accutane with 86 glioblastoma patients with recurrent tumors was less impressive. (132). 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 (133). 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.

 Because accutane's toxicity is very different from that of chemotherapy, it has also been used in combination with chemotherapy, notably temodar. When temodar was used alone for recurrent glioblastomas, the percentage of patient alive without tumor progression six months after the start of treatment was 21%. When accutane was used in combination with temodar, the corresponding number was 32%. In the earlier section on drug combinations involving temodar, I discussed two recent studies that combined accutane with temodar in patients receiving their initial treatment. Unfortunately, the results from the two studies appear to be in conflict: the larger prospective study produced a median survival of only 57 weeks while the second, retrospective study produced a median survival greater than two years.

There is also experimental evidence that accutane is synergistic with other drugs that are known to cause cell differentiation (134). This approach to cancer treatment will be discussed more fully in a later section.

While previously very expensive, isotretinoin is now off-patent and sold generically under a variety of trade names. In some countries it does not require a prescription and can be obtained via the internet.

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, especially melanoma, Kaposi's sarcoma, and prostate cancer. Unfortunately, a considerable amount of paperwork is necessary, both by the pharmacist who supplies it and the physician who prescribes it, 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. In the first clinical trial using thalidomide as a single agent for the treatment of recurrent tumors (135), involving 36 patients with GBM or AA-III tumors, there were two partial regressions, two minor regressions, and 12 patients with stable disease for a minimum of 8 weeks. Median survival times were 74 weeks for those with tumor regression, 30 weeks for those with stable disease, and 22 weeks for those classified as nonresponders. However, PFS-6 was only 4%. The major side effects were somnolence (thalidomide was originally introduced for its sedative purposes; presumably

such effects could be counteracted by various stimulants) neuropathy of various sorts, and constipation. Because such side effects are greater with higher dosages, it is of interest to note that results very comparable to the preceding study have been obtained in Australia using substantially lower dosages. Whereas the American studies have used a maximum dose of 1200 mg/day, the Australian study use a maximum dose of 500 mg/day (136). The best results using thalidomide as a single agent comes from a small study performed in Switzerland (63). 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 he median progression-free survival was 36 weeks.

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 (137). 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.

Thalidomide has also been studied in combination with BCNU (138) with patients with recurrent high-grade gliomas. Although the PFS-6 for all patients was only slightly better than temodar alone (27% vs. 21%), 9 of 40 patients had major tumor regressions while an additional 9 had stable disease. Both of these are higher than when temodar is used as a single agent in a similar population. Because of the disparity in the two different measures of treatment efficacy, any evaluation of the combination still remains unclear.

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 are believed to play an important role in inflammation, so that COX-2 inhibitors should reduce angiogenesis and inhibit tumor growth (139, 140). 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 (see discussion in a later section) many 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 scores of new 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 almost all concluded there appeared to be a significant benefit, including two clinical trials using such a combination with glioblastomas.

The two clinical trials reported to date that have used celebrex in the treatment of gliomas combined it with temodar (70) or CPT-11 (62) and are described in the section on chemotherapy.

Because of the mild toxicity of NSAIDS, considerable recent research has investigated the mechanisms of its 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 (141).   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 cyclogenase enzyme that is the target of COX-2 inhibitors correlates strongly with the proliferation rate of glioblastoma tumors and correlates inversely with survival time (142, 143).

Chlorimipramine

This old FDA-approved drug was first used for the treatment of depression, and now is used also for treatment of obsessive-compulsive neuroses. Its rationale as a treatment for gliomas (144) 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 (145) 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 among the promising new treatments, 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 (146).

Dichloroacetate (DCA).

This simple chemical compound has been used for the treatment of 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 aerobic metabolism, a very inefficient process, even in the presence of sufficient oxygen. DCA affects the membrane of the mitochondria, thus inhibiting the aerobic metabolism, which results in changes in the cells micro-environment 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 (147). 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. All of the others are 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. These results with DCA are an exciting development and a larger clinical trial is now underway.

Bortezomib (Velcade)

Velcade is a proteasome inhibitor that has FDA approval for multiple myeloma and mantle cell leukemia. Proteasomes are enzymes that play an important role in regulating cell function and growth by controlling the breakdown of important proteins. Velcade blocks the activity of proteasomes, thus disrupting processes related to the growth and survival of cancer cells. To date only one small clinical trial has tested Velcade as a treatment for glioma (148). Eleven newly diagnosed glioblastoma patients and two grade III patients received Velcade in combination with the radiation phase of the Stupp protocol, but not thereafter. Median survival was 16.9 months. In addition four patients with recurrent GBM tumors and two with recurrent grade III tumors had a median survival of 14.4 months, an unusually long survival for patients with recurrent tumors. However, patients with recurrent tumors also received a second round of radiation, about half of that they received prior to their tumors' recurrence. Despite the complexity of

how the results were reported, Velcade seems to have significant activity as a treatment for high-grade gliomas, although it has considerable toxicity as well, mainly neuropathy.

Vorinostat (Zolinza)

Vorinostat, which is FDA-approved for the treatment of cutaneous T-cell lymphoma, is a histone deacetylase (HDAC) inhibitor. 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, vorinostat re-activates the genes that have been silenced, resulting in apoptosis for the mutated cells. To date one small clinical trial has tested vorinostat with patients with recurrent GBM (149). While PFS-6 was only 15%, several patients had extended progression-free intervals. Despite these mediocre results with vorinostat as a single agent, it appears to hold considerable promise, as experimental results show it to be synergistic with velcade, gleevec., and chloroquine, among others. For example, a case report of a patient with a pineoblastoma (150) 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).

"Supplements" with Demonstrated Efficacy

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 (151). 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 (152) 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 time was significantly longer 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, the effect of melatonin was statistically reliable even with the small number of subjects. Moreover, comparable effects have been reported in a similar design for the use of melatonin with advanced lung cancer (153). 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 (154). 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 nonsmall-cell lung cancer (155), 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 (2) or partial (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 (156). 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 robust and of major 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 (157).

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 (158). 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 anti-oxidant 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 (159), 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 second example involved patients with either stage II or stage III colorectal cancer, who were randomized to receive either the standard chemotherapy or the standard chemotherapy in combination with 3.0 g/day of PSK. 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 (160). The survival rate after one, two, and three years was 77%, 49%, and 47%, 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. However, the abstract of the study (the study was in an inaccessible Japanese journal) did not report the results separately for glioblastomas versus grade III gliomas.

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, reisha, and shitake 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 recent laboratory study of chemically induced tumors in mice (161). 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. At least 100 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 (162, 163) 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 (164) 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 recent clinical trial involving its use for breast cancer substantiates that it does (165). 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 any health food store, 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, 13% had partial regression of their tumors, while 81% had stable disease. For tamoxifen + GLA the corresponding percentages were 5, 37, and 55%, a significant improvement.

The use of GLA as a cancer treatment is controversial because one of its major metabolites is arachnidonic acid, which is the precursor to both the lipoxygenase and cyclogenase 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. Part of the source of confusion is that the effects of GLA are dose-dependent. In laboratory studies low dosages may stimulate tumor growth, while at higher dosages the effect is clearly cytotoxic. (166,167). A second important factor is the interaction with n-3 fatty acids (fish oil being the most common). When fish oil is also present, its metabolic pathway competes for enzymes that also are involved in GLA metabolism, thus preventing the formation of arachnidonic acid. The optimal use of GLA may therefore be in combination with fish oil, not as a single agent.

The major fatty acids found in fish oil, eicosapentenoic acid (EPA) and docosahexanoic acid (DHA), have also been demonstrated to have potent cytotoxic effects on cancer cells in numerous 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 (168).

A clinical trial comparing fish-oil supplements versus a placebo has also been reported, involving patients with several different types of advanced cancer (169). 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 (170) 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 (171). . Patients previously had failed both chemotherapy and hormone treatments and many had multiple metastases, including many with liver metastases. Because this was a phase II trial, there was no control group that received chemotherapy alone, but patients were subdivided by 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.

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 (172). 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 (173), 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 that number of long-term survivors is remarkable. There is also strong reason to believe that Vitamin D is synergistic with retinoids such as accutane (174). Its effectiveness is also increased in the presence of dexamethesome (175) and a variety of anti-oxidants, notably carnosic acid, but also lycopene, curcumin, silibinin, and selenium (176).

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. One source that several members of the brain tumor community have used is Masters Marketing. Its web address is http://www.mastersmarketing.com. Undoubtedly there is a number of other possible suppliers. 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 (177 178, 179) 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 (180) 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 I.U.//day appear to be safe. Recently, it has become common for women suffering from osteroporosis with low Vitamin D levels to be given as much as 50,000, I. U./day. 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. Eighty-nine patients with recurrent glioblastoma, who had had at least three relapses after receiving radiation and several traditional chemotherapy agents, were compared with 52 matched GBM patients with similar clinical histories but now were

receiving only supportive care (181).   Patients were grouped according to whether their tumors were de nova (primary GBM), or had evolved from lower-grade tumors (secondary GBM).

Conflicting features of the data presentation hinder evaluation of the trial results. While patients receiving the treatment clearly survived longer than the control patients, the mean survivals reported (5.9 months for primary GBM, 11.2 for secondary GBM vs. 2.3 months) for matched controls) appear to conflict with the Kaplan-Meier survival curves, as the curves indicate that the longest survival of any patient was less than six months. The basis of the conflict is unclear. Nevertheless, two features of the results are noteworthy: (1) patients with secondary GBM survived significantly longer than those with primary GBM (but note that only six secondary GBM patients were studied and they were significantly younger); (2). Patients with deep tumors in the midbrain survived longer than patients with tumors in the cerebral lobes, a finding opposite that usually obtained.

Other Supplements

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 review of the 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 # 182.

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 be highly cytotoxic to many different types of cancer, including glioma cells. In addition to the laboratory evidence, there is also substantial epidemiological evidence that high dietary intakes of soy products decrease cancer mortality by at approximately 50%. Only recently has it begun to be studied in clinical trials, mainly for prostate cancer, the results of which have been mixed.

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; website: lef.org). It may also be possible to purchase it wholesale in the form of a product named NovaSoy, manufactured by the Archer-Daniels-Midland Corporation.

Although there is as of yet no strong evidence of the clinical effectiveness of genistein, the laboratory studies that are available make a strong case for its potential efficacy. In one representative laboratory experiment mice received different concentrations of genistein added to their regular diet (183). The measure of its effect was the number of lung metastases caused by melanoma cells injected into the mice. The number of lung tumors was reduced by 50-75% depending upon the amount of genistein added to the diet. Interestingly, even greater inhibition of tumor growth was observed in another study

when whole soy extracts were added to the diet, rather than genistein alone (soy contains numerous isoflavones other than genistein).

Recent experimental studies have examined the mechanisms whereby genistein produces its anti-cancer effects (184). The consensus is that this results from its ability to inhibit tyrosine kinase activity. This is a general class of chemical signals that strongly stimulate cell division. The epidermal growth factor, discussed earlier with respect to the mechanism of accutane's effect, is one member of this class of signals, and some investigators believe that genistein blocks the EGF receptor. 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 glioblastomas cells were treated with a combination of genistein and BCNU (185). The result was a highly synergistic suppression of the rate of growth.

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 (186). In a representative study of chemically induced tumors in mice (187), 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 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 (188).

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 (189). 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.

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 (190). However, this interference effect appears to be unique to velcade due to its chemical structure.

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. It currently is being investigated in phase-1 clinical trials. Given that apples are one of its major sources, it is interesting that a story in *Nature* (June 22, 2000) reported that material extracted from fresh apples inhibited in a dose-dependent manner the growth of both colon and liver cancer cell lines.

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 (191). Like genistein and quercetin, it inhibits the tyrosine kinase signaling and also inhibits angiogenesis. Perhaps most importantly, it inhibits proteins that prevent damaged cells from undergoing apoptosis. 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.

Silibinin (an ingredient of Silymarin)

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 (192). 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 (193) (see the section on tamoxifen), and the inhibition of angiogenesis (194). It also inhibits the 5-lipoxygenase inflammatory pathway and suppresses nuclear factor kappa B, which is a primary antagonist to apoptosis (195). It also appears to protect against common chemotherapy toxicities (196), while at the same time increasing the effectiveness of chemotherapy (197).

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 does not get transformed into Vitamin A, and thus has no hepatic toxicity. In a small clinical trial involving prostate cancer patients about to undergo surgery (198), those who consumed lycopene for several weeks before surgery

had a reduction in both the size and malignancy of their tumors relative control patients not receiving lycopene. In an experimental study involving both cell cultures and implanted glioma tumors in rats (199), 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. (200). Also of interest is evidence that it synergizes with Vitamin D (201).

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 that assessed the effect of adding 8 mg/day of lycopene versus a placebo to a protocol involving radiation + taxol (202). 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 that they contain 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 sulphoraphane as do 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 (203). Broccoli sprouts are also very tasty additions to salads.

Ellagic Acid

 This is a phenolic compound 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 with prostate cancer demonstrate its potential (204). 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. The results were that pomegranate juice produced an increase in PSA doubling time, from 15 months at baseline to 54 months after consuming the juice. Of the 40 patients in the trial, 85% exhibited a notable increase in the doubling time.

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 (205), 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. (206)

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 leukemia, prostate, breast, and colon cancer. 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 (207), 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.

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 (208). It is also a potent inhibitor of histone de-acetylase (HDAC), which will be considered in a later section.

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 (209). In the most recent paper (210), cannabinoids were shown to significantly inhibit angiogenesis in gliomas

implanted in mice, which was accompanied by significant inhibition of glioma growth. The result is noteworthy because cannabis is among the more potent anti-nausea agents for controlling the side effects of chemotherapy. A recent 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 case chemotherapy), and produced a median survival time after treatment of 24 weeks (211). 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, and that 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.

There is also evidence that supplements may be synergistic when combined. For example (212), prostate cancer patients with rising PSA levels used a combination of supplements, including soy isoflavones, lycopene, silymarin, and a mixture of various low-dose anti-oxidants. Treatment periods of 10 weeks using the supplements were alternated with 10-week periods using a placebo, separated by 4-week washout periods. The results were a 2.6 fold increase in PSA doubling time during supplement periods relative to that during placebo periods.

An experimental demonstration of synergy between supplements with glioma cells studied the combination of resveratrol and sulphoraphane (213). 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.

 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 other 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. It is important to emphasize that cancer treatment of all types is probabilistic in its outcome. Thus, any agent that adds even a small amount to the probability that a treatment program will be successful, and which also has no toxicity, is something that should be taken seriously as an additional component of a multi-faceted treatment program.

The Role of Radiation

For many years the only treatment (other then surgery) offered to patients with glioblastomas was radiation, based on the findings that radiation was 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 15-20% 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 (214). Three-year-old normal rhesus normal 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 (215). A recent randomized study of radiosurgery (216) similarly failed to show a benefit. Gliasite has yet to be studied in a randomized trial.

The standard 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 (217), 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 gliasite was used as part of the initial treatment (218), patients were partitioned according to according to established prognostic variables, and

then each partition was compared to its appropriate historical control. In all cases, survival time was greater for patients receiving gliasite.

Perhaps the best results reported involving radiation boosts comes from the combination of permanent radioactive iodine seeds with gliadel (219). 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.

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.

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 (220), high-grade glioma patients received the standard radiation protocol with the addition of hyperbaric oxygen 15 minutes prior to each radiation session. For the 31 glioblastoma patients, the median survival time was 17 months, with a very high rate of tumor regression. No data were available for 2-year survival. The use of hyperbaric oxygen was also reported to decrease the toxicity of radiation, although here too no long-term results were available.

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 (221). 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 that from 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 (222). In the first study that reported using this approach as initial treatment (223) 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 (224) 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 (225) 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 (226). 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.

Noteworthy Clinical Trials

The treatments that have been discussed involve agents that are generally available, limited only by the willingness of oncologists to prescribe them "off-label". Many of the clinical trials that have been discussed have involved such off-label use, often in combinations with other drugs (e.g., temodar + thalidomide). No doubt future clinical trials will test a variety of other combinations, hopefully beyond simple two-way combinations. Unfortunately, it typically takes a long time from the initial demonstration of a promising new treatment to when it is accepted as a standard treatment. This is time that a patient with a glioblastoma tumor does not have. But there is no reason that an individual patient could not receive novel drug combinations outside of clinical trials, depending on the cooperation of a licensed physician (although insurance companies often will not pay for off-label drug use). At various points in the preceding discussion I described new combinations of drugs that have strong preliminary evidence of producing major improvements in clinical outcome (e.g.; the addition of chloroquine to chemotherapy), as well as modifications of standard protocols that similarly improve outcomes (e.g., the switch to the daily schedule or alternating week schedule of temozolomide). There is nothing in principle that prevents the combination of these

potential improvements to produce a maximum benefit. There is of course always some risk of interactions producing unanticipated toxicities, but anyone with a glioblastoma diagnosis has a dire prognosis that requires moving beyond existing treatments that have been shown to be ineffective. Dying from one's tumor is an ugly reality that is by far the greater danger.

While an individual patient can do a great deal on his/her own to improve the chances of treatment success, many promising new treatment agents are not available outside of clinical trials, so that anyone wanting access to them must participate in such trials. The next section describes the major types of clinical trials that are now being conducted, some of which seem quite promising.

Inhibition of Angiogenesis

 In order for tumors to grow they must recruit new blood vessels to meet the greatly increased energy demands. If the growth of new blood vessels could be prevented, the tumor would necessarily stabilize or decrease, thus giving other treatments the opportunity to kill the cancerous cells. This approach has been increasingly supported by recent results. Thalidomide is the first anti-angiogenic drug used for brain cancer, although it has other mechanisms of action as well. Recently it has been joined by Avastin and Gleevec, (see their separate discussion in previous sections). The even newer drugs, Sutent and Nexaver, have only begun to be studied with brain cancer, but as yet no successful clinical results with gliomas have been reported. In addition, agents developed for other purposes, including celebrex, tamoxifen, Vitamin D, and accutane, all have shown anti-angiogenic properties in experimental settings.

It is important to appreciate the complexity of the angiogenic process. Numerous different growth factors are secreted by tumors to stimulate blood vessel growth. At least a dozen such factors have been identified, the most important being fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor (VEGF), which is generally regarded as the most important. The multiplicity of growth factors is important to note because it implies that redundant processes stimulate blood vessel

growth, which in turn suggests that targeting individual growth factors alone is unlikely to be an optimal approach. It may be necessary to combine several different treatment agents, each targeting a different signaling channel, for angiogenesis to be suppressed completely.

Because anti-angiogenesis drugs are considered one of the most promising new approaches to cancer treatment, dozens of drug companies are developing their own approach to this new treatment modality. Whereas the target for avastin is VEGF itself, a second drug, PTK787 (also known as vatalanib) blocks the VEGF receptors (of which there are at least three), along with the receptor for PDGF. When studied as a single agent for 47 patients with recurrent GBM, there were 2 partial tumor regressions, and 31 with stable disease, along with clear evidence that blood vessel growth had been inhibited (227). When studied in combination with the standard temodar protocol for 17 newly diagnosed glioblastoma patients (228), median PFS was 18+ months and median overall survival had not been reached at the time of the preliminary report. Despite these promising results, the pharmaceutical company developing the drug has discontinued its development.

A third anti-angiogenic drug, currently being studied in clinical trials at the National Cancer Institute, LY31765 (also known as enzastaurin), targets a variant of protein kinase C that has been shown to be a critical part of the signaling pathway for VEGF. Of 92 patients reported on at the 2005 meeting of ASCO (229), tumor regressions occurred in 22% of GBM patients and 25% of patients with anaplastic astrocytomas. and stable disease in a significant number of others. In addition, the treatment seems to have minimal toxicity. Because of the early promising results, enzastuarin was advanced quickly into a phase III randomized trial comparing enzastaurin with lomustine (CCNU) for patients with recurrent glioblastomas. There was no significant difference in PFS-6 values for the two treatments (230). But enzastaurin had much less toxicity. Moreover, it is important to keep in mind that many anti-angiogenic drugs have not worked well as single agents but are more effective in combination with chemotherapy or other treatments.

Enzastaurin has also been combined with the standard treatment protocol of temozolomide and radiation for newly diagnosed patients (231). Median survival was 76 weeks, approximately 4 months longer that the 14-15 months when temodar and radiation were used alone.

The most impressive results for an anti-angiogenic drug with respect to its ability to shrink recurrent GBM tumors has been reported for a drug named Cediranib (also known as AZD 2171 and Recentin), which like vatalanib targets the three known VEGF receptors. Cediranib also differs from avastin in being taken orally rather than intravenously. Thirty-one recurrent GBM patients were studied in the initial clinical trial (232): tumor regression occurred for 57% of patients, which allowed a major reduction in steroid use, but PFS-6 was only 26%.

Still another new anti-angiogenic drug under development is celingitide, which disrupts the molecular processes that allow individual cells to be joined to form mature blood vessels. In an early-stage clinical trial (233) 40 recurrent GBM patients received a low dose (500 mg) and 40 received a high dose (2000 mg); survival was consistently greater at the high dose level (which had little toxicity), with 37% survival rate after one-year and 22% survival at two years. Median survival was 10 months. The most recent clinical trial added celingitide to the standard temozolomide + radiation protocol for newly diagnosed GBM patients (234). One year after diagnosis 68% of patients were still alive, and the median survival time was 16.1 months. Two-year survival was 35%. Results were substantially better for the subgroup of patients with an inactive MGMT gene, as the one-year survival rate was 91%, median survival was 23 months and two-year survival was 46%. Note that the dose of cilengitide used in this trial was 500 mg, the low dose in the single-agent clinical trial just described. When a 2000 mg dose was used in combination with temodar and radiation in a different clinical trial, median survival was 21 months (235). It is also important to note that the mechanism of celingitide is totally different from that of the other anti-angiogenic drugs just discussed. Given its low toxicity level, it would seem an excellent candidate for combinations with drugs like avastin, gleevec, etc.

All of the agents just discussed (and several similar drugs) continue to be studied in clinical trials and will likely not be generally available for another 2-3 years.

Given that brain tumor patients are unlikely to have access to these new treatments for some time to come, it is of interest to note that at least a half-dozen agents, already discussed in earlier contexts, possess significant degrees of anti-angiogenic activity. These include tamoxifen, accutane, gamma-linolenic acid, genistein, PSK, selenium, curcumin, silibinin and green tea. Vitamin D3 also has potent anti-angiogenic effects.

A class of existing drugs that has significant anti-angiogenic effects is the tetracycline antibiotic family, specifically minocycline and doxycycline (236). These drugs also inhibit metalloproteinases, which are enzymes that break down the cell matrix of the surrounding cells that allows cancer cells to invade that tissue (237).

The mechanisms underlying the anti-angiogenesis effects of each of these agents are often unknown and possibly very different. Nevertheless, it seems feasible that a combination of these different agents might produce inhibition perhaps sufficient to be effective in its right, but also to substantially increase the effectiveness of traditional treatments, and that of other anti-angiogenic agents. For example, one laboratory study has shown that the combination of thalidomide and sulindac (an anti-inflammatory analgesic used for arthritis) produced substantially greater inhibition of new blood vessel growth than did either agent in isolation (238). A number of other studies have also shown synergistic effects from combinations of different anti-angiogenic drugs.

Receptor/Antigen Targeting

The underlying rationale of this approach is that cancerous cells have proteins expressed on their surface that are not expressed on normal cells. Thus, by addressing this protein with some type of toxic payload the tumor cells can be killed with minimal damage to the normal tissues. The difficulty of this approach is that even though a number of antigens

are highly expressed by all malignant glioma cells, few are unique to glioma cells, so inevitably some toxicity to normal cells will occur.

An example of this type of treatment approach has already been discussed in the section on radiation (224), involving monoclonal antibodies targeting tenascin, an antigen present on almost all high-grade gliomas, while carrying a radiation load. Median survival from the time of diagnosis was approximately 25 months. The therapy was associated with hematologic and neurologic toxicity in 27% and 15% of patients, respectively.

The most recent variation of antigen targeting approach involves a molecule named TM-601, which is derived from scorpion venom and has a very high affinity for selective binding with brain tumor cells. This molecule was combined with a radioactive iodine compound and single dose was administered intracranially to 18 patients with recurrent tumors. (239) There was minimal toxicity and five patients had either a tumor regression or a long-lasting stable disease. A later report compared the effects of three vs. six doses of the drug, which produced median survivals of 9.1 and 11.9 months, respectively. (240). TM-601 as a single agent also has anti-angiogenic properties, is believed to cross the blood-brain barrier, and currently is being investigated when used via intravenous injections.

As promising as these targeted treatments appear to be, they may be limited by their use of delivery directly into the brain. Such substances do not diffuse widely throughout the neuropil, so that the toxic agent may not contact portions of the tumor not immediately accessible from the site of infusion. This problem of making contact with all of the tumor cells is inherent in any approach that uses intracranial infusion, including those involving monoclonal antibodies and gene therapy. It is of course possible that this problem can be mitigated by repeated presentations of the therapeutic procedure, or the use of a low-pressure diffusion system that spreads the treatment agent over a wider area of the brain.

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 aversive side-effects, as do cytokines such as interleukin-2 and tumor necrosis factor, because their modus operandi is 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.

One of the more successful examples of the use of cytokine-based immunological treatment was reported in *Cancer* in 1995 (241). Mixing the white blood cells of individual patients with those of unrelated donors, then allowing them to incubate 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 dosages of IL-2. Patents received this regimen for multiple cycles until disease progression. The results were a median survival time of 53 weeks for patents 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 (242). 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 suppresser 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 (243). 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. However, a more recent multi-center clinical trial with recurrent AA-III tumors produced less impressive results (244), 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 (245). No chemotherapy was given. One-year survival was 69% and median survival was 65 weeks. Both values are superior to historical studies using only radiation without chemotherapy. In the second study with 83 newly diagnosed glioblastoma patients (246), 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.

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 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. In a phase -I clinical trial (247) 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 (248) 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 (249).

Long-term outcome data from the use of the vaccine in combination with the standard temodar protocol have been reported in a recent news release from ImmunoCellular Therapeutics, one of the biotech companies sponsoring this approach. One-year disease-free survival was 75% (compared to 27% for historical controls), while 2-year survival was 80% (250). Median survival had not been reached at 26-month analysis point, but an earlier report indicated it was 34 months.

DC vaccination was incorporated into the standard temozolomide protocol in a second recent study involving 42 patients (251). Here the median survival time was 21 months and the two-year survival rate was 44%. However, this clinical trial was done by a different clinical group than the results previously described, and it is possible there are significant differences in the preparation of the vaccine for different groups.

One recent development has been the documentation of a strong correlation between treatment outcome and immunological response, as measured by the level of interferon-gamma blood concentration (252). Of 36 patients, 21 of whom had recurrent tumors, 19 had significant increases in their IFN-gamma levels, while 17 did not reach the criterion for an immune response. Median survival for those with an immune response was 642 days, and 430 days for those without the immune response. For patients with recurrent tumors, the corresponding numbers were 599 vs. 401 days. Note that all patients received chemotherapy in addition to the vaccine.

Although the clinical outcomes across these various trials have been somewhat variable, which may be due to differences in the method of vaccine preparation and the amount of vaccine injected, the overall results seem markedly better than those from most other treatment protocols. But it should be noted that patients eligible for these trials must have tumors that can be safely resected with minimal residual tumor after surgery. How much this patient selection provides a positive outcome bias is difficult to evaluate.

EGFR-variant III 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.

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 (253).

The sponsor of the vaccine (now called CDX-110) 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 (254).

Virus-Based Vaccines.

Newcastle 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 recent 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 (255). Some tumor regressions were observed, along with clear responses of the immune system to the tumor tissue. A clinical trial (256) 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.

ReoVirus. A second virus, under investigation in Calgary, Canada is the reovirus, which is found commonly in the human intestines and respiratory system but is innocuous. However, it is apparently lethal to glioma cells, both in the laboratory and in rodents implanted with glioma tumors (257). Its mechanism of action is to co-opt the RAS oncogene pathway, which is activated only in cancer cells. No data from ongoing clinical trials have yet been reported.

Herpes Virus. Still a third virus 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 (258), 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 (259).

The newest virus-based approach relies on the finding that GBM cells serve as a refuge for the cytomegalovirus, a common herpes virus almost universally present in humans. However, GBM cells have a high incidence (by some estimates over 90%) of the virus being present 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 (260). Median survival time was not reached by the time of the report (a convention abstract) but was greater than 20 months.

A different method of utilizing the CMV is simply to kill it by using the anti-herpes drug, valcyte (an oral form of ganciclovir). The premise of the approach is that killing the virus inhabiting the tumor cell kills both the virus and the tumor cell. A small clinical trial using this approach has been conducted at the Karolinski Institute in Sweden. Results should soon be available. If successful, this would represent a major advance, given the simplicity of the approach.

Other Promising Treatments

Differentiation/Apoptotic Agents

Cancer cells share much in common with fetal cells. Rather than having the specialized properties of mature tissue, they divide rapidly without maturing into the adult form for which they were intended. Differentiation into mature cells is under genetic control, so

one approach to treating cancer is to upregulate the genes that cause the maturation process to occur. Several agents have been identified that serve this differentiation function. Already discussed have been accutane (13-cis retinoic acid) and Vitamin D, but also included in this category are members of the category of aromatic fatty acids, such as phenylbutyrate and phenylacetate. Valproic acid, a common anti-convulsant, also is included in this category. Closely related to the control of differentiation are tumor suppressor genes (p53 and p21 are the most well-known) that signal the cell to undergo programmed cell death (apoptosis) when abnormal functions are detected. There is now increasing reason to believe that many cancers, including glioblastomas, grow uncontrollably because the genes normally regulating differentiation and apoptosis are inactive due to various types of mutations.

One source of this de-activation is an enzyme named histone deacetylase (HDAC), which interferes with the normal uncoiling of the DNA strand that is necessary for normal cell replication. The result is that various genes do not function, including several regulatory genes necessary for monitoring genetic mutations. Currently in clinical trials are various drugs that inhibit this enzyme, based on the assumption that such inhibition will allow the gene function to be restored. Already discussed above was the new drug, vorinostat, which has been subjected to an initial-stage clinical trial with gliomas. While its results as a single agent have not been impressive with respect to PFS, some patients had long survival times. Moreover, there are considerable data suggesting it should be synergistic with many other agents, especially retinoids like accutane.

Given this new interest in gene silencing and activation, it is of interest that the well-known Burzynski anti-neoplaston treatment protocol has the restoration of normal function for tumor-suppressor genes as its modus operandi. Because Burzynski has generated enormous controversy. I devoted several pages of discussion of Burzynski"s treatment in my book, cited at the beginning of this article. Unlike the opinion of many neuro-oncologists, that discussion concluded that his treatment had merit, with the critical issue being how its results compared with conventional treatment protocols.

After years of conflict with the FDA, Burzynski now has approval to conduct clinical trials under FDA oversight. Part of the terms of this agreement is that he supplies detailed records of each of the patients receiving his treatment. Presumably this means that his other reports of his results are reliable. A recent review of those results is presented in an alternative medicine journal (261). Of 80 patients with recurrent glioblastoma tumors, 19% had tumor regressions of greater than 50%, 9% had minor regressions, and 2% had stable disease. Median survival time from the start of treatment was 9 months. A subsequent report (262) of the results from 22 patients had a PFS-6 value of 50%. The most recent results for the anti-neoplaston treatment were for newly diagnosed AA-3 patients, who received neither radiation nor chemotherapy (263). For the 20 patients in the trial, complete responses were achieved for 25%and the overall survival rate at two years was 45%.

One of the individual components of his antineoplaston package is phenylacetate, which is a common aromatic fatty acid that smells much like urine, from which it was originally derived. Phenylacetate has been shown to be a potent inhibitor of glioma growth in vitro (cell cultures), and has been studied as a single agent in a phase II clinical trial (264). Of forty patients with recurrent gliomas three had significant tumor regression, while another seven had stable diseases. In a second more recent clinical trial using a different dosing schedule (265) there were no objective tumor regressions, but the median survival time was nine months, which is above the norm for patients receiving treatment for recurrent tumors. While the overall response rate in both studies was low, it is important to recognize that phenylacetate is only one of the components of the Burzynski's treatment.

Also promising is phenylbutyrate, which is a prodrug for phenylacetate (meaning that it metabolizes into phenylacetate). Laboratory studies have shown that it strongly inhibits the growth of glioma cells (266), and a recent clinical study has reported a complete regression of an anaplastic astrocytoma tumor, which previously had failed to respond to conventional chemotherapy (267). However, a later report by the same research group indicated that this was the only clinical response out of a substantial number of patients.

Phenylbutyrate is especially interesting because in laboratory studies it has been shown to be synergistic in its effects with accutane (268).

As noted above, a common anti-epileptic drug, valproic acid, is also an inhibitor of histone acetylase. It also has the advantage of not inducing liver enzymes that reduce the concentration of chemotherapy agents in the serum, which does occur in 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 (269).

A potentially important sidelight on histone deacetylation is that the critical component of broccoli sprouts, sulforaphane, discussed in an earlier section, 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 (270). The same article also noted that garlic compounds and butyrate had a similar effect.

AntiSense Treatment

Antisense molecules are artificially constructed genes that contain RNA that is the complement of the RNA that controls the production of the proteins involved in driving cancer growth. By combining with this RNA, antisense molecules de-activate their growth stimulating effects. One gene that is the final common pathway for a number of common oncogenes is transforming growth factor beta-2. As described in a report presented at the 2007 ASCO meeting, a new drug named AP 12009 (also known as trebersen), which is an antisense molecule of TGF-Beta-2, was presented via catheters into the brains of patients with recurrent glioblastomas. (271). Out of 95 patients, 28 received a low dose of the drug, 33 received a high dose, and 34 received standard chemotherapy. Survival rates at 18 months were 21%, 24%, and 18%, and not

significantly different. However, the authors did note that several long-term survivors occurred in the two anti-sense groups.

A second similar trial restricted to patients with recurrent grade 3 gliomas (anaplastic astrocytomas) was also reported. (272) Median survival in the chemotherapy group was 21 months, while that for the low-dose AP12009 group had not been reached at the time of the report. Moreover, survival rate at that point was 42% for the chemotherapy group but 67% for the antisense group. An updated report of the results using the low dose of the drug had survival rates at 1, 2, and 3 years of 92%. 82%, and 53%, compared to 67%, 42%, and 40% for the chemotherapy control group.

PhotoDynamic Therapy

When brain tumor cells absorb a molecule named haemetaporphyrin (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 (273). 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-3 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 (274) 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.

Electrical Field Therapy

A small biotech company in Israel has developed a device called Novo-TTF, which uses electrical fields to disrupt tumor growth by interfering with cell division of cancerous cells, causing them to die instead of proliferating. Healthy brain cells rarely divide and thus are unaffected. The treatment involves wearing a collection of electrodes for 18 hours/day, which allows the patient to live otherwise normally. Of ten patients with recurrent glioblastomas, the median time to progression was 26 weeks, the PFS-6 was 50%, the one-year survival was 68%, and the median survival was 62 weeks, all substantially better than most prior treatments for recurrent tumors (275). Moreover, two of ten patients were progression free for more than two years. A subsequent study involved ten newly diagnosed GBM patients, who first received the standard radiation + temodar protocol, with the electrical fields applied after radiation was completed (276). Median time to tumor progression was 155 weeks, compared to 31 weeks for those trained with the radiation + chemotherapy protocol alone. Median overall survival time had not been reached at the time of the report, but exceeded 40 months. Eight of the ten patients were still alive at the end of the trial.

The most recent Novacure clinical trial (277) compared it to the "best standard of care" for patients with recurrent GBM. The best standard of care was not specified in the abstract report of the trial, but slides from the presentation show a heterogeneous assortment of treatments, with avastin being used for only 13% of patients (however, 20% of patients in both groups had previously failed avastin). Median survival for patients actually receiving treatments (as opposed to "intent to treat") was 7.8 months for Novacure and 6 months for the best standard of care, which was statistically significant. PFS-6 was 18% in both groups. Tumor responses occurred in 15% of Novacure patients and 5.1% of the controls, which was significantly different. The biggest difference was treatment toxicity, which was much greater for the best standard of care. Two issues are raised by these results. The first is whether a different outcome occurred if the comparison was between NovaCure and Avastin, rather than with avastin and a collection of other treatments. The second is why the PFS-6 value was so much lower than the earlier single arm report. The PFS-6 value for the control patients was also much lower than commonly reported for avastin. Currently in progress is a randomized trial

comparing the standard of care for newly diagnosed GBM (the Stupp protocol) with the same protocol along with the Novacure treatment.

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. Equally 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.

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 level of expression of the gene that controls the MGMT enzyme, which predicts whether the standard treatment protocol involving temodar will be successful. If a high level of activity is detected, the standard protocol seems not to work any better than radiation, so a different treatment protocol is advisable. The second test is for the presence of the epidermal growth factor variant III mutation. The vaccine under development that targets that specific mutation seems extremely promising, so anyone with that mutation should seriously consider using the vaccine as a first treatment option, assuming that it soon

becomes generally available. 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 EPGFR 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 fourth test is for the presence of overexpressed platelet-derived growth factor (PDGFR), which is the target of gleevec. Gleevec has been generally ineffective when applied to the entire patient population, but can be effective if the PDGF 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 three vaccines: the DC-VAX vaccine developed at UCLA and Cedars Sinai, the vaccine for the EPGFR variant III developed at M. D. Anderson and Duke, and the vaccine for the cytomegalovirus virus, 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 Novacure electrical field therapy, which seems at least comparable, if not better, than the various vaccine results. If the initial results of the Novacure clinical trial with only ten patients can be extended to a larger number, this may turn out to be the best treatment option of all. It is also compatible with almost any other treatment modality.

Also extremely 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.

An additional recommended new treatment protocol uses Avastin as an upfront treatment in combination with the standard temodar treatment. While the early results with this approach have been from only a few patients, this protocol also seems very promising. Finally, for patients whose tumors are well localized, the monoclonal antibody treatment developed at Duke that targets the tenascin antigen is promising, although more long-term survival data would be useful (e. 3-year survival).

For those whose options are restricted to chemotherapy, the best results have come from the combination of temodar and CCNU (39). Median survival from that combination was 23 months and 3-year survival rate was 26%. However, the combination did produce considerable toxicity.

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. The second change is to substitute either daily or alternating week schedule of temodar for the standard days 1-5 of each monthly cycle.

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 probably not during radiation), celebrex (which should be used during radiation), low doses of thalidomide, and tamoxifen. Also worthwhile is the calcium blocker

verapamil and the stomach acid drug. Tagamet. 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 much more complex, because the previous treatments used by a patient affect the success or failure of subsequent treatments At present the best option for patients with recurrent tumors, assuming avastin has not been used as part of upfront treatment, seems to be avastin + CPT-11, although much work is needed to increase the durability of its benefits. It is possible that the addition of other treatment agents such as thalidomide or chloroquine might be helpful, but at present we have no meaningful information.

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 (278), both better than the results obtained when avastin has been used for recurrent tumors.

A second alternative to avastin for recurrent tumors is the use of extremely low-dose temodar in combination with celebrex (35). Patients received 20 mg/day/meter-squared of temodar twice per day, along with 200 mg of celebrex. For 28 patients receiving this protocol, PFS-6 = 43% and median survival was 16.8 months. Treatment toxicity was minimal.

Enrolling in clinical trials is another option, as numerous new promising treatments are under development, especially those that target angiogenesis. A combination of anti-angiogenic agents that work by different mechanisms (e.g., celingitide with either avastin or enzastaurin) seems especially promising. Combinations involving the Novacure device are also very promising.

One important new finding is that when the standard temodar protocol has failed, substantial benefit still can be gained by switching to temodar on a "metronomic" daily low-dose schedule, which targets the growth of new blood vessels as well as the tumor itself. It is possible that this metronomic schedule may be profitably combined with other treatment protocols.

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 de-acetylase improves clinical outcome. This assumes, of course, that Depakote is as effective as the alternative medicines in controlling seizures and has acceptable side effects. In a similar vein, for patients needing anti-emetic medication, marijuana is advisable, Not only does sit avoid the constipation problem caused by the standard drugs (Zofran and Kytril), it appears to have anti-tumor properties in its own right.

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 in this category. POLY ICLC should also be helpful (with little toxicity), assuming it receives FDA approval.

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 (279). Also of significant interest is low-dose naltrexone, which has produced positive clinical results with pancreatic cancer (280)

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