Eating at the Diner!

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Did You Save Room for Dessert?

Before you order that slice of coconut cream pie, consider the effects that obesity has on cancer treatment. Did you know that obesity:

- doubles the amount of α1-acid glycoprotein in the bloodstream resulting in less drug bioavailability?
- increases the volume of distribution for lipid soluble drugs and decreases it for water soluble drugs?
- increases clearance of cisplatin and paclitaxel in particular?
- may alter tubular secretion of drugs?

Chemotherapy dosing in obese patients is a challenge since prospective studies evaluating AUC, volume of distribution, clearance, and subsequent toxicity are lacking. You can bet a dozen donuts that weight descriptors vary widely throughout the country. The best approach is to keep consistent methods for dose calculation, monitor for dose-limiting toxicities, and make dose adjustments in a step-wise fashion. In the meantime, "Pass me the fruit salad!"

INSIDE PMB

February 2010

Pay at the Table, or Pay at the Register?

PMB ships agents based on the most appropriate method of delivery, considering things like the agent's storage, stability, and classification. We realize there are times when a site may need to receive an agent with very short turn-around. When this occurs and our normal shipping isn't fast enough to get the agent to the site when they need it, the site has to pick up the tab. How? We'll grill you for an express courier account to expedite delivery. Due to the number of shipments and processes in place at the NCI Clinical Repository, we can't accommodate alternatives, such as billing the recipient at a later time or accepting site-provided express courier shipping labels. We have also had sites inform us that their institution will not allow provision of account numbers due to internal business practices. We suggest discussing this issue with the appropriate parties at your institution. Unfortunately, should you waffle, PMB will ship the agent according to the shipping mode for the agent.

New on the Menu!

Beginning the last week of January, you will start seeing a newly formatted Shipment Record of Clinical Drug Request in your agent shipments. Please continue to check packages carefully and retain all copies of the Shipment Record! Depending on what is contained in the package, there may be multiple Shipment Records in your shipment.

PMB strives to be like the diner!

Diners:
When you patronize them, you get a recognizable, fairly uniform place and product nationwide. Their food is consistent, especially within a region, as are the prices. We think of diners as a step above fast food—their menus are more varied and the staff can be, well, kitschy. But they slap that food on the formica fast!

PMB strives to deliver a uniform service nationwide. Worldwide, actually. And we value consistency and service. This issue of INSIDE PMB is full of news about recent and future changes, and appetizer-sized education. Enjoy!

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Soup of the Day: Alphabet

The world of adverse event reporting is getting a number of new looks–the acronyms and roll out can be confusing.

•CTC: Common Toxicity Criteria. Version 1 was developed by CTEP in 1982 to begin the standardization and codification of adverse events on CTEP-sponsored clinical trials.

- CTCAE: Common Terminology Criteria for Adverse Events. As the CTC evolved so did the name. CTEP released the third version of the CTC, now called CTCAE v3.0, in 2003. Version 4 of the CTCAE, released in 2009, was a joint project between caBIG and CTEP where the big change is that CTCAE is now completely MedDRA based. Use of MedDRA terms is a step toward global harmonization.
- CAEPR: Comprehensive Adverse Event and Potential Risk List. A CTEP-created document for CTEP IND agents that summarizes the adverse events for a specific investigational agent. When a sufficient number of patients have been treated, the CAEPR is updated to also include frequency categories. CAEPRs are updated as new events become known, usually on an annual basis after the new IB version is released.
- ASAEL: Agent Specific Adverse Event List. A subset of the CAEPR that is used solely to determine which adverse events need to be reported to CTEP in an expedited fashion.
- AdEERS: Adverse Event Expedited Reporting System. Used to report serious/unexpected adverse events to CTEP electronically.
- caAERS: Cancer Adverse Event Reporting System. A new open source software tool used to collect, process, and report adverse events. This will be used to report all adverse events, not just those requiring expedited reporting, and has been integrated with AdEERS.

With the release of the new CTCAE version, all protocols will need to be amended. All new protocols began using the CTEP Active Version of the CTCAE (currently v4) as of October 1, 2009. On-going protocols are converting to the CTEP Active Version of the CTCAE in a (slowly) rolling fashion and will continue to use what they are currently using—either CTC v2 or CTCAE v3–until the infrastructure is ready to support the conversion and the protocol is amended.

If that's not confusing enough, all agent CAEPRs are being updated from CTCAE v3.0 language to v4.0 language. There will be a lot of mismatches between CAEPRs and protocols for a while. And although this can be very confusing at the global level, at the individual protocol level things are set up such that when you go to enter an AdEERS report, the correct CTCAE version for your protocol will appear. And when data is loaded through CDUS the system knows what version your protocol will be reported in. The system updates required to support this and the data mapping are the major reason for the very slow roll out.

The icing on the cake? Once protocols are amended to use the CTEP Active Version, that part of the protocol won't have to be updated when the next version(s) of CTCAE roll out.

Investigator Brochure Distribution: Not a Jukebox Selection

Jukeboxes offer a section of tunes that you can play whenever you want. The word "juke" is a derivative of a Gullah word meaning, "disorderly, rowdy, or wicked." While we like disorderly, rowdy, or wicked as much as the next office, we can't be disorderly, rowdy, or wicked.

The Pharmaceutical Management Branch catalogues and distributes Investigator Brochures (IBs) for our industry partners. Just like most modern jukeboxes use CDs rather than vinyl records, we now send all Investigator Brochures (IB) electronically or on a CD. CTEP's agreements require that we maintain a very high level of confidentiality when distributing new and vital information to those involved in clinical trials. Part of that agreement is that we mustn't allow sites to redistribute IBs. Balancing the needs of the partner against the needs of the investigator is like carrying a tray full of pancakes while wiping down a table!

When we receive a new or updated version of the document, we distribute it to

- Principal Investigators (PIs) on approved LOIs.
- PIs on protocols with non-terminal status.
- The Operations Office of specific Cooperative Groups when the Group is leading a trial using the agent.
- Any investigator who has ever ordered agent from us on a study that is still treating patients.

In addition, the PMB web site lists the IBs we distribute with their version date. This information is updated frequently to help investigators verify that they have the most current version. This list can be found at the following web site:

http://tinyurl.com/yg3pd5v

So, PIs receive IBs as soon as CTEP approves their LOIs, and can request a subsequent IB for Investigational Review Board (IRB) submission. Once CTEP approves the actual protocol, any participating investigator (with appropriate affiliation) can request and receive an IB at any time. In this way, those sites that actually plan on participating can request an IB when they need it for their IRB's review. And, once investigators order agent from PMB, they'll automatically receive an IB if it is updated.

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"Can I take your order?"

Coming Summer of 2010 … OAOP (Online Agent Order Processing)

What is "OAOP"?

• OAOP is a web application that will allow you to order PMB-supplied investigational agents online, eliminating the paper "Clinical Drug Request" and the need to fax it to PMB.

OAOP will include lots of helpful features such as…

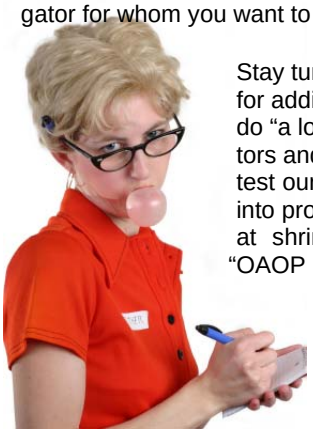
• Providing ability to query by investigator name or NCI investigator number to insure that your investigator name and number match.
• Checking that your investigator's current investigator registration status is "active."
• Displaying your investigator's shipping address so you'll know exactly where we will send the agent shipment.
• Assuring that your investigator is eligible to order agent on the selected protocol.
• Checking all those important but pesky agent details (e.g., NSC, agent name, and agent strength / unit / form).
• Validating any provided FedEx account numbers.

Plus additional checks for blinded, patient-specific orders including…

• Reminding you that a patient ID is required.
• Checking that the patient ID is associated with the selected investigator.
• Alerting you that body weight is required for patient-specific agents dosed on body weight (e.g., bevacizumab).

Sounds pretty cool, right? So, what can you do today to get ready?

• Access to OAOP Online will require an IAM user name and password. If you haven't done so already, establish an IAM account at http://tinyurl.com/yzx65le.
• Check that you are listed as either the "shipping designee" (box 10) or an "ordering designee" (box 11) on the Supplemental Investigator Data Form (See http://tinyurl.com/yc85c8j) for each investigator for whom you want to be eligible to order agents.



Stay tuned to future editions of "Inside PMB" for additional information. And, if you currently do "a lot" of drug ordering for your investigators and would be interested in helping us beta test our new web application before it goes into production, please e-mail Donna Shriner at shrinerd@mail.nih.gov with a subject of "OAOP Beta Tester."

Oops! Manager's Note

There was an error in the April 2009 AZD6244 IB. This has since been corrected. AZD6244 should be taken on an empty stomach either 1 hour before or 2 hours after meals.

Blue Plate Specials

Every once in a while, it's good to look at what's on the menu in most oncology pharmacies. We conducted a brief survey, and here's what we found were the most popular specials:

Platinums

Classic CISplatin never goes out of style. If you can't stomach its renal toxicity, ototoxicity, and serious nausea/vomiting, lighter CARBOplatin and OXALIplatin offer a different taste of toxicities such as myelosuppression and cold neuropathies. Note a potential for anaphylaxis…keep the crash cart handy!

Cyclophosphamide

Just like a good meatloaf, you can always count on cyclophosphamide to beef up the toxicities in any menu. Besides myelosuppression, alopecia, and nausea, expect a healthy serving of renal toxicity, possible infertility and sadly, hemorrhagic cystitis.

Taxanes

The daily selection allows you to chose paclitaxel or docetaxel. Highly recommended with ample portions of steroids and antihistamines to compliment the hypersensitivity reactions and help prevent that nasty edema. Other than the usual toxicities, you can expect to see neuropathies and nail disorders.

Gemcitabine

Just when you feel like you've tried everything on the menu, we offer gemcitabine. It's everything you expect from a blue plate special and more—rash, edema, a dollop of increased hepatoxicity, and a pinch of nail changes.

Anthracyclines

Known for brightening body fluids, these red entrees take away the winter blues with their cardiotoxocity, mucositis and myelosuppression. Extravasation risk and radiation recall make anthracyclines even more unique.

Fluorouracil

Not for the faint of heart, fluorouracil can cause angina. But if mucositis, hand-foot syndrome and nail loss are flavors you're craving, this special is for you! Order it either of two ways—fast or really slow to savor the...ahem…chemotherapy experience.

Special Sides

Antihistamines

A one, two combination will really smooth out pesky paclitaxel side effects. And they're good for allergies, too!

5HT$_3$ antagonists

Come and get it! An essential for almost every blue plate special we offer!

Bevacizumab

Like an exquisite sauce, guaranteed to make any entree richer.

Cetuximab

Almost as good as bevacizumab, plus a rash.

Steroids

Good for whatever ails you! And so much more!.

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What do Diners and Cancer Patients Have in Common?

No, not diarrhea, but you're close! Stools! The NCI Common Terminology Criteria for Adverse Events (CTCAE) defines diarrhea as "a disorder characterized by frequent and watery bowel movements." Simply put, diarrhea occurs when water in the intestine is not absorbed back into the body, and the stool's fluid and electrolyte concentration increases, and POW! Diarrhea.

Chemotherapy, radiation, or surgery often cause diarrhea in cancer patients by harming the lining of the gastrointestinal (GI) tract or altering GI motility. Drugs such as 5-FU and CPT-11 use to treat colorectal cancer and cancers of the gastrointestinal tract usually cause diarrhea. Other drugs that commonly cause diarrhea are actinomycin, arsenic trioxide, bortezomib, capecitabine, docetaxel, fulvestrant, gefitinib, gemtuzumab, imatinib mesylate, paclitaxel, sagramostim, and pemetrexed.

Other causes include infection; toxins; stress; GI pathology; supplemental feedings containing large amounts of vitamins, minerals, sugar, and electrolytes; and tumor growth itself. Diarrhea can be life-threatening if not treated appropriately causing dehydration, electrolyte imbalance, low immune function, and pain/or bleeding due to an increase in number of bowel movements. Severe sodium depletion can lead to seizure or coma; low potassium levels lead to abnormal heart function.

- Viral or bacterial-induced diarrhea is a self-limited illness that usually requires fluid intake and a clear liquid diet. Antibiotics are prescribed only if analysis of stool samples reveals a specific pathogen or fecal leukocytes.
- Toxin or drug-induced diarrhea is best treated by discontinuing the causative agent when possible.
- Chronic diarrhea is a result from the over use of laxatives, lactose intolerance, inflammatory bowel disease, irritable bowel syndrome and other disorders.

Foods that worsen diarrhea include dairy products such as milk, cheese, and sour cream. Spicy, greasy, or fried foods can, too. Broccoli and cabbage cause gas. Foods with high fiber content such as whole wheat breads, granola, and bran cereals, and raw fruits or vegetables can also aggravate diarrhea.

Several interventions can be used to manage diarrhea. Advise patients to eat 5 to 6 small meals and snacks daily. They should drink clear broth, ginger ale, or Gatorade®, and eat low-fiber food such as bananas, white rice, white toast, and plain yogurt.

In terms of drugs, we tend to use loperamide for cancer-related diarrhea. Opioids are commonly prescribed to cancer patients for pain relief. They have a depressant effect on the central nervous system. They also act on intestinal motility (μ receptor), intestinal secretion (δ receptor), or absorption (both μ and δ receptors). Chronic use of narcotics leads to severe constipation.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Liver 'n Onions, Hold the Onions

The American diner is one of the last refuges for the liver 'n onions lover. Slap a side of mashed potatoes on the plate, and voila! A nutritious, high protein dinner full of vitamin A and folic acid reminiscent of the 50s!

Here are a few facts about liver—the human liver, that is:

- Why is the liver such a big deal in drug metabolism? Because it's large, and it's the first organ perfused by chemicals absorbed in the gut. It also has high concentrations of most drug-metabolizing enzyme systems relative to other organs.
- The liver metabolizes drugs in Phase I and Phase II reactions. Phase I reactions usually precede Phase II, but not always.
- If you're a regular diner (or a diner regular) and have put on a few pounds because of it, your liver might behave normally. Or, your phase I reactions (oxidation, reduction, and hydrolysis) may be a little faster. Your phase II glucuronidation and sulfation reactions will be faster than a normally sized counterpart.
- When investigators do pK studies to identify possible drug interactions involving hepatic enzymes, they often use the following CYP450 substrates in combination with the investigational agent: midazolam (CYP3A4), omeprazole (CYP2C19), tolbutamide (CYP2C9) and dextromethorphan (CYP2D6). Rifampin is a good pan (3A4, 2C9, 2D6) cytochrome p450 enzyme inducer, and ketoconazole is a preferred CYP3A4 inhibitor.
- Generally, fetal, neonatal and elderly humans and animals metabolize drugs more slowly than adults.
- Patients who have kidney or cardiac disease may have impaired hepatic metabolism.