The Role of Supplements (including Anti-Oxidants) in Cancer Treatment

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Introduction

No issue better exemplifies the differences between conventional medical practice and that of complementary/integrative medicine than their recommendations about the use of vitamins and other nutriceuticals in the treatment of cancer. Oncologists who practice conventional medicine typically recommend against supplements, based on their belief that they may interfere with the treatment benefits of radiation and chemotherapy. Physicians who practice complementary medicine typically recommend in their favor, although often with caveats, because supplements can ameliorate the side effects of conventional treatment, and may also increase the effectiveness of conventional oncology protocols. Given that many cancer patients use supplements, evaluating these opposing views is of considerable importance.

There have been numerous previous reviews of the evidence on this issue (1-16), some recommending in favor of supplements and some against. In part this reflects the complexity of the issue, as there are many different kinds of supplements, each of which may have multiple properties. Moreover, radiation and chemotherapy may themselves be affected differently by supplements, as may different chemotherapy agents. But also involved in the continued disagreement are differences in philosophy, and in some cases selective reporting of the evidence.

Despite the large number of reviews on this issue, the data from clinical trials, at least those that yield interpretable results, are sparse. However, the experimental literature, using both in vitro and in vivo models, is huge. This disparity reflects the difficulty of conducting clinical trials using treatment agents that cannot be patented, which precludes the financial incentives essential for randomized trials. This creates a Catch-22 for those recommending the use of supplements. Conventional oncologists argue, indeed insist, that no treatment agents be prescribed that have not been shown to provide a benefit in clinical trials. But these "necessary" trials will never be conducted because of the lack of the essential funding. Thus, complementary medicine often must rely on the experimental evidence for their recommendations.

Contrasting Views of Anti-Oxidants

The major focus of the debate has been supplements with anti-oxidant properties (AOs). Both radiation and chemotherapy create free radicals, or more broadly, reactive oxygen species (ROS), which are believed to be essential to the effectiveness of conventional treatment. Thus, many oncologists believe that any agent that neutralizes ROS will interfere with the therapeutic benefits. However, ROS also damage normal tissue, and may themselves initiate carcinogenesis. Critical to the trade-off between these dueling effects is a better understanding of the actual role of ROS in causing malignant cells to die. The long-standing assumption is that the damaging effect of ROS is critical, but much recent research (17-21) has advanced the view that only a small portion of the cytotoxic mechanism of radiation and chemotherapy is due to ROS directly killing the malignant cell; instead, cells often are only damaged and this damage may either be repaired, or induce a series of events that produce apoptosis (programmed cell death).

This decision is regulated by a complex collection of pro-apoptotic and anti-apoptotic proteins, the expression of which can be affected by the cellular balance of ROS and AOs. Moreover, cell damage induces a variety of changes in gene expression, which may lead to evolution of treatment resistance.

It is important to recognize that ROS are constantly produced by normal metabolism, and that all cells produce endogenous AOs to regulate the level of ROS. Because of this homeostatic control, understanding the role of treatment-induced ROS depends on their interaction with the homeostatic system. An important fact is that the level of endogenous AOs of cancer cells is already substantially below that of normal cells, both because of their higher metabolism, and because of differences in manner of energy production (i.e., the Warburg effect). The level of endogenous AOs is further reduced by radiation and chemotherapy.

A further complexity is that there are several different types of ROS, which vary in their effects, depending on the intracellular milieu. Moreover, these effects vary with their concentration. Whereas the prevailing view of conventional oncology has been that ROS inflict fatal damage to cancer cells, which is true for high levels of specific ROS (the hydroxyl radical), increasing evidence has shown that low-to moderate ROS levels may spur the growth of those cells (18), in part due to stimulating angiogenesis (22), along with blocking expression of pro-apoptotic proteins (20). High ROS levels also affect the cell cycle, by retarding the transition from the nonproliferative phase (G0), prolonging the G1 phase, and inhibiting DNA synthesis during the S phase (14). Given that chemotherapy agents only kill cells in the process of division, this retardation of cell division reduces the population of cells vulnerable to chemotherapy. The multi-faceted

and complex role of ROS precludes any "in principle" argument about the harmful vs. beneficial effects of AOs on treatment outcome.

Conflicting views on the use of AOs in cancer treatment are evident even among those who are viewed as practitioners of complementary/integrative medicine. K. N. Prasad and colleagues have presented detailed recommendations about AO use during cancer treatment. They argue that low-dose supplements (doses similar to those in a daily multi-vitamin) should not be used, based on their criterion that a useful dose-specific supplement must inhibit cancer cell growth. They also distinguish between endogenous AOs (e.g., glutathione) vs. dietary supplements, and recommend against agents (alpha-lipoic acid, N-acetylcysteine, selenium) that increase the level of endogenous AOs. These should be avoided because they protect both normal cells and cancerous cells. Thus, only high doses of specific AOs should be used, ideally in combination. An example protocol is provided, including 10g/day of Vitamin C, 1000 I.U. of the alpha-tocopherol succinate form of Vitamin E, 10,000 I. U. of Vitamin A, and 60 mg/day of beta-carotene. This combination should be started at least 48 hours before radiation or chemotherapy, continued throughout treatment, and for at least one month after treatment. Prasad presented the early results of this protocol in a randomized clinical trial with patients with advanced non-small cell lung cancer who were receiving chemotherapy (1). The one-year survival rate was 33% for those with chemotherapy only, while survival rate was 54% for those receiving the supplements as well. Corresponding median survival times were 8 months and 13 months. (No statistical tests were presented).

A different view of the role of AOs has been offered by Kenneth Conklin (14). He notes that several hundred experimental studies have shown that AOs do not generally interfere with chemotherapy effectiveness, although some AOs (selenium, glutathione, N-acetylcysteine)) may directly bind platinum-based chemotherapy agents, making them inactive. An important criterion for whether a specific AO may interfere with chemotherapy effects is whether the AO prevents side effects such as hair loss and bone marrow suppression. If such side effects are reduced, it is likely that the toxicity of the chemotherapy agent for cancer cells is also reduced. Because AOs decrease the level of oxidative stress, they may nevertheless improve chemotherapy, given that the rate of cell division is inversely related to the degree of oxidative stress, and chemotherapy is only effective while cell division is occurring. Moreover, aldehydes generated by ROS directly inhibit components of the apoptosis pathway. According to Conklin, Vitamin E is one example of an AO that does not prevent hair loss and bone marrow suppression, and increases chemotherapy effectiveness.

Clinical Trials of Traditional Anti-Oxidants in Cancer Protocols

Because the above recommendations about the use of AOs are based almost entirely on experimental, not clinical studies, the critical issue is whether the benefits seen in the experimental studies translate into the clinic. Block and colleagues have reviewed the randomized trials that have compared chemotherapy alone with chemotherapy plus anti-oxidants, restricting the corpus to those trials that reported survival or tumor response outcome data (16). Of the 19 trials included, none of the trials reported evidence of significant decreases in efficacy from AO supplementation. In fact, the majority of the trials reported increased survival time, or increased tumor response, as

well as decreased toxicity, due to the addition of the AOs, although most of the differences did not attain conventional levels of statistical significance.

While the review of Block and colleagues makes a strong case that AOs do not interfere with standard chemotherapy treatments, it is useful to examine the clinical trials most often cited to support this conclusion. The most impressive example of the utility of AOs in cancer treatment comes from a randomized, double-blind clinical trial for bladder cancer (23) in which 65 patients received Bacillus Calmette Guerin (BCG).). In addition, patients were randomized to receive either a multiple vitamin supplement in the recommended daily allowance or a high dose supplement regimen, consisting of 40,000 I.U of Vitamin A, 100 mg of Vitamin B6, 2000 mg of Vitamin C, 400 units of Vitamin E, and 90 mg of zinc. The 5-year rate of tumor recurrence was 91% in those receiving only the RDA amount of the supplements, while those on the high-dose regimen had a recurrence rate of only 41%.

While these results make an impressive case for the value of high-dose supplements, they are only tangentially relevant to the present issue. BCG is an immunological agent, and presumably works by very different mechanisms than do either radiation or cytotoxic chemotherapy.

More directly related to the effects of AOs on cytotoxic chemotherapy are two trials involving the use of glutathione (GSH) in combination with cisplatin. Colombo et al (24) randomized 33 patients with relapsed ovarian cancer to receive either weekly cisplatin or weekly cisplatin + GSH. GSH was administered intravenously immediately before cisplatin infusion. All patients had received cisplatin previously, and were viewed as at high risk for neurological side effects given the cumulative toxicity from the

addition of the cisplatin to the previous dosages. The major dependent variables were effects on nerve conduction and effects on hearing. Both types of toxicity were reduced by GSH, but the difference did not meet standard levels of statistical significance. Clinical outcome was also numerically improved by GSH. In the cisplatin-only group, response rate (complete or partial responses) was 60%, while the rate for cisplatin + GSH was 75%. Median survival for the cisplatin-only group was 15.9 months; median survival for cisplatin + GSH was 21 months. Neither measure of clinical outcome was statistically significant.

Smyth et al. (25) also investigated the effects of adding GSH to the standard cisplatin treatment of 152 patients with ovarian cancer in a double blind multi-center clinical trial. Either saline or GSH was infused immediately prior to cisplatin. The aim of the study was to determine if GSH increased the number of patients who could receive six cycles of cisplatin at the starting dose. The proportion of patients completing the full six cycles was 58% in the GSH group, compared to 39% in the cisplatin-only group, which was statistically significant. Total dose of cisplatin was also slightly higher for the GSH group, but this difference was not statistically significant. Kidney toxicity was significantly less for the GSH group, and neurological toxicity was also in favor of the GSH group, although not statistically significant. Quality of life assessment also was significantly in favor of the GSH group. There was no difference in treatment efficacy as measured by Cox's proportional hazards analysis, as the survival curves were indistinguishable.

A fourth clinical trial, again randomized and double blind used GSH in combination with a multi-drug protocol that included oxaliplatin for patients with

advanced colon cancer (26). The major aim of the study was to determine if the usual toxicity caused by oxaliplatin would be reduced by GSH. After eight cycles of chemotherapy 79% of patients in the placebo arm had clinical neuropathy, compared to 43% of the GSH group, a difference that was statistically significant. Response rate was also slightly in favor of the GSH group (27% vs. 23%), but was not statistically significant.

The three clinical trials just described make a strong case that glutathione can substantially reduce the toxicity of platinum-based chemotherapy. Moreover, this improvement in toxicity did not occur at the expense of treatment efficacy in any of the four trials, as the differences in clinical outcome, while not statistically significant, were in favor of patients receiving GSH. Although these results speak strongly against the claim that AOs reduce chemotherapy effectiveness, they are of limited value in assessing whether cancer patients should use AOs on their own. All of the above studies administered GSH intravenously, which is impractical for cancer patients taking supplements on their own. The results are relevant to the concerns of Prasad et al that endogenous supplements should not be used, and of Conklin that GSH may combine with platinum compounds, thereby neutralizing them.

More relevant to what cancer patients can actually implement is a clinical trial that combined high-dose supplements with chemotherapy (for advanced non-small cell lung cancer). One hundred and thirty-six patients were randomized to receive chemotherapy (taxol and carboplatin) alone, or chemotherapy in combination of with a daily regimen of 6100 mg of Vitamin C, 1050 mg of alpha-tocopherol, and 60 mg of Vitamin A (27). There were no significant differences in any type of toxicity. The

overall response rate for the chemotherapy-only group was 33%, while response rate was 37% in the combination group. Corresponding one-year survival rates for the two groups were 33% vs. 39%; two-year survival rates were 11% vs. 16%, and median survival was 9 months vs. 11 months. None of these differences was statistically significant. The direction of the effects is nevertheless important because it makes implausible the claim that the study failed to detect a detrimental effect because it was insufficiently powered.

A different AO, lycopene, was combined with chemotherapy and radiation for fifty high-grade glioma patients (28). All patients received radiation in combination with taxol, which is believed to be a radiation sensitizer. Fifty patients were randomized to receive a placebo or 8 mg/day of lycopene. Of those receiving lycopene, 40% had a complete response and 40% had a partial response. Of those receiving placebo, 20% had a CR and 24% had a PR. Median time to disease progression was 41 weeks for the lycopene group and 27 weeks for the placebo group. Neither the difference in response rate (p= .10), nor the time to progression was statistically significant (p=. 14). Nevertheless, the results provide significant evidence that lycopene did not interfere with the radiation therapy, and strongly suggest that it provided a clinical benefit.

Amifostine

Among the most widely cited evidence that AOs do not interfere with the effectiveness of standard cancer treatments are the results obtained with the synthetic AO, amifostine, which was developed by the military for the purpose of ameliorating radiation toxicity. The drug received FDA approval based on numerous clinical trials. The large number of required clinical trials is not surprising given that FDA review panels consist largely of oncologists who needed to be convinced that the conventional

wisdom - that AOs interfere with cancer treatments- is not valid. Two separate meta-analyses of the results of these clinical trials have been published. The first, which included clinical trials on the effect of amifostine on the outcome of radiation treatment (29), concluded that amifostine significantly reduced various kinds of radiation toxicity (mucositis, esophagitis, xerostomia, dysphagia, etc.) without any effect on overall response rate. In addition, the complete response rate was significantly greater for patients receiving amifostine. The second meta-analysis (30) was restricted to seven clinical trials with patients with advanced non-small-cell lung cancer. While there were no significant differences in any clinical outcome measure, there was a numerical advantage in terms of overall and complete response rates for patients receiving amifostine.

Block and Gyllenhaal (31) have provided the most detailed and comprehensive review of clinical trials using amifostine with either radiation or chemotherapy. Their conclusions concurred with the results of the two meta-analyses: the great majority of trials showed a significant reduction in toxicity, and none of the trials showed a significantly reduced clinical outcome.

Although the clinical trials included in the above reviews should allay concerns that anti-oxidants interfere with radiation and chemotherapy, it is important to recognize that amifostine has unique properties that prevent its results from being generalized to other AOs. The major AO properties of amifostine are due to its active metabolite, WR-1065, which depends on membrane-bound alkaline phosphatase. Because normal cells have higher levels of alkaline phosphatase than do cancer cells, this results in relatively greater concentrations of WR-1065 in normal cells, which produces relative greater

cytoprotection for the normal cells. Some degree of protection of cancer cells could possibly occur, but is outweighed by the greater protection of normal cells. Because other AOs do not depend upon alkaline phosphatase, amifostine's results may have little applicability to the effect of these other AOs. Moreover, as a practical issue, the cytoprotection of normal cells provided by amifostine is offset by the substantial side effects of its own.

Melatonin: Anti-Oxidant with Additional Benefits

In addition to amifostine and the standard AO vitamins and minerals, there are numerous other potential treatment agents that have strong AO properties. Of these, melatonin has the most substantial clinical literature. While melatonin's primary function is regulation of the circadian rhythm, it is also a potent AO. It also has properties beyond being an anti-oxidant, but is considered here because conventional oncologists routinely recommend against its use because of its AO potency. Melatonin has now been used in numerous clinical trials, involving several different kinds of cancer. Mills et al. (32) performed a meta-analysis on ten different randomized trials in which the combination of melatonin with conventional treatment was compared to conventional treatment alone. All trials were performed at the same medical center in Italy and were unblinded. Across all trials the relative risk of death at one year for those that used melatonin was .66, a significant and meaningful reduction.

The great majority of these clinical trials were with advanced cancer in which melatonin was added to conventional chemotherapy. One clinical trial, with glioblastoma brain tumors (33), investigated the effects of adding melatonin to radiation therapy only. GBM patients were randomly assigned 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 patients 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.

Of the randomized clinical trials that compared chemotherapy alone with chemotherapy with melatonin, the most extensive involved 250 patients with advanced metastatic cancer of various types (34). 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 second large trial, involving 100 patients with metastatic non-small-cell lung cancer (35), 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 patients receiving chemotherapy + melatonin had either a complete (2) or partial (15) regression. Twenty percent of the chemotherapy-alone patients survived for one year and zero for two years, while the corresponding numbers for chemotherapy + melatonin were 40% and 30%. Melatonin not only increased the efficacy of chemotherapy, but also significantly reduced its toxicity. These trials demonstrate that the effects of melatonin are robust and clinically significant.

One exception to the preceding generalization was a large clinical trial involving patients with metastatic brain tumors originating from various types of cancer (36). Patients received whole-brain radiation only or radiation plus melatonin. Patients receiving melatonin had a median survival of 3.1 months; those who had only radiation had a median survival of 4.1 months, a difference that was nonsignificant. There was also no significant difference between the patients with melatonin and historical data from a comparable group of patients.

Although the results of Berk et al. provide no meaningful evidence that melatonin interferes with conventional treatment. Its failure to find a benefit possibly reflects a difference in the measure of treatment efficacy. When one-year survival was estimated from their survival curves, approximately 17% of those receiving melatonin were alive, while only 12 % of those receiving radiation alone were alive.

From reviews of the basis of the melatonin's anti-cancer effects (37, 38) several mechanisms have been identified. In addition to melatonin's potent AO properties, it has been shown to inhibit cell division by retarding mitosis. It also restores immunological deficiency by stimulating the production of interferon and various interleukins. Thus, it is unclear whether melatonin's benefits result from its AO properties or from its immunological effects. However, the fact that melatonin is a powerful AO is not a sound basis for recommending against its use.

Other Promising Supplements with AO Properties

There are a significant number of other supplements that have a strong case for clinical utility based on extensive experimental research, including many "in vivo" animal cancer experiments Among these for which there are reviews of their efficacy are

curcumin (39,40), green tea (41), genistein (42), quercetin (43), ellagic acid (44), lycopene (45), silymarin (46), and resveratrol (47). A more general review has been provided by Aggarwal and Shishodia (48).

Clinical Trials Showing Supplements Improve Clinical Outcomes

Although the above review provides little basis for the concern that supplements interfere with conventional treatment, they also offer only weak evidence that they improve clinical outcomes, except for their non-trivial benefit of reducing toxicity. Part of the reason for the lack of positive evidence is that minimal clinical research has been conducted using these supplements. The notable exception is melatonin, for which the benefits may be due to a variety of mechanisms that are independent of its anti-oxidant status.

However, several clinical trials using supplements with AO properties support their benefits in the treatment of cancer, although here also the benefits may be independent of their AO properties. The bulk of these clinical trials have involved prostate cancer, in part because PSA offers a surrogate measure of disease status that can be monitored throughout treatment. One positive prostate cancer trial involved patients whose PSA levels were rising after initial treatment with either surgery or radiation, who drank pomegranate juice (8 oz/ daily), which contains high levels of eligitannnins (precursors to ellagic acid, which also is found in blueberries, strawberries, raspberries and walnuts, (49). The dependent measure was the rate of increase in the PSA level, which typically rises at a steady rate for this category of patients. Pomegranate juice produced an increase in PSA doubling time, from 15 months at baseline to 54 months after consuming the juice. Of the 40 patients in the trial, 85% exhibited a notable

increase in the doubling time, and 40% had an actual PSA reduction (four of which were greater than 50%).

A similar trial using pomegranate extract rather than whole juice (50) obtained a similar but smaller increase in PSA doubling time. No differences were obtained between two different dose levels (1 vs. 3 g of extract), but combined over doses the PSA doubling time increased from 11.5 months at baseline to 18.5 months after treatment. Declining PSA levels were noted in 13 of 104 patients.

Neither of the above studies included a control group that received no pomegranate juice, but given that the natural history of the disease is that PSA increases regularly after the failure of initial treatment, it is plausible to assume that the reduction in the rate of disease progression was due to the consumption of the pomegranate.

Lycopene also has been shown to slow the progression of prostate cancer (51). Twenty-six patients newly diagnosed with prostate cancer were randomly assigned to receive a tomato extract containing 30 mg of lycopene or no supplementation for three weeks before radical prostatectomy. Tissue analysis and tumor assessment were performed on the excised tumor tissue. Patients receiving lycopene had significantly smaller tumors, less high-grade neoplasia, and less involvement in the tumor margins. PSA levels were also significantly lower in the lycopene group.

There is also evidence that soy isoflavones, especially genistein, can slow the rate of prostate cancer progression (52). Forty-one patients with prostate cancer and rising PSA levels were composed of three categories: those with no prior treatment but on "watchful waiting"; those after initial treatment with surgery or radiation; those whose PSA level was rising despite initial treatment and subsequent hormone therapy. All

patients received 100 mg/day of genistein plus assorted other soy components. None of the patients showed a reduction in PSA value, but 18/22 patients in groups 1 and 2 had stable PSA values for the six months of the study, while 6/17 patients in group 3 had no further PSA rise. For all patients combined there was a statistically significant decrease in the rate of PSA rise, indicating that soy isoflavones did in fact slow disease progression. The authors also reviewed several previous studies using soy as a treatment for prostate, which had similar results: no reduction in PSA value, but a decrease in the rate of disease progression.

Like all cancer treatments, single-agent treatments involving dietary supplements are likely to be less effective than combinations of agents. An important demonstration of the potency of combination treatments comes from a British study (53) that combined extracts from four different foods, pomegranate, green tea, broccoli, and turmeric, in a placebo-controlled, double-blind design. Prostate cancer patients (N=199) were randomly assigned to receive the capsule of combined food, or an identical placebo for six months. Slightly more than half of the men had no prior treatment and were being monitored by periodic PSA tests (watchful waiting), while the remainder had prior initial treatment, but had relapsed with climbing PSA levels. In the placebo group, PSA rose by approximately 80% over the 6-month period, while that of the supplement group rose by only 14%. In half of the supplement group, PSA remained stable or decreased over the six months.

A second example of a combination treatment (54) also involved PSA levels in prostate cancer patients, but using a different combination of supplements, including soy isoflavones, lycopene, silymarin and a mixture of low doses of various AOs. 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.

Failures of combination treatments have also been reported. In one of these (55) the combination included Vitamin E, selenium, Vitamin C, and coenzyme Q10, which was administered to 36 hormonally untreated prostate cancer patients with rising PSAs, and compared to 34 comparable patients receiving a placebo. Here no differences in PSA levels were detected. This failure to find a benefit is perhaps instructive because all of the components of the combination have AO properties, which suggests that AO properties, per se, may not be the critical factor in determining whether specific supplements have clinical benefit.

Combinations of supplements are not necessarily synergistic, nor even additive in their effects. In a study of 71 prostate cancer patients with rising PSA levels (56), patients were randomly assigned to receive lycopene alone (30 mg/day) or lycopene in combination with a soy isoflavone mixture (80 mg). For those receiving only lycopene 35 of 37 had stable PSAs; for those receiving the combination, 22 of 33 had stable PSAs.

Although the weight of the evidence indicates that AOs provide benefits rather than harm, it is important to appreciate that specific AOs may have idiosyncratic interactions with various cancer treatment agents. The possibility that glutathione can bind to platinum-based chemotherapy was noted above, although the clinical trials using glutathione failed to substantiate this concern. A second example involves the proteasome inhibitor bortezomib (Velcade), which is FDA-approved for the treatment of multiple myeloma. When green tea's active ingredient, EGCG, was combined with bortezomib

both in vitro and in vivo, bortezomib no longer induced cell death by apoptosis (57). Although no clinical data are available that support this negative interaction, prudence dictates avoiding green tea when using bortezomib. It should be noted, however that this negation of bortezomib's therapeutic effects is due to binding of EGCG to the boronic acid component of bortezomib, and is not relevant to cancer treatment agents generally. The finding does highlight the importance of considering the specific character of the treatment agent along with the specific AO that is combined with it.

Useful Supplements without AO Properties

Although this discussion has focused on supplements that have AO properties, it is important to recognize that some useful supplements are not AOs, and may in fact be pro-oxidant in their effect. Important examples are polyunsaturated fatty acids (PUFAs), notably the main components of fish oil, eicosapentaenoic acid (EPA) and docasahexaenoic acid (DHA). Also often used is gamma-linolenic (GLA), which is derived from various plant-based substances (e.g., borage oil, primrose oil, black currant seed oil). All three of these fatty acids have an extensive experimental literature showing they increase the effectiveness of both radiation and chemotherapy, and some clinical evidence for extending survival. However, one of their mechanisms of action is the generation of ROS, and there is evidence that AOs (e.g., Vitamin E) neutralize their toxicity to cancer cells. Additionally, however, these PUFAs affect the nature of prostaglandin production, and thereby moderate important components of the inflammatory process that plays an important role in cancer cell proliferation. PUFAs also increase the permeability of the cellular membrane, perhaps allowing chemotherapy agents to have increased access to the cell nucleus. Also potentially important is their

property of serving as a ligand for PPAR-gamma, which has been shown to strongly inhibit cancer cell growth. Conklin (58) has suggested that the maximum benefit of PUFA is obtained when they are combined with AOs, as this neutralizes their pro-oxidant properties while retaining their other benefits. In support of this hypothesis are the results of a study of mice with injected Lewis lung cancer cells in their feet (59). The measure of interest was the extent of metastases of the initial tumor to the lung. Two different experiments were conducted. The first compared the amount of tumor growth under three diets, soybean oil as the control, fish oil, or fish oil supplemented with Vitamins C and E. Tumor growth was greatly reduced by the fish-oil -only diet, and significantly less reduced by the combination of fish oil with the AO vitamins. The results of this experiment demonstrate that AOs may reduce the treatment benefits of fish oil as a single agent. However, in the second experiment the same three diets were combined with cisplatin chemotherapy. Here, the greatest suppression of tumor growth occurred with the cisplatin + fish oil + AO vitamins, a reversal of the pattern obtained without the cisplatin. Some property of fish oil other than its pro-oxidant properties must therefore have been responsible for its facilitation of the treatment benefit of cisplatin.

A clinical trial comparing fish-oil supplements versus a placebo has also been reported, involving patients with several different types of advanced cancer (60). 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 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 (61). Patients previously had failed both chemotherapy and hormone treatments and many had multiple metastases, including many liver metastases. Because this was a phase II trial, there was no control group that received chemotherapy alone, but patients were subdivided according to their level of plasma DHA. The two groups were approximately equal with respect to all major prognostic variables. Median survival for the high DHA patients was 34 months, vs. 18 months for the low-DHA patients.

A second clinical trial presented 2200 mg of EPA plus 240 mg of DHA to patients with advanced nonsmall cell lung cancer (62). Patients either received only the standard of care of chemotherapy, or the same treatment in combination with daily fish oil. Response rate (tumor regressions) was 60% in the fish oil group and 26% in those receiving only the standard of care. One-year survival was 60% in the fish oil group versus 39% in those receiving only chemotherapy. Chemotherapy toxicity was also decreased in those using fish oil.

The complex literature on PUFAs illustrate the difficulty of understanding the best use of AOs in cancer treatment, and demonstrate again the importance of the evidence pertaining to particular combination of specific treatment agents with specific

AOs. Any **general** statement about AOs increasing or decreasing cancer treatment effectiveness is unwarranted, given the current state of the evidence.

A second example of beneficial supplements without AO properties are mushroom extracts. The most extensively researched (primarily in Japan) is an extract from *the Coriolus Versicolor* mushroom known as polysaccharide krestin (PSK). Numerous clinical trials have been conducted in which PSK has been added to standard chemotherapy protocols. In one representative study, with non-small cell lung cancer (63), 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 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 (64). The three-year disease-free survival rate was 81% for patients receiving PSK, compared to 69% for those receiving only chemotherapy, again a statistically significant improvement.

The presumed basis for PSK's benefits is its effects on the immune system, including 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.

Special mention is warranted for Co-enzyme Q-10 (ubiquinone, ubiquinol) for its role in protecting against the cardiotoxicity that occurs for patients undergoing anthracycline- based chemotherapy. Co-Q10 is an intrinsic part of the cellular respiratory

process, serving as a powerful AO that protects the mitochondrial membrane from damage by high ROS levels. Because of their idiosyncratic structure and high respiratory level, heart cells are especially susceptible to ROS damage, resulting in extreme cases in congestive heart failure. Co-administration of Co-Q10 with the chemotherapy has been shown to prevent this damage from occurring (65). There has been no evidence that CoQ10 diminishes chemotherapy effectiveness, although this possibility has not been adequately assessed in clinical trials.

The Opposing View of Conventional Oncology Reiterated

While many in conventional medicine concur that the issue of supplements during cancer treatment is a complex issue, most nevertheless oppose their usage. Labriola and Livingston (66) provide a representative rendition of this opinion, as they argue that AOs are likely to have the same effect as a reduction in dosage of the treatment agent, due to their neutralizing the ROS that serve as an important basis of the treatment's benefits. While they conceded there are no convincing clinical results that support their position, the absence of evidence that supplements improve long-term clinical outcome, and the fact that AOs neutralize ROS provides a primae facie basis for recommending against their usage.

As noted above, a major difficulty for his conventional view is that more recent research has challenged whether ROS actually play the decisive role in the cytotoxic mechanisms by which cancer cells die. While ROS may damage cancer cells (and normal cells), the evidence cited above suggests that this damage is usually repaired, and that the critical event is the decision of whether the repair processes are instigated, or

whether the machinery of apoptosis is initiated instead. Gene regulation of the apoptotic pathway is affected both by ROS and AOs, with the result that it is not possible to make a generalization about AO detrimental effects based on first principles.

Clinical Results Supporting an Adverse Effect of Anti-Oxidants ?

Lawenda and colleagues have provided a vigorous restatement of the views of conventional oncologists in the authoritative *Journal of the National Cancer Institute* (10). They acknowledge the complexity of the issue, noting the possible differences among chemotherapy agents and different kinds of dietary AOs. They also acknowledge that AOs may affect apoptosis, and the importance of the dose of AOs. , Nevertheless, they caution against any use of AOs until further research clarifies the issue. More importantly, they argue that the existing clinical literature supports the likelihood that AOs interfere with conventional cancer treatment.

Although they provide a comprehensive listing of relevant clinical trials, only three are spotlighted for discussion. The first of these involved 90 unilateral, non-metastatic breast cancer patients treated by a single physician (Adam Hofer, who at one time worked with Linus Pauling), who prescribed high doses of beta-carotene, niacin B3, Vitamin C, selenium, Coenzyme Q10, and zinc. Patients were advised to follow this protocol regardless of subsequent treatment, which included radiation, tamoxifen, and chemotherapy, which varied among patients. Using the British Columbia breast cancer database, Lesperance and colleagues (67) selected control patients who matched the individual patients receiving the supplements on eight different variables. Survival rates at five years were 72% for the patients taking the supplements, and 81% for the control patients. Ten-year survival rates were 65% and 76%. Neither breast cancer specific

survival (p = .16) nor disease-free survival (p =. 07) reached conventional levels of statistical significance. Nevertheless, the trend for interference due to the AOs raises important concerns.

The validity of the conclusions from the Lesperance et al study depends critically on the adequacy of the matching of the control patients to those receiving the supplements. Moss (9) and others have noted an important difference between the two groups of patients: Patients prescribed supplements were more likely to reject radiotherapy, which is important because the combination of no radiation and lumpectomy has been shown to result in a higher incidence of cancer in the ipsilateral breast than those receiving both lumpectomy and radiation.

A second study cited by Lawenda et al. in support of their concern about adverse effects of AOs was a double-blind random-assignment study of patients with oral cancer receiving radiation treatment (68). Fifty-four patients were randomly assigned to rinse their mouths with 400 mg of vitamin E (alpha-tocopherol) immediately prior to each radiation session, and again each night, or to a control group that received a "placebo" solution of primrose oil. The major purpose of the study was to determine if Vitamin E could reduce the high level of mucositis typically caused by radiation to the oral cavity. A significant reduction in the severity of oral toxicity was reported, along with a significant increase in food intake. However, survival results were in the opposite direction: median survival for the Vitamin E patients was 8.5 months, while that for the placebo patients was 12.5 months, a difference that was not statistically significant (p = .126). Two-year survival rates also favored the placebo group, 63% vs. 32%, also not statistically significant. Despite these differences suggesting a deleterious effect of Vitamin E on

survival, the investigators reporting the study concluded that there was no interference with the radiation therapy effectiveness, due to the lack of statistical significance and the fact that a higher percentage of Vitamin E patients had stage III or IV cancer (86%) than patients in the placebo group (62%).

A second major issue in the above study was the nature of the placebo. Primrose oil contains a high percentage of gamma linolenic acid, which prior studies have shown to be an effective topical treatment for superficial bladder cancer (69). Moreover, experimental studies have demonstrated that GLA improves the effectiveness of radiation. Thus, primrose oil may have had therapeutic benefits of its own that obscured the benefits of Vitamin E.

The most important report of deleterious effects of AO supplements comes from a large randomized, double-blind, placebo-controlled clinical trial conducted in Quebec (70), in which head-and-neck cancer patients received radiation treatment with or without AO supplements. Initially, the supplements were 400 mg of alpha-tocopherol and 30 mg of beta-carotene. The components of the placebo were not identified. Use of the supplements continued for three years after radiation was completed. Follow-up continued for eight years. The study was complicated by the fact that midway through the recruitment of patients, the beta-carotene was no longer used. Thus, there were two separate studies, the initial study with the combination of AOs, involving 156 patients, and then the continuation of the study with alpha-tocopherol alone that included 384 patients.

The initial report of the study focused on time to local recurrence in the first three years of the study (70). Combined over both parts of the study, the hazard -odds ratio for

local recurrence was 1.37, which was significantly greater than 1.0, indicating that patients receiving the supplements were more likely to have an earlier recurrence-apparently clear evidence that the supplements interfered with the radiation treatment effects. The supplements also reduced the toxicity of the radiation, with an odds ratio of .38, which was a significant reduction for those receiving supplements. Further analysis indicated that a significant reduction in toxicity occurred when both beta carotene and alpha-tocopherol were used, but not when alpha-tocopherol was used alone.

A second report focused on all-cause mortality as a function of supplement use (71). For the placebo group, 77 deaths occurred, while 102 occurred for the supplement group. There was also a significant hazard ratio (1.38) for patients receiving the supplements, again apparently clear evidence that the supplements interfered with radiation effectiveness.

The dependent variable for a third report (72) was cancer-free survival, including both the absence of recurrence of the original tumor and absence of the development of any other primary cancers. Here the results were complicated by the finding of a discontinuity in the occurrence rate of cancer while the supplements were being used, versus after they were no longer provided. Separate analyses were done on the first 3.5 years of follow-up, versus after 3.5 years. For the first 3.5 years, relative risk was 2.42, indicating that patients receiving supplements were more likely to have recurrences or develop new tumors. However, for the period after the 3.5 years, when supplements were no longer provided by the study protocol, the relative risk was .57, indicating that those who had received supplements were less likely to develop new tumors or recurrences. Because the different time periods had the opposite pattern of results, the total number of

patients who were tumor free at the end of the 8-year follow-up was not significantly different.

When the analysis was restricted to recurrences of the original tumor, a discontinuity in the survival curves was not detected, allowing a unified analysis of the entire follow-up period. The result was a hazard ratio of 1.41, indicating a greater risk of recurrence for patients receiving supplements.

An important observation from this analysis was that the patient's smoking history prior to the study had no effect on the hazard ratios, either for cancer-free survival, or time to recurrence.

The differences in the outcome measures (e.g., mortality rate vs. cancer-free survival) raise various questions of interpretation, but some insight may be provided by a re-analysis of the results as a function of whether patients continued to smoke throughout the period they were receiving radiation (73). Whereas the initial report had shown that the history of smoking prior to radiation did not predict outcome, whether the patient actually smoked during radiation was critically important. For this subpopulation, supplement use produced a relative risk of cancer recurrence of 2.38 and a relative risk of all-cause mortality of 3.38. For those who did not smoke during radiation therapy, including those with a prior history of smoking, there was no increase in risk for any measure. Thus, the combination of AOs and smoking undermined the effectiveness of the radiation, while AOs alone did not negatively impact radiation effectiveness. Moreover, the use of AOs did significantly reduce the side effects of radiation, although a statistically significant protection effect occurred only with the combination of beta-carotene and alpha-tocopherol, not with alpha-tocopherol alone.

One anomalous result of this array of results is that the initial paper reported that a significant hazard ratio was obtained for both patients who were smokers and those who were nonsmokers. Presumably the nonsmokers did not begin smoking during radiation treatment, given they had not smoked before. Yet the last study described (73) ascribed all of the deleterious effects of using supplements to those subjects who smoked during radiation. How this apparent contradiction is to be resolved is unclear.

Conclusions

The preceding discussion reveals no convincing clinical evidence supporting the view that supplements containing AOs generally interfere with the effectiveness of chemotherapy. The major caveat is that the clinical trials addressing this issue have involved a limited number of types of cancer and also a limited number of chemotherapy agents. Nevertheless, the evidence supports the view that the likely effect of adding supplements to chemotherapy protocols is to improve clinical outcome, not interfere with it.

The issue is more debatable for radiation, as some studies (68,70) do have suggestive trends for interference effects. However, upon detailed examination these effects are confounded by other variables, or are limited to a specific subpopulation. Moreover, there are specific supplements (e.g., melatonin) that have potent AO properties but nevertheless improve clinical outcomes, while others (e.g., genistein, curcumin) have impressive resumes from in vivo animal models. Given the potential, and already demonstrated benefits of such supplements, and the fact that AOs generally do reduce the toxicity of both radiation and chemotherapy to normal cells, a judicious use of supplements offers more benefit than harm. However, caveats are still in order. Optimal

supplement dosages have not been determined, nor has the optimal combinations. It is also important to determine whether a specific AO has some idiosyncratic interaction with the specific cancer treatments, most importantly in terms of hepatic drug clearance. While this information is generally available from the Physicians Desk Reference, the majority of cancer patients will benefit from consultation with a nutritionist familiar with these issues.

Almost all of the clinical results described above were cited by Lawenda et al. (10). Why then do they recommend so against the use of AOs? They acknowledge the complexity of the different effects of AOs and the possible benefits of AOs for reducing damage to normal tissue. They also cite (but do not elaborate) the results of the clinical trials that showed no interference with the efficacy of conventional treatment. But these are largely discounted because they are small and thus underpowered to detect interference effects. However, this concern must be suspect because in several cases the numerical outcomes, while nonsignificant, were in the direction of improving clinical outcome, not reducing it. Increasing the statistical power by increasing the number of patients typically amplifies the small differences seen with the smaller N studies; rarely does increasing the number of patients reverse the direction of the effect.

One hypothesis for the basis of Lawenda et al.'s recommendations against supplements is that supplement use is strongly associated with the practice of alternative medicine and must therefore be resisted. This opposition is widespread among conventional oncologists wary of "snake-oil" treatments, which unfortunately may produce a slanting of the interpretation of clinical trial outcomes. Two examples from the Lawenda et al. review illustrate this possibility. The first involves the Bairatti et al study

described in detail above. While Lawenda et al do include all of the studies cited above, including the finding that the deleterious effect of AOs on cancer-free survival occurred only for those who smoked during radiation treatment, in the next sentence they cite the finding that AOs produced an overall higher mortality rate, without acknowledging that this effect also was confined to those who smoked during treatment.

A second example of possible bias involves their interpretation of the results showing the benefits of amifostine. While they cite both of the meta-analyses described above, they described only one of them, which concluded that "at most" there could be only a 2% reduction in treatment effectiveness, and used this conclusion to argue that patients should be concerned, despite this being a hypothetical worst-case scenario, not the most likely scenario. Their omission of any discussion of the second meta-analysis is instructive because it concluded that not only was there no reduction in treatment effectiveness, but also that there were significantly more complete responses to treatment when amifostine was used.

The essential part of Lawenda et al's argument is that the evidence they review still leaves open the possibility that AOs interfere with conventional cancer treatment effectiveness. Thus, adherence to the Hippocratic Oath's dictum of "Do no harm" mandates that AOs not be prescribed until shown to be beneficial. It is not enough for proponents of AOs to demonstrate that AOs reduce the side effects of conventional treatment; they must also demonstrate beyond doubt that they do not interfere with clinical outcome.

To this reader of the clinical evidence, the argument presented by Lawenda et al., which is pervasive among conventional oncologists, is self-serving. Although there have

been notable successes with some forms of targeted therapy (e.g., gleevec), it remains true that conventional oncology treatments consist largely of "slash, burn, and poison". It is essential to recognize that a significant number of cancer patients die from the toxicities of their treatments rather than from their malignancy. Moreover, for many types of cancer (e.g., glioblastoma, pancreatic cancer, the great majority of metastatic cancers), conventional cancer treatments have an abysmal record of failure, even while patients endure considerable impairment to their quality of life. Given that harm is already being done, the critical issue is whether the "harm" outweighs the benefits of that harm. Adjudicating that issue demands that the playing field be level. When AOs are shown to reduce toxicity, and concurrently there is no clear evidence for reduction in treatment effectiveness, the burden of proof falls on conventional oncologists to demonstrate that there actually is a reduction in treatment benefits. Simply raising that possibility is neither sound argument nor real adherence to the Hippocratic Oath.

For cancer patients, whether to use or not use supplements is a complex decision. The greatest mistake is to adhere to a "one size fits all" approach. If conventional treatment for the patient's malignancy has a high rate of success, prudence would suggest that a conservative approach is in order, although for some situations, such as radiation for head-and neck cancer, the side effects, while temporary, can be extremely debilitating. But for many cancer patients, conventional treatment is not effective, so recommendations against the use of supplements, is unwarranted, especially given evidence they ameliorate the treatment's toxicity. Moreover, given that some supplements have clear clinical evidence of providing benefit (melatonin, Vitamin D, PSK, and fish oil), while others have impressive support from animal models (curcumin,

silibinin, lycopene, genistein, green tea, and ellagic acid), the possible benefits greatly outweigh the hypothetical harm.

References

1. Prasad, K.N. (2004). Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. Integr Cancer Ther. 3, 310-322

2. D'Andrea, G.M, (2005). Use of antioxidants during chemotherapy and radiotherapy should be avoided. CA Cancer J. Clin (2005), 55(5), 319-21

3. Seifried, H.E., McDonald, S.S., Andersen, D.E., et al. (2003). The antioxidant conundrum in cancer. Cancer Res., 63, 4295-98

4. Ladas, E. J., Jacobson, J. S., Kennedy, D. D., et al., (2004). Antioxidants and cancer therapy. A systematic review. J Clin Oncol., 22(3), 517-528

5. Lamson, D. W., and Brignall, M. S. (1999). Antioxidants in cancer therapy: Their actions and interactions with oncologic therapies. Altern Med Rev, 4(5), 304-329

6. Hardy, M. L. (2008). Dietary supplement use in cancer care: Help or harm. Hematol/Oncol Clin, N Am, 22, 581-617

7. Drisko, J.A., Chapman, J., and Hunter, V. J. (2003). The use of antioxidant therapies during chemotherapy. Gynecol Oncol, 88, 434-39

8. Whiteside, M. A., Heimburger, M. D., and Johanning, G. L. (2004), Micronutrients and cancer therapy. Nutr Rev, 62(4), 142-47

9. Moss, R. W. (2006). Should patients undergoing chemotherapy and radiotherapy be prescribed antioxidants? Integr Cancer Ther., 5(1) 63-82

10. Lawenda, B. D., Kelly, K. M., Ladas, E. J., et al. (2008). Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? J. National Cancer Inst., 100, 773-783

11. Prasad, K. N., Cole, W. C., Kumar, B., et al. (2002). Pros and cons of antioxidant use during radiation therapy. Cancer Treat. Rev, 28(2), 79-91

12. Simone, C. B., Simone, N., Simone, V., et al. (2007). Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, Part 1. Altern Ther Health Med, 13(1). 22-28

13. Simone, C. B., Simone, N., Simone, V., et al. (2007). Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, Part 2. Altern Ther Health Med. 13(2), 40-47

14. Conklin, K. A., (2000), and Dietary antioxidants during cancer chemotherapy: Impact on chemotherapeutic effectiveness and development of side effects. Nutr. Cancer, 37(1), 1-18

15. Borek, C. (2004). Dietary antioxidants and human cancer. Integr Cancer Rev. 3(4), 333-341

16. Block, K. I., Koch, A. C., Mead, M. N.,et al. (2007). Impact of antioxidant supplementation on chemotherapeutic efficacy: A systematic review of the evidence from randomized controlled trials. Cancer Treat Rev,

17. Storz, P. (2005). Reactive oxygen species in tumor progression. Front. Biosci. 10, 1881-1896

18. Peervaiz, S, and Clement, M. V. (2004). Tumor intracellular redox status and drug resistance – serendipity or a causal relationship? Curr Pharm Des., 10 (16), 1969-77

19. Shklar, G. (1998). Mechanisms of cancer inhibition by anti-oxidant nutrients. Oral Oncol. 34(1), 24-29

20. Ozben, T. (2007). Oxidative stress and apoptosis: Impact on cancer therapy. J Pharm Sci, 96(9), 2181-96

21. Mates, J. M., and Sanchez-Jimenez, F. M. (2000). Role of reactive oxygen species in apoptosis: implications for cancer therapy. Int J Biochem Cell Biol., 32, 157-170

22. Xia, C., Meng, Q., Ling-Zhi, L, et al. (2007) Reactive oxygen species regulate angiogenesis and tumor growth through vascular endothelial growth factor. Cancer Res, 67(22), 10823-30

23. Lamm, D. L., Riggs, D. R., Shriver, J. S., et al.(1994) . Megadose vitamins in bladder cancer: a double-blind clinical trial, J. Urol. 151(1), 21-26

24. Colombo, N., Bini, S., Miceli, D. et al. (1995). Weekly cisplatin +/- glutathione in relapsed ovarian carcinoma. Int J Gynecol Cancer, 5, 81-86

25. Smyth, J. F., Bowman, A., Perren, T. , et al. (1997). Annals of oncology, 8, 569-73

26. Cascinu, S., Catalano, V., Cordella, L., et al. (2002). Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: A randomized double-blind, placebo-controlled trial. J. Clin. Oncol. 20 (16), 3478-83

27. Pathak, A. K., Bhutani, M., Guleria, R., et al. (2005). Chemotherapy alone vs. chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer. J Am Coll Nutr. 24 (1), 16-21

28. Puri T., Goyal, S Julka, P. K., Nair, O., et al. (2010). Lycopene in the treatment of high-grade glioma: a pilot study. Neurologica India, 58. 20-23

29. Sasse, A. D., Clark, L. G., Sasse, E. C., & Clark, O. A. (2006). Amifostine reduces side effects and improves complete response during radiotherapy: results of a meta-analysis. Int. J. Radiat Oncol Biol. Phys., 64 (3), 784-91

30. Mell, L. K., Malik, R., Komak, R.,et al. (2007). Effect of amifostine on response rates in locally advanced non-small-cell lung cancer patients treated on randomized controlled trials: a meta-analysis. Int J Radiat. Oncol Biol. Phys. 68(1), 111-18

31. Block, K. I., & Gyllenhaal, C. (2005). Commentary: The pharmacological antioxidant amifostine – Implications of recent research for integrative cancer care. Integr. Cancer Ther. 4(4), 329-351

32. Mills, E., Wu, P., Seely, D., & Guyatt, G. (2005). Melatonin in the treatment of cancer: a systematic review of randomized controlled trials and meta-analysis. 39, 360-66

33. Lissoni, P., Meregalli, S., Nosetto, L., et al. (1996). Increased survival time in brain glioblastomas by a radio-neuroendocrine strategy with radiotherapy plus melatonin compared to radiotherapy alone. Oncol, 1996, 53, 43-46

34. Lissoni, P.,Barni, S., Mandala, M. et al. (1999). Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in

metastatic solid tumor patients with poor clinical status. Eur J Cancer, 35, 1688-1692

35. Lissoni, P., Barni, S., Ardizzoia, A. et al.. (1992) Randomized study with the pineal hormone melatonin versus supportive care alone in advanced non-small cell lung cancer resistant to a first-line chemotherapy containing cisplatin. Oncol, 49, 336-339

36. Berk, L., Berkey, B., Rich, T., et al. (2007). Randomized phase II trial of high-dose melatonin and radiation therapy for RPA class 2 patients with brain metastases (RTOG 0119). Int J Radiat Oncol Biol Phys., 68 (3) 852-57

37. Srinivasn, V., Spence, D. W, Pandi-Perumal, R., et al. (2008). Therapeutic actions of melatonin cancer: Possible mechanisms. Integr Cancer Ther. 7, 189-202

38. Vijayalaxmi, B., Thomas, C. R., Reiter, R. J., and Herman, T. S. (2002). Melatonin: From basic research to cancer treatment clinics, J Clin Oncol. 20(10), 2575-2601

39. Kunnumakkara, A. B., Anand, P., and Aggarwal, B. B. (2009). Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer Let., 269(2), 199-225

40. Lopez-Lazaaro, M. (2008). Anticancer and carcinogenic properties of curcumin: considerations for its clinical development as a cancer chemopreventive and chemotherapeutic agent. Mol Nut Food Res. 52 Suppl 1, S103-127

41.Khan, N., & Mukhtar, H. (2009). Multitargeted therapy of cancer by green tea polyphenols. Cancer Let, 269(2), 269-280

42. Banerrjee, S., Li, Y., Wang, Z., and Sarkar, F. H. (2009). Multitargeted therapy of cancer by genistein. Cancer Let, 269(2), 226-242

43. Murakami, A., Ashida, H., and Terao, J. (2009). Multitargeted cancer prevention by quercetin, Cancer Let, 269(2), 315-325

44.Heber, D. (2009). Multitargeted therapy of cancer by ellagitannins, Cancer Let., 269(2), 262-68

45. van Breemen, R. V. and Pajkovic, N. (2009). Multitargeted therapy of cancer by lycopene. , Cancer Let, 269(2), 339-351

46. Ramasamy, K., and Agarwal, R. (2009). Multitargeted therapy of cancer by silymarin. , Cancer Let, 269(2), 352-362

47. Kundu, J. K., and Surh, Y-J. (2009). Cancer chemopreventive and therapeutic potential of resveratrol: Mechanistic perspectives. , Cancer Let, 269(2), 243-261

48. Aggarwal, B. B., & Shishodia (2006). Molecular targets of dietary agents for prevention and therapy of cancer. Biochem Pharm., 71,1397-1421

49. Pantuck, A. J., Leppert, J.T. Zomorodian, N., et al. (2006). Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. Clin Cancer Res., 12(13), 4018-26

50. Paller, C. J., Xe, X., Wozniak, P. J., Gillespie, B. K., et al. (2013). A randomized phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer. Prostate, Cancer & Prostatic Disease, 2013, 16 (1), 50-55

51. Kucuk, O., Sarkar, F. H., Djuric, Z., et al. (2002). Effects of lycopene supplementation in patients with localized prostate cancer. Experimental Biology and Medicine, 227 (10), 881-85

52. Hussain, M., Banerjee, M. Sarkar, F. H., et al. (2003). Soy isoflavones in the treatment of prostate cancer. Nutrition and Cancer, 47(2), 111-17

53. Thomas, R., Williams, M., Sharmaa, H., et al. (2014). A double-blind, placebo-controlled randomized trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer – the UK NCRN Pomi-T study. Prostate Cancer and Prostatic Disease, 17(2), 180-6

54. Schroeder, F. H. Roobol, M.J., Boeve, E. R., et al. (2005). Randomized, double-blind, placebo-controlled crossover study in men with prostate cancer and rising PSA: effectiveness of a dietary supplement. Eur Urol. 48(6), 922-930

55. Hoenjet, K. M., Dagnelie, P. C., Delaere, K. P., et al. (2005). Effect of a nutritional supplement containing Vitamin E, selenium, vitamin c and coenzyme Q10 on serum PSA in patients with hormonally untreated carcinoma of the prostate: a randomized placebo-controlled study. European Urology, 47 (4), 433-39

56. Valshampayan, U., Hussain, M., Banerjee, M., et al. (2007). Lycopene and soy isoflavones in the treatment of prostate cancer. Nutrition and Cancer, 59 (1), 1-7

57. Golden, E.B., Lam, P. Y., Kardosh, A., et al. (2009). Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteosome inhibitors. Blood, e-pub ahead of print (Feb. 3)

58. Conklin, K. A. (2002). Dietary polyunsaturated fatty acids: Impact on cancer chemotherapy and radiation. Altern Med Rev. 7(1), 4-21

59. Yam, D., Peled, A., & Shinitsky, M. (2001) Suppression of tumor growth and metastasis by dietary fish oil combined with vitamins E and C and cisplatin. Cancer Chemother Pharmacol. 47, 34-456.

60. Gogos, C. A., et al. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy: a randomized control trial. Cancer, 1998, Vol. 82, pp. 395-402

61. Bougnoux, P., Hajjaji, N., Ferrasson, M. N. et al. Improving outcome of chemotherapy of metastatic breast cancer by docasahexaenoic acid: a phase II trial. Br. J Cancer, 2009, 101, 1978-1985

62. Murphy, R. A., Mourtzakis, M., Chu, QW. S., et al. Supplementation with fish oil increases first-line chemotherapy efficacy in patients with advanced nonsmall cell lung cancer. Cancer, 2011, 117(16), 3774-80

63. Hayakawa, K., et al. Effect of krestin (PSK) as adjuvant treatment on the prognosis after radical radiotherapy in patients with non-small cell lung cancer. Anticancer Res, 1993, 13, 1815-1820

64.. Ohwada, S., Ikeya, T., Yokomori, T. et al. (2004). Adjuvant immunochemotherapy with oral Tegafur/Uracil plus PSK in patients with stage II or III colorectal cancer: a randomized controlled study. Br J Cancer, 90(5), 1003-10

65. Iarussi, D., Auricchio, U., Agretto, A., et al. (1994). Protective effect of coenzyme Q10 on anthracyclines cardiotoxicity: control study in children with acute lymphoblastic leukemia and non-Hodgkin lymphoma. Mol. Aspects Med.,15 Supple, S207-12

66. Labriola, D., and Livingston, R. (1999). Possible interactions between dietary antioxidants and chemotherapy. Oncol, 13(7), 1003-1008

67. Lesperance, M. L., Olivoto, L. A., Forde, N., et al. (2002). Mega-dose vitamins and minerals in the treatment of non-metastatic breast cancer: an historical cohort study. Breast Cancer Res & Treat. 76, 137-143

68. Ferreira, P. R., Fleck, J. F., Diehl, A., et al. (2004). .Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucostiis: A double-blind randomized trial. Head & Neck, 26(4), 313-321

69. Harris N. M., Crook, T. J., Dyer, J. P., et al. (2002). Intravesical meglumine gamma-linolenic acid in superficial bladder cancer: an efficacy study. Eur Urol. 42(1), 39-42

70. Bairati, I., Meyer, F., Gelinas, M., et al. (2005). Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. Journal of Clinical Oncology, 23 (24), 5805-13

71. . Bairati, I. , Meyer, F., Jobin, E., et al. (2006). Antioxidant vitamins supplementation and mortality: A randomized trial in head and neck cancer patients. Int J Cancer, 119, 2222-24

72. Bairati, I., Meyer, F., Gelinas, M., et al. (2005). A randomized trial of antioxidant vitamins to prevent second primary cancers in head and neck cancer patients. Journal of the National Cancer Institute, 97 (7), 481-488

73. Meyer, F., Bairati, I., Fortin, A., et al. (2008). Interaction between antioxidant vitamin supplementation and cigarette smoking during radiation therapy in relation to long-term effects on recurrence and mortality: A randomized trial among head and neck cancer patients. International Journal of Cancer, 122, 1679-83