

INSIDE PMB Jungle Safari MAY 2007



The dawn alarm sounds early here in the concrete jungle, and working at Pharmaceutical Management Branch is like being on a safari. We have many rules that have one goal: safety. We'd like to remind you of three cardinal rules as you begin this excursion:

- Although most safaris ban solitary walks (you might be devoured by a leopard!), PMB-supplied agents must make the long journey back to the NCI Repository by themselves. Translating from the Swahili: You must return only those agents that came from NCI to the NCI.
- Avoid loose scree lacking permanent footpaths: Don't leave the beaten path. Check the Investigators Handbook or call us if you are uncertain about any situation.
- Dusk is short and darkness comes quickly in Africa, and the same is true for expired investigational agents. Once you receive a stock recovery letter for any PMB-supplied agent, please return it to our Repository within 90 days.

So, join our three page safari. You won't need a spotlight to pick out animals' luminous eyes and shadowy forms. You'll have to imagine the scent of frangipani and mimosa. But take a break, graze like a gazelle while you read, and in no time you'll head back to camp.

Jungle Fever? No. Neutropenic Fever

Jungle fever is a severe form of malaria that occurs in the tropics. In the presence of neutropenia, fever—a single temperature greater than 38.3°C orally or greater than or equal to 38°C over one hour without obvious cause—is an early, non-specific sign of infection. Other signs are often absent or muted. Reflecting immunocompromised cancer patients' heterogeneity and the range of pathogens to which they are susceptible, the NCCN just expanded their "Fever and Neutropenia" guidelines to create guidelines on "Prevention and Treatment of Cancer-Related Infections." (See http://nccn.org/professionals/physician_gls/PDF/fever.pdf)

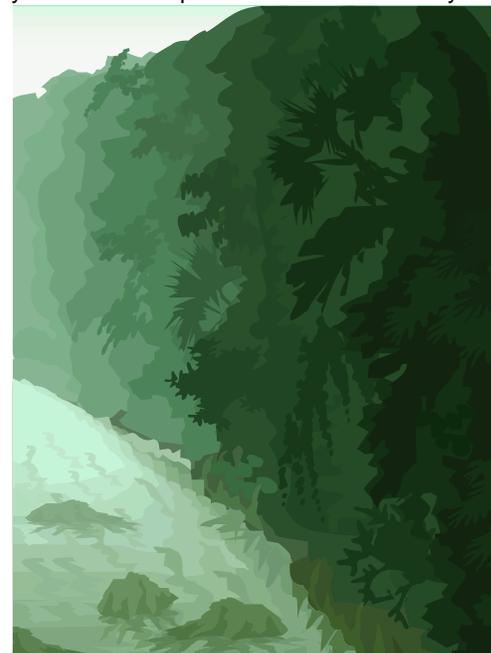
- Below 500/mm³, susceptibility to infection increases. Ten to 20% of patients with neutrophil counts less than 100/mm³ (yes, one hundred!) develop septicemia.
- Patients receiving chemo and biologic therapy may develop "flu-like syndrome (FLS)." FLS's fevers usually peak at 40°C (104°F) and often spike after a severe chill.
- Corticosteroids may blunt the fever response and hide signs of infection.
- Early in neutropenic fever's course, bacteria mainly cause initial infection. Antibiotic-resistant bacteria, yeast, fungi and viruses often follow.
- Initial evaluation should include a site-specific history and physical exam, thorough assessment of common sites of infection (such as alimentary tract, groin, skin, lungs, sinus, ears, perivagina, perirectum, and IV access device sites), cultures, laboratory evaluation.
- Initiate empiric antibiotic therapy soon after fever is noticed.
- Base initial therapy on infection risk assessment, potential organisms, infection site, local antibiotic susceptibility patterns, organ dysfunction, drug allergy, broad spectrum of activity, and previous antibiotic therapy.
- For risk assessment, check out the NCCN guidelines. Patients may be categorized into high- or low-risk groups. Risk criteria are derived from validated clinical prediction rules based on classification systems developed by Talcott and colleagues and the Multinational Association of Supportive Care in Cancer.

NCCN's comprehensive management guideline suggests treating neutropenic patients empirically with broad-spectrum antibiotics at the first sign of infection. However, before initiating monotherapy, institutional bacterial susceptibilities should be determined because antibiotic sensitivity changes are emerging.

Efficiency & Sloth: Intelligent Laziness

PMB is asking its ordering designees to get in touch with their inner sloth. Sloths have made extraordinary adaptations to survive economically on difficult-to-digest leaves that provide very little energy or nutrition. Symbiotic bacteria process tough leaves in large, specialized, stomachs that contain up to two-thirds of a sloth's body-weight. Digestion can take a month or more. Sloths deal with this "poor energy availability" issue with economy measures: metabolic rates less than half that of other animals their size, low body temperatures when active, and lower temperatures when resting.

NCI's energy source (the budget) is stressed right now, and we need symbiosis to deal with it. The message: Whenever possible, please s-l-o-w down and batch the orders destined for PMB. Ask, "Can I wait and send this later?" Rather than ordering an item or two every day, if you could order more along the lines of once per week, we could realize shipping efficiencies. (Think like a sloth: you send fewer orders, you unpack fewer orders.) We recognize it isn't always possible to plan ahead, but we appreciate any and all efforts you make to help us save time and money.



Casablanca: The PMB Version

The scene: A clinical site somewhere in the jungle that has an NCI-sponsored cilengitide study open. A surveyor (played by a wildebeest) enters the agent storage area and meets with the person responsible for maintaining investigational agents (played by a dodo bird).

Sam Dodo: Thinks, "Of all the gin joints in all the towns in all the world, she walks into mine." Says, "What in heaven's name brought you to Casablanca?"

Ilsa Wildebeest: "Here's looking at you; your cilengitide is stored improperly. Round up the usual suspects."

Sam Dodo, snatching the vial off the shelf and squinting at the label, which clearly says *Store at 2° to 8° C:* "I was misinformed."

Ilsa Wildebeest: "Tell me, who was it that left this here? Was it Laszlo, or were there others in between? Or ... aren't you the kind that tells?"

Sam Dodo, lies unconvincingly: "I don't know what you mean, Miss Ilsa!"

Ilsa Wildebeest: "Order it once, Sam, for old times' sake. Order it again, Sam. And return this lot to the NCI Repository."



You must remember this
 A kiss is just a kiss, a sigh is just a sigh.
 The fundamental things apply
 As time goes by

Always read agent labeling.
 Please refrigerate your cilengitide (EMD121974, NSC 707544).



**Important carboxypeptidase
 News on page 3**

Pithy Responses = Tasty Cookies...

Three readers were selected from among the many contestants in February's quiz. A Big ROAR for :

Michael Wortman, Cancer Research Nurse
 Mission Hospitals, Asheville, NC

Sharon Denison, Investigational Drug Pharmacist
 City of Hope Medical Center, Duarte, California

Kristin Henderson, Clinical Research Associate
 Great Falls Clinic, Great Falls MT

Easy Contest:

Lovely Bunch of Coconuts

Are your forms obsolete? Jane of the Jungle knows they are, because she routinely sees Drug Return Lists from the 80s that YOU (yes YOU!) have sent to our Repository. Stop monkeying around with this...

First, get those forms "all standing in a pretty row (deedileede), big ones small ones..." Then check <http://ctep.cancer.gov/forms/index.html> for the most up-to-date versions of the Clinical Drug Request (CDR), Drug Accountability Record Form (DARF), and Agent Transfer Form, Return Drug List, 1572, Supplemental Investigator Data Form, and Financial Disclosure Form. Many of these forms are now in a writable pdf version for your convenience. Please discard obsolete versions and start using the newest versions immediately.

When you are done, E-mail pmbafterhours@mail.nih.gov using the subject line, "Coconut Contest," and tell us (1) that you did it, and (2) how old your oldest obsolete form was. You'll be entered in the quarterly drawing for home baked cookies or dog biscuits (that may be stale, having been baked in 1986).

Verging on Extinction

Ispinesib (SB-715992; NSC 727990): 5 mg vial will be discontinued. Look for a 10 mg (1 mg/mL) vial.

It's sundown on the grassy floodplain for a pride of agents in Pat's portfolio: BPU (NSC 639829) and PZA (NSC 366140) were closed, EF5 (NSC 734904) was transferred.

Migrating Species

PMB will distribute commercially labeled irinotecan (CPT-11, Camptosar®, NSC 616348) for protocols E1304 and RTOG-0625. Note: We do not hold the IND.

Lapatinib (GW572016, Tykerb®, NSC 727989) Now FDA-approved, lapatinib with remain in our herd of kinase inhibitors as our IND studies continue.

New Species

Trials using AZD6244 (NSC 741078) will start this summer. Due to solubility problems, AZD6244 will be supplied with a special anionically charged sulfobutyl ether β-cyclodextrin (Captisol*).

It's sunrise over the mystical mountains for a ruck (yes, a ruck) of agents in Pat's portfolio: tempol (NSC 142784), batracylin (NSC 320826), 1-MT(NSC 721782) and FAU (NSC 678515).

**Watch Captisol and products like it. Traditional formulation systems for very insoluble and/or unstable drugs (think: creosol) have involved a combination of organic solvents, surfactants and extreme pH conditions. These formulations are often irritating to patients and plagued with adverse reactions. Many drugs are up to 90 times more soluble in Captisol than in water.*

Elephants Never Forget!



Jumbo, pharmacy technician,
 Went on a Riviera vacation
 Took his flawless memory with him
 Sans remorse or trepidation.

Ena the screaming pharmacist
 Didn't have a clue
 How (or when) to order
 Or when study patients were due

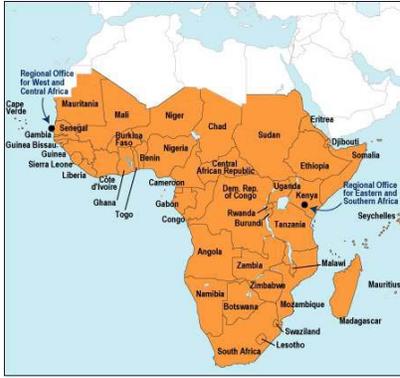


Loquacious clerk Polly
 Had never missed a trick
 She was able to parrot
 How to contact PMB really quick!

Need an answer when PMB is closed,
 but lack that elephantine ability to remember to call tomorrow?
 E-mail pmbafterhours@mail.nih.gov.

Expect an answer within one business day.

Sub-Saharan Africa: Cancers



Sub-Saharan Africa is the term used to describe countries on the African continent not considered part of political North Africa and geographically at or south of the southern edge of the Sahara Desert. Many countries such as Chad, Mali, Sudan, Niger, and Mauritania thus belong to both regions, and for this reason the term can be inexact. Sub-Saharan Africa is the poorest region in the world, and contains many of the least developed countries. Its 42 countries located on the

sub-Saharan African mainland, and an additional six island nations hosted a population of 705 million in 1997.

Cancers in Sub-Saharan Africa have had little visibility in global health communities for many years. The most obvious reason: the high incidence of HIV/AIDS on the African continent took priority and continued to be the emerging and consuming global health issue, specifically in sub-Saharan Africa. About 24.5 million sub-Saharan Africans were living with HIV at the end of 2005 and an additional 2.7 million people were infected with HIV in that year. In total, an estimated 2 million have died and more than twelve million children have been orphaned by AIDS in Africa. Many governments have had difficulties implementing policies that would mitigate the effects of the AIDS-pandemic. Often, the biggest stumbling block is lack of technical support.

Mortality and morbidity data and death registries in sub-Saharan Africa indicate that cancers are emergent health issues needing immediate action in order to sustain the current infrastructure of public health. World Cancer Report of 2002 estimated about half a million cancers occur annually, with approximately 250,000 in males and 279,000 in females. Unlike in more developed countries,

- Cancer registration is almost non-existent
- The incidence is probably underestimated considerably
- 95% of cancer patients present with late disease
- Almost all Africans who develop cancer will die of their disease

In sub-Saharan Africa, the top six leading cancers in males are Kaposi's sarcoma (15.9%), liver (13.3%), prostate (10.7%), esophagus (6.0%), non-Hodgkin's lymphoma (5.8%), and stomach (4.5%). The top six leading cancers in females are cervix (25.4%), breast (17.4%), Kaposi's sarcoma (6.2%), liver (5.5%), stomach (3.8%), and non-Hodgkin's lymphoma (3.8%).

Some factors contributing to cancers are not unexpected considering the prevalence of various health epidemics in some regions of Africa; human herpes virus-8 (HHV8), *Helicobacter pylori* infection, hepatitis B and C infections, human papilloma virus, and Epstein-Barr virus infection play an important role in the development of some cancers. In addition, poverty, lifestyle factors such as smoking and alcohol consumption, lack of education, and lack of accessibility to basic health care (only available in urban centers) are also problems.

Evaluating the relative importance of the leading causes of cancers and their distribution in Africa is difficult. Few clinical trials examining cancers and/or on carcinogenic exposures have been available. Given the multi-ethnic population, multiple life styles, disease patterns, and variation in genetics in Africa, long term surveillance is sorely needed, and would improve the efficacy of cancer control measures.

Simply to Confuse you...

Recently, we sent a letter to sites indicating that Millennium has extended the expiration date for PS-341 (NSC 681239), lot IZ022K. It asked you to make a note of it on any supplies in your possession, and indicated future supplies shipped by NCI will have the old date blackened.

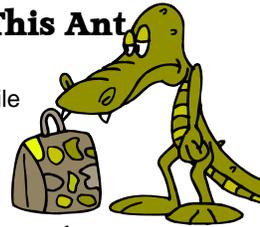
Several sites that host to both NCI-sponsored and company-sponsored trials have called indicating that they received a different letter from Millennium--a letter dated March 30 from J.C. Tetreault indicating this lot will expire.

We have checked with Millennium, and confirmed that lot IZ022K, and specifically the NCI supplies, has been extended for one year.

Please call Millennium's Kate Brown at (617) 551-3839 if you have questions. She will be able to explain/confirm why Millennium sent the letter; what alternatives they have with company sponsored supplies; and that the NCI supplies of this lot have been extended.

The Ants March In. This Ant Marches Out...

We don't want to see any crocodile tears but the NCI's carboxypeptidase IND was inactivated on April 30, 2007. If you are trying to hunt down supplies, you will have to call the manufacturer Protherics using your land lion at 1-888-327-1027.



Since the IND has been inactivated, canoe return all remaining NCI-provided supplies to the NCI ASAP?

Saving YOUR Krugerrands. Spending Ours

In the lower middle of the Clinical Drug Request (NIH-986) there's a sneaky little box that says, "MISCELLANEOUS: Urgent shipments must be accompanied by an express courier account number."

Note this:

- 1 A courier account number on your drug order is a request to ship using this account. If you do not want to be charged, please delete the account number from the CDR!*
- 2 Using your account can speed up a shipment normally sent by Priority Mail by at least 2 days.
- 3 Requests for Saturday delivery must include your institution's courier account number (e.g. Fed-Ex, UPS, Airborne, etc.)
- 4 Urgent orders are subject to the same deadlines and requirements as all other orders
- 5 If your request is truly urgent, please fax it and call us with a head's up

* The taxpayers of the United States thank those very efficient people who have photocopied stacks of CDRs with courier account number pre-filled and are paying for all of their shipments by accident.