

The Microenvironment

Save the Date!



May 9 – 11, 2019

REGISTRATION: Opens—Nov. 15, 2018
ABSTRACT SUBMISSION

Deadline—Jan. 28, 2019

TRAVEL AWARD APPLICATION
Deadline—Jan. 28, 2019

<https://www.islh.org/2019/index.php>



Co-hosted by the CHS



CHS CH

THE CANADIAN
HEMATOLOGY
SOCIETY

SOCIÉTÉ
CANADIENNE
D'HÉMATOLOGIE

November 2018

NEWSLETTER

See you in San Diego!



DON'T MISS IT!

- ♦ Awards
- ♦ Networking
- ♦ Ambiance
- ♦ Dining

Canadian Hematology Society

Members Reception,

Awards and Dinner

at ASH

7:00 pm, Sun., Dec. 2, 2018

*The Westin, Gaslamp Quarter
910 Broadway Cir, San Diego, CA*

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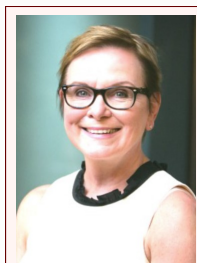
MICROENVIRONMENT

Editor	Dr. Tom Nevill
Co-Editor	Dr. Danielle Hammond

CANADIAN HEMATOLOGY SOCIETY
199—435 St. Laurent Blvd.
Ottawa, ON K1K 2Z8 CANADA
Phone: 613-748-9613
Fax: 613-748-6392
Website: canadianhematologysociety.org
Email: chs@uniserve.com

MESSAGE FROM THE PRESIDENT

CHS hosts successful International Society of Hematology (ISH) 2018 Congress, Vancouver BC



Dr. Nicole Laferriere
President, CHS

Dear Colleagues,

On behalf of the CHS it was my great pleasure to welcome the delegates to the 37th World Congress of the International Society of Hematology in Vancouver.

Thank you to our co-chairs **Dr. Gail Rock**, Chair of the Organizing Committee and **Dr. Tom Nevill**, Chair of the Scientific Program Committee. Both of these former CHS

presidents worked tirelessly to organize this important meeting. Delegates travelled from over 50 countries and there were over 300 Canadian Hematologists in attendance. It was a pleasure to see so many Colleagues and meet Hematologists from around the globe.

In his opening remarks, Dr. Nevill spoke of the rich history of Hematology in Canada. We had strong representation from Canadian Hematologists from across the country as members of the Speaker Panel and I thank them for their time and expertise.

CHS at ASH: December 2, 2018

The CHS works to advance the professional, educational and research aspects of Hematology practice in Canada. We will continue this work year with the Annual Members Reception at ASH, awarding of the Paper of the Year, Abstract Awards, the John H Crookston Award and the Lifetime Achievement Award.

ISLH 2019: May 9 – 11, Vancouver

The Canadian Hematology Society is very pleased to partner with the International Society for Laboratory Hematology (ISLH), North American Specialized Coagulation Laboratory Association (NASCOLA), and the Canadian Association of Pathologists (CAP), to host ISLH 2019: the XXXII International Symposium on Technological Innovations in Laboratory Hematology.

Plan to join your laboratory hematology colleagues in Vancouver, Canada at the Vancouver Convention Center from May 9-11, 2019. The pre-meeting educational workshop will be held on May 8, 2019.



I look forward to seeing you in San Diego on December 2, 2018 at ASH – and in Vancouver in May for ISLH 2019!

Nicole

Dr Nicole Laferriere,
President CHS

Le message du Président e

La SCH organise le congrès 2018 de la Société internationale d'hématologie qui s'est déroulé avec succès, à Vancouver, en Colombie-Britannique

Chers collègues

Au nom de la société canadienne d'hématologie (SCH), j'ai eu le grand plaisir d'accueillir les délégués au 37e Congrès mondial de la Société internationale d'hématologie à Vancouver. Merci à nos coprésidents, la présidente du comité organisateur, Docteur **Gail Rock**, et le président du comité du programme scientifique, Docteur **Tom Nevill**. Ces deux anciens présidents de la SCH n'ont ménagé aucun effort pour l'organisation de cette réunion importante. Les délégués venaient de plus de 50 pays et plus de 300 hématologues canadiens étaient présents. Ce fut un plaisir de rencontrer autant de collègues et de rencontrer des hématologues du monde entier.

Dans son allocution d'ouverture, le Dr Nevill a parlé du riche passé de l'hématologie au Canada. Les hématologues canadiens de partout dans le pays étaient bien représentés au comité des conférenciers et je les remercie pour leur temps et leur expertise.

La SCH à l'ASH : 2 décembre 2018 La SCH travaille à faire progresser les aspects professionnels, éducatifs et de recherche de l'exercice de l'hématologie au Canada. Nous poursuivons cette année de travail

avec la réception annuelle des membres de l'ASH, pour la remise du prix des meilleurs articles scientifiques, du prix des meilleurs résumés, du prix John H Crookston et du prix d'excellence pour l'ensemble des réalisations.

ISHL 2019 : du 9 au 11 mai, Vancouver La Société canadienne d'hématologie est ravie de s'associer à la Société internationale de laboratoire d'hématologie (ISLH), à la NASCOLA (Association nord-américaine des laboratoires spécialisés en matière de coagulation) et à l'Association canadienne des pathologistes (ACP) pour accueillir l'ISHL 2019 : le 32e Symposium international sur les innovations technologiques dans le laboratoire d'hématologie. Rejoignez vos collègues de laboratoire d'hématologie à Vancouver au Canada, au Vancouver Convention Center du 9 au 11 mai 2019. La réunion préliminaire à l'atelier de formation se tiendra le 8 mai 2019.

Je suis impatiente de vous voir à San Diego le 2 décembre 2018 lors de l'ASH - et à Vancouver en mai lors de l'ISHL 2019!

Nicole

Dr. Nicole Laferriere, Présidente, SCH

2018 - 2019 CHS Executive Board



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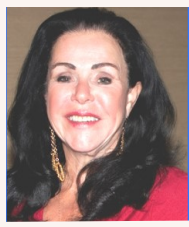
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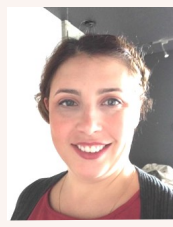
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HISTORY CORNER

Dr Hans Messner: "treated patients, not diseases"

By Dr Tom Nevill
Editor

The Microenvironment

Hans Messner was born in Brunn, Czechoslovakia on May 26, 1941. His family was ethnic German and were relocated to Fulda, Germany, where he was raised, at the end of WWII. Hans went on to study Medicine in Freiberg, Germany and moved to Canada in 1969 to complete a PhD at the University of Toronto. He met his wife, **Sandy Shuve**, the day that he arrived in Canada. They married in 1973 and went on to have four children together.

Dr. Messner studied stem cells under the guidance of **Dr. Ernest McCulloch**, one of the fathers of stem cell science (see November 2011 issue of *The Microenvironment*), before he accepted a position at Princess Margaret Hospital in 1975.



Dr Hans MESSNER

(1941—2018)

At PMH, he performed the first stem cell transplantation procedure in Ontario in August of 1976 and served as the first Director of the Allogeneic BMT Program for the next 30 years. Hans was asked by the CHS in 1977 to review the options for introducing BMT treatments across Canada. He was a founding member of the Canadian Bone Marrow Transplant Group (CBMTG). The CBMTG was incorporated in December 1989 following four years of planning and development.

He acted as the Director of the Philip S. Orsino Cell Therapy Facility after it was established at PMH in 2004 and was a driving force behind an Expert Working Group reviewing Canadian standards for transplantation of cells, tissues and organs. Dr. Messner was also a key member of the Provincial Ministry's working group that sought to improve patient flow through both the inpatient and outpatient units at PMH.

Hans Messner became a friend, mentor and advisor to many during his years at PMH; he was a compassionate physician who, in his words, "*treated patients, not diseases.*" He was an avid cycling participant in the **Ride to Conquer Cancer** (photo, right) – a member of the "Heme Team" – for 10 years until

2017 when his open battle with metastatic bladder cancer made it impossible for him to continue.

Hans took all of this in stride and learned from his experience as an Oncologist and as a cancer patient. "*The medical prowess is only one side of the coin. The smile, soft touch, embrace when spirits drop....the prowess and humane delivery (of care) is what signifies the PMH Cancer Centre.*"

He was still assisting with patient care in the months before his death and was there when PMH's Allogeneic Transplant Program was renamed the **Messner Allogeneic Transplant Program**. Dr. Hans Messner died on July 24, 2018.



Dr. Messner was not one to seek out recognition for his medical achievements; nonetheless, they were rightfully acknowledged. He received the **CBS Lifetime Achievement Award** in 2007, the **Order of Ontario** in 2015 recognizing his many contributions to cancer care and the **ASBMT Lifetime Achievement Award** in 2017. The CBMTG recently introduced the **Hans Messner New Investigator Award**, as a way of acknowledging his key role in establishing their organization in 1989.



REPORT FROM THE 37TH CONGRESS OF THE INTERNATIONAL SOCIETY OF HEMATOLOGY



The Canadian Hematology Society was pleased to host the 37th Congress of the International Society of Hematology, the oldest hematology association—having been formed on November 23, 1946—in Vancouver, September 13 - 16, 2018.

Dr. Gail Rock (Ottawa), the Organizing Chair, and **Dr. Thomas Nevill (Vancouver)**, the Scientific Chair, had spent almost five years developing the program and were pleased to welcome **600 delegates from over 50 countries**. The program had 140 oral presentations combining educational sessions, original research and Meet-the-Expert talks as well as 9 Corporate Symposia and 100 poster presentations divided into two sessions on Friday and Saturday. The opening ceremony on Thursday September 13 included a welcome from: Dr. Rock; **Dr. Emin Kansu (Ankara, Turkey)**, the Chair of Council, ISH; and **Dr. Nicole Laferriere**, the President of CHS.

This was followed by a welcome from a local group of **Indigenous performers** who sang, danced and educated conference attendees on First Nations history. Delegates were then invited to the Welcome Reception in the adjacent Ballroom. **The Scientific Program** was packed with interesting and informative presentations from around the

world and some of the content is **summarized in the following pages**. The Gala was held on the evening of Saturday September 15 and featured the spectacular menu of the **West Conference Centre** built in 2009 and those



attending were also entertained by an eclectic musical trio. The closing ceremony took place at noon on Sunday, September 16 where the ISH flag was passed from the Vancouver organizers to representatives from **Bangkok, Thailand** – the host city for the 38th Congress of the International Society of Hematology, scheduled for September 13-16, 2020.



Do you know the diagnosis?

Dr. Tom Nevill, Editor, Microenvironment

A 63 year-old man presented with:

- a one month history of fatigue, night sweats and right cervical lymphadenopathy.
- A CBC showed hemoglobin 130 g/L, WBC $2.8 \times 10^9/L$, ANC $0.4 \times 10^9/L$ and platelets $57 \times 10^9/L$.
- Chemistry was normal except for AST 74 U/L (ULN 55) and LDH 903 U/L (ULN 240).
- CT scan revealed bilateral neck, axillary, mediastinal and retroperitoneal lymphadenopathy with splenomegaly.
- A bone marrow examination was performed (Figure 1-4).

What is your diagnosis?

Answer: Page 24

Figure 1

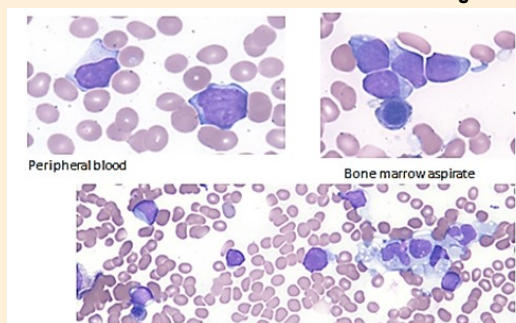


Figure 2

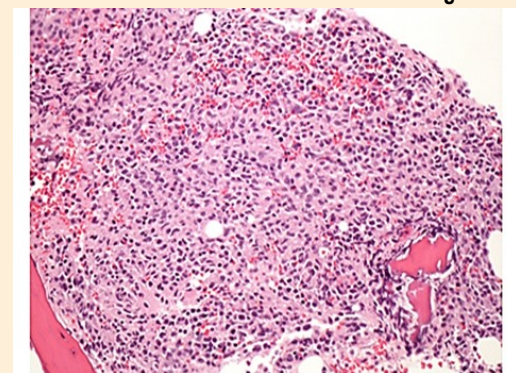


Figure 3

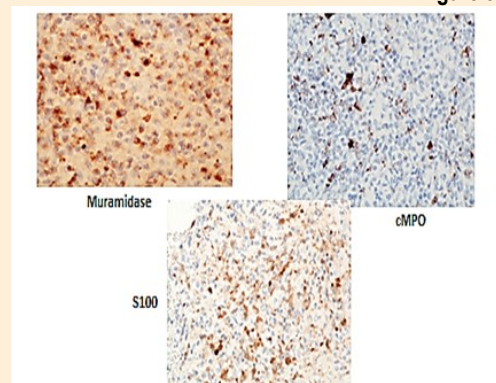
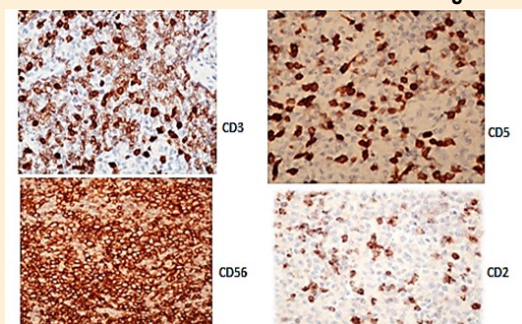


Figure 4



SUMMARY: 37th ISH Congress Scientific Program

37th ISH Congress Summary, page 5—page 23,
by Dr Tomas Nevil, Editor, the Microenvironment

Marrow Failure Syndromes Update

Dr. Phillip Scheinberg (Sao Paulo, Brazil) spoke on Saturday September 15 on the etiology, pathogenesis and therapy of aplastic anemia (AA). AA was first described by Dr. Paul Ehrlich in 1888 and has a typical biphasic age distribution with peaks between 15 and 30 years of age (when males predominate) and between 50 and 70 years of age (with no gender dominance). It has geographic variability with an incidence of 2/million in the Western world but an incidence that is twice as high in Thailand and four times higher in China. Its etiology remains mysterious in the vast majority of cases. However, it is known to be immune-mediated with studies showing oligoclonal T-cell proliferation, upregulation of interferon-gamma and T-bet transcription factor and secretion of TNF and Fas ligand leading to apoptosis of hematopoietic cells.



**Dr. Phillip
Scheinberg**

Dr. Scheinberg discussed the evolving understanding of the role of genetics in the development of AA. Studies over the past decade have shown that AA patients have short telomeres; some of these patients have identifiable mutations in telomere-related genes – including TERC and TERT – without any of the manifestations typically seen in dyskeratosis congenita. While these AA patients may respond to immunosuppression, those patients with the shortest telomeres have the highest risk of relapse (~40%).

It is interesting to note that a recent study (Townesley, 2016) showed that Danazol increases telomerase activity, lengthens telomeres and can produce durable improvement in blood counts in telomeropathy patients – although hemoglobin increases were much better sustained. Genetic predisposition to AA is also supported by the HLA-DR15 association with the disease and the discovery of predisposing mutations in interferon-gamma and TNF genes in some patients. Acquired somatic mutations have become a hot topic in AA and, excluding the PIG-A mutation expected in a sizeable number of individuals, 20-25% of AA patients have mutations in leukemia-related genes (Yoshizato, 2015). Aging-related “DTA” mutations are the most common (15%) but BCOR/BCOR-L1 (5-10%) have the most unique relationship and are

predictive of response to immunosuppression.

Treatment of AA is in evolution with results with immunosuppression at the NIH from 2005-2010 being a 68% overall response and a 96% 3-year survival. However, there is a 30% relapse rate, higher if Cyclosporine is stopped at 6 months rather than 2 years, and a 20% risk of clonal evolution. Randomized studies have definitively shown that as primary treatment, response rate and overall survival are significantly better with horse rather than rabbit ATG. Efforts to improve outcomes with immunosuppression have focused on the addition of a third agent to standard Cyclosporine/ATG. G-CSF, Sirolimus and MMF all failed to increase response rates in serial studies but the discovery of a 40% response rate – including trilineage improvements – with Eltrombopag in refractory AA patients has created interest in using this earlier in treatment. The NIH has reported on an upfront trial in newly diagnosed AA patients adding Eltrombopag (for the first 6 months) to standard immunosuppression (Townesley, 2017). A 58% CR rate and 94% PR+CR rate have been encouraging with a 3-year survival of 99%. Clonal evolution has been observed, especially monosomy 7, but the 2-year risk (~8%) is similar to historic controls. Further study is needed and the SOAR trial has been launched looking at Cyclosporine and Eltrombopag alone as initial therapy in AA.

Dr. Thomas Loughran (Charlottesville, VA) was the first to describe large granular lymphocyte (LGL) leukemia as a clonal disease in 1985. He provided a description of the key presenting features: large granular lymphocytosis ($>0.5 \times 10^9/L$), hematologic cytopenias – especially neutropenia, splenomegaly and concurrent autoimmune disease – especially rheumatoid arthritis, creating overlap with Felty's syndrome. Dr. Loughran subsequently recognized the two key subtypes of the condition, the T-cell type and the NK cell type, and their characteristic flow cytometry findings – CD3/8/16/56/57+, CD5(low) for the former and CD16 (high)/56/57+, CD3/5- for the latter. The T cell type is TCR gene rearrangement positive but the NK type is not; clonality

Figure 1

IL-15 in LGLL

- Identified as a master regulator in leukemic LGL survival
- Presence of IL-15 sufficient to reproduce all deregulations in T-LGLL.
- Increased IL-15 mRNA found in patient PBMC



in the NK type may be suggested by flow cytometry testing of the KIR repertoire (CD94, CD161 and NKB1). The more recent developments in LGL leukemia have been in understanding the molecular pathogenesis of the condition. There is now clear evidence that IL-15 upregulation is the “master regulator” of LGL survival (Figure 1) with PDGF upregulation being a concurrent event. A number of signalling pathways are subsequently activated but it appears that the JAK/STAT pathway is integral to the pathogenesis. In fact, whole exome sequencing has shown that somatic STAT3 (and also STAT5b) mutations lead to pathway activation in LGL leukemia resulting in impaired apoptosis.

Dr. Loughran reviewed the treatments available for LGL leukemia with historic review of pooled results suggesting a response rate of ~60% for each of: weekly Methotrexate, daily Cyclophosphamide and twice daily Cyclosporine. More instructive were the results of his prospective ECOG study, published in 2010, using MTX upfront and Cyclophosphamide for MTX failures, both with Prednisone for the first 8 weeks. The CR+PR rate for MTX was only 37%, although STAT3-mutated patients did respond better. Surprisingly, the response rate with Cyclophosphamide after failing MTX was 64%, suggesting this might be better for frontline treatment. However, the most important development is a new IL15 inhibitor (BNZ-1) which is being used in a phase I/II study expected to complete enrollment by the end of 2018.

Dr. Mikkael Sekares (Cleveland Clinic, OH) discussed the importance of accurately stratifying myelodysplastic syndrome

(MDS) patients by prognosis to allow for appropriate treatment decisions. The IPSS score (Greenberg, 1997) has been in use for 20 years but a newer IPSS-R is now in widespread use. The former can be practically split into two groups, lower-risk MDS (low and INT-1 risk patients) and higher-risk MDS (INT-2 and high risk patients). However, the IPSS-R has 5 categories with the middle category being “intermediate”. Dr. Sekares reviewed a key publication relating to this subgroup (Pfeilstocker, 2016) in which patients with an IPSS-R score of >3.5 had a survival of ~20 months (similar to “high-risk patients”) while those with scores ≤3.5 had a survival (~70 months) similar to “low-risk” patients. Thus, he suggested that the following should be considered higher-risk MDS and treated as such: IPSS INT-2/high; IPSS-R intermediate with score >3.5, high or very high-risk; and all MDS with excess blasts [regardless of IPSS-(R) score]. The most recent prognostic information that has been introduced for MDS patients is somatic mutations. These can be categorized by the role of the gene involved (i.e. epigenetic regulation, pre-mRNA splicing), the frequency of the mutation (from common – larger circle) to rare (smaller circle) and the prognostic impact (favourable, neutral or adverse) (see Figure 2).

Dr. Sekares introduced the Cleveland Clinic management algorithm for lower-risk MDS and higher-risk MDS. The former focused on observation and supportive care for many with clinical trial participation recommended for all patients whenever possible. However, those patients with isolated

cytopenias, growth factors (EPO or TPO agonist) were felt to be appropriate first options; for those with multiple cytopenias, Azacitidine or immunosuppression could be considered.

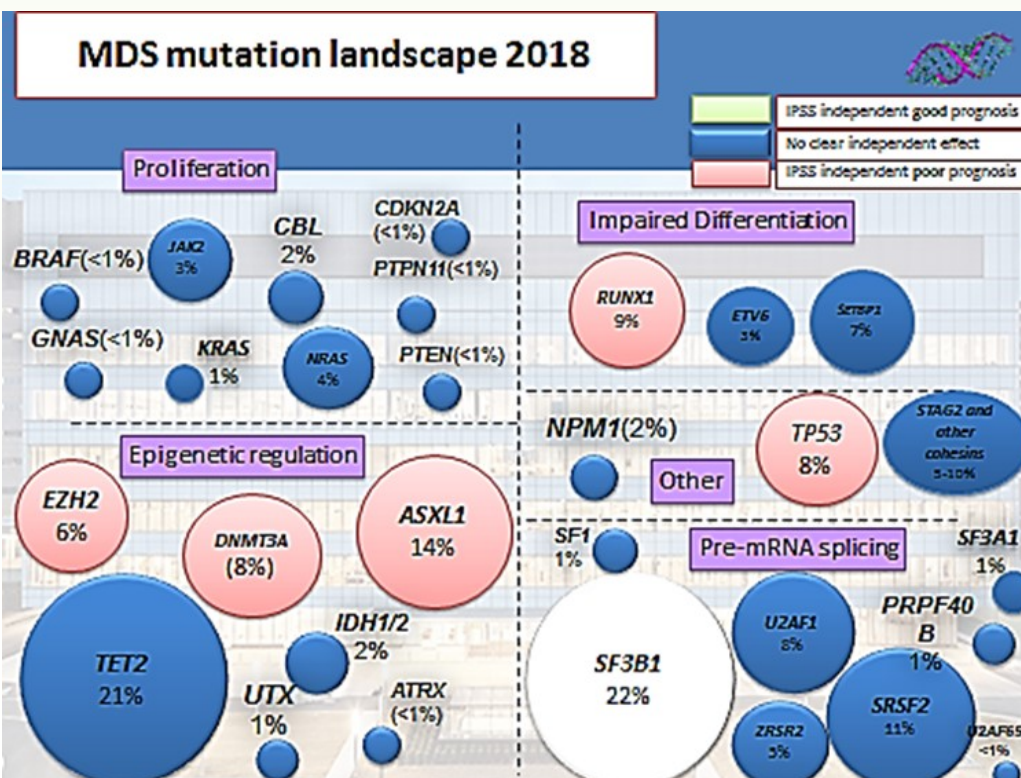


Figure 2.

An International retrospective study of immunosuppression in lower-risk MDS (Stahl, 2017) suggested a response rate of 50% although the vast majority were only “hematologic improvement”. The isolated anemia patient that fails EPO is often started on Lenalidomide alone (the combination appears no more effective than the IMiD by itself). If the patient has del (5q), the response rate is at least 60% with a median duration of 2.2 years; for the non-del(5q) patient, responses are only seen in ~30% and median duration is ~8 months. A novel

emerging therapy in EPO-refractory patients is Luspatercept, a modified activin receptor fusion protein with the ability to suppress SMAD 2/3 activation and correct ineffective erythropoiesis. Given as a subcutaneous injection every 3 weeks, about 50% of ring sideroblast MDS patients have become transfusion-independent, regardless of baseline EPO level and prior rhEPO exposure.

Higher-risk MDS patients in Cleveland are immediately treated with Azacitidine or, if transplant-eligible with a higher blast count and normal karyotype, standard AML induction; stem cell transplantation is the ultimate goal in these patients when feasible. A randomized study, with Dr. Sekares as the PI, looked at the value of adding Lenalidomide or Vorinostat to Azacitidine in this patient population (J Clin Oncol, 2017). Overall response rate was better with the Azacitidine/Lenalidomide combination (49% vs. 38% with Azacitidine alone) but this was not statistically significant and survival was no different. Finally, Dr. Sekares discussed novel agents that have shown considerable promise in MDS patients. These included: SY-1425 (Tamibarotene), a RARA/IRF8 agonist that promotes differentiation; H3B-8800, an oral modulator of the SF3B1 complex for use in spliceosome-mutated myeloid neoplasms; ASTX727, an oral combination of Decitabine and a cytidine deaminase inhibitor (that prevents degradation of Decitabine in the gut and liver); and Enasidenib, an IDH2 inhibitor with a reported 60% response rate in mutated MDS patients.

Progress in Laboratory Hematology

Dr. Catherine Hayward (McMaster University, Hamilton, ON) gave an overview of the challenges faced when investigating patients with suspected platelet dysfunction.



**Dr. Catherine
HAYWARD**

The laboratory testing focuses on light transmission aggregometry (LTA) which measures platelet aggregation to a series of agonists – typically thrombin, collagen, ristocetin, ADP, arachidonic acid and ADP -- and lumiaggregometry (LA), evaluating ATP-induced dense granule secretion. Flow cytometry for GPIb (deficient in Bernard Soulier syndrome), GPIIb/IIIa (deficient in Glanzman's thrombasthenia) and other platelet surface glycoproteins as well as electron microscopy to evaluate the dense granule count (low in dense granule deficiency) can be useful supplementary tests.

For the patient with platelet-type bleeding, with or without a family history, the first step is to do a platelet count, blood smear morphology and VWF screening. If VWF screening is normal and severe thrombocytopenia is excluded, platelet function studies are indicated. Dr. Hayward stressed that the LTA and LA are the key initial tests but are not offered widely, require fresh samples, are labour-intensive, need proper controls and validation and are not well-standardized. Furthermore, interpretation is highly variable with one study showing that only 60% of real cases are correctly interpreted by at least ¾ of the testing laboratories. Most problematic are the patient whose sample reacts to only a single agonist or has a response that is interpreted as abnormal but is actually a normal variant. Studies have shown that an individual with an abnormal LTA with at least two agonists has an odds ratio of 20-30 of having a bleeding disorder. For comparison, an abnormal bleeding time – not recommended as a test in these patients – has an OR of only 3.7 of predicting an underlying bleeding disorder.

Dr. Roland Walter (Seattle Cancer Care Alliance, Seattle, WA) spoke on minimal residual disease (MRD) testing in acute myelogenous leukemia (AML). This field has been limited by the fact that a “perfect” MRD test – able to detect a small population of cells that will lead to relapse but indifferent to cells that will not -- has not yet been identified. Next generation sequencing (NGS) has been proposed as an MRD test in AML but has recognized disadvantages. There are many mutations in AML, often several in any one patient, some mutations do not contribute to recurrence (e.g. DNMT3A) and new mutations can drive relapse. An alternative approach is multiparameter flow cytometry (MFC) which relies on identifying leukemia-associated immunophenotype (LAIP) from the diagnostic AML specimen or aberrant differentiation/maturation surface antigens (different from normal or DfN) at follow-up.

MFC has significant advantages over NGS in MRD monitoring; it is easier to do, quick in yielding results and provides quantification of leukemia clones – at least down to 0.1%. However, there remain some challenges; it is operator-dependent, has a definite learning curve, is hard to standardize between laboratories and a LAIP is not always identified at diagnosis. Nonetheless, experience to date has shown that MRD positivity at day 15, after 1 or 2 cycles of induction, pre-stem cell transplantation and post-remission therapy all predict for AML relapse. It appears that there may be a role for combining NGS and MFC MRD testing in AML as shown in a recent publication (Jongen-Lavrenic, 2018) examining 430 AML patients in morphologic CR1. If MRD was positive with both techniques, risk of relapse was 75%, 50% if only one technique was positive and only 25% in both were negative. Dr. Walter indicated that morphology and MFC are often

It is time to move to MRD-based definition of complete remission in AML

- Post-HCT outcome of adults with MRD+ remission \approx outcome of adults with active disease (n=359)

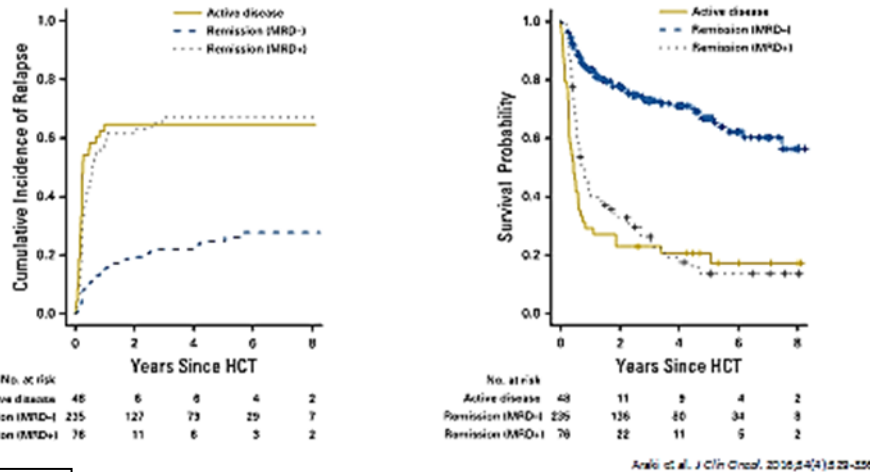


Figure 3.

discordant in determining CR in AML and that the time has come to move to a MRD-based definition of CR. To support this, he presented the results of a study examining post-transplantation outcomes for patients based upon pre-SCT MRD status. For MRD-negative patients, relapse was 25% and event-free survival was 60%; for MRD-positive patients, relapse was 65% and EFS 15%, virtually identical to a group of patients transplanted with active AML (Figure 3). In closing, Dr. Walter suggested that MFC was a valuable tool for assessing remission and for risk stratification but felt it was not yet ready to be used to guide treatment decisions.

Disorders of Hemostasis

Dr. Guy Young (Children's Hospital, Los Angeles, CA) provided a thorough review of novel antibody therapies that have been developed for hemophilia. Conventional factor replacement in this disorder has required intravenous infusion of products – frequently, in many patients – is associated with the development of inhibitors, is costly and is not curative. Novel approaches have included gene therapy – with the potential to rid patients of the condition – and antibody treatments that either “mimic” factor VIII or tip the natural procoagulant-anticoagulant balance in humans.

The antibody product that is furthest in its

development is Emicizumab, a factor VIII mimetic that is bispecific, capable of bridging factor IXa and factor X. The drawbacks of this treatment are that it is only effective in hemophilia A, is not easily monitored with blood tests, may be associated with antibody formation and has the theoretic risk of inciting thrombosis. However, a preliminary study done in 18 hemophilia A patients yielded impressive results (Shima, 2016). Emicizumab was administered subcutaneously once weekly and led to a reduction in annualized bleeding rates from a median of 18 to 0, including no bleeding in 8 of 11 patients with factor VIII inhibitors. No patients developed antibodies to the product and no thrombosis was seen.

The second product to be developed is Fitusiran, a small interfering RNA that acts on anti-thrombin, one of the anticoagulants for the coagulation cascade (Figure 4). In a phase I/II trial, it was given subcutaneously once monthly to 26 hemophilia A and 6 hemophilia B patients. With doses of ≥ 450 mcg/kg, the anti-thrombin was reduced by a median of $>75\%$, thrombin generation was increased by a median of almost 3 fold and bleeding events were reduced to a minimum (3 bleeds in 9 patients).

On the basis of these results, a phase III trial (ATLAS) was proposed but, after one patient in the phase I/II study died of a brain hemorrhage, the study was put on hold. It was later determined that this patient had suffered a primary thrombotic event with secondary hemorrhage. After appropriate steps to

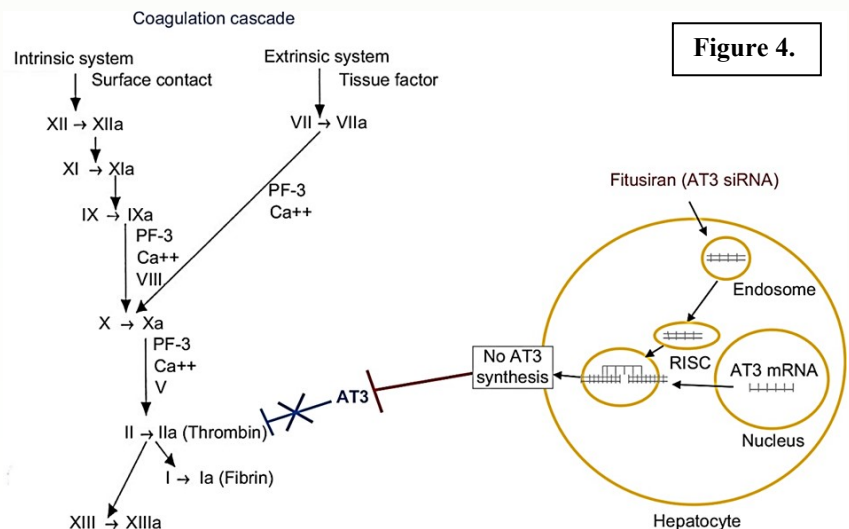


Figure 4.

mitigate risk of such events, ATLAS began enrolling patients in 2018 and the results are awaited.

The final product that Dr. Young discussed was Concizumab, an anti-tissue factor pathway inhibitor (TFPI) that binds to the Kunitz-type protease inhibitor 2 of TFPI. In a phase I study of 14 normal and hemophilia patients treated with subcutaneous Concizumab, prothrombin and D-dimers were shown to increase, consistent with a procoagulant effect – proof of principle. No thrombosis was seen and further phase I/II studies are underway using this novel treatment.

Professor Adrian Newland (Royal London Hospital, UK) spoke on current controversies in the management of immune thrombocytopenic purpura. He indicated that both morbidity and mortality in ITP was low unless there were mitigating comorbidities present.

Historically, treatment has been given to the majority of ITP patients with platelet counts <30 with the goal to achieve “safe” – not normal – platelet counts. In adults, initial therapy is with corticosteroids, often with IVIg, with other immunosuppressive agents forming the backbone of second-line therapy, albeit with CR rates of only ~15%. The specifics of the therapy selected depends upon a number of patient-specific variables – age, co-morbidities, occupation, lifestyle and history of bleeding.

The treatment algorithm for Prednisone-requiring ITP has increasingly included Rituximab with initial response rates of ~60% but durable responses are seen in only ~15% of individuals. Furthermore, hypogammaglobulinemia with recurrent infections and rarely, progressive multifocal leukoencephalopathy are recognized complications of this treatment. Thrombopoietin agonists – Romiplostim and Eltrombopag – have a response rate of 80-90% in steroid-

refractory ITP. TPO agonists need to be continued indefinitely in most patients but ~30% will maintain their platelet count at acceptable levels after discontinuation.

Dr. Newland suggested that the next major step forward in ITP management will be based upon a better understanding of the underlying biology of the condition. The most exciting new agent that has entered the clinic is Fostamatinib, an oral inhibitor of the macrophage-associated spleen tyrosine kinase (Syk) (Figure 5). Early trials have shown a ~50% response rate in ITP patients, some of which had failed TPO agonists. Its primary toxicities are GI side effects, with other adverse effects being uncommon. Follow-up phase II trials (FIT-1, FIT-2 and FIT-3) have shown a ~20% response rate in refractory ITP patients, ½ of whom had received TPO agonists and 1/3 of whom had previously undergone splenectomy.

Therapies for Hemoglobinopathy

Dr. Richard Ward (University Health Network, Toronto, ON) provided an update on new therapies available for β thalassemia. His talk focused on improved management of iron overload and development of alternatives to blood transfusions but did touch on the “holy grail” – the potential to cure the condition with gene therapies that are undergoing clinical trial around the world.

Luspatercept is a modified activin receptor-IgGFc fusion protein that promotes late stage erythroid differentiation and is being evaluated in transfusion-dependent MDS. However, it has also been shown to reduce α globin aggregates, reduce hemolysis and thereby reduce iron burden. In a study by Rivella (2015), ¾ of β thalassemia patients experienced a >33% reduction in transfusion burden following q3weekly Luspatercept infusions. Ruxolitinib, a JAK2 inhibitor used in chronic MPNs, was evaluated in a phase IIa involving 27 patients with β thalassemia (Taher, 2018). Participants had a mean 26% reduction in spleen size at 30 weeks and a mean 6% reduction in transfusion burden.



**Dr. Richard
WARD**

Dr. Ward reported on results with AG-348, a pyruvate kinase (PK) activator in β thalassemia. ATP is a key component of antioxidant systems and low ATP levels are characteristic of β thalassemia. Within the erythrocyte, PK is involved in the final step of ATP production. A PK inhibitor could significantly improve erythrocyte survival in β thalassemia. Hemoglobin

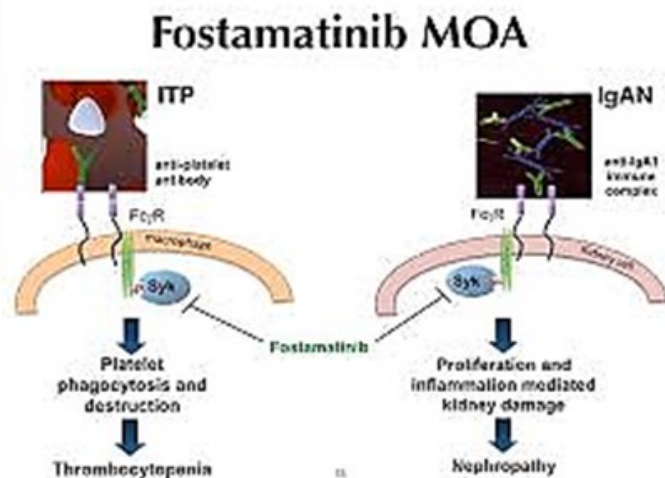


Figure 5.

gene modification might be another approach to mitigating the effects of β thalassemia with either increasing fetal hemoglobin with Metformin – the subject of a clinical trial in non-transfusion-dependent β thalassemia – or downregulation of the α gene – with CRISPR/Cas9 gene editing -- to alter globin gene imbalance being viable approaches.

Transferrin has also been used as a treatment strategy in β thalassemia and this has been shown to reduce spleen size and thereby double erythrocyte survival time (Li, 2010). Transferrin also modulates iron metabolism, increases hepcidin, normalizes plasma iron and increases hemoglobin production – although not to a clinically relevant level to date. Hepcidin agonists – “mini hepcidins” -- are currently in development and have the potential to limit iron absorption and alter storage.

This could benefit both β thalassemia and hemochromatosis patients and mouse models have shown reduction in spleen size and improvement in hemoglobin through correction of ineffective erythropoiesis. Finally, Dr. Ward did reiterate the results of one older (Oudit, 2003) and one more recent (Eghbali, 2017) study that both showed Amlodipine to be effective at reducing cardiac tissue iron and, when combined with iron chelation, was superior to chelation alone (Fernandes, 2016).

Dr. Christina Peters (Vienna, Austria) spoke about the role of allogeneic stem cell transplantation (SCT) in patients with hemoglobinopathies. She emphasized that these disorders constitute the largest population of non-malignant disease patients with an indication for SCT and that sustained engraftment leads to resolution of the signs and symptoms for affected individuals. Furthermore, delays in proceeding to SCT only increases risk of graft rejection and GVHD and leads to more treatment-related mortality (TRM) – especially due to complications of iron overload. For young patients without organ dysfunction (especially hepatic impairment), disease-free survival with matched sibling SCT is >90%. With the development of novel conditioning for alternative donor SCT, disease-free survival is ~80% (Shenoy, 2018) although the incidence of acute and chronic GVHD are in the order of 25-30% when alternative donors are used.

Dr. Peters expressed her feelings that myeloablative regimens are needed in hemoglobinopathies as the risk of graft rejection is unacceptably high with reduced-intensity conditioning. In this regard, she presented data on SCT in over 2000 patients with non-malignant disorders, ~600 of whom had

hemoglobinopathies. This retrospective review showed that the lowest TRM (8%) and the highest survival (90%) was seen when Treosulfan, Fludarabine and Thiotepa conditioning was used. When the analysis was confined to β thalassemia major, the same conditioning yielded the best results although the difference from other conditioning regimens was not significant (Figure 6).

Figure 6.

TM: Primary Outcomes

Outcomes	Strata	Endpoint with 95% CI	p value*
1 yr OS	Bu/Flu	92.6 [88.3-97.2]	0.42
	Treo/Flu+TT	95.9 [92.9-98.9]	
	BU/Flu+TT	93.5 [88.5-98.7]	
100d TRM	Bu/Flu	5.4 [1.7-9]	0.21
	Treo/Flu+TT	2.2 [0-4.3]	
	BU/Flu+TT	2.8 [0-6]	
1 yr TRM	Bu/Flu	7.5 [2.8-11.9]	
	Treo/Flu+TT	2.9 [0.3-5.5]	
	BU/Flu+TT	5.5 [0.6-10.2]	

Finally, Dr. Peters presented the results from 1000 matched sibling SCTs for sickle cell disease that was recently published (Gluckman, 2017). This study showed an overall survival (OAS) of 93% (95% for patients <16 years and 80% for patients ≥16 years) with a 5-year event-free survival (EFS) of 70%. Although uncommon, acute GVHD was seen in 15% of patients and a similar percentage developed chronic GVHD. In a smaller study involving 30 patients, unrelated donor SCT yielded similar outcomes (OAS 90%, EFS 70%) but a higher risk of acute (28%) and chronic (62%) GVHD and a dramatic incidence (~30%) of posterior reversible encephalopathy syndrome (PRES).

Lymphoproliferative disease

Dr. Cynthia Toze (Vancouver, BC) delivered a presentation on chronic lymphocytic leukemia that focused on the increasing challenges of prognostic stratification in deciding appropriate treatment in CLL. Allogeneic stem cell transplantation used to be the only treatment associated with long-term survival in “high-risk” patients but the definition of

high-risk has evolved as novel treatment options have expanded. Patients with chemoimmunotherapy refractory disease should be referred for a SCT opinion as should patients with del(17p) and, when available, TP53 mutations – although novel agents such as Ibrutinib may effectively control disease in these patients if used early in the course of the condition. IgVH unmutated status is an adverse disease feature but patients may respond well to novel agents (again, when used early). Certainly, novel agent use is associated with lower risk of morbidity and mortality than SCT and, intuitively, a better quality of life. However, Ibrutinib can cause cardiac toxicity, Idelalisib is associated with colitis and pneumonitis and Venetoclax may produce life-threatening tumour lysis.

However, immune recovery is not possible without SCT – although this is not guaranteed with this approach. More concerning for clinicians is the durability of the response to novel agents and the salvageability of patients with high-risk disease if they progress on Ibrutinib – potentially preventing a patient from proceeding to SCT. There is a general consensus that CLL patients who experience Richter's transformation (RT) should be stabilized and promptly taken to SCT and Dr. Toze indicated that some patients will develop RT within a few months of starting Ibrutinib.



**Dr. Cynthia
TOZE**

Regarding the specifics of SCT in CLL, Dr. Toze emphasized the importance of screening family donors for a CD5+ B cell clone with flow cytometry before committing to using them as a donor as there is a definite familial predisposition to CLL. Conditioning of CLL patients for SCT should be done with reduced-intensity regimens as this is associated with lower risk of TRM and the most favourable outcomes. One of the unusual quirks of SCT for CLL is that a post-transplant relapse

does not necessarily translate into a short survival. In fact, studies show that 10-year overall survival for CLL patients is identical for patients with post-SCT relapse as for individuals without recurrent CLL.

In summarizing results for SCT in CLL, Dr. Toze showed the 5-year outcomes for almost 2600 patients reported to a SCT registry (Schetelig, 2017). Overall survival was 50% (40% event-free) with a TRM of 30% and a relapse rate of 30%. Of interest, there was a gender difference in that EFS for females was 15-20% better, regardless of whether the CLL was good-risk or poor-risk.

Dr. Doug Stewart (Calgary, AB) provided an overview of primary CNS lymphoma (PCNSL) with a special focus on the outcomes with high-dose therapy. PCNSL is only 1% of all lymphomas and is usually characterized by a single supratentorial enhancing lesion although ~20% present with ocular involvement. ~90% of PCNSL are BCL2+ DLBCL, non-GCB type with chromosome 9p24.1 abnormalities being common – consistent with an immune evasion etiology. Outcomes for patients <age 60 years are superior to outcomes for those ≥60 years. Treatment of PCNSL (Figure 7) should focus on CNS-directed therapy and induction with high-dose Methotrexate (HD-MTX) and/or high-dose Ara-C (HDAC) [using both may lead to a better progression-free survival (PFS)] is preferred.

Historically, whole brain radiotherapy (WBRT) has been used in these patients and, while it may improve PFS, neurotoxicity is a problem – negatively impacting quality of life – and overall survival is not improved. Novel therapies – Ibrutinib, IMiDs and PD1 inhibitors – have had interesting activity in small numbers of PCNSL patients but their role in treatment has not yet been established. Dr. Stewart is a proponent of Thiotepe-based high-dose therapy with autologous stem cell transplantation (ASCT), early in the course of the disease, and offered personal and literature results to support this assertion.

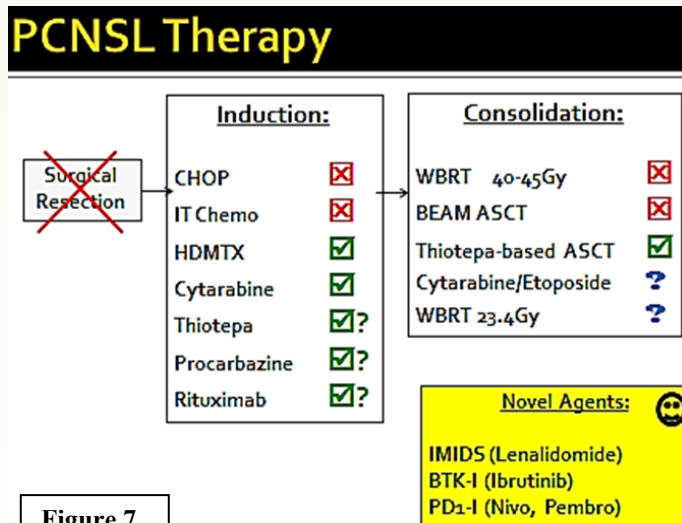


Figure 7.

Multicentre reports have shown a PFS in relapsed/refractory PCNSL of 30-40% with an early TRM of 6-8%. However, the French multicentre phase II PRECIS trial for newly diagnosed PCNSL patients (Houllier, 2016) randomized patients to ASCT or WBRT following HD-MTX + HDAC induction. The reported 2-year PFS was 87% in the ASCT arm and 63% in the WBRT arm. The IELSG-32 study took 219 patients with PCNSL and randomized to every 3 week induction with HD-MTX/HIDAC, the same + Rituxan or the same + Rituxan and Thiotepe. All three arms were mobilized for stem cell collections after two cycles with patients with at least stable disease being

randomized to ASCT versus WBRT. The third arm (MATRIX) had the highest percentage of patients randomized (64%) and the highest 3-year PFS although the ASCT and WBRT treatments had a similar PFS overall. Dr. Stewart highlighted that almost half of all patients in the study did not proceed to ASCT and questioned whether optimizing induction was not as important as getting as many patients to ASCT as possible.

In his final slides, Dr. Stewart reported on the results of ASCT for PCNSL in Alberta between 2011 and 2018. Four cycles of induction incorporating HD-MTX, HIDAC, Rituxan ± Procarbazine are given with stem cell collection after the first 2 cycles. A two-drug preparative regimen is used (Busulfan and Thiotepa) as a three-drug regimen (including Cyclophosphamide) was not as well-tolerated, particularly in patients >age 60 years. In 38 patients so treated, there has been no TRM and 3-year PFS is 77%.

Dr. Kerry Savage (Vancouver, BC) spoke on the use of checkpoint inhibitors in lymphomas, a treatment that has been directed at this malignancy's ability to evade immune attack. One of the mechanisms that lymphomas use is the PDL-1/PDL-2 present on the tumour cell which act on the PD-1 receptor present on effector T-cells. When the ligand interacts with the receptor, the immune response is "checked". Checkpoint inhibitors can restore T-cell immune response by blocking inhibitory receptors or by stimulating activating receptors (Figure 8). Dr. Savage put classical Hodgkin lymphoma (cHL) forward as the "poster child" for PD-1 inhibition.

There are many potential sites for checkpoint receptor inhibition

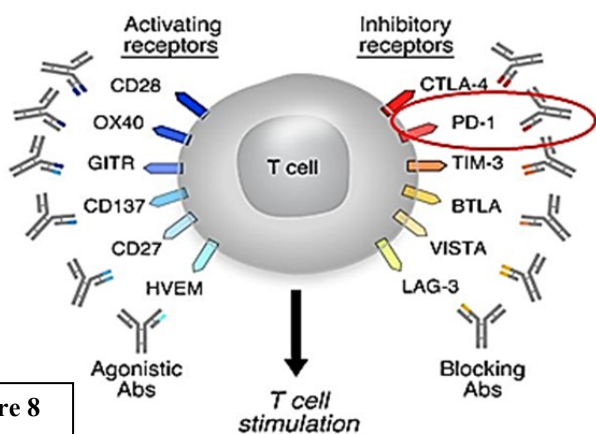


Figure 8

cHL is often EBV-driven and is characterized by alteration or amplification of chromosome 9p24.1, the site of the genes encoding PDL-1 and PDL-2. Both EBV and 9p24.1 aberrations lead to increased expression of PDL-1/2 on the Reed-Sternberg cells, allowing them to avoid immune surveillance. Not surprisingly, PD-1 inhibitors have shown dramatic activity

in cHL with 27/29 patients responding to Pembrolizumab (Moscovitz, 2014) and 20/23 patients achieving PR/CR with Nivolumab (Ansell, 2015) in phase I studies. Subsequent phase II studies have confirmed a ~70% response rate in patients relapsing after ASCT and failing Brentuximab vedotin (Younes, 2016; Chen, 2017). Even more intriguing is the fact that CRs increase over time and are durable with >70% of CRs maintained beyond 18 months. However, Dr. Savage did describe the significant side effects that can occur with these agents including hypersensitivity infusion reactions, cytokine release syndrome, skin rash, hyper/hypothyroidism, hepatitis and pneumonitis – in fact, virtually any organ may be affected.

With the noted efficacy of PD-1 inhibitors in cHL, these agents have been used in a variety of non-Hodgkin lymphoma with much less impressive results. In general, response rates have been lower (≤40%) and shorter (a few months) although there are specific exceptions. Primary mediastinal B cell lymphomas and Gray zone lymphomas are both disorders with a significant incidence of 9p24.1 abnormalities and have been associated with the highest response rates. EBV+ DLBCL and lymphomas involving immune privilege sites (primary CNS or testicular) are diseases where PDL-1/2 are upregulated and excellent responses have been described. T/NK cell lymphomas, especially extranodal (nasal or liver), cutaneous (mycosis fungoides) and anaplastic large cell lymphoma all have a biologic basis to respond to PD-1 inhibitors.

Curiously, the use of checkpoint inhibitors in adult T-cell lymphoma leukemia and multiple myeloma has led to inferior outcomes due to rapid disease progression and severe toxicities, respectively. In closing, Dr. Savage proposed that combination therapy in cHL may further improve outcomes with there being a strong scientific reason to use Nivolumab and Brentuximab vedotin in relapsed/refractory disease. Preliminary studies suggest a >80% response rate with this combination although infusion reactions have been an issue in almost ½ of patients.

PLENARY SESSION FOR BEST ABSTRACTS

GOLD MEDAL WINNER

Identification of CD248 as a novel cofactor for tissue factor activation of coagulation

Piyush Kapopora, Centre for Blood Research, University of British Columbia, Vancouver, Canada

Venous thromboembolism (VTE) is the third leading cause of vascular disease, is increasing in incidence and tissue factor (TF) is a key trigger of coagulation. CD248 is expressed on inflammatory monocytes and vascular smooth muscle cells.

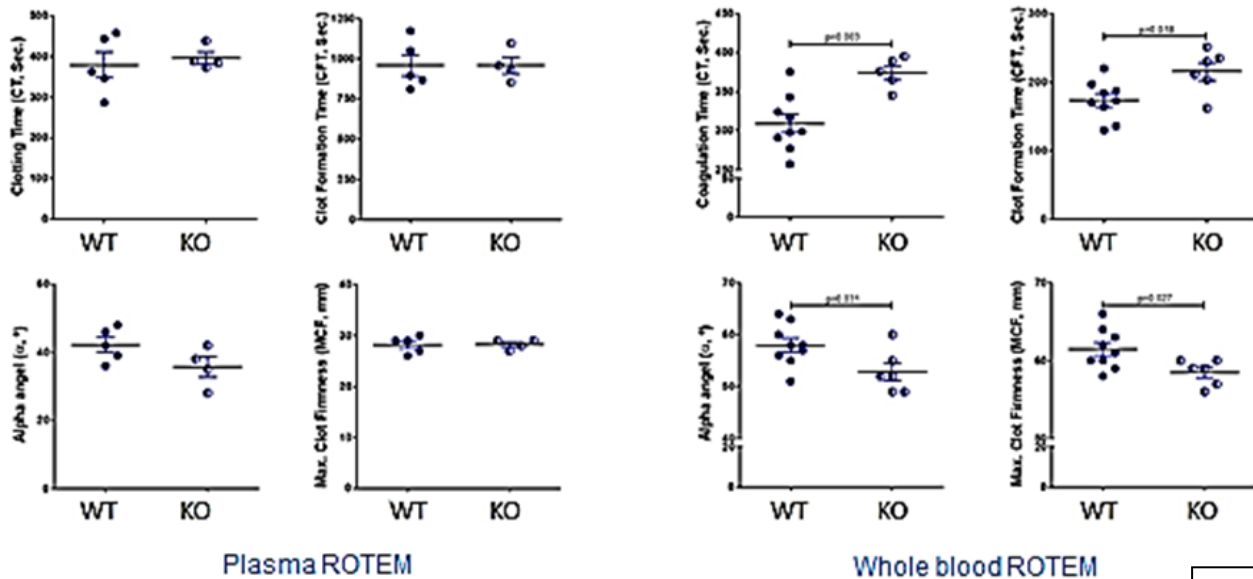


Figure 9.

This study employed CD248 knockout mice to examine the potential role of CD248 as a co-factor in TF-dependent extrinsic pathway activation.

Using rotational thromboelastometry (ROTEM) for evaluating hemostasis in vitro, the investigator was able to show that CD248 knockout mice had significantly longer coagulation times ($p=0.003$), clot formation times ($p=0.018$) and maximal clot firmness ($p=0.027$) when compared to wild-type mice (Figure 9). This strongly supported that CD248 is an important cofactor in thrombin-mediated clot formation and provides yet another potential therapeutic target for prevention of VTE.

RUNNER-UP ABSTRACTS

Safety, efficacy and PK/PD profile of the anti-C1s antibody (Sutimlimab) in primary cold agglutinin disease patients

Ulrich Jäger, Division of Hematology, Medical University of Vienna, Vienna, Austria

Cold agglutinin disease (CAD) is an autoimmune hemolytic anemia caused by IgM antibodies, usually affecting an elderly patient population. Symptoms relate to the anemia itself, the agglutination or venous or arterial thromboembolism and 5-year survival is in the order of 60%.

Sutimlimab is a humanized antibody directed against C1s that prevents activation of the classical complement pathway and is

administered by weekly 1-hour intravenous infusion. In this study, 10 patients with CAD, with a mean pre-treatment hemoglobin of 78 g/L, were given weekly Sutimlimab infusions for four weeks and re-evaluated. All patients became transfusion independent with 70% of subjects having a >20 g/L rise in their hemoglobin level (Figure 10).

Patients with primary CAD generally responded better than those with secondary CAD. Side effects were very uncommon with one patient developing rash and one reporting alopecia.

Best Overall Hemoglobin Response to Sutimlimab in Patients with Cold Agglutinin Disease (N=10)

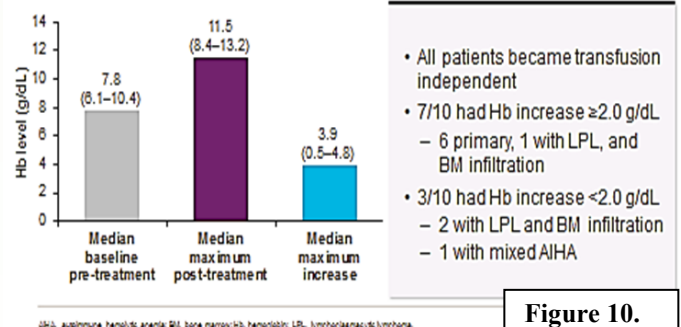


Figure 10.

The investigative team is moving forward with plans to carry out a randomized placebo-controlled study to confirm the superiority of this new agent.

Clinical significance of ASXL2 and ZBTB7A mutations and AML1-ETO9a expression in AML with t(8;21): the JALSG AML201 study

Naomi Kawashima, Department of Hematology and Oncology, Nagoya University School of Medicine, Nagoya, Japan

Core binding factor AML has a favourable prognosis although ~50% of patients experience a relapse. This study examined the prognostic significance of additional driver mutations in t(8;21) AML in a study of over 1000 de novo AML patients in Japan. There were 41 patients identified with this translocation and ASXL2, an epigenetic modifier, was found to be mutated in one-third of this cohort. These patients presented with a higher white cell count, were less likely to have an associated sex chromosome loss – a frequent finding in t(8;21) disease – and none had concurrent ASXL1 mutations. However, the presence of an ASXL2 mutation had no influence on CR, DFS or OAS rates. ZBTB7A, a transcription factor gene, was found to be mutated in 4 patients (10%). Although the ZBTB7A-mutated group was small, their DFS was only 20% compared to 61% in the wild-type patients ($p=0.14$) and may be useful in deciding on post-remission therapy in t(8;21) disease.

Clinical outcomes following lentiglobin gene therapy for transfusion-dependent β -thalassemia in the Northstar HGB-204 study

Suradej Hongeng, Ramithibodi Hospital, Bangkok, Thailand

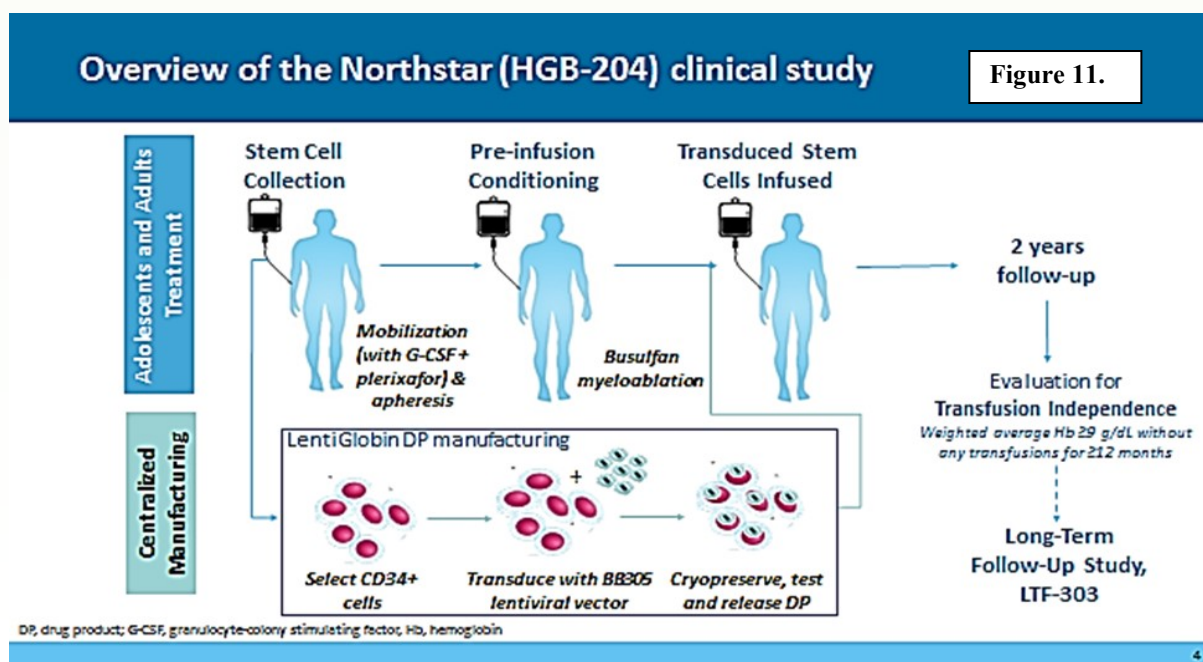
This presentation was made on behalf of the Northstar HGB-204 Study investigators and detailed the results of an

international phase I/II study of gene therapy in adolescents and young adults with β -thalassemia. Iron overload remains a major contributor to morbidity and mortality in this patient population. Stem cell transplantation (SCT) can be curative in this condition and while outcomes are good with matched sibling SCT, results with alternative donors are much less favourable and new therapies are needed.

The approach used in this study was to condition patients with high-dose Busulfan and reinfuse cryopreserved autologous CD34+ stem cells transduced ex vivo with BB305 lentiviral vector encoding the B-globin gene with a T87Q amino acid substitution (Figure 11).

The investigators have treated 18 patients, median age 21-24 years (maximum 36 years), with a median follow-up of almost 3 years and a minimum follow-up of 2 years. The median CD34+cell transduction rate was 29-32% and all subjects had neutrophil engraftment by 30 days; 94% had platelet engraftment by day +100. Stomatitis and febrile neutropenia were the common \geq grade 2 non-hematologic toxicity; two patients developed hepatic VOD, two patients had a thrombotic event and no lentivirus vector was detected in recipients of the product.

Although all patients experienced a decrease in PRBC needs (median of ~50%), the key end-point – transfusion-independence – was reached in 8 of 10 non- $\beta\beta$ genotypes (7 patients within 4 months) and 3 of 8 $\beta\beta$ genotypes (with 2 patients taking 18 months to do so). Investigators are currently enrolling patients on the randomized Northstar-2 (non- $\beta\beta$ genotypes) and Northstar-3 ($\beta\beta$ genotypes) clinical trials.



Heparin-induced Thrombocytopenia, DIC and the Ischemic Limb

Dr. Ted Warkentin (McMaster University, Hamilton, ON) delivered an entertaining and informative talk on limb ischemia to open the scientific program. He emphasized that when dealing with an ischemic limb, the first triage point is decided by the presence or absence of a pulse. If the latter, this become a surgical emergency and appropriate consultation is warranted. If the pulse is present and there is evidence of DIC – as there is in ~90% of such cases -- this is a hematologic emergency.

ISTH Scoring System For Overt Disseminated Intravascular Coagulation

1. Risk assessment: does the patient have an underlying disorder known to be associated with overt DIC?

✓ If Yes: Proceed

If No: Do not use this algorithm

2. Order global coagulation tests:

	Normal	Patient
Platelet count:	160-400	XXX
Fibrin-specific marker: e.g., d-dimer:	< 500	XXX
INR (PT):	0.8-1.2	XXX
Fibrinogen:	1.6-4.0	XXX

4. Calculate score:

If ≥ 5 : Compatible with overt DIC

If < 5 : suggestive (not affirmative) for non-overt DIC

3. Score global coagulation test results:

Platelet count:	>100 = 0	<input type="checkbox"/>
	<100 = 1	<input type="checkbox"/>
	< 50 = 2	<input type="checkbox"/>
Elevated Fibrin related markers (e.g., Fibrin D-dimer):	no increase = 0	<input type="checkbox"/>
	moderate increase = 2	<input type="checkbox"/>
	strong increase = 3	<input type="checkbox"/>
Prolonged INR:	INR ≤ 1.2 = 0	<input type="checkbox"/>
	1.3-1.6 = 1	<input type="checkbox"/>
	≥ 1.7 = 2	<input type="checkbox"/>
Fibrinogen level:	≥ 1.0 g/L = 0	<input type="checkbox"/>
	<1.0 g/L = 1	<input type="checkbox"/>
TOTAL		<input type="checkbox"/>

Modified from Toh and others. Scoring system of the Scientific and Standardization Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 2-year overview. Journal of Thrombosis and Haemostasis 2007;7:604-609.

Determining whether there is evidence of DIC in a rigorous and validated fashion is important and Dr. Warkentin introduced the ISTH Scoring System that can be applied in situations known to be associated with DIC (Figure 12).

In evaluating a patient with an ischemic limb, palpable pulses and DIC, there are two conditions to be considered – venous limb gangrene (VLG) and symmetrical peripheral gangrene (SPG), with the latter sometimes manifesting as purpura fulminans. Both VLG and SPG are associated with mild to moderate thrombocytopenia. VLG is seen with heparin-induced thrombocytopenia (HIT) and cancer-associated DIC. Cancer-associated VLG typically occurs in a patient with known venous thromboembolism during their transition from Heparin to Warfarin. It mimics HIT and presents with acral extremity necrosis that is a consequence of Warfarin depletion of Vitamin K-dependent Protein C leading to procoagulant/anticoagulant imbalance and microthrombosis. This usually develops on day 2-5 of Warfarin when the INR is supratherapeutic (>3.5), a surrogate marker for severe Protein C depletion. Not surprisingly, an important therapeutic intervention in these patients is Vitamin K administration.

Individuals develop SLG in the context of septic or cardiogenic shock. Classic teaching has attributed SLG to vasopressor administration in the face of profound hypotension. Dr. Warkentin has re-examined this thinking and notes that these patients typically develop shock liver on day 2-5 followed by symmetrical acral extremity necrosis. Laboratory studies support that Protein C (and anti-thrombin) are both markedly depleted at this time providing a unifying pathogenetic mechanism for VLG and SPG.

Updates in Multiple Myeloma Molecular Biology and Treatment

Dr. Brian Walker (Little Rock, AR) gave a presentation on the rapidly expanding area of genetic changes in multiple myeloma (MM) (Figure 13); these changes tend to accumulate over time as MM progresses.

“Primary” genetic events – IGH translocations and hyperdiploidy -- are equally common in MGUS, smoldering myeloma and frank MM. This is not true for “secondary” events – copy number alterations [del(1p), del(17p), del(13q) and 1q+], DNA hypomethylation and acquired

mutations [t(8;14)] – which increase in frequency across the plasma cell dyscrasia spectrum. Nonetheless, both primary genetic events [e.g. t(4;14) and t(14;16)] and secondary genetic events [del(1p), del(17p) and 1q+] can be associated with adverse outcomes. There is also evidence for cooperative and synergistic effects of certain genetic changes. IGH translocations are closely linked to 1q+ and del(17p) and all

Myeloma Genome: Summary

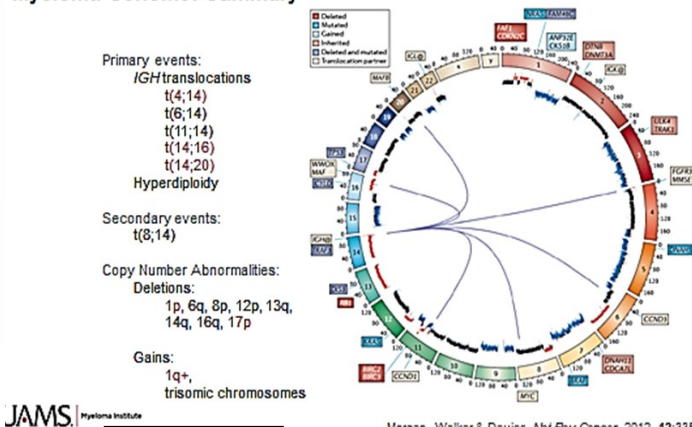


Figure 13

Morgan, Walker & Davies. Nat Rev Cancer 2012 12:335

three abnormalities may coexist, producing an inferior prognosis to patients with two abnormalities which, in turn, is worse than a patient with just one of these genetic changes.

Recent next generation sequencing studies have given a better understanding of the mutational landscape in MM. As a general rule, mutations in oncogenes are much more common than mutations in tumour suppressor genes in this disease. The most common mutations occur in the MEK/ERK pathway genes with NRAS, KRAS and BRAF V600E being most frequent. DIS3 mutations are particularly common in t(4;14) and t(14;16) disease patients. Mutational analysis has shown that t(14;16) and t(14;20) MM have the highest mutational load and may be a unique subset of patients in their sensitivity to PD-1 inhibitors.

Dr. Kevin Song (Vancouver, BC) followed with a thorough review of evolving antibody therapies that have the potential to further improve outcomes in MM. The “naked” antibodies are the furthest along in development and include Daratumumab and Isatuximab, both targeting CD38 and Elotuzumab, targeting SLAMF-7. These agents are all directed at extracellular targets and while they do have single agent activity, the best results have been seen in combination with IMiDs or proteasome inhibitors and Dexamethasone. Daratumumab is an interesting agent in that it has been demonstrated to have both “direct” toxicity and an “indirect” effect on MM by depleting immunoregulatory cells leading to T-cell activation and expansion.



**Dr. Kevin
SONG**

Newer antibody products for MM patients are being widely developed with B Cell Maturation Antigen (BCMA) being a favourite target. Antibody conjugates including DM1 toxin are in phase I trials but the most promising agent in this class is GSK2857916. This product is a BCMA-monomethyl auristatin-F conjugate that has high single agent activity (60%) but does have ocular toxicity. It has moved into phase II and phase III trials and holds considerable promise in combination therapy.

Bispecific antibodies have been developed for B-cell ALL and hemophilia A and are also undergoing phase I studies in MM with BCMA being the target for AMG 701 and JNJ-857. Perhaps the most intriguing product in this area is BCMA-directed CAR T-cells although the experience with this therapy in MM is small. Nevertheless, the early results from the largest study involving 18 MM patients (Bluebird Bio) are encouraging -- 4 CRs, 7 VGPRs and 5 PRs.

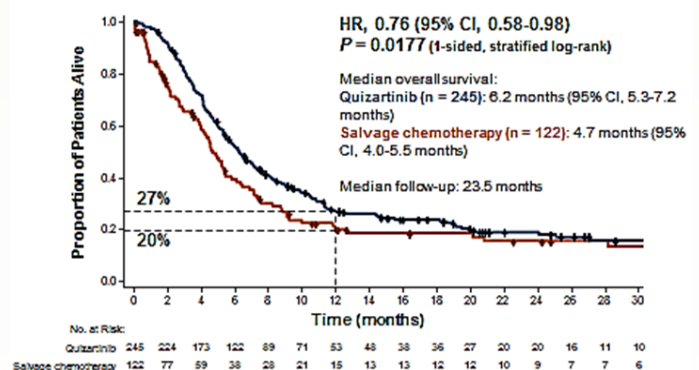
ISH-ASH Joint Symposium: Targeted Therapies in Hematology

Dr. Donna Hogge (Vancouver, BC) began this symposium with a talk directed at gene inhibitor therapies in AML. FLT3-positive AML is a poor prognosis subgroup and, not surprisingly, FLT3 inhibitors have been a focus of drug development over the past several years. The first approved agent for this patient population is Midostaurin and the results of the pivotal Phase III trial were presented (Stone, 2017). In this randomized, placebo-controlled study, Midostaurin was given orally from day 8-21 in FLT3+ patients with 7+3 induction, HIDAC consolidation and maintenance – although patients were allowed to proceed to allogeneic SCT when appropriate. The OAS curve for the Midostaurin arm separated out early (within the first 6-9 months) from the placebo arm. Median OAS was 74.7 months in the Midostaurin arm and 25.6 months in the placebo arm ($p=0.009$). The survival advantage was seen in all FLT3-mutated patients --TKD, ITD low and ITD high.

Second generation FLT3 inhibitors – Quizartinib and Gilteritinib – are more specific and more potent. The Quantum-R study evaluated Quizartinib in the refractory/first relapse setting with the standard arm receiving one of three salvage regimens; patient in both arms could proceed to SCT where appropriate. The Quizartinib arm ($n=245$, 2:1 randomization) had a “composite” CR rate of 48% (44% were CRi or CRp) and the standard arm ($n=122$) had a CR rate of 27% (all but one CRi). Median overall survival was modest but better in the Quizartinib cohort (6.2 vs. 4.7 months; $p=0.018$) (Figure 14).

Primary Endpoint: Overall Survival by Kaplan-Meier Method

Figure 14



IDH inhibitors have moved to the fore in AML with the IDH2 inhibitor, Enasidenib, nearing approval in Canada. IDH2 mutations are seen in 12% of AML patients and portend an intermediate or poor prognosis, depending upon concurrent mutations. These mutations cause enzymatic activity that

increases 2-hydroxyglutarate, increases DNA hypermethylation and blocks differentiation. In a study of 239 relapsed/refractory AML patients (Stein, 2017), Enasidenib had a 26% composite CR but, unlike FLT3 inhibitors, most (20%) were true CRs and duration was longer (~9 months). However, as these agents act through differentiation, median time to CR is 4 months and differentiation syndrome occurs in 5-7% of patients.

Ivosidenib is an IDH1 inhibitor – IDH1 mutations are found in ~10% of AML – that has also been evaluated in 258 relapsed/refractory AML patients with this genetic lesion (DiNardo, 2018). A composite CR rate of 34% was seen (2/3 were CRs), with the same time to CR (3 months) and 5% incidence of differentiation syndrome seen with IDH2 inhibitors. QT prolongation – a problem seen with both IDH and FLT3 inhibitors -- was observed in 8% of subjects. Of interest, ~20% of patients cleared their IDH1 mutation and this subgroup had a much longer survival.

Dr. Ruben Mesa (San Antonio, TX) related his experience with JAK inhibitors in myeloproliferative neoplasms. While a number of JAK inhibitors are seeking approval – Pacritinib, Fedratinib and Momelotinib -- the only JAK inhibitor that is currently approved in North America is Ruxolitinib. This agent has a well-established role in primary (and post-PV/ET) myelofibrosis based upon the Comfort-I (randomized, placebo-controlled) and the Comfort-II [randomized versus best available therapy (BAT)].

In summary, both studies show a 30-40% spleen response (pre-defined as $\geq 35\%$ reduction in volume) and convincing improvement in constitutional symptoms (night sweats, pruritus and MSK pain). Pooled 5-year survival data (Figure 15) from the two studies show a median survival of ~5 years with Ruxolitinib, 3.5 years with BAT (although crossover to

Ruxolitinib was allowed) and 2.5 years for control patients censored at crossover.

With its role in myelofibrosis solidified, Ruxolitinib has now been evaluated in Hydroxyurea/Interferon-resistant/intolerant PV (Response Trial; standard arm of BAT) and is undergoing evaluation in Hydroxyurea-resistant/intolerant ET (Reset trial; standard arm of Anagrelide). In the Response trial (PV), Ruxolitinib was twice as effective at controlling hematocrit and the only arm that saw a reduction in spleen volume. The hematocrit control was durable with >80% of subjects having a satisfactory hematocrit at 3 years. The WBC and platelet counts were also better controlled and thromboembolic events were reduced. As in the myelofibrosis population, amelioration of MPN symptoms was superior in the Ruxolitinib cohort.

Dr. Mesa also spoke of the JAK inhibitors that are on the treatment horizon. Firstly, Pacritinib is of interest for low-platelet myelofibrosis patients. Persist I evaluated this new agent versus BAT and showed similar results to the Comfort II trial – better relief of symptoms and reduction in spleen size. Twice daily dosing was superior to once daily, particularly in comparing overall survival to BAT. Fedratinib has been put forward as a third JAK inhibitor with a high response rate in the Jakarta-I trial – almost 50% of patients experienced a spleen response. However, 30% of patients became anemic and there has been concern about the possibility of this agent precipitating Wernicke's encephalopathy.

Finally, Momelotinib has been compared to Ruxolitinib in inhibitor-naïve myelofibrosis patients – the Simplify-1 study. Spleen response was similar in the two arms but Momelotinib was inferior in controlling MPN symptoms. However, this agent was clearly superior to Ruxolitinib at maintaining hemoglobin and platelet counts.

A Pooled Overall Survival Analysis of 5-Year Data from the COMFORT-I and COMFORT-II Trials of Ruxolitinib for the Treatment of Myelofibrosis

Srdan Verstovsek, MD, PhD,^{1*} Vikas Gupta, MD, FRCP, FRCPATH,² Jason R. Gotlib, MD,³ Ruben A. Mesa, MD,⁴ Alessandro M. Vannucchi, MD,⁵ Jean-Jacques Kiladjan, MD, PhD,⁶ Francisco Cervantes, MD, PhD,⁷ William Sun, PhD,⁸ Jessy Gao, MA,⁹ Tuoquan Dong,⁹ Ahmad Naim, MD,⁹ Prashanthi Gopalakrishna, MBBS, MRCS,¹⁰ Claire N. Harrison, DM, FRCP, FRCPATH¹¹

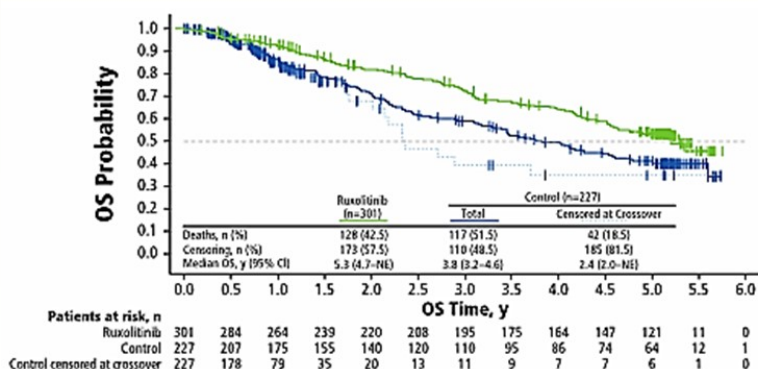
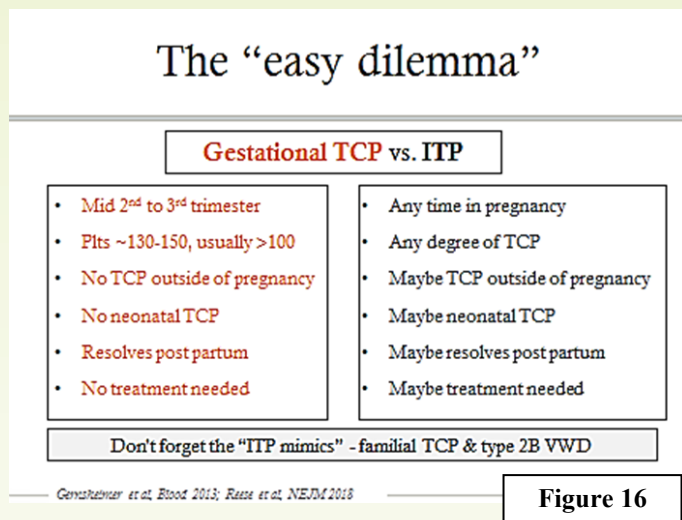


Figure 15

Thrombocytopenia in Pregnancy

Dr. Leslie Zypchen (Vancouver, BC) addressed what she described as the “two dilemmas” encountered when facing a pregnant woman with thrombocytopenia (TCP). The “easier” dilemma is deciding on whether the woman has gestational TCP or ITP – with the rare sidebar possibilities being drug-induced TCP or type IIB Von Willebrand disease (VWD) (Figure 16). These causes of TCP would fall under a general classification of “non-dangerous”, with the exception of heparin-induced thrombocytopenia. The second TCP in pregnancy dilemma deals with the thrombotic microangiopathies – TTP, atypical HUS (aHUS) and preeclampsia/HELLP syndrome; these disorders

(along with the rare patient with a primary marrow disorder or acute fatty liver of pregnancy) would be classified as “dangerous”.



There is new data on gestational platelet counts (Reese, 2018) that shows that TCP develops in 10% of uncomplicated pregnancies, usually in the late second or third trimester. Gestational TCP is typically mild (130-150 x 10⁹/L) but 10% drop their count below 100. Factors supporting this diagnosis (rather than ITP) would include no prior TCP, no neonatal TCP and platelet counts that return to normal post-partum. ITP can present at any time in pregnancy, can be of any severity, and can be mimicked by a familial TCP or type IIB VWD. Unlike gestational TCP, treatment is needed in ~40% of women although response to treatment is not as favourable as it is outside of pregnancy.

Response to IVIg and corticosteroids is seen in ~40% of patients and higher doses of steroid are often required. A new therapy, rhTPO has shown considerable promise in 31 refractory ITPs in pregnancy with a 74% response rate, no major adverse events and no evidence that this agent crosses the placenta (Kong, 2017). Even in the presence of ITP, ~2/3 of women have successful vaginal deliveries although epidural anaesthesia is often avoided. Bleeding is seen in 5% antepartum and 10% post-partum; neonatal outcomes are excellent (1% fetal loss or major bleed) although up to 15% of neonates have a nadir of <50 a few days post-partum that requires treatment.

The thrombotic microangiopathies of pregnancy are more difficult to diagnose, the patient is often quite unwell and treatments and outcomes vary by diagnosis. TTP is a disorder in which the pathogenesis is well-known – ADAMSTS13 deficiency, either from a congenital gene mutation or acquired. This leads to an increase in ultra-large VWF multimers (VWF levels normally increase in the third trimester), formation of

WVF-platelet complexes (consuming platelets) which obstruct small vessels, shearing erythrocytes (hemolysis) and prompting tissue ischemia. Dr. Zypchen pointed out that ADAMSTS13 levels normally decrease in the 2nd and 3rd trimester and that this persists post-partum. The two largest studies of TTP in pregnancy (Moatti-Cohen, 2012; Scully, 2012) reported on a combined 74 pregnant women. TTP presented in all trimesters but ~50% occurred in the third trimester or post-partum.

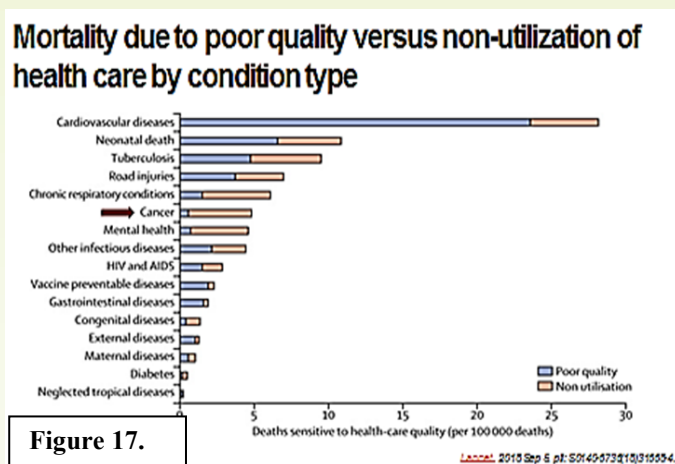
Maternal deaths were rare and live births were seen in almost 70% of cases – although TTP in the 2nd trimester led to a far lower success rate (<20%). Of interest, it was emphasized that 60% of these cases had a congenital mutation – first pregnancy is not an uncommon presentation of someone with such a mutation. Outcomes with future pregnancies for both congenital and acquired TTP are favourable with preemptive treatment – plasma infusion/exchange (if ADAMSTS13 levels fall below 10%), ASA ± LMWH.

Dr. Zypchen discussed two final microangiopathic conditions in pregnant women, HELLP syndrome – the treatment for which is delivery and supportive care – and aHUS. In aHUS, there is prominent renal damage that results from uncontrolled activation of the alternate complement pathway leading to endothelial injury. The TCP observed is often mild and renal function outcomes are generally poor with >50% of patients ending up on dialysis. Its etiology is often complement pathway gene mutations and/or anti-factor H antibodies (~50%) although affected patients require a trigger to develop aHUS – pregnancy being a classic trigger. In 75% of women, aHUS develops in the first pregnancy and does so in the post-partum period. While plasma exchange has been used in this disorder, the modern (and most effective) management of aHUS focuses on the anti-C5 antibody product Eculizumab.

Treatment of Leukemia and Lymphoma in Less Developed Countries

Dr. David Gómez-Almaguer (Monterrey, Mexico) provided a sobering overview of the challenges of caring for hematologic malignancies in less developed countries (LDCs). LDCs are defined by income, human assets and economic vulnerability and, from a medical standpoint, the key issues are lack of financial support and inadequate education in these countries. Mortality rates for a wide spectrum of health conditions are higher in LDCs and this can be attributed to two factors – poor quality of health care and non-utilization. The

contribution of one factor over the other is dependent upon the specific type of disease. For cardiovascular disease, >80% of mortality has been attributed to poor quality of care; for tuberculosis, the two factors each contribute ~50% to the mortality rates. Unfortunately, for malignant diseases, >90% of the mortality is due to non-utilization of health care (Figure 17).



Studies have shown that patients with low socioeconomic status have an inferior progression-free and overall survival, both in LDCs and in the United States. In Mexico, the challenges faced by Dr. Gómez-Almaguer and his colleagues include poor access to public health care, late diagnosis, lack of accessible staging procedures and, as a consequence, under-treatment of the disease. Not surprisingly, cancer mortality rates are almost double in LDCs when compared to developed countries.

Dr. Gómez-Almaguer noted that the relative frequency of adult ALL and AML in Mexico is different than what is seen in developed countries. In patients ≥ 16 years of age, ALL and AML are equally common. Furthermore, the incidence of high-risk ALL is 3 times that of standard-risk disease with survival in these patients being particularly unfavourable (<20%). Of note, Ph+ ALL patients are given TKI agents in only 2/3 of the cases. Furthermore, the use of “pediatric-type” protocols has only increased survival in high-risk ALL to ~35%. AML patients tend to be younger than ALL patients in Mexico and APL is especially common. The standard approach to APL in Mexico, for logistic reasons, continues to be ATRA + anthracycline with satisfactory long-term survival.

In a study from Northeast Mexico, Hodgkin lymphoma -- which has a higher incidence than NHL -- was shown to be associated with advanced disease in 2/3 of patients at presentation. This led to a low progression-free survival, even after autologous stem cell transplantation, although overall survival was similar to what has been observed in developed countries.

Approach to Blood Product Transfusion in Hematology/ Oncology Patients

Dr. Andrew Shih (Vancouver, BC) did a thorough review of ideal transfusion practice in the hematology/oncology patient population. He started with basic recommendations for red cell support –give each unit over 2-4 hours and monitor closely for TACO (transfusion-associated circulatory overload). Dr. Shih emphasized that TACO is the leading cause of transfusion-related mortality in the United States, occurring after 1-5% of transfusions and is associated with need for ICU care in ~20% of cases. Patients at highest risk are those ≥ 70 years of age, patients with a reduced ejection fraction or eGFR and those with a prior history of heart failure; pre-emptive Furosemide is strongly recommended when these factors are present.

Febrile and allergic reactions were much more common after platelet transfusions and while acetaminophen and antihistamine \pm hydrocortisone are often used as treatment and subsequent prophylaxis, studies to support this practice are of poor quality. For the problematic patient with persistent reactions, plasma reduction or washing of platelets has been suggested but this leads to platelet loss and potential introduction of bacteria; furthermore, these techniques are used so infrequently that it is challenging for the transfusion service to maintain competence.

Dr. Shih discussed the rare complication of transfusion-associated graft-versus-host disease (TA-GVHD) which develops in the immunocompromised and has a mortality rate of >90%. There is no satisfactory therapy for this condition and preventative irradiation of cellular products is the most effective strategy. However, irradiating all products is expensive, time consuming, impractical and results in red cell destruction – especially if the irradiated product has been stored for more than 2 weeks. Dr. Shih stressed that the risk of TA-GVHD is exceedingly low in Canada as a result of standard leukoreduction and the usual practice of using the oldest unit in the inventory. Non-leukoreduced products are responsible for 95% of TA-GVHD cases and the responsible unit is <10 days (and often <48 hours) old in 75% of those affected. As a result, the current recommendation is that irradiation be used only for: Hodgkin lymphoma (lifetime), NHL having received a purine analogue (lifetime), aplastic anemia patients treated with ATG or Alemtuzumab (duration unclear), autologous stem cell transplant patients (from 1 week prior to cell collection to 3 months post-SCT), allogeneic stem cell transplant patients until off all immunosuppression (and no chronic GVHD is present) and for HLA-matched platelets.

Figure 18

Figure 1. Comparison of 30-Day Mortality Using Restrictive vs Liberal Hemoglobin Transfusion Thresholds in Randomized Clinical Trials



Special Hematology Session: Nuclear Terrorism

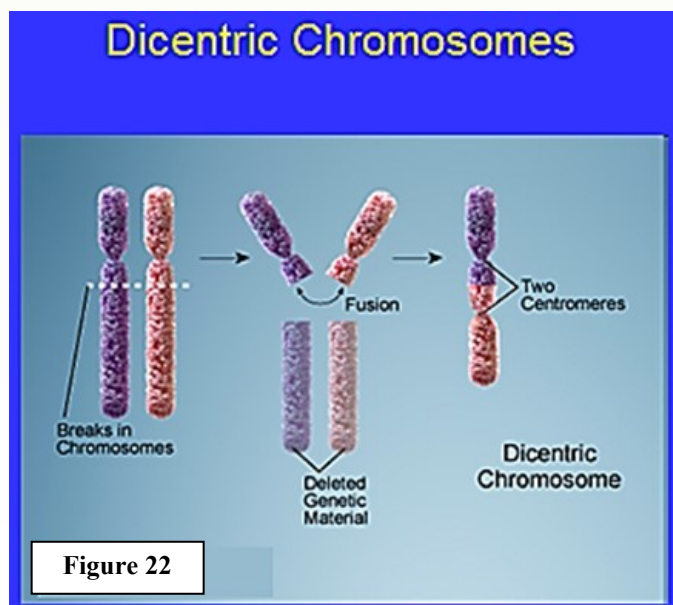
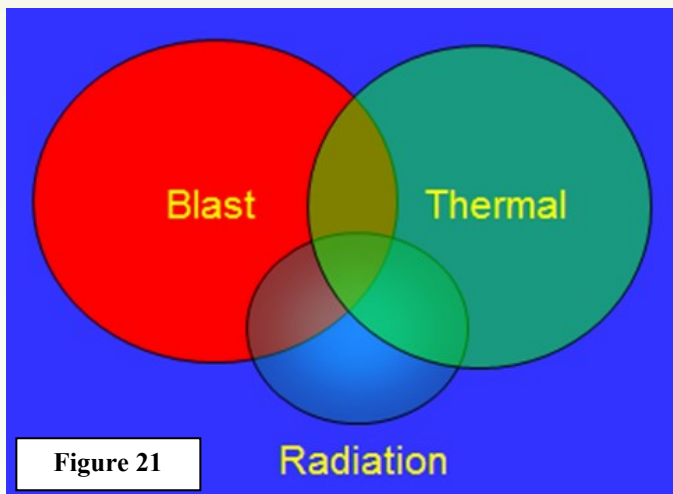
Figure 19



Figure 20



Injuries resulting from a nuclear device can be classified as blast, radiation and thermal injury (Figure 21). Dr. Gale focused on the radiation injury component and indicated that acute radiation syndromes are rare below 200 cGy (when only observation is required) and inevitable above 1000 cGy (where death is likely without intervention). Acute radiation injury affects the skin and GI tract first (100-300 cGy) and then begins to affect the bone marrow with the classical development of dicentric chromosomes – fusion of the top half and centromere of one chromosome with the bottom half and centromere of another forming a single chromosome with two centromeres (Figure 22). Cardiac and central nervous system toxicity occurs when exposures are >1200 cGy. It was stressed that dealing with radiation syndromes requires knowledge on dose, dose-rate, field, other concurrent exposures, age and prior health. If the radiation exposure is “survivable”, irreversible bone marrow damage does not occur; temporary blood product, growth factor and antimicrobial support may be needed. However, exposures of ≥800 cGy are not survivable without allogeneic stem cell transplantation.



Dr. Gale shifted into the potential for using nuclear devices in terrorism attacks. Criminal acts involving nuclear materials to date have included theft (80% -- 85% involving <1 kg) and sabotage (20%). Attacks could be in the form of a radiological “dispersion” device (radioactive material dispersed with a bomb), a radiological “exposure” device (planting radioactive material in a crowded space) and an improvised nuclear device (IND) – not to be confused with a nuclear war involving weapons of mass destruction. The effects of the IND would depend upon its size/weight; a 0.1 kiloton IND would cause light damage for ¾ mile with a narrow “dangerous fallout zone” of 1.5 miles while a 10 kiloton device would cause heavy damage for ½ mile, light damage for 3 miles and a wide 8-mile fallout zone.

New Understanding of Genetic Changes in ALL and CAR T-cell Therapy

Dr. Kirk Schultz (Vancouver, BC) provided an update on the genetics of pediatric ALL and how it might allow us to move forward with new therapies in high-risk groups. COG trials in pediatric ALL have shown a steady improvement in survival over the past 40 years – 20% in the early 1970s, 75% by the mid-1980s and ≥90% by the 2000s. Improvements have been realized in all age groups although the prognosis for adolescents and especially infants remains inferior. T-cell disease had a less favourable outcome in the early 1990s but has now nearly caught up with B-ALL in the pediatric population. Poor prognosis pediatric ALL is increasingly being determined by genetic markers.

The most frequent genetic markers -- hyperdiploidy >50 and t(12;21) (ETV6;RUNX1) – are seen in 50% of patients and are associated with a favourable outcome. Abnormalities that predict for a poor prognosis with chemotherapy alone include MLL rearrangements (8%), CRFL2 overexpression ± JAK2 mutation – referred to as “Ph-like” (6%), hypodiploidy (5%), BCR/ABL+ (3%) and iAMP21 (2%). Targeted therapy in BCR/ABL+ ALL with Imatinib and chemotherapy has been shown to result in a 72% 7-year survival, much better than historic controls (27%) and even better than historic BMT results (60-65%). However, the addition of Imatinib to induction followed by BMT in CR1 has improved transplantation outcomes up to 80%, continuing to make this a challenging choice.

Genetic profiling in ALL has led to the recent description of a group of patients with an expression profile that resembles BCR/ABL+ ALL. This cohort has genetic changes that lead to constitutive activation of cytokine receptor or tyrosine kinase

signaling and are referred to as Ph-like ALL, a poor-prognosis patient population (5-year EFS of 20%). The incidence of Ph-like ALL increases with age; it is more common in adolescent pediatric patients (~20%) and even more common in adults age 21-39 (~30%); males are more frequently affected and often present with high WBC counts. However, the two age groups differ in their mutation profile in that adolescents tend to be JAK2mut and young adults tend to be JAK2WT (see below).

Ph-like ALL seems to have two distinct subgroups, each comprising ~50% of cases. Half of patients have CRFL2 rearrangements, with or without JAK2 and IKZF1 mutations. These patients are predicted to be responsive to JAK2 inhibitors. The other half of patients have other kinase alterations with the two largest groups being “ABL Class” rearrangements (ZM1Z1-ABL1, PAC1-ABL2, SSBP2-CSF1R and EBF1-PDGFRB) (Figure 23) – predicting for responsiveness to TKIs (especially Dasatinib) -- and “EPOR/

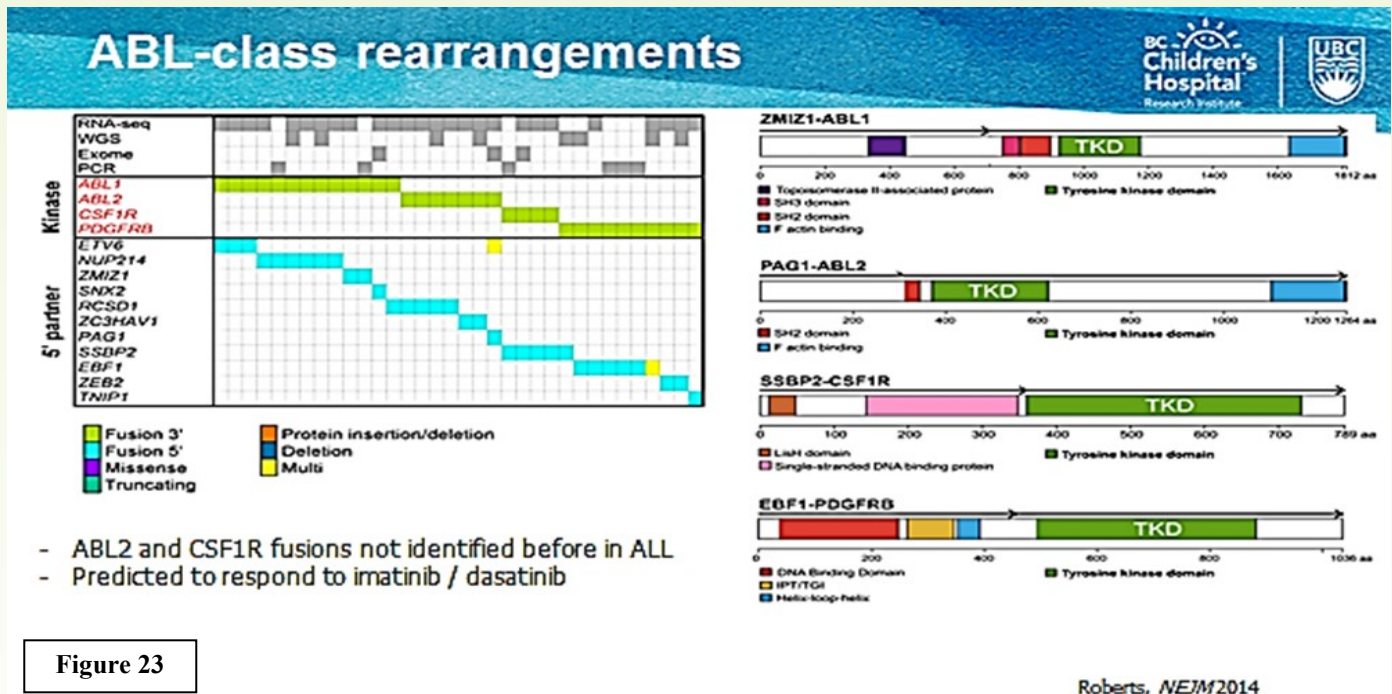


Figure 23

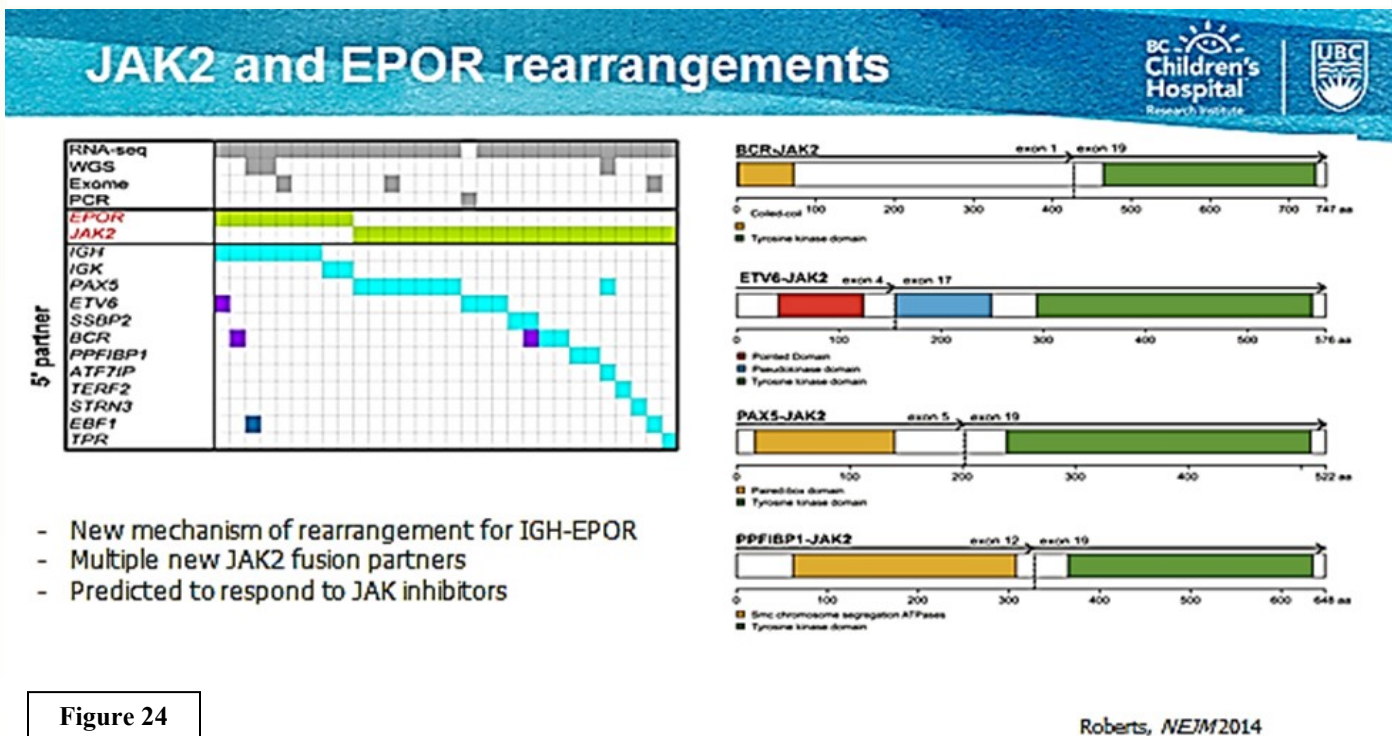


Figure 24

JAK2" rearrangements (BCR-JAK2, ETV6-JAK2, PAX5-JAK2 and PPF1BRP1-JAK2) (Figure 24) – also expected to be responsive to JAK2 inhibitors. Each of these two groups comprise 15-20% of all Ph-like ALL and are most frequently found in high-risk pediatric ALL patients. A much smaller number of Ph-like ALL patients have other kinase alterations, which may be sensitive to alternative targeted treatments – TYK2-MYB (TYK2 inhibitor), NTRK3-ETV6 (Crizotinib), PTK2B-KDM6A (FAK inhibitor) and IL2RB (JAK 1/3 inhibitor).

Dr. Shannon Maude (Philadelphia, PA) spoke on one of the hottest topics in oncology today – CAR T-cell therapy. This treatment is based upon the knowledge that our immune system deals with potentially malignant cells every day. However, these cells are able to use our own immune system controls to evade recognition, including immune "checkpoints".

CAR (chimeric antigen receptor) links extracellular antibody (that is designed to recognize an antigenic target on the tumour cell) with intracellular T-cell signaling domains. The extracellular antibody is attached to a receptor stabilizing costimulatory domain (typically CD28 or 4-1BB) which is attached to CD3-zeta, a T-cell activation signal that stimulates immune cell proliferation (Figure 25).

patient where they engage tumour antigen. This leads to in vivo T-cell proliferation – a critical event for the success of the treatment – and cytotoxicity. The longer that the CAR T-cells persist, the greater the chance of long-term control of disease.

Dr. Maude reported on her experience with the phase I/IIa CTL019 pediatric ALL study that involved 60 patients with relapsed/refractory ALL, median age 11 years (maximum 24 years); 2/3 of the patients had relapsed post-SCT. The CAR was directed against CD19 and 4-1BB was the co-stimulatory domain. A CR was seen in 56/60 patients (93%) with a 2-year relapse-free survival of 53%. The major toxicity was cytokine release syndrome with its severity directly proportional to the disease burden at the time of CART infusion. This syndrome resembles HLH with neurotoxicity not uncommon, and the mainstay of treatment is IL6 antibody.

Prolonged cytopenias can be seen and chronic B cell aplasia can develop requiring IVIg replacement. Follow-up trials from Memorial Sloan Kettering and Fred Hutchison Cancer Centre have confirmed the high CR rate with this therapy in relapsed/refractory adult ALL with responses being better in patients with blast counts <5% (90%) versus ≥5% (75%). Long-term follow-up has suggested an EFS of ~20%, including 9 patients who received no further therapy after CART.

Cellular Immunotherapy with CAR T cells

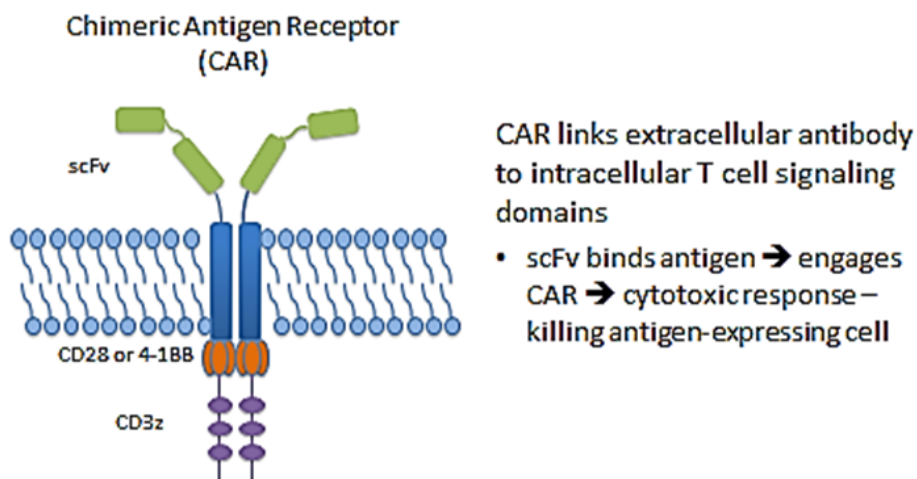


Figure 25

Dr. Maude's centre is now focusing on the mechanisms of relapse post-CART and has found that short persistence of the CART cells is correlated with relapse. Hypothesizing that this represents immune rejection of the murine antibody in their original product, they have designed a humanized CTL019 that has produced 100% CR rates in CAR-naïve patients to date.

Building on the possibility of T cell exhaustion as the mechanism for short persistence of CART cells, PD-1 inhibitors (Pembrolizumab every 3 weeks from day +14) are being combined with their CART therapy to prolong survival of the CARTs.

Finally, although both CD19+ and CD19- relapses can occur after CART therapy, a CD22 CART in combination with the CD19CART is being evaluated to prevent the occurrence of the former.

CAR T-cell therapy entails collecting T-cells from the patient and using a lentiviral vector to introduce a gene encoding the CAR. T cells are then expanded ex vivo and reinfused into the





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Annual Reception, Dinner & Awards Evening**

December 3, 2018

San Diego, California, USA

Contact: chs@uniserve.com

**INTERNATIONAL SOCIETY FOR LABORATORY
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**XXIII International Symposium on Technical
Innovations in Laboratory Hematology**

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Vancouver, BC

Contact: <https://www.islh.org/2019/>

American Society for Apheresis (ASFA)

2019 Annual Meeting

May 15—18, 2019

Portland, OR, USA

Contact: <http://www.apheresis.org/>

**Canadian Blood and Marrow Transplant Group
(CBMTG)**

2019 Annual Meeting & Conference

June 5—8, 2019

Calgary, Alberta

Contact: <http://www.cbmtg.org/>

**European Hematology Association (EHA) 23rd
Congress**

June 13-16, 2019

Amsterdam, The Netherlands

Contact: <https://ehaweb.org/congress/eha24/key-information/>



**38th World Congress of the
International Society of
Hematology (ISH)**

September 13—16, 2020

Bangkok, Thailand



the diagnosis...

ANSWER

...FROM PAGE 4

This patient's bone marrow was diffusely infiltrated with blasts that were CD3+, CD5+, CD56+ and cytoplasmic myeloperoxidase (cMPO) +, consistent with mixed phenotype acute leukemia (MPAL), T/myeloid. Karyotype was normal male, TcR gene rearrangements were positive and a myeloid gene sequencing panel showed mutations in DNMT3A, ETV6 and IDH2.

The additional marrow finding of interest was focal proliferations of mature histiocytes (area denoted by arrows in Figure 2) that were positive on immunohistochemistry for muramidase, S100 and CD56 (see Figure 3 and 4) as well as CD1a and CD68; BRAF V600E IHC was negative. These latter findings were felt to be consistent with Langerhans-Cell histiocytosis (LCH). A biopsy of the cervical lymph node showed both the acute MPAL and the LH.

Formerly referred to as Histiocytosis X, Langerhans-Cell Histiocytosis is the most common histiocytic disorder. In this

condition, there is a proliferation of CD207 (langerin)-positive mononuclear phagocytes. These cells are clonal dendritic cells, not monocytes or macrophages, and can produce multi-organ infiltrates, especially involving skin, lungs, bone/marrow and liver/spleen. 85% of patients have MAPK pathway mutations, the vast majority being BRAF V600E mutations.

“Low-risk” LCH results from a mutation in a tissue-derived/committed dendritic cell and involves only a single organ – skin, lymph node, bone or pituitary.

“High-risk” LCH is a multi-organ disease involving marrow, liver, spleen and lungs and is a myeloid neoplasia. In these patients, the MAPK mutation occurs in pluripotent hematopoietic cells.

This patient was treated with anthracycline, Vincristine and Prednisone and entered a complete remission. A search for a suitable stem cell donor was underway when his MPAL relapsed and he was transitioned to supportive care.



Canadian Hematology Society / Société Canadienne d'Hématologie

2019 RK Smiley Research Grant

Established in 2011 to mark the Fortieth Anniversary of the Canadian Hematology Society's service and to support hematology practitioners in Canada, this award is named in honour of the CHS Founding President, Dr. R. Kennedy Smiley. Many impressive submissions from across Canada have been funded under the previous invitations to submit applications to this research grant program since its inception.

The CHS Executive Committee is very pleased to announce that the next deadline for submissions to the R K Smiley Award is Friday, February 22, 2019.

The R K Smiley Research Grant provides **start up grants of \$20,000** for pilot projects expected to lead to larger follow-up studies funded by CIHR or other grant funding agencies.

Funds are to be used within one year of the award being granted.

ELIGIBILITY CRITERIA:

- Applicants may be clinicians or scientists with a project relevant to the field of hematology.
- The Principal Investigator must be a member-in-good-standing of the Canadian Hematology Society.
- Preference will be given to groups who will benefit maximally from the limited start up funds.
- Only one application will be received per applicant in a given year.
- The principal applicant should be able to hold grant at his or her institution.

APPLICATIONS SHOULD INCLUDE

1—The proposal: 1 page, maximum length should include:

- ⇒ Title of project
- ⇒ Name of Principal Investigator
- ⇒ Names of Co-investigators
- ⇒ Project Background
- ⇒ Relevance to hematology

2—The Budget: 1 additional page, maximum

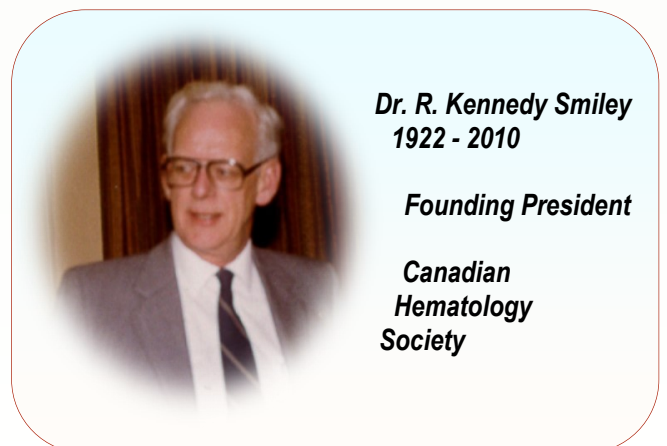
3—CV of Principal Investigator, 5 pages, maximum

FORMAT REQUIREMENTS

- ⇒ MS Word format
- ⇒ Double-spaced
- ⇒ Font size 12

N.B.

- Submit by email to: chs@uniserve.com
- **By: 1800 hrs EDT, Friday, February 22, 2019.**
- We will confirm receipt of all proposals.
- Decisions will be announced in May 2019.



Sponsored in part by the pharmaceutical industry.

FELLOWSHIPS

LEUKEMIA FELLOWSHIP PROGRAM

The Leukemia Fellowship Program is a 1-year clinical fellowship designed to train hematologists with special knowledge and expertise in leukemia and related disorders (acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes, bone marrow failure syndromes, myeloproliferative neoplasms).

This fellowship is funded by the Ontario Ministry of Health through Cancer Care Ontario and has a 2-year return of service. Applicants must submit a letter of intent, CV, 3 reference letters; and have completed 3 years internal medicine and 2 years hematology residency. Application timing is flexible; for further information:

STEM CELL TRANSPLANT FELLOWSHIP PROGRAM

The Stem Cell Transplant (SCT) Program is a 2-year clinical/research fellowship. Scholarly activity is a required part of the fellowship, and will be tailored to the trainee pending interest and career plan. Those with a stronger research interest may pursue a relevant Masters Degree.

This fellowship is funded by the Ontario Ministry of Health through Cancer Care Ontario and has an associated 2-year return of service. The applicant must submit a letter of intent, curriculum vitae, and 3 reference letters. Applicants must have a minimum of 3 years of internal medicine residency and 2 years of hematology residency. Application timing is flexible; for further information:



Dr. Arleigh McCurdy, Program Director
Malignant Hematology and Stem Cell Transplant
Box 704-501 Smyth Road, Ottawa ON, K1H 8L6
613-737-8899 x 71286
amccurdy@toh.ca



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or email at medical.staff@horizonnb.ca

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- Curriculum Vitae
- names / addresses of three references to

Susan Schelleman by email at susan.schelleman@nshealth.ca

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St. Michael's

Inspired Care. Inspiring Science. **Keenan Research Centre for Biomedical Science**

The Keenan Research Centre for Biomedical Research of St. Michael's Hospital, University of Toronto.

- Closing date: 29/11/18.
- Position for a Canada Research Tier 2 Chair.

Qualifications

- PhD or an MD or an equivalent
- research excellence, including research funding, fellowships & publications.
- unique, skills to establish independent research and enhance the profile of the platelet biology research group.
- proficiency in cellular/molecular biology, biochemistry, advanced imaging and/or physiological/pathological studies.
- ability to work independently and to collaborate with other scientists.
- English proficiency

Please submit

- A current curriculum vitae
- A brief statement (1-2 pages) of research accomplishments and future plans.

Contact HugginsEL@smh.ca

JOB POSTINGS

HEAD, DIVISION OF HEMATOLOGY: UNIVERSITY OF OTTAWA, THE OTTAWA HOSPITAL



An inspirational leader is sought to drive change and advance the academic enterprise of the Division of Hematology over the next five years. The ideal candidate will be a visionary leader, will meaningfully engage the academic leadership of the University and the affiliated teaching hospitals to build strong cross-department and cross-discipline collaboration, bridge diverse groups, strengthen capacity in research across disciplines, and provide strong mentorship.

The position is a five-year term appointment with the possibility of reappointment for an additional five-year term. Interested applicants, please forward a letter of interest and up-to-date curriculum vitae to **Charlene D'Silva** on behalf of **Dr. Philip Wells**, Chair & Chief, Department of Medicine at cdsilva@toh.ca

PART TIME LOCUM FOR HEMATOLOGIST IN MYELOMA/LYMPHOMA—Toronto



The locum will provide clinical cover for two half-day clinics per week at Princess Margaret Cancer Centre for a period of 6 weeks. Dates are flexible; early 2019 is preferred. The clinics comprise outpatient myeloma and lymphoma patients and typically include one new myeloma patient referral and 10-14 follow up visits per clinic.

A number of new patient referrals are for autologous stem cell transplant. Hematology fellows are currently attached to both clinics, offering both support and the opportunity for teaching. Some patients are enrolled in clinical studies.

Dr. Rodger E. Tiedemann, Associate Professor of Medicine, U. of T.
101 College Street, Suite 12-306, Toronto, ON M5G 1L7
Tel: 416-946-2359 | Fax: 416-946-4563
rodger.tiedemann@uhn.ca

HEMATOLOGIST—ONCOLOGY: WINDSOR REGIONAL HOSPITAL—Windsor, ON

The Oncology Dept. is recruiting a full time Hematologist to join its multidisciplinary team of Oncologists, Hematologists, Nursing and Allied Health—to provide consultative services in collaboration with a group of 16 Oncologists/Hematologists. One primary focus will be management of patients with complex hematologic malignancies. Radiation Oncology, Oncology and



Hematology services are well established as well as a 28 bed In-Patient Oncology Unit with a roster of Oncology Hospitalists.

Qualifications

- Candidates must hold, or be eligible for, certification in Internal Medicine from the Royal College of Physicians and Surgeons of Canada with a subspecialty in Hematology
- Eligible to practice: College of Physicians & Surgeons of Ontario
- French language an asset

Expressions of Interest should be forwarded along with your CV to:

Dr. Sindu Kanjeekal, Chief, Oncology

c/o Jessica Bennett, Director, Medical Affairs

Windsor Regional Hospital

Jessica.bennett@wrh.on.ca

PROVINCIAL DIRECTOR, LEUKEMIA, BONE MARROW TRANSPLANT AND MALIGNANT HEMATOLOGY PROVINCIAL PROGRAM—Vancouver, BC



The Leukemia, Bone Marrow Transplant (LBMT) and Malignant Hematology Program—a new provincial initiative—provides leadership within BC Cancer and provincially.

Successful applicant will have:

- experience/working knowledge of implementation and oversight of operational plans, budgets, policy development, and relating to internal and external stakeholders
- a level of education, training, and experience equivalent to a Master's Degree in Health Services Administration, Business Administration, Nursing or
- relevant health care discipline with a minimum of seven (7) year's recent, related experience.

Contact Linda Hand, Manager, Talent Acquisition – Clinical Services
at (604) 875-7216 or email lhand@phsa.ca

www.bccancer.bc.ca

DIVISION CHIEF, HEMATOLOGY—Calgary, Alberta



UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE



**Alberta Health
Services**

The Department of Medicine, seeks a full-time Hematologist (Associate or Full Professor), Hematology Division, Cumming School of Medicine.

Qualifications include:

- MD, FRCPC (Hematology) or equivalent
- Eligibility for specialist licensure in the province of Alberta
- Established reputation for clinical excellence
- Strategic thinker / administrative and leadership experience
- A track record of scholarly productivity
- Excellent interpersonal skills.

Send CV, cover letter and names of three referees by Dec 15, 2018:

Richard Leigh, PhD, FRCPC

Professor and Head, Department of Medicine

University of Calgary, Foothills Medical Centre

1403 29th St. NW – 930 North Tower, Calgary AB, T2N 2T9 Canada

OR—send electronically to sandy.hafez@ahs.ca

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 500 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 making sustained contributions to clinical or laboratory hematology practice or hematology research in Canada.

Active members only 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 ... if you have not sent your \$75 dues payment for 2018, it is now past due.

Please Note Rate Change

The CHS Annual Dues for 2019 is \$100.
Payable on January 1, 2019; due on March 1, 2019.

Annual dues payments 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:



2019 Membership Renewal / Address Change: Canadian Hematology Society

Membership Status

Active ☐

Associate ☐

Emeritus ☐

Has your status changed?

Yes ☐

No ☐

Name: _____

Title: _____

Email: _____

Work Address: _____

Work Phone: _____

Work Fax: _____