Pharmaceutical Management Branch

Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
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Already on Your Shelves!

All bevacizumab/placebo and patient-specific bevacizumab used on blinded studies has been transitioned to the easier-to-use 400 mg vials.

INSIDE PMB

November 2010

This issue's theme: Good Groceries!

This issue of INSIDE PMB takes you on a trip through the grocery store. We here at Pharmaceutical Management Branch (PMB) love grocery stores. We know grocery store etiquette, and abide by its every nuance, yielding the right-of-way to older or more aggressive shoppers, parking our carts way to the sides of crowded isles, and having our payment methods in hand as we check out. Just like YOU always check your stock levels before you order, include all the information we need on your forms, order with plenty of time for delivery, and check shipments in as soon as they arrive! PMB and its customers are simply perfect.

As you'll see in this issue, working with PMB and Cancer Therapy Evaluation Program (CTEP) and grocery shopping have similarities (and if they don't, we will make them!). This issue is peppered with useful tidbits, so grab a cart or a basket, and stroll down our aisles.

The Old Switcheroo!

We've all found wonderful products, purchased them regularly and faithfully, only to see them discontinued—or replaced by "new, improved" products. If you're perusing the shelf looking for AZD6244's Mix and Drink formulation (NSC 741078) and can't find it, that's because it is joining fels naptha flakes and Dastardy Mash ice cream. They're in the annals of history, and this formulation will join them on December 31, 2010. No longer treating patients with this formulation? Please return unused supplies to the NCI Clinical Repository. Protocols 7918 and GOG-0239 are still treating patients with this formulation; an amendment is being processed that will convert existing patients to the AZD6244 hydrogen sulfate formulation capsules (NSC 748727–note the NSC change!). Watch for the amendment and prepare to switch agents within two months.

Another Week, Another Circular

CTEP uses action letters much like grocery stores use the weekly circular. You should too. When you see those coupons, you need to take advantage of weekly specials right away. You need to act on Action Letters right away, too.

CTEP recently mailed an Action Letter asking sites to amend protocols that use AUC-based carboplatin dosing. Why? The National Institute for Standards and Technology has standardized methods of measuring serum creatinine by Isotope Dilution Mass Spectrometry (IDMS). The new method reduces interlaboratory variation in creatinine assay calibration—now, estimates of glomerular filtration rate (eGFR) are much more accurate. All clinical laboratories will switch to IDMS by December 31, 2010. This amendment educates sites that may be unaware of the change. It corrects non-standard dosing formulas that might result in carboplatin overdosing and cause unnecessary toxicity, particularly in patients who have low serum creatinine.

You'll find CTEP's Action Letter dated October 1, 2010 at this link: http://ctep.cancer.gov/content/docs/Carboplatin_Information_Letter.pdf.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

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Cut Back on Groceries: Three Good Reasons

It's a given: you run into the grocery store to pick up three or four items, and leave with a sack full! Sometimes it's because you remember a few other things you need, but other times it's because those tasty cakes and chips jumped into your cart. Cutting back on groceries is a good idea for three reasons, especially in these cash-strapped, go-green times:
(1) Americans waste unbelievable amounts of energy—the equivalent of 350 million barrels of oil annually or 2% of our total energy use—when we waste food and it ends up in the garbage. Spoiled food wastes not only the unconsumed calories in the food, but the cost of making, processing, packaging and transporting it! Buying just for immediate needs (and locally-produced food) saves energy and money.

(2) The cost of overeating averages $258,000 per person over a lifetime. No kidding! Obesity costs about $4900/year for women, and $2700/ year for men.

(3) Obesity is associated with a higher risk of cancer, and since doses are often weight-based, obese individuals need higher doses of antineoplastics. That usually means a higher cost, and it may mean greater toxicity. This last point raises an issue for sites ordering CTEP-distributed investigational agents.

For every protocol that has CTEP-distributed agent, PMB pharmacists do one last thing before CTEP approves the protocol—we calculate the anticipated eight week supply for the average patient and enter it in our database. Most of us:

- Calculate the dose estimating an average patient weight of 85 kg or 2 mg/m^2.
- Round up if that dose represents a partial vial
- Enter the eight week supply in the drug-ordering data base.

Our drug authorizers (the staff who process your orders) refer to the eight week supply when they fill Clinical Drug Requests. If you ask for more than the usual eight week supply, the drug authorizer will automatically cut the order to only the eight week supply. He or she will also add a note to the shipping documents indicating you ordered more than we usually distribute, and telling you the quantity was cut–a good reason to scrutinize your shipping documents!

Often, sites receive this lesser amount of agent and then call back and explain why they need more. You can save a step if you use the "comments" section to explain that you are treating a large patient when you order. Jot down the patient's weight and the actual amount of agent you need, and the drug authorizer will ask the pharmacist to override the eight week supply.

We thank Mimi Passerello who used NSABP's data base to provide some updated information for us:

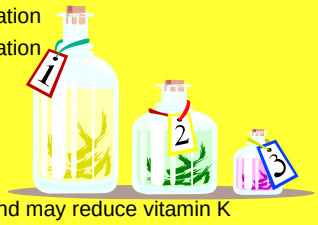
- The mean weight among breast cancer patients (N = 4894) is 77.9 kg
- The mean weight among colorectal cancer patients (N= 2710) is 81.3 kg overall; 89 kg for males and 73.6 kg for females.

Patient Information

The grocery aisle that has bright shelves of herbal, complementary and alternative medicine is magnetic for many people. They peruse the shelves looking for natural cures for the annoying little health issues we all experience. Cancer patients often need routine and chronic anticoagulation, and for these patients, a few doses of a natural remedy can spell trouble! Coenzyme 10, a vitamin K antagonist, and St. John's Wort, by mechanisms that are unknown, can reduce anticoagulants' effects. Many other increase anticoagulation (see table below). Be sure to ask about patients' use of these products.

Products with Additive Anticoagulant Effect

Product	Mechanism
Alfalfa	Contains coumarin medicagol
Anise	Contains coumarin constituents
Arnica	Contains scopoletin and umbelliferone
Astragalus	Increases fibrinolysis, including thromboxane synthesis and prostglandin 12
Bilberry	Contains vaccinium myrtilis
Black current seed oil	Contains gamma-linolenic and alphalinolenic acids, inhibits platelet aggregation
Bladderwrack	Contains fucoidan which has antithrombin activity
Bogbean	Contains coumarin scopeletin
Boldo	May have antiplatelet activity
Borage Oil	Inhibits platelet aggregation
Buchu	Unknown
Capsacin	Inhibits platelets; effect more pronounced in Asians
Cat's claw	Contains rhynochophylline, which may inhibit platelet aggregation
Celery	May inhibit thomboxane and contains coumarin derivatives
Chapparral	Contains nordihydroguaiaretic acid which interferes with platelet adhesion and aggregation
Chincona bark	Contains quinine-type alkaloids, which decrease Vitamin K production
Clove oil	Contains various concentrations of eugenol, which inhibits platelet aggregation
Dandelion	Platelet inhibitor (contains ample vitamin A)
Dong quai	Contains numerous coumarin derivatives
Evening primrose oil	Decreases platelet aggregation
Fenugeek	Unknown
Feverfew	Inhibits platelet aggregation
Garlic	Inhibits platelet aggregation
Ginger	Inhibits platelet aggregation
Ginkgo	Unknown
Guggul	Has fibrinolytic activity
Papaya extract	Unknown
Red clover	Contains coumarins
Rhubarb	Inhibits thromboxane and may reduce vitamin K absorption
Safflower oil	Decreases platelet aggregation
Skullcap	Inhibits platelet aggregation; contains flavenoids
Tan-shen	Inhibits platelet aggregation
Vitamin A	Platelet inhibitor



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Thank You, Volunteers!

PMB thanks each of you for taste-testing our new on-line ordering system! Your bravery and selflessness will benefit all ordering designees!

OAOP Volunteers	Practice Location
Brad Christensen, Susan Wescott, and Jackie Heim	Mayo Clinic, Rochester, MN
Don Chalupa, Jane Varney and Michele Murphy	Ohio State University
Dana Kelley	Washington University, St. Louis, MO
Wendy Laraway	Spectrum Health, Grand Rapids, MI
Veronica Hudson	Providence Saint Joseph Medical Center, Burbank, CA
Elizabeth Kennedy	Saint Vincent Hospital, Indianapolis, IN
Janet Szucs and Amy Porter	Cleveland Clinic Foundation, Cleveland, OH
Scott Freeswick, Anna Woo and Hyun Jin Byun	Memorial Sloan Kettering Cancer Center, New York, NY
Emmanuel Semmes, Phyllis Newson and Mark Miller	University of Chicago, Chicago, IL
Gopal Patil, Susan Huddock and Janine Stewart	Johns Hopkins, Baltimore, MD

On-line Ordering: Your On-Line Shopping Cart!

Over the last several months, a few mystery-shopping clinical sites have done some testing for PMB (see the box above), and we thank them for their efforts. They used our new Online Agent Order Processing (OAOP) application to "check out" this application and ensure that it replicates and improves the current manual process. All PMB customers who order investigational agent can now find this application at https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Very shortly, on-line ordering will replace the fill-out-the-form-and fax-it-and-hope-it-goes-through process for most sites. It's full of e-mail notifications and self check-out options!

OAOP is like the self-serve kiosk at the grocery store! The first time you use it will be the hardest. Ordering investigational agents is simple once you do a few things:

If you don't have one, establish an "active" account status and a "current" password in CTEP Identity and Access Management (IAM).

- Access IAM from the PMB page on the CTEP web site http://ctep.cancer.gov/branches/pmb/associate_registration.htm or directly via the URL https://eapps-ctep.nci.nih.gov/iam/.
- An "active" account status requires an initial registration and annual re-registration, both of which can be completed online using IAM. You'll receive a "Re-registration Notification" email from "CTEP Identity and Access Management" 14 days in advance to let you know it's time to re-register.
- A "current" password requires you to change your alpha-numeric-and-special-character laden password every 60 days (yeah … we love that one, too). OAOP will alert you if you try to login with an expired password, and will allow you to change your password.

To use OAOP, you must produce documentation that you are either the shipping designee (box 11) or an ordering designee (box 12) on the most recent Supplemental Investigator Data Form on file with PMB for each investigator for whom you want to order investigational agent.

- This is the same as the current requirement designating who can sign the Clinical Drug Request for a given investigator.
- For assistance with updating the shipping and ordering designees on an investigator's Supplemental Investigator Data Form, contact the PMB Registration Help Desk PMBRegPend@ctep.nci.nih.gov.

If you decide to brave the new world of online agent ordering, please let us know if you have questions or comments and, perhaps most importantly, if you encounter glitches. Be sure to add the web link https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx to your favorite places or desktop!

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Superfruits in the Produce Aisle? Orange we glad you asked…

Inundated with ads for nutritional supplements and beverages containing a so-called superfruit? Açaí, noni, gogi berries, and jujube fruit are among the more exotic fruits being marketed. The claim is they promote health—from causing weight loss to preventing cancer. Superfruits do contain a cornucopia of beneficial phytochemicals, such as flavonoids, phenolic acids, stilbenes, coumarins and tannins. They also show cytotoxic activity in a petri dish, but clinical trials haven't proven that superfruits confer a cancer prevention benefit. Past clinical trials have only looked at the benefit of fruits and vegetables in general.

Case-controlled studies conducted 15 years ago suggested that eating plenty of fruits and vegetables prevented cancer, but numerous randomized trials conducted since then have been unable to link this benefit to fruits alone. The most recent large-scale trial, European Prospective Investigation into Cancer and Nutrition (EPIC), prospectively analyzed a large cohort of patients over eight years. The results show that consuming greater than 200 grams/day of vegetables and fruits lowered overall cancer incidence by a few percentage points. Multiple reports stemming from EPIC show there appear to be variable inverse associations between fruit or vegetable intake and incidence of specific types of cancer. Multiple factors, such as type of fruit or vegetable eaten, smoking status, alcohol use, physical activity and gender complicate interpretation. Without further investigation, experts are hesitant to change current recommendations for risk reduction. The good news is that fruit and vegetable consumption significantly decreases blood pressure and reduces cardiovascular disease.

The US Department of Agriculture (refer to 2010 dietary guidelines) still thinks most people "underconsume" fruits and vegetables. So be nice to your heart and forget the exotic superfruits that you can only find in a can. Look no farther than your local fruit stand for the more domestic, fresh superfruits, like blueberries, cranberries, pomegranate and strawberries.

Where are the Edamame Beans?

Grocery aisles are loaded with soy products, from beverages to cheese and burgers. Soy-based food isn't just for vegetarians and the lactose-intolerant. It's a health-conscientious consumer's low fat, high protein choice. Some people claim that soy-based food consumption may lower cholesterol, lower the incidence of breast cancer and prostate cancer, and minimize menopausal symptoms. Soybean contains isoflavone, a phytoestrogen compound with a structure similar to the hormone estrogen.

The U.S. Food and Drug Administration recommends 25 grams of soy protein daily for lowering cholesterol. This is equivalent to one cup of soy milk or three ounces of tofu that contains roughly 6 to 8 grams of protein per ounce. Any LDL reduction may simply be due to soy' high-quality protein that is low in saturated fat and high in polyunsaturated fat replacing other dietary proteins. Science communities agree that daily consumption of soy protein may lower LDL slightly; however, there are not enough data to prove that soy supplementation is of benefit for other health concerns.

Soy's role in breast cancer risk is inconclusive. Isoflavone's estrogenic effect may promote tumor recurrence, however, so most experts advise breast cancer survivors to avoid it.

With prescribers using conventional hormone replacement therapy less frequently than before, having a natural approach to treat hot flashes is of interest to menopausal women. Isoflavone seemed to be the answer, and many commercial soy products are available. Many clinical trials explored this claim. Most found what Tice et al (2010) did in a randomized controlled trial exploring phytoestrogen supplements for the treatment of hot flashes. The data could not confirm any clinical effect on hot flashes or any other symptoms.

Soy can cause or contribute to minor gastrointestinal problems like nausea, bloating, and constipation. Allergic reaction is possible, usually indicated by breathing problems or rash.

Squeezing the Most From the Container

It's a dilemma when you pick up a favorite packaged food and after a few uses, it's impossible to get any more out of the container. Usually, condiments like ketchup, peanut butter, mayonnaise and barbeque sauce are the biggest challenge. Lately, producers are packaging these in "big mouth" jars. PMB doesn't have any big mouths (at least not in agent packaging). Here are our two most frequent dose-squeezing questions:

Question: Two patients receive the same agent on the same open label NCI study at the same institution. Can we share vials?
Answer: If the patients are being treated on the same day, this is acceptable. Document this on the DARF by noting patient initials/number used 1 vial and patient initials/number used 0 vials. Tie the lines together with a "]". Document each of the patients' actual doses on the DARF.

Question: Our patient's dose of bananaplatin is 104 mg, and the NCI supplied vials contain 100 mg in 5 mL, but they have ample overfill. If we can draw 5.2 mL from the vial, can we use it instead of opening another vial?
Answer: You bet, especially if the vial was filled by the manufacturer. If the product is lyophylized, however, please make sure that you reconstituted it exactly as directed, and the overfill isn't the result of an error. (Please note that you might want to suggest to your physicians that the difference between 104 mg and 100 mg is very small, and they can round to 100 mg without a problem in most cases.)

Find more Frequently Asked Questions at http://ctep.cancer.gov/branches/pmb/faq.htm.