Canadian Hematology Society announces exciting initiatives

Dear Colleagues,

The fall season has been busy for the Canadian Hematology Society (CHS) with a number of new and exciting initiatives.

CHS to host ISH 2018

I am delighted to announce that the Canadian Hematology Society will be hosting the 2018 International Society of Hematology (ISH) meeting in Vancouver.

A special thank you to Drs. Tom Nevill and Gail Rock for all of their hard work in securing this international meeting.

Dr. Tom Nevill will serve as the scientific chair of the meeting and

continued, page 2
Dr. Gail Rock will serve as organizing chair.

Over the next several months, they will be reaching out to the Canadian community as they establish their scientific and organizing committees and subcommittees. ISH will be an outstanding venue to showcase the great research being conducted by Canadian hematologists and an opportunity for significant representation and participation from our membership.

**Choosing Wisely Canada**

Dr. Chris Hillis and colleagues recently announced the Canadian Hematology Choosing Wisely list for hematology.

The CHS was delighted to participate in this process and you can view the list through the link on the CHS website. We hope you will find the list a springboard for discussion quality initiatives and best practices in the field.

**The CHS at ASH 2014**

The CHS annual gala and meeting will be held this year on Sunday December 7, 2014 at the Four Seasons Hotel in San Francisco during ASH. If you have not done so already, please RSVP for this great evening.

The CHS gala is a fantastic opportunity to reconnect with colleagues and establish new collaborations and contacts. Again this year, we will be presenting awards for the top abstracts being presented at ASH by our residents and fellows. Over 30 submissions have been received and include many outstanding studies.

For the first time this year, we will also be presenting recognition for paper-of-the-year. **We will recognize the Best in Canadian Hematology.** The response to this call has been tremendous with many practice changing publications from our CHS members. We will continue to offer this competition next year and hope you will consider submitting your paper next year.

**Interactive web-portal planned**

Finally, in the new year, we will launch an interactive web-portal that we hope will provide exciting and useful content for our members. Among the many new features will be listings of province-specific criteria for reimbursement of hematology drugs. We hope this site can serve as a “one-stop-shop” for questions around drug reimbursement – something that is often not easily found in other formats.

This site will also provide a means to network and connect with your colleagues. In addition, we will be offering monthly interactive quizzes in Royal College format to help the trainees prepare for their exams and help our members keep up-to-date with current developments in hematology. Watch for emails announcing this initiative. In closing, I appreciate your ongoing interest and involvement in the CHS and hope to see you at the ASH meeting.

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**The R Kennedy Smiley Research Grant 2015**

**to be announced at CHS December 7 meeting**

The Canadian Hematology Society established a research award in honour of our founding President, Dr. R. Kennedy Smiley, to mark our 40th Anniversary in 2011.

This Research Grant offers start-up funds of $10,000 aimed at pilot projects which are expected to lead to larger follow-up studies funded by CIHR or other grant funding agencies.

**Watch for more details of the 2015 competition, to be announced at the CHS AGM at ASH, December 7th, 2014.**
Avec un nombre d’initiatives nouvelles et passionnantes, l’automne a été une saison très occupée pour la Société Canadienne d’Hématologie (SCH).

Je suis ravie d’annoncer que cette dernière sera l’hôte de la réunion de la SIH (Société Internationale d’Hématologie) qui prendra place à Vancouver en 2018.

Un remerciement spécial aux Drs. Tom Nevill et Gail Rock pour leur travail acharné afin d’assurer cette rencontre internationale. Dr. Tom Nevill servira sous le titre du président scientifique de la réunion et Dr. Gail Rock servira sous le titre de la présidente organisatrice. Au cours des prochains mois, ils vont approcher la communauté Canadienne alors qu’ils établissent leurs comités et sous-comités scientifiques et organisationnels.

La SIH sera une excellente vitrine qui mettra en valeur la grande recherche menée par les hématologues Canadiens, elle représentera également une opportunité pour une participation et une représentation significative de nos membres.

Dr. Chris Hills et ses collègues ont annoncé récemment la liste Canadienne d’Hématologie, cette dernière a été judicieusement choisie pour l’hématologie.

La SCH a été ravie de participer à ce processus et vous pouvez visionner la liste travers le lien du site web de la SCH. Nous espérons que cette liste représentera un tremplin pour les meilleures pratiques dans le domaine, ainsi que pour l’initiation de discussions de qualité.

Le gala et la réunion annuels de la CHS auront lieu cette année le dimanche, 7 décembre 2014 à l’hôtel quatre saisons à San Francisco durant la réunion d’ASH. Si vous ne l’avez pas déjà fait, veuillez RSVP pour cette merveilleuse soirée.

Le gala de la CHS est opportunité fantastique pour rétablir les reconnections avec les collègues et également pour établir de nouveaux contacts et de nouvelles collaborations.

Cette année encore, nous allons décerner des prix pour les meilleurs résumés présentés à ASH par nos résidents et fellows. Plus de 30 mémoires incluant plusieurs études remarquables ont été reçus.

Pour la première fois cette année, on présentera également une reconnaissance pour le papier de l’année. On reconnaîtra le meilleur de l’Hématologie Canadienne.

La réponse à cet appel a été énorme avec plusieurs modifications dans la publication des pratiques de nos membres de la CHS. L’année prochaine, Nous continuerons à organiser cette compétition et nous espérons que vous considéreriez de soumettre votre papier.

Le site fournira également un moyen de réseautage et de connexion avec vos collègues. En outre, nous offrirons mensuellement des quizzes interactifs dans le format du Collège Royal afin d’aider les stagiaires à préparer leurs examens et à aider nos membres à se tenir à jour avec les développements actuels en hématologie. Guettez les emails annonçant cette initiative

En terminant, je vous remercie pour votre intérêt et votre implication dans la SCH, et on espère vous voir à la réunion d’ASH.

Dr. Aaron Schimmer
President, CHS
A 45-year-old woman was referred for investigation of asymptomatic bicytopenia that had been found on routine blood testing nine months previously. In the past year, she had also been found to have deranged liver function tests for which she was seeing a Hepatologist.

- Past medical history was significant for a history of B\textsubscript{12} deficiency diagnosed at age 10 and treated with parenteral B\textsubscript{12} for one year followed by sporadic oral supplementation.
- She also had a history of recurrent renal lithiasis dating back to age 14 for which she had been treated with multiple lithotripsy procedures. She had one healthy daughter, age 20.
- Her only medications were a multivitamin and calcium supplements.
- Her mother and father were both healthy as were her two younger brothers.
- Physical examination revealed a middle aged woman with a slight build (5 feet tall and 45 kg) and dentition as shown in Figure 1.
- Chest and cardiac exams were normal.
- Her liver was palpable 4 cm below the right costal margin and 12 cm in span; she did not have a palpable spleen.
- The remainder of her examination was normal.
- CBC revealed a hemoglobin of 121 g/L (MCV 110), WBC 4.6 x 10\textsuperscript{9}/L, ANC 1.4 x 10\textsuperscript{9}/L and platelets 113 x 10\textsuperscript{9}/L.
- Urea, creatinine, electrolytes and liver function were normal except ALT 85 U/L and AST 56 U/L.
- Lymphocyte telomere length analysis was at the 60th percentile.
- Bone marrow examination is shown in Figure 2; karyotype revealed 70% of the metaphases were 46,XX and 30% contained del(20q).

- Figure 1
- Figure 2

**What is the diagnosis?** … SEE PAGE 15

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**Upcoming Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Date/Location</th>
</tr>
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<tbody>
<tr>
<td>Canadian Hematology Society (CHS)</td>
<td>Annual Reception, Dinner &amp; Awards Evening&lt;br&gt;December 7, 2014, San Francisco</td>
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<tr>
<td>International Society of Thrombosis and Haemostasis (ISTH)</td>
<td>25th World Congress&lt;br&gt;July 11—17, 2015, Toronto, Ontario</td>
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<tr>
<td>Canadian Blood and Marrow Transplant Group (CBMTG)</td>
<td>Annual Conference&lt;br&gt;May 13-16, 2015, Montreal, Quebec</td>
</tr>
<tr>
<td>International Society for Laboratory Hematology (ISLH)</td>
<td>28th International Symposium&lt;br&gt;May 19-21, 2015, Chicago, Il</td>
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The Canadian Hematology Society has recently developed new bylaws as part of its legal obligation to transition its charter documents to comply with the new *Canada Not-for-profit Corporations Act*.

A copy of the new CHS bylaws can be found on our website: http://canadianhematologysociety.org/

**Background:**
All Canadian not-for-profit corporations were required by the Government of Canada to meet a transition deadline of October 17, 2014, or they were to be considered inactive and dissolved.

The transition to comply with the new act required that a corporation replace its letters patent, supplementary letters patent (if any) and by-laws with new charter documents. This meant that the CHS was required to submit articles of continuance to obtain a Certificate of Continuance, and to create and file new by-laws to comply with the new act. These charter documents set out the primary rules governing the corporation.

**Bylaws Ratification Vote:**
The CHS is also legally bound under the new Act, to hold membership vote though a standard motion to ratify the new bylaws at its next regular meeting of the membership, which will be the December 7, 2014 AGM as part of the CHS events at ASH.

**Expansion of CHS Executive:**
Further, the CHS Executive at its recent fall retreat (October 24, 2014) has also voted in favour of splitting the Executive Board position currently defined as “Secretary-Treasurer” into the two separate positions: one position of “Secretary” and a separate position of “Treasurer”. A key benefit of this division of roles and the addition of one additional position on the executive is that it will help to preserve institutional memory.

**A motion to amend the bylaws to allow for this division of roles on the Executive Committee will also be put to a vote at the December 7th meeting.**

**2014 Nominations:**
Our currently serving Secretary-Treasurer, Dr. Molly Warner, is nominated to remain on the Executive Board as Secretary for at least the next year, and possibly for the next two years. Dr. Julie Stakiw, has been nominated for the new position of Treasurer.

Originally from Saskatchewan, Dr. Stakiw completed her Bachelor of Science, MD and internal medicine training at the University of Saskatchewan prior to moving to Ontario to complete hematology training at Queen’s university followed by a one-year fellowship at PMH in Lymphoma and Stem Cell Transplant. After working as a hematologist-oncologist at Peel Regional Cancer Center in Mississauga, Ontario for 3 years, she then moved back to Saskatchewan in 2010 to be closer to family, where she soon took on the role of Provincial Leader of Hematology for Saskatchewan & Medical Director of the Provincial Blood and Marrow Transplant Program. Recently the Ministry of Health introduced the LEAN management system province wide and Dr. Stakiw is one of the first physicians in the province to become LEAN LEADER certified.

Additional nominations from the floor at the December 7 meeting for each of these new positions will also be accepted prior to the membership vote on the composition of the new board.
Jack Hirsh was born January 7, 1935 in Lodz, Poland but obtained his MBBS and MD degrees from the University of Melbourne in Australia.

He trained in hematology at Washington University in St. Louis, Missouri in the early 1960s and then pursued further studies at the London Postgraduate Medical School in England.

It was in London that Dr. Hirsh received a visit from Dr. Fraser Mustard (see Fall 2013 Microenvironment) who, as he later acknowledged, was hugely influential in his research career development.

Dr. Hirsh moved to Toronto to work in Dr. Mustard’s laboratory at the University of Toronto. Their work together led to the co-authoring of two key papers: “Streptokinase effects on hemostasis” (Blood, 1968) and “Effect of platelet age on adherence” (J Clin Invest, 1968).

His subsequent investigation of warfarin and heparin led to the development of the INR as the method of monitoring warfarin therapy and a landmark paper, “The aPTT in the control of heparin treatment” (Australas Ann Med, 1970).

In 1973, Dr. Hirsh joined the Faculty of Medicine of McMaster University where he founded the Clinical Thromboembolism Group and, in 1988, established the Hamilton Civic Hospitals Research Centre [now the Thrombosis and Atherosclerosis Research Institute (TAARI)].

Dr. Hirsh fostered the development of an entire generation of thromboembolism researchers and has been actively involved in multiple pharmaceutical firms focusing on clinical products aimed at cardiovascular, inflammatory and malignant diseases.

He is a former Chairman of the Department of Medicine at McMaster University and was made a member of the Order of Canada in 1999. The following year, he was awarded the International Gairdner Research Award for his pioneering efforts in the understanding of diagnosis, prevention and treatment of thromboembolic disorders.

Dr. Hirsh has authored 19 books, 231 book chapters and over 650 papers and in 2000, he was inducted into the Canadian Medical Hall of Fame. In 2014, McMaster University established the Jack Hirsh Professorship in Thrombosis.

He remains Professor Emeritus, Division of Hematology and Thromboembolism, Department of Medicine; his career reflects his own words of advice for young researchers: “My advice for budding researchers is to be passionate about your research, train with the best in your area of interest and spend as long as it takes to develop the skills required to be an independent researcher”.

By Dr. Tom Nevill, Editor
The Microenvironment

**History Corner**

Dr. Jack Hirsh, Professor Emeritus, McMaster University

**Invitation to submit**...

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

Queries should be directed to:
- Dr. Tom Nevill, The Editor, The Microenvironment
- Email: chs@uniserve.com
AZACITIDINE TREATMENT FOR MDS: THE BRITISH COLUMBIA EXPERIENCE

Madeleine Ankenman
Summer Student
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Azacitidine (Vidaza®), is a drug developed to prolong the survival and decrease transfusion dependence in patients with Myelodysplastic Syndrome (MDS) who are not eligible for other treatment options.

Traditional chemotherapy acts against rapidly proliferating cells by interfering with the DNA cell cycle, forcing the cell to prematurely undergo apoptosis. While Azacitidine was initially used as a traditional chemotherapy agent, it has been found to be more effective in lower doses (75mg/m²/day) as a hypomethylating agent. Hypomethylating agents work on epigenetic changes -- alterations to the chromosome that do not involve changes in the actual DNA sequence. DNA methylation is an example of an epigenetic change in which methyl groups are added to cytosine-phosphodiester-guanine (CpG) sites on the chromosome.

Many CpG sites are found in gene promoter regions where DNA methylation prevents transcription factors from binding to the promoter. This in turn prevents transcription of many crucial genes including tumour suppressor genes (TSGs).

The enzyme DNA methyltransferase binds the methyl groups to the chromosome. Azacitidine blocks this enzyme, detaching the methyl groups, allowing transcription factors to bind and restoring the promotion of TSGs.

The bar graph in Figure 1 shows the number of patients treated each year of the study period. The median age for this group of patients was 71 years [range was 1-90 and included 3 pediatric patients (<13 years)] and 71% were male with the most common diagnoses being oligoblastic AML (33%) and refractory anemia with excess blasts-2 (25%). It was found when analyzing the doses that only 80% of patients started treatment at the recommended dose of 75mg/m², and only 50% of patients remained at that dose for their entire treatment. In addition, one third of patients received three cycles or less, regardless of the recommendation that response be evaluated following a minimum of four cycles. In fact, approximately 20% of patients only received one cycle of Vidaza. The two academic hospitals in Vancouver administered Vidaza to 45% of the patients in the cohort; of these patients, 38% received less than four cycles, similar to the 34% of patients receiving less than four cycles at non-teaching hospitals.

Response rates (Figure 2) were determined based upon the International Working Group (IWG) criteria; 12% of patients experienced a complete (CR) or partial (PR) response. This project involved the collection of data on 181 patients who had been administered Vidaza in British Columbia from 2010-2014, following the licensing of the drug in Canada for higher-risk MDS patients.
remission and an additional 26% had a hematologic improvement (HI). These results are inferior to those found in the pivotal randomized study (Aza 001) in which 29% of the patients had a CR/PR and an additional 20% had a HI.

When analyzing the HI patients in our study (Figure 3), hemoglobin was found to be the most common parameter that increased with Vidaza (64% of patients).

The overall response rates were further classified according to the seven diagnostic categories in our cohort: MDS unclassified, RCMD, CMML, t-MDS/t-AML, RAEB-1/RAEB-2 and AML. The treatment-related MDS/AML patients responded poorly in comparison to the other diagnoses, as only 5% of patients achieved PR or CR. However, 53% of patients in this group received ≤ 3 cycles of the drug, potentially skewing results. It is also noteworthy that the patients with CMML did just as well as patients with other diagnoses - 18% of patients achieved CR/PR and 12% had a HI.

Responses were then classified according to IPSS cytogenetic risk group at commencement of Azacitidine: poor-risk, intermediate-risk and good-risk/normal karyotype; 45 patients did not have an available chromosome analysis. The analysis indicated that all cytogenetic groups had a similar response rate; notably, patients with complex karyotypes seemed to do as well as the other cytogenetic categories (Figure 4).

In attempting to analyze the cytogenetic response of patients to Azacitidine, it was found that follow-up cytogenetics were performed infrequently -- only 9 of 138 patients with informative cytogenetics (6%) had a follow-up karyotype analysis.

The median survival time for our Vidaza-treated cohort was 7 months, with a range of <1 month to 3.1 years; 37% of the patients are still alive. When patients who received ≤ 3 cycles were excluded from the survival analysis, the median survival was 1.1 years. This was only ~50% of the 2.2 years seen in the Aza 001 study.

The most common side effects seen in our Vidaza patients were hematologic -- neutropenia and thrombocytopenia, which occurred in 59% and 38% respectively. Of the non-hematologic side effects, injection site inflammation, nausea, disturbance in bowel habit (constipation/diarrhea) and fever/infection were all seen in ~50% of patients. While 39% of patients ceased their treatment without evidence of disease progression, the most common reason for stopping Vidaza was progression of MDS/AML (28% of patients).

Progression typically occurred early -- within 12 months in 75% of individuals. Not surprisingly, disease progression was the most common cause of death (50% of patients) with infection a distant second (10% of patients).

The response rates and survival time in our study may have been inferior to the Aza 001 study for a number of reasons. Firstly, it appears that the drug was not administered as aggressively as it was in the Aza 001 study. This may have been because...
By Thomas J. Nevill, MD, FRCPC

The 35th World Congress of the International Society of Hematology took place September 4-7, 2014 in Beijing, China, hosted by the Chinese Society of Hematology.

The International Society of Hematology was founded in 1946 as a professional body interested in advancing scientific research as well as the practice of clinical and laboratory hematology.

ISH is composed of three divisions - Intra-American, Asian & Pacific and European & African – and its journal is Hematology.

The CHS sent a delegation to Beijing this past September, to present a bid to the ISH Council, asking for the opportunity to host the 37th World Congress in Vancouver in 2018.

The presentation was well-received and CHS was subsequently informed that their bid was successful; the CHS Organizing Committee will travel to Glasgow, Scotland in 2016 to receive the ISH banner at the 36th World Congress.

Below—and on the next few pages—is a summary of the highlights of the recent ISH 2014 meeting in Beijing.

Acute myelogenous leukemia and myelodysplasia

The World Congress opened with the Miwa Lecture being given by Dr. Zhu Chen from Shanghai, China: “Acute promyelocytic leukemia: achievement, challenges and expectations.”

This topic was an appropriate choice as two of the cornerstones of modern APL treatment were developed in China in the 1980s (all-trans retinoic acid, ATRA) and 1990s (arsenic trioxide, ATO). ATRA and ATO are now being used as standard induction therapy in China (and elsewhere) with a 3-year event-free survival of ~90% for low and intermediate-risk patients (Li, Int J Hematol, 2014). Unfortunately, outcomes in high-risk APL are less favourable (EFS of ~65%) and more aggressive treatment strategies incorporating anthracyclines are being used in this subgroup of patients.

Oral tetra-arsenic tetrathiolide is also being evaluated as an oral agent in APL since a randomized trial has confirmed similar efficacy to ATO (Zhu, J Clin Oncol, 2013).

Dr. Martin Tallman, Memorial Sloan-Kettering (New York, NY) provided an eloquent talk on recent developments in AML therapy, focusing on the contribution of genetic mutations to risk stratification and newer targeted therapy in AML.

While NPM1 mutations have been reported to confer a favourable outcome in normal karyotype, FLT3...
wild-type AML, newer evidence suggests a more complicated risk stratification. In NPM1 mutated patients, concurrent IDH1/2 mutations provide a more favourable outcome while those also having mutations in TET2 (Tian, Int J Hematol, 2014) or DNMT3 (Loghavi, J Hematol/Oncol, 2014) are better categorized as unfavourable.

Dr. Tallman indicated that patients with favourable-risk AML may have better outcomes with the incorporation of Gemtuzumab ozogomicin into their treatment regimen, especially in the older patient population (Loke, Ann Hematol, 2014). Other targeted therapies may have a role in AML including Dasatinib in t(8;21) disease (Herrmann, Exp Hematol, 2014) and inhibitors of the MAPK and PI3K pathways in MLL-rearranged AML (Kampen, Leukemia, 2014). Only 6 genes were found to be mutated in >10% of patients in the study – TET2, RUNX1, DNMT3A, SRSF2, SF3B1 and ASXL1 (Haferlach, Leukemia, 2014). Detailed analysis revealed a specific temporal order of mutation development. The splicing mutations and TET2 appear to be early events, followed by the development of IDH 1/2 and DNMT3A mutations. Late mutational events involve the TP53, ASXL1 and EZH2 genes.

Dr. Seishi Ogawa from Kyoto, Japan provided an overview of somatic mutations in MDS during the opening day of the 35th World Congress.

Professor Ogawa presented gene analysis data on 944 patients with MDS that showed that 92% of patients had at least one mutation in a key gene with the mean number of mutations per patient being three.

It was stressed that one needs to use experience with pattern recognition in order to remember some of the rarer causes of anaemia and the potential for multiple co-existent causes that may obscure classic features seen in anaemia resulting from a single etiology.

The standard approach to anaemia is to divide diagnoses into categories based upon the red cell size, as measured by the MCV. However, this algorithmic approach has its pitfalls if it is followed too rigidly.

Dr. Green presented a case of an African-American woman in her 20s who presented with a normocytic anaemia (Hb 81 g/L), thrombocytopenia (platelets 51 x 109/L), a markedly elevated LDH (>12,000 U/L) and prominent anisopoikilocytosis on blood film. Thrombotic thrombocytopenic purpura (TTP) was suspected and the patient was treated with (and appeared to respond to) plasma exchange (PLEX). However, when her condition deteriorated soon thereafter, hypersegmented neutrophils were identified in her blood film. Serum B12 level was markedly reduced and she was found to have concurrent α-thalassemia trait.

This case illustrated how an unexpected diagnosis (B12 deficiency in a young adult) can mislead a physician, especially if there are multiple co-existent causes (B12 deficiency and hemoglobinopathy) in which apparent response to therapy (PLEX) provided false reassurance.

A second interesting case was outlined by Dr. Green in which a middle-aged woman with a history of a prior gastric bypass surgery presented with fatigue and numbness in a stocking/glove distribution. She was found to have a marked anemia with and MCV of 83, WBC of 1.4 x 109/L and a platelet count of 145 x 109/L. She had a normal serum ferritin and RBC folate level; bone marrow exam was slightly hypercellular with mild erythroid and granulocytic dysplasia.

Based on her presenting sensory symptoms, B12 deficiency was considered but its serum level was also normal. Myelodysplastic syndrome was the provisional diagnosis but her serum copper level was markedly reduced and zinc level was increased. It was emphasized that gastric bypass surgery can increase the risk of hematological disorders including iron and other micronutrient deficiencies (including B12 and copper).

Copper deficiency anemia is often macrocytic but can be normocytic or microcytic. This entity may further confuse clinicians as leukopenia and thrombocytopenia can both occur and the bone marrow may have dysplasia and ring sideroblasts. Copper deficiency can cause neurologic...
deficits including dorsal and lateral column dysfunction similar to that seen in B12 deficiency. Curiously, copper deficiency may also be precipitated by excessive zinc supplementation through herbal products and through denture adhesives.

**Hematologic manifestations of celiac disease**

Dr. Subhash Varma (Chandigarh, India) lectured at ISH 2014 on “Relevance of celiac disease in hematology practice”.

Professor Varma indicated that celiac disease (gluten-sensitive enteropathy) is characterized, in its "classic" form, by frank diarrhea / steatorrhea and failure to thrive in childhood.

However, the disorder is now increasingly diagnosed in individuals of all ages and may affect up to 1% of the population. In adults with celiac disease, ~50% will not provide a history of abnormal bowel movements – the "atypical" form of the condition.

The diagnosis of celiac disease can usually be made with serum anti-tissue transglutaminase antibody (anti-tTG Ab) testing although concurrent IgA deficiency can reduce the sensitivity of this test to 90%. The gold standard for diagnosis remains small bowel biopsy which shows characteristic villous atrophy.

The hematologic manifestations of celiac disease are protean, with the most common being iron deficiency anemia, occurring in ~50% of atypical or silent cases. This anemia may be resistant to therapy and Dr. Varma emphasized that 20% of patients with refractory iron deficiency anemia (RIDA) have celiac disease. Furthermore, even when the anti-tTG Ab and small bowel biopsies are negative, RIDA may respond to a gluten-free diet.

Other micronutrients can be malabsorbed in celiac disease, which can lead to folate, B12 and/or copper deficiency, all of which can lead to anemia and other cytopenias. Thrombocytosis has been described in up to 60% of patients with celiac disease and has been attributed to inflammatory mediators, concurrent iron deficiency or functional hyposplenism; the latter is much more common in adult celiacs and has been associated with anecdotal reports of severe/fatal bacterial infections. IgA deficiency is seen in 5-10% of patients with gluten-sensitive enteropathy and is a risk factor for developing inflammatory bowel disease and chronic parasitic infections such as Giardiasis; it can also lead to anaphylactic reactions to blood product transfusions.

The relationship of celiac disease to intestinal lymphoma bears specific mention. Enteropathy-type T-cell lymphoma (ETL), a rare disorder, arises from clonal proliferation of intraepithelial lymphocytes (IEL) and patients with refractory celiac disease have been shown to harbour clonal IELs.

The odds ratio for developing ETL in the setting of celiac disease appears to be in the 15-20 range, although celiac patients are also at higher risk for the more common intestinal B-cell and extraintestinal T-cell lymphomas.

Finally, Professor Varma highlighted the increased risk of venous (and possibly arterial) thromboembolism (VTE) in celiac disease. In fact, VTE may be the presenting feature of gluten-sensitive enteropathy with its etiology linked to hyperhomocysteinemia, decreased levels of vitamin K-dependent anticoagulants (proteins C and S) and increased levels of thrombin-activatable fibrinolysis inhibitor (TAFI).

Photo BELOW: China National Convention Centre, Beijing
**An Update On Light Chain Amyloidosis**

**Introduction**

Amyloidosis is a rare disorder in which aberrant precursor proteins misfold resulting in stable aggregates of amyloid fibrils that deposit within different organs leading to impairment and eventually failure. Light chain amyloidosis (AL) is the most common variant of this disease. The amyloidogenic light chain protein is produced by an underlying B-cell based clone. This is commonly a plasma cell dyscrasia but the disease is also seen in indolent B-cell lymphoma.

**Clinical presenting features and diagnostic procedures**

Patients with AL amyloidosis can present with a multitude of symptoms reflecting the spectrum of involved organs. Presentation is often late, with the heavy amyloid burden negatively impacting prognosis. It is thus important to consider AL amyloidosis in the workup of all plasma cell dyscrasias from monoclonal gammopathy of undetermined significance or overt CRAB-defined myeloma.

Tissue from an affected organ or surrogate sites such as fat, rectum or bone marrow, is ultimately needed for confirmation. Observing the typical apple-green birefringence with Congo red staining under crossed-polarized light is diagnostic for amyloid. Immunohistochemistry, immuno-electron microscopy and proteomic analysis can be used to determine the underlying fibril subtype. Once the diagnosis has been confirmed it is important to establish the systemic burden of disease and organ involvement. Table 1 illustrates the baseline assessment of organ function. Cardiac involvement is the dominant prognostic factor. Echocardiography and cardiac magnetic resonance imaging have emerged as important tools for establishing cardiac deposition. However, a simple approach using NT-proBNP and HS Troponin T has evolved as the standard for prognostication; identifying those at high risk of early death. Recognizing the poor outcomes in Mayo stage III patients, further stratification of these individuals has been proposed. Using NT-proBNP >8500 ng/L and a systolic blood pressure <100mmHg, this group can be further separated identifying those with ultra high-risk disease. Paradoxically these patients have the greatest need for therapy but are the least likely to tolerate it, raising the need for more refined treatment strategies emphasizing supportive care.

**Treatment of systemic AL amyloidosis**

While the disease is incurable it is manageable. The primary goal of treatment is to suppress the production of the amyloidogenic free light chains by targeting the underlying clone. Over time the body may degrade existing amyloid deposits leading to further organ improvement and increased survival. Deep clonal responses are integral to long term survival and organ responses with patients attaining a dFLC-VGPR (<40mg/L) or better having the markedly improved outcomes.

**Autologous Stem cell transplantation (ASCT)**

Prior to the era of rigorous patient selection this modality of therapy resulted in unacceptable levels of transplant related morbidity (TRM). With modern selection criteria focusing on cardiac involvement, the TRM now approaches that expected in eligible myeloma patients. Recent publications have reported median OS of over 6 years. In those attaining a CR the median OS may be as long as 13.2 years. Marked improvements in TRM to <6% is also seen in appropriately selected patients.

Interestingly, long-term outcomes may be similar irrespective of whether the transplant is done as first line therapy or at relapse. An NT-proBNP > 5000 pg/ml and troponin T > 0.06ng/L are important predictors of outcome post-ASCT. With serum levels below these thresholds the TRM may be as low as 1%. Approaches incorporating novel agents into induction and conditioning are being explored.

**Combination chemotherapy**

While effective, high-dose chemotherapy is applicable to less than 25% of patients. Most are treated with low-dose combinations.
Alkylating agents in conjunction with steroids have been used for over 40 years. While complete response (CR) rates of around 20-30% are achievable responses tend to be slow. Immunomodulatory drugs such as thalidomide, lenalidomide and pomalidomide have emerged as important agents. Initial studies with thalidomide demonstrated more rapid clonal responses with about 20% achieving a CR. Toxicity was high however, with 60% experiencing ≥3 grade adverse events. Treatment with lenalidomide and dexamethasone has shown promise with responses of 48% and median OS and PFS of 28 and 14 months respectively. Continuous therapy may be a key component to durable responses when IMiDs are used.

The largest therapeutic gains have been made with the advent of proteosome inhibitor-based regimens. Prospective studies have shown deep and rapid responses. Various groups have investigated bortezomib in triplet combinations based on a steroid/alkylator backbone. In those surviving long enough to maximally benefit from therapy CR rates of up to 65% are reported, especially when used in the upfront setting. Even in Mayo stage III patients an unprecedented 1-year OS of over 50% has been reported. Two recent case-control studies examining a bortezomib-alkylator-steroid combination compared with two standard regimens (melphalan and dexamethasone and CTD) have corroborated these findings.

Prospective studies are currently awaited to validate these findings. Studies with next generation proteosome inhibitors including such as carfilzomib and ixazomib are under way including a recently reported phase I trial with the latter.

**Targeted therapy for amyloidosis**

In the clinical realm, the targeted removal of amyloid fibrils is lacking.

### Table 1: Diagnostic and baseline investigations for systemic AL amyloidosis.

<table>
<thead>
<tr>
<th>Tissue diagnosis</th>
<th>Abdominal fat aspirate</th>
<th>Bone marrow biopsy</th>
<th>Salivary gland or rectal biopsy</th>
<th>Biopsy of involved organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid typing</td>
<td>Immunohistochemistry</td>
<td>Mass spectrometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies to detect an underlying plasma/B cell clone</td>
<td>Serum and urine electrophoresis and immunofixation</td>
<td>Serum Free light chain measurement</td>
<td>Bone marrow aspirate / biopsy</td>
<td></td>
</tr>
<tr>
<td>Assessment of organ involvement and staging</td>
<td>Cardiac</td>
<td>Renal</td>
<td>Liver</td>
<td>Nerves</td>
</tr>
<tr>
<td></td>
<td>NT-proBNP (or BNP), cTnT (or hs-cTnT, or cTnI)</td>
<td>ECG (plus Holter ECG)</td>
<td>Liver function tests (alkaline phosphatase)</td>
<td>Nerve conduction studies (if indicated)</td>
</tr>
<tr>
<td></td>
<td>Echocardiography (plus strain imaging)</td>
<td>Cardiac MRI</td>
<td>Liver US / CT scan</td>
<td>Autonomic testing</td>
</tr>
<tr>
<td></td>
<td>Renal MRI</td>
<td>24 h urinary protein</td>
<td>Nerves</td>
<td>Sural nerve biopsy (if indicated)</td>
</tr>
<tr>
<td></td>
<td>Renal MRI</td>
<td>Serum creatinine (and eGFR)</td>
<td>Whole body amyloid load</td>
<td></td>
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<tr>
<td></td>
<td>Cardiac</td>
<td>Liver</td>
<td></td>
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<tr>
<td></td>
<td>Liver US / CT scan</td>
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</tbody>
</table>

NT-proBNP - N-terminal prohormone of brain natriuretic peptide; BNP – brain natriuretic peptide; cTnT or cTnI – troponin T or I; hs-cTnT – high sensitivity troponin T; ECG – electrocardiograph; 99mTc-DPD scan - 99mTc-dicarboxypropane diphosphonate scan; eGFR – estimated glomerular filtration rate; US – ultrasound; CT – computed tomography; MRI – magnetic resonance imaging; SAP – serum amyloid P.
Proof-of-concept has been demonstrated using a transgenic mouse model of AA amyloidosis treated with antibodies targeting SAP; a molecule associated with all amyloid fibrils, irrespective of the subtype28.

Early phase clinical trials using this strategy are underway. A similar approach using a monoclonal antibody targeting AL and AA is also under investigation29. In combination with current cytotoxic approaches direct anti-amyloid fibril therapy will serve as the next generation of therapeutic approaches in this disease.

Conclusion

Systemic AL amyloidosis is a serious and yet under-diagnosed condition. Effective treatment exists but should be tailored based on the extent and severity of organ involvement, minimizing toxicity and maximizing depth of response. Prompt diagnosis and early initiation of therapy is crucial for long-term control of the underlying clone; paramount for improving survival. Future efforts combining cytotoxic approaches with direct anti-fibril treatments will usher in a new era in the management of this disease.

References

**Opportunities**

**Locum Hematologist, 3 Month Term, Dept. of Medicine, Dalhousie / Capital District Health**

The Department of Medicine, Dalhousie University/Capital District Health Authority seeks applications for a position as locum Hematologist in the Division of Hematology, at the QEII Health Sciences Centre, Halifax, Nova Scotia. The position will be for a three month term. The Division of Hematology is an integral part of the Department of Medicine and provides services for the Capital District Health Authority. Interested applicants should forward their curriculum vitae and three references to:

Dr. Stephen Couban, Head/Chief, Division of Hematology
Room 417, Bethune Building, 1276 South Park Street, Halifax, NS, B3H 2Y9
Email: stephen.couban@cdha.nshealth.ca

**Fellowships**

**LEUKEMIA/BONE MARROW TRANSPLANTATION FELLOWSHIP VANCOUVER**

The Leukemia/Bone Marrow Transplantation Program of British Columbia offers 1 or 2 Year fellowships to provide advanced training in the management of adults with hematological malignancies including all aspects of allogeneic and autologous hematopoietic stem cell transplantation (HSCT). Candidates should be registered in, or completed a recognized hematology or oncology training program. Interested candidates should submit a CV and names of three references to: Dr. Donna Forrest, Fellowship Director Leukemia/BMT Program, BC Cancer Agency & Vancouver General Hospital

Phone: (604) 875-4089
Fax: (604) 875-4763
Email: dforrest@bccancer.bc.ca

**The Diagnosis? Answer:** (from Page 4)

This middle-aged woman was suspected to have myelodysplastic syndrome and, after one of her brothers was found to be HLA-identical, was referred for allogeneic stem cell transplantation.

- Physical examination revealed microdontia; the bone marrow biopsy shows marked hypocellularity (10%). Review of blood work done 30 years previously at the time of her first lithotripsy revealed a virtually identical CBC with hemoglobin 131, MCV 106, ANC 1.2 and platelets 120.

- Blood testing was sent for genetic analysis and she was found to have two pathogenic mutations within the SBDS gene (c.183_184delTAlncGT and c.258+2T>C) found in 33% and 58% of individuals, respectively, with Shwachmann Diamond syndrome. This disorder is characterized by short stature, exocrine pancreatic deficiency and progressive bone marrow failure. The steatorrhea, for reasons that are unclear, improves with age and 50% of SDS adults will have no GI symptoms.

Patients with SDS also commonly have mild hepatic dysfunction and may have skeletal/dental, urinary tract or cardiac abnormalities. They are at risk for developing MDS and AML but clonal cytogenetic abnormalities may fluctuate spontaneously.

Allogeneic stem cell transplantation is curative in ~65% of SDS patients although they may be at risk for excessive toxicity with myeloablative conditioning regimens.
Membership Matters

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

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

Only active members shall:
- vote
- hold office
- receive CHS grants, and
- pay dues.

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

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

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

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

CHS members are reminded … that dues for the year 2014, were due on January 1, 2014.

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

Or by mail to: Canadian Hematology Society, 199-435 St. Laurent Blvd., Ottawa, Ontario K1K 2Z8

Please provide the following information with your payment:

2014 Membership Renewal: Canadian Hematology Society

Membership Status
Active □
Associate □
Emeritus □

Has your status changed?
Yes □
No □

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Work Fax: ___________________________