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Tongues are Wagging: INSIDE PMB Celebrates Six Years!

It's August, and that means that we change our newsletter template to bring in a new year of INSIDE PMB, and celebrate our anniversary. This newsletter has evolved over the years, and its readership has grown to include all kinds of clinical trials clinicians. We've tried to cover issues of importance to you, and help you learn with laughter. We appreciate your kind words of praise after especially good issues, and we have addressed the three complaints we received (LOL–you know who you are!).

We hope everyone nose that when PMB identifies critical information we don't let it get stuck on the tip of our tongues. We send it directly to investigators and shipping designees in a formal, timely communication. INSIDE PMB supplements and summarizes information that you should have already received.

Go to http://tinyurl.com/nplwks for previous issues.

INSIDE PMB

August 2009

Elbow Expectation Explanation Into Your Practice!

We like to keep you abreast of latest developments, so here's a new buzz phrase for you: "managing patient expectations." It's nothing really new. It's been a big deal in chronic pain management; clinicians are often frustrated because patients expect that analgesics will relieve all of their pain, which is often not the case. Teaching patients that they will probably not be pain-free helps a lot—it manages patient expectations, and they appreciate the relief they get from treatment more (and complain less). In cancer, we need to do a better job of managing expectations.

The key here is communication.

•Don't waist time with jargon or information your patient doesn't need. Get to the point!

•Explain what to expect during treatment, and do it in terms of mobility and function. Tell patients incapacitated by nausea that antiemetics may not take away all their nausea, but will take away enough that doing laundry, gardening, or walking is possible.

•Tell patients about possible side effects. Study after study has confirmed that patients don't develop side effects just because you tell them they might occur.

•Talk about the near and not-so-near future, and do it at every visit. Repetition is important, as is telling people how long a side effect will last. Saying, "You'll have this treatment every three weeks for six months," is fine. Telling Farmer John, "You'll feel like growing tomatoes again by March," is even better.

•If you know something usually distresses patients (the cost of a prescription, the usual waiting time, a procedure's discomfort), tell patients as soon as you can so they are prepared for it.

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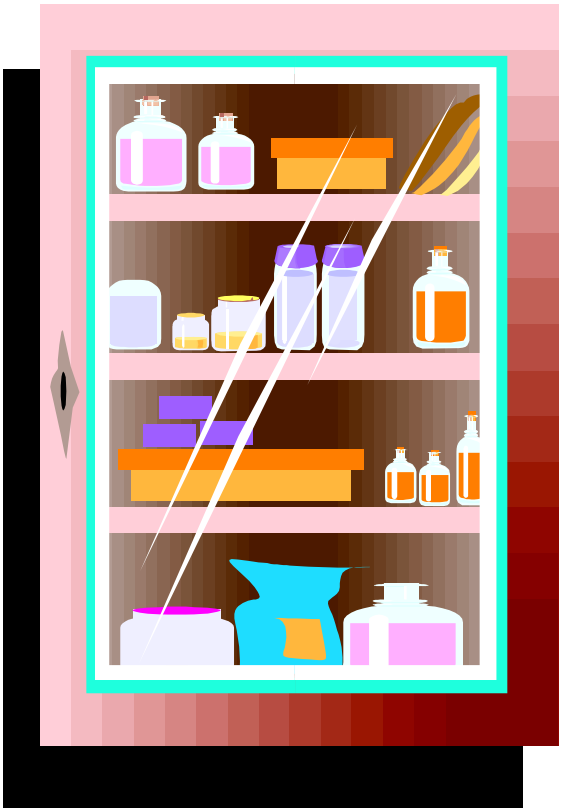
Head-to-Toe Physical: The Perfect Dose Modification Section (if you can stomach it)!

Sometimes, CTEP receives protocols for review that have a good skeleton, butt when we get to the dose modification section, the thigh bone is not connected to the head bone or something like that. The best dose escalation sections

- define the maximum number of allowable dose reductions before treatment must stop
- include consistent descriptions of modifications among a study's treatment arms for the same agent
- use consistent terminology for the same meaning (i.e., < grade 3 or ≤ grade 2)
- describe exactly how a toxicity must resolve before treatment can be resumed or doses re-escalated
- explain exactly how modifications are to be handled during a cycle or at the start of the next cycle
- specify how modifying or stopping therapy of one agent impacts the rest of the treatment regimen
- Describe dose modifications as actual doses, e.g. X mg/m^2, and not as a percent of the previous dose
- use values for CTCAE grades consistent with the actual definition
- and, finally, this one is tricky but it's a problem. For dose escalation studies (particularly for patients treated at the initial dose levels), the maximum number of allowable dose level reductions in the dose modification section must be less than or equal to the number of available dose levels defined in the treatment section. (You may have to read this one a few times, but it will not be a waist of time.)



Gut Reaction: Mouths of Babes ♥ TLC

Increasingly, our protocols are using oral antineoplastics. As is usually the case, once the adult trials show favorable results, the next step is pediatric trials. This raises the issue of how to get that agent into–and through and then out of–itty bitty bodies.

- Review the instructions on the label, and tell the patient what it is for.
- Make sure it says "give by mouth," or "to be given orally"
- Include appropriate auxiliary stickers such as "shake well" or "do not take with food"
- Show the patient the capsules or tablets and point out the color, size, shape.
- If they get two different strengths, explain which is which.
- If dosage form must be altered or crushed at home, explain how to do it. (If it cannot be altered or crushed, explain that it must be swallowed whole.)
  - ❑ Does the caretaker need safe handling instructions?
  - ❑ Are you supposed to provide diluents, syringes, oral cups, gloves or supplies?
  - ❑ Is the altered product for "immediate-use" only?
  - ❑ What should they do if the child does not take the medication within that time window (e.g., 5 to 15 minutes)?
  - ❑ Is there a "use by" date for any solution, slurry, or mixture prepared at home?
- What are the storage requirements for the agent?
  - ❑ Are the storage conditions different if they alter the dose?
- If instruction is for a teaspoon, explain that a kitchen teaspoon may be too big or too small, and why a measured teaspoon is important.
- Explain how to record the dose, time, and date of agent administration on the pill diary.
  - ❑ **Really good clinical trials clinicians also tell patients how to correct errors if they make them, and not to "batch" entries on the patient diary.**
- When should the agent be considered expired, and how should they dispose of any leftover agent?

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The Anatomy of a..... SHIPPING DOCUMENT!

Let's do a quick head-to-toe review of a shipping document. This exercise is a little like scratching someone else's back. You'll need to listen and go to the right, to the left, a little higher, a little lower. Pull out a couple of your most recent shipment records, and make note of the following:

- Upper right quadrant, Need by Date: This is the date you say you need the drug. ASAP, by the way, is not a date. ASAP here at PMB means, "Alarming Site Acquisition Problem."
- Right midriff, Manufacturer and Lot Number Column: This is the lot number you need to copy to the DARF. It's also the lot number that PMB will use when issuing Stock Recovery Letters.
- Belly button area, under the line item, "order comment" or a "package insert": An order comment will tell you something new or important about the order. Our most frequent order comments are listed in Table 1 to the right. Our most frequent package insert is a notation that the agent is a dangerous good. You'll also find the agent's PREP DATE here if there is no prep or expiration date on the label.
- Lower right hand corner, around the knees, Order Number: It starts with the year and is a Julian date with a sequence number. This helps if you call with a question. We can identify the order quickly.
- Middle section, bottom left, Order Message: This is an impersonal but very important message sent to everyone who receives orders during a specified period. The most important of these is, "A new issue of INSIDE PMB is now available at http://tinyurl.com/nplwks."

Please note that very soon, the shipping document is going to look slightly different as we abandon pin feed documents and move to laser printing. All of the information discussed h-ear-in will still be present on the form, and in approximately the same places.

PMBafterhours

Do you have a question and need an answer soon, but not necessarily right this minute?
E-mail pmbafterhours@mail.nih.gov
Any time day or night!
Expect an answer on the next business day.

Table 1. PMB's Most Frequent Order Comments

1. "One 8 week supply for this protocol is *X* vials per patient" indicating your original clinical drug request asked for more drug than we can send.
2. "Please place a single 8 week order for all patients participating on this trial. Do not order by individual patient." That means we sent this agent within the last 10 days, and you are probably ordering for one patient at a time. Give yourself (and PMB) a break and save some time. And money.
3. "Bevacizumab 400mg vials are shipped in multiples of 2," means we are not going to send you seven, even if it is your favorite number.
4. "Oxaliplatin vials are shipped in multiples of 4." We won't send seven of these, either.
5. "PMB does not supply Bevacizumab 100mg vials. Please note that bevacizumab 400mg vials have been substituted to complete this order." This means that you are operating in the past in terms of open label studies. We've been sending 400 mg open label vials for years. (And soon, blinded studies will, too!)

Don't Be a Heel

If you're part of the large minority (36%) of our customers who are using out-of-date forms, please update them ASAP (which in this case means "As Simple As P-eye"):

- The most recent Clinical Drug Request is dated 02/2007
- The most recent NIH 2564 NCI Investigational Drug Accountability Record Form expires 02/2011
- The most recent NCI Transfer Investigational Agent Form is dated 06/06
- The most recent NCI Return Investigational Agent Form is dated 03/09 (look on the form's right shoulder)
- Note that the FDA Form 1572 has expired. We are waiting for the FDA to receive approval for their new form.

Go to http://ctep.cancer.gov/forms/ and download new forms. Most of these are "fillable PDFs," which means you can type information into them and print. Just click the area where you want to type!

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Chemo Brain: All in Their Head?

Clinicians and patients often notice chemotherapy-induced cognitive impairment—it occurs in 15 to 70% of cancer patients. Although it isn't an accepted medical term, "chemo brain" is the most popular vernacular term used. Chemo brain's spectrum of weakened cognitive abilities includes concentration, memory, learning, and language ability deficits following chemotherapy. The changes may be subtle or may drastically reduce patients' abilities to perform home and business functions.

Chemo brain is best described in breast cancer but has also been reported in testicular cancer, lymphoma, leukemia, small cell lung cancer, ovarian, and pediatric tumors. Causative agents include cyclophosphamide, 5-fluorouracil, methotrexate, cytarabine, carmustine, cisplatin, doxorubicin, and antiestrogens. It seems ironic that these agents cause chemo brain, because they are inactive against central nervous system (CNS) tumors or metastases.

Some experts have doubted chemo brain exists, attributing cognitive changes to confounding factors including anemia, anxiety, depression, supportive care medications, and menopausal status. Studies before and after patients receive chemotherapy have shown chemo brain symptoms despite confounding variables. Neuroimaging studies revealed gray and white matter abnormalities. Other studies used objective assessment tools commonly used in other dementias (e.g. Alzheimer's disease). Researchers wonder if these tools are sensitive enough for chemo brain's sometimes subtle changes. It's a conundrum. Neuroimaging and/or neuropsychological tests are negative in some symptomatic patients, while other patients with objective findings on imaging don't manifest symptoms.

The mechanism by which chemotherapy causes chemo brain is unclear. Likely mechanisms include direct neurotoxicity producing demyelination, inflammatory/immune mechanisms involving the release of cytokines, and microvascular injury resulting in CNS ischemia.

Lack of an etiology has made treatment of chemo brain difficult. Erythropoietin has helped improve cognitive function in anemic cancer patients, but the FDA and some professional organizations like NCCN don't recommend it in the absence of anemia. Several experimental treatments including methylphenidate and hormone replacement therapy (HRT) failed to show clinical benefit.

With increased awareness of chemo brain, large prospective studies to assess cognitive function before and after chemotherapy are needed. They'll need to use validated instruments to assess the cognitive domains in chemo brain. Until a treatment or prevention method is found, clinicians should continue to educate patients about ways to minimize the impact of cognitive decline on their quality of life. Such measures include reduced multitasking, external memory aids, and psychosocial intervention.

Hirsutism

Cancer patients typically experience alopecia due to chemotherapy and radiotherapy treatments. They rarely experience the reverse: hirsutism, a condition that produces excess body (chest) and facial hair. Hirsutism is caused by excess production of androgens from the ovaries, the adrenal glands, or exogenous sources. Perimenopausal and menopausal women often go through an abrupt imbalance of testosterone, estrogen and progesterone making them prone to increased hair growth. Ovarian tumors can cause errant hair growth. Insulin resistance syndrome is another hirsutism-causing disease and is also associated with polycystic ovarian syndrome (PCOS), a condition that generates plenty of follicles without producing eggs each month. PCOS account for approximately 80% of hirsute cases.

Hirsutism has also been observed in children with Cushing's Syndrome, wherein the body elevates cortisol hormone for a long period of time. Adrenal tumors can induce similar hair growth. It can also be from exogenous high dose corticosteroid medication used in asthma, lupus, rheumatoid arthritis and some cancers.

Drugs causing hirsutism include androgenics (testosterone, ACTH, phenothiazine, danazol), anabolic steroids, androgenic progestins (levonorgestril, norgestril, and norethindrone), acetazolamide, and valproic acid. Among the nonandrogenic medications are cyclosporine, phenytoin, diazoxide, minoxidil, high dose glucocorticoids, penicillamine, metoclopramide, and reserpine. That said, valproic acid has been tested in a few phase 1 clinical trials such as in children with recurrent or progressive solid tumors; in combination therapy in NSCLC, or a combination therapy in NHL; and in Kaposi's Sarcoma. Dexamethasone, used routinely as a myeloma treatment, and metoclopramide are being used as supportive care.

These drugs might induce hirsutism, but because they are typically used only short-term, patients might be spared from that condition.