The Microenvironment

August 2015

THE CANADIAN HEMATOLOGY SOCIETY

SOCIÉTÉ CANADIENNE D'HÉMATOLOGIE

CHSCH

NEWSLETTER

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2015 CHS Executive

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Past-President	Dr. Stephen Couban
Vice-President	Dr. Lynne Savoie
Treasurer	Dr. Julie Stakiw
Secretary	Dr. Molly Warner
Executive Vice-President	Dr. Gail Rock
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MESSAGE FROM THE PRESIDENT

Dr. Aaron Schimmer
President, CHS

Dear Colleagues,

As the new academic year begins, I would like to update you on some of the exciting initiatives underway at the Canadian Hematology Society (CHS).

CHS webportal

The new CHS webportal is very active thanks to the dedication of **Dr. Hassan Sibai**. Each month, a new case and related educational review is posted.

Through the interactive nature of the web portal, a discussion of the topic occurs. The cases cover the spectrum of benign and malignant hematology. Feedback on the cases has been exceptionally positive. I would like to thank the many members across the country who have participated in the cases and have posted feedback on the webportal.

(Accessible via: canadianhematologysociety.org)

These cases are a great way to stay up to date in hematology and test your knowledge. Please visit the portal at **www.chsportal.ca** and check out the current and past cases. Don't forget, if you are among the first five people to answer the questions correctly, you win great CHS prizes.

Hematology drugs listing

In the very near future, we will launch the next installment to the webportal. The CHS will provide a province-specific listing of reimbursement criteria for hematology drugs. We recognize that navigating the complex world of drug reimbursement can be challenging and we hope to provide the "go-to" site when faced with questions on drug reimbursement and coverage for your patients.

As an additional benefit, I anticipate this site will spark discussion as the coverage criteria for drugs is compared between provinces.

Chief Canadian Hematology Resident

I would like to warmly welcome **Dr. Eric Tseng** as our inaugural Chief Canadian Hematology Resident. Dr. Tseng is a senior hematology resident at the University of Toronto with an academic interest in education. In his role as Chief Canadian Resident, Eric will join our executive team to represent the trainees across the

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country and ensure that CHS activities are meeting the needs of this important group of our members. Dr. Tseng's term will run until July 1, 2016.

Trainee abstracts
Supporting research among our trainees continues to be a priority for the CHS. We will again be recognizing the best trainee abstracts presented at ASH. I would like to encourage all of our trainees to submit their abstracts for consideration of CHS merit awards. Details of how to submit your abstract and the deadlines will be available on our website and flyers that will be distributed. We look forward to showcasing your work and recognizing your achievements at our annual business meeting and gala that will be held at the 2015 ASH meeting.

2015 Paper of the Year
As part of the 2015 CHS gala held annually at ASH, we will be recognizing the best paper in Canadian hematology. Following the success of the initial competition last year, we are again requesting nominations from all CHS members to identify the best manuscript published this past year in the field of hematology. Both clinical and lab-based papers spanning benign and malignant hematology are being considered.

The Best in Canadian Hematology Award is an important mechanism to highlight the tremendous hematology research being conducted in Canada and recognize our CHS members who are international leaders in their field.

In closing, I would like to thank our executive members and staff for their hard work and time they devote to the CHS. I would also like to thank you for your support of the CHS and your continued membership in the Society.

Dr. Aaron Schimmer
President, CHS

Le message du Président

En ce début de la nouvelle année scolaire, je veux faire le point sur certaines des initiatives intéressantes en cours à la Société Canadienne d'Hématologie (SCH).

Portail web de la SCH

Le nouveau portail web de la SCH est très actif grâce au dévouement du **Dr. Hassan Sibai**. Chaque mois, on affiche un nouveau cas avec un examen pédagogique connexe. Grâce à la nature interactive du portail web, une discussion sur le sujet s'ensuit.

Les cas couvrent l'éventail de l'hématologie bénigne et maligne. Les commentaires sur les cas ont été exceptionnellement positifs et je tiens à remercier les nombreux membres partout au pays qui ont participé à la discussion de ces cas et qui ont posté des commentaires sur le portail web.

Ces cas sont un excellent moyen pour rester à jour en hématologie et tester vos connaissances. Veuillez visiter le portail web au www.chsportal.ca et explorer les cas actuels et passés. N'oubliez pas, si vous êtes parmi les 5 premiers à répondre correctement aux questions, vous gagnerez de superbes prix de la SCH.

Liste de médicaments d'hématologie

Dans un avenir très proche, nous allons lancer le prochain volet de notre portail web. La SCH fournira la liste des critères de remboursement pour les médicaments d'hématologie correspondant à chaque province. Nous sommes conscients que le monde du remboursement des médicaments peut parfois être très compliqué et nous espérons devenir le site «expert» pour les questions sur le remboursement des médicaments et de la couverture pour vos patients. Le site offrira un avantage supplémentaire, celui de provoquer des discussions sur la comparaison des critères de couverture des médicaments d'une province à une autre.

Résident en chef en hématologie du Canada

Je tiens à saluer chaleureusement le **Dr. Eric Tseng** qui est notre premier résident en chef en hématologie. Le docteur Tseng est le résident principal en hématologie de l'Université de Toronto qui s'intéresse vivement à l'enseignement. En tant que résident en chef du Canada, Eric se joindra à notre équipe de direction pour représenter les stagiaires dans tout le pays et faire en sorte que les activités de la SCH répondent aux besoins de ce groupe important de nos membres. La durée du mandat du docteur Tseng s'étendra jusqu'au 1er juillet 2016.

Exposés des stagiaires

La priorité pour la SCH est de continuer à soutenir la recherche parmi nos stagiaires. Nous choisirons à nouveau les stagiaires avec les meilleurs exposés qui seront présentés à ASH. Je voudrais encourager tous nos stagiaires à soumettre leurs exposés pour une évaluation en vue des prix de mérite de la SCH. Des détails sur la façon de soumettre votre exposé et sur les délais seront disponibles sur notre site web et dans des

UPDATE

ISH-CHS 2018 Vancouver

The joint meeting of the Canadian Hematology Society and the International Society of Hematology is scheduled for September 13 to 17, 2018.

The venue is the Vancouver Convention Centre, located in one of the world's most beautiful settings on the downtown waterfront with a dramatic mountain background.

The exciting three-day event will highlight:

- **Canadian activities and practitioners**
- **A Plenary Session**
- **Educational and abstract presentations**

Please send suggestions for scientific program articles to the Chair of the Scientific Program, Dr. Tom Nevill, Email: TNevill@bccancer.bc.ca

A great social program and post congress tours will be featured. Want to cruise the inland waterway? You can do it ! Join us for a great time. Plan now to be there then. Vancouver 2018.

Conference Co-Chairs:

- **Dr. Tom Nevill, Scientific Committee Chair**
- **Dr. Gail Rock, Organizing Committee Chair**

dépliants qui seront distribués. Nous avons hâte de présenter votre travail et de partager vos réalisations lors de notre assemblée générale annuelle et notre gala qui auront lieu à la réunion de ASH en 2015.

Rapport clinique de l'année pour 2015

Dans le cadre du gala 2015 de la SCH qui a lieu à chaque année à ASH, nous attribuerons le prix du meilleur article rapport clinique en hématologie du Canada. Suite au succès de la première compétition l'an dernier, nous demandons encore une fois à tous les membres de la SCH de soumettre des candidats pour identifier le meilleur manuscrit publié cette année dans le domaine de l'hématologie. Des études cliniques et en laboratoire couvrant l'hématologie bénigne et maligne seront envisagées. Le Prix du meilleur article rapport clinique en hématologie au Canada est un mécanisme important pour souligner l'excellence de la recherche en hématologie en cours au Canada et pour reconnaître les membres de la SCH qui sont des chefs de file internationaux dans leur domaine.

En terminant, je tiens à remercier nos membres exécutifs et notre personnel pour leur travail acharné et le temps qu'ils consacrent à la SCH. Je tiens également à vous remercier pour votre soutien et votre adhésion renouvelée à la Société.

Dr. Aaron Schimmer
Président, SHC

Do you know the diagnosis?

A 19-year-old woman, a first year university commerce student, presented to a walk-in clinic with a sore throat and a fever of 38.5 ºC.

- She had no prior medical problems and had never been hospitalized. She was not on any medications and had no known allergies.
- Her mother, father and older brother were healthy and there was no family history of hematologic disease or malignancy.
- Physical examination revealed the aforementioned fever, a heart rate of 104 per minute, a respiratory rate of 14 per minute and a blood pressure of 100/50.
- She had enlarged tonsils with an overlying exudate and slightly tender, rubbery 1.5 cm jugulodigastric lymph nodes bilaterally.
- Chest, cardiac and abdominal examination were all unremarkable.
- Examination of the extremities was significant for the findings shown in Figure 1 and Figure 2.
- A CBC showed a hemoglobin of 105 g/L, MCV of 110, WBC of 2.8 x 10^9/L, ANC of 1.3 x 10^9/L and platelets of 57 x 10^9/L.
- Peripheral smear did not show any abnormal cells. A bone marrow examination was performed.

Do you know the diagnosis?

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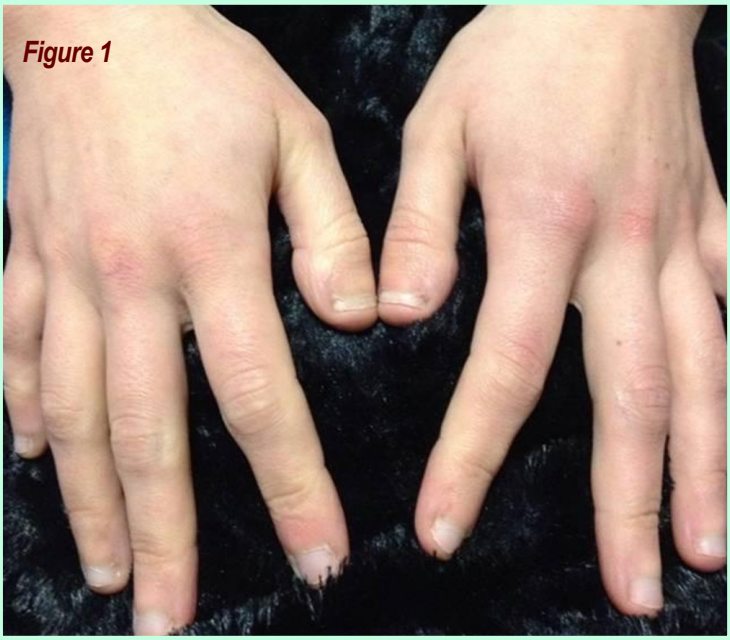

Figure 1

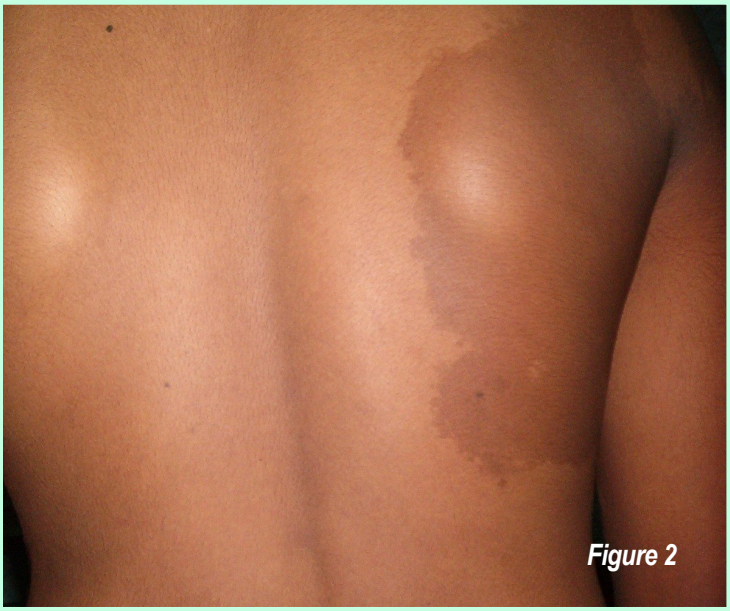

Figure 2

CHS 2015 Executive Committee

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Dr. Gail Rock

2015 R.K. Smiley Award Winners

By Dr. Tom NEVILL

Genome-wide Identification of p53-Regulated Genes in Hematopoietic Stem Cell Progenitor Cells

Dr. Anastasiya Nijnik

Assistant Professor
Dept. of Physiology
McGill University
Montréal, QC

Dr. Ana Nijnik's recent research has focused on a transcriptional regulator, MYSM1, which plays an essential role in hematopoiesis and hematopoietic stem cells (HSCs) in both mice and humans.

Her research team has demonstrated that MYSM1 binds to p53, localizes to the promoters of p53 target genes and antagonizes their expression. In murine models, the loss of MYSM1 results in p53-driven hematopoietic failure and their laboratory is currently conducting a genome-wide analysis of MYSM1-regulated genes in HSCs.

With Dr. Ninjik's current proposal, her team aims to identify the p53-regulated genes in HSCs through a genome-wide analysis similar to their previous work with MYMS1. RNA-Seq will be performed on HSCs and multipotent stem cells that will be FACS-sorted from the bone marrow of control and $p53^{-/-}$ mice. ChIP-Seq will then be carried out to identify p53-binding sites across the genome of HPC7 cells, recognized as models of HSC transcriptional regulation.

Dr. Nijnik plans to use this in concert with their previously collected MYSM1 dataset to provide insight into the cross-talk between MYSM1 and p53 in transcriptional programs.

It is hoped that this insight will increase our knowledge of p53 regulation in hematopoiesis, leading to future therapeutic strategies.

Setting the Benchmark Metric for Red Blood Cell Transfusion to Allow for Assessment of Optimal Transfusion Care: A Pilot Quality Project at 10 Hospitals

Dr. Yulia Lin

Transfusion Medicine Specialist
Dept. of Clinical Pathology
Sunnybrook Health Sci. Centre
Toronto, ON

The appropriate use of red cell transfusions (RBC) has become an important focus for clinicians, medical institutions and national organizations that fund and supply these products.

Choosing Wisely recommends not to transfuse patients based on an arbitrary hemoglobin threshold. The Canadian Society of Transfusion Medicine further suggests not to transfuse more than one red cell unit at a time. Studies have attempted to bench-mark this problem using a number of variables – surgical RBC rates, RBC per 100 inpatient days and RBC per 1000 population. Unfortunately, none of these studies have answered the question of which RBC given are appropriate, an analysis that would require time-consuming chart audits.

With this research proposal, Dr. Lin plans to perform a 10-site pilot study that will lead to a larger national audit of RBC practices at 100 Canadian hospitals. She plans to perform RBC audits – the gold standard – using an audit tool developed by ORBCAN, with each unit of RBC given adjudicated independently by 2 physicians for compliance with guidelines based on pre-set criteria.

At least 30 consecutive RBC units will be adjudicated per site with blocks of 10 units added until there is a <3% change in appropriateness per site. The appropriateness rating per site will be compared with simple-to-obtain benchmark metrics – RBC per 100 patient days, proportion of RBC with a pre-transfusion trigger of <80 g/L and post-transfusion level <90 g/L and proportion of one unit RBC administered. Undertransfusion due to restrictive strategies will also be evaluated by reviewing all patients with a hemoglobin <60 g/L.

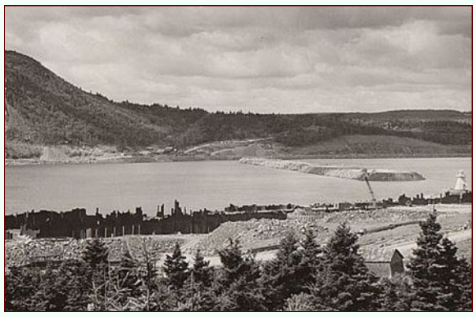
HISTORY CORNER

By Dr. Tom NEVILL

Remembering a devoted groundbreaker in Canadian hematology: Dr. G. Ross Langley

Dr. G. Ross Langley was a pioneer in the field of hematology in Atlantic Canada demonstrating a boundless devotion to physician education and research in a career that spanned more than half a century.

Ross Langley was born in Sydney on Cape Breton Island, some twenty-five years before the Canso Causeway was built to link the island with the Nova Scotia mainland.



The Canso Causeway, still under construction in this photo, was completed and officially opened in May 1955.

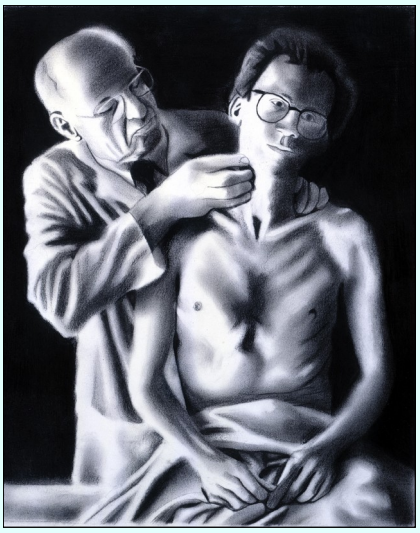
He attended school in Port Hawkesbury and New Glasgow before receiving his Bachelor of Arts degree from Mount Allison University in 1952. He went on to medical school at Dalhousie University in Halifax and graduated with his MD in 1957.

Ross Langley trained in Internal Medicine in St. John's, Halifax and Toronto before pursuing research in hematology at the University of Rochester on a Medical Research Council of Canada scholarship. After further studies at the University of Melbourne in Australia, he returned to Nova Scotia in 1961 to take a position in the Department of Medicine as the John and Mary R. Markle Scholar in Academic Medicine.

In 1968, he was appointed a Professor of Medicine, became the Chief of Medicine at Camp Hill Hospital and then served as the Head of Medicine at Dalhousie University and Victoria General Hospital. He also played an early role in the Canadian Hematology Society as a key member of the CHS Executive in the 1970s.

Throughout his distinguished career, Dr. Langley trained countless hematologists and showed particular interest in medical ethics. Along with Dr. Heather MacDougall, he co-authored a highly influential paper on the subject for the Royal College of Physicians and Surgeons in 2009 – "***Medical Ethics: Past, Present & Future***".

He also volunteered for the National Cancer Institute of Canada and was a strong advocate for many patients, including the renowned **Nova Scotia artist Robert Pope**, who succumbed to complications of Hodgkin lymphoma while under his care. Dr. Langley assisted in the creation of the **Robert Pope Foundation** and served as its director and as an advisor for two decades.



Self portrait of Robert Pope being examined by Dr. G. Ross Langley

In recognition of his work in the establishment of the hematology specialty in Nova Scotia, Ross Langley was awarded the Queen Elizabeth II Silver Medal in 1977 and the Golden Jubilee Medal in 2002.

He was appointed Emeritus Professor of Medicine at Dalhousie later in 2002 and went on to receive the Dalhousie Lifetime Achievement Award in Medical Education and Research and was named the Medical Alumnus of the Year.

When he retired in 2007, he was made a Master of the American College of Physicians and in May 2015, he was honored with an Honorary Doctor of Laws. Dr. Langley died in Victoria General Hospital on June 19, 2015.

By Dr. Tom NEVILL

CANADIAN RESEARCH AT EHA 2015

The 20th Congress of the European Haematology Association was held in Vienna, Austria June 11-14, 2015. The weather was spectacular, the historic city was enchanting and the conference program was packed full of interesting presentations. Canada was well-represented in the program and the best of Canadian research projects are summarized in the following pages.

Optimal duration of anticoagulant therapy for the treatment of cancer-associated thrombosis

Dr. Chatree Chai-Adisaksopha, McMaster University, Hamilton, ON

Patients who develop venous thromboembolism (VTE) have a high-risk of recurrent events when treated with conventional-intensity Warfarin. The risk of a second event is lower when low-molecular weight Heparin is used but the required duration of such therapy remains uncertain. This study involved an analysis of 2 groups of cancer patients that were enrolled consecutively in the RIETE registry – 2937 patients that received LMW Heparin for <6 months and 1523 patients that were similarly treated for >6 months. These patients were followed for 5 years for the development of recurrent VTE. The investigators found that the group that received <6 months of anticoagulation had significantly higher risks of recurrent VTE (RR 2.86), all-cause mortality (RR 5.88) and VTE-related death (6.25). The group that was on LMW Heparin for >6 months did not have a higher risk of hemorrhagic events.

This study strongly supports prolonged anticoagulation for patients with cancer-related VTE although the optimal duration has not yet been determined.

Hydroxyurea for ß-thalassemia: a meta-analysis

Dr. Ali Algiraigri, University of Calgary, Calgary, AB

ß-thalassemia is one of the most common inherited diseases with its more severe forms requiring life-long transfusions that lead to iron overload. Hydroxyurea is an agent that can increase hemoglobin levels in this patient population and thereby reduce red cell transfusion needs. To evaluate this drug's benefits in ß-thalassemia patients, a meta-analysis was performed by searching Medline, EMBASE, CENTRAL and conference proceedings to identify randomized controlled trials (RCT) or observational studies with a sample size ≥ 5 in which Hydroxyurea was used alone for ≥ 3 months. ß-thalassemia was classified as ß-thal major (BTM) and severe or mild non-transfusion-dependent ß-thal (NTDBT).

There were 11 observational studies involving 620 patient in BTM. This analysis showed a 41% CR rate and, when including patients with a ≥ 50% reduction in transfusion needs, a 71% overall response (OR) rate. There were 8 studies involving severe NTDBT patients (n=305), including one RCT, in which Hydroxyurea was associated with a 55% CR rate and a 79% OR rate. For the mild NTDBT patient population there were 14 studies (one RCT) that included 344 patients. Using a response rate (RR) definition of an increase in hemoglobin of ≥ 10 g/L, RR was 54%. Adverse events in all studies were uncommon and were either transient or decreased with dose-reduction or, rarely, drug discontinuation. The researchers did caution that this meta-analysis largely involved observational studies with a small sample size and lacked a comparison group.

This study clearly suggests that Hydroxyurea has significant efficacy in different forms of ß-thalassemia with minimal side effects. Although the logistics would be challenging, a large randomized trial would be ideal in order to more thoroughly evaluate this treatment option.

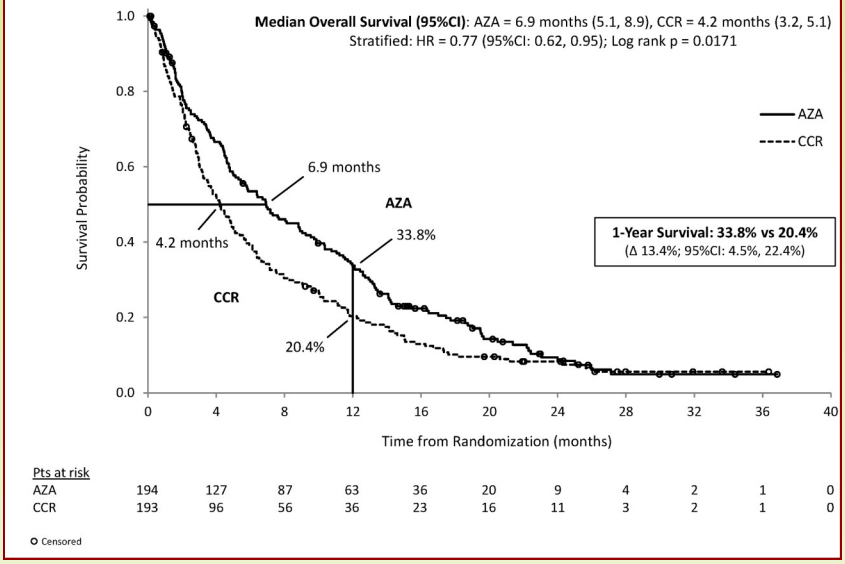
The effect of Azacitidine on overall survival (without CR) and health-related quality of life in older AML patients on the Aza-AML-001 trial

Dr. Andre Schuh & Dr. Mark Minden, Princess Margaret Hospital, Toronto, ON

The Aza-AML-001 study randomized AML patients ≥ 65 years of age with intermediate- or adverse-risk karyotypes to Azacitdine (Aza) or one of 3 pre-specified conventional care regimens (CCR) – induction

chemotherapy (IC), low-dose Ara-C (LDAC) or best supportive care. This trial was similarly designed to the Aza-001 study in higher-risk MDS which demonstrated a survival advantage of more than 9 months for the Aza arm despite the fact that complete remissions were uncommon with this agent. Whether this is true in AML patients treated with Aza was not known. The investigators reported on the overall survival (OAS) advantage seen in the Aza arm – 10 months versus 6.5 months in the CCR arm (p=0.10).

Figure. Overall survival for patients who did not achieve CR

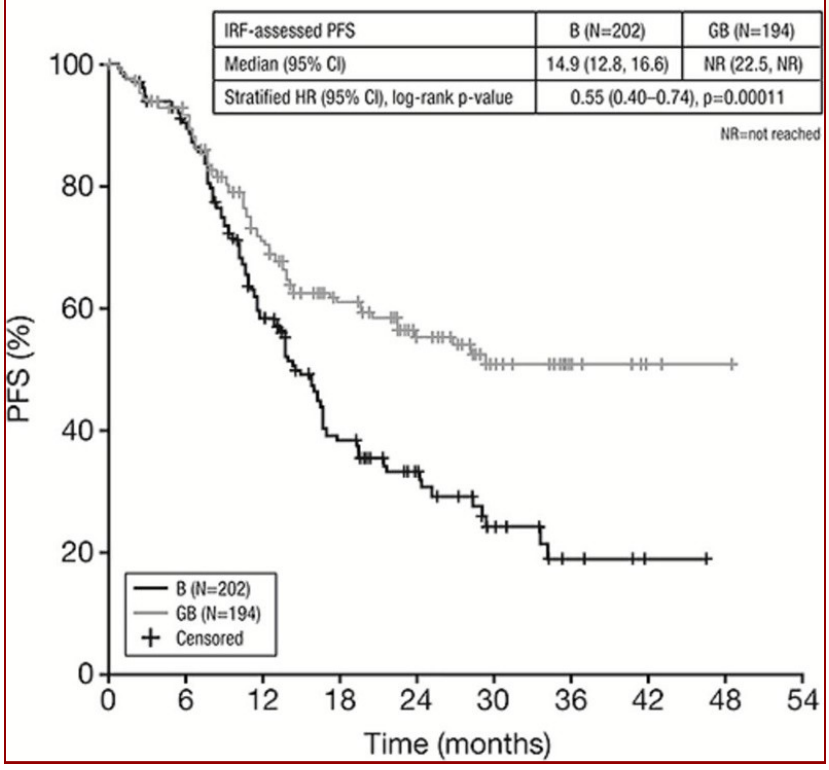


To evaluate the importance of achieving CR, the 47 patients in the Aza arm (19.5%) and the 54 patients in the CCR arm (21.9%) who entered CR were excluded from a subset analysis. In the subset that did not enter CR, the OAS was 6.9 months in the Aza patients and 4.2 months in the CCR arm (p=0.17) with a 1-year OAS of 33.8% and 20.4%, respectively) (*Figure i*).

In further subset analyses, Aza was superior to LDAC pre-selection (1-year OAS of 36.8% versus 16.4%, p=NS) and identical to IC pre-selection (1-year OAS of 40% for both). Health-related quality of life (HRQL) was a designated secondary end-point of the study with the EORTC QLQ-C30 performed at baseline, day 1 of every treatment and, when possible, at the end of study. Only patients that completed at least one follow-up questionnaire were included in the HRQL analysis. There were 157 evaluable patients in the Aza arm and 247 evaluable patients in in the CCR arm, 64% of whom were selected for LDAC.

In the four key domains analyzed in the HRQL -- physical functioning, fatigue, global health status and dyspnea – improvement was the norm for all treatments given although few reached statistical significance and even fewer were clinically meaningful (Figure ii). However, patients in the Aza arm did demonstrate a meaningful improvement in the fatigue domain.

Figure. IRF-assessed median PFS in the GADOLIN study



The Aza-AML-001 study has shown that Azacitidine can prolong survival compared to conventional care regimens in elderly AML patients and -- similar to the published experience in MDS -- even when a CR is not attained. However, the survival advantage is not as dramatic as that observed in MDS and the quality of life data is inconclusive. It remains to be determined what role Aza will play in the treatment of AML in the elderly.

Hodgkin lymphoma is a shelterin-associated disease: disruption of telomere-TRF2 interaction on 3D immuno-FISH analysis of Hodgkin and Reed-Sternberg cells

Dr. Hans Knecht, Jewish General Hospital, McGill University, Montréal, QC

In Hodgkin lymphoma (HL) cell lines, the transition from Hodgkin to Reed-Sternberg (RS) cells is associated with progression of 3D telomere dysfunction, changes in the telomere-protecting shelterin complex, chromosomal rearrangements and formation of giant "zebra" chromosomes. Analogous findings are observed in post-germinal centre B-cell in vitro models for EBV-associated HL. The EBV-encoded oncogene LMP1 mediates multinuclearity through down-regulation of TRF2. 3D interaction of TRF2 and telomeres is primordial to the formation of Hodgkin and RS cells.

In this study, investigators performed combined TRF2-telomere 3D immuno-FISH on cultured diploid fibroblasts and B cell suspensions of diagnostic lymph nodes from 6 patients with classical HL. Normal fibroblasts and many lymphocytes showed intact quantitative and qualitative interaction of TRF2-telomeres. Hodgkin cells displayed variable disruption of steric interaction – a few to many TRF2-dependent – as well as short telomeres; these changes were more pronounced in R-S cells.

The most dramatic loss of TRF2 expression was in a LMP1-expressing case and in one case, with clinically aggressive disease, some lymphocytes had lost TRF2 signals and huge multinucleated R-S ghost cells with no telomeres but internuclear bridging were seen.

This interesting study solidifies the relationship between TRF2, telomeres and the pathogenesis of HL. The 3D cytological appearance and behaviour of Hodgkin and R-S cells in this study support that HL may indeed be a shelterin- associated disease.

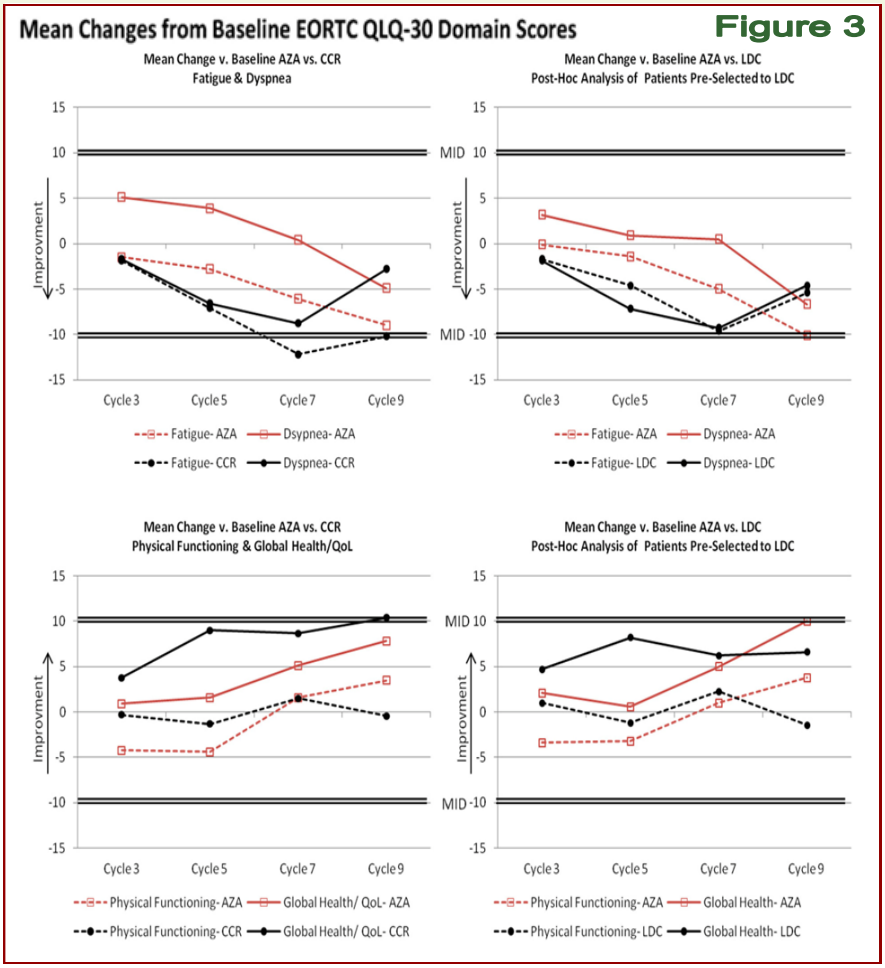
Primary results from a phase III study of Obinutuzumab (GA101) plus Bendamustine versus Bendamustine in Rituximab-refractory indolent NHL

Dr. Laurie Sehn, British Columbia Cancer Agency, University of BC, Vancouver, BC

Obinutuzumab (GA101) is a glycoengineered type II anti-CD20 antibody which, in preclinical studies, has demonstrated synergistic activity with Bendamustine. In this clinical trial, 198 patients with Rituximab-refractory indolent non-Hodgkin lymphoma (~80% follicular lymphoma) were randomized to receive Bendamustine 120 mg/m^2 on days 1 and 2 for 6 cycles (B arm) and 194 to receive Bendamustine 90 mg/m^2 days 1 and 2 plus GA101 (GB arm) for 6 cycles.

The GA101 was given on days 1, 8 and 15 in cycle 1 and day 1 in cycles 2-6; if there was no evidence of progression, GA101 was continued every 2 months for 2 years (median duration in study participants was 10.8 months). In February 2015, the DSMC recommended at the time of a specified interim analysis that the data be unblinded and released to the scientific

Figure 3



community. The median age of the participants was 63 years. Progression-free survival (PFS) was the primary endpoint and median observation time at the interim analysis was 20 months in the B arm and 22 months in the GB arm. Median PFS in the B arm was 14.9 months and not reached in the GB arm (p <0.0001; Figure iii). However, there was no difference in response rate (63% vs. 69%, respectively), CR rate ((12% vs. 11%) or median overall survival (not reached in either arm).

Grade 3 or greater adverse events were less with B (62% vs. 68%), especially neutropenia (26% vs. 33%), than with GB (which also was associated with more infusion-related reactions, 8.8% vs. 3.5% with B alone). The B arm did have more ≥ grade 3 thrombocytopenia (16% vs. 11%), anemia (10.1% vs. 7.7%) and pneumonia (5.6% vs. 2.6%).

The treatment landscape in indolent lymphoma continues to evolve rapidly and it is increasingly challenging trying to prioritize newer therapies. This study does show that GA101, much like Rituximab, may have a role in the treatment of this condition but the best time to use it still needs to be defined. To complicate matters, newer targeted agents are already being used in clinical practice that will compete for this patient population.

Prolonged survival of heavily pretreated DLBCL patients responding to treatment with Selinexor

Dr. John Kuruvilla, Princess Margaret Hospital, Toronto, ON

Nuclear export protein XPO1 is overexpressed in all lymphomas, including diffuse large B cell lymphoma (DLBCL). Relapsed/refractory DLBCL is associated with a median survival of less than 1 year. Selinexor is an oral selective inhibitor of export protein (SINE) that inhibits XPO1 to force nuclear retention and activation of multiple tumour suppressor proteins (including p53) and reduces levels of C-MYC and BCL2.

In this phase I study, Selinexor was given in increasing doses (3-80 mg/m^2) for 8-10 days on a 28-day cycle to 33 heavily pre-treated DLBCL patients (median of 3 prior therapies). Thirty-one patients received ≥ 1 cycle and 12 patients responded (39%) – 12 PRs (26%) and 4 CRs (13%), with responses similar in the ABC and GCB DLBCL genotypes. The median progression-free survival in the responders was 329 days versus 49 days in the 19 non-responding patients (p <0.001); median overall survival was 571 days and 108 days, respectively. The most common grade 1-2 adverse effects were fatigue (43%), nausea (29%) and dysgeusia (25%); the most frequent grade 3-4 toxicities were thrombocytopenia (62%), anemia (24%) and neutropenia (24%).

SINE agents are of great interest in a number of malignancies and have both significant efficacy and the ability to produce durable responses. Nonetheless, the focus for these agents has already begun to shift towards combination therapy and identifying clinical and molecular predictors of response.

Real life analysis of second-line therapy in CML indicates that treatment is frequently discontinued prematurely due to intolerance

Dr. Lambert Busque, Hôpital Maisonneuve-Rosemont, Université de Montréal, Montréal, QC

A variety of treatment guidelines exist to help guide tyrosine kinase inhibitor (TKI) treatment but non-adherence in practice may depend on drug availability, patient choice and definition of intolerance and resistance to a TKI. In this study, the investigators, reporting on behalf of the Groupe Québécois de Researche en LMC-NMP describe second-line/subsequent TKI treatment in 266 patients diagnosed since 2002.

Primary TKI therapy was Imatinib in 83%, Dasatinib in 8.6% and Nilotinib in 5.6%; 44% of patients required second-line treatment (2TKI), usually for resistance (45%) or intolerance (42%). 2TKI was most commonly Dasatinib (43%); Nilotinib was used in 29% and stem cell transplantation in 8.5%. 2TKI with Dasatinib was discontinued in 48% of patients at a mean of only 9.6 months – most frequently due to intolerance (48%) although resistance was also not uncommon (28%). 2TKI with Nilotinib was discontinued in 55% at a mean of 15 months, 53% due to intolerance and 26% as a result of resistance.

Third-line treatment (3TKI) was most commonly Nilotinib (33%) but Dasatinib (29%) and stem cell transplantation (16%) were also utilized. 3TKI with Nilotinib was for a mean duration of 24 months and with Dasatinib for a mean of 25 months. Intolerance was the reason for discontinuation in only 20% and 10% of these patients, respectively.

In the flexibility of real life practice, as opposed to protocol-driven clinical trials, intolerance is a much more frequent reason for switching to alternative TKI therapy in CML patients. It is only when patients reach 3TKI that disease resistance become the most frequent reason for discontinuing a therapy.

Outcomes of allogeneic stem cell transplantation in JAK 1/2 inhibitor-treated myelofibrosis patients

Dr. Mohamed Shanavas, Princess Margaret Hospital, Toronto, ON

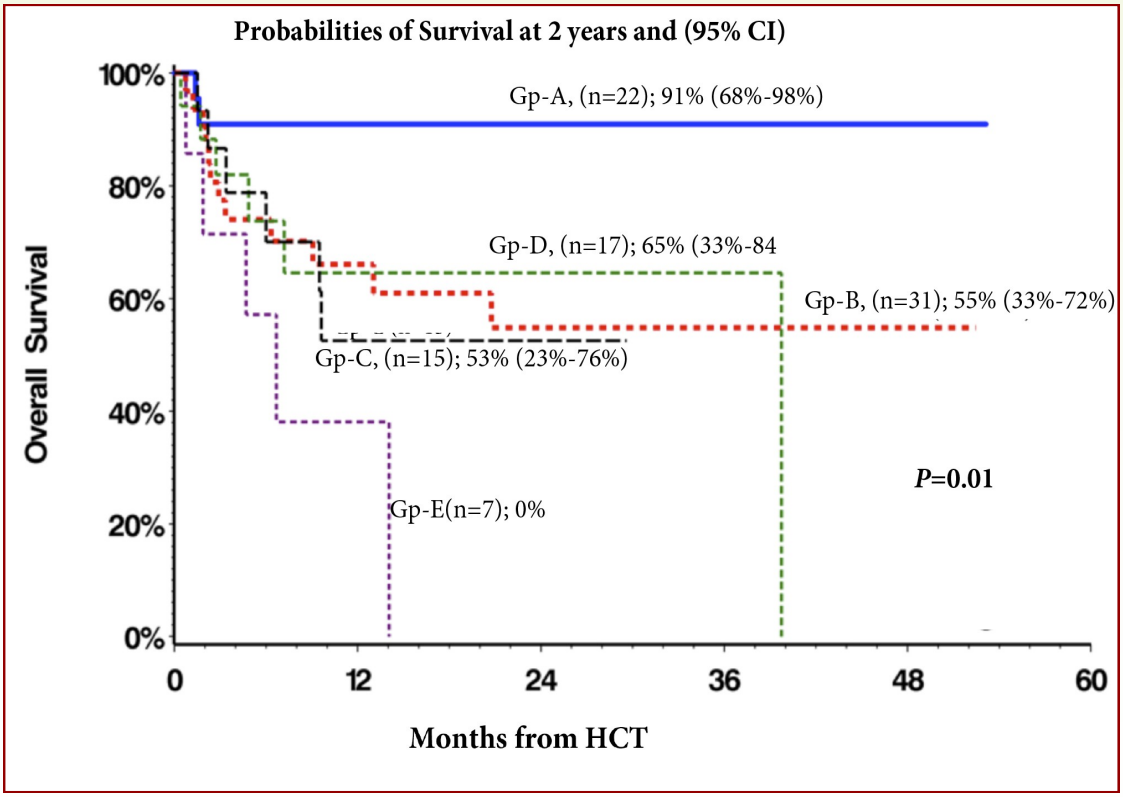
JAK 1/2 inhibitors (JAKI) can improve clinical status in patients with myelofibrosis (MF) prior to hematopoietic stem cell transplantation (HSCT) although their influence on post-HSCT survival is uncertain.

This multi-institutional study analyzed the outcomes for 93 patients with primary MF (n=53), post-polycythemia MF (n=20) or post-essential thrombocythemia MF (n=20) that underwent allogeneic HSCT following treatment with JAKI. Median age was 59 years; by DIPSS-plus score, 52% were INT-2 and 24% were high-risk.

The JAKI was Ruxolitinib in 84 patients, Momelotinib in 6 patients and other JAKI in 3 patients. Unrelated donors were used in 51% of patients, matched sibling donors in 39% and 10% received alternative donor HSCT. The conditioning regimen was myeloablative in 45% and reduced-intensity in 55%. Disease status at HSCT was classified as "A" to "E" with the "A" group having responded to JAKI with a ≥50% reduction in spleen size, "B" patients having stable disease, "C" patients having developed new anemia or having 10-19% blasts, "D" patients having lost spleen response or had progressive splenomegaly on JAKI and "E" patients having frank acute leukemia.

JAKI was stopped within 16 days of HSCT in 70% of patients and a withdrawal syndrome developed in 10 patients, almost exclusively in patients that stopped it 7-16 days prior to HSCT. Graft failure was seen in 3 patients and the incidence of grade ≥II acute and chronic GVHD was 44% and 53%, respectively. Overall survival (OAS) was 62% for the entire cohort with group "A" having a superior outcome (Figure iv).

Relapse was seen in 13% of patients and 33% of patients have died. In multivariate analysis for OAS, the most significant predictor was responsiveness to JAKI (p=0.004) although DIPSS-plus high-risk patients (p=0.04) and those receiving mismatched or haploidentical HSCT (p=0.04) had inferior outcomes.



While allogeneic HSCT is an effective curative strategy for primary and post-PV/ET MF, outcomes depend upon disease biology and, with the advent of JAKIs, status following treatment with these new agents. Advances in stem cell transplantation and the development of even more effective target therapies will continue to guide and refine the treatment algorithm in MF.

Impact of response to continuous treatment in MM-020 for transplant-ineligible newly diagnosed multiple myeloma patients

Dr. Nizar Bahlis, Tom Baker Cancer Centre, Calgary, AB

In the phase III FIRST trial, transplant ineligible multiple myeloma patient were randomized to receive one of three treatments: (1) continuous Revlimid/ Dexamethasone (RD); (2) RD for 18 cycles (RD18) and (3) Melphalan/Prednisone/Thalidomide (MPT) for 12 cycles. For patients that achieved a CR, the median progression-free survival (PFS) was superior in the RD arm (not reached) compared to MPT (44.6 months) and RD18 (45.2 months). PFS was also superior for RD in the subgroups that had a ≥VGPR (not reached, 34.7 month and 31 months, respectively) or a ≥PR (35 months, 22.3 months and 22.1 months, respectively). Overall survival was not statistically different for the entire cohort by treatment designation nor was it different in any of the three subgroup analyses by treatment response.

Keeping up with the management of multiple myeloma in the era of novel therapies has become one of the greatest challenges for the clinical hematologist over the past 5 years. This study provides new information on the treatment of transplant-ineligible multiple myeloma; unfortunately, a direct head-to-head comparison of immunomodulatory with proteasome inhibitor-based initial therapy for this patient population is not provided by this study.

Treatment of higher-risk MDS with Azacitidine in British Columbia

Madeleine Ankenman, British Columbia Cancer Agency, Vancouver, BC

Azacitidine (Aza) received its notice of compliance in Canada in October 2009 and in January 2010 the British Columbia Cancer Agency started funding this hypomethylating agent for the treatment of higher-risk myelodysplastic syndrome (MDS). This study involved the review of 181 consecutive patients treated with Aza between January 2010 and April 2014 -- 60 oligoblastic AML, 69 RAEB, 19 therapy-related neoplasm, 16 CMMoL, 14 RCMD and 3 MDS, unclassifiable. Karyotype was available in 136 patients with IPSS classification assigned as good-risk in 34%, intermediate-risk in 40% and poor-risk in 26%.

Patients were treated at Vancouver teaching hospitals (VAN) in 72 cases, peripheral BCCA sites in 44 cases and at one of 14 community oncology clinics (CON) in 65 cases. The starting dose of Aza was the recommended 75 mg/m^2 in only 78%, a lower dose in 15% and a higher dose in 7%. One-half of the patients treated received the full-dose of 75 mg/m^2 throughout their treatment cycles; there were 36% that had ≥ one, 29% ≥ two and 12% ≥ three dose-reductions.

The median number of cycles delivered was 5 cycles with 19% of patients receiving only 1 cycle and an additional 20% of patients receiving 2-3 cycles. For patients commencing treatment in 2010-2011, the median number of cycles given was 6; for patients starting treatment in 2012-2013, the median number of cycles administered was 4. The proportion of patients receiving ≤ 3 cycles was 42% at VAN sites, 30% at BCCA sites and 45% at CON sites.

The IWG responses were evaluable in 163 patients; 11% of patients had a CR, 2% a PR and 29% hematologic improvement [overall response rate (RR) 42%]. RR was 52% in the IPSS good-risk karyotype group and 44% in the poor-risk karyotype group. Median overall survival (OAS) was only 7 months for the entire cohort but for patients receiving ≥ 4 cycles of Aza, the median OAS was 13 months.

Azacitidine is an effective treatment for higher-risk MDS patients and has been shown to improve quality of life compared to conventional care regimens. However, there is a "learning curve" for all new therapies and this study demonstrates some of the issues faced even in a population-based strategic approach. It is important that treating physicians and the facilities delivering the drug be educated on the importance of an adequate trial of Azacitidine in this challenging hematologic disorder.

CHS Paper of the Year

- The Canadian Hematology Society is now accepting nominations for ***"the best hematology paper in Canada"***.
  - Individuals may nominate themselves or may nominate others.

Please include:

- A PDF of the paper
- A one-paragraph description of the work and its significance to hematology

Eligibility requirements:

- Papers must have been published **between August 31, 2014 to August 31 2015.**
- Nominated individuals must be CHS members in good standing.
- The recipient or designate must be available to accept the award.
- Awards will be presented at the at ASH, December 6, 2015 in Orlando, Florida.
- Papers addressing clinical or lab-based hematology research will be considered.
- Applicants of all levels are encouraged to apply.

Nominations:

- Are now open
- Material must be submitted to the Canadian Hematology Society office by email to chs@uniserve.com
- **by the deadline, September 15, 2015.**

INVITATION TO SUBMIT STUDENT RESEARCH ARTICLES

The Microenvironment **will be happy to consider for publication, articles submitted by members who have sponsored student summer projects.**

Queries should be directed to:

- **Dr. Tom Nevill, The Editor,** ***The Microenvironment***
- **Email: chs@uniserve.com**

Upcoming Events

Mark your calendar - Save the date!

Canadian Hematology Society (CHS)
Annual Reception, Dinner & Awards Evening
Sunday, December 6, 2015
Orlando, Florida
- **Contact: chs@uniserve.com**

Canadian Apheresis Group
35th Annual General Meeting
September 18-20, 2015
Gatineau, Quebec
- **Information: cag@cagcanada.ca**

CBMTG 2016 Annual Conference
April 24—27, 2016
Westin Bayshore Hotel in Vancouver, BC
- **http://cbmtg.org/2016-annual-conference**

Lymphoma & Myeloma 2015: An International Congress on Hematologic Malignancies
October 22—24, 2015
New York, NY, USA
- **http://www.imedex.com/lymphoma-myeloma-conference/index.asp**

The DIAGNOSIS? Answer: (from Page 4)

The physical examination showed bilateral hypoplastic thumbs (Figure 1; confirmed on routine X-ray of the hands) and a large café-au-lait spot on her trunk (Figure 2). Bone marrow examination revealed marked hypocellularity (5%) with no dysplasia, no increase in blast cells and no abnormal infiltrates; cytogenetic analysis showed 46,XX in all 25 metaphases analyzed. Flow cytometry did not show any GPI-deficient blood cells.

Peripheral blood chromosome fragility studies showed an increased number of breaks with Diepoxybutane (DEB) and Mitomycin C (MMC) consistent with a diagnosis of Fanconi anemia (FA). The patient's sibling was not HLA identical and an unrelated donor search was initiated.

FA is a constitutional marrow failure syndrome that results from a group of 15 known gene mutations named (alphabetically) FANC A to FANC N. The disease is autosomal recessive in 99% of patients (X -linked recessive is rare) and is caused by homozygous or double heterozygous inheritance of the affected genes.

Most of the gene protein products interact with other proteins involved in DNA repair. Manifestations are highly variable and include birth defects that are protean: short stature, microcephaly/microphthalmia, limb defects (such as radial or thumb abnormalities), café-au-lait spots/hypopigmentation, genitourinary and cardiac anomalies. The presence of these congenital abnormalities generally leads to an early diagnosis (median age of 7 years) and the more severely affected individuals develop early aplastic anemia.

However, 25% of FA patients do not have any identifiable birth defects and this may delay the diagnosis until adulthood (having even been recognized for the first time in some patients in their 40s). These less severely affected FA patients tend to develop MDS/AML or head and neck/esophageal/ vulvovaginal cancers as young adults (cumulative incidence of 15-20% and 25% by age 50, respectively). The diagnosis can be confirmed in these patients by the chromosomal fragility that is typical of FA patients when peripheral blood lymphocytes are exposed to DNA cross-linking agents such as DEB and MMC.

While the hematologic cytopenias may respond to androgens, the most effective treatment for the marrow failure that develops in FA is allogeneic stem cell transplantation. AlloSCT has produced unfavourable results in this unique disorder in the past due to FA patients being especially sensitive to organ toxicity when exposed to conventional doses of radiation and/or alkylating agents. Results with tailored, reduced-intensity conditioning regimens have improved the outcome with AlloSCT in FA.

Unfortunately, AlloSCT does not prevent the development of head and neck, esophageal and genital tract malignancies seen in this patient population and it may actually increase the risk of their development.

Fellowships

LEUKEMIA/BONE MARROW TRANSPLANTATION FELLOWSHIP VANCOUVER

The Leukemia/Bone Marrow Transplantation Program of British Columbia

- offers 1 or 2 Year fellowships
- to provide advanced training in the management of adults with hematological malignancies
- including all aspects of allogeneic and autologous hematopoietic stem cell transplantation (HSCT).

Candidates should be registered in, or completed a recognized hematology or oncology training program.

For details: leukemiabmtprogram.org

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

Interested candidates should submit a CV and names of three references to:

Dr. Donna Forrest, Fellowship Director Leukemia/BMT Program, BC Cancer Agency & Vancouver General Hospital
Phone: (604) 875-4089 FAX: (604) 875-4763
Email: dforrest@bccancer.bc.ca

Clinical or translational research fellowship in Myeloproliferative Neoplasms

The Elizabeth and Tony Comper MPN program at Princess Margaret Cancer Center offers a unique opportunity for a one or two-year clinical or translational fellowship in MPN. The MPN program works closely with a team of leukemia and transplant physicians, and there will be opportunity to train in other aspects of myeloid malignancies and allogeneic transplantation depending on candidate's interest and career goals.

We are actively involved in clinical, laboratory, and translational research, and have a large portfolio of clinical trials. In addition to gaining clinical experience, fellows will have the opportunity to participate in clinical and translational research projects, the design of clinical trials, to learn the principles of conducting research, and to participate in the academic activities of the program.

UHN Princess Margaret Cancer Centre

Candidates must have completed training in internal medicine, and sub-specialty training in hematology or medical oncology. Overseas candidates should have Canadian equivalent training in the above disciplines.

For additional information or an informal discussion, please contact: Dr. Vikas Gupta, MD, FRCP, FRCPath Princess Margaret Cancer Centre 610 University Avenue, 5-303C Toronto, ON CANADA M5G 2M9 tel: (416) 946-4521; fax: (416) 946-6546 email: **vikas.gupta@uhn.ca**

McGill University Thrombosis Fellowship 2016-17
Jewish General Hospital in Montreal, Quebec

The JGH Thrombosis Program is currently accepting applications for a one year fellowship (July 1, 2016 - June 30, 2017) to acquire and consolidate expertise in Thrombosis.

Specific areas of clinical activity include the Thrombosis Clinic, Anticoagulation Clinic and In-patient Thrombosis Consultation Service.

Our Thrombosis Program also encompasses a broad range of research activities that relate to diagnosis, risk factors and treatment of venous and arterial thromboembolic disease.

Hôpital général juif
Jewish General Hospital

To obtain more information please contact **Dr. Susan Kahn** or **Maureen Morganstein** 514-340-7587
maureen.morganstein@ladydavis.ca

The Microenvironment August 2015

Your Canadian Hematology Society
Société Canadienne d' Hématologie Newsletter

Membership Matters

The Canadian Hematology Society has represented all physicians and scientists with an interest in the discipline in Canada since it was founded in 1971, and currently has over 400 members.

Active Membership

- Physicians in the practice of clinical or laboratory hematology in Canada
- Scientists with PhD degrees making continuing contributions to research related to hematology in Canada
- Allied Health Professionals with university degrees making sustained contributions to clinical or laboratory hematology practice or hematology research in Canada.

Only active members shall:

- **vote**
- **hold office**
- **receive CHS grants, and**
- **pay dues.**

Associate Members

- Residents and fellows engaged in hematology training
- Masters and PhD graduate students
- Post-doctoral fellows engaged in hematology research

Associate members will not be required to pay dues until completion of their training.

Emeritus Members

- All individuals who have retired from full time hematology practice or research, or those who were active members and request a transfer of status with adequate reason.

Honorary Membership

- Non-members may be invited to become Honorary Members of the corporation by virtue of their outstanding contributions to any discipline which is of importance to hematology.

CHS members are reminded … that dues for the year 2015, were due on January 1, 2015.

Your $75. annual dues payment may be made online at the CHS website:
www.canadianhematologysociety.org

Or by mail to: **Canadian Hematology Society, 199-435 St. Laurent Blvd., Ottawa, Ontario K1K 2Z8**
Please provide the following information with your payment:

2015 Membership Renewal: Canadian Hematology Society

Membership Status

Active ☐
Associate ☐
Emeritus ☐

Has your status changed?

Yes ☐
No ☐

Name: _____

Title: _____

Email: _____

Work Address: _____

_____

Work Phone: _____

Work Fax: _____