The Microenvironment

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THE CANADIAN HEMATOLOGY SOCIETY

SOCIÉTÉ CANADIENNE D'HÉMATOLOGIE

NEWSLETTER

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2013 CHS Executive Committee

President	Dr. Stephen Couban
Past-President & Editor, The Microenvironment	Dr. Tom Nevill
Vice-President	Dr. Aaron Schimmer
Secretary Treasurer	Dr. Molly Warner
Executive Vice-President	Dr. Gail Rock

Message from the President

Dear Colleagues,

Dr. Stephen Couban

I hope all of you are enjoying the summer. The CHS continues to be active on your behalf and I have a number of issues to report on:

The CHS Executive held its Spring Retreat in May, 2013. I do want to thank my colleagues on the Executive including Aaron Schimmer, Vice-President, Molly Warner, Secretary-Treasurer, Tom Nevill, Immediate Past President, Gail Rock, Executive Director, Darrell White, Chair, Hematology Speciality Committee and Marciano Rees, Chair, Hematopathology Speciality Committee.

The CHS is in the process of working with ASH and the RCPSC to get Canadian accreditation of the ASH SAP. We surveyed the CHS membership and the overwhelming feedback was that it would be valuable to have the ASH SAP accredited by the Royal College so that it can be counted in the MOC program. Kevin Imrie is assisting us in completing this project and I hope that I can report that this undertaking is completed in the near future.

The CHS Executive is continuing to review submissions for Areas of Focused Competency on a case by case basis. There is no question that the submissions which we have received to date have been extraordinarily well prepared and thorough. One of the concerns of the CHS Executive with this process is that as more and more Areas of Focused Competency are developed, for example in Adolescent and Young Adult Medicine, Thrombosis, Bleeding, Blood and Marrow Transplantation and Hemoglobinopathies, it may diminish the value of training in hematology by itself. The CHS Executive continues to welcome feedback on this issue from our membership.

Gena Piliotis and **Chris Chen** continue to organize the highly successful annual Residents Retreat including Jerry Scott Day for trainees in hematology. The

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Save the Date!

CHS AT ASH
Sunday, Dec. 8, 2013
New Orleans

I look forward to welcoming you to the
CHS Reception, Awards and Dinner
at the W Hotel
only 3 blocks from the Congress Centre and near the famous French Quarter.

Stephen Couban, President CHS

CHS is very pleased to have had a presence at this event recently in Toronto. This is an excellent opportunity for us to increase the visibility of our Society to those just entering the field and we have noted a marked increase in applications for membership from our younger colleagues in the field!

We continue to work to try and re-establish an annual Canadian meeting with a focus in hematology. For a number of years, the Canadian Blood and Marrow Transplant Group (CBMTG) and the Canadian Apheresis Group (CAG) have held meetings at the same time. In 2014, I am very pleased to announce that a number of Canadian groups with interests in hematology have agreed to meet in Halifax in June, 2014. On Friday June 13, 2014, the CHS and the CBMTG will be hosting a morning symposium and Dr. Neal Young will be the plenary speaker. He will speak about the diagnosis and management of patients with aplastic anemia. Also during that morning, recent winners of the RK Smiley Award will be asked to make brief oral presentations about their work. A number of Canadian groups have agreed to gather in Halifax at that time including the Canadian Blood and Marrow Transplant Group (CBMTG), the Canadian Apheresis Group (CAG), Vector which is the Canadian thrombosis interest group, Myeloma Canada, and the Canadian myeloproliferative disorders interest group. I look forward to this event and hope it will provide a forum for further collaborations and interactions among the various hematology interest groups.

I look forward to seeing everyone at the Canadian Hematology Society evening at ASH in New Orleans in December, 2013. This event is a high point of the ASH meeting. It is a chance to catch up with Canadian colleagues and also to acknowledge fellows and young investigators who have won awards.

Thank you to Tom Nevill for his continued work as Editor of the Microenvironment and to Jean O'Brien-Louis in our central office for supervising the production of this newsletter. Finally, please pay your CHS dues!

Sincerely,
Stephen Couban

Message du Président

Chers Collègues,

J'espère que vous profitez de l'été. La SCH continue de plaider pour vous et j'ai plusieurs problèmes que je veux aborder ici.

Le comité exécutif de la SCH a organisé sa retraite de printemps en mai 2013. Je tiens à remercier mes collègues du comité 'exécutif, parmi lesquels Aaron Schimmer, vice-président, Molly Warner, secrétaire-trésorier, Tom Nevill, président sortant, Gail Rock, directeur exécutif, Darrell White, président du Comité de spécialité en hématologie et Marciano Rees, président du Comité de spécialité en hémato-pathologie
La SHC est en train de travailler avec la Société américaine d'hématologie (SAH) et le Collège royal des médecins et chirurgiens du Canada (CRMCC) pour faire en sorte que le programme d'autoévaluation de la Société américaine d'hématologie (SAH) soit accrédité au Canada. Nous avons mené une enquête parmi les membres de la SCH et la vaste majorité d'entre eux ont répondu qu'il serait bien si le Programme d'autoévaluation de la SAH était accrédité par le Collège royal afin qu'il puisse être intégré dans le programme de maintien du certificat (programme de MDC). Kevin Imrie nous assiste dans la réalisation de ce projet et j'espère que, dans un avenir proche, je pourrai vous dire que le projet a été finalisé

Le comité exécutif de la SCH continue d'examiner les demandes de domaines de compétence ciblée au cas par cas. Sans doute, les mémoires que nous avons reçus à ce jour ont été extraordinairement bien préparés et complets. L'une des préoccupations du comité exécutif de la SCH est, qu'au fur et à mesure que des domaines de compétence ciblée sont développés, dans des secteurs comme la médecine de l'adolescent et du jeune adulte, thrombose, hémorragie, greffes de moelle et de sang, hémoglobinopathies, la valeur de la formation en hématologie pourrait être diminuée. Le comité exécutif de la SCH accueille les commentaires de tous ses membres.

Gena Piliotis et Chris Chen continuent à organiser la Retraite annuelle des résidents, y compris le Jour Jerry Scott pour les stagiaires en hématologie. La SCH est très heureuse d'avoir participé à cet événement récemment organisé à Toronto. C'était une excellente occasion d'augmenter la visibilité de notre société auprès de ceux qui viennent de commencer leur carrière dans ce domaine et nous avons remarqué une augmentation marquée des demandes d'adhésion de la part de nos collègues plus jeunes.

Nous continuons à travailler pour essayer de réinstaurer la tradition d'une réunion annuelle canadienne se concentrant sur l'hématologie. Depuis quelques années déjà, le Groupe canadien de transplantation de moelle et de sang et le Groupe canadien d'aphérèse (GCA) ont tenu des réunions simultanées. En 2014, je suis très heureux d'annoncer que plusieurs groupes canadiens ayant des intérêts en hématologie ont convenu de se rencontrer à Halifax, en juin 2014. Le vendredi 13 Juin 2014, la SHC et le Groupe canadien de transplantation de moelle et de sang organiseront un symposium dans la matinée et Dr. Neal Jeunes sera le conférencier plénier. Il parlera du diagnostic et de la gestion des patients atteints d'anémie aplasique. Également, au cours de la matinée, les récents gagnants du Prix RK Smiley seront invités à faire de brèves présentations orales sur leur travail.

Plusieurs groupes canadiens ont convenu de se réunir à Halifax à cette date, y compris le Groupe canadien de greffe de moelle et de sang, le Groupe canadien d'aphérèse (GCA), Vector qui est le Groupe de travail sur la thrombose du Canada, Myélome Canada, et le Groupe canadien d'intérêt en syndromes myéloprolifératifs. Je me réjouis de cet événement et j'espère qu'il fournira un cadre pour de plus amples collaborations et interactions entre les divers groupes d'intérêt en 'hématologie

J'ai hâte de voir tout le monde à la soirée de la Société canadienne d'hématologie organisée au siège de la Société américaine d'hématologie, à la Nouvelle Orléans, en décembre 2013. Cette soirée est l'un des événements-clés de la réunion de la SAH. C'est une

Successful Annual Hematology Resident Retreat

Submitted by
Dr. Christine Chen

The 7th Annual Hematology Resident Retreat was held on July 19-21, 2013 in Toronto. The Hematology Retreat is a key educational event for hematology residents across Canada who gather to share ideas, experiences, and participate in scholarly activities. The three-day weekend event was comprised of multiple educational and social activities. On Friday, residents participated in a mock oral examination using eight case scenarios in an OSCE format with 16 faculty examiners from programs across the country. On Friday evening, program directors and educators from across Canada gathered for the Canadian Hematology Training Programs Meeting. During this meeting, retreat details, Royal College updates, and cross-Canada education initiatives were discussed.

Hematology Education Award

A Canadian Hematology Training Programs Fund, contributed to by adult Hematology Training Programs within Canada, was initiated by this meeting committee, providing support for the retreat and the Canadian Hematology Trainee Education Award. The Education Award is awarded to two resident projects per year focusing on medical education/ quality research and is in part supported by the **Canadian Hematology Society** (CHS).

Hematology residents from across Canada gather at a key educational event held recently in Toronto. The annual three-day weekend event is comprised of multiple educational and social activities.

On Saturday morning, residents participated in a Transfusion Workshop comprised of two didactic lectures followed by small group case discussions. For the didactic talks, **Dr. Yulia Lin** presented a nuts and bolts talk on *Serologic Testing in Transfusion Medicine* and **Dr. Christine Cserti-Gazdewich** presented on the *Transfusion Needs of Special Populations*, such as sickle cell and pregnant patients. These lectures set the stage for the small group, hands-on, case discussions, guided by transfusion experts.

The Transfusion Workshop was followed by a Meet and Greet Luncheon for all residents and faculty, during which residents had the opportunity to review a job and fellowship job board, mingle with our industry supporters, and sign up for CHS membership with our CHS representative, Jean O'Brien-Louis, who was in attendance.

Jerry Scott Educational Events

Saturday afternoon was devoted to the Jerry Scott Educational Half-Day. **Dr. Jerry Scott** was a cherished and much lauded educator at the University of Toronto, acting as Hematology Divisional Head from 1992-1996. Following his death in 1996, Dr. Scott's teaching accomplishments were commemorated with an educational forum for local hematology residents and it has since blossomed into an annual lecture series held within the National Hematology Retreat.

Topics and speakers from across Canada are invited to speak. This year, **Dr. Shannon Bates** from McMaster University presented on *Antiphospholipid Antibody Syndrome*, **Dr. Raewyn Broady** from UBC presented on the *Longterm Complications of Allogeneic Transplantation,* **Dr. Jillian Baker** from U of T Pediatrics presented on *Neonatal Hematology: Lessons from*

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(Message du Président)

chance d'entrer en contact avec des collègues canadiens et également de saluer les boursiers et les jeunes chercheurs qui ont remporté des prix.

Je tiens à remercier Tom Nevill pour son travail continu en tant que rédacteur en chef du Microenvironnement ainsi que Jean O'Brien-Louis dans notre bureau central pour avoir supervisé la production de ce bulletin. Enfin, s'il vous plaît, payez vos cotisations SCH!

Cordialement,
Stephen Couban

RESIDENTS RETREAT continued from page 3

the NICU, and **Dr. Christine Chen** from U of T presented on *What's New in CLL*. In addition, the two winners of the 2012 Hematology Medical Education Award presented their project proposals: **Dr. David Sanford** from University of Waterloo presented on *Test Enhanced Learning Project in Hematology* and **Dr. Jovana Yudin** from McMaster University presented on *Resident Remediation*.

The Saturday events concluded with a dinner at a local restaurant, allowing the residents and faculty to relax after a very full day of activities, whilst providing participants a setting to network and to establish contacts for future collaborations.

The final event of the weekend started bright and early on Sunday morning with the morphology exam and teaching session. Using digitally scanned blood and marrow films, the morphology exam is comprised of 30 slides viewable by an online program developed by **Dr. Doug Tkachuk**.

Following completion of the exam, slide content was reviewed in a very popular morphology teaching session by **Dr. David Barth**, University of Toronto hematopathology.

In conjunction with the activities of the Hematology Retreat weekend, an online mock written examination was offered to all residents in early July with results analyzed by PGY year and university to provide residents and program directors with serial, formative feedback.

The Hematology Resident Retreat was founded and is organized by Drs. Christine Chen and Gena Piliotis, U of T educators. It has grown immensely over the seven years since inception with over 80 residents and 40 faculty from across the country participating this year.

We thank CHS for support of our Education Award and our industry sponsors: **Roche, Janssen, Alexion, Merck, Amgen, Celgene, Novartis,** allowing us to provide resources, venue, and free hotel accommodation

Participants at the 7th Annual Hematology Resident Retreat, held July 19-21, 2013 in Toronto, organized by Drs. Christine Chen and Gena Piliotis, University of Toronto.

Do you know the diagnosis?

A 22 year-old woman presented with pancytopenia [Hemoglobin 75 g/L, WBC 1.0 x 10e9/L(neutrophils 0.2, lymphocytes 0.6, monocytes 0.2) and platelets 18 x 10^9/L], having just had a spontaneous abortion at 11 weeks gestation.

- Bone marrow examination showed less than 10% cellularity with no dysplasia, no increase in blast cells and no abnormal infiltrates.
- Chromosomal analysis is shown in Panel A ***(next page)***.
- She was treated with oral Cyclosporine 200 mg twice daily and horse anti-thymocyte globulin (ATGAM) IV daily for four days.
- Over the next four months, her blood counts slowly improved and she became red cell/platelet transfusion-independent.
- Beginning at one year, the Cyclosporine was tapered and at two years from diagnosis, it was discontinued.
- Three months after stopping the Cyclosporine, her hemoglobin was 116 g/L, WBC 4.1, Neutrophils 1.7 and platelets 135.
- Blood counts were monitored monthly and were stable until 9 months later when her CBC showed: hemoglobin 94 g/L, WBC 2.8, Neutrophils 0.7 and platelets 48.
- Peripheral blood flow cytometry revealed a 4.5% GPI-deficient (PNH) clone in the neutrophils.
- A repeat bone marrow exam showed 25% cellularity with no dysplasia, increase in blast cells or abnormal infiltrate.
- Repeat chromosome analysis is shown in Panel B ***(next page)***.
- ***What is the diagnosis?*** ***… SEE PAGE 14***

Panel A

Panel B

HISTORY CORNER

CSH and ASH meet in San Diego to prepare for ISH in Montreal

Photograph and historical details provided by Dr. G. Ross Langley

The year was 1977 and the Canadian Society of Hematology had been awarded the opportunity to host the next plus one meeting of the International Society of Hematology of which Dr. Maxwell M. Wintrobe was President.

Pictured to the left are the Presidents and Vice -Presidents of the CSH and ASH and the Secretary of ASH. FROM LEFT: Thomas Bradley, Ross Langley,[1] Samuel Rapaport,[2] Bernard Cooper[3] and Ernest Beutler[4]. (Missing from the photograph is Dr. Maxwell M. Wintrobe,[5] President of ISH, who later joined the meeting).

The financial resources necessary to prepare for this first ever meeting of ISH in Canada were daunting to the Canadians. When ASH was contacted for advice, their President, **Sam Rapaport** suggested a breakfast meeting at the ASH annual meeting in San Diego.

The counsel of Dr. Wintrobe was felt to be essential and he was subsequently invited to the second day of meetings to help resolve an important issue. That problem was resolved permitting ASH to fully participate and a successful ISH meeting in Montreal was held.

[1] **Dr. G. Ross Langley** received his MD from Dalhousie University in Halifax, NS in 1957. After obtaining his fellowship in Hematology from the University of Melbourne, he returned to Dalhousie University where he became the Head of the Department of Medicine and practiced hematology for 46 years. He retired in 2007 with a Hematology Lectureship subsequently named in his honour and is a Professor Emeritus of Medicine at Dalhousie.

[2] **Dr. Samuel I. Rapaport** was born in Los Angeles, CA, received his undergraduate degree from UCLA and then his MD from USC in 1945. He founded a clinical and research coagulation laboratory at Long Beach VA. He played a key role in the development of the American Society of Hematology, acting as one of its Presidents, and went on to establish a Hematology Division at USC in 1974. He became the Chief of Medicine at the VA San Diego, retiring in 1996. He died in December 2011 at age 90.

[3] **Dr. Bernard Cooper** graduated from McGill University in 1953 and became a Hematologist at the Royal Victoria Hospital in Montreal. He worked there until 1991 when he took a sabbatical with the eminent transplant physician, the late Dr. Karl Blume, at Stanford University. Dr. Cooper enjoyed Palo Alto, CA so much that he moved there in 1993 to work in a Hematology/Oncology practice and was an Emeritus Clinical Professor of Medicine (Hematology) until his recent retirement. He and his wife continue to live in Palo Alto.

[4] **Dr. Ernest Beutler** was born in Berlin, Germany with his family emigrating to the United States in 1935 to escape Nazi persecution. Raised in Milwaukee, he was enrolled at the University of Chicago at age 15. At age 21, he was the valedictorian of his 1950 medical school class. Following residency, he joined the US Army, spending time investigating anemia produced by anti-malarial drugs. Dr. Beutler identified G6PD deficiency as the defect that led to red cell lysis under stress. He helped describe X-inactivation as the basis for tissue mosaicism in female mammals and became interested in iron metabolism and other hemolytic anemias. Dr. Beutler was the first to attempt pharmacologic modification of fetal hemoglobin levels in sickle cell disease and was integral in the development of 2-chlordeoxyadenosine (2-CDA). He was the editor of Williams Hematology and another Past President of ASH. Dr. Beutler became the Chairman of Medicine at City of

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RK SMILEY RESEARCH AWARDS: 2013 WINNERS

Dr. Nathalie A. Johnson

The Role of FAS Mutations in Chemotherapy-Resistant Lymphomas.

Dr. Nathalie A. Johnson, Jewish General Hospital, Montreal, QC.

The investigators note that one in 30 Canadians are diagnosed with lymphoma and only ~50% are cured of the disease. FAS is the prototypical death receptor and once activated by FAS ligand, initiates the apoptotic pathway. FAS gene mutations are uncommon in lymphomas at diagnosis but are found in ~20% of lymphomas at the time of relapse. This study involves transfection of a murine lymphoma cell line with either FAS Y232* mutant or FAS wild-type; changes in tumour growth and response to Doxorubicin will be monitored using 3D ultrasound. B and T cells involved in the immune response will also be evaluated for changes in FAS and FASL.

White Matter Integrity and Neurocognition in Sickle Cell Patients.

Dr. Isaac Odame, Hospital for Sick Children, Toronto, ON.

Dr. Isaac Odame

Ischemic white matter events are thought to lead to cognitive morbidity in children with sickle cell disease (SCD). The researchers have previously shown in a retrospective study that subtle white matter changes in the right frontal lobe of SCD patients predicted for impaired processing. The current study is designed to prospectively identify behavioural and imaging correlates in a longitudinal fashion. Ten patients with SCD and 10 healthy sibling controls will undergo Diffusion Tensor Imaging (DTI) to determine the structural integrity across 12 regions of white matter. Participants will also have neurocognitive assessments performed. The objective of the study is to develop a better understanding of the mechanics of cognitive impairment in SCD to allow for the introduction of effective interventions.

Dr. Brent Williams

Treatment of AML Xenografted Mice with CD16+NK-92 and Anti-CD123 Antibody.

Dr. Brent Williams, University Health Network, Toronto, ON

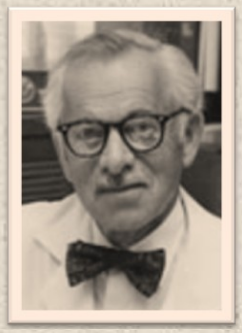
The investigators have previously shown that NK-92, a permanent NK cell line, preferentially kills leukemic stem cells. Furthermore, they have also demonstrated that a gene-modified variant of NK-92 that expresses CD16 can enhance killing of CD123+ targets (leukemic stem cells) coated with a murine anti-CD123 antibody (7G3). In murine experiments, an 8 mcg dose of 7G3 improves survival of AML xenografts treated with CD16+ NK-92 but higher doses have been associated with significant toxicity. The proposed study will focus on finding the dose of 7G3 that will optimize survival in AML xenografts.

HISTORY CORNER

CSH and ASH continued from page 6

Hope Medical Center in 1959 and assumed the Chairmanship of the Department of clinical Research at the Scripps Clinic in 1979, which he maintained until his death in 2008.

[5] **Dr. Maxwell M. Wintrobe** was born in 1901 in Sanok, Poland, (then part of the Austrian Empire). The family immigrated to Halifax, Nova Scotia in 1906 as his mother (whose maiden name was Zwerling) had four brothers living in that city at that time. In 1912 the family moved to Winnipeg, Manitoba and Dr. Wintrobe began his studies at the University of Manitoba at age 15. He went on to graduate from the Faculty of Medicine in 1926 of the University of Manitoba. During his second year of medicine, to improve his finances, he took a job in the hospital's blood bank. He told Dr. Herbert L. Fred MD, MACP, that working in the blood bank "was the spark that ignited his passion for hematology." He moved to the US



Dr. Maxwell M. Wintrobe
(1901—1986)

to continue his studies and obtained a PhD from Tulane University in New Orleans, LA. He became a faculty member at Johns Hopkins University but moved to Utah in 1943. Dr. Wintrobe became the first Chairman of the Department of Medicine at Salt Lake County General Hospital where he did research in hereditary, metabolic and cardiovascular disorders. He pioneered the measurement of MCV, MCH and MCHC and was involved in the early work in pernicious anemia, copper metabolism and cancer chemotherapy. He was the editor of Clinical Hematology from its inception in 1942 until he retired in 1965. Dr. Wintrobe died in December 1986.

ASK THE HEMATOLOGIST

CASE 1: Upper extremity deep vein thrombosis

Dr. Erica Peterson

CASE 1: **A 58 year-old man, with a history of IgG kappa multiple myeloma, presented one year post-autologous stem cell transplantation with pain in his left upper arm that began after he slipped in the shower and grabbed a handrail. X-ray showed a pathologic fracture of the left humeral neck in the area of a new lytic lesion.**

Blood work showed a mild anemia (100 g/L) and azotemia (serum creatinine 140 µmol/L, creatinine clearance (CrCl) 39 mL/min) with a rising serum IgG M-protein.

He required open reduction and internal fixation of the humeral fracture and was started on Lenalidomide 10 mg daily for three out of every four weeks and Dexamethasone 40 mg once weekly, ASA was added for venous thromboembolism (VTE) prophylaxis.

At his first follow-up appointment three weeks later, he complains of increased swelling of his left upper extremity from the shoulder down to the hand. Doppler ultrasound revealed thrombosis of the left subclavian vein lateral to the entrance of the cephalic vein with extension into the medial aspect of the axillary vein.

The Thrombosis Service was asked to review the patient.

Dr. Erica Peterson *is a Hematologist who trained in Vancouver. She is currently doing a Thrombosis Fellowship at Vancouver General Hospital.*

Upper extremity deep vein thrombosis (UEDVT), defined as thrombus involving the subclavian, axillary and/or brachial veins, accounts for only 10% of all DVTs.

Reported complications of UEDVT include symptomatic pulmonary embolism (PE) in 2 -9%, recurrence at 12 months in 2-4% and post-thrombotic syndrome (PTS) in 7-47% of affected individuals.[1] Thus, the goals of therapy in patients with UEDVT are not only to alleviate symptoms and prevent DVT extension, but also to reduce the risk of PE and PTS.

Limited evidence exists for initial and long-term management of UEDVT; therefore treatment recommendations are extrapolated from studies of lower extremity DVT.

Acute treatment of UEDVT consists of parenteral anticoagulation with low molecular weight heparin (LMWH), fondaparinux or unfractionated heparin (UFH).[2,3] Catheter directed thrombolysis may be considered in selected patients with severe symptoms, acute DVT onset and low bleeding risk.[2]

Anticoagulation should be continued for a minimum of 3 months. Extending anticoagulation beyond 3 months is recommended if ongoing risk factors for recurrent VTE, such as active cancer or an indwelling catheter, are present.[2,3]

In cancer patients, the anticoagulant of choice for initial and long-term treatment is LMWH, as this agent is more efficacious than vitamin K antagonists (VKA), does not require monitoring and has no drug or dietary interactions.[3,4]

For case 1, a symptomatic UEDVT was diagnosed in the setting of active malignancy, ongoing chemotherapy and

continued , following page

recent humeral fracture with impaired mobility of the affected limb. In the absence of active bleeding, anticoagulation with weight-based LMWH should be initiated.

Although the UEDVT occurred in conjunction with a transient risk factor, the patient has continuing risk factors for recurrent VTE (active cancer, chemotherapy) and would therefore benefit from extended anticoagulation.

Regular follow-up should be scheduled every 3-6 months to review the risk/benefit ratio of ongoing anticoagulation.

The underlying renal dysfunction poses a therapeutic challenge in this case. Impaired renal excretion of LMWH seen in patients with significant renal insufficiency (defined as a CrCl <30 mL/min) can lead to bioaccumulation of active drug.

The degree of bioaccumulation observed is dependent on the LMWH formulation. For example, enoxaparin demonstrates significant bioaccumulation and leads to increased bleeding risk, while little or no bioaccumulation is seen with tinzaparin.[5] Therefore, in patients with a CrCl <30 mL/min, consensus guidelines recommend dose-adjustment of LMWH based on anti-Xa levels.[3,4]

As our patient has a CrCl of 39 mL/min, LMWH can be initiated without dose-adjustment; however, close monitoring of the renal function is required. Should the CrCl drop below 30 mL/min, the LMWH dose should be adjusted based on manufacturer recommendations and anti-Xa levels.

If anti-Xa monitoring is unavailable, parenteral anticoagulation with UFH with bridging to a VKA would be the preferred option. Although our patient currently has a normal platelet count, thrombocytopenia is a well-recognized complication of lenalidomide treatment.

Full weight-based LMWH is recommended in patients with a platelet count >50 x 10^9/L.[6] If the platelet count drops to 25-50 x 10^9/L, LMWH should be reduced by 50% or to a prophylactic dose depending on an individualized assessment of bleeding risk. LMWH should be held in patients with a platelet count <25 x 10^9/L.

In patients with extensive acute DVT, transfusion support to allow ongoing anticoagulation is an alternate option.

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CASE 2: Large B-cell lymphoma

Dr. Alina S. Gerrie

A 50 year-old man presented with a two-week history of severe left upper quadrant pain such that he is unable to work, associated with early satiety and a 5 kg weight loss.

A CT scan of the abdomen showed an 18 cm abdominal mass with associated retroperitoneal lymphadenopathy.

CBC was normal but serum lactate dehydrogenase was elevated. HIV testing was negative.

Ultrasound-guided biopsy of the mass was felt to show diffuse large B-cell lymphoma, CD10+, with a Ki-67 proliferative rate of 95% but the EBV RNA stain was negative.

Immunostains were positive for BCL2; MYC staining was not performed. Imaging revealed lymphadenopathy within the neck, axillae and mediastinum with a bone marrow biopsy showing a single paratrabecular aggregate of small lymphoid cells that were CD10, CD20 and kappa light chain-restricted.

Further examination of the tissue taken from the abdominal mass revealed an *IGH/BCL2* rearrangement and a *MYC* rearrangement that did not involve *IGH*.

The Lymphoma Service was asked to review this patient.

Dr. Alina Gerrie *is a Hematologist with the Leukemia/BMT Program at Vancouver General Hospital and the Lymphoma Tumour Group at the BC Cancer Agency. She was a winner of a CHS Resident Research Award in 2010 for her work on FISH analysis in chronic lymphocytic leukemia.*

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype and is curable in over 60% of patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP). Discordant marrow involvement is detected in approximately 7% of DLBCL cases and its negative impact is encompassed within the International Prognostic Index (IPI).[1] This patient had bulky stage 4A discordant DLBCL with indolent B-cell lymphoma in the marrow. Based on a high-intermediate risk IPI score of 3 (ECOG performance status 2, elevated lactate dehyrogenase, and stage 4), his predicted 3-year overall survival (OS) approached 65% in the rituximab era.[2] Furthermore, he had germinal centre-type (GCB) DLBCL (CD10+), which is associated with improved outcomes compared to non-GCB DLBCL.

Additional genetic analysis in this case, however, revealed concerning findings. BCL2 overexpression in the context of GCB-DLBCL is associated with inferior survival among patients treated with RCHOP.[3] In GCB-DLBCL, BCL2 overexpression is generally due to a translocation between *IGH* on chromosome 14q32 and *BCL2* on chromosome 18q21 [t (14;18)], detected in one-third of DLBCL cases. Indeed, our patient has an *IGH/BCL2* rearrangement. This translocation as a sole abnormality does not negatively impact outcomes; however, our patient also harboured a *MYC* rearrangement. *MYC* rearrangements, the hallmark of classical Burkitt lymphoma (BL), are detected in 5-14% of DLBCL cases and are associated with inferior outcomes independent of the IPI. In one series, *MYC*-rearranged DLBCL cases had a 2-year OS of 35% versus 61% in the non-rearranged group.[4]

continued , following page

The combination of dual translocations of *BCL2* and *MYC* is termed "double-hit lymphoma" (DHL), detected in up to 10% of non-Hodgkin lymphomas.[5] *MYC* translocations involve a non-*IGH* partner in nearly half of cases.

MYC protein overexpression by immunohistochemistry can identify additional patients with *MYC*-driven DLBCL; however increased MYC protein appears to be predictive of outcome only if associated with concurrent BCL2 overexpression.[6]

Patients with DHL have a very poor outcome when treated with standard RCHOP chemotherapy, with median survival less than 2 years.[5] Alternative regimens are urgently needed.

One strategy may be to employ similarly aggressive therapies as those used in BL, such as CODOX-M/IVAC combined with rituximab; however this approach has not been prospectively studied in DHL patients. Dose-adjusted EPOCH -R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab) has shown promising activity in BL and is currently being evaluated in a US Intergroup trial in patients with *MYC*-driven DLBCL, including DHL.[5]

Novel targeted agents such as ABT-263 (BCL2 inhibitor) and enzastaurin (PKCβ inhibitor), among others, are being tested in clinical trials in DLBCL patients. The utility of consolidative autologous stem cell transplantation (ASCT) after standard chemotherapy for DLBCL patients is inconclusive, although a recent phase III US/ Canadian Intergroup trial has shown a benefit in both progression-free and overall survival in the subgroup of patients with high-risk IPI.[7]

There is no standard therapy for DHL; however given the dismal outcomes with RCHOP, it is clear that alternate regimens are needed, even outside a clinical trial.

Since 2003, the BC Cancer Agency has adopted the use of intensive chemotherapy with CODOX-M/IVAC+R followed by high-dose chemotherapy and ASCT as definitive treatment for eligible DHL patients, including for the patient presented above.

Given the discordant indolent lymphoma in the marrow in this case, an allogeneic transplant may be favoured if a suitable matched donor is identified.

An alternate strategy, particularly for elderly patients with DHL, is to consider dose-adjusted EPOCH-R since it has demonstrated activity in BL and is well tolerated.[5]

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The Lymphoid Cancer Families Study

Ruth Thomas
and
Dr. Angela Brooks-Wilson
BC Cancer Agency, Vancouver, BC

The Lymphoid Cancer Families Study is a research study focused on identifying genetic risk variants for lymphoid cancers such as *Hodgkin Lymphoma, non-Hodgkin lymphoma, myeloma or lymphocytic leukemia.*

As a group, lymphoid cancers comprise the 5th most common type of cancer [1,2]. The lifetime risk of developing a lymphoid cancer is over 3% [3], and the outcome is frequently poor. Different lymphoid cancers are sometimes observed in several individuals in the same family[4].

The overrepresentation of lymphoid cancers in some families suggests the existence of common susceptibility factors, including shared genetic factors. Genetic factors that convey risk of lymphoid cancers remain largely unknown.

The Lymphoid Cancer Families study is analyzing families where two or more individuals have been diagnosed with a lymphoid cancer. Over 230 families with 2 to 7 relatives with lymphoid cancer have been referred to the study. Participation consists of subjects answering questions regarding health and family history by telephone interview, providing a blood or saliva sample, and providing contact information for close relatives interested in participating.

BC Cancer Agency
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An agency of the Provincial Health Services Authority

It is possible for family members to participate even if they don't live near their relatives, if they live in another country, or if most of their affected relatives are no longer living.

The study takes a multidisciplinary approach involving researchers from the Genome Sciences Centre and the Centre for Lymphoid Cancer, clinicians and pathologists at the BC Cancer Agency and a genetic counselor.

We are still actively recruiting families.

If you have a patient or a family that meets the criteria for this study or would like to learn more about the Lymphoid Cancer Families Study, please contact the Project Coordinator, Ruth Thomas, at 604-675-8172 or at rthomas@bcgsc.ca

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Time for a new CHS board

The time has come around again when Canadian Hematology Society members are being asked to consider nominations to the Executive Committee.

In accordance with the CHS Bylaws, a three-member Nominating Committee, Chaired by the Immediate Past-President is being organized to prepare a slate of nominees.

Nominees must give consent to having their names put forward. The head office will distribute the nomination list, compiled by the committee, at least one month before the Annual Meeting, which is to be held during ASH on Sunday, December 7, 2013, at the W Hotel in New Orleans. (*Watch the next issue of the Microenvironment for more details about the December events.)*

Please note that further nominations may be submitted in writing to the Secretary-Treasurer, if signed by five active members and accompanied by the written consent of the nominees.

The current board appointments were made as follows:

President	**Dr. Stephen Couban**	**Dec. 2011—Dec. 2013**
Past-President	**Dr. Tom Nevill**	**Dec. 2011—Dec. 2013**
Vice-President	**Dr. Aaron Schimmer**	**Dec. 2011—Dec. 2013**
Secretary-Treasurer	**Dr. Molly Warner**	**Dec. 2011—Dec. 2014**

According to the Bylaws, the elections for President and Vice-President are held every two years, whereas that of Secretary-Treasurer is every three years.

As the Vice-President will become President, **only one position, that of Vice-President is open at this time**. Nominations or suggestions for the nominating committee should be sent to the Head Office at **canadianhematology@uniserve.com**

The Microenvironment

Your
Canadian Hematology
Society
NEWSLETTER

Member Submissions Welcome!

C H S C H

Reminder - Save the Date

CHS AT ASH

Sunday, December 8, 2013
New Orleans

CHS ANNUAL RECEPTION, DINNER AND AWARDS EVENING
at the W Hotel

only 3 blocks from the Congress Centre
& steps from the famous French Quarter.

UPCOMING EVENTS

CHS Annual Reception, Dinner & Awards Evening
Sunday, December 7, 2013
New Orleans Contact: www.cbmtg.org

ASFA & WAA Joint Congress
April 2—5, 2014
San Francisco Contact: asfa@apheresis.org

Canadian Apheresis Group and Canadian Association of Apheresis Nurses Annual General Meeting and Scientific Sessions
June 13—15, 2014
Halifax, Nova Scotia Contact: cag@cagcanada.ca

Canadian Blood and Marrow Transplant Group Annual Conference
June 11—14, 2014
Halifax, Nova Scotia Contact: www.cbmtg.org

International Society of Thrombosis and Haemostasis (ISTH) 25th World Congress
July 11—17, 2015
Toronto, Ontario

...from Pages 4 & 5:

The DIAGNOSIS? Answer:

- This woman has developed a monosomy 7 bone marrow clone following immunosuppressive treatment for severe aplastic anemia (i.e. myelodysplastic syndrome).
- Although this would predict for a poor response to immunosuppression, she was restarted on Cyclosporine 200 mg twice daily.
- Over the next few months, her blood counts deteriorated. She did not have a matched sibling and an unrelated donor search was commenced.
- Unfortunately, 5 months into her second course of immunosuppression, she developed acute myeloid leukemia and was treated with Cytosine arabinoside and Daunorubicin ("7+3").
- She was refractory to induction chemotherapy and subsequently died of pneumonia.

Fellowships

Thrombosis Fellowship 2012-2013 Jewish General Hospital, McGill University

The JGH Thrombosis Program is currently accepting applications for a one year fellowship (July 1, 2014—June 30, 2015) to acquire and consolidate expertise in Thrombosis. Specific areas of clinical activity include the Thrombosis Clinic, Anticoagulation Clinic and In-patient Thrombosis Consultation Service. Our Thrombosis Program also encompasses a broad range of research activities that relate to diagnosis, risk factors and treatment of venous and arterial thromboembolic disease.

Jewish General Hospital

For information, please contact:

Dr. Susan Kahn
514-340-7587
susan.kahn@mcgill.ca

Thrombosis Clinical & Research Fellowships - Up to 3 positions

Applications are encouraged from MDs who have completed or who will complete General Internal Medicine, Respirology and/or Hematology training. Foreign medical graduates with equivalent qualifications are eligible.

Applicants may apply to one of three training streams:
1.) Clinical Fellowship, one-year—To consolidate expertise in thrombosis.
2.) Clinical and Research Fellowship, 2-3 years (to become a clinician investigator in thrombosis (Fellows enroll in the Master's of Clinical Epidemiology Program at the University of Ottawa).
3.) Clinical and Education Fellowship, 2-3 years (to become a clinician educator in Thrombosis. (Fellows enroll in a Master's in Education).

To apply, please contact:
nlanglois@ohri.ca

THE OTTAWA HOSPITAL
L'HÔPITAL D'OTTAWA

Details are also available on the CHS website.

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

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

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

The Microenvironment

August 2013

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 its founding 40 years ago in 1971. Our society now has over 300 members.

Active Membership is open to physicians engaged in the practice of clinical or laboratory hematology in Canada and to any persons doing scholarly research in hematology in Canada.

In appropriate cases, the requirement for a university degree or other qualifications may be waived if in the opinion of the Executive Committee the candidate is making significant continuing contributions to science.

We welcome residents and fellows in approved university training programs in hematology or hematological pathology as ***Associate Members***. Associate members will not be required to pay dues until the completion of training.

Emeritus Membership is open to individuals at the age of 65 or those who were active members and request a transfer of status with adequate reason. Emeritus members will not be required to pay a membership fee.

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 ...

to please remit your 2013 Annual Dues. **Your $75. annual dues payment** may be made online at the CHS website: **www.canadianhematologysociety.org**

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

Please provide the following information with your payment:

2013 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: _____