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Message from the President

Dear Colleagues,

It was wonderful to see many of you at the CHS Reception at the ASH Meeting in Atlanta in December, 2012. The reception, the business meeting and the awards dinner were all well attended and it was heartening to see both familiar faces but also many new members!

In this issue, the CHS Abstract Award winners are highlighted. The encouragement, support and acknowledgement of the academic accomplishments of trainees and junior faculty remains a key focus and effort of the Canadian Hematology Society. Congratulations again to all the winners!

As announced at the CHS Reception, we are keenly waiting to hear whether Vancouver will be chosen as the venue for the 2018 ISH meeting. Tom Nevill, Gail Rock and the CHS Administrative Team have submitted a very strong bid!

The CHS Executive will be holding a retreat later in the Spring. We are considering having a CHS Reception and Awards presentation without a full dinner at ASH 2014 and are eager to hear from the membership on this issue.

continued on page

2013 CHS Executive Committee

President Dr. Stephen Couban
Past-President & Editor, The Microenvironment Dr. Tom Nevill
The Microenvironment Dr. Aaron Schimmer
Vice-President Dr. Molly Warner
Secretary Treasurer Dr. Gail Rock
Executive Vice-President
Another important issue is that we are often asked by third parties to distribute information to our members. Some requests, such as the announcement of openings and opportunities for hematologists, seem very reasonable and we have always supported these announcements. Other requests, particularly with respect to promotional material for a medication or a commercial event, present more questions. While we very much want to serve the needs of our members, we don't want to become a conduit for unreviewed promotional material. Again, the thoughts and feedback of our members would be very much appreciated.

Thanks for continuing to support the CHS!  Stephen Couban

Message du Président

Chers Collègues,

C’était merveilleux de voir beaucoup d’entre vous à la Réception SCH à la Réunion SAH à Atlanta en décembre 2012.

La réception, la réunion d’affaires et le dîner de remise des prix ont attiré un nombre considérable de personnes et c’était encourageant de voir des visages familiers ainsi que beaucoup de nouveaux membres!

Dans ce numéro, les gagnants du Prix Abstract de la SCH sont présentés. L’encouragement, le soutien et la reconnaissance des réalisations universitaires des stagiaires et des professeurs débutants demeurent l’objectif central et l’effort de la Société Canadienne d’Hématologie. Encore une fois félicitations à tous les gagnants!

Tel qu’annoncé lors de la Réception SCH, nous attendons de savoir si Vancouver sera choisi comme lieu pour la réunion ISH de 2018. Tom Nevill, Gail Rock et l’Équipe Administrative de SCH ont soumis une candidature très solide!

Le Comité Exécutif de SCH organisera une retraite plus tard au cours du printemps. Nous envisageons d’organiser une Réception SCH et de présenter des Prix sans un dîner complet pour l’ASH de 2014 et sommes impatients d’entendre ce que les membres ont à dire sur la question.

Une autre importante question est que de tiers parties nous demandent souvent de diffuser les informations à nos membres. Certaines demandes, telles que l’annonce d'opportunités et d’offres pour les hématologues, semblent très raisonnables et nous avons toujours appuyé ces déclarations. D’autres demandes, surtout en ce qui concerne le matériel promotionnel pour un médicament ou un événement commercial, présentent plus de questions.

Alors que nous voulons beaucoup servir les besoins de nos membres, ne nous voulons pas devenir un conduit de matériel promotionnel non révisé. Encore une fois, les pensées et les commentaires de nos membres seraient très appréciés.

Merci pour votre soutien constant du SCH!  Stephen Couban
The CHS 2012 Research Awards were presented on December 9, at the Annual Business Meeting, Reception and Awards Gala, which was held during ASH in Atlanta, Ga.

Annette E. Hay, a fellow at the Cancer Research Institute in Kingston, Ontario, was the winner of the most prestigious of the five awards—the John H. Crookston Award. The 2012 winners in the category of Residents & Fellows, Oksana Prokopchuk-Gauk, Hematology Fellow at the Foothills Medical Centre in Calgary, Alberta; and Tyler W. Smith, Thrombosis Fellow (Hematology) at Vancouver General Hospital, BC. In the category of PhD & Postdoctoral, the 2012 winners were Laura L. Swystun, Postdoctoral Fellow at Queens University, Kingston; and Fong Chun Chan, PhD student, BC Cancer Agency, Vancouver. Read more about these five winning entries on the following three pages.

The John H. Crookston Award is presented each year by the Canadian Hematology Society for the best paper given by a resident. It is the most prestigious of the CHS Annual Awards.

This award is named for the late John Hamill Crookston (1922-1987) who was the Laboratory Hematologist-in Chief at Toronto General Hospital and a Professor of Medicine and Pathology at the University of Toronto from 1957 until his death in 1987.
A 45 year-old man presents with fatigue and easy bruising and a CBC shows a hemoglobin of 103 g/L, a WBC of 8.4 x 10^9/L (with 60% blast cells) and a platelet count of 28 x 10^9/L.

Bone marrow aspirate confirms pre-B acute lymphoblastic leukemia with karyotype showing 70% of the metaphases contain t(9;22) and 30% of the metaphases are normal male. He was commenced on Daunorubicin, Vincristine and Prednisone and did not develop any evidence of tumour lysis syndrome. He was afebrile for his first 10 days in hospital and was discharged at that point with daily visits to the Outpatient Clinic planned.

He was given red cell and platelet transfusions prior to discharge and because his WBC count was 0.2, was discharged on Ciprofloxacin, Valtrex and Fluconazole prophylaxis.

The following morning, he called into the Outpatient Clinic with a fever of 39.5 degrees Celsius, a heart rate of 120/minute, a respiratory rate of 30/minute and a blood pressure of 80/40. Blood work was drawn and the ICU was consulted. His peripheral smear from his initial blood work is shown.

Do you know the diagnosis?
Patients who undergo coronary artery bypass grafting (CABG) are at an increased risk of bleeding. Both topical and intravenous anti-fibrinolytic agents have been used to reduce blood loss during and after CABG. In this study, the investigators conducted a prospective, randomized, double-blind trial in 41 patients undergoing CABG. All participants received intravenous tranexamic acid (TXA) prior to initiation of circulatory bypass. In addition, 23 patients were randomized to intraoperative cardiac bath with TXA solution prior to sternotomy closure with the other 18 patients randomized to a normal saline bath (placebo). Mean chest tube blood loss was 632 ml in the TXA group and 789 ml in the placebo group (p=0.049). Further, 72.2% of the placebo group experienced >700 ml blood loss versus only 30.4% of the TXA cohort (p=0.008). Chest tubes remained in situ for similar times in the two groups (TXA 19 hours; placebo 20 hours) and none of the patients on study required post-operative blood transfusions.

This study supports that topical TXA application prior to sternotomy closure reduces post-operative blood loss in patients undergoing CABG. However, it has not yet been established that this relatively simple intervention influences patient morbidity or resource utilization.

The effects of the new oral anticoagulants Dabigatran and Rivaroxaban on standard coagulation assays have been evaluated in the past using normal pooled plasma spiked with known concentrations of drug. In this study, the investigators decided to take actual blood plasma samples from patients on Dabigatran and Rivaroxaban in order to study, while accounting for patient-to-patient variability, the effects of these new anticoagulants on INR, aPTT, thrombin time (TT), protein S/antithrombin levels, dilute Russell’s viper venom times (DRVVT) and factor VIII (FVIII) activity. In the cohort analyzed, 43 patients were on Dabigatran and 10 patients were on Rivaroxaban. The INR in the majority of patients was ≤1.3 although 73% of patients on Dabigatran had an elevated aPTT, albeit most were only mildly elevated. Only one patient on Rivaroxaban had an elevated aPTT. The TT was elevated in all patients on Dabigatran but none of the patients on Rivaroxaban. Dabigatran patients also had falsely elevated protein S and antithrombin levels which was not observed with Rivaroxaban. However, both agents artificially suppressed FVIII activity and frequently prolonged the DRVVT.

The authors have shown in this study that normal INR and aPTT levels in patients on Dabigatran and, especially Rivaroxaban do not necessarily indicate lack of therapeutic anticoagulation effect. It is also clear that clotting-based thrombophilia testing can be influenced by the use of these newer anticoagulants.
2012 CHS PhD and Post-Doctoral Fellow Awards

Large-scale high resolution integration of copy number and gene expression in DLBCL reveals focal and frequent deletions in chromatin modifying genes with outcome correlation

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(Supervisor: Dr. Christian Steidl)

Prognosis for individuals with diffuse large B cell lymphoma (DLBCL) has improved with the incorporation of Rituximab into the newer chemotherapy regimens but still ~1/3 of patients are not cured by this treatment approach. It has been shown that gene expression profiles and copy number help explain some of the heterogeneity in clinical outcomes in DLBCL. The investigators in this study sought to integrate gene expression profiles and copy number in 151 DLBCL patients and then to correlate these results with clinical outcome. All subjects were treated at the BC Cancer Agency with R-CHOP-like regimens and pre-treatment biopsies underwent Affymetrix SNP 6.0 microarray and DriverNet analyses to identify key genes and to distinguish functionally relevant from passenger genomic aberrations. The SNP 6.0 microarray analysis revealed hotspots at 3q26-q28 (BCL6, TP63 and TBL1XR1), 17p12 (NCOR1 and MAP2K4), 18q11.1-q11.2 (RBBP8) and 22q11.21 (BID and IL17RA) linking these genomic locations to the pathogenesis of DLBCL. Novel focal deletions were found in the chromatin modifying genes LCOR (8% of patients), RCOR1 (10% of patients) and NCOR1 (19% of patients). DriverNet analysis identified RCOR1 deletions as a main driver alteration. Moreover, RCOR1 deletions were associated with an inferior 5-year progression-free survival (40%) compared to patient without this deletion (75%, p=0.019).

These exciting results move the field closer to understanding the pathogenesis of DLBCL. Perhaps of greater relevance to clinicians is the discovery of a key genetic marker, RCOR1 deletions, which predict for an unfavourable outcome in DLBCL. This provides yet another target for novel therapeutic agents. -ed.

Genetic variability of the CLEC4M endothelial lectin receptor modulates binding and internalization of VWF and contributes to variance in plasma VWF levels

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(Supervisor: Dr. David Lillicrap)

Type I von Willebrand’s disease (vWD) can result from decreased synthesis or increased clearance of von Willebrand’s factor (vWF) with ~1/3 of patients lacking an identifiable vWF gene mutation. Other genes may contribute to the pathophysiology of vWD and, in this study, the investigators focused on C-type lectin domain family 4 member M (CLEC4M) as a gene that had recently been linked to plasma vWF levels in normal individuals. Previous work done in the same laboratory on 555 vWD patients and their families had shown that the most common CLEC4M alleles were VNTR 7 (53% of subjects), VNTR 5 (29%) and VNTR 6 (15%). The current study assessed the binding of vWF to a CLEC4M-Fc chimera using a modified ELISA assay. Results demonstrated that CLEC4M bound to Humate P and recombinant vWF in a dose-dependent manner but there was a 75% decrease in binding with a de-N-glycosylated Humate P (p=0.046). Binding and internalization of vWF by HEK293 cells expressing CLEC4M was assessed by immunofluorescence and ELISA assay. CLEC4M and vWF were shown to co-localize with early endosomal antigen-1, indicating that CLEC4M participates in receptor-mediated endocytosis of vWF. Studies examining the influence of genetic variability of CLEC4M on vWF binding/internalization revealed a 60% reduction with the VNTR 4 allele (p<0.001) and a 45% reduction with the VNTR 9 allele (p=0.006) compared to the common VNTR 7 allele.

This elegant research demonstrates that CLEC4M binds to vWF leading to N-glycan-dependent endocytosis. CLEC4M polymorphisms may well contribute to variations in plasma vWF levels although other genes may still be involved in the pathogenesis of vWD. -ed.
The treatment of multiple myeloma (MM) has been a source of debate for decades. However, following the publication of the results of a pivotal randomized trial in 1996, the gold standard of treatment for MM has been high-dose chemotherapy and autologous stem cell transplant (ASCT). At the present time, international standards recommend an age limit of 65 years for ASCT in MM. This criterion is based upon evidence that survival following ASCT decreases with age leading to the suggestion that outcomes in MM patients do not warrant this intervention beyond the age of 65 years. Bearing in mind the median age of diagnosis in MM is 69 years for males and 72 years for females, this age limit creates a significant gap in the myeloma treatment algorithm. Taking into account the demographics of MM, a review of the literature was undertaken to assess the impact of patient age on survival after ASCT. The clinical question to be addressed was: How does ASCT influence survival in patients older than 65 years of age when compared to younger patients?

Studies by Reece et al and by O’Shea et al examined prognostic factors for outcome in MM patients that underwent high-dose chemotherapy and ASCT. Median age of patients in these studies was 63 years (range 60–73) and 56 years (range 26–72), respectively. Pre-transplant characteristics evaluated for influence on progression-free survival (PFS) and overall survival (OAS) included patient age, serum B2-microglobulin (B2M) level, MM isotype, time from diagnosis to ASCT, number of prior lines of chemotherapy and disease status at time of ASCT. Notable, is the lack of reliable cytogenetic data in both studies as this has become a key prognostic variable in multiple myeloma.

The Reece study involved a comparative analysis of IBMTR registry data for 382 patients age <60 years and 110 patients age ≥60 years that underwent ASCT for MM between 1994 and 1998. The two groups were similar in disease features aside from higher B2M levels in the age ≥60 years cohort. The day+100 treatment-related mortality (TRM) was 6% in patients age <60 years and 5% in the older cohort (Figure 1). While 3-year PFS was higher in the younger cohort (44% vs. 35% in patients ≥60 years), this difference was not significant (p=0.16) and the 3-year OAS was comparable (55% vs. 58%, respectively) (Figure 2).

The O’Shea study reported results from a single institution, Hammersmith Hospital, on 211 MM patients that received high-dose therapy with ASCT between 1994 and 2004. The entire cohort had a TRM of only 1.4% and age was not predictive of OAS in univariate or limited multivariate analysis.

What emerged as a common theme in both the O’Shea and the Reece study was that other variables such as serum B2M, time from diagnosis to ASCT, pre-treatment and disease status at ASCT are more important determinants of PFS and OAS in MM patients. Both studies concluded that select older MM patients (>60 years) could experience the same benefit with ASCT as younger patients (<60 years).

Based on the available evidence,
**STUDENT RESEARCH, cont’d from page 7**

chronological age should not be considered an absolute exclusion criterion for ASCT. The treatment choices in MM patients should rather be guided by "biological" age,² taking into account medical co-morbidities and performance status, and other disease-related factors that have previously been shown to result in unfavourable ASCT outcomes.³,⁴ Although it may be that chronological age does impact outcome following ASCT in MM, review of the relevant literature suggests that age should not be considered as the main determinant of whether an individual patient will benefit from this procedure. **Acknowledgements:** Special thanks to Dr. Sudeep Shivakumar for his guidance and editorial work. **References:** (continued from Student Research, Page 7)


**Norman Bethune: A blood transfusion innovator**

Henry Norman Bethune was born on March 4, 1890, in Gravenhurst, Ontario, where his father was a pastor. Despite this inauspicious beginning, he actually belonged to a prominent Scottish Canadian family.

His great-great grandfather, John Bethune, established the first Presbyterian Church in Montreal in 1786 (and was also the great-great grandfather of famous actor Christopher Plummer).

His great grandfather, Angus Bethune was an explorer and fur trader for the Hudson’s Bay Company and was later elected to Toronto City Council as an alderman. His grandfather, also Norman Bethune, was a physician trained at Guy’s Hospital in London, England and became a founder of the Upper Canada School of Medicine, which was ultimately incorporated into Trinity College, Toronto in 1849.

Norman Bethune graduated from Owen Sound Collegiate Institute in 1909 and enrolled at the University of Toronto to study medicine. He interrupted his education to become a stretcher bearer with the Canadian Army during WW I. He was wounded and spent three months in hospital before returning to Toronto to obtain his MD in 1916.

In 1917, Bethune joined the Royal navy as a Surgeon-Lieutenant in England where he met a Scottish woman, Frances Penny. They married in 1924 and moved to Detroit, Michigan where he took up private practice and instructed at a local medical school.

In 1926, he contracted tuberculosis and was institutionalized in Trudeau Sanitorium in New York State. His health remained poor until he insisted on having a radical new treatment, induced pneumothorax, which led to Bethune’s complete recovery.

In 1929, Bethune joined Dr. Edward Archibald, a pioneering thoracic surgeon, at the Royal Victoria Hospital in Montreal.

Over the next seven years, he became an exceptional thoracic surgeon, developing more than a dozen new surgical tools as well as publishing 14 articles on his surgical innovations. It was also during this time period, in the midst of the Great Depression, that Bethune became increasingly concerned about the socioeconomics of disease. He lobbied the Canadian government for medical care reform and was a strong proponent of socialized medicine. In 1935, he travelled to the Soviet Union to learn from their system of health care delivery and upon his return, joined the Communist Party of Canada.

Following the outbreak of the Spanish Civil War in 1936, Bethune conceived his greatest hematologic innovation. He was intrigued by the fact that soldiers with relatively minor injuries were dying of hypovolemic shock secondary to blood loss. Bethune decided to administer blood transfusions to soldiers in the field of battle, organized a blood donor service, developed the world’s first mobile medical unit [the precursor of the mobile army surgical hospital (“MASH Unit”)] and saved countless lives.

Although Bethune returned to Canada for 6 months in June 1937, he left again in January 1938. On this occasion, he
travelled to Yan’an, China to organize medical services for the Chinese communists, led by Mao Zedong, in their battle against Japanese invaders.

There, he performed emergency battlefield surgery and also trained doctors, nurses and orderlies.

While stationed with the Communist Party’s 8th Route Army in Huang Shiko, China, Bethune suffered a finger laceration while operating without gloves and developed septicemia.

He died on November 12, 1939 at the age of 49 and is buried in the Revolutionary Martyrs’ Cemetery in Hebei Province, as is Reverend Eric Liddell, the Scottish sprinter of Chariots of Fire fame, who died in a Japanese POW camp.

Dr. Norman Bethune was little known in Canada during his lifetime but became an iconic figure in China primarily due to praise from Mao Zedong. Mao brought Bethune to international prominence by publishing an essay entitled “In Memory of Norman Bethune”.

In it he wrote “Comrade Bethune’s spirit, his utter devotion to others without any thought of self, was shown in his great sense of responsibility in his work and his great warm-heartedness towards all comrades and the people.”

Chairman Mao made this essay required reading in Chinese elementary schools during the Cultural Revolution in the 1960s and it remains so today.

Numerous statues of Bethune have been erected in China and the Norman Bethune University of Medical Sciences was founded in Jilin, China. The Norman Bethune Medal is the highest medical honour in China and is awarded for outstanding contributions in the medical field.

It was only after Prime Minister Pierre Trudeau’s visit to China in 1973 that the Canadian government purchased Bethune’s original house in Gravenhurst and opened it to the public 3 years later as a National Historic Site. In March 1990, both Canada and China issued postage stamps commemorating the 100th anniversary of Bethune’s birth.

In 1998, Norman Bethune was inducted into the Canadian Medical Hall of Fame.

The Bethune Memorial House, (AFTER) a National Historic Site of Canada in Gravenhurst, Ontario, Canada, commemorates the life and achievements of Dr. Henry Norman Bethune.

The house was built in 1880 to serve as the manse of Knox Presbyterian Church. Malcolm Bethune became the minister of Knox Church in 1889 and, a year later, his son Norman was born in the manse.

The Bethune family remained in Gravenhurst until 1893 when they moved to Beaverton, Ontario. Thereafter, the house was occupied by a succession of ministers.

In 1973 the house was purchased by the federal government's Department of External Affairs. Restoration of the building was subsequently undertaken by Parks Canada, which is now responsible for its operation.
Advances in the use of bortezomib (Velcade®)
in the treatment of newly diagnosed multiple myeloma

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Introduction
Multiple myeloma (MM) is a hematologic neoplasm characterized by the proliferation of malignant plasma cells. While still an incurable disease for the overwhelming majority of patients, the last decade has seen significant improvements in our understanding of the molecular biology of myeloma and in treatment outcomes. These discoveries have been translated to patient care as we now routinely identify molecular and genetic abnormalities found in patients’ myeloma cells and use these data for risk stratification, prediction of the natural history of their disease, and prediction of its response to treatment.

Myeloma patients can be stratified into risk classifications according to key cytogenetic features (1). Specifically, approximately 15% of patients have high risk cytogenetic abnormalities (t(14;16), t(14;20), or del17p13) and have a median overall survival (OS) of less than 2-3 years despite aggressive chemotherapy and autologous stem cell transplant (ASCT). Patients with t(4;14), deletion 13, or hypodiploidy were previously also classified as high risk, however, since the introduction of the proteasome inhibitor bortezomib (PS-341, Velcade®, Millenium Pharmaceuticals and Johnson & Johnson) in the treatment of these patients, their outcome has improved. Patients who do not fall into either of the above categories are classified as standard risk with a median survival of 6-7 years.

Along with refinement in risk stratification, the therapeutic options for patients with MM have also improved over the last decade. One of the most notable advances in this respect has been the development of proteasome inhibitors and their introduction into the armamentarium of therapies for MM (2). Over the last decade, proteasome inhibitors have advanced from agents used in the treatment of patients with relapsed and refractory disease to become the backbone of up-front therapeutic regimens for newly diagnosed patients. This review will summarize some of the important clinical advances recently published on the use of bortezomib in patients with newly diagnosed MM.

The ubiquitin-proteasome pathway
The integrity of protein degradation machinery, such as the 26S proteasome, is essential for cellular homeostasis. Composed of a 20S core particle and one or two 19S regulatory particles, this large multi-subunit complex catalyzes the proteolysis of both damaged or misfolded proteins and undamaged proteins requiring rapid turnover, as recently described in detail (3, 4). These latter substrates include regulators of inflammation, apoptosis, and the cell cycle, among other processes. Proteins destined for proteasomal degradation are first tagged with chains of the small peptide ubiquitin in a specific conformation. This polyubiquitylation is tightly regulated, catalyzed in concert by three enzymes: an E1 ubiquitin activating enzyme, an E2 ubiquitin conjugating enzyme, and finally an E3 ubiquitin ligase enzyme. Polyubiquitylated substrates are recognized and unfolded by the 19S regulatory particle and translocated into the 20S core particle. This barrel-like core particle is formed by four stacked rings of seven subunits. Three subunits localized in the inner two rings possess trypsin-like, chymotrypsin-like or caspase-like proteolytic activity, catalyzing substrate degradation in an ATP-dependent manner.

Bortezomib
Bortezomib was identified in a screen of 13 peptide-based proteasome inhibitors in 60 tumour cell lines as a potent and effective therapeutic candidate (5). It subsequently became a first-in-class anticancer agent, obtaining Health Canada approval for use in relapsed refractory MM in 2005, and for frontline combination therapy in newly diagnosed non-transplant eligible patients in 2008 (6). While bortezomib has historically been administered as an intravenous bolus, the subcutaneous route of administration has recently been approved and has entered routine clinical practice (6).

Bortezomib is a water-soluble dipeptide boronic acid, modified from the amino acids leucine and phenylalanine. It binds to the chymotrypsin-like subunits of the 20S core particle, acting as a

Dr. Jimenez-Zepeda is currently a post-doctoral fellow with the Multiple Myeloma Clinical and Research program at Princess Margaret Hospital in Toronto. He completed medical school at the University of Guadalajara in Mexico, and took Internal Medicine and Hematology training at the National Institute of Medical Sciences and Nutrition in Mexico City. He obtained specialized training in lymphoma and myeloma under the mentorships of Drs. Joan Blade and Armando Lopez-Guillermo in Barcelona, Spain. From 2007-2009, obtained bench training in genetics and myeloma under the supervision of Drs. Rafael Fonseca and Leif Bergsagel at the Mayo Clinic in Scottsdale, Arizona. Dr Zepeda joined the myeloma research group at the Princess Margaret Hospital in July of 2009 and quickly expressed interest in research projects in both the clinical and basic field. Dr Zepeda is member of ASH and the International Myeloma Society. Recently he was awarded with the MMRF Research fellow award with a project on STAT3 inhibition in Multiple Myeloma. He was awarded the ASH Abstract achievement award in 2012. Dr Zepeda has ~90 journal publications and abstracts to his credit. He has served as a reviewer for Journal of Clinical Oncology, American Journal of Clinical Oncology, British Journal of Hematology, International Journal of Laboratory and Clinical Hematology, Journal of Pathology and the World Journal of Surgical Procedures. Dr. Zepeda is soon to be relocated to Calgary, AB where he will receive a faculty position as an Associate Professor and Scientist Clinician at the Tom Baker Cancer Centre in the Multiple Myeloma group.
potent, competitive and reversible inhibitor (3, 7). While the
details of its clinical mechanism of action remain to be clarified,
bortezomib is thought to exert its antимyeloma effects in part by:
(i) disrupting cell survival, proliferation and adhesion signalling
mediated by the NFκB pathway; (ii) tipping the balance of pro-
and anti-apoptotic regulators to favour cell death; (iii) stabilizing
cell cycle checkpoint regulators; and (iv) inducing endoplasmic
reticulum stress responses (2, 3, 8). In addition, these activities
may allow bortezomib to potentiate the effects of several other
therapeutic agents.

As is the case for virtually all new therapeutic agents,
bortezomib was initially evaluated in patients with advanced
disease (2). As a single agent in a relapsed patient population,
bortezomib produced response rates of 43% and improved OS
when compared in a Phase III trial to high dose dexamethasone
alone. Survival at one year was 80% vs 66% (p=0.003) for
bortezomib compared to pulse dexamethasone. These exciting
results sparked several areas of clinical investigation including
the use of bortezomib-based drug combinations to further
improve response rates and survival. The drug has also been
evaluated in the upfront setting, and as maintenance after ASCT
to prolong time to progression.

In addition, different schedules and routes of administration
have been evaluated with the intention of decreasing toxicity
and improving ease of administration. Finally, new proteasome
inhibitors with different biochemical mechanisms and selectivity
distinct from bortezomib have been developed (7). For
example, carfilzomib is an irreversible inhibitor of the
chymotrypsin-like enzymatic activity of the proteasome . This
drug has efficacy in patients resistant to bortezomib and has
recently been approved by the Federal Drug Administration
(FDA) for patients with relapsed refractory MM.

Given that bortezomib has improved survival outcomes of
relapsed myeloma patients it had been anticipated that the use of
bortezomib in the frontline setting, either prior to stem cell
transplant or in the non-transplant eligible patient population,
would portend even greater clinical impact. Indeed, the past
several years has seen the publication of several high-impact
randomized trials of bortezomib-containing regimens that firmly
validate its use for newly diagnosed patients.

**Up-front bortezomib-based regimens in transplant eligible
patients**

The initial treatment of symptomatic myeloma is primarily
determined by eligibility for ASCT. Transplant eligible patients,
usually under 65-70 years of age, are first treated with induction
therapy prior to high dose chemotherapy and stem cell
transplant. Historically the use of vincristine, adriamycin and
dexamethasone (VAD) induction chemotherapy followed by
high dose melphalan with stem cell transplant produced major
response rates (partial response (PR) or better) of approximately
60%. Subsequently, Harousseau et al reported that the use of
bortezomib and dexamethasone induction significantly
improved post-induction and post-transplantation complete
response (CR) and very good partial response rates (VGPR)
rates compared with VAD. Further, in this randomized trial an
observed trend towards improved progression free survival
(PFS; 36 month vs. 29.7 months) led to the conclusion that
bortezomib plus dexamethasone should be considered the new
standard of care in this setting. (9)

Efforts to further improve transplant outcomes have focused on
achieving greater depths of response by optimizing induction
regimens or introducing consolidation treatment after ASCT as
well as improving duration of responses by the use of
maintenance strategies post transplant. Thus studies have
evaluated the use of bortezomib in 3 and 4 drug induction
regimens as well as the use of bortezomib consolidation and
and/or maintenance. In a recently published randomized
phase II trial of bortezomib combinations, patients received
bortezomib 1.3 mg/m2 (days 1, 4, 8, 11) and dexamethasone 40
mg (days 1, 8, 15), with either cyclophosphamide 500 mg/m2
(days 1, 8) and lenalidomide 15 mg (days 1-14; VDCR),
lenalidomide 25 mg (days 1-14; VDR), or cyclophosphamide
500 mg/m2 (days 1, 8; VDC) or cyclophosphamide 500 mg/m2
(days 1, 8, 15; VDC-mod) in 3-week cycles (maximum 8
cycles), followed by maintenance with bortezomib 1.3 mg/m2
(days 1, 8, 15, 22) for four 6-week cycles (all arms). High grade
responses, VGPR or greater, were seen in 58%, 51%, 41%, and
53% of patients receiving VDCR, VDR, VCD, and VCD-mod,
respectively; the corresponding 1-year PFS was 86%, 83%,
93%, and 100%, respectively. All regimens were highly active
and well tolerated in previously untreated MM, and, based
on this trial, VDR and VCD-mod are preferred for clinical practice
and further comparative testing (10) Consistent with these
results, in a phase II study of induction bortezomib combined
with cyclophosphamide and dexamethasone (CyBorD) we
observed high grade responses (VGPR or greater) in 60%
patients (11). Further, patients in the once weekly bortezomib
(1.5 mg/m2 weekly) cohort achieved responses similar to the
twice weekly (1.3 mg/m2 days 1, 4, 8 and 11) cohort (ORR 93%
vs. 88%, ≥ VGPR 60% vs. 61%) and experienced less grade 3/4
adverse events (AEs; 37%/3% vs. 48%/12%) and fewer dose
reductions of bortezomib and dexamethasone. These data
support the use of CyBorD as an effective and safe induction
regimen in untreated MM patients. Finally, a recent mixed
model meta-analysis demonstrated that the addition of
bortezomib to the induction regimens of transplant-eligible MM
patients results in improved overall response rate (ORR), PFS
and OS compared with the non-bortezomib-containing induction
regimens. The pooled hazard ratios for 3-year PFS and OS were
0.7 and 0.7, respectively, favoring bortezomib-containing induction
regimens. Thus the pooled estimates of response and
survival strongly favor inclusion of bortezomib in the induction
regimens (12)

Currently, novel agents, including bortezomib, are also being
tested post-ASCT, with the objective of further improving depth
of response and duration of response. Single-agent bortezomib
consolidation after ASCT has been investigated by the Nordic
group, in a phase III trial in which 370 patients were randomized
to receive no treatment or bortezomib (13) . Preliminary results
indicated that bortezomib consolidation was feasible and
toxicity was low, with 5% grade 3 or 4 peripheral neuropathy.
The 6-month post-randomization CR/nCR rate was 35% versus
45% with for no treatment versus bortezomib (P < .05). This
translated into an improvement in median PFS, from 20 to 27
months (P = .04). (12), Recently, Sonneveld et al., reported the
results of a randomized phase III study of bortezomib
maintenance in newly diagnosed MM that were eligible for
ASCT (14). Patients (827) were randomized to: (i) VAD
followed by ASCT and thalidomide maintenance; or (ii) PAD
(bortezomib, doxorubicin, and dexamethasone) followed by
ASCT and bortezomib maintenance. In this study, patients
treated with bortezomib fared better. Consistent with other
induction trials, response rates in the bortezomib arm were
higher, both after induction chemotherapy as well as after
transplant. Complete response (CR, including near CR (nCR),
was superior after combination of PAD (15% v 31%; P < .001)
and bortezomib maintenance (34% v 49%; P < .001). Importantly, after a median follow-up of 41 months, PFS was superior in the arm that was treated with the bortezomib-based regimen that included maintenance (median of 28 months v 35 months; hazard ratio [HR], 0.75; 95% CI, 0.62 to 0.90; P = .002). (14)

Thus, these randomized studies highlight the therapeutic benefit of up-front bortezomib-based regimens in newly diagnosed patients who are eligible for transplant. Furthermore, they emphasize the need to balance high response rates with increased monitoring for higher rates of peripheral neuropathy as an adverse event, which may be alleviated by using weekly dosing regimens in 3-drug combinations and routes of administration.

**Up-front bortezomib-based regimens in transplant ineligible patients**

In patients not eligible for transplant due to age and/or comorbidities, the selection of up-front therapy needs to balance efficacy and toxicity. In the past year, San Miguel, et al. (15) presented the final analysis of the phase III VISTA trial comparing VMP (bortezomib, melphalan, and prednisone) to MP (melphalan and prednisone) in 682 patients with myeloma who were not eligible for transplant. After a 5-year median follow-up, median OS was higher in patients receiving VMP (56.4 months) compared to those receiving MP (43.1 months). The survival benefit was seen across multiple patient subgroups except those with high risk disease. Patients with poor risk cytogenetics did poorly regardless of therapy. Despite the improved survival outcome approximately one-third of patients discontinued VMP treatment or discontinued only bortezomib because of AEs, most frequently as a result of bortezomib induced peripheral neuropathy. (16). It does not come as a surprise therefore, that in a subsequent phase III trial, comparing bortezomib-melphalan-prednisone-thalidomide followed by maintenance bortezomib-thalidomide (VMP-VT) to VMP the protocol was amended so that both arms received once-weekly instead of the initial twice-weekly bortezomib infusions (17). In a post-hoc analysis the impact of the schedule change on clinical outcomes and safety was evaluated. Long-term outcomes including 3-year PFS and OS for the once-weekly vs the twice-weekly group were comparable (P > .999 and P = .54, respectively). Importantly, non-hematologic grade 3/4 AEs were significantly less in the once-weekly patients compared to the twice-weekly patients (35% vs. 51%, respectively; P = .003) and in particular, the incidence of grade 3/4 peripheral neuropathy was markedly reduced from 28% in the twice-weekly group to 8% in the once-weekly group (P < .001).

Finally, as has been observed the transplant setting, maintenance regimens that include bortezomib post-induction also appear to confer an important clinical benefit in the non-transplant eligible patient population. At this years, American Society of Hematology meeting, Palumbo reported that VMPT followed by VT maintenance significantly prolonged OS compared to VMP with no maintenance, demonstrating a 4-year OS of 64.6% for the VMPT-VT arm compared to 49.7 for the VMP arm (P=0.02) (18). Thus, the addition of bortezomib to the standard MP regimen is reasonably well tolerated and improves outcomes compared to the historical standard of MP in patients not eligible for transplant.

**Conclusions**

The last 10 years has seen major advances in the therapy of MM with the addition of novel therapies including proteasome inhibitors. In addition to their use in the relapsed setting, studies have demonstrated the efficacy of the proteasome inhibitor bortezomib in the treatment of newly diagnosed disease both in patients eligible and ineligible for ASCT. Despite this progress, several clinical challenges remain in the up-front treatment of this disease. Among these hurdles is the need for better therapies for patients with high-risk disease who continue to respond poorly to standard induction therapy. In addition, while there are many trials of multi-drug combinations in patients with newly diagnosed disease, it is unclear how to incorporate these regimens into clinical practice in the absence of randomized trials. Finally, in the near future, we will need to address how to incorporate newer proteasome inhibitors such as the irreversible inhibitor carfilzomib or the orally bioavailable reversible inhibitor MLN9708 into up-front therapy.

Currently, the myeloma group at the Princess Margaret Cancer Center has balanced the benefits, toxicity, and cost of the available regimens and uses the following algorithm for patients with newly diagnosed MM. First, when available, all patients are encouraged to enrol in a clinical trial. If patients are not eligible for available trials, decisions regarding up-front therapy are based on risk classification and eligibility for ASCT. Patients eligible for transplant receive induction with CyBorD (bortezomib, cyclophosphamide, and dexamethasone) with weekly dosing to reduce neurotoxicity. (11) Patient with high risk disease (defined by 17p deletion, t(4;14) or t(14;16) FISH abnormalities) undergo tandem transplants. Maintenance treatment with lenalidomide post-ASCT is recommended for all patients. Patients who are not candidates for transplant and have standard risk disease are recommended either VMP or MPT (melphalan, prednisone and thalidomide) with choice based on toxicity profiles, need for rapid response, patient comorbidities and patient preference while patients with high risk disease as defined above are recommended VMP.

It is our hope that, as more clinical and molecular data become available over the next few years, our understanding of how to best exploit proteasome inhibitors in the treatment of newly diagnosed myeloma patients will advance in parallel, ultimately refining clinical practice and improving patient care.

**References**


Figure 1. The ubiquitin-proteasome pathway

Figure 2. Princess Margaret Cancer Centre treatment algorithm for the treatment of newly diagnosed multiple myeloma

New Diagnosis of Multiple Myeloma

Transplant eligible

Enrol in Clinical trial if Eligible

Non Transplant eligible

Standard or intermediate risk

High risk

CyBoRd inductionX4

ASCT and LEN Maintenance

Intermediate or standard risk

High risk

VMP

MPV or MPT

Tandem ASCT and LEN Maintenance

High risk is defined by the presence of t(4;14) with high β2-microglobulin, t(14;16) or del17p, Intermediate risk represents t(4;14) with low β2-microglobulin and standard risk is hyperdiploid MM or normal/pseudodiploid without the above mentioned abnormalities. LEN=lenalidomide

Welcome!

Your Canadian Hematology Society NEWSLETTER

Member Submissions Welcome!

Editor
The Microenvironment
Dr. Tom Nevill
The patient rapidly deteriorated following initial assessment at the hospital and required intubation and commencement of inotropic support.

Despite aggressive use of pressors, his blood pressure was not supportable and he died of multiorgan failure within 6 hours of presentation.

The initial blood film showed numerous large gram positive rods and the blood cultures drawn on admission grew a Bacillus species in 4/4 bottles.

Cause of death was felt to be overwhelming Bacillus septicemia with resultant multiorgan failure.

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

Queries should be directed to:
- The Editor, The Microenvironment
- Email: chs@uniserve.com

( Student Research article from Haley Augustine, Dalhousie University in Halifax, NS, is featured on Page 7 of this issue.)
**Thrombosis Fellowship 2012-2013 Jewish General Hospital, McGill University**

The JGH Thrombosis Program is currently accepting applications for a one year fellowship (July 1, 2013 - June 30, 2014) 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.

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  
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
**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.

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**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:

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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.