Interactions of natural health products with biomedical cancer treatments

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ABSTRACT

The use of complementary and alternative medicine (CAM), including the ingestion of natural health products (NHPs), is common among cancer patients. Of concern to clinicians and patients alike is the possibility that CAM, used concurrently with biomedical therapy, may interact poorly with that therapy, especially chemotherapy and radiotherapy. Proponents of NHPs argue that taking such products can help to reduce the side effects of conventional therapy and can provide an additional anticancer effect. However, opponents insist that the potential for harm is too great to warrant the risk of concurrent administration. There are promising examples of specific NHPs that may provide patient benefit even when given in close proximity both to chemotherapy and to radiotherapy, but unfortunately, in part because of a rather limited evidence base, caution is warranted when considering the issue of therapeutic interactions. Strategic application of NHPs before or after conventional therapy may be considered; however, concurrent application should be avoided as a general principle until further evidence is available regarding specific interactions.

KEY WORDS

Complementary medicine, CAM, natural health products, NHPs, chemotherapy, radiotherapy, antioxidants, drug–herb interactions, pharmacology

1. INTRODUCTION

A diagnosis of cancer can generate a great deal of anxiety and often leads people to seek out any and all therapies that they believe may make a difference to their prognosis. Generally speaking, most patients with a cancer diagnosis want optimal care provided within the biomedical model, but they will also often look beyond the conventional options available [1]. Many patients will arrive at a point where they choose to incorporate complementary and alternative medicine (CAM), including natural health products (NHPs), into their care [2]. The choice to use CAM, comprising therapies not provided nor typically supported by the established Western medical system [3], may well also create some anxiety on the part of the attending biomedical health care practitioners. One of the greatest concerns for oncologists, and in many cases for patients as well, is the potential for negative interactions between biomedical cancer therapies and NHPs [4].

Clinician concerns focus on possible detrimental interactions between NHPs and conventional treatments, including surgical resection, radiation therapy, chemotherapy, and increasingly, targeted molecular therapies. Patients with cancer are often subjected to highly invasive therapies with narrow therapeutic windows that need to function as reliably as possible without risk of significant alteration. That said, it is also important to recognize the potential for adjunctive agents, complementary or not, to enhance quality of life, to act as anticancer agents in their own right, and possibly even to enhance the effectiveness of conventional biomedical therapies.

In this paper, we begin by describing ways in which interactions between NHPs and biomedical therapies might occur, with most attention paid to pharmacologically-based interactions. Then, we discuss examples of interaction that are most relevant to clinical practice. Specifically, we focus on how NHPs may affect chemotherapy or radiation therapy.

2. EVIDENCE FROM THE LITERATURE

2.1 Mechanisms of Interaction

The varying abilities to cause both harm and benefit are two characteristics that define the usability and value of any therapeutic intervention. These criteria also provide a foundation for understanding interactions. In pharmacology, whether a drug serves as an over-the-counter painkiller, an anaesthetic, or a chemotherapeutic agent, there exists a concentration level at which the benefit-to-risk ratio is maximized. Agreed-on acceptable limits of this ratio define the therapeutic window of the agent in question. The same basic principle applies in the case of radiotherapy for cancer: too much ionizing radiation causes damage to innocent healthy

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tissue, but too little fails to provide the desired effect. Interactions become relevant when co-administration of two or more therapies results in alteration of either of these parameters—harm or benefit (or, more specifically, toxicity or efficacy).

With respect to drug pharmacology, the two principal ways in which toxicity and efficacy of a drug can be altered are through changes to its pharmacokinetic and pharmacodynamic profiles [5]. The pharmacokinetic profile relates to distribution and elimination of a drug in the body. Alterations to this profile can lead to increased toxicity or lowered efficacy through, respectively, higher retention or higher elimination of the drug. The pharmacodynamic profile relates to the functionality of the drug, and changes here can lead to reduced effect and potentially even to a synergistic and augmented therapeutic effect. Table I provides a summary of both types of pharmacologically-based interactions and how they could result in harm or benefit.

When pharmacokinetic interactions are at play, the culprits most often responsible are metabolic enzymes involved in the body's ability to metabolize and eliminate xenobiotics. Induction or inhibition of these enzymes can lead to altered expression levels and activity. The enzymes most commonly associated with this process include the liver-active cytochrome P450s and, to a lesser degree, the uridine diphosphate glucuonosyltransferases also involved in detoxification [6]. In addition, the proper functioning of elimination organs, including the liver and kidneys, needs to be considered in relation to a compound's pharmacokinetics.

The issue of pharmacodynamic interactions arises in cases in which a drug's effect may be altered by the interaction. Two obvious possibilities come up: the drug becomes more toxic, or the drug's effect is attenuated. The latter situation has been of most concern and has raised red flags in situations in which antioxidants are taken concurrently with either chemotherapy or radiotherapy [7]. Both of these biomedical therapies rely, in part, on their ability to cause oxidative damage to the replicative machinery of cancer cells, and antioxidants might conceivably interfere with this therapeutic process. The argument is a rational one, but the evidence to date indicates that this concern may be overstated. In fact, in some cases, benefits—including a synergistic augmentation of therapeutic effect—can be achieved [5,8,9].

For example, the potential to use CAM to reduce chemotherapy- or radiation-induced toxicity to healthy tissue without concomitant reductions in anticancer activity have been demonstrated in animal models with green tea, selenium, and curcumin [5]. Evidence is limited, but some clinical data in humans indicates the same possible effect using melatonin concurrently with conventional biomedical therapy [10]. Given that the evidence in this area is still in its infancy, it is probably best to continue to treat these combinations with caution.

2.2 NHPs and Chemotherapy

Natural health products that induce or inhibit the CYP450 enzyme system or that affect the efflux proteins can lead to subtherapeutic or toxic levels of chemotherapeutic agents. St. John's wort is one of the best known and well-studied herbs found to be responsible for pharmacokinetic interactions. When St. John's wort was used in combination with irinotecan, plasma levels of SN-38, the active metabolite of irinotecan,

TABLE I Ways in which harmful interactions and beneficial interactions might occur from co-administration of chemotherapy with biologically based complementary therapies

Pharmacologic effect	*Harmful interactions*		*Beneficial interactions*	
	Effectiveness	*Toxicity*	*Effectiveness*	*Toxicity*
Kinetic	Lowered, because of a higher rate of elimination	Raised, because of a lower rate of elimination	In theory, a potential to reduce costs is available if judicious co-administration of natural health products with chemotherapy leads to reduced drug use by increasing retention time.	
	Lowered, because of a higher rate of metabolite deactivation	Raised, because of a higher rate of conversion from prodrug to active metabolite		
Dynamic	Lowered, because of an antagonistic interference—that is, antioxidant quenching	Theoretically raised, because of an additive increase in drug toxicity to normal tissue; unlikely (no examples seen in literature)	Raised, because of synergistic and cancer-specific cytotoxicity	Lowered, because of protection of normal healthy tissue
	Lowered, because of an upregulation of phosphoglycolate phosphatase (PgP) and other drug efflux proteins		Raised, because of downregulation of PgP and other drug efflux proteins	Lowered, because of improved function of organs of elimination

decreased by 42% [11]. Healthy subjects taking imatinib with St. John's wort showed a 43% greater imatinib clearance, with up to a 32% lower mean area under the concentration curve [12]. Greater docetaxel metabolism can also be expected in patients chronically using St. John's wort [13]. Other NHPs shown to inhibit CYP enzymes include: garlic [14], *Ginkgo biloba* [14,15], kava [14], ginseng [16], *Echinacea purpurea* [15], milk thistle (silybin) [17,18], and evening primrose oil (*cis*-linoleic acid) [14].

Another way in which NHPs may modulate chemotherapeutic effect is through alterations in the functional activity of cellular efflux proteins. One of the main identified efflux proteins is P-glycoprotein, which has been found to be inhibited by specific compounds derived from NHPs including curcuminoids, ginsenosides, piperine, green tea catechins, quercetin, and silymarin [19–22].

Although opponents hold that any risk of pharmacokinetic modulation is too high, proponents argue that co-administration of antioxidants may in fact provide benefit when given concurrently with chemotherapy. A proposed model of benefit from antioxidant use alongside chemotherapy is reasoned as follows: Oxidative stress interferes with many cellular functions, such as cell cycle progression and apoptotic pathways, so that the ability of anti-neoplastic agents to kill cancer cells is reduced. The effects are mediated, most likely, by the many aldehydes that result from oxidative stress–induced lipid peroxidation. During cancer chemotherapy, oxidative stress–induced lipid peroxidation generates numerous electrophilic aldehydes that can attack many cellular targets. These products of oxidative stress can slow the cell-cycle progression of cancer cells and cause cell-cycle checkpoint arrest. The aldehydes may also inhibit drug-induced apoptosis by inactivating death receptors and inhibiting caspase activity. These effects also diminish the efficacy of the treatment.

The use of antioxidants during chemotherapy may enhance therapy by reducing the generation of oxidative stress–induced aldehydes. In this model, the antioxidant's ability to quench aldehydes would actually improve or accelerate the cytotoxic effects of oxidative chemotherapies, thereby improving their efficacy. All antioxidants cannot be viewed as equal when evaluating their potential impact on cancer chemotherapy, and the individual antioxidants cannot be anticipated to have the same effect on the activity of all chemotherapeutic agents. The chemotherapy agents that generate high levels of reactive oxygen species include anthracyclines, alkylating agents, platinum coordination complexes, epipodophyllotoxins, and camptothecins. The anthracyclines generate by far the highest levels of oxidative stress; in contrast, taxanes (for example, paclitaxel and docetaxel), vinca alkaloids (for example, vincristine and vinblastine), antimetabolites such as the antifolates, and the nucleoside and nucleotide analogues generate only low levels of oxidative stress [23–25].

In vitro and *in vivo* data suggest that certain antioxidants selectively inhibit the growth of tumour cells, may induce cellular differentiation, and may alter the intracellular redox state, thereby enhancing the effects of cytotoxic therapy [26]. Observed effects of dietary antioxidants in cancer include decreased carcinogen formation, DNA mutation, cell proliferation, and metastasis [27]; however, a number of variables make it difficult to clearly extrapolate these findings to clinical practice. These variables include a lack of methodologic rigor in clinical studies, limited clinical endpoints, and uncertainties as to antioxidant dosing regimens, including treatment timing, duration, and dosage considerations [27]. Several studies report modestly diminished treatment-related side effects with concurrent administration of both dietary and pharmaceutical antioxidants during cytotoxic regimens [28–33].

Ladas *et al*. conducted a systematic review of trials and observational studies published between July 2000 and January 2002 to investigate the effect of conventional chemotherapy with or without radiation on antioxidant status, the effect of antioxidant status on treatment-related toxicities and event-free survival, the effect of antioxidant supplementation in combination with conventional chemotherapy with or without radiation on antioxidant status, and the effect of antioxidant supplementation on treatment-related toxicities and event-free survival [26]. This review of observational studies of the effects of chemotherapy on antioxidant levels supports the hypothesis that chemotherapy lowers total antioxidant status; however, that outcome was assessed only in a limited number of studies. An explanation for the lack of consistent change in antioxidant status after chemotherapy treatment may be that some patients were depleted of antioxidants before initiation of treatment. These observations suggest that low antioxidant status may be associated with neoplastic activity and subsequent poor health, supporting the idea that antioxidant supplementation could benefit cancer patients. However, the published studies assessed in the review did not provide evidence that individual antioxidant vitamin supplements reduce the toxicity associated with anticancer therapy. The authors proposed that either antioxidants do not reduce toxicity or that more potent antioxidants or higher doses of individual antioxidants may be needed to minimize the side effects of anticancer therapy.

Another issue that arises is the timing of antioxidant supplementation. Timing is important to consider because supplementation may need to be introduced early, before cumulative doses can lead to physiologically therapeutic levels [26].

Simone *et al*. reviewed two medical databases from 1965 to November 2003 to examine the effects of antioxidants and other nutrients used during chemotherapy or radiation therapy (or both). These authors found that, since the 1970s, 280 peer-reviewed *in vitro* and *in vivo* studies, including fifty human studies involving 8521 patients, 5081 of whom were given

nutrients, consistently demonstrated that non-prescription antioxidants and other nutrients did not interfere with standard therapeutic cancer treatments. Of the fifty human studies, forty-seven indicated that nutrients reduce the side effects of treatment, and the other three studies showed no difference. In addition, many of the studies reported that nutrients produce higher response rates and higher survival rates when administered concomitantly with chemotherapy and radiation therapy [34,35].

A critique of the review found that, of the sixteen controlled trials in the review, ten randomized fewer than 50 patients, reflecting a sample size that was too small to provide confidence in the findings of equivalent survival. Of the six randomized trials with 50 patients or more, only one tested an antioxidant [27].

Lawenda *et al.* reviewed sixteen randomized clinical trials that studied the concurrent use of antioxidant supplements and chemotherapy, six of which included a placebo control. Although no decrements in tumour response rates or survival rates were observed in the studies that reported response data, the studies were not powered to evaluate these endpoints, and the conclusions may have reflected the authors' biases [27].

2.3 NHPs and Radiation Therapy

A number of randomized controlled clinical trials have investigated the possible radio-modifying effects of concurrent administration of antioxidants on normal tissues and tumours [27]. Bairati *et al.* randomized 540 head-and-neck cancer patients to receive either α-tocopherol (with or without β-carotene) or placebo, concurrent with radiation therapy; the result was a 38% reduction in severe acute side effects with treatment. However, the rate of local recurrence of the head-and-neck tumours tended to be higher in the supplement arm of the trial [32,36]. A follow-up study by Bairati *et al.* showed a significantly poorer overall survival in patients receiving antioxidants [37]. However, in a subgroup analysis of the second study, the negative interaction between antioxidant supplementation was only found in patients who smoked during radiation therapy [38]. The combination of radiotherapy, smoking, and supplementation was associated with an increase in both disease recurrence and in cancer-specific mortality. It should be noted that no increase in either of these outcome measures was observed for the non-smokers [38].

Several other studies provide evidence that antioxidants can reduce the effectiveness of chemotherapy or radiation therapy. Ferreira *et al.* randomized 54 patients undergoing radiation therapy for head-and-neck cancers to receive a concurrent oil-based oral rinse containing either vitamin E or placebo before and after each daily dose of radiation. Vitamin E supplementation was associated with a 36% reduction in symptomatic mucositis, but the 2-year overall survival with treatment was 32% as compared with 63% for the placebo [33]. This trend could have been confounded by the greater percentage of stage III and IV tumours found in the former group.

Lesperance *et al.* investigated 90 patients with nonmetastatic breast cancer receiving either conventional treatment (surgery, chemotherapy, radiation therapy, hormonal therapy) alone or the same treatment combined with high doses of one or more of β-carotene, vitamin C, niacin, selenium, coenzyme Q10, and zinc. Breast cancer–specific survival and disease-free survival were shorter in the nutrient-supplemented cohort, although the difference between the supplement and non-supplement arms was of only borderline significance [39].

Lissoni *et al.* tested melatonin in brain glioblastomas and found that radiotherapy combined with α-tocopherol or melatonin supplementation increased survival [40]. However, the implication of tumour-specific radiosensitization was not confirmed by Berk *et al.* in a randomized trial of radiation therapy and high-dose melatonin in brain metastases [27,41].

3. DISCUSSION

With respect to radiation therapy, reductions in treatment-related side effects appear possible with NHP use; however, of much greater concern is the evidence for reduced effectiveness of radiation therapy when combined with antioxidant NHPs. In considering chemotherapy, the evidence indicates greater potential for benefit through the inclusion of NHPs, but this conclusion is still highly controversial. Given the limited evidence and continued potential for negative interactions of antioxidants with the pharmacodynamic properties of chemotherapeutic agents, concomitant administration cannot be recommended in good conscience.

In a paper detailing similar issues of interaction with respect to pediatric cancer and chemotherapy, we propose a strategy of "approach" to avoid interactions based on the elimination half-lives of both chemotherapy and NHPs [5]. Essentially, if a potential interaction is suspected, the strategy requires stopping administration of the NHP within 3–5 half-lives before the start of chemotherapy and restarting the NHP only after 3–5 half-lives of the chemotherapy have elapsed. Passage of at least 3 elimination half-lives ensures that more than 80% of the compound or compounds are gone from the system, thereby greatly reducing the chance of pharmacodynamic interaction. In the case of radiotherapy, the same basic principle can be applied, the key difference being that radiation acts within a very short period, thus allowing the rapid use of NHPs following radiotherapy if desired.

The idea behind this strategy is essentially to create windows of time wherein no interactions between CAM and conventional therapies are likely. These windows may then allow the use of NHPs between rounds of biomedical therapies, thus addressing more of a patient's need and desire to use CAM without risking

potentially negative interactions. However, determining such windows is not necessarily easy; it requires knowledge of the product's pharmacokinetics and potential to interact pharmacodynamically with either chemotherapy or radiotherapy.

4. CONCLUSIONS

The evidence to support the use of NHPs during chemotherapy and radiotherapy is conflicting and unfortunately provides little basis for strong recommendations. One positive goal of combining therapies is the achievement of reduced toxicity to normal tissue without losing any anticancer efficacy. There appears to be some basis for this kind of synergism, especially in chemotherapy; however, the lack of clinical evidence warrants caution. The first principle in medicine, *primum non nocere*, does not allow the conscientious application of some NHPs with biomedical therapy, especially in cases in which the biomedical therapies have proven to be effective. Until further research provides clearer answers, creating a buffer zone and recommending that patients avoid NHPs *at least* for a few days before either chemotherapy or radiotherapy and after chemotherapy remains the safest course of action.

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