Antioxidant Supplementation in Cancer: Potential Interactions with Conventional Chemotherapy and Radiation Therapy

Introduction

The use of supra-dietary doses of chemical antioxidants has attracted increasing interest as a possible primary and secondary cancer prevention strategy. It is possible that some cancer patients have an inherently impaired capacity to contend with oxidative stress because of genetic or environmental factors. Specifically, higher levels of intracellular antioxidants may protect against chromosomal injury induced by UV radiation and xenobiotic induced oxidative stress. Vitamin A and carotenoids, vitamin C, vitamin E, selenium, and glutathione may alone or in combination afford protection. Chemotherapy and radiation therapy result in depletion of tissue antioxidant stores. Antioxidant supplementation may be an important part of recovery from conventional therapy and perhaps have impact on secondary prevention.

However, currently the greatest controversy surrounds the **concomitant** administration of supra-dietary doses of antioxidant agents during chemotherapy and/or radiation therapy. The remainder of this section intends to clarify the major issues surrounding this controversy by reviewing the current state of understanding about potential and established interaction between antioxidants and conventional oncological therapies. Toward this end it is useful to consider four focus questions:

1. Does the co-administration of antioxidants decrease the effectiveness of chemotherapy and radiation therapy?
2. Does the co-administration of antioxidants increase the effectiveness of chemotherapy and radiation therapy?
3. Does the co-administration of antioxidants mitigate some of the side effects of chemotherapy and radiation therapy and improve quality of life?
4. Does the co-administration of antioxidants favorably or unfavorably affect long-term survival rates?

Historical position and rationale of medical and radiation oncologists. Chemotherapy-induced formation of free radicals is well demonstrated most notably with alkylating agents, anthracyclines, epipdophyllotoxins (eg. etoposide and teniposide), and antitumor antibiotics (mitomycin, bleomycin) [1,2]. Therefore, theoretical concerns exist regarding the use of antioxidant vitamins in combination with at least the above-mentioned standard tumor therapeutic agents. The fear is that antioxidant vitamins may protect normal and cancer cells against free radicals that are generated by chemotherapy and radiation therapy. Other agents, not known to generate free radicals, pose less concern. These include hormonal therapy, biological agents, antimetabolites, vinca alkaloids, and taxanes [3].

Historical position and rationale of practitioners of nutritional medicine. Practitioners of nutritional medicine have historically utilized antioxidant dietary supplements concomitant with chemotherapy and radiation. In part the rationale for the use of antioxidants during chemotherapy is based on studies that suggest antioxidant levels are reduced in cancer patients during chemotherapy [4,5]. Additionally, albeit limited in number, all of clinical studies to date investigating the combination of chemotherapy/radiation therapy and antioxidants have demonstrated either beneficial effects or lack of interference.

Chemotherapy and Antioxidants: Evidence Review

Evidence supporting the concomitant use of antioxidants and chemotherapy

In vitro studies:
In a murine neuroblastoma model, administration of vitamin E enhanced antitumor activity of cisplatin in vivo [12]. In vitro studies with neuroblastoma, melanoma and non-small cell lung cancer cell lines have also shown that antioxidants can enhance the antitumor effects of 5-FU, cisplatin, doxorubicin and dacarbazine [13-15]. In vitro, vitamin C is reported to improve the antineoplastic activity of doxorubicin, cisplatin, and paclitaxil in human breast carcinoma cells [16].

The interactions between antioxidants and chemotherapy appear to be more complex than might be predicted solely on the basis of oxidative mechanisms. Antioxidants have been shown to increase cell death by triggering apoptosis. A recent in vitro study demonstrated vitamin E induced apoptosis in colorectal cancer cells, and significantly enhanced tumor growth inhibition by 5-FU and doxorubicin [29]. This stimulation of apoptotic pathways may explain the synergistic effects of chemotherapy and radiation with antioxidant therapy.

Animal studies:
Despite the fact that chemotherapy-induced formation of free radicals is well demonstrated, both in vitro and animal studies have shown that the co-administration of antioxidants did not reduce the antitumor effect of cytostatic agents such as doxorubicicn and cisplatin. Furthermore, the survival of animals co-administered antioxidants was increased compared to the survival of animals that received chemotherapy alone [6-9].

Vitamin E pre-treatment did not interfere with the action of doxorubicin in rats with myeloid leukemia, but it did reduce cardiotoxicity [10]. A combination of vitamins A, C, and E, enhanced antitumor effects of doxorubicin on transplanted tumors in mice [11].

Clinical studies:
In clinical studies, synthetic antioxidants did not alter the antitumor effect of chemotherapy [24-26]. In a randomized trial evaluating 100 breast cancer patients taking cyclophosphamide or doxorubicin, supplementation with vitamin A improved response rate to chemotherapy [27]. A combination of vitamins A (15,000 IU), C (2,000 mg.), E (300IU), beta-carotene (10,000IU), and selenium (800 mcg.) was co-administered with chemotherapy and radiation in an open trail of patients with small cell lung cancer. Two-year survival was greater than historical control [28]. A clinical trial in advanced non-small cell lung cancer randomized 70 patients to receive chemotherapy alone or chemotherapy plus the hormone antioxidant melatonin. The response rate and one year survival was significantly greater in the

melatonin plus chemotherapy cohort [41]. Additionally myelosuppression, neurotoxicity, and cachexia were all reduced in the melatonin treated group.

A good deal of evidence suggests that reactive oxygen species have an important role in certain chemotherapy-induced side effects. Examples include doxorubicin-induced cardiotoxicity, bleomycin-induced pulmonary fibrosis, and cisplatin nephrotoxicity, ototoxicity and neurotoxicity. A recent review of the literature by Weijl et al. reports on numerous in vitro, animal and clinical studies (264 references) demonstrating a reduction in adverse effects from these chemotherapeutic agents with co-administration of various antioxidants [30]. Synthetic antioxidant cytoprotectants are routinely used by oncologists to attentuate the toxicity of chemotherapeutic agents and radiation therapy while preserving the effectiveness of such therapy. Examples include mesna for ifosfamide induced hemorrhagic cystitis, dexrazoxane for adriamycin cardiotoxicity and amifostine for cisplatin nephrotoxicity. These agents have been scrutinized through pre-clinical and clinical testing and found to be safe and efficacious [24-26]. This further lends support to the argument that natural antioxidant supplementation could safely be combined with chemotherapy and radiation therapy.

*Evidence supporting the **avoidance** of antioxidants with chemotherapy*

In vitro studies:

Other in vitro studies, however, have shown a *reduction* in antitumor effect when antioxidants (N-acetylcysteine, selenium, superoxide dismutase and catalase) and iron chelating agents were co-administered with doxorubicin [17]. A similar in vitro effect was shown with vitamin A and doxorubicin [18]. Beta –carotene has been shown to reduce the effect of 5-FU in a murine fibrosarcoma model [19]. Vitamin C enhanced doxorubicin resistance in human breast cancer cell lines [20]. Furthermore, it has been demonstrated that vitamin C reduced the cytotoxic effects of methotrexate and DTIC on neuroblastoma cell lines [40].

Animal studies:

N-acetylcysteine has been shown to reduce the effect of doxoxrubicin in one animal study and reduce the effect of cisplatin in vitro[21,22]. The bioflavinoid tangeretin, has been shown to inhibit the effect of tamoxifen on mammary cancer in a mouse model [23].

Radiation Therapy and Antioxidants: Evidence Review

*Evidence supporting the **concomitant use** of antioxidants and radiation therapy*

Animal studies:

Ionizing radiation generates free radicals that damage DNA. Apoptosis may ensue as a result of radiation-induced cellular damage in normal and tumor cells. Limited studies are available in animals and humans, examining the effect of antioxidants administered during radiation therapy. Vitamin A and beta-carotene co-administered with local radiation, decreased tumor size and increased survival time in mice bearing human breast tumor cell lines, compared to treatment with radiation alone [31]. In mice, vitamin C has demonstrated a radio-sensitizing effect on tumors and a radio-protective effect on normal tissue [33]. The limited animal data on vitamin E suggest that typical therapeutic doses (<1,200 IU)

enhance the effect of radiation therapy while extremely high doses (35,000IU) may have the opposite effect [35].

Clinical Studies:
Vitamin A (cis-retinoic acid) and radiotherapy improved the tumor response rate in a clinical trial of locally advanced cervical cancer compared to historical controls [32]. A randomized human trial of 50 patients evaluated the effect of combined Vitamin C 5gms/day and radiotherapy in different tumor types and noted more complete responses to radiation in the vitamin C group [34]. Radiotherapy co-administered with melatonin 20 mg./day in 30 patients with glioblastoma demonstrated improved survival at one year compared to radiation therapy alone. Fewer radiation- induced side effects were observed in the melatonin treated group [36]. Patients randomized to receive intravenous glutathione (1200 mg.) administered just prior to adjuvant pelvic radiotherapy for endometrial cancer showed a significant reduction in radiation induced diarrhea compared to controls receiving radiation only [37].

Clinical Options Regarding Combining Antioxidants with Chemotherapy or Radiation Therapy

We recognize that randomized controlled trials designed to determine the optimal dose and timing of antioxidants administered during chemotherapy and radiation are desirable. However it is also clear that patients are increasingly self-prescribing antioxidant therapy during chemotherapy and radiation therapy. Several options are presented to help inform treatment decisions. The rationale for each is presented based on available evidence.

Option A: Withhold any antioxidant therapy until all chemotherapy and radiation therapy is completed. As noted in the above discussion, only a limited number of clinical trials have been performed investigating the combination of chemotherapy/radiation therapy and antioxidants. Despite a suggestion of a beneficial effect from these studies, there have been no large randomized long-term clinical trials evaluating the effect of antioxidants administered concomitantly with chemotherapy or radiation therapy. The most conventional approach would therefore be to avoid antioxidant supplementation entirely until chemotherapy and radiation are completed.

Option B: Avoid combining antioxidant therapy only with those chemotherapeutic agents known to induce formation of free radicals, and with radiation therapy. *Alkylating agents*, *antitumor antibiotics*, and *topisomerase II inhibitors* depend on the generation of free radicals for their therapeutic action. *Ionizing radiation* generates free radicals that damage DNA. Therefore, concurrent administration of antioxidants would theoretically, <u>not</u> be advisable for:

<u>Alkylating Agents</u>: Busulfan, Carmustine, Lomustine, Chlorambucil, Cyclophosphamide, Cisplatin, Carboplatin, Ifosamide, Mechlorethamine, Melphalan, Thiotepa, Dacarbazine, Procarbazine
<u>Antitumor Antibiotics</u>: Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, Mitomycin, Mitoxantrone, Plicamycin.
<u>Topoisomerase II inhibitor</u>: Etoposide, Teniposide
<u>Radiation Therapy</u>

On the other hand, certain chemotherapeutic agents are not known to rely on oxidative mechanisms for their effect. Interference with the action of these agents by antioxidants is thus unlikely. These include *hormonal therapy*, *biological agents*, *antimetabolites*, *vinca alkaloids*, *taxanes*, and *topoisomerase II inhibitors***.**

Antimetabolites: Cytarabine, Fludarabine, Fluorouracil, Mercaptopurine, Methotrexate, Thioguanine, Gemcitabine, Hydroxyurea
Mitotic inhibitors: Vincristine, Vinblastine, Vinorelbine
Topoisomerase Inhibitors: Topotecan, Irenotecan
Miscellaneous: Paclitaxel, Docetaxel, Asparaginase

Option C: Antioxidant therapy might safely be considered if administered during a defined period of time so as not to interfere with the biologic activity of chemotherapy and radiation therapy. For chemotherapeutic agents which induce free radical production, the introduction of antioxidants could be timed so as to avoid a critical period defined by the pharmacodynamic properties of the chemotherapeutic agent involved.

Pharmakodynamic Data for Chemotherapeutic Agents on the TJUH Formulary			
Drug	**Onset (days)**	**Nadir (days)**	**Recovery (days)**
Alkylating Agents			
Bulsufan	7-10	14-21	28
Carboplatin	NA*	NA	NA
Carmustine	7-14	21-35	42-56
Chlorambucil	7	14	28
Cisplatin	NA	NA	NA
Cyclophosphamide	7	10-14	21
Ifosfamide	7-14	21-28	21-28
Lomustine	10-14	4-6	6-8
Mechlorethamine	4-7	14	21
Melphalan	7	8-32	42-50
Thiotepa	7-10	14-30	NA
Antibiotics			
Bleomycin	7	14	21
Dactinomycin	7	14-21	21-28
Daunarubicin	7	10-14	21-28
Doxorubicin	7	10-14	21-28
Liposomal Idarubicin	7	10-14	21-28
Mitomycin	21	36	42-56
Mitoxantrone	7-10	14	21
Plicamycin	7-10	14	21
Antimetabolites			
Cytarabine	4-7	14-18	21-28
Floxuridine	NA	NA	NA
Fludarabine	NA	8	5-7 wks
Fluorouracil	7-10	14	21
Mercaptopurine	7-10	14	21
Methotrexate	7	10	21
Thioguanine	7-10	14	21
Mitotic Inhibitors			
Etoposide	10	7-14	21
Vinblastine	4-7	4-10	17
Vincristine	7	10	21
Vinorelbine	4-7	7-10	14-21

Miscellaneous			
Aldesleukin	NA	NA	NA
Azathioprine	NA	NA	NA
Cladribine	NA	NA	NA
Dacarbazine	7	21-25	21-28

*Data not available

Option D: Allow the use of antioxidants concomitant with chemotherapy and radiation therapy. As documented in the preceding discussion, the overwhelming majority of available evidence to date suggests that neither natural or synthetic antioxidants reduce the toxicity of chemotherapy and radiation therapy without interfering with short term cytotoxic effects. However, most of the evidence cited above is either from in vitro or animal studies. Only a limited number of human trials of antioxidant supplementation have been completed in patients with breast and lung cancer [27,28,38,39]. These trials have demonstrated an increase in survival but are limited by their small sample sizes, limited duration, and comparisons based on historical controls.

As to the documented safety of antioxidant supplementation with chemotherapy and radiation therapy, notable exceptions exist. Until further data emerges, these exceptions can be used to alert clinicians and patients to potential adverse interactions between antioxidants and chemotherapy. Based solely on in vitro and animal studies cited above, the following precautions are recommended:

- Avoid high doses of vitamin C with methotrexate and DTIC [40].
- Avoid vitamin A, vitamin C, selenium, and N-acetyl cysteine, with doxorubicin [17,18,20].
- Avoid beta carotene with 5-FU [19].
- Avoid N-acetylcysteine with cisplatin [21,22].
- Avoid citrus bioflavinoid supplements with tamoxifen [23].

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