Understanding the interaction between food and treatment

What, how much, and when patients eat, as well as dietary supplement use, can have a significant impact on the efficacy of cancer therapy.

St. John's wort flowers and pills

© SANTJE / SHUTTERSTOCK

BRYANT FURLOW

Eating habits can change dramatically for cancer patients. Loss of appetite; the effects of treatment on digestion; changing nutritional demands; the timing of meals relative to administration of medications; and dietary supplements taken by patients as folk remedies or to treat the symptoms of cancer and side effects of chemotherapy or radiation treatments all play important roles in patients' dietary shifts. Cancer can trigger cachexia and malnutrition, compounded or hastened by nausea, vomiting, anorexia, or constipation.

An often-neglected facet of the diet-cancer treatment equation is food-treatment interaction, or the impact dietary practices can have on the efficacy of chemotherapy or radiation therapy. Drugs can affect nutritional states, but foods can also significantly modulate the bioavailability and absorption time profiles of chemotherapeutic drugs, potentially in ways that could reduce the efficacy of the medications (**Table 1**). Interactions may be driven by the chemistry of the food, beverage, or dietary supplement on a drug's bioavailability; increased or, more frequently, decreased metabolic rates after meals; reduced digestive tract pH soon after meals; and the effects of food fats on drug absorption in the digestive tract (**Table 2**). The effects of patients' dietary practices on drug absorption and efficacy have been proposed as one explanation for the wide variation in toxicity and treatment outcomes experienced by cancer patients.[1]

Continued on page 30

DRUG INTERACTIONS WITH FOOD AND MEALS

Food and drug chemistry, timing and composition of meals, and meal size can all affect drug bioavailability. Recent meals can interfere with the bioavailability of oral chemotherapy drugs, such as lapatinib (used to treat metastatic breast cancer or other solid tumors) or nilotinib (used to treat chronic myeloid leukemia [CML]).

The fat content of food eaten may magnify the impact of a meal on absorption times and absorbed doses of these drugs.[2,3] High-fat food may slow the absorption time of nilotinib in patients with CML by as much as 50%. Nilotinib should be taken on a minimum 2-hour fast only, and the patient should fast for 1 hour after taking the drug.[3] Taking oral chemotherapy drugs with soft drinks or fruit juices, particularly acidic grapefruit or orange juice, can alter stomach and intestinal pH and transporter protein activity in the digestive tract, potentially increasing or decreasing the drug's absorption rate.[4] Many chemotherapeutic drugs have narrow windows between absorption of therapeutic levels and minimum toxic doses and may therefore be particularly affected by some dietary practices.[1]

TABLE 1. Dietary interactions of selected cancer drugs

Drug	Dietary interaction
Bexarotene	Grapefruit juice may increase absorption, toxicity
Methotrexate	Alcohol may amplify liver damage
Plicamycin	Calcium and vitamin D supplements may impair absorption
Procarbazine	• Alcohol may cause toxic interaction • Caffeine may raise BP
Temozolomide	Meals decrease and delay absorption

Data from US National Cancer Institute. www.cancer.gov/cancertopics/pdq/supportive-care/nutrition/Patient/page6#Section_92. Accessed July 18, 2010.

TABLE 2. General food-drug interactions[4]

Accelerated drug absorption
Decreased drug absorption
Delayed drug absorption
Increased drug absorption
Neutral (no interaction)
Toxic interaction

Much of the recent literature on the interactions of diet and dietary supplement use with cancer treatment is anecdotal. Studies are typically based on findings among small numbers of patients, and proposed food-drug interactions are frequently based on preclinical laboratory findings rather than clinical studies.[5] Conclusions about clinical implications are therefore rarely without controversy.

> Antioxidant supplements may well be counterproductive for cancer patients, possibly protecting tumor cells from molecular damage.

A recent search of the medical literature identified no meta-analyses on specific food-cancer drug interactions, and no systematic framework exists for predicting food-drug interactions. The best nurses can do for their patients is to identify associations between specific drugs and foods or supplements, or between drugs and the timing of meals. Communicating food-drug interactions to patients may be even more critical for the elderly than for younger patients because aging processes also alter drug absorption profiles, increasing the risk of insufficient dosing or overdosing.[4]

Many claims in the popular media regarding anticancer diets and dietary or diet-supplement cancer cures are extremely speculative and poorly supported by empirical evidence. Curative claims for diets should not be confused with diets intended to improve cancer patients' nutritional status and comfort during treatment; the latter can make a significant contribution toward improved quality of life for patients (**Table 3**).

POPULAR DIETARY SUPPLEMENTS

Unproven diets and dietary supplements, such as garlic, mistletoe, Essiac, Lingzhi, St. John's wort, and astragalus, are popular among cancer patients.[6] For example, a recent survey in the United Kingdom found that 22% of patients with newly-diagnosed cancer used herbal supplements.[7] These supplements are frequently self-administered by patients in the hope of controlling tumor growth or to reduce the toxic side effects of prescribed chemotherapies.[6]

Although some dietary supplements, such as cod liver oil or fish oil, appear to be associated with reduced cancer risk

TABLE 3. Cookbooks and dietary guides

Betty Crocker's Living with Cancer Cookbook: Easy Recipes and Tips through Treatment and Beyond New York, NY: Hungry Minds Inc; 2001 ($24.95)
Eating Well Through Cancer: Easy Recipes and Recommendations During and After Treatment Nashville, TN: Favorite Recipes Press; 2006 ($24.95)
The Cancer Lifeline Cookbook: Recipes, Ideas and Advice to Optimize the Lives of People Living with Cancer, 2nd ed Seattle, WA: Sasquatch Books; 2004 ($19.95)
What to Eat During Cancer Treatment: 100 Great-tasting, Family-friendly Recipes to Help You Cope Atlanta, GA: American Cancer Society; 2009 ($19.95)

and improved quality of life (eg, improved depression), available empiric evidence of the benefits of most supplements remains very weak. Sadly, clinical research suggests some supplements can interfere with chemotherapy (**Table 4**). St. John's wort reduces the concentration and bioavailability of the chemotherapeutic metabolite of irinotecan (SN-38) by 42% and imatinib by 32%.[6]

Antioxidant supplements remain controversial; widely used for their reported anticancer properties, they may actually be counterproductive for cancer patients, possibly protecting tumor cells from molecular damage from radiation therapy and chemotherapy.[8] Vitamin C (ascorbic acid) is an antioxidant that has been tied to reduced clinical activity of the antimyeloma drug bortezomib in a human xenograft mouse model of myeloma, prompting a recent recommendation that vitamin C supplements be avoided during bortezomib therapy.[9]

COMMUNICATION IS KEY

A lack of knowledge about patient dietary practices makes patient education and communication crucial to improving the probability of successful treatment. Without doctors or nurses telling them about potential adverse food-drug interactions, many patients would simply not know about the issue's importance. Similarly, unless they are directly asked, patients may not volunteer information about their use of herbs that can interfere with their medically prescribed treatments.[10] Many, perhaps most, labels on herbal remedies fail to include warnings about adverse interactions with medications.[10] Communicating known adverse interactions and the importance of carefully timing treatment and meals can be crucially important, as is directly asking patients about their use of herbs, such as St. John's wort.

Even when epidemiologic associations between diet and cancer treatment outcomes are identified and reach statistical significance, the biological mechanisms underlying such associations frequently remain unclear and cannot be easily conveyed to patients. For example, a higher intake of red meat, fats, and refined grains may increase the risk of recurrence and mortality in patients with a diagnosis of advanced colon cancer, compared with a diet high in fruits, vegetables, poultry, and fish.[11] But it is not known whether the association is due to impaired treatment efficacy, continuing colon exposure to dietary carcinogens, or other factors. High-fat Western dietary patterns are associated with increased insulin levels, for example, and insulin may hasten incipient tumor growth; however, what, if any, role this potential mechanism plays in the reported association between high-fat diets and colon tumor recurrence is not clear.[11] Nevertheless, patients should be told even when only limited evidence suggests a possibly harmful drug-dietary interaction.

FOOD-DRUG INTERACTIONS

One way that foods, juices, and dietary supplements can modulate the bioavailability of chemotherapy drugs appears to be through inhibition or activation of P-glycoproteins in the gut.[1] These transporter proteins play an important role in absorption of anticancer drugs, and their activity appears to be alterable by dietary factors.[1]

St. John's wort (*Hypericum perforatum*) should be avoided during chemotherapy. St. John's wort herbal supplements are widely used among cancer patients as a preventive or remedy for depression. But as described earlier, the supplement can markedly reduce plasma concentrations of irinotecan's active metabolite and imatinib.[6] Both findings suggest that St. John's wort may result in reduced chemotherapeutic dosing and ineffective treatment. The effects of St. John's wort on imatinib may be sufficient to reduce plasma concentrations below the minimum therapeutic dose concentration (for a standard 400-mg dose).[12] Laboratory studies of human liver

> Even when associations between diet and treatment outcomes are known, the underlying mechanisms cannot be easily conveyed to patients.

The clinical implications of laboratory studies on the interaction between dietary garlic and chemotherapy drugs are still far from clear.

cells suggest docetaxel metabolism may be hastened among cancer patients who regularly consume the herb.[12]

Fruit juices, especially grapefruit juice, can significantly modulate the metabolism and bioavailability of several drugs, including hypertension and hypercholesterolemia drugs, immunosuppressant drugs used to reduce organ rejection in transplant patients, and cancer chemotherapy drugs. This interaction may be related to stomach pH or the physiologic effects of the juice in the intestinal epithelia. Grapefruit juice markedly reduces the peak concentration of oral nilotinib, a tyrosine kinase inhibitor used to treat imatinib-resistant Philadelphia chromosome-positive chronic myeloid leukemia.[3] Grapefruit juice reduces oral etoposide concentrations and bioavailability by 48%.[12]

Green tea (*Camellia sinesis*) contains polyphenols, catechins, flavonols, and flavonoids that exhibit antioxidant properties. It may be consumed as a traditional drink or as a dietary supplement in pill or capsule form. Because the main catechin in green tea, epigallocatechin-3-gallate, and green tea polyphenols are proteasome inhibitors that block antitumor activity of other proteasome inhibitors through competitive interference, the antitumor efficacy of bortezomib could be reduced by regular green tea consumption.[12] Green tea should be discouraged among patients undergoing bortezomib therapy even though no clinical study has established an interaction between green tea and chemotherapy drugs.

Garlic (*Allium sativum*) is widely used as a folk remedy for hypertension, atherosclerosis, and cancer. Garlic may also change docetaxel clearance in breast cancer patients, though this finding is preliminary.[6] Docetaxel is metabolized by CYP enzymes modulated by chemicals from garlic, particularly allicin.[12] Laboratory and animal studies suggest both inhibition and activation of these enzymes. Garlic has been shown to alter the interaction between two antiretroviral drugs affected by CYP enzymes.[12] However, the clinical implications of laboratory studies on the interaction between dietary garlic and chemotherapy drugs are far from clear.

Docetaxel is metabolized by the enzyme CYP3A4, and drug clearance has been found to be progressively slower through time in the presence of garlic allicin, although the trend has not reached statistical significance in available studies.[12] Clinical data suggest garlic may inhibit docetaxel metabolism in some patients, but clinical results have been inconsistent.[12] Until more is known, patients should be discouraged from using it during cancer chemotherapy.

Ginkgo biloba is a folk remedy used by some cancer patients for memory loss and dementia. Patients undergoing radiation and chemotherapy frequently experience neuropathies and impaired cognitive performance. Drug interactions between ginkgo and blood thinners have been identified. However, the metabolic pathways and enzyme interactions of ginkgo-derived chemicals in the gut are not known. Laboratory and animal studies suggest gingko chemicals can both activate and inhibit CYP enzymes involved in drug metabolism, leading some authors to suggest that clinically relevant drug interactions are possible or likely.[12] Laboratory animal studies suggest gingko alters the metabolism for heart drugs, asthma and emphysema drugs, and psychiatric drugs, such as alprazolam.[12] Human studies have been inconsistent, however, and the effects of ginkgo on chemotherapy drug metabolism is unknown. Caution dictates that until more is known, it should not be used by cancer patients undergoing chemotherapy.

Fish and fish oil consumption are associated with lower rates of several cancers. Many fish are rich in anti-inflammatory omega-3 fatty acids and docosahexaenoic acid, both of which have been tied epidemiologically to a reduced risk of numerous

TABLE 4. Interactions of dietary supplements

Supplement	Interaction
Ascorbic acid (vitamin C)	Reduces bioactivity of bortezomib (in animal studies)
Black cohosh	• Increases absorption and toxicity of tamoxifen • May lower blood lipids
Echinacea	May interfere with immune system-based anticancer therapies
Garlic	May increase bleeding when used with blood thinners (aspirin, dipyridamole, or warfarin)
Ginkgo biloba	May increase bleeding when used with blood thinners (aspirin, dipyradamole, or warfarin)
St. John's wort	• May cause toxicity with antidepressants • May reduce absorption of anticancer drugs (irinotecan and imatinib)

Data from US National Cancer Institute. www.cancer.gov/cancertopics/pdq/supportive-care/nutrition/Patient/page6#Section_92. Accessed July 18, 2010.

cancers. The fatty acids in fish oil may have an influence on the effectiveness of chemotherapy drugs; however, no human clinical trials have confirmed any suggestive findings from animal and in vitro laboratory studies.[13] ■

Bryant Furlow is a medical writer in Albuquerque, New Mexico.

DRUGS MENTIONED

Alprazolam (Niravam, Xanax, generics)
Bortezomib (Velcade)
Docetaxel (Taxotere)
Etoposide (VePesid, generics)
Imatinib (Gleevec)
Irinotecan (Camptosar, generics)
Lapatinib (Tykerb)
Nilotinib (Tasigna)

REFERENCES

1. Marchetti S, Mazzanti R, Beinjnen JH, Schellens JH. Concise review: Clinical relevance of drug drug and herb drug interactions mediated by the ABC transporter ABCB1 (MDR1, P-glycoprotein). *Oncologist*. 2007;12(8):927-941.
2. Koch KM, Reddy NJ, Cohen RB, et al. Effects of food on the relative bioavailability of lapatinib in cancer patients. *J Clin Oncol*. 2009;27(8):1191-1196.
3. Tanaka C, Yin OP, Sethuraman V, et al. Clinical pharmacokinetics of the BCR-ABL tyrosine kinase inhibitor nilotinib. *Clin Pharmacol Ther*. 2010;87(2):197-203.
4. Singh BN. Effects of food on clinical pharmacokinetics. *Clin Pharmacokinet*. 1999;37(3):213-255.
5. Bar-Sela G, Epelbaum R, Schaffer M. Curcumin as an anti-cancer agent: review of the gap between basic and clinical applications. *Curr Med Chem*. 2010;17(3):190-197.
6. Yang AK, He SM, Liu L, et al. Herbal interactions with anticancer drugs: mechanistic and clinical considerations. *Curr Med Chem*. 2010; 17(16):1635-1678.
7. Corner J, Yardley J, Maher EJ, et al. Patterns of complementary and alternative medicine use among patients undergoing cancer treatment. *Eur J Cancer Care (Engl)*. 2009;18(3):271-279.
8. Lawenda BD, Kelly KM, Ladas EJ, et al. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? *J Natl Cancer Inst*. 2008;100(11):773-783.
9. Perrone G, Hideshima T, Ikeda H, et al. Ascorbic acid inhibits antitumor activity of bortezomib in vivo. *Leukemia*. 2009;23(9):1679-1686.
10. Clauson KA, Santamarina ML, Rutledge JC. Clinically relevant safety issues associated with St. John's wort product labels. *BMC Complement Altern Med*. 2008;8:42.
11. Meyerhardt JA, Niedzwiecki D, Hollis D, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. *JAMA*. 2007;298(7):754-764.
12. Meirjerman I, Beijnen JH, Schellens JH. Herb-drug interactions in oncology: focus on mechanisms of induction. *Oncologist*. 2006;11(7):742-752.
13. Shaikh IA, Brown I, Wahle KW, Heys SD. Enhancing cytotoxic therapies for breast and prostate cancers with polyunsaturated fatty acids. *Nutr Cancer*. 2010;62(3):284-296.

EGFR Inhibitors **Continued from page 23**

CONCLUSION

EGFR inhibitors are a mainstay in the treatment of lung cancer, and oncology nurses play a vital role in their effective use. Prevention and management of EGFR inhibitor side effects can allow the patient to remain on therapy at either a full or decreased dose, an important goal if the patient's cancer is responding well to treatment. Educating patients about strategies to prevent and manage EGFR inhibitor side effects is a key factor to helping them maintain body image while on these medications and remain adherent to therapy. ■

Beth Eaby-Sandy is a nurse practitioner at the Abramson Cancer Center of the University of Pennsylvania, Philadelphia, Pennsylvania.

REFERENCES

1. American Cancer Society Facts & Figures 2009. http://209.135.47.118/downloads/STT/500809web.pdf. Accessed July 22, 2010.
2. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353(2):123-132.
3. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomized phase III trial. *Lancet*. 2009;373(9674):1525-1531.
4. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet*. 2005;366(9496):1527-1537.
5. Cohen MH, Williams GA, Sridhara R, et al. FDA drug approval summary: gefitinib (ZD1839) (Iressa) tablets. *Oncologist*. 2003;8(4):303-306.
6. National Cancer Institute. Common terminology criteria for adverse events (CTCAE). Version 4.0. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. May 28, 2009 (v4.03: June 14, 2010). Accessed August 4, 2010.
7. Lacouture ME, Maitland ML, Segaert S, et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. *Support Care Cancer*. 2010;18(4):509-522. Epub 2010 Feb 10. http://www.ncbi.nlm.nih.gov/pubmed/20145956. Accessed August 4, 2010.
8. Lynch TJ, Kim ES, Eaby B, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *Oncologist*. 2007;12(5):610-621.
9. Lacouture M, Basti S, Patel J, Benson A 3rd. The SERIES Clinic: an interdisciplinary approach to the management of toxicities of EGFR inhibitors. *J Support Oncol*. 2006;4(5):236-238.
10. Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a Phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol*. 2010;28(8):1351-1357.