A Pilot Study of Website Information Regarding Aromatase Inhibitors: Dietary Supplement Interactions

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Abstract

Objectives: Patients who have hormone receptor–positive breast cancer and who are taking aromatase inhibitors (AIs) should understand the benefits and risks of concomitant dietary supplement (DS) use. The International Society for Integrative Oncology (SIO) encourages patients to discuss DS use with their health care practitioners. The objective was to conduct a pilot study rating Internet websites from the perspective of health care practitioners for information about AI–DS interactions.

Design: Five (5) Internet websites suggested by SIO were evaluated using the DISCERN instrument rating tool. The available AI–DS information on these websites was rated by 4 evaluators: 2 naturopathic doctors, 1 oncology pharmacy resident, and a pharmacy student.

Results: The overall rankings ranged from 1.6 to 3.9, with considerable variability in the type of information available from the websites. The interevaluator rankings of the websites ranged from 0.44 to 0.89. The evaluators consistently found the most reliable, unbiased, and comprehensive information on AI–DS interactions at the Natural Medicines Comprehensive Database and Memorial Sloan-Kettering Cancer Center websites. However, more than one database was needed for provision of optimal patient information on AI–DS interactions.

Conclusions: In order to effectively advise patients regarding AI–DS interactions, more than one website should be evaluated to assess the potential efficacy and safety of DS in women whose breast cancer is being treated with an AI.

Introduction

THE MAJORITY (i.e., 69%–78%) of patients with cancer receiving cytotoxic chemotherapy report concomitant dietary supplement (DS) use.^{1–3} Despite the concern regarding adverse drug–DS interactions,^{4–7} there is a paucity of data regarding the actual health risk experienced from adverse chemotherapy–DS interactions during cancer care.^{1,2,8} Open communication is essential for quality patient care, as our previous study observed that most (>85%) patients who are receiving chemotherapy while also taking DS would discontinue their DS or ask their medical oncologist for advice if a detrimental chemotherapy–DS interaction was suspected.¹

Among patients with cancer, those with breast cancer report the highest frequency of DS use.^{9,10} Patients with hormone-receptor–positive breast cancer have the risk for DS interactions not only with cytotoxic chemotherapy, but also

with endocrine therapy such as tamoxifen and the third-generation aromatase inhibitors (AIs). The AIs are increasingly being used instead of tamoxifen, with the duration of AI therapy ranging from 5 to 10 years.^{11,12} Although the potential for interactions between tamoxifen and DS have been analyzed,^{13–15} the differences in the mechanism of action and pharmacokinetic profiles of the AIs compared to tamoxifen suggest the need for data specific to AI–DS interactions.

Patients who have cancer use DS for various reasons, among them to improve their quality of life (QOL) and to improve their tolerance of chemotherapy.^{1,2,16} Postmenopausal women receiving endocrine therapy can experience treatment-related toxicities that negatively impact health-related QOL and adherence to treatment. Nonadherence rates range from 25% to 55% in patients with breast cancer, with nonadherence being primarily due to drug toxicity.^{16,17} Common toxicities to the AIs include musculoskeletal

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TABLE 1. COMMON TOXICITIES OF AROMATASE INHIBITORS

Toxicity	Incidence of toxicity by specific AI		
	Anastrozole ²⁰	Exemestane ²¹	Letrozole ²²
Arthralgias/myalgias	13% arthralgia 2%–6% myalgia	14.6%–28.8% arthralgia 5.5% myalgia	8%–22% arthralgia 6.4%–6.7% myalgia
Depression	Up to 13%	6.2%–13%	12%
Headache	13%–18%	6.9%–13.1%	20%–30%
Hot flashes	12%–35%	13%–32.9%	5%–49.7%
Insomnia	Up to 9%	11%–13.7%	5–7%
Nausea	10%–20%	8.5%–18%	8%–17%
Osteoporosis	7%–10%	4.6%	2%–6.9%

AI, aromatase inhibitor.

symptoms such as arthralgias and myalgias, depression, headache, hot flashes/hot sweats, insomnia, nausea, and osteoporosis (Table 1).^{18–22} Of particular concern are the musculoskeletal events (i.e., arthralgias/myalgias), which occur in 5% to over 40% of patients taking AIs.²³ The optimal methods to prevent and/or treat these toxicities have yet to be identified. It is imperative that health care practitioners assist patients to mitigate toxicities common to AI use, such that the patients adhere to their AI regimen with the long-term goal of preventing a breast cancer relapse and maintaining or improving QOL.

In the context of frequent DS use by patients with breast cancer, it is critical to identify which DSs may be safely used while also recognizing which DSs may have life-threatening toxicities themselves and/or have a detrimental interaction with an AI.^{4,5} Practitioners must become well versed in this topic to better counsel their patients. Patients have reported that their most frequent primary sources of DS information are a friend or family member, while a naturopathic doctor was the most frequent information source who has educational training about DS.^{1,2}

Given the common use of DSs, all health care practitioners must be increasingly prepared for appropriately advising patients who have breast cancer and who are taking AIs about the potential benefit and risks of DS use. Notably, the International Society for Integrative Oncology (SIO) website encourages patients to ask clinicians about information regarding drug–DS interactions, and SIO guidelines recognize that clinicians have a key role in counseling patients taking AIs regarding the potential benefits and risks of integrating DS.²⁴ Additionally, the guidelines recommend that patients' DS use be evaluated prior to the start of cancer treatment to assess the appropriateness of continued use during treatment.²⁵ The SIO provided Integrative Oncology Practice Guidelines in 2007 and 2009 stating, "It is recommended that dietary supplements, including botanicals and megadoses of vitamins and minerals, be evaluated for side effects and potential interaction with other drugs. Those that are likely to interact with other drugs, including chemotherapeutic agents, should not be used concurrently with immunotherapy, chemotherapy or radiation or prior to surgery" (Table 2). Therefore, a pilot study was conducted utilizing the DISCERN instrument to evaluate some of the available websites from the perspective of the health care practitioner advising patients regarding DS use concomitant (i.e., at the same time) with AI.

Materials and Methods

Websites evaluated

The SIO is an international organization established to encourage scientific evaluation, dissemination of evidence-based information, and appropriate clinical integration of complementary and alternative medicine (CAM) for patients with cancer. Per the 2007 guidelines, the SIO recommends seven websites for evidence-based resources: the American Botanical Council, Cochrane Review Organization, M.D. Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center (MSKCC), National Cancer Institute's Office of Cancer Complementary and Alternative Medicine, Natural Medicines Comprehensive Database (NMCD), and Natural Standard. Those databases that are readily available to all the evaluators (i.e., all but the American Botanical Council and Natural Standard) were assessed using DISCERN. Of note, some websites, such as the NMCD, require a fee for access and thus may not be readily available to patients or practitioners.

The SIO's practice guidelines for clinicians and researchers categorize CAM into five categories: biologically based therapies (e.g., vitamins, DS, and herbal remedies); mind-body therapies (e.g., meditation); manipulative and body-based practices (e.g., massage and reflexology); energy therapies (e.g., *Reiki* or *qigong*); and ancient medical systems (e.g., Traditional Chinese Medicine).²⁶ SIO recommendations are then graded into six categories ranging from 1A to 2C based on the strength of available evidence. The SIO guidelines' recommendations specifically relevant to this study are summarized in Table 2. The authors incorporated SIO's four recommendations pertaining to biologically based therapies akin to DS, listed by strength of recommendation from strongest to weakest, into the assessment of DS recommendations from websites for completeness, accuracy, and support for these guidelines.

Evaluation questions

The aim of the current study was to evaluate and rate the websites using the DISCERN instrument, from the perspective of the health care practitioner providing information to a patient who has breast cancer and who is concomitantly using an AI and DS. A series of 10 questions (Table 3) were developed to address clinically relevant issues about potential AI–DS interactions. The questions were developed by 3

TABLE 2. GRADING RECOMMENDATIONS FROM SIO REGARDING INTEGRATIVE ONCOLOGY, INCLUDING DIETARY SUPPLEMENTS²⁵

Grade	Description of recommendation	Benefits vs. risks/burdens	Strength of evidence and implications
1A	Strong recommendation with high-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	RCTs without important limitations and overwhelming evidence from observational studies. Data can apply to most patients in most circumstances without reservation.
1B	Strong recommendation with moderate-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodology flaws, indirect or imprecise); exceptionally strong evidence from observational studies.
1C	Strong recommendation with low- or very-low-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa	Observational studies or case series; recommendation may change if better evidence available.
2A	Weak recommendation with high-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations; overwhelming evidence from observational studies. Best practice may depend on circumstances or patient's or societal values.
2B	Weak recommendation with moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise); or exceptionally strong evidence from observational studies
2C	Weak recommendation with low- or very-low-quality evidence	Uncertainty in estimates of benefits, risk, or burdens; may be closely balanced	Observational studies or case series. Very weak recommendation; other alternatives may be equally reasonable.

SIO, International Society for Integrative Oncology; RCTs, randomized, controlled trials.

oncology pharmacists, with review by 2 naturopathic doctors. Question 1 focused upon DS contraindicated in patients with breast cancer. The second question evaluated DS that may affect the efficacy and/or toxicity of AIs in patients with breast cancer. Four (4) questions focused upon potential DS toxicities, specifically their acknowledged and/or theoretical

risks (question 9) and the potential for detrimental AI-DS interactions. Regarding the potential detrimental AI-DS interactions, question 3 focused upon pharmacokinetic interactions, which are interactions where the DS could change the systemic exposure to the AIs, and questions 4, 5, and 10 focused upon pharmacodynamic interactions where the DS could change the effect of the AIs. Questions 6–8 sought to identify DS that could alleviate common toxicities to the AIs, which are listed in Table 1.

TABLE 3. CONTENT QUESTIONS REGARDING AROMATASE INHIBITOR (AI)–DIETARY SUPPLEMENT (DS) INTERACTION QUESTIONS EVALUATED USING DISCERN

1. Does the website identify DS that are contraindicated in breast cancer patients?
2. Does the website specifically address DS that could affect the efficacy and/or toxicity of AI in patients with breast cancer?
3. Does the website address the pharmacokinetic interactions, specifically if the DS affects how the body absorbs and breaks down the AIs?
4. Does the website identify DS that possess estrogenic and/or progesterone effects?
5. Does the website identify DS that possess anti-estrogen and/or anti-progesterone qualities?
6. Does the website identify any DS that alleviate hot flashes?
7. Does the website identify any DS that improve bone health?
8. Does the website identify any DS that improve arthralgias (i.e., joint and/or musculoskeletal pain)?
9. Does the website describe the risks of the DS?
10. Does the website describe if the DS affects plasma concentrations of hormones used to assess menopause (e.g., follicle-stimulating hormone, luteinizing hormone, estradiol)?

Website quality rating

The websites were evaluated using DISCERN rankings after completion of the 10 content questions. DISCERN was designed to be used by health consumers and does not require previous knowledge of the research topic. The DISCERN instrument is a validated rating tool that is freely available online (www.discrim.org.uk) and can be used by health consumers and professionals alike.²⁷ A downloadable instruction handbook is available from the DISCERN website. A series of 15 questions (Table 4) are asked about the website's content, and the user responds to each question on a scale of 1–5, with a higher score being more favorable. Each evaluator independently completed a 10×16 cell matrix to analyze each website given the 10 content questions (Table 3) and 16 DISCERN-related questions (i.e., 15 questions plus an overall rating, which are listed in Table 4).

Using DISCERN, each website was evaluated on a scale of 1–5, assessing the clarity of and support available for information available on the websites. A rating of 5 was given if the quality criterion had been completely fulfilled. Ratings between 2 and 4 were given if the information offered by the websites met the criterion in question to some extent; this partial rating depends largely on the evaluator's judgment. A

TABLE 4. MEDIAN OF EVALUATOR'S RANKING OF DISCERN QUESTIONS (1=Low, 5=High) FOR EACH WEBSITE

	Cochrane	MedlinePlus	MSKCC	NCCAM	NMCD
1. Are the aims clear?	4.2	2.6	4.4	3.5	3.7
2. Does it achieve its aims?	4.2	2.4	4.9	3.4	4.4
3. Is it relevant?	3.0	3.5	4.9	4.1	4.8
4. What sources of information were used?	5.0	4.7	5.0	3.9	5.0
5. When was the information published?	4.9	4.8	5.0	4.8	5.0
6. Is it balanced and unbiased?	4.9	4.1	5.0	3.7	4.9
7. Were additional sources of information provided?	3.8	4.4	4.9	4.8	4.5
8. Does it refer to areas of uncertainty?	3.2	3.7	4.5	3.8	4.7
9. Does it describe how each treatment worked?	2.5	2.9	4.9	2.1	4.8
10. Does it describe the benefits of treatment?	3.5	3.0	4.6	3.4	4.7
11. Does it describe the risks of treatment?	3.2	4.0	5.0	3.5	4.9
12. Does it describe what could happen if no treatment is used?	1.5	1.0	1.0	1.0	1.4
13. Does it describe how treatment affects quality of life?	1.0	1.0	2.0	1.4	1.6
14. Is it clear there is more than one treatment choice?	1.8	2.2	2.8	2.4	2.9
15. Does it describe support for shared decision-making?	2.0	2.7	3.4	3.3	2.3
16. Overall ranking of website	2.4	2.9	3.9	1.6	3.1

MSKCC, Memorial Sloan-Kettering Cancer Center; NCCAM, National Center for Complementary and Alternative Medicine; NMCD, Natural Medicines Comprehensive Database.

rating of 1 was given if the criterion of the question was not fulfilled at all. A total score provided an overall rating of the available websites. Quality review of the websites was based on their ability to answer the drug interaction questions listed in Table 3. In the absence of science-based standards on DS use, the pharmacist and naturopaths reviewed content of each database by evaluating cited references and assessing the accuracy of information presented. Erroneous information was recorded and described.

Each website was graded by 4 independent evaluators. Two (2) evaluators were naturopathic doctors (ESS and KMT) who had expert knowledge in DS, 1 evaluator was a pharmacy student well versed in the use of DISCERN (CLM), and the other evaluator was a pharmacist who at the time was an oncology pharmacy resident (AAH). All evaluators reviewed all five websites.

Statistical methods

Descriptive statistics were used to analyze the data. The interevaluator variability was measured by the Spearman

correlation coefficient (r). Microsoft Excel (Redmond, WA) was used in the analysis.

Results

Table 4 contains the median ranking for each DISCERN question by website. The overall ranking of each website—calculated by calculating the median of the rankings of the 15 DISCERN questions—is also included. The overall rankings ranged from 1.6 to 3.9. MSKCC and NMCD had the highest ranked websites at 3.9 and 3.1, respectively. Overall, the evaluators found that all websites were evaluated highly as they showed sources of information, information publication dates, and were felt to be fair and/or unbiased. Conversely, all websites had lower evaluation rankings (ranging from 1.0 to 2.0) for not listing QOL information or what might happen if no treatment was used.

A median of the rankings by each DISCERN question varied considerably, as shown in Table 4. The interevaluator rankings of the websites were evaluated by Spearman correlation coefficient of each website, providing 27 correlation

FIG. 1. Interevaluator rankings of website for information about AI-DS interactions: Highest (A) and lowest (B).

coefficients that were closely correlated. The rankings by the naturopathic doctors and the pharmacy-trained evaluators were similar (Fig. 1).

Discussion

The AIs are self-administered daily for 5–10 years^{11,12} and therefore, patient adherence to AIs is critical. The amelioration of toxicities to AIs—potentially via DS—is likely to be of interest to patients with breast cancer; however, the optimal methods to prevent and/or treat these toxicities have yet to be identified.^{16,17} The use of DS should be assessed individually for each patient to allow for the best possible short-term (i.e., mitigation of toxicities, improved adherence to AIs, improved QOL) and long-term clinical outcomes (i.e., remission and secondary prevention). This is an important step in recognizing the therapeutic potential of DS use and acknowledging the importance that patients with cancer place on the value of integrative oncology. Although the potential for interactions between tamoxifen and DS have been analyzed,^{13–15} the differences in the mechanism of action and pharmacokinetic profiles of the AIs compared to tamoxifen suggest that data specific to AI–DS interactions is needed. There is a paucity of data regarding AI–DS interactions, and we sought to identify websites that provide information regarding this difficult clinical scenario. NMCD and MSKCC had the highest-ranked websites (Table 4). In addition to the findings in this study, others have noted that NMCD on a personal digital assistant had the highest scope, completeness, and composite score compared to other DS personal digital assistant tools.²⁸ Faubert et al. found that the NMCD and the Natural Standard Database identified a similar number of potential medication–DS interactions.²⁹

SIO guidelines acknowledge that only a few complementary therapies have been evaluated with randomized controlled clinical trials. This has left a knowledge gap between the currently available scientific evidence and the information needed to provide evidence-based advice.²⁵ Given this knowledge gap, the authors sought to identify which SIO-supported websites would be best to rapidly identify clinical issues regarding AI–DS interactions.

A study limitation is restricting the number of websites to those mentioned by the 2007 SIO guidelines. Although it is recognized that other websites provide information related to integrative oncology,³⁰ this study focused upon the information needs of the health care provider rather than those of the patient. This focus was chosen to best facilitate health care practitioners counseling patients taking AIs about DS. The data from this pilot study suggest that there is heterogeneity in the information available upon each website, suggesting that at least two websites should be evaluated. However, evaluations with more websites are needed to confirm these findings.

One strength of this study is the inclusion of naturopaths to aid in this study's evaluation, because naturopaths seek to teach their patients to use diet, exercise, lifestyle changes, and natural therapies to enhance their bodies' ability to ward off and combat disease.³¹ Naturopaths have training in patient counseling, nutrition, acupuncture, homeopathy, botanical medicine, and medical training.³² However, naturopaths are licensed in a limited number of states and are not readily accessible to many patients with cancer.

Boddy et al. have identified good quality information sources, also using DISCERN, about integrative oncology for health care providers and their patients while observing the quality variation in online resources for integrative oncology.³⁰ The Cochrane and PubMed databases plus the MSKCC and National Center for Complementary and Alternative Medicine websites were included within their summary. Simulating the perspective of a patient or their family member seeking information about CAM, Brauer et al. evaluated websites from 41 National Cancer Institute–designated cancer centers using a 4-point Likert scale.³³ This evaluation regarding CAM information noted considerable variability in the quality and ease of navigation of these websites, with 20% of cancer centers not having functional websites. In this pilot study, variability was also observed in the information provided by the evaluated websites. Therefore, at least two websites should be evaluated for AI–DS interactions.

A challenge that continues to face integrative oncology is the scarcity of data regarding the actual health risk from drug–DS interactions.^{1,2,8} With the prevalent use of DS in patients with breast cancer, it is important to emphasize that many of the drug–DS interactions are theoretical ones rather than interactions observed in clinical studies as noted by Frenkel and Gupta.³⁴ The recent SIO guidelines clearly state that “all patients with cancer should receive guidance about the advantages and limitations of complementary therapies in an open, evidence-based, and patient centered manner by a qualified professional. Patients should be fully informed of the treatment approach, the nature of the specific therapies, potential risks/benefits, and realistic expectations” (Recommendation 2, grade of recommendation 1C). This pilot study focused upon evaluating websites identifying the advantages and limitations of DS that are a component of complementary therapies.

Given the heterogeneity of information on websites as shown from the authors' pilot study, health care practitioners may encounter problems accurately following Recommendation 2 of the 2009 SIO guidelines until more data are available regarding the potential benefits and risks of AI–DS use. Nevertheless, health care practitioners must advise patients with the limited data currently available, consulting multiple websites to optimally advise patients. There are numerous issues that arise when considering potential AI–DS interactions, as summarized in Table 3. First, the DS that may be of most interest to patients taking AIs should be identified based on those DSs that may ameliorate the most common toxicities to the AIs, as summarized in Table 1. For example, because nausea is a common AI toxicity while urticaria is not, a patient taking an AI may seek a DS that alleviates nausea more often than one that relieves urticaria. Subsequently, because the actual risk is not known currently, the theoretical risk of AI–DS interactions should be assessed to identify those DSs with a low likelihood of interacting with AIs. As with drug–drug interactions, AI–DS interactions can occur because the DS changes how an AI moves throughout the body or it is broken down in the body (Question 3 of Table 3). These are termed pharmacokinetic interactions, or basically that the DS changes what the body does to the AI. Unfortunately, it is not known whether changing the plasma AI concentrations changes the efficacy or toxicity of the AIs and thus, the potential importance of pharmacokinetic interactions with AIs cannot be estimated at

this current time point. The DS could also change how well the AI works, which is termed a pharmacodynamic interaction (Questions 4, 5, and 10 of Table 3). However, it should be clearly noted that effectiveness and the toxicities of concomitant AI-DS use are difficult to estimate because of the lack of published clinical trials of concomitant AI-DS use.

A variety of DSs may ameliorate the toxicities to the AIs, with the current data suggesting a low likelihood for an adverse AI-DS interaction. Below there is a summary of some of the DSs with more well-characterized toxicity profiles. The arthralgias/myalgias due to the AIs may be prevented and/or treated by the amino acid glutamine based on case reports in patients treated with the taxanes.³⁵ Early *in vitro* data indicated that cancer cells preferably consume glutamine, which led to concern regarding its use. Kuhn et al. recently completed a comprehensive review of both preclinical and clinical data and concluded that exogenous glutamine supply is safe and can beneficially contribute to diminish risks of high-dose chemotherapy and radiation.³⁶ Headaches due to the AIs may be ameliorated by the free-radical scavenger coenzyme Q10. Co-enzyme Q10 has antioxidant activity and membrane-stabilizing properties that may help to protect against and repair DNA damage caused by free radicals.³⁷ In their systematic review, Roffe et al. concluded that further investigations are necessary to determine whether coenzyme Q10 can improve the tolerability of cancer treatments. A more recent study suggests that coenzyme Q10, in combination with riboflavin and niacin (the CoRN regimen), can be safely administered with tamoxifen,³⁸ although no data could be found with concomitant AI use. The potential for AI-induced osteopenia may be decreased by calcium and vitamin D supplements. Calcium is recommended as a preventative supplement against osteoporosis by the American Society of Clinical Oncology and the National Comprehensive Cancer Network and is not expected to interact with the AIs.³⁹ Vitamin D may be recommended in conjunction with calcium for the prevention of osteoporosis in patients taking AIs. There is debate regarding vitamin D dosing, but notably daily doses over 10,000 international units (IUs) daily may have greater toxicity.⁴⁰ No potential pharmacokinetic or pharmacodynamic interaction could be identified between AIs and calcium or vitamin D. The examples of glutamine, coenzyme Q10, calcium, and vitamin D demonstrate that DS may potentially decrease the toxicities of the AIs with no apparent mechanism for a pharmacokinetic or pharmacodynamic interaction, although further information is needed.

It is critical that health care professionals question patients who have breast cancer and who are taking AIs regarding their use of complementary therapies and be receptive when patients disclose their use.²⁵ These questions can lead to open communication regarding the patient's expectations and experience with integrative medicine. It is particularly important to assess the support received by the patient from their family, community, and friends, because patients with cancer usually rely on information sources other than health care professionals to learn about DS.² Open communication is a critical aspect of optimally advising patients regarding AI-DS interactions. Further studies are needed to identify the optimal websites for information regarding integrative oncology not only for health care practitioners, as evaluated in the pilot study reported here, but also for the lay public.

Conclusions

Critically evaluated websites have the potential to offer health care practitioners updated and evidence-based information to counsel patients taking AIs in conjunction with DS. The NMCD and MSKCC most consistently provide reliable information regarding the concomitant use of AI-DS.

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