The Microenvironment

November 2014

THE CANADIAN HEMATOLOGY SOCIETY

SOCIÉTÉ CANADIENNE D'HÉMATOLOGIE

NEWSLETTER

Inside this Issue...

The Canadian Hematology Society

Annual Reception
Awards Presentations
and Dinner at ASH

Sunday, December 7, 2014
at 6:30 pm

Four Seasons Hotel
757 Market Street
San Francisco

RSVP by November 21st to:
CHSatASH2014@gmail.com

MESSAGE FROM THE PRESIDENT

Canadian Hematology Society announces exciting initiatives

Dr. Aaron Schimmer
President, CHS

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 →

2014 CHS Executive Committee

President	Dr. Aaron Schimmer
Past-President	Dr. Stephen Couban
Vice-President	Dr. Lynne Savoie
Secretary Treasurer	Dr. Molly Warner
Executive Vice-President	Dr. Gail Rock
Editor: Microenvironment	Dr. Tom Nevill

Canadian Hematology Society
199—435 St. Laurent Blvd.
Ottawa, ON K1K 2Z8 CANADA
Phone: 613-748-9613
Website: canadianhematologysociety.org
Email: chs@uniserve.com

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 on-going interest and involvement in the CHS and hope to see you at the ASH meeting.

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.

Canadian Hematology Society
Société Canadienne d'Hématologie

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.

Message du Président

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 reconnaitra le meilleure 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.

Finalement au cours de la nouvelle année, nous lancerons un portail web interactif. Nous espérons que ce dernier fournira un contenu passionnant et utile à nos membres. Parmi les nombreuses nouvelles fonctionnalités seront listés les critères spécifiques à chaque province concernant le remboursement des médicaments d'hématologie.

Nous espérons que ce site pourra servir de « guichet unique » pour les questions concernant le remboursement des médicaments – quelque chose qui n'est pas facile à trouver dans d'autres formats-.

Ce 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

Do you know the diagnosis?

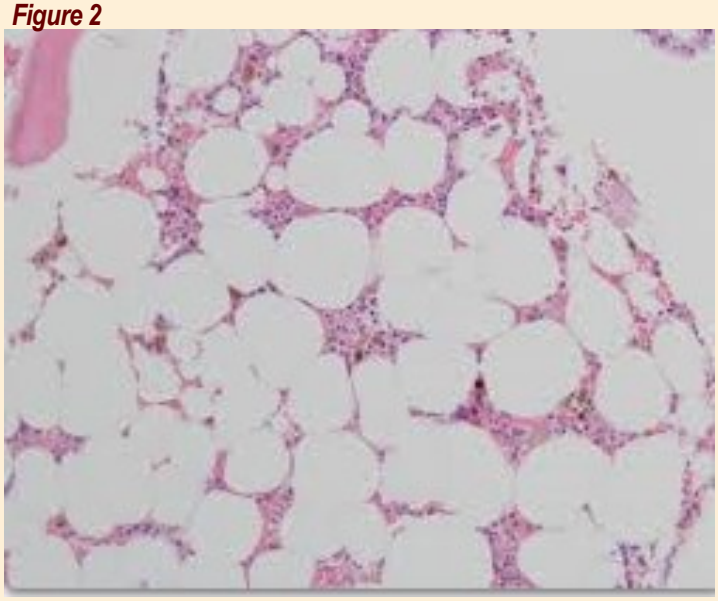
A 45-year-old woman was referred for investigation of asymptomatic bicytopenia that had been found on routine blood testing nine months previously. In the past year, she had also been found to have deranged liver function tests for which she was seeing a Hepatologist.

- Past medical history was significant for a history of B_{12} deficiency diagnosed at age 10 and treated with parenteral B_{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 10^9/L, ANC 1.4 x 10^9/L and platelets 113 x 10^9/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).

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

Figure 1

Figure 2



Upcoming Events — Mark your calendar - Save the date!

Canadian Hematology Society (CHS)
Annual Reception, Dinner & Awards Evening
Sunday, December 7, 2014
San Francisco
Contact: chs@uniserve.com

International Society of Thrombosis and Haemostasis (ISTH)
25th World Congress
July 11—17, 2015, Toronto, Ontario
Contact: https://www.isth.org

Canadian Blood and Marrow Transplant Group (CBMTG)
Annual Conference
May 13-16, 2015, Montreal, Quebec
http://www.cbmtg.org

International Society for Laboratory Hematology (ISLH)
28th International Symposium
Chicago, Il, May 19-21, 2015
Contact: http://www.islh.org/

Upcoming membership vote to ratify new CHS bylaws

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.

CHS EXECUTIVE BOARD

President

Dr. Aaron Schimmer

Past-President

Dr. Stephen Couban

Vice-President

Dr. Lynn Savoie

Secretary Treasurer

Dr. Molly Warner

Executive Vice-President

Dr. Gail Rock

YOUR CHS NEWSLETTER

Member submissions welcome!

History Corner — Dr. Jack Hirsh, Professor Emeritus, McMaster University

Jack Hirsh was born January 7, 1935 in Lodz, Poland but obtained his MBBS and MD degrees from the University of Melbourne in Australia.

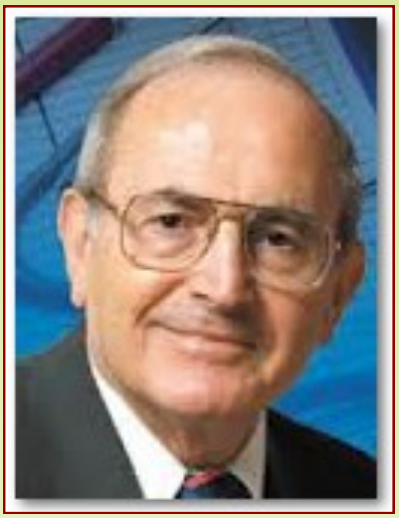
He trained in hematology at Washington University in St. Louis, Missouri in the early 1960s and then pursued further studies at the London Postgraduate Medical School in England.

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. Jack Hirsh
Professor Emeritus,
Division of Hematology & Thromboembolism,
Department of Medicine,
McMaster University

His work in Hamilton contributed to the discovery of low-molecular weight heparin and helped define its clinical advantages.

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

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**

STUDENT RESEARCH ARTICLES

Student Article | Summer project data analysis report

AZACITIDINE TREATMENT FOR MDS: THE BRITISH COLUMBIA EXPERIENCE

Madeleine Ankenman
Summer Student
Simon Fraser University
Burnaby, BC

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).

Madeleine Ankenman
Simon Fraser University
Burnaby, BC

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.

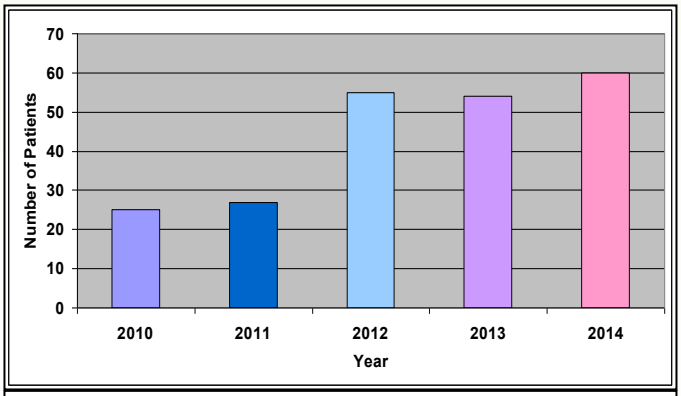


Figure 1: The number of patients initiating Vidaza each year

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.

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.

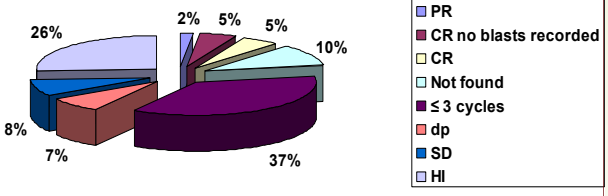


Figure 2: the overall response of MDS patients to Azacitidine following the IWG criteria

Response rates (Figure 2) were determined based upon the International Working Group (IWG) criteria; 12% of patients experienced a complete (CR) or partial (PR)

continued, page 8 ⟶

(Student Article – CONTINUED from page 7)

remission and an additional 26% had a hematologic improvement (HI). These results are inferior to those found in the pivotal randomized study (Aza 001)[1] 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.

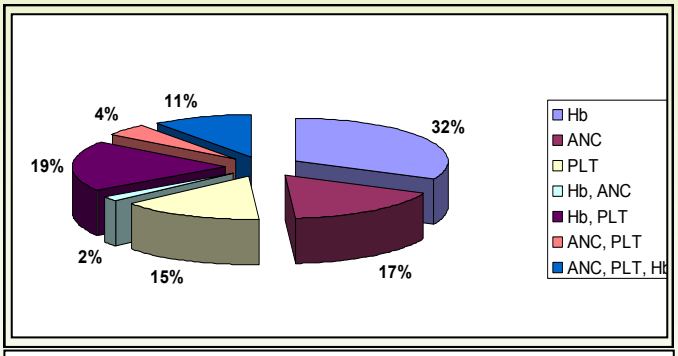


Figure 3: Hematologic improvement divided into the relevant components.

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.

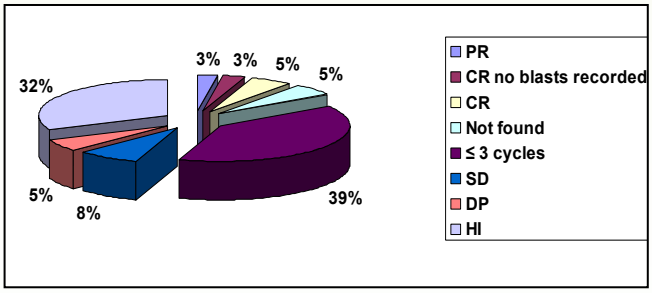
The median survival time for our Vidaza-treated cohort was 7 months, with a range of <1 month to 3.1 years; 37% of the patients are still alive. When patients who received ≤ 3 cycles were excluded from the survival analysis, the median survival was 1.1 years. This was only ~50% of the 2.2 years seen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

The most common side effects seen in our Vidaza patients were hematologic -- neutropenia and thrombocytopenia, which occurred in 59% and 38% of the patients, 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).

***Supervisor*:**
Dr. Tom Nevill
Clinical Professor, Hematology
University of BC

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 of the many side effects and the lack of familiarity with these by both the



continued, page 9 ⟶

ISH 2014 HIGHLIGHTS FROM THE 35th WORLD CONGRESS - Beijing, China

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 division - Intra-American, Asian & Pacific and European & African – and its journal is Hematology.

ISH has biennial meetings hosted, in rotation, by each of its divisions. Canada, under the auspices of the Canadian Hematology Society, last hosted ISH in Toronto in 2000 -- the 28th World Congress.

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.

(Student Article – CONTINUED from page 8)

care team and the patients. It appears that many patients did not continue the drug beyond the initial (expected) decrease in counts and may not have been given the proper medication to prevent the gastrointestinal side effects of Azacitidine. These adverse effects may have placed too much burden on the site of drug administration and the patient themselves.

It also must be said that it is difficult to evaluate the responses to Vidaza without detailed follow-up notes and without routine bone marrow re-evaluation. A CR/PR cannot be assigned without a follow-up bone marrow according to the IWG criteria. Although this analysis had its limitations, Azacitidine appears to be an effective drug in a significant proportion of higher-risk MDS patients, and was shown to be particularly useful in poor- risk karyotype MDS and CMML.

HIGHLIGHTS

XXXV World Congress of the International Society of HEMATOLOGY
September 4–7, 2014

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".

Dr. Zhu Chen

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 tetrasulfide 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.

Dr. Martin Tallman

While NPM1 mutations have been reported to confer a favourable outcome in normal karyotype, FLT3

continued, page 10 →

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).

Dr. Seishi Ogawa

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.

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.

Micronutrient deficiency anemias

Dr. Donald Green (University of California, Davis) spoke at ISH 2014 on "Micronutrients in hematology: building blocks for the blood".

Professor Green's talk focused on "unexplained" anemias -- what possibilities to consider and how to diagnose the underlying cause.

Dr. Donald Green

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

The standard approach to anemia 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 anemia (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 therafter, 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

continued, page 11 ⟶

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".

Dr. Subhash Varma

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 failure1. 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 lymphoma1.

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. Immunohistochemistry2, immuno-electron microscopy3 and proteomic analysis4 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 death5. 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 disease6. 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.

Christopher P. Venner, MD, FRCPC
Cross Cancer Institute
Department of Medical Oncology
University of Alberta

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 outcomes7.

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)8. 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 years9-12. In those attaining a CR the median OS may be as long as 13.2 years10. Marked improvements in TRM to < 6% is also seen in appropriately selected patients10.

Interestingly, long-term outcomes may be similar irrespective of whether the transplant is done as first line therapy or at relapse12. 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 of 1%13. Approaches incorporating novel agents into induction and conditioning are being explored14.

Combination chemotherapy

While effective, high-dose chemotherapy is applicable to less than 25% of patients. Most are treated with low-dose combinations.

continued, page 13 →

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 slow15.

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 events16,17.

Treatment with lenalidomide and dexamethasone has shown reasonable response rates of up to 67% (CR = 29%)18,19. Pomalidomide has also shown promise with responses of 48% and median OS and PFS of 28 and 14 months respectively20. Continuous therapy may be a key component to durable responses when IMiDs are used21.

The largest therapeutic gains have been made with the advent of proteosome inhibitor-based regimens. Prospective studies have shown deep and rapid responses 22. Various groups have investigated bortezomib in triplet combinations based on a steroid/alkylator backbone 23-26.

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 reported24. 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 25, 26.

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, 27

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.

Tissue diagnosis	Abdominal fat aspirate Bone marrow biopsy Salivary gland or rectal biopsy Biopsy of involved organ
Amyloid typing	Immunohistochemistry Mass spectometry
Studies to detect an underlying plasma/B cell clone	Serum and urine electrophoresis and immunofixation Serum Free light chain measurement Bone marrow aspirate / biopsy
Assessment of organ involvement and staging	**Cardiac** NT-proBNP (or BNP), cTnT (or hs-cTnT, or cTnI) Echocardiography (plus strain imaging) ECG (plus Holter ECG) Cardiac MRI **Renal** 24 h urinary protein Serum creatinine (and eGFR) **Liver** Liver function tests (alkaline phosphatase) Liver US / CT scan **Nerves** Nerve conduction studies (if indicated) Autonomic testing Sural nerve biopsy (if indicated) **Whole body amyloid load** ^{123}I labelled SAP scintigraphy (if available)

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.

continued, page 14 ⟶

continued, from page 13

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

1. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin. Hematol. 1995;32 (1):45–59.
2. Schonland SO, Hegenbart U, Bochtler T, et al. Immunohistochemistry in the classification of systemic forms of amyloidosis: a systematic investigation of 117 patients. Blood. 2012;119(2):488–493.
3. Arbustini E, Verga L, Concardi M, et al. Electron and immuno-electron microscopy of abdominal fat identifies and characterizes amyloid fibrils in suspected cardiac amyloidosis. Amyloid. 2002;9(2):108–114.
4. Vrana JA, Gamez JD, Madden BJ, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009;114(24):4957–4959.
5. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. Journal of Clinical Oncology. 2004;22(18):3751–3757.
6. Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood. 2013;121(17):3420–3427.
7. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J. Clin. Oncol. 2012;30 (36):4541–4549.
8. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. 2007;357 (11):1083–1093.
9. Gertz MA, Lacy MQ, Dispenzieri A, et al. Trends in day 100 and 2-year survival after auto-SCT for AL amyloidosis: outcomes before and after 2006. 2010;46(7):970–975.
10. Cibeira MT, Sanchorawala V, Seldin DC, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. 2011;118(16):4346–4352.
11. Jimenez-Zepeda VH, Franke N, Reece DE, et al. Autologous stem cell transplant is an effective therapy for carefully selected patients with AL amyloidosis: experience of a single institution. Br J Haematol. 2013;164(5):722–728.
12. Venner CP, Gillmore JD, Sachchithanantham S, et al. Stringent patient selection improves outcomes in AL amyloidosis after autologous stem cell transplantation in the upfront and relapsed setting. Haematologica. 2014.
13. Gertz MA, Lacy MQ, Dispenzieri A, et al. Refinement in patient selection to reduce treatment-related mortality from autologous stem cell transplantation in amyloidosis. Bone Marrow Transplantation. 2012;48(4):557–561.
14. Landau H, Hassoun H, Rosenzweig MA, et al. Bortezomib and dexamethasone consolidation following risk-adapted melphalan and stem cell transplantation for patients with newly diagnosed light-chain amyloidosis. Leukemia. 2012;27(4):823–828.
15. Palladini G, Milani P, Foli A, et al. Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. Haematologica. 2014;99(4):743–750.
16. Palladini G. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). Blood. 2005;105(7):2949–2951.
17. Wechalekar AD, Goodman HJB, Lachmann HJ, et al. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. Blood. 2007;109(2):457–464.
18. Sanchorawala V, Patel JM, Sloan JM, et al. Melphalan, lenalidomide and dexamethasone for the treatment of immunoglobulin light chain amyloidosis: results of a phase II trial. Haematologica. 2013;98(5):789–792.
19. Moreau P, Jaccard A, Benboubker L, et al. Lenalidomide in combination with melphalan and dexamethasone in patients with newly diagnosed AL amyloidosis: a multicenter phase 1/2 dose-escalation study. Blood. 2010;116(23):4777–4782.
20. Dispenzieri A, Buadi F, Laumann K, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. Blood. 2012;119(23):5397–5404.
21. Mahmood S, Venner CP, Sachchithanantham S, et al. Lenalidomide and dexamethasone for Systemic AL Amyloidosis following prior treatment with thalidomide or bortezomib regimens. Br J Haematol. 2014.
22. Reece DE, Hegenbart U, Sanchorawala V, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study. Blood. 2011;118(4):865–873.
23. Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood. 2012;119(19):4387–4390.
24. Jaccard A, Comenzo RL, Hari P, et al. Efficacy of bortezomib, cyclophosphamide and dexamethasone in treatment-naïve patients with high-risk cardiac AL amyloidosis (Mayo Clinic stage III). Haematologica. 2014;99 (9):1479–1485.
25. Palladini G, Milani P, Foli A, et al. Melphalan and dexamethasone with or without bortezomib in newly diagnosed AL amyloidosis: a matched case-control study on 174 patients. Leukemia. 2014, epub ahead of print.
26. Venner CP, Gillmore JD, Sachchithanantham S, et al. A Matched Comparison of Cyclophosphamide, Bortezomib and Dexamethasone (CVD) versus risk adapted Cyclophosphamide, Thalidomide and Dexamethasone (CTD) in AL Amyloidosis. Leukemia. 2014, epub ahead of print.
27. Merlini G, Sanchorawala V, Zonder JA. MLN9708, a novel, investigational oral proteasome inhibitor, in patients with relapsed or refractory light-chain amyloidosis (AL): results of a phase 1 study. 120: Abstract 731
28. Bodin K, Ellmerich S, Kahan MC, et al. Antibodies to human serum amyloid P component eliminate visceral amyloid deposits. Nature. 2010;468(7320):93–97.
29. Wall JS, Kennel SJ, Williams A, et al. AL amyloid imaging and therapy with a monoclonal antibody to a cryptic epitope on amyloid fibrils. PLoS ONE. 2012;7 (12):e52686.

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. Candidates must hold FRCPC certification (or equivalent) in Internal Medicine with subspecialty certification in Hematology.

All qualified candidates are encouraged to apply, however Canadians and permanent residents will be given priority. Dalhousie University is an employment equity, affirmative action employer. The University encourages applications from qualified First Nations Peoples, as well as persons with a disability, racially visible persons and women.

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

DALHOUSIE UNIVERSITY *Inspiring Minds*

Capital Health *A different today. A better tomorrow.*

Fellowships

LEUKEMIA/BONE MARROW TRANSPLANTATION FELLOWSHIP VANCOUVER

The Leukemia/Bone Marrow Transplantation Program of British Columbia offers 1 or 2 Year fellowships to provide advanced training in the management of adults with hematological malignancies including all aspects of allogeneic and autologous hematopoietic stem cell transplantation (HSCT). Candidates should be registered in, or completed a recognized hematology or oncology training program. **For more information: leukemiabmtprogram.org** 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**

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

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_184delTAinsCT 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.

The Microenvironment

November 2014

Your Canadian Hematology Society
Société Canadienne d' Hématologie Newsletter

Membership Matters

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

Active Membership

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

Only active members shall:

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

Associate Members

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

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

Emeritus Members

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

Honorary Membership

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

CHS members are reminded … that dues for the year 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 ☐

Name: _____

Title: _____

Email: _____

Work Address: _____

_____

Work Phone: _____

Work Fax: _____