Nutritional Supplements and Docetaxel: Avoid or Combine?

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One of the main concerns that oncologists have in the use of complementary and alternative medicine (CAM) is the possibility of the negative interactions of nutritional supplements with chemotherapy, causing reduced effectiveness of the cancer treatment. The purpose of this study was to search commonly used databases and look for actual research data (in vitro, in vivo, or human studies) that document any interactions (positive or negative) of nutritional supplements with docetaxel, a commonly used chemotherapeutic drug. The search revealed 24 articles that document interaction with docetaxel and certain nutritional supplements such as L-glutamine, fish oil, vitamin D, garlic, black cohosh, and others. Twenty-two of the studies documented some benefit in the combined use in terms of improving the apoptotic and cytotoxic effects of docetaxel on the tumors as well as reducting the toxicity and side effects involved in the use of docetaxel. From the current search, it seems as if more evidence supports the combined use of certain nutritional supplements with docetaxel in terms of beneficial effects. On the other hand, one needs to be cautious as well as certain supplements can have a negative effect, such as reducing the effectiveness of the drug. There is a dire need to further evaluate the negative and positive interactions of nutritional supplements and chemotherapeutic drugs.

Key words: *alternative medicine, cancer care, complementary medicine, docetaxel, herb–drug interaction, integrative medicine, integrative oncology, medicinal herbs, nutritional supplements*

The National Center of Complementary and Alternative Medicine (http://nccam.nih.gov/health/whatiscam) defines "complementary and alternative medicine" (CAM) as a group of diverse medical and health care systems, practices, and products that are not generally considered to be part of conventional medicine. Recently, the use of CAM has increased considerably in the United States, and CAM is now being used for a variety of purposes, from back pain to adjuvant in cancer therapy.[1] The 2008 National Health Statistics report estimated that almost 4 of 10 adults (38.3%) used some type of CAM in the previous 12 months.[1] Nutritional supplements were the most frequently used CAM modalities (18% of those who used some kind of CAM), followed by deep-breathing exercises (13%).[1] CAM is increasingly being used by cancer patients in conjunction with their cancer therapy. Estimating the number of cancer patients who use CAM is difficult because studies show varied results. Reported CAM use ranges from 30% in some studies to 83% in others, averaging around 50%, which is much higher than CAM use in the general population.[2,3] Use of CAM also varies by the type of cancer, with the highest use among breast cancer patients (approximately 86%),[4] followed by patients with brain tumors (approximately 30%).[5] The majority of cancer patients who use CAM do so to boost their immune systems. CAM is also used to improve patients' quality of life, avert treatment drugs' side effects, improve cancer-related symptoms, and prevent cancer recurrence; CAM is also used for its direct anticancer effects.[6] It is also believed to be beneficial in helping patients cope with pain, distress, negative emotions, and anxiety.

More and more patients are combining CAM with their conventional medications, but the majority do not discuss CAM use with their physicians. It is estimated that 38 to 60% of cancer patients participate in CAM practices without informing their attending physicians.[2] A recent survey revealed that 36 to 64% of physicians estimated that less than 25% of their patients used CAM, whereas 34% of the patients said they did so.[7] Many physicians admit they are concerned about the pharmacodynamic interactions between prescribed treatment drugs and supplements that patients use. This is highlighted by a study in which 84% of attending physicians thought they needed to learn more about CAM to sufficiently address patients' concerns.[8] Another study showed that 24% of primary care physicians never referred patients to complementary medicine physicians, 69% did so occasionally, and 70% admitted they had little or no knowledge of herbal

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DOI 10.2310/7200.2009.0027

remedies.[9] Physicians are understandably worried about the safety of their patients and thus do not recommend any CAM therapies about which they are not very sure.

The lack of knowledge about CAM among conventional physicians is compounded by uncertainty about how CAM therapies and conventional chemotherapies interact. Some authorities have expressed concern about the use of CAM with chemotherapy because of the potential risk for negative interactions between the two. Thus, many attending physicians are limited in their ability to effectively treat their patients not only because they are unaware of the possible interactions between conventional drugs and the dietary supplements used in CAM but also because they are unaware of their patients' CAM use because patients are hesitant to discuss CAM with their attending physicians.[10,11] Data on the potential interactions between the majority of the herbal supplements and chemotherapeutic drugs have been inconsistent. Numerous recommendations have been deduced theoretically on the basis of the potential influence of herbs on the metabolism of the drugs, which affects the drug's pharmacokinetic and pharmacodynamic properties. Herbs can alter all aspects of a drug's pharmacokinetics, including absorption (by altering the absorption rate), distribution (by causing protein-binding displacement), metabolism (by affecting the CYP enzymes), and excretion.[12] The most important and widely accepted interaction is the alteration of a drug's metabolism by affecting the CYP enzymes.[13,14] This class of enzymes is responsible for the metabolism of drugs in the human body, so any increase or decrease in activity may lead to failure of the therapy or increased toxicity.

Most clinicians raise a concern about the potential interaction that herbs might have with conventional drugs. Garlic, a common dietary supplement, has been said to affect several CYP enzymes (CYP2C9, CYP2C19, CYP3A4, CYP3A5, and CYP3A7) and thus may interfere with the action of various drugs that are also metabolized along the CYP pathway, such as docetaxel, etoposide, imatinib mesylate, irinotecan, and paclitaxel, and may cause partial metabolism of other drugs, such as cyclophosphamide, ifosfamide, tamoxifen, vinblastine, and vincristine.[15] The same concern is present for other herbs, including *Echinacea angustifolia*, ginkgo, ginseng, grapeseed, grapefruit juice and peel, and soy, which are also thought to affect the CYP3A4 enzyme and thus might affect the metabolism of these chemotherapy drugs.[12] Because of this, more caution is necessary when considering the combination of these herbs and drugs. Likewise, Sparreboom and colleagues have expressed concern over combining chemotherapy drugs, especially taxanes, with certain herbs, such as echinacea, St. John's wort, kava, and grapeseed.[12]

We chose to focus on one chemotherapeutic drug, docetaxel, which is commonly used for breast cancer, ovarian cancer, lung cancer, and other malignancies. In this study, we searched for evidence of interactions between docetaxel and nutritional supplements. We looked for either positive or negative interactions. We felt that searching the interactions with this commonly used chemotherapeutic drug as an example could help in clarifying the combined use of nutritional supplements and chemotherapy in terms of harm or benefit.

Methods

Databases

In February 2009, investigators at The University of Texas M. D. Anderson Cancer Center in Houston, Texas, conducted a systematic search in eight electronic databases for data about possible interactions between docetaxel and nutritional supplements and herbs. The databases searched were *SCOPUS* (Elsevier; 1880 to February 20, 2009), *Medline* (Ovid, PubMed, National Institutes of Health; 1966 to February 22, 2009), *Natural Medicine Comprehensive Database* (www.naturaldatabse.com; February 22, 2009), *Herb and Nutrient Drug Interactions* (searched on February 22, 2009), *CINAHL* (1982 to February 22, 2009), *Natural and Alternative Treatments* (1997 to February 23, 2009), *Natural Standard* (searched on February 23, 2009), and *Cancer LIT* (1975 to February 24, 2009).

Data Collection and Analysis

Investigators searched for studies that addressed the issue of nutritional supplement interaction with docetaxel using the search terms as mentioned previously.

The studies were then categorized based on the study type (in vitro, in vivo, or human trial) and outcome (beneficial or adverse effects). Based on these categories, we performed analysis of all of the data to compare the potential interactions suggested by each study's authors with the actual data from all studies. We also compared the supplements that had shown positive interactions with those that had shown negative interactions.

Results

The search for various interactions of docetaxel with CAM therapies yielded 24 relevant studies. Of these, 13 were in vitro studies, 1 was based on an animal model, and 10 were human trials (randomized control trial, case report, nonrandomized trial) (Table 1). In the process of this search, additional articles were found that mainly discussed the possible theoretical

interactions between various supplements and docetaxel; these results are outlined in Table 2. The main findings are summarized in Table 3, which summarizes all of the studies that actually documented positive or negative interactions of nutritional supplements with docetaxel. Twenty-two of the 24 studies showed beneficial effects of supplements combined with docetaxel, whereas only two studies showed adverse effects. Of the 22 studies showing benefits, 11 were in vitro and 11 were in vivo (1 animal, 10 human). Both studies that found adverse effects were in vitro studies.

We found seven nutritional supplements (fish oil, β-carotene, β-elemene, fatty acids, black cohosh, St. John's wort, and garlic) for which only in vitro studies were done. In these studies, most of the beneficial effects were proposed to be due to potentiating the cytotoxic and apoptotic effects of docetaxel. The only herb that had a negative effect was St. John's wort, which appeared to induce the metabolism of docetaxel and potentially reduce the drug to subtherapeutic levels in humans.

Table 1. Studies of Supplement–Drug Interactions ($n = 24$)

Type of Study	n
In vitro studies	13
Animal models	1
Human trials	10
Case reports	2
Nonrandomized controlled trials	3
Randomized controlled trials	2
Case control study	1
Phase II clinical trials	2

Table 2. Theoretical Interactions of Complementary and Alternative Medicine with Docetaxel

Herb/Supplement	*Mechanism Proposed*	*Recommendation*
St. John's wort[24,25]	Induces cytochrome CYP3A4, thus affecting metabolism of drug and decreasing its efficacy	Avoid
Grapefruit[24]	Can inhibit CYP3A4 metabolism of drugs, causing increased drug levels and potentially increasing the risk of adverse effects	Avoid
Garlic[24]	Affects cytochrome CYP3A4 isoenzymes; some garlic preparations contain allicin, which appears to induce activity of CYP3A4	Avoid
Feverfew[25]	Might inhibit cytochrome CYP3A4 enzyme	Potential benefit
Glutamine[24]	Might alter the pharmacokinetics of chemotherapeutic drugs or reduce effectiveness by enhancing tumor growth	Avoid

Table 3. Interactions Found by Research Studies

Herb/Supplement	*Mechanism Proposed*	*Recommendation*
Vitamin B_6[26–28]	Helps reduce hand-foot syndrome (cutaneous reaction) caused by docetaxel in human trials	Potential benefit
L-Glutamine[19–21]	Helps reduce oral mucositis and nerve damage caused by docetaxel in human trials	Potential benefit
γ-Linolenic acid (fatty acids)[29]	Potentiates the cytotoxic action of docetaxel in in vitro study	Potential benefit
Fish oil[30,31]	Potentiates the cytotoxicity and apoptosis caused by docetaxel in vitro studies	Potential benefit
Vitamin D[16,32–36]	Potentiates the cytotoxic effects of docetaxel in animal and human trials	Potential benefit
β-Elemene (Chinese herb, Zedoary)[37]	Potentiates the cytotoxic effects of docetaxel in in vitro study	Potential benefit
β-Carotene (vitamin A)[38–42]	Potentiates the cytotoxic effects of docetaxel in in vitro studies	Potential benefit
Black cohosh[43]	Potentiates the cytotoxic effects of docetaxel in in vitro study	Potential benefit
Garlic[44]	Increases the apoptotic effects of docetaxel	Potential benefit
St. John's wort[45]	Induces the metabolism of docetaxel	Avoid

The human trials included only three supplements (L-glutamine, vitamin B_6, and vitamin D), in which all had the beneficial effect of reducing the toxicity and side effects associated with this drug, such as hand-foot syndrome, oral mucositis, and nerve damage.

Discussion

The findings in this study suggest that the majority of potentially harmful interactions that have been suggested in theoretical discussions were not supported by much research evidence. On the contrary, most scientific studies have found beneficial effects of combining docetaxel with nutritional supplements. Many of these beneficial interactions were found only in in vitro studies; for instance, fatty acids seemed to potentiate the cytotoxicity of docetaxel.[16] No in vivo studies have been done specifically to test these beneficial interactions, so the in vitro results may not be very relevant in terms of practical applications to humans. There is a need to further establish the usefulness of supplements through in vivo studies. On the other hand, other nutritional supplements have shown beneficial effects in human studies. For example, vitamin B_6 reduces the occurrence of hand-foot syndrome caused by docetaxel, L-glutamine reduces the incidence of oral mucositis, and vitamin D potentiates the cytotoxicity of docetaxel.

Although many nutritional supplements, such as garlic, St. John's wort, and echinacea, are thought to have negative effects on chemotherapy drugs, only two studies found evidence of negative interactions between docetaxel and nutritional supplements. Both studies on which these negative assumptions are based have been in vitro studies, with the results generalized to humans. It must be kept in mind that all in vitro results may not be relevant in vivo because of numerous variations and differences in the environments. There has been a concern about garlic uses with drugs metabolized through CYP3A4 enzymes, including docetaxel, but our search retrieved only two studies of garlic interacting with docetaxel. First, one found that garlic did not affect pharmacokinetics (ie, drug clearance). This study of women with metastatic breast cancer showed that the pharmacokinetics of docetaxel was not significantly changed when patients took garlic supplements; thus, garlic supplementation did not have much effect on enzyme induction in these patients.[17] Second, garlic proved to be beneficial to hormone-refractory prostate cancer cells, in which it was observed that garlic extract may promote docetaxel-induced cell death by promoting cell cycle arrest at the G_2/M phase and apoptosis.[18] This implies a potential role for garlic in improving docetaxel-based treatment of hormone-refractory prostate cancer. The same effect was seen with L-glutamine, which has been proposed to interact with docetaxel and decreases some of the side effects of this drug.[19–21] Human trials for the management of nerve damage and hand-foot syndrome (one of the major side effects of docetaxel) also found that L-glutamine proved to be beneficial in patients with oral mucositis, peripheral nerve damage, and hand-foot syndrome, thus establishing the utility of L-glutamine use with this drug.[19–21]

There has also been concern over the use of grapefruit, echinacea, and feverfew with docetaxel, but our search found no relevant studies that showed such interactions. It is of concern that recommendations have been made and are being followed without relevant research having been conducted. One in vitro study showed some interaction between St. John's wort and docetaxel.[22] In this study, hepatocytes isolated from human donors were first exposed to hyperforin (an active constituent in St. John's wort) and later to docetaxel. It was found that hyperforin induced the metabolism of the drug, thus reducing the drug's efficacy. However, this study used much higher concentrations of both St. John's wort and docetaxel than can be achieved in cancer patients treated with both drugs. Also, the negative interaction was seen only when hepatocyte cell cultures were exposed to St. John's wort for a long time and at very high concentration levels. Thus, the result of this in vitro study might not be very relevant in vivo. Realistic in vivo studies are therefore needed.

Another concern has been the increased use of black cohosh in women diagnosed with breast cancer when starting chemotherapy and/or radiotherapy. Black cohosh is thought to be beneficial in treating menopausal symptoms but was found to increase the cytotoxicity of docetaxel.[23] It is unclear whether this is a beneficial or adverse side effect because this study did not look for increased toxicity in this combination. Thus, it is not clear whether black cohosh might be useful by permitting a decrease in the concentration of the drug needed for patients or harmful by increasing the drug's toxicity.

From the current search, it seems as if more evidence supports the combined use of certain nutritional supplements with docetaxel in terms of beneficial effects, such as improving cytotoxic effects and reducing the side effects of the drug. On the other hand, one needs to be cautious as well as certain supplements can have a negative effect, such as reducing the effectiveness of the drug. Therefore, further studies and evaluation of the negative and positive interactions of nutritional supplements and chemotherapeutic drugs are needed to clarify this complicated issue.

Acknowledgment

Financial disclosure of authors and reviewers: None reported.

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