

## An update for Low and Average Risk B-Cell precursor Pediatric Acute Lymphoblastic Leukemia

By Dr. Christopher Fryer FRCP(C)

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Acute Lymphoblastic Leukemia (ALL) is the most common paediatric malignancy and accounts for 21% of cancers in <17 years age group with 5 year survival rates now approaching 90%. Patients commonly present with anemia, bone pain, fever and sometimes hepato/splenomegaly. Investigations usually reveal abnormalities in at least 2 of the 3 cell lines (hemoglobin, white blood cells and platelets). Patients suspected of having leukemia should be referred to BC Children's Hospital (BCCH) Oncology division for definitive diagnosis which is undertaken looking at the morphology and immunophenotype of the bone marrow blast cells. Patients have a central line inserted (usually a venous access device) for chemotherapy administration once the diagnosis is confirmed.



DR. CHRIS  
FRYER

ALL is a heterogeneous disease comprised of morphologically identical leukemias arising from different biological

mechanisms. Flow cytometry immunophenotyping differentiates the common B-cell precursors from T-cell and biphenotypic leukemias.

Treatment depends on risk stratification. The 2008 WHO classification incorporated the category B-lymphoblastic leukemia/lymphoma into the precursor lymphoid malignancies.

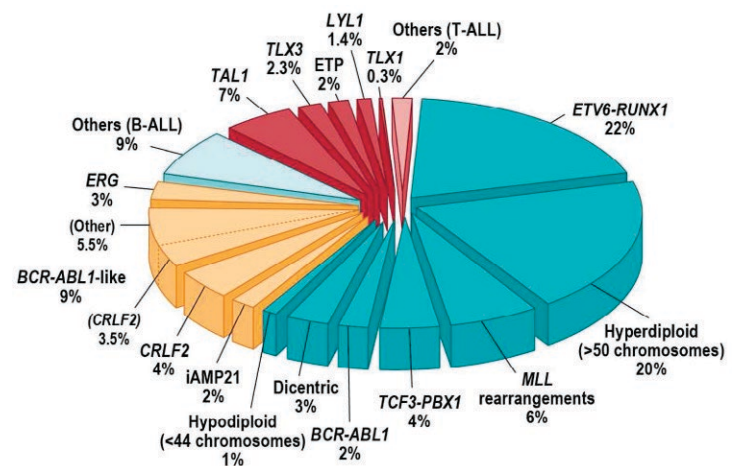
For B-cell precursor ALL, the NCI/Rome classification identifies 3 risk groups viz:

- Standard Risk: age 1-9 years and WBC <50,000
- High Risk: age 10+ years or WBC >50,000
- Infants: age <1 year

Approximately 75% of childhood ALL harbor chromosomal aberrations detectable by karyotyping, FISH or molecular techniques that may incur a favorable or unfavorable prognosis.

### Estimated frequency of specific genotypes in childhood ALL

From Inaba H. et al. Lancet 2013;381:1943-55



The genetic lesions associated with B-cell precursor ALL are in blue and yellow. Unfavorable genetics are: hypodiploid <44; BCR-ABL1; intrachromosomal amplification of chromosome 21. Favourable genetics are: hyperdiploidy >50; trisomies 4, 10&17; ETV6-RUNX1.

B-cell precursor ALL is now risk classified using a combination of NCI (National Cancer Institute) risk group, sentinel cytogenetic lesions, clinical variables (CNS and testicular status) and early treatment response evaluating minimal residual disease (MRD) in peripheral blood (PB) at Day 8 and in the bone marrow (BM) sample at Day 29 of Induction phase.

Based on these findings, patients with B-cell precursor ALL are stratified into one of 4 risk groups for post-Induction therapy:

Low Risk (LR)	5-year Event Free Survival (EFS) rates of >95%
Average Risk (AR)	5-year EFS rates of 90-95%
High Risk (HR)	5-year EFS rates of 75-90%
Very High Risk (VHR)	5-year EFS rates of <75%

**Patients with Low or Average Risk** (50% of population) has the following characteristics: Age 1-9 years; WBC <50,000; CNS and Testicular negative, No unfavorable genetics. MRD day 8 <1%; MRD day 29 <0.01%.

*continued on page 2*

## Low and Average Risk B-Cell precursor Pediatric ALL continued from page 1

All patients age 1-9 years with WBC <50,000 are treated according to the Children's Oncology Group (COG) AALL0932 protocol (open study). They receive a standard 29 day 3-drug induction phase consist of:

### 1) INDUCTION

Vincristine (VCR), Dexamethasone (DEX), Pegaspargase (PEG ASP) and Intrathecal Cytarabine (IT ARAC)/Methotrexate (IT MTX)

### 2) CONSOLIDATION for 4 wks

Vincristine, Mercaptopurine (MP) and Intrathecal Methotrexate (IT MTX)

### 3) INTERIM MAINTENANCE #1 (IM I) for 8wks

Vincristine, escalating IV Methotrexate and Intrathecal Methotrexate

### 4) DELAYED INTENSIFICATION (DI) for 8wks

Vincristine, Dexamethasone, Doxorubicin (DOXO), Pegaspargase, Cyclophosphamide (CPM), Thioguanine (TG), Cytarabine (ARAC), Intrathecal Methotrexate

### 5) INTERIM MAINTENANCE #2 (IM II) for 8wks

Vincristine, escalating IV Methotrexate and Intrathecal Methotrexate

### 6) MAINTENANCE This study compares different arms of therapies for maintenance. Consented patients are randomized to 1 of 4 arms:

Arm A (Standard Arm): VCR/DEX pulses q 4-weeks and oral MTX at 20 mg/m<sup>2</sup>/week;

Arm B: VCR/DEX pulses q 4 weeks and oral MTX at 40 mg/m<sup>2</sup>/week;

Arm C: VCR/DEX pulses q 12 weeks and oral MTX at 20 mg/m<sup>2</sup>/week

Arm D: VCR/DEX pulses q 12 weeks and oral MTX at 40 mg/m<sup>2</sup>/week

Patients on all arms receive oral MP daily and Intrathecal MTX q 12 wks  
Duration of maintenance is 2 years in girls and 3 years in boys from the start of Interim Maintenance #1.

Induction phase is always started at BCCH. Consolidation, Interim maintenance, Delayed Intensification, and Maintenance phases could be given in communities. Care is provided by local physicians and nurses with experience in providing chemotherapy to children. Local care is directed and supervised by medical specialists from BCCH. The goal is to provide high quality, safe and effective clinical and supportive care in an appropriate environment as close to a patient's home as possible.

Ref: Community based – levels of care: [www.bcchildrens.ca/NR/rdonlyres/A5F3189A-BBE2-4F14-A83E-958A75E73760/o/LevelsofCareoct2011rev.pdf](http://www.bcchildrens.ca/NR/rdonlyres/A5F3189A-BBE2-4F14-A83E-958A75E73760/o/LevelsofCareoct2011rev.pdf)

## Supportive Care during Treatment

**Pneumocystis prophylaxis:** All patients receive trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of TMP 5 mg/kg/day divided bid 2-3 sequential days per week.

**Transfusions:** Current recommendations are to use irradiated blood products and transfuse if hemoglobin <70g/L or platelets <10 x 10<sup>9</sup> /L

**Immunization:** Live vaccines should be avoided while the patient is on chemotherapy (immunocompromised)

**Fever and neutropenia:** see [www.bcchildrens.ca/Services/Onc-HemBMT/for-professionals/resources/default.htm](http://www.bcchildrens.ca/Services/Onc-HemBMT/for-professionals/resources/default.htm)

## Surveillance Post Treatment

It is recommended to perform physical examination, testicular examination, BMI and Tanner staging. CBC/diff/plts every 2-3 monthly for year 1 and 2, 3 monthly for year 3; and 6 monthly for year 4 and then annually. For information on long term follow up guidelines, please visit: [www.bcchildrens.ca/Services/Onc-HemBMT/survivors/long-term-follow-up-guidelines.htm](http://www.bcchildrens.ca/Services/Onc-HemBMT/survivors/long-term-follow-up-guidelines.htm)

Recurrence beyond 5 years from diagnosis is extremely rare in this treated population.

### Reimmunization:

On completion of chemotherapy individuals should be immunized according to past immunization history. Ref: BC Centre for disease Control:

[www.bccdc.ca/NR/rdonlyres/3E63F4F8-BD1A-4F4D-B716-3D77B25046E2/o/SectionIII\\_ImmunizationofSpecialPopulations.pdf](http://www.bccdc.ca/NR/rdonlyres/3E63F4F8-BD1A-4F4D-B716-3D77B25046E2/o/SectionIII_ImmunizationofSpecialPopulations.pdf)

The vast majority of survivors in this population are unlikely to have major health issues related to their therapy. We recommend all 5 year + survivors have an annual physical by their pediatrician and/or their primary health care provider. Patients are followed until age 17 years and 5 years post treatment. They are then counseled, provided with their medical summary including any existing or potential health risks and individualized surveillance recommendations and then transitioned to their primary health care provider. They are also consented to be placed on an annual letter follow up program which is managed by the long term follow up nurse clinicians in the Oncology division at BCCH. For more information on Long term follow up clinics, please visit: [www.bcchildrens.ca/Services/Onc-HemBMT/survivors/Default.htm](http://www.bcchildrens.ca/Services/Onc-HemBMT/survivors/Default.htm)

## Potential late sequelae

**Osteonecrosis:** The risk is very low (<1%) and appears within 2 years of diagnosis. Symptoms are persistent bone pain. Investigate with MRI or bone scan.

**Osteopenia:** Rare but all patients should take supplemental Vitamin D and Calcium.

**Obesity:** Survivors are at an increased risk, although the reasons are unclear, and appropriate nutritional counseling and exercise should be provided.

**Neurocognitive issues:** These are rare in this population since methotrexate doses are relatively low and patients do not receive cranial radiation.

**Fertility:** Unlikely to be affected as cyclophosphamide dose is low (1Gm/m<sup>2</sup>)

**Cardiac function:** Unlikely to be affected as anthracycline dose is low (75mg/m<sup>2</sup>).

For more information on Acute Lymphoblastic Leukemia, please visit Pediatric Oncology Education Material: [www.pedsoncologyeducation.com/ALLReferences.asp](http://www.pedsoncologyeducation.com/ALLReferences.asp)



# Commonly Used Chemotherapeutic Agents in Pediatric Acute Lymphoblastic Leukemia

By Roberta Esau BSc Pharm

Acute Lymphoblastic Leukemia (ALL) is the most common childhood malignancy and requires the longest treatment: 2.5 years for



girls, 3.5 years for boys from start to finish. It is, therefore, great help to families if the treatment can be given closer to home. The side effects and administration methods for a few of the chemotherapy agents that might be given outside of BC Children's Hospital (BCCH) will be discussed in this article.

## Corticosteroids

Corticosteroids, either prednisone or dexamethasone, are backbone of ALL treatment.

### Side effects

Each of the usual steroid side effects can be expected, though hyperglycemia is more commonly seen with the induction phase of treatment when steroids are given daily for 14 to 28 days. Hyperglycemia is managed with diet if possible and occasionally with insulin. In most cases it resolves at the end of induction phase and does not recur with subsequent steroid pulses (5 days of treatment).

Aseptic necrosis (also known as osteonecrosis, avascular necrosis or AVN) can be a painful and debilitating effect of corticosteroids in children, particularly those greater than 10 years of age. It is not an acute effect; it usually presents later in the maintenance phase of treatment. There has been much research into this side effect. Methods of decreasing the incidence have been examined, such as using different steroids in different age groups (prednisone is used in patients >10 years of age) and using different schedules to find a minimal effective dose.

Management of AVN is controversial. Some centres use bisphosphonates to relieve pain. However, studies of small number of patients have not shown consistent improvement with this treatment. Definitive treatment is joint replacement. Patients must be examined for bone or joint pain at each visit and notify oncologist of any findings. Steroid therapy may be interrupted in the maintenance phase of treatment if symptoms are severe.

Gastrointestinal irritation is commonly seen and patients are usually prescribed a course of ranitidine with each course of steroid.

Psychological effects are common in children. Parents can testify how they dread the 5 day pulses of steroids and the accompanying symptoms of insomnia, tearfulness, irritability, argumentative behavior or tiredness. Patience and reassurance are required.

## Cytarabine (ARAC)

Cytarabine is given intrathecal (IT) on the first day of induction phase of ALL therapy. Subsequent doses in other treatment phases are given intravenous (IV) or subcutaneous (SC).

### Side effects

The dose-limiting toxicity of cytarabine is myelosuppression. Two common side effects are fever and nausea and vomiting. Fever which is confounding in our patients as we are never sure if this caused by infection or cytarabine. Patients are assessed for a source of infection. In the event that the fever does signify an infection, ceftriaxone is often used. Using anti emetics such as ondansetron 30-60 minutes before administering cytarabine is effective in reducing the incidence of nausea and vomiting. It is important to instruct parents to administer ondansetron regularly while the patient is receiving cytarabine.

Cytarabine in high doses (2 g/m<sup>2</sup>/dose or greater) can cause neurotoxicity but this is rarely seen at the doses used for treatment of ALL.

### Administration

Doses of 75 mg/m<sup>2</sup>/dose are drawn up in the biohazard hood in the pharmacy and given undiluted by IV push. Cytarabine can also be given by SC route but this is not popular with children.

## Doxorubicin and daunorubicin

These 2 anthracycline agents are used sparingly in low or average risk ALL protocols.

These drugs are vesicants. Severe tissue damage will result from extravasation. The risk of extravasation is greatly reduced when administered through central lines.

### Side effects

Cardiac toxicities (subclinical cardiac dysfunction, congestive heart failure) dominate the toxicity profiles. Patient's cardiac function is monitored by echocardiograms specifically looking at shortening fraction (SF). Doses may be held according to the protocols' modifications for toxicity. An Anthracycline Cumulative Dose Record is kept and aims to keep the maximum cumulative dose for all patients less than 300 mg/m<sup>2</sup>. The cumulative dose in most patients with low or average risk ALL is about 75 mg/m<sup>2</sup>. The bright red colour of doxorubicin and bright orange colour of daunorubicin may manifest in patients as pink or red urine, sweat, tears or saliva. This can be alarming so patients and families need to be reassured that they are not seeing blood. Other common side effects of these two drugs are nausea and vomiting, myelosuppression and mucositis.

### Administration

Doses up to and including 25 mg/m<sup>2</sup>/dose are given undiluted by IV push at BCCH. Larger doses (not used in ALL protocols) are diluted in 25 mL normal saline or D5W minibags and infused over 30-60 minutes or as instructed by the protocol.

*continued on page 4*



Commonly Used Chemotherapeutic Agents  
continued from page 3

## Mercaptopurine (MP) and thioguanine (TG)

These oral (PO) agents are commonly given in several phases of ALL treatment.

### Side effects

Most common side effect is myelosuppression. Monthly complete blood counts (CBC) is drawn during maintenance phase. The blood results are used to guide dosing. In most cases, oncologists at BCCH determines if doses should be adjusted in order to achieve the absolute neutrophil count (ANC) and platelet count range described in each treatment protocol.

## Methotrexate (MTX)

Methotrexate is given by the IT, IV and PO routes during ALL treatment in a variety of doses. Patients are given weekly (NOT daily!) PO MTX throughout maintenance phase, but not on the days that they get IT MTX.

### Side effects

Myelosuppression is common with MTX. As the mercaptopurine dosage is guided by monthly CBC so is the MTX dosage which is adjusted as appropriate. Mouth sores are also frequent with MTX, although not with the PO doses used in ALL treatment

Drug interactions: Penicillins, proton-pump inhibitors (e.g. omeprazole, pantoprazole), cotrimoxazole and non-steroidal anti-inflammatory agents (NSAIDs) compete for excretion at the renal tubule in the kidney and can delay the excretion of MTX. This interaction is not significant with IT or PO doses of MTX. Co-administration of these agents while patients are getting high IV doses of MTX (greater than 1000 mg/m<sup>2</sup>/dose) is contraindicated. When these drugs are given concurrently with high IV doses of MTX, excretion is prolonged significantly and toxic effects (renal toxicity from precipitation in the renal tubules and mucositis) are observed.

### Administration

IT doses are prepared in syringes in volumes appropriate for patient. The syringes have distinctive bright green IT stickers on the syringe and outer packaging.



IV doses up to 350 mg/m<sup>2</sup>/dose are added to 25 mL D5W minibags and infused over 10-15 minutes which results in less nausea and vomiting than giving these doses via IV push. High doses (greater than 1000 mg/m<sup>2</sup>/dose) are administered in large volumes of fluid. Patients are given generous hydration before and after each dose. Oral doses should be handled as per the guidelines in the resource listed.

Families are given “Chemotherapy Safety at Home” pamphlet before they are discharged from the hospital. [http://www.cw.bc.ca/library/pdf/pamphlets/BCCH1466\\_ChemotherapySafetyHome\\_2012.pdf](http://www.cw.bc.ca/library/pdf/pamphlets/BCCH1466_ChemotherapySafetyHome_2012.pdf)

## Vincristine (VCR)

Vincristine like corticosteroids is also the backbone of ALL therapy and is given throughout treatment.

### Side effects

VCR does not cause significant myelosuppression so doses are usually given without regard to white blood cell (WBC), absolute neutrophil count (ANC) or platelet counts. The lack of myelosuppression and low emetogenicity makes VCR different from many chemotherapeutic agents. The distinctive and primary dose-limiting toxicities of VCR are those of neuropathy, which can be peripheral (tingling of fingers, foot drop, decreased deep tendon reflexes, ataxia), autonomic (decreased intestinal motility) or central (headache, seizures, SIADH). Patients should be examined for abnormal gait and reflexes, as well as questioned about signs of peripheral neuropathy (e.g. decreased writing skills or difficulty buttoning clothing). Other neuropathies

include vocal cord paralysis and ptosis. Severe neuropathies are managed by withholding VCR doses until symptoms resolve and then reintroducing the drug in small increments as described in the “modifications for toxicity” section of each treatment protocol. Constipation is avoided with diet, if possible, but often with the help of laxatives: polyethylene glycol crystals are frequently prescribed (but must be taken with adequate fluid intake to be effective). Suppositories are *contraindicated* due to the risk of anal fissures and the introduction of fecal bacteria into the bloodstream.

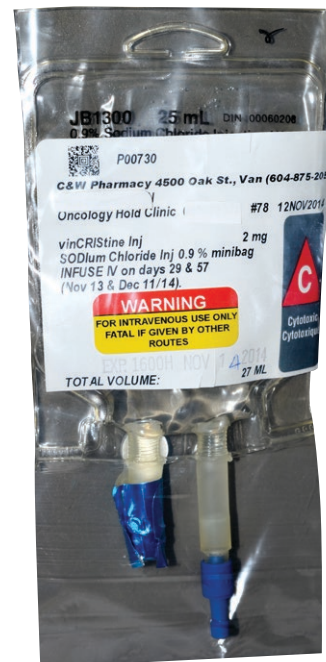
### Administration

At BCCH, all doses of VCR, to all ages and sizes of patients, are prepared in 25 mL normal saline minibags. The measured dose is added to the minibag. Nurses administer the content of the bag, labeled “for IV use only” by IV infusion over 1 to 2 minutes. VCR is considered to be a vesicant but the risk of extravasation is greatly reduced when doses are given through central lines. VCR administered by the IT route is universally **fatal** and extreme care must be

taken to avoid this devastating error.

On days when both VCR and IT medication are to be given to a patient, the BCCH pharmacy sends only IT medication for that patient to the oncology ward. Once the IT medication is given, the patient’s completed sedation record is scanned to the pharmacy. The scanned sedation record indicates that the patient has left the procedure room and is ready

to receive other chemotherapeutic agents. Only then, pharmacy will send the other chemo agents to the oncology ward.



## Thoughts from Dr. C Strahlendorf – Division Head of Oncology Hematology BMT

We are entering a new era in the fields of both pediatric oncology and hematology – an era where understanding the tumour



**DR. CARON  
STRAHLENDORF**

genetics is allowing us to better understand the biology of the disease, and hence find more targeted therapies. Certainly in oncology a personalized approach to therapy is already a reality. Treatments targeting specific pathways are available while the knowledge of the host genetics allows the delivery of therapy with less toxicity. Our successes in pediatric oncology are to be celebrated, but we still have the task of finding the cure for all children and continue to be challenged to prevent late effects from treatment. We are also entering

a new era for bone marrow transplant in which we can now provide transplants for more complex diseases, malignant diseases, hematological disorders, immune and biochemical diseases and some genetic disorders. These are generally high risk transplants requiring innovative approaches and substantial support for the child and their families.

These advances make this a truly exciting field to be in, but one that continues to challenge us as health care providers. We are privileged to treat children diagnosed with cancer and blood disorders and to offer support to their families as they navigate their child's disease and treatment. As we venture into this challenging new era I am excited at the prospect of leading BC's pediatric oncology and hematology team – a team dedicated to the care of our province's children and their families and committed to research and education.

### New Leadership Announcement

Dr Caron Strahlendorf MB.BCh. FCP, FRCPC is the new Head of the Division of Pediatric Hematology/Oncology/ Bone Marrow Transplantation effective September 1, 2014. She graduated from the University of the Witwatersrand Medical School in Johannesburg and underwent subspecialty medical training in South Africa, England and Canada. She is the Principal Investigator for the Children's Oncology Group (COG), Director of the Pediatric Apheresis Program, and member of the Clinical Research Ethics Board. Her research interests are in hematopoietic stem cells and their role in pediatric solid tumors and in medical bioethics and end-of life care. Caron also has a long-standing interest in global health. She is currently pursuing a PhD (Health) at the University of Bath. She has several awards including the 2013 Cancer Society Volunteer Award of Excellence; the 2013 UBC Pediatric Resident Faculty Mentor of the Year award and in 2014 was the finalist for the YMCA Women of Distinction Award.

## We welcome the following physicians to the Oncology Hematology BMT Division at BC Children's Hospital (BCCH)...

**Dr. Sylvia Cheng** joined us in 2014 after completing a fellowship at the Hospital for Sick Children in Toronto. Dr. Cheng represents an exciting addition to the brain tumour group.

**Dr. Rebecca Deyell** completed her fellowship at BCCH in 2010. She worked with the neuroblastoma and developmental therapeutics teams, as well as doing neuroblastoma research at Children's Hospital of Philadelphia from 2010 to 2012. Dr. Deyell came on staff at BCCH in March 2012. Her focus is oncology with interests in neuroblastoma and developmental therapeutics.

**Dr. Jess Halparin** completed her fellowship at BCCH in 2013 and then joined us as an attending with special interest in benign hematology, thrombosis and hematologic malignancies.

**Dr. Melissa Harvey** completed her fellowship at BCCH in 2014 and then joined us as an attending with special interest in sarcomas and medical education.



**SAVE THE DATE – Monday, January 26, 2015 (6-8:30 pm)  
 at the Coast Bastion Hotel, Nanaimo, BC**

The Provincial Pediatric Oncology Hematology Network will be conducting an education session in Nanaimo, BC. Roberta Esau, pharmacist at the Oncology/Hematology BMT division of BC Children's Hospital will share her knowledge on pediatric oncology specifically on how to read pediatric protocols and mixing chemotherapeutic agents for pediatric patients. The target audience is pharmacists and pharmacy technicians but other health care professionals are welcomed. Dinner will be provided.

Please contact Paulina Chen, network coordinator at [ppchen@cw.bc.ca](mailto:ppchen@cw.bc.ca) for more information.



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 Christmas season and  
 a wonderful new year!



Our mission is to improve the health and welfare of children in BC with cancer and blood disorders through research, education, and care.

**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 healthcare 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**

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