



BC PROVINCIAL  
Pediatric Oncology  
Hematology Network

# Newsletter



BC Cancer Agency  
CARE & RESEARCH  
An Agency of the Provincial Health Services Authority



BC CHILDREN'S  
HOSPITAL  
An Agency of the Provincial Health Services Authority

www.kidscancer.bc.ca

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## COMPLICATIONS AND TOXICITIES FROM CHEMOTHERAPEUTIC AGENTS COMMONLY GIVEN IN THE COMMUNITY

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Chemotherapy is one of the treatment modalities commonly used to treat childhood cancer. While such medicines have many different mechanisms of action, most are effective because they kill rapidly dividing cells (eg. cancer cells). Ideally, differences between cancer cells and normal cells will be the target for such therapies<sup>1</sup>. However, this is not always the case, and because many chemotherapy drugs affect all rapidly dividing cells, many normal tissues are affected as well. Such tissues include the hair, the lining of the intestine and the bone marrow. Chemotherapy dosing and timing is often limited by toxicity to normal tissues. The goal of therapy is to balance maximal killing of tumor cells while minimizing harm to the rest of the child's body. Several chemotherapy drugs commonly administered in the community will be reviewed here, with a focus on side effects and toxicities.

**Vincristine** is a chemotherapy drug used in the treatment of acute lymphoblastic leukemia as well as many solid tumors. It is one of the vinca alkaloid chemotherapy agents, and acts by affecting cell division and structure<sup>1</sup>. Vincristine is given intravenously, and care must be given during its administration to avoid accidental extravasation into the tissues\*\* as it is highly toxic to subcutaneous tissues (ie. vesicant). It is metabolized in the liver, and excreted in the bile<sup>1</sup>. Patients with hepatic dysfunction with elevated direct bilirubin levels may require modifications to their dosage. Vincristine also acts on microtubules in the peripheral nerves and, as a result, may cause peripheral neuropathy. The nerves which stimulate bowel contraction are often impacted, resulting in constipation. Regular bowel movements must be maintained while receiving this medication. Many children require laxatives such as lactulose while receiving vincristine. Other nerves which can be affected include nerves important for motor

function in the feet and hands. Many children experience "foot drop", meaning they have weakness on flexion of their ankle, and diminished deep tendon reflexes due to vincristine neuropathy. Parents may notice that their child slaps his feet on the ground while walking. Physiotherapists are essential team members in the assessment and treatment (eg. possible splinting) of vincristine related hand or foot neuropathy. Some children develop a burning sensation or paresthesiae of palms and soles. A rare (but serious) manifestation of peripheral neuropathy is vocal cord paralysis. Children with this dangerous complication may present with a weak or hoarse voice. If both vocal cords are affected, respiratory failure may result. If vocal cord paralysis is suspected, an urgent Otolaryngology consult is mandatory. Other side effects to note include SIADH and associated hyponatremia.

\*\*For treatment of extravasation refer to: <http://www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Policies.htm>

*Continued on page 2...Complications and Toxicities*

### PEDIATRIC ONCOLOGY DAY

DECEMBER 1, 2007

### BRAIN TUMOURS IN CHILDREN

Part of the  
BC Cancer Agency Annual Cancer Conference  
November 29 to December 1, 2007  
Westin Bayshore, Vancouver, BC  
"Technology and Innovation -  
From Bench to Bedside"

### PEDIATRIC ONCOLOGY - PRELIMINARY SCHEDULE

#### Brain Tumours

- ~ Overview of Brain Tumours
- ~ Neurological Assessment
- ~ Neuro-Imaging
- ~ Surgical Issues
- ~ Emerging Therapies

#### Care for the Health Care Team

- ~ Coping with Stress and Preventing Burnout

Enabling Hope in the Midst of Suffering

### **Mercaptopurine and Thioguanine**

are purine analogs, and are part of the thiopurine and antimetabolite group of chemotherapy agents<sup>1</sup>. They interfere with purine synthesis, which is essential for DNA formation. Rapidly dividing cells must produce new DNA quickly, and are thus vulnerable to the effects of these drugs. They are usually given orally and are metabolized in the liver. Some patients are deficient in the enzyme required for their metabolism and are more sensitive to the drugs as a result<sup>1</sup>. Lower doses may be required in these patients. The most common side effects are bone marrow suppression and liver toxicity. Rarely patients may develop a severe form of hepatic dysfunction called veno-occlusive disease. This is a severe and potentially life threatening complication, manifested by jaundice, hyperbilirubinemia, abdominal pain and weight gain due to ascites.



**Asparaginase** is an enzyme produced by bacteria which degrades asparagine<sup>1</sup>. Asparagine is an important nutrient for lymphoblastic leukemia and lymphoma cells, so asparaginase is an important chemotherapeutic agent in the treatment of both of these cancers. Asparaginase may be given in a short acting (L'-asparaginase) or long-acting preparation (PEG-asparaginase). Due to the high incidence of allergic reactions, it is given intramuscularly. Allergic reactions may range from local redness to anaphylaxis. As a result, patients who receive L'-asparaginase are monitored for 1 hour after the injection, and those who receive PEG-asparaginase are monitored for 3 hours after the injection. Other important side effects of this agent include pancreatitis and hepatitis, which may occur days or weeks after administration (especially if the PEG preparation is given)<sup>1</sup>. Abnormalities of the coagulation system may result in bleeding or clotting. Sagittal

sinus thrombosis, a clot in one of the cerebral vessels, is a rare complication.

**Methotrexate** is a chemotherapy agent which can be given intravenously, subcutaneously, intramuscularly, orally or intrathecally (in the spinal fluid). This drug interferes with folate metabolism, and is part of the antimetabolite class of chemotherapeutic drugs<sup>1</sup>. It is used in the treatment of acute lymphoblastic leukemia, lymphoblastic lymphoma and sarcomas. When given in high doses, folic acid is given to bypass this metabolic blockade, with preferential uptake and rescue in normal cells. Common side effects of methotrexate include mucositis, particularly after high dose infusions (> 1g/m<sup>2</sup>) and liver toxicity. Both intrathecal and high dose intravenous methotrexate can cause leukoencephalopathy, which is central nervous system white matter damage from the drug<sup>2</sup>. Leukoencephalopathy is seen most often in patients who have had extensive treatment to the central nervous system, including radiation therapy.

**Doxorubicin** is an antibiotic chemotherapeutic agent in the class of drugs known as anthracyclines<sup>2</sup>. It is also a vesicant like vincristine. Doxorubicin is used to treat acute leukemias, sarcomas and many other solid tumors. Anthracyclines are well known to cause cardiac toxicity, particularly dilated cardiomyopathy<sup>1</sup>. They are also known to cause arrhythmias. Such cardiac side effects may occur shortly after the drug is administered, or even up to 10 years later. Consequently, cardiac function is followed closely while the child is on treatment and for years afterward. While any dose can cause cardiac damage, doses beyond 350 mg/m<sup>2</sup> are associated with greater risk<sup>1</sup>. At British Columbia's Children's Hospital, any dose above 25 mg/m<sup>2</sup> is infused over at least 6 hours to decrease the likelihood of cardiotoxicity. Sometimes dexrazoxane, a chelating agent, is given with anthracyclines to reduce iron-associated free radical damage to the heart<sup>1</sup>. Doxorubicin is metabolized in the liver, and can cause elevation in the transaminases or bilirubin levels<sup>2</sup>. In addition to nausea, vomiting and diarrhea, doxorubicin may also cause significant mucositis<sup>1</sup>.

**Cyclophosphamide** is a nitrogen mustard derivative, and a drug in the class of alkylating agents<sup>1</sup>. These agents damage DNA and result in cell death. They are used to treat



Dr. Guilcher has been appointed a staff Pediatric Hematologist/Oncologist at Alberta Children's Hospital in Calgary

leukemias, lymphomas and solid tumors. Cyclophosphamide is given in various different doses. Smaller doses require less monitoring and supportive care than higher doses, although adequate hydration is a mainstay of supportive care. In addition to nausea, vomiting and myelosuppression, one of the major side effects to consider is hemorrhagic cystitis<sup>1</sup>. This condition is due to one of the toxic metabolites of cyclophosphamide called acrolein<sup>1</sup>. The risk of hemorrhagic cystitis is dose related, and when higher doses are given, another drug called Mesna is often co-administered to bind acrolein and reduce toxicity. High doses may be associated with sterility especially in males and secondary malignancies.

**Dexamethasone** and **Prednisone** are glucocorticoid steroids used in the treatment of acute lymphoblastic leukemia. They are administered monthly for five days when children are in the maintenance phase of their treatment. Common side effects include increased appetite, fluid retention and weight gain, acne, mood and sleep disturbance, hyperglycemia, bony pain, osteoporosis, hypertension and gastric ulceration. Due to possibility of gastrointestinal upset and bleeding, patients are given ranitidine to decrease gastric acid production while receiving steroids. Steroids also make children more vulnerable to viral and fungal infections. Long term use of steroids may result in adrenal suppression, and this should be kept in mind if a child presents in shock. Another important side effect to consider is avascular necrosis (AVN). Teenagers, especially females, are showing increasingly high rates of AVN due to steroid use. When suspected, appropriate radiologic investigations and referral to an orthopedic surgeon are required. Osteopenia and osteoporosis may occur as a result of steroid therapy.

While this list of medications and their side effects is not exhaustive, it serves as an introduction to guide those involved in the care of the children receiving them. Advances in the treatment of childhood cancer has improved in great part due to the improved dosing and scheduling of known medications, and a better understanding of the associated supportive care required<sup>1</sup>.

#### References

1. Pizzo PA, Poplack DG. Principles and practice of pediatric oncology. Fifth Edition ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2006.
2. Altman AJ. Supportive care of children with cancer. Third ed. Altman AJ, editor. Baltimore: The Johns Hopkins University Press; 2004.

## ADVERSE EVENTS IN PEDIATRIC ONCOLOGY THE GATC CANCER STUDY

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BC Children's Hospital

Cure rates for children with cancer have increased dramatically over the last few decades with currently over 75% of children being cured of their disease. However, the improvement in cure rates has come at a significant price – many of these survivors are left with life-threatening or life-altering late effects. In children, it is estimated that adverse reactions to medications account for 22% of all pediatric oncology patient hospital admissions. There is no current explanation as to why a child has an adverse event to chemotherapy, while a similar child receiving the exact same drug combination does not. The GATC Cancer Study is a partnership between the Division of Oncology at BC Children's Hospital (Drs. Rassekh and Rogers), and the Center of Molecular Medicine and Therapeutics (Dr. Hayden) and the Pharmaceutical Outcomes Programme & Policy Innovations (Dr. Carleton) that hopes to answer this very important question.

Although many factors influence the effect of medications (i.e. age, organ function, and drug interactions), it has been estimated that genetic factors account for 20-95% of drug response variability and contribute to an estimated half of all adverse drug reactions (ADRs). Many of these ADRs become apparent during the course of therapy, such as vincristine neuropathy that, if severe, will cause the oncologist to withhold or use lower doses of this

agent. However, many of these ADRs may not become evident until months or years after treatment has concluded and the child is cancer-free. For example, it is well known that children who receive anthracyclines, especially at high cumulative doses, are at risk for developing cardiac dysfunction years after their treatment has been completed. These late-effects are the key reason why long term follow-up of survivors of childhood cancer needs to be a priority.

The GATC Cancer Study is designed to evaluate genetic factors that may predispose a child to an adverse event. We have embarked on a study to investigate the hypothesis that the reason that only certain children have an ADR to a particular drug is that there are very subtle genetic differences in key drug metabolizing and transporting genes that cause different responses to different medications. This project functions under the umbrella of the general pediatric GATC study which is funded through Genome BC and Genome Canada, and is one of the studies in the new and exciting field known as Pharmacogenetics. This field has become possible due to the development of incredible technology made possible by the interest in the Human Genome Project. The basis of pharmacogenetics is the study of single nucleotide polymorphisms (SNPs). The single nucleotide (encoded by one of 4 nucleotides: G, A, T and C) is the basic building block of DNA. It has been shown that individuals have single nucleotide differences every 1200 base pairs, meaning that any two individuals



### Canadian Association of Nurses in Oncology

*CANO's mission is to lead nursing excellence in cancer control for Canadians, with a vision of being an international nursing leader in cancer control*

19th Annual Conference  
"Using Hearts, Minds and Voices:  
Oncology Nurses Influencing Cancer Care"  
October 28 to 31, 2007  
Hyatt Regency, Vancouver, BC

have approximately 5 million SNPs different between them. A SNP differs from a mutation in that at least 1% of the population must carry the SNP. For example, a hypothetical gene may have a particular SNP where different people have different genotypes – 60% of the population may have a GG genotype, while 30% of the population has a GT genotype, while the other 10% has a TT genotype. The person with the TT genotype may metabolize a drug much faster than the person with the GG genotype – and therefore require a much higher dose of that particular drug. The person with the GT genotype being a heterozygote with both a T and a G will typically need a drug dose in between the other two genotypes. Therefore the population can be broken down into three groups: those requiring normal dosing (GG genotype), those needing intermediate dosing (GT genotype) and those requiring low dosing (TT genotype). Pediatric oncology already has a classic example of a SNP that has been shown to confer different dosing for a medication - the TPMT polymorphisms leading to different doses of 6-mercaptopurine (6-MP). It is well established that a particular SNP at this TPMT gene can predict a subset of the population (approx 10%) that are heterozygotes and need smaller doses of 6-MP, and another subset that needs 5% dosing of this drug (found in 0.3% of the population). In the next few years, this TPMT SNP testing will likely become the standard of care for children with leukemia in order to

correctly select their starting 6-MP dose. Gone will be the days where we start everyone at 100% dosing of 6-MP and then 'wait and see' who becomes profoundly neutropenic and then discontinue the drug until count recovery. In the future, we will likely individualize the starting dose of 6-MP based on which SNP an individual has in his TPMT gene.

The GATC study has been actively investigating all severe ADRs seen in patients being followed through BC Children's Hospital. Children with ADRs are being identified both prospectively and retrospectively through the Long Term Follow-up Clinic. In 551 children attending this clinic we have identified that 146 (24.5%) have had at least one significant ADR (only Grade 3 or 4 toxicities have been called significant in this study). The ADRs that have been identified thus far include: anthracycline cardiotoxicity (45 subjects), cisplatin induced hearing loss (34), severe vincristine neuropathy (26), methotrexate severe adverse event (15), asparaginase anaphylaxis or pancreatitis (28), and veno-occlusive disease (13). Of note is the fact that many individuals unfortunately suffer from more than one significant ADR – in fact 22 of the 551 children and young adults had 2 significant ADRs, 4 patients had 3 ADRs, and 2 unfortunately had 4 ADRs.

We decided to focus our initial study on two particular ADRs: cisplatin-induced hearing loss and anthracycline-

induced cardiac failure. It is estimated that 10-25% of children receiving cisplatin will have significant hearing loss, while the rest only have mild hearing loss at the high frequencies (not in the speech frequencies). It is estimated that 7-10% of children receiving anthracyclines will have measurable cardiac dysfunction, with possibly up to 40% having mild but detectable cardiac effects. This case-control study design will identify 100 ADRs for each of these two drugs and match them with 400 controls who received the same chemotherapeutic combination. The hearing loss cases are those who have > 20 dB hearing loss in the speech frequencies, while the anthracycline cases are those with evidence of congestive heart failure or a shortening fraction of below 29% on echocardiogram at any point during therapy. Preliminary results which have been obtained in 17 cisplatin ADRs and 26 anthracycline ADRs have been very encouraging. Using a spit or blood sample collected from cases and controls, we run the samples on a SNP chip which has been specifically designed for this project to look at 220 drug metabolizing or transporting genes. Each chip contains the ability to look at 3072 different SNPs at the 220 pre-selected genes. Our early results have found that a promising SNP has been identified that appears to be associated with cisplatin hearing loss. This particular SNP has biologic plausibility for contributing to hearing loss, as it codes for a gene involved that helps rescue cells from free-

radical damage. A SNP of interest has also been identified for anthracycline cardiac damage and this SNP codes for a drug transporter that moves anthracycline derivatives out of cardiac muscle. Therefore, the early results are very encouraging and, through the generosity of the C17 Research Network, we have been able to expand the study to all 17 pediatric oncology centers in Canada in order to complete accrual by July 2008.

The study has been very well received by the children, teens, young adults, and their parents that have been approached to participate. Without their support, along with the support of the long term follow-up clinic and the booking clerks, this project would not be possible. In fact, it has been humbling to see that so many families are participating in this study to try and minimize adverse events for future generations. Our goal is to make the treatment of cancer safer for all children so that we not only try and cure every child or young adult, but to minimize the late-effects of therapy. This study is only the first step to try and make chemotherapy safer for any particular individual. Our goal is to first identify individuals at high risk for chemotherapy ADRs using a simple blood or spit sample. Subsequent studies will then be needed in those identified high risk subjects in order to see whether we can dose adjust, use alternative chemotherapy, or use protective agents to try and maintain (or even improve) cure rates and decrease the rates of significant adverse events. We may not be far away from the day that we dose chemotherapy not by weight or body surface area, but by a person's genetic profile at key drug metabolizing enzymes.

For further information on the GATC Cancer Study, or to refer any patient to be included in this study, please do not hesitate to contact me at: rrassek@cw.bc.ca.



Dr. Rassekh will be on staff at BC Children's Hospital as a Pediatric Hematologist and Oncologist effective July 2007

### SIBLINGS COPING TOGETHER (SCT)

The Oncology Program at BC Children's Hospital is offering a group program for brothers and sisters of children being treated for cancer. Healthy siblings may experience difficulties with family members, school life, and peers. Even those who are coping well with their situation can benefit from additional support during this difficult time. The goals of the Siblings Coping Together group are to provide social interaction, educational opportunities, and a safe setting for expressing thoughts and feelings.

- Who may participate:** Siblings between the ages of 6 and 16 years
- When is the next group:** Spring 2007
- For more information:** Call Dr. Joanna Chung, Psychologist (604) 875-2345 ext 3003



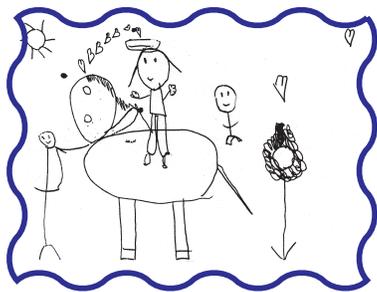
From some of the campers at Zajac Camp  
Date of camp: October 13 to 15, 2006  
Campers: Children with cancer and blood disorders and their siblings

Sponsored by Balding for Dollars and supported by the Oncology/Hematology/BMT department at BC Children's Hospital



From Brendan.

Dan took me to camp with my cousin Stephen. The hardest part of the climbing wall was getting off the cargo net. My goal was to climb up the upside down part but I really didn't get to touch it. I love Archery. When I shot my arrow it went right into the board. It wasn't a bull's-eye, but it was the next ring from the bull's-eye and I was so proud. Everybody called me Robin Hood from that day on. Seriously they did. Camp was lots of fun. Thanks for letting us come.



TO: ZAJAC RANCH

Thank you SO much for inviting me!

I had the time of my life!!!

I can't tell you how much fun I had.

So could you ~~pretty~~ please invite me and my little sister Ella again!!!

Thank you so much

SARAH HAYSON AGE 9 1/2



I liked the climbing wall and the crafts the best. I had fun with everybody, and when we sneaked up on the boys they yelled and...

I wish I could go there again, like 100 times and we actually weren't there three days, it was a special new friends. I met we're Julia, Hailey, Ella and Sarah. I forget all the rest of the names.

One boy there was walk sleeping, but I forget his name.

Thank you for letting me go to camp Zajac Ranch. Paige Timmers



Return Undeliverable Canadian Addresses to  
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## The Provincial Pediatric Oncology/Hematology Network

The Network is an interdisciplinary organization whose goal is to ensure appropriate diagnosis, management, follow-up, and end-of-life care for pediatric patients with malignancies and blood disorders.

The Network supports community hospitals and practitioners, and develops partnerships with other health care facilities to enable seamless and integrated care for patients and families on treatment and off treatment.

It will further develop and enhance the research programs of basic, translational, and clinical research to better childhood cancer control and improve outcomes for these patients and their families.

### For More Information

To learn more about the Provincial Pediatric Oncology/Hematology Network, or to submit articles or stories to this newsletter, please contact:

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# TEEN ADVENTURES SPIRIT QUEST 2007



Surfs Up  
April 27-30, 2007

Tofino  
Chesterman on the Point



Kayaks & Killer Whales  
June 30 - July 4, 2007

Johnstone Straits  
Power to Be



Horse & Howdies  
July 20-23, 2007

Chilcotin/Cariboo  
Crystal Waters Ranch



River Rafting  
August 26-29, 2007

Thompson &  
Fraser Rivers  
Kumsheen

All activities are sponsored by the Oncology/Hematology/BMT Department through Balding for Dollars.

For more information about Teen Adventures/Spirit Quest 2007 or to register for one of these activities, please contact Dan Mornar or Nita Takeuchi:  
Dan Mornar, dmornar@cw.bc.ca, 604-875-2345 ext 6477  
Nita Takeuchi, ntakeuchi@cw.bc.ca, 604-875-2664

## CCSSBC CHILDHOOD CANCER SURVIVOR'S SOCIETY OF BRITISH COLUMBIA

"ALL CANCER SURVIVORS LIVING THEIR VISION"

Survivor: *someone who has survived or been affected by cancer, and who thinks, defines or considers himself or herself to be a survivor*

We are a group of young adult cancer survivors who want to stay connected to the hospital community and each other.

Our main focus is not to be a support group but to be a social outlet for young adults who have gone through cancer treatment.

Meetings:  
Last Thursday of each month  
Odd Fellows Hall \*90  
1443 W. 8th Avenue  
Vancouver, BC



For more information about the CCSSBC, please contact any of the following:  
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