DO ANTIOXIDANTS INTERFERE WITH RADIATION THERAPY FOR CANCER?

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Abstract

Despite recent comprehensive review articles concluding that supplemental antioxidants do *not* undermine the effectiveness of cytotoxic therapies, the use of antioxidants during cancer treatment remains controversial. Many oncologists take the position that antioxidants by their nature undermine the free radical mechanism of chemotherapy and radiotherapy, and should therefore generally be avoided during treatment. For their part, many integrative practitioners believe that antioxidants taken during cancer treatment not only alleviate some of the adverse effects of that treatment, but also enhance the efficacy of cancer therapy. Until recently, most research attention has focused primarily on the interaction of antioxidants with chemotherapy; relatively little attention has been paid to the interaction of antioxidants with radiotherapy. This paper reviews clinical literature on the question of whether antioxidants do in fact interfere with radiation therapy. Studies have variously investigated the use of alpha-tocopherol for the amelioration of radiation-induced mucositis; pentoxifylline and vitamin E to correct the adverse effects of radiotherapy; melatonin alongside radiotherapy in the treatment of brain cancer; retinol palmitate as a treatment for radiation-induced proctopathy; a combination of antioxidants (and other naturopathic treatments) and external beam radiation therapy as definitive treatment for prostate cancer; and the use of synthetic antioxidants, amifostine, dexrazoxane and mesna, as radioprotectants. With few exceptions, most of the above mentioned studies draw positive conclusions about the interaction of antioxidants and radiotherapy. Although further studies are needed, the preponderance of evidence supports a provisional conclusion that dietary antioxidants do not conflict with the use of radiotherapy in the treatment of a wide variety of cancers, and may significantly mitigate the adverse effects of that treatment.

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Few topics generate as much controversy as the nutritional component of cancer patients' care. In particular, the concurrent use of antioxidants and conventional cancer treatments has become a flash point in the relationship between conventional oncologists and complementary and alternative medical (CAM) practitioners Although CAM practitioners draw on a wide spectrum of healing traditions, and hold diverse opinions on many aspects of cancer care, they are generally unanimous in their belief that improved diet and lifestyle, including judicious dietary supplementation, can decrease the adverse

effects of conventional treatment and thereby render the patient better able to endure cytotoxic treatment modalities.

Oncologists on the whole are inclined to take the view that antioxidants are capable of diminishing the effectiveness of chemo- and radiation therapy.[i] However, within the profession there is great variation in the degree of concern over this issue, with some oncologists taking a laissez-faire attitude towards the use of antioxidants during conventional therapy while others have publicly expressed alarm over such usage.[ii]

The basis of the anti-concurrent use argument is that radiotherapy, like much chemotherapy, destroys cancer cells through the creation of free radicals. The ingestion of dietary antioxidants supposedly results in neutralization, and, potentially, nullification, of these therapeutic moieties. Statements about the putative harm of antioxidants during conventional treatment are often grounded in these theoretical concerns or on selective interpretations of a few high-profile studies. It is rare to find a dispassionate overview by oncologists of the relevant clinical data in its totality.

Kenneth Conklin, MD, PhD, University of California, Los Angeles (UCLA) Medical Center, has questioned the theoretical basis for the argument against concurrent usage. He has posited an alternate model, acknowledging that while radiation does indeed kill cells by generating high levels of free radicals, this does not necessarily preclude the use of antioxidants as adjuvant dietary supplements during treatment. Conklin points out that radiotherapy is most effective in well-oxygenated tissues. However, tumors, particularly larger ones, are often hypoxic at their core, diminishing the effectiveness of radiation.[iii]

Antioxidants, as a class, improve blood flow and therefore promote the normal oxygenation of tissues, thereby rendering tumors more – not less – susceptible to radiation.[iv] Conklin has suggested that since the degree of free radical generation is proportional to the oxygen tension in the tissue, antioxidants pre-administered in amounts sufficient to improve blood flow, yet not in amounts to actually quench a significant proportion of free radicals, may result in an improved antineoplastic effect.[v]

A similar perspective has been put forward by Carmia Borek, PhD, at a National Institutes of Health (NIH) conference on “Free Radicals: The Pros and Cons of Antioxidants” on June 26-27, 2003.[vi] Borek, who is Professor of Community Health, and Director, Nutrition and Infectious Diseases, Tufts University School of Medicine, Boston, Mass., stated that an important goal of radiotherapy is to administer enough radiation to kill tumor cells without killing adjacent normal cells. DNA is the primary target of radiotherapy; damage to DNA occurs through a direct effect but two thirds of the damage occurs through an indirect effect, by free radicals: superoxide, hydroxyl radicals and nitric oxide metabolites. Cells are most sensitive to radiation during the G1-M phase of the cell cycle; oxygen concentration and cyclins will modify radiation response. Irradiation of non-dividing or slow dividing cells results in apoptotic death.

Borek reiterated the fact that radiation itself is capable of inducing cancer, and that vitamin E and selenium protect against radiation-induced malignancy *in vitro*. The use of

combinations of antioxidants can help decrease damage expected from radiotherapy, especially high dose radiotherapy.[6]

Furthermore, there is considerable experimental and clinical evidence that radiation reduces tissue antioxidants. In laboratory animals, for example, radiation exposure has been demonstrated to reduce cellular vitamin E levels. In other studies, radiation has been shown to reduce bone marrow vitamin C and E levels, and in clinical studies in breast cancer patients, vitamin A, C, and E, and selenium levels were found to be reduced during cancer radiotherapy. The question remains whether supplementing antioxidants during radiotherapy is beneficial to cancer patients or might have an adverse effect.[6]

Kedar Prasad, PhD, formerly of the Center for Vitamin and Cancer Research, Department of Radiology, University of Colorado, Denver, has long advocated the concurrent use of selected antioxidants during radiotherapy. In numerous articles, he has presented a scientific rationale for a micronutrient protocol that includes high doses of dietary antioxidants (vitamin C, vitamin E succinate and natural beta-carotene) that can be used adjunctively with radiation therapy.[vii]

Two recent comprehensive surveys of the literature on concurrent administration of antioxidants alongside cytotoxic therapy drew similarly positive conclusions. Keith Block et al[viii] and Charles Simone et al[ix] both found that antioxidants were at the very least harmless when given in the context of conventional therapy.

Charles Simone et al surveyed the peer-reviewed literature on the use of dietary antioxidants administered with chemotherapy and radiation therapy from 1996 though 2003. These investigators identified 280 peer-reviewed articles on this topic, of which 50 were clinical trials involving a total of 8,521 patients. Of these patients, 5,081 received over-the-counter supplements such as beta-carotene; vitamins A, C, and E; selenium; cysteine; B vitamins; vitamin D3; vitamin K3; and glutathione, as single agents or in combination. Simone (a medical and radiation oncologist) concluded that these studies have “consistently shown that non-prescription antioxidants and other nutrients do not interfere with therapeutic modalities for cancer”.[9]

In fact, he and his colleagues maintained that the use of antioxidants actually enhanced the effectiveness of standard therapeutic modalities, while diminishing adverse effects and protecting normal tissue. In 15 of the studies, 3,738 patients who took supplemental non-prescription antioxidants, and other supplemental nutrients, had improved survival, which contradicts the claim made by others that antioxidants diminish survival in this context.[9]

For their part, Block et al focused primarily on the interaction of antioxidants with chemotherapy, but this comprehensive review had implications for radiotherapy as well. The authors surveyed 845 peer-reviewed articles and identified 19 clinical trials that met strict inclusion criteria. Most study participants had advanced or recurrent disease, and were administered, variously, glutathione (7 trials), melatonin (4), vitamin A (2), an

antioxidant mixture (2), vitamin C (1), N-acetylcysteine (1), vitamin E (1) and ellagic acid (1).

These authors concluded: "None of the trials reported evidence of significant decreases in efficacy from antioxidant supplementation during chemotherapy." [8] By contrast, many studies showed that antioxidant supplementation was associated with "increased survival times, increased tumor responses, or both, as well as fewer toxicities than controls".[8]

However, as Block, Borek, Conklin, Prasad, Simone and others have indicated, there have already been a number of *in vitro* and clinical studies on this topic.[x,xi] Not all of the clinical studies are large, North American or Western European multi-centric trials (the kind most likely to carry weight in the oncology community). However, there are enough data on which to base some preliminary conclusions. While one randomized controlled trial (RCT) drew negative conclusions,[xii,xiii,xiv] the majority of the published clinical studies (not to mention the preponderance of laboratory experiments) show a beneficial interaction between antioxidants and cancer treatment.

Radiation Decreases Antioxidant Levels

The use of antioxidants in the course of conventional oncologic treatment is sometimes presented as an irrational intervention by patients who are attempting to meddle in their own treatment, against the better judgment of their oncologists.[2] However, an alternative view is that oncologists as a class often fail to monitor all the relevant biochemical and/or nutritional changes in their patients before, during and after chemotherapy and radiotherapy. If they did so they themselves might see the need to adjust antioxidant intake in conformity with dynamic test results.

Studies have shown that both chemotherapy and radiotherapy decrease plasma antioxidant levels. This "may reflect a failure of the antioxidant defense mechanism against oxidative damage induced by commonly used anticancer drugs" [xv] as well as by radiotherapy.[xvi,xvii,xviii] It is generally recognized that adequate levels of antioxidants are a precondition for optimal health. In addition to having tumoricidal effects, the free radicals generated by radiotherapy may upset the oxidant-antioxidant equilibrium, causing acute, intermediate and long-term damage that can result, among other things, in second cancers.[xix] Free radicals can also exacerbate comorbid conditions that either predate the cancer or emerge as a result of treatment itself.

As Ellen F. Manzullo, MD, of the University of Texas M. D. Anderson Cancer Center, Houston, put it, "It's important to keep comorbid conditions in mind for the sake of the entire patient and not just focus on the cancer, because the patient can do extremely well as far as their cancer is concerned but subsequently die of coronary artery disease or stroke".[xx]

The damage caused by radiation to the body's intrinsic antioxidant balance has mainly been studied in the context of total body irradiation (TBI), used for conditioning patients

for stem cell and bone marrow transplantation (BMT). Clemens et al reported on vitamin E and beta-carotene levels in the serum of 19 patients, as well as their levels of lipid hydroperoxides (i.e., free radicals), before and after TBI. Clemens found that lipid hydroperoxides were significantly increased among patients undergoing a greater-than-normal exposure to TBI, whereas the other group, receiving no additional TBI, showed no significant change. The authors therefore suggested the use of supplemental antioxidants for patients undergoing TBI prior to BMT.[xxi]

Researchers in Atlanta similarly reported that both chemotherapy and radiation therapy resulted in increased free radical formation and depletion of intrinsic tissue antioxidants.[xxii] They studied the plasma antioxidant status of 24 BMT patients and found that plasma glutathione (GSH) and alpha- and gamma-tocopherol concentrations decreased and the GSH redox state became more oxidized after conditioning treatment. They concluded: "A significant decline in GSH-glutathione disulfide, cysteine-cystine, and vitamin E status occurs after chemotherapy and BMT."[22]

Lin et al studied antioxidant status in 19 patients undergoing BMT. Ten patients were randomized to receive vitamin C (300 mg/d) and vitamin E (600 mg/d) consecutively for 15 days before BMT. The control group received BMT with this prior vitamin administration. Four measurements of antioxidant levels were carried out before and after BMT. The authors concluded: "Exogenous supplementation of antioxidant vitamins before BMT may improve the antioxidant capacity and reduce lipid peroxidation in patients with BMT, effectively alleviating their peroxide stress induced by high-dose chemo/radiotherapy."[xxiii]

Bhuvarahamurthy et al showed that after radiotherapy and chemoradiotherapy the antioxidants glutathione, vitamin E and selenium were reduced in cervical cancer patients. Conversely, erythrocyte lipid peroxide (E-LPx) and erythrocyte membrane lipid peroxide (EM-LPx) were increased in all stages of uterine cervical carcinoma. The endogenous antioxidant enzyme systems such as erythrocyte superoxide dismutase (E-SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione-S-transferase (GST) and glucose-6-phosphate dehydrogenase (G6PDH) were also decreased in uterine cervical carcinoma. Eventually, they said, these "altered biochemical parameters were reversed to normal." But this took varied degrees of time depending on the radiotherapy protocol.[xxiv]

In general, antioxidant systems do not rapidly rebound in a spontaneous fashion. Indeed, the opposite seems to be the case. Research carried out at Leiden University Medical Center, Holland, established that the levels of the endogenous antioxidant compounds, bilirubin, albumin, and uric acid remained depressed for several months after irradiation, as did the ratio of vitamin E to cholesterol and triglycerides. The investigators characterized this as "a failure of the antioxidant defense mechanism against oxidative damage," [15] caused by commonly used cytotoxic treatments.

Elango et al collected blood samples from 63 stage III oral cancer patients before initiating radiotherapy. Twenty-seven of these patients were given radiotherapy alone

while 36 were given selenium (400 µg/day for 6 months) during and following radiation treatment. The authors evaluated a broad array of systemic antioxidants, including the plasma selenium concentration, non-enzymatic systems including GSH, vitamins A, C and E, ceruloplasmin and enzymatic antioxidant systems including superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase.[xxv]

The authors found that concentrations of all were significantly lowered in patients who received radiotherapy. By contrast, in the selenium-supplemented group there was a marked increase in the concentrations of selenium as well as the general antioxidant status at 6 months compared to the radiation group. The authors concluded: "The observed result represents the antioxidant property of selenium through the improvement of antioxidant defense system. Selenium supplementation could be of great interest in protecting cells against oxidative stress."[25]

Alpha-tocopherol for Radiation-Induced Mucositis

In a 2004 RCT, 54 patients with cancer of the oral cavity and oropharynx were randomly assigned either to rinse their mouths with a solution containing the antioxidant alpha-tocopherol (vitamin E) or with a placebo mouthwash. Patients rinsed their mouths before each administration of radiation, and again 8 to 12 hours later, throughout 5 to 7 weeks of treatment.

Among patients administered alpha-tocopherol mouthwashes, there was a 21.6% incidence of radiation-induced mucositis vs. 33.5% among the placebo group. Vitamin E was thus associated with a 12.9% mucositis risk reduction. It was also associated with a five-fold reduction in WHO grades 2 and 3 pain during radiation treatment (53.8% in the placebo group vs. 10.7% in the vitamin E group).

While no significant differences in survival were noted, the authors concluded that alpha-tocopherol "decreased the incidence of symptomatic oral radio[therapy, ed.]-induced mucositis in patients with cancer of the oropharynx and oral cavity."[xxvi]

Pentoxifylline and Radiotherapy

Pentoxifylline (PTX) is a xanthine-derived antioxidant commonly used to improve blood flow and to reduce aching, cramping, and tiredness in the hands and feet. It decreases the viscosity of blood, allowing it to flow more easily.[xxvii] There have been studies on the concurrent use of PTX and over-the-counter antioxidant vitamins with radiotherapy: 64 such papers are presently listed in PubMed, 15 reporting RCTs.

Some of these trials involve the use of PTX after the completion of radiotherapy. While they therefore do not directly address the question of concurrent use they nevertheless bear mentioning.

PTX has been used with vitamin E in the successful treatment of radiation-induced fibrosis[xxviii,xxix] as well as osteoradionecrosis.[xxx] When given along with vitamin E, PTX was also found to improve embryo implantation rate in women who had previously received irradiation to the pelvis, sometimes decades before. "In young women who want to bear children, the combination of pentoxifylline and vitamin E can reduce fibroatrophic uterine lesions after childhood irradiation," these French authors wrote.[xxxi] PTX also exerted a modest therapeutic effect in patients who had radiation-induced trismus.[xxxii] In 1992, Lee et al of the University of Minnesota showed that PTX, along with the B vitamin nicotinamide, "increased the radio-response of tumors by improving tumor oxygenation".[xxxiii] PTX has also been found to convey "a significant protective effect" for both early and late lung radiotoxicity.[xxxiv]

In 2000, H.C. Kwon et al of the University of Minnesota Medical School, Minneapolis, MN, demonstrated increased survival in patients who received PTX concurrently with conventional radiotherapy (RT).[xxxv] Out of 64 non-small cell lung cancer (NSCLC) patients, 47 had measurable tumors on chest x-ray views. These 47 patients were randomly divided into a radiotherapy-alone group (20 patients) and a PTX+RT group (27 patients). Each patient received a total tumor dose of 65-70 Gy. PTX was given at a daily dose of 1200 mg during radiotherapy (Table 1).

Table 1.
Effects of Radiotherapy + PTX vs. Radiotherapy Alone in NSCLC
(Data from Kwon 2000*)*

	Complete response	Partial response	Stable disease	Time to relapse	Median survival	1-yr survival	2-yr survival
RT alone	15%	65%	20%	9 mo.	7 mo.	35%	12%
RT + PTX	11%	48%	11%	11 mo.	18 mo.	60%	18%

The complete response (CR), partial response (PR), and stable disease rates in the two groups (RT alone vs. RT + PTX) were comparable, although they trended towards a diminished response rate in the PTX-added group. However, surprisingly, patients who received the supplemental antioxidant had a median survival 18 months vs. 7 months for those receiving radiotherapy alone, for an increase of 260%.[35]

In addition, the median time to relapse in the PTX+RT group was 11 months, which was 2 months longer than for the RT alone group. These results were statistically significant. The median survival was 18 months in the PTX+RT group and 7 months in the RT alone group. The 1-year survival rate was 60% in the PTX+RT group and 35% in the RT alone group; the 2-year survival rate was 18% in the PTX+RT group and 12% in the RT alone group. The authors report that the latter differences were not statistically significant.

These largely positive findings were clearly not consistent with the notion that antioxidants interfere with radiotherapy. Indeed, the authors themselves concluded that PTX was "a modestly effective radiation response modifier and provides benefit in the treatment of non-small cell lung cancer".[35]

A 2006 RCT studied the effect of PTX and alpha-tocopherol on the clinical outcome of 66 patients with stage IIIB non-small cell lung cancer.[xxxvi] All patients received 46 Gy of external beam radiotherapy to their primary tumors and to regional lymph nodes, followed by a boost of 14 Gy to the primary. Half the patients also received PTX (400 mg, 3X daily) and alpha-tocopherol, (300 mg, 2X daily) concurrently with radiotherapy. This was followed by 400 mg of PTX and 300 mg of alpha-tocopherol daily for 3 months after completion of radiotherapy. A control group of 33 patients received radiotherapy alone.

After a mean follow-up of 12 months, a total of 18 patients (27.3%) remained alive. There were local recurrences in 14 patients and distant metastases in 18 patients during follow-up. In patients receiving PXT and alpha-tocopherol, 1- and 2-year overall survival rates were 55% and 30%, respectively. Median survival was 18 months. In control patients, 1- and 2-year overall survival rates were 40% and 14%, respectively, with a median survival of 10 months. These differences were statistically significant (Table 2).

Table 2
Overall Survival After Radiotherapy With and Without PTX and Vitamin E
(Data from Misirlioglu 2006)

	1 Year Overall Survival	2 Year Overall Survival	Median Survival
PTX + Vit E Group	55%	30%	18 months
Radiation Group	40%	14%	10 months

Patients who also received PTX and alpha-tocopherol had progression-free survival rates of 48% (1 year) and 23% (2 year); median survival was 12 months. In the control group, the corresponding rates were 24% and 18%; median survival in this group was 8 months (Table 3).[36]

Table 3
Progression-Free Survival (PFS) After PTX and alpha-tocopherol vs. Control
(Data from Misirlioglu 2006)

	1 Yr P.F.S.	2 Yr P.F.S.	Median Survival
PTX + alpha-tocopherol	48%	23%	12 months
Control Group	24%	18%	8 months

If the dominant paradigm among oncologists were correct, one would expect to see significantly *decreased* response rates and survival curves when antioxidants such as PTX and alpha-tocopherol were administered concurrently with radiotherapy. Yet in these clinical trials one sees the opposite.

Melatonin and Radiotherapy

The pituitary hormone melatonin (MLT) has many biological functions, including acting as an antioxidant in the body. Paolo Lissoni, San Gerardo Hospital, Monza, Italy et al have published numerous articles on the concurrent use of melatonin and chemo- and radiotherapy.

In one RCT involving patients with stage IV glioblastoma multiforme, 30 patients received 60 Gy of radiotherapy alone or radiotherapy plus 20 mg/daily oral doses of melatonin, until disease progression. Lissoni et al reported: "Both the survival curve and the percent of survival at 1 year were significantly higher in patients treated with RT plus MLT than in those receiving RT alone."[xxxvii] Six out of 14 melatonin-treated patients were alive at one year vs. just 1 out of 16 in the radiotherapy group.[37]

The authors also reported that radiotherapy- or steroid therapy-related toxicities "were lower in patients concomitantly treated" with melatonin.[37] The addition of the antioxidant melatonin prolonged survival time and improved quality of life in patients affected by glioblastoma multiforme.

Retinol Palmitate and Radiation Proctopathy

The antioxidant retinol palmitate (i.e., vitamin A) has been shown to prevent or reverse some adverse effects of radiotherapy without interfering with its efficacy. Ehrenpreis et al of the University of Chicago Medical Center tested oral retinol palmitate for reducing symptoms of radiation proctopathy such as diarrhea, urgency, rectal pain, tenesmus, and fecal incontinence. The study was designed to see if vitamin A (an antioxidant noted for its ability to accelerate healing) could reduce these troublesome side effects. The study was a double-blind RCT of 10,000 IU of vitamin A by mouth for 90 days vs. placebo.

Patients, all of whom had significant symptoms, were recruited more than six months after pelvic irradiation. Most of them had been irradiated for prostate disease.[xxxviii]

Nineteen patients were randomized: 10 to receive oral doses of retinol palmitate and 9 to placebo. Five of the placebo non-responders were eventually crossed over to the retinol palmitate arm for another 90 days. Seven of 10 retinol palmitate patients responded, whereas only 2 of 9 responded to placebo.

Additionally, all 5 placebo non-responders who were crossed over to treatment with retinol palmitate then responded to treatment. The authors concluded that vitamin A "significantly reduced rectal symptoms of radiation proctopathy, perhaps because of wound-healing effects. The current results can serve as the foundation for future trials examining retinol palmitate in the multi-institutional setting." Douglas K. Rex, MD, of *Journal Watch Gastroenterology*, commented: "If substantiated by additional studies, this discovery would dramatically advance the treatment of a difficult clinical problem."[xxxix]

CTCA Study

In 2006, Timothy C. Birdsall, ND, and colleagues at the Cancer Treatment Centers of America (CTCA), Midwestern Regional Medical Center, Zion, IL presented a paper at the Society for Integrative Oncology (SIO) meeting on the "Effect of Concomitant Naturopathic Therapies on Clinical Tumor Response to External Beam Radiation Therapy for Prostate Cancer."[xl] An updated version of this study will be presented at the American Society of Clinical Oncology (ASCO) meeting in Chicago, June 2007.[xli]

In the 2006 study, 13 patients received naturopathic therapy including antioxidants (CAM group) and 9 individuals did not (non-CAM group). External beam radiation therapy (EBRT) of up to 72 Gy was given to all patients on a conventional 8-week treatment regimen. Tumor responses were based on PSA scores, time to PSA nadirs, and durability of PSA levels. All patients were then monitored for at least 12 months (range 12-42) and no patient received concomitant hormonal therapy. All patients in the CAM group received at least one antioxidant supplement (range=1-7). The most frequent antioxidant supplements included green tea extract (11/13); melatonin (10/13); and a high-potency multivitamin, vitamin C or vitamin E (8/13). The number of antioxidant supplements taken per patient in the CAM group was 2.9 ± 1.7 (Table 4).

Table 4
CTCA Study of EBRT w/wo Antioxidants for Prostate Cancer
(Data from Birdsall 2006)

	Low risk patients	Pretreatment PSA	Median PSA nadir	Time to PSA nadir	Treatment failures
Non-CAM group	9/9	5.4 ng/mL	0.66 ng/mL	16.0 months	1
CAM group	9/13	5.8 ng/mL	0.59 ng/mL	16.0 months	0

In the 9 patients who did not receive antioxidants, the median pretreatment PSA level was 5.4 ng/mL, the median PSA nadir was 0.66 ng/mL, and the median time to PSA nadir was 16.0 months. In the 13 patients who received antioxidants, the corresponding values were 5.8 ng/mL; 0.59 ng/mL; and 16.0 months. There was 1 tumor treatment failure in the non-CAM group based on PSA elevation > 2 ng from nadir which occurred at 14 months; no treatment failures were seen in the 13 patients who received CAM regimens.

It is noteworthy that 9/9 patients in the non-CAM group were considered low risk (i.e., pretreatment PSA levels of 4-10 ng) whereas 3 patients in the CAM group were classified as intermediate risk (PSA >10-20 ng) and 1 patient as high risk (PSA >20 ng).

The authors conclude:

> "Thus, concomitant naturopathic treatment does not appear to inhibit the capacity of external beam radiation therapy to control localized prostate cancer, and does not interfere with either the magnitude of the response, the velocity of the response, or its durability for at least 1 year. These results provide definitive evidence that antioxidant-based CAM modalities, designed to improve patient tolerance, quality of life, and possibly improve survival, do not inhibit tumor responses that depend on oxidative killing mechanisms elicited by external beam radiation therapy. This sort of investigation in well-defined, homogeneous cancer populations that receive consistent, definitive single treatment modalities offers the opportunity to investigate the positive benefits of selected CAM regimens in cancer patient management."[40]

Finnish Clinical Trial

In 1992, Kaarlo Jaakkola, MD et al of the University of Jyvaskyla, Finland, compared the treatment of patients receiving radiotherapy (and chemotherapy) for small cell lung cancer (SCLC) with or without over-the-counter antioxidants. They concluded:

> "Antioxidant treatment, in combination with chemotherapy and irradiation, prolonged the survival time of patients with small cell lung cancer compared to most published combination treatment regimens alone. We also noticed that the patients receiving antioxidants were able to tolerate chemotherapy and radiation treatment well. Surviving patients started antioxidant treatment in general earlier than those who succumbed."[xlii]

Synthetic Antioxidants

The oncology profession does not uniformly proscribe all antioxidants during radiotherapy. In fact, it makes several conspicuous exceptions. Prominent among these is the drug amifostine (Ethyol), a powerful synthetic antioxidant that scavenges three types of free radicals – superoxide, hydroxyl, and lipoperoxyl.[xliii] Amifostine is an analog of the antioxidant cysteamine. It is classed as a phosphorylated aminothiol pro-drug, which exerts its effects as a selective cytoprotective agent for normal tissues against the toxicities of chemotherapy and/or radiation.

Amifostine was developed at Walter Reed Army Institute of Research (hence its original designation, WR-2721) to protect military personnel from radioactive fallout. It was the first antioxidant to be approved by the FDA and international health agencies.[xliv] Amifostine was evaluated in a multicenter, multinational phase III clinical trial that enrolled women with stage III/IV ovarian cancer. This, and additional clinical trials, showed that amifostine "can protect normal tissues from the toxic effects of alkylating agents, organoplatinums, anthracyclines, taxanes, and radiation."[xlv]

Does it simultaneously diminish the positive effects of treatment? Apparently not. In clinical trials, amifostine significantly reduced cumulative kidney damage associated with cisplatin, without undermining cisplatin's anticancer effects. [xlvi] The FDA approved amifostine because objective response rates, time to progression, and the duration of survival were similar in the amifostine and control study groups.[xlvii]

According to the FDA's meta-analysis, the median progression-free survival was 4.14 months in the amifostine arm and 4.73 months in the control arm. This difference was not statistically significant. The median overall survival was 8.75 months in the amifostine arm and 9.93 months in the control arm. Again, the difference was not statistically significant (FDA n.d.). However, amifostine had a significant effect on nephrotoxicity, which is defined as a 25% or more decrease from baseline in creatinine clearance at the completion of therapy. There was a highly significant reduction in the incidence of nephrotoxicity between the placebo (35%) and amifostine (21%) arms.

In one RCT carried out at Eastern Virginia Medical School, Norfolk, while 24% of the cisplatin-only patients had to discontinue treatment because of toxicity, only 9% of the amifostine-added patients did so – a 267% improvement.[46]

In addition to being approved for reducing toxicity in patients undergoing treatment for advanced ovarian cancer (1995) and non-small cell lung cancer (1996), amifostine was approved for the management of post-irradiation xerostomia (1999). At this writing, there are over 470 PubMed-listed articles referencing amifostine and radiotherapy. In one study, researchers at Thomas Jefferson Hospital, Philadelphia, found that in head and neck cancer patients receiving radiotherapy "the incidence of acute xerostomia was lower than reported previously with no amifostine in a controlled study."[xlviii]

There continues to be a considerable degree of scientific controversy over this issue. "The major concern related to radioprotectors is the potential hazard of collateral tumor protection", wrote Christian N. Andreassen et al in 2003. While the authors point out that

several clinical studies have concluded that amifostine does *not* reduce antitumor efficacy, they nevertheless caution that "not even the largest study conducted, with over 300 patients, has sufficient statistical power to detect a clinically significant reduction in tumor control rate." They concluded: "To put this issue ultimately to a rest, a clinical trial with a sufficient accrual to definitely rule out a tumor protective effect of amifostine needs to be conducted."[xlix]

However, in 2007, Mell et al published a meta-analysis of all the randomized trials utilizing amifostine in locally advanced non-small cell lung cancer patients. This was the most complete rigorous study to date. The authors identified 7 randomized trials involving 601 patients who met the inclusion criteria. Response rate data were available for 6 of the studies, involving 552 patients.

The overall, complete and partial response rates among those who were given amifostine were not significantly different from those who were not. While the authors concede that radiographic response rates are a less than perfect measure of tumor control, and that variations in amifostine dosage and scheduling across studies could have masked the extent of tissue protection, they nonetheless found no evidence of an adverse effect of amifostine on tumor control.[l]

The authors conclude: "Amifostine has no effect on tumor response in patients with locally advanced non-small-cell lung cancer treated with radiotherapy with or without chemotherapy." [50] In another trial, not only did amifostine protect against mucositis and dysphagia, clinical response rates were better. There were complete responses in 90.9% of patients in the amifostine-treated group vs. 78.3% in the controls. Cytoprotection with amifostine was not judged to adversely affect treatment outcome.[li]

Moreover, the authors point out that amifostine's effectiveness as a radioprotectant diminishes at high oxygen tension. Conversely, the effectiveness of radiation is enhanced by higher oxygen tension. Therefore the conditions that favor radiation's cytotoxic effects are precisely those that would simultaneously reduce any tumor protective effect of amifostine.[49]

There are currently at least nine clinical trials in progress utilizing amifostine, and the results of those trials – as well as other potential trials – are still unknown. It would be premature to anticipate that none of these trials might reveal a tumor protective effect for amifostine. However, if the results of previous studies, including the aforementioned Mell meta-analysis of lung cancer trials, hold true, it seems unlikely that amifostine will be shown to actually diminish the efficacy of cytotoxic treatments.

Dexrazoxane

Another exception to the "no antioxidants during cancer treatment" rule is the synthetic antioxidant, dexrazoxane (Zinecard, razoxane, ICRF-187), a derivative of the chelating agent, EDTA. This drug was approved by the FDA as a radioprotectant in 2004, and its concurrent use with radiotherapy is the subject of over 70 PubMed-listed papers.

Dexrazoxane is sometimes given as a cardioprotectant to patients who are also receiving doxorubicin (Adriamycin), a drug which carries a significant risk of cardiotoxicity.

A randomized trial of adjuvant dexrazoxane in patients with soft tissue sarcoma concluded:

> "…[T]he treatment with radiotherapy and [dex]razoxane led to an increased response rate compared to photon irradiation alone (74% vs. 49%). The local control rate was likewise improved…Radiotherapy combined with [dex]razoxane seems to improve the local control in inoperable, residual, or recurrent STS [soft tissue sarcoma, *ed.*] compared to radiotherapy alone."[lii]

A 2007 RCT from the University of Montréal similarly concluded:

> "Dexrazoxane did not have a significant impact on the 5-year EFS [event-free survival, *ed.*] of high-risk patients, and there was no significant difference in outcome....We conclude that …dexrazoxane does not interfere with the antileukemic effect of doxorubicin…"[liii]

Mesna and Radiotherapy

Mesna (sodium 2-mercaptoethane-sulfonate, Mexnex, Uromitexan) is a synthetic antioxidant that was developed as a prophylactic agent to reduce the risk of hemorrhagic cystitis induced by the chemotherapeutic drug, ifosfamide. Mesna disulfide is physiologically reduced to the free thiol compound, mesna, which reacts chemically with ifosfamide metabolites, resulting in their detoxification. Mesna's widespread use has almost eliminated ifosfamide-induced hemorrhagic cystitis and has reduced the drug's nephrotoxicity.[liv] According to its FDA-mandated package label, in multiple human xenograft or rodent tumor models, mesna in combination with ifosfamide has failed to demonstrate any interference with antitumor efficacy.[lv]

Since mesna is sometimes administered in multimodal treatments that include radiotherapy, the issue of its possible interference with radiation has been investigated, although rarely in isolation from concomitantly administered chemotherapy. In 1983 Becher et al did investigate the isolated impact of mesna on radiotherapy in PHA-stimulated lymphocytes *in vitro*. They concluded: "The possibility of a radioprotective effect of mesna could not be supported by the results obtained in this test system."[lvi]

According to Kangarloo et al, mesna "does not significantly influence the pharmacokinetics of cisplatin and carboplatin in pediatric cancer patients."[lvii] In a 1994 randomized trial of chemoradiation (including mesna) vs. radiation alone for locally advanced cervical cancer, there was no significant difference in overall and disease-free survival between the two groups.[lviii] There is no RCT evidence that mesna interferes with the effectiveness of either chemotherapeutic or radiation-containing regimens, or

combinations thereof, and the product insert contains no warning concerning interaction with these modalities.

If synthetic antioxidants such as amifostine, dexrazoxane and mesna interfered with radiotherapy, this should have become apparent over the past decade or more of standard use around the globe. However, the general picture that emerges from clinical experience and more than 3,000 scientific articles on these synthetic antioxidants is one of their safe concurrent usage with chemotherapy, radiotherapy or their combinations. Opponents of the concurrent use of natural antioxidants have a difficult time explaining why non-prescription supplements such as vitamins A, C and E allegedly interfere with radiotherapy, while three powerful synthetic antioxidants do not.

Bairati Study

One study that is frequently cited as evidence that the use of antioxidants with radiotherapy is harmful was carried out by Isabelle Bairati et al of the Université Laval, Québec, and published in 2005 in both the *Journal of Clinical Oncology (JCO*) and the *Journal of the National Cancer Institute (JNCI*).[12,13] Bairati and colleagues set out to determine whether supplementation with antioxidants could reduce the incidence and severity of treatment-related side effects in 540 patients undergoing radiotherapy for head and neck cancers, without reducing the effectiveness of treatment.

The results were mixed. On the one hand, the authors concluded that supplementation with high doses of alpha-tocopherol (vitamin E) and/or beta-carotene significantly mitigated adverse effects of radiation in patients undergoing treatment for head and neck cancer. (There was a 62% reduction in severe adverse effects to the larynx and other anatomical sites in those who were randomized to receive both antioxidants.)

On the other hand, there was also a non-significant trend towards developing second primary cancers during supplementation, which began during radiotherapy and extended for three years afterwards. The rate of local recurrence was also higher in the supplemented group during the period of supplementation, but reverted to normal risk over the ensuing 8 years.[12]

In 2006, Bairati et al published a further analysis showing that during the follow-up period (median 6.5 years), 179 deaths were recorded in both groups. All-cause mortality in the vitamin E group was increased by 38%. Cause-specific mortality rates also tended to be higher in the supplement than the placebo arm. These results, they said, concurred with their earlier reports, suggesting that high-dose vitamin E could be harmful in head-and-neck patients receiving conventional therapy.[14]

The negative findings of this study generated a great deal of adverse publicity for the concurrent use of antioxidants and radiotherapy. Much was made of the fact that patients receiving supplementation in addition to radiation had a higher rate of second primaries and local recurrences while receiving the vitamins.

But, as a close reading of these studies makes clear, patients also had a lower rate of such recurrences and second primaries once the supplementation was discontinued. In fact, by the completion of the study, 8 years after start of radiotherapy, there were *fewer* second primaries or recurrences in the supplementation group compared to those receiving a placebo (113 vs. 119 participants, respectively)[12]. In addition, a majority of supplemented patients were spared the worst adverse effects of treatment. This pointed to a potential strategy for both minimizing adverse effects (by enabling patients to better tolerate the therapeutic dose) while not increasing the long-term recurrence rate. But these mitigating facts were generally downplayed or ignored in a storm of negative publicity that was generated around the Bairati trial, especially after publication of the *JCO* article on the topic.[12]

The Québec authors themselves called for further trials to explore the various effects of antioxidants with radiotherapy:

> "Given the current true uncertainty surrounding these issues among patients, their treating physicians, and in the medical community, randomized controlled trials should be conducted to provide clear scientific evidence regarding the efficacy and safety of antioxidant use as adjuvant therapies for cancer."[12]

One question that needs answering was whether, even temporarily, these two over-the-counter antioxidants actually had the capacity to quench the free radicals generated by radiotherapy. In an accompanying *JCO* editorial, Kevin A. Camphausen, MD, et al of the US National Cancer Institute, and colleagues cast doubt on the widespread notion that supplemental antioxidants could possibly be taken by patients in sufficient quantity or strength to interfere with the primary and secondary free radical species produced by radiation therapy.[lix]

They speculated that, instead, antioxidants might suppress continued free radical production that arises from an inflammatory response following radiation therapy. This could possibly impede anti-tumor activity, they wrote, although it is not known if this inflammatory response does actually occur in tumor tissue.[lx]

Camphausen et al concede that most phytochemical antioxidants, far from being simple scavengers of free radicals, also trigger complicated signal transduction pathways, which may ultimately result in tumor cell death. A few of these pathways, however, may also lead to tumor cell survival. These authors conclude that while patients should avoid what they call "unnecessary supplementation" during and after radiotherapy, using antioxidants to improve the therapeutic index of radiotherapy is a reasonable and commendable goal. Further investigations should be conducted in cancers in which there is an effective salvage therapy, in case second primaries or recurrences do occur.[54] This was a wise recommendation, which left the door open for further research into this complex interaction. For many physicians, however, the takeaway message of Bairati was to avoid concurrent use of supplemental antioxidants during all forms of radiotherapy and chemotherapy.

Conclusions

The preponderance of laboratory and clinical evidence leads to the conclusion that dietary antioxidants do not interfere with the beneficial effects of radiotherapy. It is possible that the judicious use of antioxidants may in fact enhance therapeutic results. There are indications that, post-therapy, selective antioxidants may reverse some of the adverse effects of radiotherapy.

Both chemo- and radiotherapy diminish antioxidant levels. The widespread self-administration of dietary antioxidants by patients can be seen, in this context, as an attempt to correct treatment-induced hypovitaminosis. Admittedly, patients' specific actions in this regard are sometimes poorly informed. But those who complain about patients' use of supplements during radiotherapy have a professional responsibility to inform themselves of the clinical and physiological effect of cytotoxic treatment on antioxidants and to remediate any deficiencies. If they refuse to educate themselves, they can hardly be surprised if patients take it upon themselves – however inexpertly – to correct for the deleterious aspects of conventional treatment.

When oncologists indiscriminately oppose the ingestion of supplemental antioxidants during radiotherapy, they are in effect embracing the notion that the treatment-induced diminution of endogenous antioxidants is an integral part of their proposed treatment strategy. Is iatrogenic hypovitaminosis now to be regarded as a component of standard treatment? By what medical theory can such a strategy be defended? Conversely, if nutritional depletion is *not* part of standard treatment, aren't oncologists then obligated to at the very least replace antioxidants and other nutrients that are lost as a result of aggressive treatment?

If antioxidants can indeed be safely and beneficially administered in various clinical settings, without apparently interfering with cytotoxic treatment, this contradicts the rationale for prohibiting their concurrent use during radiotherapy.

At the 2003 NIH conference on free radicals and antioxidants, it was acknowledged that there was a critical need to use an evidence-based approach for summarizing data, reaching conclusions and drawing up guidelines on antioxidant usage, including further clinical trials to build on existing *in vitro* and preclinical data.

In a similar vein, Block et al have conceded that a lack of adequate statistical power is a consistent limitation of studies in this field. They have made a case for large, well-designed studies of the interaction of antioxidant supplementation with chemotherapy.[8] However, there appears to be little wide-scale interest in doing adequate studies. Clinical trials of the sort recommended at the 2003 NIH conference are not currently mentioned at the National Center for Complementary and Alternative Medicine (NCCAM) Web site.

A search of www.clinicaltrials.gov, using the terms "antioxidants" and "radiotherapy," returns but a single entry, "Safety of Oral Antioxidants and Intravenous Vitamin C

During GYN Cancer Care." The principal investigator on this pilot study is Jeanne Drisko, MD, University of Kansas Medical Center, Wichita, Kansas. But this study involves less than 50 patients, so even a highly positive outcome would be unlikely to change the minds of many oncologists.[lxi]

While the preponderance of data does support the concurrent use of selected dietary antioxidants with radiotherapy, there is a pressing need for professional consensus on this issue. The surest way of attaining such an agreement would be upon the successful completion of well-designed and executed clinical trials. Until such clinical investigations have been carried out, however, both clinicians and patients have little choice but to make difficult treatment decisions based on the existing admittedly scant, and sometimes contradictory, data. The preponderance of that data suggests that antioxidants do *not* conflict with the effectiveness of radiotherapy, and may in fact increase the possibility of a beneficial outcome.

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