Bikes & Trikes

Dudes on Bikes...see page 2

inside PMB

November 2008

Registration Coordinators!

Shift Gears, Please!!!

PMB thanks Registration Coordinators for their winning response to our pleas in August. Specifically, we thank you for facilitating completion and submission of Investigator Registration documents before your investigators' registrations expire.

The NCI's Cancer Therapy Evaluation Program is making a concerted effort to conserve resources, and PMB is asking for your help again to streamline the registration process. We ask a lot, we know, we try not to tire you out. But, to save time, funds, and paper, we would like to send your investigators' annual re-registration documents to you either by e-mail or on a CD.

To receive your annual investigator registration packets electronically, please e-mail ctepreghelp@ctep.nci.nih.gov with the subject line "Electronic Investigator Re-Registration Documents," or call CTEP Registration Help Desk at (703) 738-9171.

LOOK INSIDE FOR

Hit the Brakes on Protocol GOG-0218!

Consider this: a person bicycling at 10-15 mph (15-25 km/h), using just the energy required to walk, is generally the most energy-efficient means of transportation available. Air drag (with up to 75% of it caused by the rider's body) increases dramatically as speed increases, requiring more work. Every clinician who dispenses, prepares or administers investigational agent would like the process to be as efficient and drag-free as riding a bicycle. That said, please increase efficiency and decrease drag on GOG-0218. Why? Because errors on this study represent more than half of all errors reported to PMB. What kind of errors, you ask?

•Using Phase A drug supply for Phase B treatment. Some pharmacies have used left-over vials from Phase A to start Phase B cycle 7. Screech….bad idea! The patient may have been randomized to active agent in phase A and placebo in phase B!

•Using wrong patient's drug supply. This error seems to occur when the regular pharmacist is away, and someone else covers. Blinded supplies' patient-specific 10 digit patient ID numbers (###-0218-###) reflect the site code, study number and patient number enrolled at that site and may look very similar. If the site enrolls multiple patients, patient ID numbers may differ only at the tenth digit.

•Making dose modification errors for modest patient weight changes. GOG-0218 keeps the same bevacizumab/placebo and paclitaxel dose if the weight change is less than 10%! PMB calculates the number of vials to send based on patient weight at enrollment in Phase A. When registering for Phase B treatment or faxing an order to PMB, please note the Phase A enrollment weight unless it changes by at least 10%.

•Using commercial bevacizumab (Avastin) in place of the patient-specific NCI-supplies of active drug or placebo. Duh. PMB will not replace commercial agent, and you cannot charge the patient.

•Removing vials from the original tamper-evident box to facilitate storage or combine supplies from different shipments into one box. This removes important identification (i.e., Phase A or B, Julian date/lot number). Vials will still have the patient ID on them, but there is no way to discern supplies for different Phases or shipments. Mixing Phase A and B vials presents a problem at cross-over.

In the conduct of GOG-0218, most "drag" is created by humans involved in the study. Slow down, decrease your drag, and do this:

•Keep phase-specific accountability logs.
•Require GOG patient-specific ID numbers on local physician order sets and require prescribers to mark orders, "Patient is on a clinical trial."
•Double-check that the patient ID number corresponds to the correct initials for the patient.
•Return vials left-over at Phase A's end to CTEP *pronto*.
•Mandate that the pharmacist highlight the patient's name, GOG patient ID number and Phase of treatment (A or B) with a yellow marker on each patient's drug supply container.
•Keep the same bevacizumab/placebo dose if the weight change is less than 10%!
•Leave supplies in their original tamper-evident box until they are used.

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Pedal Over to the CTSU Members Web Site

The Cancer Therapy Evaluation Program (CTEP) created Identity and Access Management (IAM) accounts primarily to provide access to the Cancer Trials Support Unit's (CTSU) members web site.

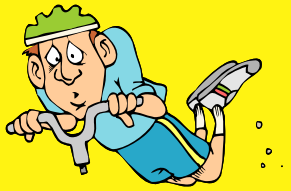
Once Associates activate their CTEP-IAM accounts, an application request is automatically forwarded to the CTSU Help Desk and they begin the approval process for access to the CTSU members web site. It will typically take the CTSU 2 to 3 days to review your application. The CTSU team will notify you by e-mail of the outcome of their review. Once you receive the approval e-mail from the CTSU, you will be able to use your new CTEP-IAM username and permanent password to access the CTSU members website.

*Associates need not take any other steps in IAM to obtain access to CTSU.

Dudes on Bikes: No Joke

The photo on page 1 is none other than our own Steve Friedman of Protocol and Information Office fame on the left, and Lance Armstrong on the right. Steve tells us they were in the "first stage of the Tour of Hope, about 40 miles outside of LA in the foothills.....this climb we're on lasted 8 miles and was about 5% grade and close to 95 degrees..." On a bike, 5% is shear dypsnea for most of us! PMB is grateful for the use of the picture, and that these dudes were wearing the right colors to match our theme!

PMB: Pumped Up and Popping Wheelies!



We're all excited over here at the PMB because the next few months are full of federal holidays. That raises issues for you, and we don't want to cause you to do a stoppie (braking so hard and fast that you generate significant stopping force at the front wheel and flip longitudinally). Keep this in mind:

• **Veterans Day is Tuesday, November 11.** The NCI Repository will ship as usual on Monday November 10, and FedEx will deliver on Tuesday. If you order for next-day delivery Monday, please confirm that you will be open on Tuesday!

• **Thanksgiving (November 27 in the US), Christmas and New Year's Day are all on Thursdays.** The NCI Repository will not ship any next day orders after Tuesday of the weeks in which they fall. With Santa monopolizing most shipping routes, your orders may take a little more time, too. Please plan accordingly.

• Double wheelie here! We in the nation's capital get an extra day off for presidential inauguration, and in 2009, I**nauguration Day falls right after Martin Luther King's Birthday.** We will be outta here for four days running: Saturday, January 17 through Tuesday, January 20! Again, please make a note of this now, and plan around it.

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Setting a Vicious Pace: On a Bike or in the Clinic!

This puts a new spin on cancer at the cellular level, doncha think?

RANK	Cycle Racing Tactic	Cell Cycle Tactic
1	Drafting: Riding directly behind and slightly to the side of another rider (in his slipstream), to save a considerable amount of energy	The cell's "division cycle" is a series of coordinated DNA replication and division. The cyclin dependent kinase (Cdk) family of serine/threonine kinases is at the core of mammalian cell division cycle. The "dependent" part of the Cdk name means that these kinases' full activity is dependent on association with one of the many regulatory subunits known as cyclins. Different cell cycle phases require different Cdks. Specific Cdks are fully active when their cyclin partners are expressed.
2	Breakaway: A group that breaks away from the main field, bunch or peloton, to have more space and freedom	The p53 gene stops the cell cycle when even tiny DNA double-strand breaks occurs. The cell produces more p53—a breakaway protein, if you will—when it is exposed to DNA-damaging agents (e.g., UV radiation), and p53 induces synthesis of another protein that inhibits Cdk-cyclin complex function.
3	Domestique: A road bicycle racer who works solely for the benefit of his or her team and leader	Cdks induce other proteins to perform their functions and relay a cell from one stage to the next by phosphorylating (adding a phosphate group) key amino acid residues, and cyclins bind to Cdks to control their ability to phosphorylate those target proteins.
4	Cycling sprinter: A road bicycle racer or track racer who finishes a race very explosively by accelerating quickly to a high speed	In addition to the protein phosphorylation cascade that acts as a domestique, the cell cycle has checkpoints to monitor completion of critical events and delay progression to the next stage if necessary. Cancer often mutates the cell cycle and its checkpoints. Because cancerous cells divide rapidly and ignore intracellular control mechanisms, they would be considered the cycling sprinters.
5	Broom wagon: The bus that follows the race to pick up injured, exhausted or straggling riders	Internal or external insults constantly damage cells and threaten their survival. Cell cycle checkpoint mechanisms also make necessary repairs. Cell cycle DNA damage, replication, spindle integrity, and restriction checkpoints would be considered the cell's broom wagon.

Gearing Up: Angiogenesis-Induced Hypertension

Cyclists use a multi-speed bicycle's gears to maintain their pedaling speed while covering rolling terrain: high gear cycling downhill, medium gear on flat roads, and low gear to avoid huffing and puffing uphill. If a bicycle's gears fail, the cyclist's legs must pedal harder to maintain constant speed!

If you use your imagination, you'll see that angiogenesis inhibitor-induced hypertension is similar. Think of microvessels (arterioles and capillaries) as gears, and angiogenesis inhibitors as oil with sand in it. If angiogenesis inhibitors prevent the microvessels from working regularly, blood pressure (BP) increases.

Bicycles are classified in different ways: e.g. by function, by number of riders, by general construction, by gearing or by means of propulsion. Mechanisms of action (MOA) are classified in a bunch of ways, too. Researchers have not elucidated the MOA leading to BP increase during angiogenesis inhibitor therapy yet. They've proposed reduced formation of nitric oxide (NO) by endothelial cells, reduced responsiveness of vascular smooth muscle cells to NO, increased production of or reaction to vasoconstricting stimuli, reduced vascular wall compliance and distensibility, and microvascular rarefaction (decrease in the density of something). Because microvessels are a major contributor to total peripheral vascular resistance, functional rarefaction (fewer perfused microvessels) or anatomic rarefaction (reduced capillary density) may play an important role in hypertension's development.

Currently, nine CTEP-sponsored angiogenesis inhibitors report hypertension as an adverse event. There had been no anti-cancer drugs with hypertension before bevacizumab pedaled up the hill and into our peloton. Other angiogenesis inhibitors have been pedaling in bevacizumab's draft, hoping to mimic or improve on its novel efficacy and toxicity profile that is a distinct improvement on cytotoxic antineoplastics' myelosuppression, vomiting, hair loss, etc.

Hypertension is common globally. However, your gears are stripped if you think the NCI-CTCAE used by oncologists to grade blood pressure is the same as the WHO/ISH criteria used by cardiologists and general physicians (see below). This is a concern since various specialists are involved in the treatment of cancer patients receiving angiogenesis inhibitors, and they aren't always involved with the study. Standardizing our terms for evaluating hypertension and establishing a standard "gear" for initial assessment, surveillance and management of blood pressure in patients treated with angiogenesis inhibitors is a pressing need.

Hypertension Criteria: A Comparison

	Grade 1	Grade 2	Grade 3	Grade 4
NCI CTCAE ver 3.0 for Hypertention	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated	Recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy indicated	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (e.g., hypertensive crisis)
WHO/ISH* classification for Hypertension (1999)	Systolic 140-159 Diastolic 90-99	Systolic 160-179 Diastolic 100-109	Systolic $\geq$ 180 Diastoclic$\geq$ 110	

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No Longer in Suspension...

►Unicycle Units: CCI-779 (temsirolimus, NSC 683864): All trials have been amended to use NCI-supplied commercial Torisel®. Please return investigationally labeled CCI-779 to NCI.

►Tandem Tease! AZD6244 is available as two different formulations with two different NSC numbers. The powder (the free base that is mixed with Captisol immediately before administration) is NSC 741078. The capsule (hydrogen sulfate salt form) is NSC 748727. Each protocol will use only one formulation. Powder and capsule are not interchangeable. Check your protocol before ordering, please.

►Roadster's Rage: Oxaliplatin (NSC 266046): For N0147, 50 mg and 100 mg vials are available. With the 85 mg/m^2 dose, please base your number of 50 mg and 100 mg vials on the patient's BSA to avoid waste.

Investigational Drug Handling Slideshow

PMB is happy to announce that we now offer a training module so you can be prepared for any old thing related to investigational drug handling. This training is the Tour de France of all training, and covers topics from investigator registration to ordering to returning investigational agent, and everything in between. And it has a touch of animation to keep you on your toes!

To access the training, go to the CTEP camp site (http://ctep.cancer.gov –with no "www" in the address, by the way). Look at the yellow vertical banner on the right and scrooooollllll down. You'll find a link called "Investigational Drug Handling Slide Show."

Double click and you will find clear directions how to proceed. These directions are only clear, however, if you read them. (HINT: The slide show has two password screens; on the second, click "Read Only."

Send your comments and questions to pmbafterhours@mail.nih.gov

Please note CTEP will have a new web site very soon!

Pediatrics & Cancer: Let's Roll!

A December 2003 Report to Congress spoke to the roughly 12,000 new cases of cancer diagnosed in children each year in the United States. Approximately 20,000 children receive treatment for cancer in a given year. Five-year survival rates have increased from 25% in the 1960s to 78% between 1992 and 1999. How did we do this? Many childhood cancers respond to surgery, radiation, and chemotherapy; the National Cancer Institute (NCI) funded a national clinical trials network to capitalize on this fact. Most importantly, about 50% of children who enroll in clinical trials choose NCI-sponsored trials.

Despite our significant progress, cancer is the reason about 2,300 children and adolescents never graduate from trikes to bikes annually—they die—and that's more than childhood deaths for asthma, diabetes, congenital abnormalities, and AIDS combined. With use of radiotherapy and surgery limited to select tumors and anatomic sites, chemotherapy is the cornerstone of treatment for most childhood malignancies. Among 120 FDA-approved cancer drugs between 1948 and January 2003, approximately 30 drugs are used in children, yet only 15 have pediatric information in the approved labeling.

The scope of that information is still limited. Many pediatric oncology centers use "off-label" indications as standard of care for kids. "Off-label" means that the drug company has not received FDA approval for a pediatric indication—but it doesn't mean there is no scientific data. Often, drug companies don't apply for pediatric indications because of the financial barriers related to meeting FDA requirements.

This leaves investigators, health care professionals, and parents/caretakers perched precariously on the handle bars, if you will. They need to go forward, but aren't in control! In pediatric clinical trials, investigators extrapolate data from adult trials and determine how the antineoplastic is best used in kids. Despite ample supporting scientific data, most oral investigational drugs are dosage forms unsuitable for young children. In addition, most are not scored, cannot be crushed, and must be swallowed whole. Lacking appropriate dosage forms, investigators and drug sponsors develop extemporaneous or special compounding guidelines for tikes. You know the score: sprinkling opened capsules or crushed tablets onto applesauce, or dissolving the drug in water. Since stability data are sparse and short-term, they advise preparing it "immediately prior to administration."

The question remains: Is the extemporaneous or special preparation safe and accurate? We know it is not ideal. The need to conduct additional trials on agent stability is imperative. Best Pharmaceuticals for Children Act (BPCA) 2002, a legislative initiative, and the Pediatric Research Equity Act (PREA) 2003 have teamed up to address pediatric formulation development. The BCPA addresses on-patent and off-patent drugs indicated in pediatrics. The PREA requires drugs and biologics trials in pediatric populations. As most pediatric oncology drugs are off label, pediatric research that improves dosing and administration in young children will improve safety and outcomes.

Contest Winners

Our last contest, "Happy Campers Get Cookies," was our most successful yet. It appears that clinical trials staff love word search problems! We are all such children, aren't we? Our lucky winners:

Teri Mahaffrey, LPN
Montana Cancer Consortium
Great falls, Montana

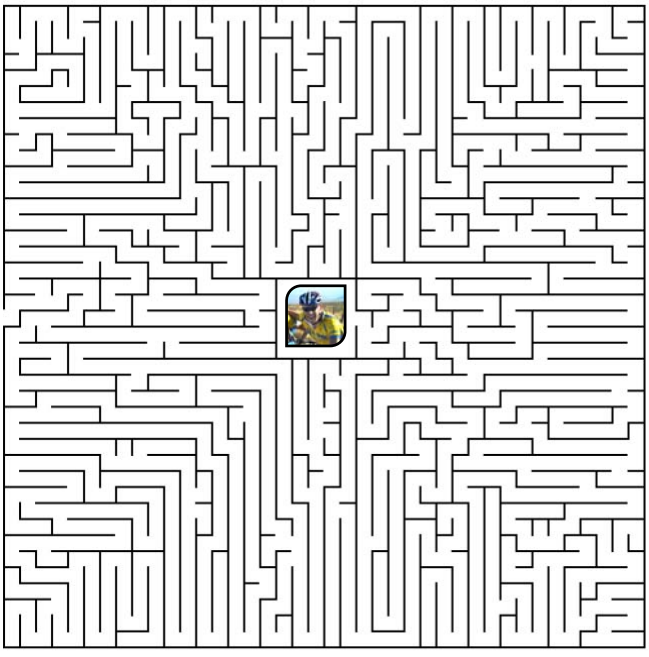
Elizabeth Baxter
Sick Childrens Hospital
Toronto, Ontario, Canada

Mary Ette Hartwick, RN, MS
Mission Hospitals Cancer Program
Ashville, NC

On July 29, 2008, President George W. Bush signed the Caroline Pryce Walker Conquer Childhood Cancer Act. Named in memory of Caroline Pryce Walker, Congresswoman Deborah Pryce's daughter who died of neuroblastoma in 1999 at age nine, the bill authorizes $30 million annually for five years for collaborative pediatric cancer clinical trials research; to create a population-based national childhood cancer database; and to further public awareness about treatment and research for children with cancer and their families.

CONTEST! Biker Dudes Need Help

Lance and Steve got separated on the aforementioned 5% climb—we can't say how or why, but we know they need to find each other. Solve this maze and fax it to (301) 402-0429, and you'll be eligible for our drawing to win homemade cookies or dog biscuits!



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.

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