

Riverside Theatre
HSANZ: Molecular Basis of Haematological Disorders
Sponsored by Celgene

0900-1030
0900

Molecular-based Risk Stratification of Multiple Myeloma: Are We There Yet?

John D Shaughnessy, Jr. and Bart Barlogie

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High-risk multiple myeloma (HRMM) is routinely defined by laboratory parameters alone or in combination in the Durie-Salmon and, more recently, the ISS staging systems. The Bartl grade, a cell morphology-based staging system, has seen limited use. The presence of abnormal cytogenetics, high BrdU labeling index, interphase FISH abnormalities and flow cytometric measures have also been used. A molecular-based classification and risk stratification of MM may improve the definition of HRMM. Global gene expression profiling (GEP) with of CD138-selected plasma cells followed by unsupervised hierarchical cluster analysis revealed that MM comprises a spectrum of seven distinct reproducible subtypes. A validated molecular classification schema has been defined as follows: **(MS = t(4;14); MF = t(14;16) or t(14;20); CD-1 = t(11;14) or t(6;14) and CD-2 = t(11;14) or t(6;14) with high CD20 and/or VPRESB3), hyperdiploidy (HY = high DKK1, FRZB, NCAM1, TNFSF10), low bone disease (LB = NF-kB signature, high CCND2, CST6 and IL6R) and proliferation (PR = high MIK67, CCNB1, CCNB2, TOP2A, and TYMS).**

Correlating GEP with outcome in two independent cohorts permitted the identification of a high-risk signature (UAMS 17-gene model), present in approximately 13% of newly diagnosed disease. GEP and high-resolution comparative genomic hybridization in 92 cases confirmed that the altered expression of the 17 genes in the model is driven by 1q gains and 1p losses. This high-risk signature is evident in a subset of all 7 molecular subtypes and negatively influences outcome. For example, low-risk MS disease fares much better than high-risk MS disease. We recently reported that the addition of bortezomib to TT3 has significantly improved outcome in low-risk MS disease, thereby demonstrating the value of GEP in evaluating benefits of new treatments that might be otherwise masked. When subjected to multivariate analysis including the International Staging System (ISS) and a gene expression-based proliferation index (GEP PI), the UAMS 17-gene model remained a significant predictor of outcome.

Mulligan and colleagues developed outcome classifiers for relapsed disease treated with single agent bortezomib or high dose dexamethasone improved upon the risk stratification provided by the ISS. These predictive models showed some specificity for bortezomib. Using U133A data from newly diagnosed disease treated with ASCT, the Mayo clinic group validated the UAMS 17-gene model, but also showed that the t(4;14) translocation remained a significant adverse variable. The IFM recently reported on a 15-gene model of high-risk (IFM 15-gene model) related to cell proliferation. Multivariate showed that the UAMS 17-gene model was significant in all datasets while the IFM 15-model was significant in a limited number. This difference might be attributed to the dependence of the IFM model to cell proliferation.

GEP on 71 paired diagnostic and relapse samples indicate that the UAMS 17-gene model score increases in 80% of the cases and a low-risk to high-risk conversion in 14 of 24 (58%) severely impacted post-relapse survival. Expression of *TP53* is a surrogate for 17p13 deletion and *TP53* expression below a specific threshold seen in approximately 10% of newly diagnosed disease, imparts a poor prognosis in low-, but not high-risk defined by the UAMS 17-gene model. In conclusion, while the majority of patients with MM can anticipate long-term disease control, approximately 25% of patients with molecularly defined HRMM do not benefit from current approaches.

Riverside Theatre
HSANZ: Molecular Basis of Haematological Disorders
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0900-1030
0945

Molecular Pathogenesis of the Myeloproliferative Disorders

Anthony Green

University of Cambridge, Department of Haematology, Cambridge Institute for Medical Research, Cambridge, United Kingdom

The human myeloproliferative disorders represent a spectrum of clonal haematological malignancies, with three main members: polycythaemia vera (PV), essential thrombocythaemia (ET) and idiopathic myelofibrosis (IMF). For over quarter of a century it has been realised that these diseases reflect transformation of a multipotent haematopoietic stem cell, but the identity of underlying target gene(s) remained elusive.

This changed dramatically in 2005 when we and others demonstrated that a single acquired V617F mutation in JAK2 is present in virtually all patients with PV and in approximately half those with either ET or IMF. The mutation is present in a variable proportion of granulocytes, alters a highly conserved valine present in the negative regulatory JH2 domain, and dysregulates kinase activity. Retroviral and transgenic studies have shown that the mutation produces cytokine-independence in cell lines and an MPD phenotype in mice.

Our subsequent results suggest that V617F-positive ET and PV form a phenotypic continuum, that homozygosity for this mutation plays a key role in the PV phenotype and that V617F-negative ET and V617F-positive ET represent distinct disorders. More recently we have made the unexpected discovery that leukaemic transformation is associated with loss of the JAK2 V617F mutation and we have identified a cluster of new JAK2 mutations which define a previously unrecognised myeloproliferative syndrome. These data, together with those of other groups, are laying the foundation for new approaches to the diagnosis, classification and therapy of the myeloproliferative disorders.

Meeting Room 4
ANZSBT: Critical Bleeding
Sponsored by CSL

0900-1030
0900

Massive Transfusion and Coagulopathy: Pathophysiology and Clinical Implications

Jean-François Hardy

Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, Québec, Canada

Coagulopathy associated with massive transfusion (MT) remains an important clinical problem. In this presentation, we review the literature in an attempt to identify the causes of coagulopathy in massively transfused, adult and previously hemostatically competent patients and to differentiate between the elective surgical and the emergency settings.

In patients undergoing elective surgery, tissue trauma is controlled, normothermia is maintained, hypovolemia and shock are avoided, monitoring of hemostasis is ongoing and blood products are available in a timely fashion. A decrease in fibrinogen concentration is observed initially while thrombocytopenia is a late occurrence. Critically low levels of coagulation factors were seldom reported when whole blood was in common use. With the use of packed red blood cells (PRBC), dilution or consumption of coagulation factors has become a significant issue requiring specific treatment with, primarily, fresh frozen plasma (FFP). Platelet transfusions are seldom required in this context.

In the emergency setting (e.g. trauma, ruptured abdominal aortic aneurysm), tissue trauma, shock, tissue anoxia and hypothermia contribute to the development of microvascular bleeding. The exact cause of microvascular bleeding remains unknown. Massive consumption of coagulation factors and platelets, disseminated intravascular coagulation, anticoagulation by activated protein C and hyperfibrinolysis are suggested mechanisms. Several recent observations (chart and database reviews) suggest that the proactive administration of large volumes of platelets and FFP improve coagulation, decrease hemorrhage and improve survival in massively bleeding trauma patients. We can only speculate that, in this specific context, the benefits of early and aggressive platelet and coagulation factor replacement are related to the ongoing consumption coagulopathy at the time of surgery.

Coagulopathy associated with MT is an intricate, multifactorial and multicellular event. Appropriate management strategies should consider the patient's situation (elective vs. urgent surgery) and, whenever possible, the results of diagnostic laboratory tests of hemostasis (Can J Anaesth 2006;53:S40-S58).

Meeting Room 4
ANZSBT: Critical Bleeding
Sponsored by CSL

0900-1030
0945

Critical Bleeding: Retrieval Service Perspective

Stephen Langford

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Abstract not received at time of going to print

Meeting Room 4
ANZSBT: Critical Bleeding
Sponsored by CSL

0900-1030
1005

Critical Bleeding: Trauma Service Perspective

Sudhakar Rao
Royal Perth Hospital, Perth, WA, Australia

Modern management of critically injured people relies on a efficient and effective trauma system. The evidence for trauma systems as opposed to individual trauma centres is compelling. An organised and properly resourced trauma system is the foundation on which other medical and pharmacological treatments of the critically ill trauma patient can be effective. Conversely, advances in surgical and medical care of injuries, (e.g. haemostasis, fluid resuscitation, critical care) will not the expected outcomes in the absence of an organised trauma system.

Trauma Care in Western Australia is multidisciplinary. The trauma service has expanded from a traditional focus of surgeons and now encompasses all surgical, medical specialities and all therapists (including clinical psychology). The outcome measures from trauma care now include more than just mortality and surgical morbidity.

Meeting Room 2/3
ASTH: Hormones, Thrombophilia and Thrombosis

0900-1030
0900

Female Hormones and Venous Thrombosis

FR Rosendaal

Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

Widespread use of female hormones began in the 1960s with the availability of oral contraceptives. The first thrombotic side effect of oral contraceptives was reported in 1961. Since first licensing in 1959, the oestrogen dose has been reduced, to either 50 µg or 30 µg ethinylloestradiol, or even less. The progestogen content has also changed over time, but here it concerned the chemical composition. Second generation progestogens include norgestrel and levonorgestrel, of which levonorgestrel is still widely used. Third generation progestogens are desogestrel and gestodene. Two other progestins are the anti-androgen cyproteronacetate and drospirenone, which is an anti-mineralocorticoid .

The most recent studies still show 2- to 6-fold increased risks of venous thrombosis caused by oral contraceptives. The absolute risk of venous thrombosis in women of reproductive age is low, and in oral contraceptive users it becomes two to three per 10 000 per year. The risk of venous thrombosis is highest during the first year of use. However, the risk does not accumulate with prolonged use. The higher the dose of oestrogen, the higher the risk of thrombosis.

A series of studies have confirmed an additional two-fold higher risk for third generation progestogens brands. Recently, it has been shown that oral contraceptives that contain cyproteronacetate confer a substantially increased risk of venous thrombosis, similar to that of third generation oral contraceptives. The safety of drospirenone is still unclear.

Obesity increases the risk of thrombosis about 2-fold, but obese women using oral contraceptives have a more than 20-fold increased risk. In familial thrombophilia oral contraceptives greatly enhance the risk of thrombosis in carriers of one of these defects.

The oestrogens in oral hormonal replacement therapy preparations are usually conjugated oestrogens retrieved from pregnant mare urine, or micronised oestradiol. The progestogen mostly used in combination preparation is medroxyprogesterone acetate (MPA). Besides oral administration, the hormones can also be administered transdermally by patches and subcutaneously.

From 1996 onwards, studies have established a clearly increased risk of venous thrombosis for users of oral hormonal replacement therapy, with a two- to fourfold increased risk compared to non-users.

As is the case for oral contraceptives, the risk of venous thrombosis is higher shortly after therapy has started, and in those with prothrombotic abnormalities. .

A6

Meeting Room 2/3
ASTH: Hormones, Thrombophilia and Thrombosis

0900-1030
0930

Update on the Protein C Anticoagulation Pathway

David Lane

Department of Haematology, Imperial College London, UK

Protein C is part of an important anticoagulant mechanism that down regulates blood coagulation. It is activated on the endothelial cell surface by thrombin/thrombomodulin complex. Activated protein C (APC), together with its cofactor protein S, proteolytically inactivates factor Va and factor VIIIa. Optimum activation of protein C to APC requires presentation of protein C to its activation complex. On large blood vessels this is achieved by specific interaction of protein C with its receptor, EPCR, an interaction mediated via its Gla domain. A number of specificity issues surrounding activation of protein C and the function of APC have been clarified recently:

By what mechanism is EPCR selectively expressed in large blood vessel endothelial cells?

How does protein C specifically recognise its receptor, EPCR?

How does APC specifically recognise protein S?

Protein S has been under the shadow of protein C for many years, perhaps reflecting the difficulty in its assay and complexity surrounding clinical manifestation of thrombotic problems arising from its deficiency. Exploring an area long been confused by methodological issues, the protein C independent functions of protein S, Hackeng and colleagues have now suggested that a key function of protein S is to enhance the inhibitory effect of TFPI against the tissue factor/factor Xa complex. If they are correct, this will indicate a bifunctional role for protein S, as a cofactor for TFPI at low tissue factor concentration and as a cofactor to APC at high tissue factor concentrations.

Protein C is also attracting increasing interest in the therapeutic context. APC is unique amongst the natural anticoagulant proteins in that it has been shown to be effective in reducing mortality of patients with severe sepsis. John Griffin and coworkers have raised an interesting question: does its effectiveness arise from its anticoagulant property or is another function responsible? A number of studies have shown that APC also has anti-inflammatory/cytoprotective properties that are mediated through cellular positioning of APC by its interaction with EPCR, subsequent cleavage of endothelial cell protease receptors and modulation of cytoprotective signalling pathways. Intriguingly, by selective mutation of its protease domain exosite loops, it has been shown that mutant forms of APC can be produced that have greatly diminished anticoagulant function but normal cytoprotective functions in vitro. It may be that such non anticoagulant functions are also the basis of beneficial effects of APC in tPA induced bleeding in small animal stroke models. APC mutants with selective cytoprotective function hold the promise of improved therapeutic agents.

Meeting Room 2/3
ASTH: Hormones, Thrombophilia and Thrombosis

0900-1030
1000

Protein C & S Gene Mutations and Regulation by Hormones

Quintin Hughes, Ross Baker

Centre for Thrombosis and Haemophilia, Royal Perth Hospital, Murdoch University, Australia.

Activated Protein C (aPC) inactivation of the procoagulants factor Va and factor VIIIa is enhanced by binding of the cofactor Protein S (PS). Approximately 60% of circulating PS is bound to C4b-binding protein (C4b-BP) leaving a remaining 40% 'free PS' fraction. Until recently it was thought that only the free form was available for aPC cofactor activity. However, recent evidence suggests that C4b-BP bound PS is able to enhance aPC proteolytic inactivation of factor Va. A separate study found that free PS exhibits cofactor activity for tissue factor pathway inhibitor (TFPI), stimulating TFPI inhibition of factor Xa. These recent findings in addition to what we already know about PS highlight its importance as a regulator of thrombin generation.

Expression of PS is affected by oestrogen and the many progestin isotypes that are both used in combined oral contraceptive formulations (COCs). We recently identified a progesterone response element (PRE) in the 5' untranslated region of the PROS1 gene that encodes PS, demonstrating differential expression in response to various progestins. This finding explains the observed differences in PS levels seen between users of 2nd and 3rd generation COCs that contain levonorgestrel and gestodene or desogestrel, respectively. Progestogenic upregulation represents a counterbalance to the downregulatory effect oestrogen has on PS production. The oestrogenic site responsible for Protein S upregulation is currently being investigated in both the 5' and 3' untranslated regions of the PROS1 gene.

Recent studies have suggested that acquired aPC resistance may be in part, a function of oestrogen driven acquired PS deficiency. Therefore, a better understanding of the exact process involved in the regulation of PS by oestrogen may provide a better insight into the acquisition of aPC resistance and the propensity of hormones to be associated with venous thrombosis.

Meeting Room 1
Nurses: Quality of Life

0900-1030
0900

Home Chemotherapy

Julie Wilkes
Royal Perth Hospital, Perth, WA, Australia

Abstract not received at time of going to print

Meeting Room 1
Nurses: Quality of Life

0900-1030
0930

QOL – Concepts and Measurement: The Patient’s Perspective

Anne Williams

Western Australian Centre for Cancer and Palliative Care, Curtin University of Technology; Centre for Nursing Research and SolarisCare Centre, Sir Charles Gairdner Hospital

This presentation explores the concept of QOL from the perspective of patients and describe a program of research in this area. The current program is based on a substantive theory “Optimising Personal Control to Facilitate Emotional Comfort” which was developed initially through a grounded theory study which investigated the experience of being a patient hospitalised in Western Australia. In that study patients were found to perceive that when they felt emotionally comfortable, healing was facilitated. A central component of emotional comfort was having a sense of personal control over their situation or environment during hospitalisation. Emotional comfort could be influenced by a number of factors such as the interpersonal interactions experienced, characteristics relating to the patient, and aspects of the hospital environment. For the purpose of this presentation the characteristics of those interpersonal interactions from healthcare staff that facilitated the state of emotional comfort will be described in terms of how they related to the patient’s perceived Level of Security, Level of Knowing, and Level of Personal Value.

An instrument to measure the interpersonal interactions experienced by patients during hospitalisation has been developed as part of this program of work. The instrument named, ‘Patient Evaluation of Emotional Care during Hospitalisation’ (PEECH) was tested through a survey of 132 patients. Encouraging reliability and validity estimates have been obtained through this preliminary psychometric testing and further directions for research have been identified.

Meeting Room 1
Nurses: Quality of Life

0900-1030
1000

What Can Qualitative Research Do for Me?

Moira Stephens

Centre for Values, Ethics and the Law in Medicine, University of Sydney, Sydney, NSW, Australia

Descartes said in 1637 “ For it seemed to me that I should find more truth in the reasonings of which a man makes with regard to matters which touch him closely..... than in the reasonings of a man of learning in his study, whose speculations remain without effect” (Tr. Wollaston 1960). This was arguably, one of the earliest comments on the strength and validity of empirical qualitative research!

This session will introduce and discuss a variety of ways of undertaking qualitative research and explore the differences in their perspectives. It will discuss ideas about methodology and rigour in qualitative research and how qualitative research is ideally situated to answer many questions and complexities evident in health care.

No conflict of interest to disclose

Meeting Room 7
BMTSAA Session

0900-1030
0900

From Stem Cells to Blood Cells

Louise Winteringham

The Western Australian Institute for Medical Research and The Centre for Medical Research The University of Western Australia, Perth, Australia

Haemopoiesis is the stepwise maturation of cells to form all the different cellular components of the blood. Haemopoiesis starts from multipotent, self renewing haemopoietic stem cells (HSC) which differentiate into multipotent progenitors that are unable to self renew but are able to differentiate. These multipotent progenitor cells become progressively lineage restricted to finally form all the mature differentiated cells of the blood. When this process fails leukemia can develop. Most often leukemias are treated with high doses of chemotherapy and radiation which target the rapidly dividing cancer cells. These therapies unfortunately also target rapidly dividing progenitor cells so bone marrow transplantation is often used to repopulate the bone marrow. However, in a number of patients the leukemia recurs. Chemotherapy and radiation fail to target the quiescent or very slow dividing HSC and research over the past 10 years has demonstrated that a small portion of these cells have the ability to reinitiate leukemia. These cells are referred to as cancer stem cells (CSC) or leukemia initiating cells (LIC). It is still not clear whether LIC arise from mutations in HSC that confer a greater ability to self renew or mutations in progenitor cells that cause "regression" and reactivation of stem cell programs. Regardless of their origin it has become clear that current treatments for leukemia do not target these LIC and this is likely to be, at least in part, the reason for relapse of patients following treatment. Current research is focused on identifying molecules that might contribute to the tumorigenic capacity of LIC, *vis.* deregulated proliferation and an inhibited ability to differentiate, and establishing which of these molecules will provide appropriate targets for consideration in future therapeutic strategies.

Meeting Room 7
BMTSAA Session0900-1030
0940**Improved Functional Recovery After Transplantation of Human Bone Marrow Stromal Stem Cells (hBMSCs) From Spinal Cord Injured Patients Into the Acute and Chronic Injured Rat Spinal Cord****Stuart Hodgetts¹**, Paul Simmons², David Haylock³ & Giles W Plant¹¹*Reds Spinal Cord Research Laboratory, UWA, Perth, Western Australia*²*Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center, Houston, USA*³*Australian Stem Cell Centre, Melbourne, Australia*

Multipotent hBMSCs from spinal cord injury (SCI) patients were used to stimulate sparing and regeneration of descending neural pathways following moderate contusive SCI. hBMSCs transduced with a retrovirus encoding GFP (hBMSC^{GFP}) were transplanted into immunologically deficient (Nude) rat hosts subjected to a moderate SCI (10g,12.5mm) using an NYU impactor device. The therapeutic potential of hBMSC^{GFP} was assessed both behaviourally (recovery of function) and anatomically using immunohistochemistry. In both *acute* and *chronic* SCI studies, hBMSC^{GFP} initially survive well in the injured host spinal cord (SC) 1wk after transplantation, induce axonal growth, produce growth promoting molecules and co-exist with host glial cells such as astrocytes and Schwann cells within the lesion site. At 1wk post-transplantation, immunostained SC sections show the presence of RT97⁺/ -III tubulin⁺ axons, GFAP⁺ astrocytes, and p75⁺ Schwann cells intermingled with hBMSCs. S100⁺ profiles were seen to be in close proximity to transplanted hBMSC^{GFP} and hBMSCs were shown to produce large quantities of laminin & fibronectin *in vivo*. Immunostaining for RT97, GFAP, p75 remains high in and around the lesion site up to 4wks post-transplantation. Virtually no donor hBMSCs were present in the lesion site after 8wks, coinciding with a large increase in ED1⁺ macrophages within the lesion and both rostral and caudal SC tissue. Rats transplanted with hBMSCs showed a reduction in the size of the injury site, compared to controls. Extensive behavioural analysis of hBMSC^{GFP}-transplanted nude rats showed a marked improvement in open field BBB scoring (15 ± 0.5^{SEM}) c.f. controls (13 ± 0.7^{SEM}) 8wks post transplantation. Additional detailed computer generated functional analysis (Catwalk gait system) was also performed. These results provide new evidence on the use of hBMSCs for the repair of the chronic injured mammalian SC.

Riverside Theatre
HSANZ: Acute Leukaemia

1100-1200
1100

Unravelling the Complexity of Chromosome Abnormalities in Acute Myeloid Leukaemia

Lynda Campbell

Victorian Cancer Cytogenetics Service, St Vincent's Hospital Melbourne, Victoria, Australia

Chromosome abnormalities are found in 55-60% acute myeloid leukaemias and aid in morphological classification and prediction of outcome. Approximately 20% of successfully karyotyped AML cases contain "complex" chromosome abnormalities. Complexity is defined as either 3 or more or 5 or more abnormalities, depending on the study and invariably denotes a poor prognosis. However, simple counting of abnormalities may be misleading. A study of hyperdiploid AMLs showed that patients with ≥ 3 extra chromosomes but without structural abnormalities were better classified in an intermediate prognostic group (Luquet *et al*, 2008).

It is assumed that complex karyotypes reflect genomic instability. Yet there are patterns to be discerned within most complex karyotypes and it seems likely that these patterns represent an accumulation of critical events in the development of AML, as is observed in solid tumours such as colon cancer.

The most frequent abnormalities observed in AML, apart from the standard balanced translocations, are unbalanced rearrangements: gains or losses of whole chromosomes or deletions of part of chromosomes, such as 5q, 7q, 17p and 20q. Monosomies of chromosomes 5, 7, 17 and 20 are also frequently observed and both loss of the whole chromosome and loss of part of one arm should result in a similar genetic outcome: effectively removing a tumour suppressor gene (TSG) from the commonly deleted region of the chromosome, for example TP53 on 17p13.

However, there is increasing evidence that true monosomy of chromosomes 5, 17 and 20 does not exist and that two copies of fragments of these chromosomes are always found if looked for using FISH. These retained segments possibly reflect a second oncogenic effect of chromosomal deletion – indicating the location of oncogenes that are activated or up-regulated by the removal of an adjacent TSG.

No conflict of interest to disclose

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Riverside Theatre
HSANZ: Acute Leukaemia

1100-1200
1130

New Strategies in Acute Promyelocytic Leukaemia

Martin Tallman

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Comprehensive Cancer Center, Chicago, IL, USA*

Since the initial description in 1957, the natural history of acute promyelocytic leukemia (APL) has changed from one characterized by high early mortality to one distinguished by a high cure rate. With routine administration of all-trans retinoic acid (ATRA) combined with chemotherapy in the early 1990's and arsenic trioxide (ATO) in the late 1990's, cure is now achieved in the majority of both newly diagnosed and relapsed patients. ATRA with anthracycline-based chemotherapy for induction and consolidation followed by ATRA plus low-dose chemotherapy maintenance is currently the standard of care for newly diagnosed patients. Early institution of ATRA and aggressive blood product support are critical to reduce induction mortality, reported to be 10% among patients entered on clinical trials, but certainly higher when all patients are considered. The relapse rate among high-risk patients is approximately 20-30% and new strategies include administration of intensified anthracyclines, intermediate- or high-dose ara-C in either induction or consolidation, or ATO as early consolidation. Central nervous system (CNS) prophylaxis for such patients and those with relapsed disease may be important to prevent subsequent extramedullary relapse. Given the excellent outcome for most patients with current therapy and potential short-and long-term toxicities, other new therapeutic strategies have focused on minimizing chemotherapy. Recent studies suggest that patients who are molecularly negative after intensive consolidation may not benefit from maintenance therapy. Most exciting is the combination of ATRA and ATO, given with minimal chemotherapy only for leukocytosis, which is a very effective new strategy for patients who are unable to tolerate anthracyclines or older adults and soon may replace conventional therapy for many, if not most, patients. A subset of patients with very low-risk disease may be cured with ATO alone. Patients with relapsed disease do well with ATO with CNS prophylaxis followed by autologous hematopoietic stem cell transplantation.

Meeting Room 4
ANZSBT: Landmark Studies

1100-1200
1100

Landmark Studies that Have Changed the Practice of Transfusion Medicine: The Top 10 RCTs

Morris A Blajchman

McMaster University and Canadian Blood Services, Canada

Evidence-based medicine (EBM) is a term coined in the late 1980s to describe the process of systematically finding, appraising, and using the available contemporary research findings as the basis for medical/scientific decision making. The process of EBM requires the application of formal rules of evidence in the evaluation of the available medical/scientific literature. The use of EBM by the medical/scientific community implies that every patient, or biomedical system, be managed using of the best evidence available at a particular point of time. Medical/scientific evidence ranges from **level 1** (the best evidence), which are mainly large randomized control trials (RCTs), to **level 5** (the poorest evidence) which comprises mainly anecdotal and other types of poor quality observational evidence. Undocumented expert opinion is thus also considered level 5 evidence! Level 1 evidence represents data from RCTs that are sufficiently large to give clear cut results as well as meta-analyses of all the available large RCTs on a topic. Over the past twenty years there have been approximately 2000 RCTs that have been done to evaluate various transfusion medicine interventions that can be used for the treatment of patients or to choose tools to assess the safety or other aspects of the blood supply. The foci of these randomized control trials have ranged widely from: (1) studying the efficacy of different platelet preparations for the treatment of patients at risk for thrombocytopenic bleeding; (2) the evaluation of leukoreduction in preventing transfusion-related immunomodulatory and other effects; (3) evaluating transfusion triggers for administering RBCs, platelets or plasma; (4) assessing the efficacy of various infectious disease markers in preventing transfusion-transmitted infections; (5) evaluating the role of various bioactive agents in reducing allogeneic transfusion requirements; or (6) studying the effects of allogeneic RBC transfusions on the post-operative length of stay in a hospital or intensive care unit. During this presentation, Dr. Blajchman will present his top ten list of Transfusion Medicine RCTs, ranking them in reverse order according to their quality and clinical impact.

References

1. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1989; 95 (Suppl. 2): 2S-4S.
2. Hébert PC, Wells G, Blajchman MA *et al.* A multicenter randomized controlled trial of transfusion requirements in critical care. *N Engl J Med* 1999; 340: 409-417.
3. Blajchman MA. Landmark studies that have changed the practice of transfusion medicine. *Transfusion* 2005; 45: 1523-1530.

Meeting Room 2/3
ASTH: Anticoagulation

1100-1200
1100

The Future of New Antithrombotics

Sanjeev Chunilal
North Shore Hospital, Waitemata Health, Auckland, New Zealand

Abstract not received at time of going to print

Meeting Room 2/3
ASTH: Anticoagulation

1100-1200
1130

Warfarin Reversal: How Long Do We Have To Wait To Get It Right?

Hatem H Salem

Australian Centre for Blood Diseases, Alfred Hospital and Monash University, Victoria

Although Warfarin was first approved for human use in 1954, we continue to evolve our understanding of the drug and how best to use it and reverse its effects. Prevention of thromboembolic events consequent to atrial fibrillation remains the main indication for the long term use of this drug. While millions around the world are candidates for anticoagulant therapy for this indication, many are denied treatment with numerous studies attesting to the underutilisation of Warfarin in this target population. The main reason for the under prescribing of the drug is related to the risk of bleeding and the need for regular close monitoring. While it is true that bleeding often occurs when the INR is within the therapeutic range, an INR above the therapeutic range is well recognised as a risk factor for bleeding. This is particularly true in the elderly, those receiving concomitant anti-platelet therapy, or those at risk of falls. In many of these patients, reversing the effects of Warfarin is recommended. Patients on warfarin with active bleeding present another indication for warfarin reversal while in others urgent reversal may be required because of emergency surgery. In many other patients receiving Warfarin reversal may be required for a planned surgical or diagnostic procedure. In 2004, the Australasian Society of Haemostasis and Thrombosis published its consensus guidelines for Warfarin reversal. The group stressed the importance of a thorough evaluation of the patient with respect for the potential of bleeding versus the risk of recurrence of thrombosis. Guidelines were presented for managing Warfarin reversal under different scenarios. Unfortunately, and despite best efforts, Warfarin reversal continues to be carried out in a sub-optimal way with many patients requiring urgent reversal receiving either high dose vitamin K alone and or large volume of fresh frozen plasma. Those lucky enough to receive PCC often are administered an inadequate dose of the product.

In my presentation, I will review the various indications for Warfarin reversal highlighting the optimal way to manage these patients. The presentation will emphasize the use of PCC as an efficient and safe method in patients who require urgent Warfarin reversal.

Meeting Room 1
Nurses: Apheresis Update

1100-1200
1100

Immunoabsorption for ABO Incompatible Renal Transplants

Jo-Anne Moodie

North West Dialysis Service, Royal Melbourne Hospital, Vic, Australia

Aim

To describe the North West Dialysis Service (NWDS) experience of performing Immunoabsorption for ABO incompatible renal transplants.

Background

Transplantation from ABO incompatible donors has been avoided in Australia because of a high risk of severe irreversible rejection, the need for splenectomy and powerful immunosuppression. Immunoabsorption of either anti A or B antibodies (Glycorex Glycosorb columns) avoids rejection mediated by anti-blood group antibodies without depletion of other proteins or the requirement for replacement fluid [1]. In 2005 the first use of this technology in Australia was undertaken at the Royal Melbourne Hospital to enable Australia's first ABO incompatible renal transplant.

Method

Since December 2005, 5 patients with ABO incompatibility have been treated by NWDS using the Glycosorb ABO Column. The treatment involves antigen specific adsorption of ABO antibodies, using the conventional Cobe Spectra plasma exchange machine and lines, with the addition of the appropriate column. Treatments are performed pre and post transplantation in conjunction with conventional plasma exchange and immunosuppression, to halt rebound of antibodies. Titre levels are taken pre and post treatment to monitor effectiveness and suitability to undergo transplant.

Results

Experience with immunoabsorption indicates removal and thus reduction of ABO antibodies. Titre levels were reduced by as much as 3 dilutions. All grafts are still functioning, and no incidence of rejection has occurred, after a minimum of 12 months follow up. The use of columns also reduces the side effects experienced during regular plasma exchange, such as decreased fibrinogen levels.

Conclusion

A number of patients with end-stage kidney disease are potentially suitable for living related and unrelated transplantation, if it were not for blood group incompatibility. The use of immunoabsorption columns reduces titre levels and is a safe adjunct to treatment without adverse effects. Performing ABO incompatible transplants at NWDS provides an opportunity to patients that otherwise may not be able to undergo a transplant.

1 Kumlien, Ullstrom, Losvall, Persson and Tyden 2005

Meeting Room 1
Nurses: Apheresis Update

1100-1200
1130

On the Road to Accreditation With a Little Help From our Friends

Susan Price, Andrew McCutchan and Joanne Kanakis

Townsville Cancer Centre, The Townsville Hospital

The Townsville Health district provides care to over 600,000 people. The Townsville Cancer Centre is the only service north of Brisbane which has an Apheresis/Bone Marrow Transplant Unit. Since 1996 The Townsville Cancer Centre at the Townsville Hospital has been performing Therapeutic Apheresis procedures and Haemopoietic Progenitor Cell (HPC) collections.

During 2004-2005 TGA developed a position statement that stated all HPC's will now be required to meet licensing requirements using the Foundation for the Accreditation of Cellular Therapy (FACT) Standards. After several meetings with identified stakeholders, it was agreed that the National Pathology Accreditation Advisory Council (NPAAC) would develop the Australian Standard based on FACT quality principles. Since the first draft was released in 2006 we have slowly been transforming our service with the goal of becoming an accredited facility. We've has great assistance from fellow Qld Health and non Qld Health facilities.

In this presentation, the Apheresis Coordinator, Bone Marrow Transplant Coordinator and Quality Manager give an insight to where we started on the accreditation journey, how far we have come and where we are planning to go.

Riverside Theatre

1200-1300

Barry Firkin Oration

Evidence-based Medicine: Wish-fulfilment or Search for Excellence?

Alex Gallus

Flinders Medical Centre, Bedford Park, SA, Australia

Abstract not available

Riverside Theatre
Combined HSANZ / BMTSAA/ Nurses: Bone Marrow Transplantation

1400-1530
1400

Timing of Transplantation and Choice of Conditioning in MDS and MPD

H Joachim Deeg^{1,2} and Bart Scott^{1,2}

¹Fred Hutchinson Cancer Research Center and ²University of Washington School of Medicine, Seattle, WA, USA

Both myelodysplastic syndromes (MDS) and myeloproliferative disorders (MPD) are clonal marrow diseases, potentially curable by hematopoietic stem cell transplantation (HCT). The optimum timing, however, and the best conditioning strategy have remained controversial, and the availability of a growing number of non-transplant modalities is raising additional questions. Factors to be considered include disease stage, prognosis with or without non-HCT therapy, patient age, and comorbid conditions. Is the patient a risk taker? Is quality of life the primary objective? With MDS, generally patients in IPSS risk groups intermediate-2 and high, and select patients with intermediate-1 risk should be considered for transplantation early in their course; the remaining patients are likely to benefit from more conservative management initially. Transfusion dependence, marrow fibrosis and phenotypic aberrancies of marrow cells may be additional reasons for earlier transplantation. Patients who present with transformation to acute leukemia should probably receive 'debulking' chemotherapy before undergoing HCT. Among patients with less advanced/low risk MDS (<5% marrow myeloblasts, generally IPSS risk groups low and intermediate-1), the 3-year survival probability is 65% to 75% with HLA-matched related and unrelated donors. Among patients with more advanced/high-risk disease (≥5% marrow blasts, IPSS risk groups intermediate-2 and high), the probability of post-transplant relapse ranges from 10%-40%, and, as a result, relapse-free survival is inferior. The karyotype is the strongest risk factor for relapse. Patients with MPD (other than CML) have generally come to HCT because of progressive myelofibrosis and peripheral blood cytopenias or transformation to acute leukemia. Post-HCT survival in remission may be as high as 75% in the first case (relapse is infrequent), but only 30–35% in the second. Both conventional and reduced-intensity conditioning (RIC) have been used successfully. RIC allows for a decrease in non-relapse mortality and for application of HCT even in patients 60–70 years of age. However, in patients with either MDS or MPD, relapse rates after RIC tend to be higher than with conventional regimens. "Re-intensification" of RIC may overcome this problem. Graft-versus-host-disease, acute and chronic, has remained a frequent and challenging problem for all patients. The impact of epigenetic modification or JAK2 inhibitors on transplant decision and outcome remains to be determined.

Riverside Theatre
Combined HSANZ / BMTSAA/ Nurses: Bone Marrow Transplantation

1400-1530
1445

Therapeutic Applications of Mesenchymal Stromal Cells in Haemopoietic Stem Cell Transplantation

Ian Lewis

Division of Haematology, SA Pathology, Adelaide SA, Australia

In addition to haemopoietic stem cells (HSC), bone marrow (BM) also contains Mesenchymal Stromal Cells (MSC), which can differentiate into multiple mesodermal lineages including bone, cartilage, muscle and fat. In the laboratory these cells are isolated from the adherent layer of BM and appear as fibroblast like cells which can be induced to differentiate into bone, cartilage, muscle and other tissues. This property has led to the suggestion that MSC may have a role in tissue repair. BM MSC support haemopoiesis and may have an important role in promoting HSC engraftment particularly following cord blood transplantation (CBT). In a NOD/SCID mouse model we compared engraftment rates of double-unit CBT with MSC co-transplantation. We show at equivalent cell dose, single and double unit CBT lead to similar engraftment, suggesting the enhanced engraftment seen with double unit CBT reflects a cell dose effect. MSC co-transplantation enhanced engraftment of both single and double unit CBT and may be a potential strategy to be explored in the clinic.

MSC have also been shown to have unique immunomodulatory properties. They possess both immunogenic and immunosuppressive properties. This property has been exploited in the treatment of severe acute graft versus host disease (aGVHD), a life threatening immunological complication of allogeneic bone marrow transplantation, with encouraging preliminary results. The Royal Adelaide Hospital has participated in an international multi-centre study to evaluate the effectiveness of MSC infusion in severe steroid refractory aGVHD. Of 55 patients treated, 30 patients had a complete response and 9 showed improvement. Complete responders had lower transplantation-related mortality 1 year after infusion than did patients with partial or no response (37% vs 72%; $p=0.002$) and higher overall survival 2 years after haemopoietic-stem-cell transplantation (53% vs 16%; $p=0.018$). In conclusion, MSC infusion is a promising modality in the treatment of steroid resistant aGVHD.

Meeting Room 4
ANZSBT: Molecular Advances in Transfusion Medicine

1400-1530
1400

Experience Using DNA-based Assays to Predict Blood Group Antigens

Marion Reid

New York Blood Center, New York, NY, USA

We have over a decade of experience using PCR-based laboratory developed tests (LDTs) to predict a blood group in two main areas. (1) In the prenatal setting: we test DNA from a fetus at risk for hemolytic disease of the newborn for *RHD*, *RHCE*c*, *KEL1/KEL2*, and other blood groups for which the molecular basis is known. Regardless of the implicated antibody(ies), we test for *RHD* to preempt a request for D-negative blood for an intrauterine transfusion. (2) In the transfusion setting: we test DNA from a patient who has been recently transfused, whose RBCs are positive in the direct antiglobulin test, to distinguish allo from auto antibodies, and to predict the presence of a weakly expressed antigen when a patient is unlikely to be immunized if transfused with antigen-positive RBC products. For patients and donors, we use PCR-based LDTs to predict the blood type when an antisera is in short supply or is weakly reactive, to resolve typing discrepancies between reagents of the same apparent specificity, to identify the molecular basis of unusual serological results and new antigens, and to type stored DNA from donors and a transplant patient after an antibody arises. We also analyze our in-house antibody identification panel for selected antigens. We have considerable experience using a beadchip platform and are currently using it to test donors to increase our antigen-negative inventory and to find donors whose RBCs lack a high-prevalence antigen. Having access to a larger number of antigen-negative donors, albeit a prediction requiring serological confirmation, should improve patient care in regard to transfusion therapy. The high-throughput technologies would make it feasible to match donor to the type of a patient, especially for RH alleles in patients with sickle cell disease. The extent to which this becomes a reality may be dictated by cost.

Meeting Room 4
ANZSBT: Molecular Advances in Transfusion Medicine

1400-1530
1445

Platelet Antigens

Paul Metcalfe

National Institute for Biological Standards and Control, Potters Bar, Hertfordshire, UK

To date 24 platelet-specific alloantigens have been defined by immune sera of which 12 are grouped in 6 bi-allelic systems (HPA-1, -2, -3, -4, -5 & -15). For the remaining 12, alloantibodies against the thetical but not the anti-thetical antigen have been observed. The molecular basis of 23 of the 24 serologically defined antigens has been resolved and these have been designated as Human Platelet Antigens (HPA). In all but one of the 23, the difference between self and non-self is defined by a single amino acid substitution, caused by a single nucleotide polymorphism (SNP) in the gene encoding the relevant membrane glycoprotein. The exception is HPA-14bw which is the result of an in-frame single codon deletion in glycoprotein IIIa. The HPA nomenclature system was adopted in 1990 to overcome problems with the previous nomenclature and was revised again in 2003.

For the 6 bi-allelic HPA systems, SNP typing has become routine and a variety of methods are in use. Several large scale studies have provided reliable information on allele frequencies and some have indicated significant differences between populations.

Meeting Room 2/3
ASTH: Von Willebrand Disease

1400-1530
1400

Molecular Aspects of vWD

David Lillicrap

Dept. Pathology & Molecular Medicine, Queen's University, Kingston, Canada

Von Willebrand disease (vWD) is the most common inherited bleeding disorder characterized in humans with a prevalence of symptomatic disease of approximately 1 in 1,000. The mucocutaneous bleeding problems that manifest in vWD are due to quantitative and/or qualitative defects in the multiligand adhesive protein von Willebrand factor (vWF).

The gene that encodes vWF is located on the short arm of chromosome 12. The gene spans 178 kb of genomic DNA and comprises 52 exons ranging in size from 40 bp (exon 50) to 1.3 kb (exon 28). Complicating the genetic analysis of vWD, there is a partial vWF pseudogene on chromosome 22 that duplicates exons 23-34 of the chromosome 12 gene with 3% sequence variation. In addition to its large size and genomic complexity, the vWF gene sequence is also highly polymorphic in nature with >80 non-synonymous single nucleotide polymorphisms in the coding region.

The three types of vWD represent either quantitative (types 1 and 3) or qualitative (type 2) traits affecting vWF hemostatic function. Type 3 vWD is the least frequent form of the disease with a prevalence of between 0.5 and 6 per million. This vWD variant is inherited as a recessive trait with transmitting parents showing no clinical or laboratory evidence of the disorder. The genetic basis of type 3 disease involves a heterogeneous collection of null mutations ranging from large vWF gene deletions to a group of missense mutations that presumably prevent secretion of the protein from its cell of synthesis.

There are four subclasses of type 2 vWD: 2A, 2B, 2M and 2N. These variants interfere with vWF's ability to interact with platelets and factor VIII, respectively. In the vast majority of cases, the genetic basis of these conditions involves missense mutations in the vWF gene.

Finally, the genetic pathology of type 1 vWD, which comprises ~80% of vWD cases, is now beginning to be characterized and appears to represent a miscellany of mutation types both at the vWF locus and at other genetic loci.

Meeting Room 2/3
ASTH: Von Willebrand Disease

1400-1530
1440

Testing for vWD

Simon Brown

Haemophilia Centre, Royal Children's Hospital, Brisbane; Queensland Blood Management Program, Queensland Health, Brisbane; Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, Queensland

Despite being the most prevalent inherited bleeding disorder, von Willebrand disease (vWD) continues to pose problems with respect to its accurate diagnosis and sub classification. The problems faced by clinicians and laboratories particularly relate to the diagnosis of a partial quantitative deficiency of von Willebrand factor (vWF). The classification of vWD has undergone a number of modifications since the immunological characterisation of vWF and factor VIII, and the description of the utility of Ristocetin in vWD diagnosis in the early 1970's. Cloning of the vWF gene in the 1980's has lead to a detailed understanding of the molecular defects underlying type 2 vWD. This molecular knowledge has contributed to a re-evaluation of laboratory tests for vWD, in particular laboratory tests of vWF function. However, two large international studies that aimed to investigate the utility of molecular testing in the diagnosis of type 1 vWD have demonstrated the complex nature of a partial quantitative deficiency of vWF (pqd vWF). To date there is no single diagnostic test for a pqd vWF. The limitations of current laboratory tests need to be considered along with the pre-analytical variables and clinical situation when approaching the diagnosis of vWD.

Meeting 2/3
ASTH: Von Willebrand Disease

1400-1530
1505

Treatment of von Willebrand Disease

Scott Dunkley

Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Issues surrounding the treatment of vWD are always highly contentious with regard to the need for therapy, the intensity of therapy and the type of therapy required. The flip side of this of course is that many patients, particularly those with type 1 vWD, do well even when subjected to a bleeding challenge such as surgery. Many persons with borderline VWF levels range may best be labelled as such rather than vWD and therapy individualised. In addition, therapy has the potential to cause harm and the spectre of blood borne disease transmission hangs over us particularly in the absence of recombinant therapy. It is appropriate to consider venous thrombosis prophylaxis in patients with vWD at times of risk including during therapy for surgical procedures.

A recent Australian retrospective study reinforced the efficacy and safety of DDAVP in mild to moderate type 1 vWD. However, in type 2 and 3 vWD, and with major surgical procedures, VWF containing factor concentrates are generally required for adequate haemostasis. The recently completed prospective Australian surgical 'Biostate' study has shed some light on dosing regimes required for surgical haemostasis and the differences compared to haemophilia A. Controversy exists on whether FVIII or VWF:RCo levels should be used to monitor such therapy and important insights have been gained from this study. Further, we will soon be faced with a choice of factor concentrates with differing FVIII to VWF:RCo ratios that may be selected depending on the specific clinical circumstance. Children with type 3 vWD are now all considered for primary prophylaxis. Finally, AHCDO have recently developed guidelines for the management of pregnancy in persons with vWD and inherited bleeding disorders and this also will be reviewed.

Riverside Theatre
HSANZ: Chronic Lymphocytic Leukaemia
Sponsored by Roche

1600-1730
1600

The Cell of Origin in Chronic Lymphocytic Leukemia

Nicholas Chiorazzi

The Feinstein Institute for Medical Research, Manhasset, New York, USA

While it has been relatively easy to determine the cell of origin of certain of the B-cell lymphoproliferative disorders (e.g. follicular cell and marginal zone lymphomas), for chronic lymphocytic leukemia (CLL) the issue is still a matter of debate. This is also complicated by the divergent clinical courses of patients whose leukemic clones differ in the presence or absence of IgV_H gene mutations, “mutated CLL” (M-CLL) and “unmutated CLL” (U-CLL), respectively. In this presentation, we will discuss the molecular, cellular, and phenotypic features of CLL cells and relate these to the known human and murine B-cell subsets.

Based on several considerations, the normal human B-cell equivalent to a CLL cell likely [1] expresses CD5, constitutively or after stimulation, as well as other markers (CD23 and CD27) indicative of activation *in vivo*, [2] resides primarily in solid lymphoid tissues, and [3] expresses characteristic BCR structural features, i.e., unmutated IgV_H genes coding for polyreactive BCRs/mAbs or somatically mutated IgV_H genes coding for oligo/mono-reactive BCRs/mAbs. In addition, it is likely that selection and drive by either autoantigens or foreign antigens or a combination of both influences the “choice” of which normal B cells or sublineage is promoted into leukemic transformation.

These parameters suggest that U-CLL and M-CLL derive from distinct normal B-cell precursors. However, gene expression profiling suggests that the two CLL subgroups do not differ from each other in a large number of differentially expressed genes. Therefore, the most parsimonious scenario is that all CLL cases, regardless of IgV_H gene subgroup, derive from marginal zone B cells, which can express unmutated or mutated Ig V genes coding for polyreactive or mono/oligoreactive Igs. On the other hand, if one considers that the similarity in the expression phenotypes of U-CLL and M-CLL reflects a common transformation process (not a common ancestral lineage), then the derivation of U-CLL from two distinct B-cell subsets is plausible (e.g., U-CLL from the human equivalent of murine B-1 cells and M-CLL from MZ B cells, which could have developed mutations at an extra-follicular site). The possibility that M-CLL derive from follicular B cells that developed IgV_H mutations in classical GCs cannot be excluded, especially if such cells subsequently migrated and took up residence in MZ.

Riverside Theatre
HSANZ: Chronic Lymphocytic Leukaemia
Sponsored by Roche

1600-1730
1635

The Yin and Yang of Therapeutic Research in CLL

Michael J Keating & William Plunkett

University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Translational research is frequently misunderstood, it implying that identifying pathways and targets will lead to successful therapy. The frequent ineffectiveness of these agents in the clinic is frustrating. Combination therapy emphasized agents with non-overlapping toxicity and different modes of action. However many clinical studies combine agents with no mechanism-based strategy, ending up as being A + B versus B + C with minor differences in outcome and subtle differences in toxicity.

The ability to obtain CLL cells from patients prior to treatment allows exploration of different mechanisms. When clinicians who understand disease work with basic scientists who understand the pharmacology/pharmacodynamics, studies often succeed. The interaction of agents with synergistic outcome is paramount. In CLL, fludarabine generated great enthusiasm. So far we still do not know how this agent works or the target. The alkylating agents are also effective and Dr Plunkett and colleagues demonstrated that fludarabine would enhance the cytotoxicity of alkylating agents leading to the development of the fludarabine/cyclophosphamide combination now established as the best combination chemotherapy program available in CLL.

In parallel studies the interaction of fludarabine (F) and cytosine arabinoside (ara-C) with platinum analogs has been informative in the development of combination therapies. The interaction between oxaliplatin (O), fludarabine, cytosine arabinoside, and rituximab (R) has been dissected. The addition of F + ara-C (A) has increased cell killing by oxaliplatin in vitro and in vivo and led to a very effective regimen (OFAR) in refractory CLL and Richter's syndrome. New agents such as flavopiridol and SNS 032 are cell cycle checkpoint inhibitors, but their interaction with RNA polymerase and down-regulation of anti-apoptotic proteins may well be a more important mechanism which can be measured in the leukemic cells and targeted and an appropriate dose selected. Nelarabine is an agent with marked activity in T-cell leukemias including T-cell prolymphocytic leukemia and surprisingly in B-cell CLL. High ara-G triphosphate levels, the active drug formed after administration of nelarabine correlate with response. Fludarabine and presumably other purine analogs enhance the formation of ara-GTP and should improve the effectiveness of these regimens. A close working relationship between the clinicians and pharmacologists emphasizes the strengths of each individual so that the synergism of the relationships leads to more effective mechanism-based therapy.

Riverside Theatre
HSANZ: Chronic Lymphocytic Leukaemia
Sponsored by Roche

1600-1730
1710

BH3 Mimetic Antagonists of BCL-2 – Potential New Therapy for CLL and Lymphoproliferative Diseases

Andrew Roberts^{1,2,3}, Kylie Mason^{1,2}, Seong Lin Khaw^{1,3}, David CS Huang^{1,3}

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³*The University of Melbourne, Parkville, Victoria, Australia*

CLL is an archetypical example of how failure of apoptosis is central to the development and phenotype of malignancy. The anti-apoptotic protein, BCL-2, is uniformly overexpressed by B-CLL cells, leading to a pathological accumulation of these cells. Further, as in other B cell lymphoproliferative diseases and other cancers, overexpression of BCL-2 results in resistance to cytotoxic agents. For these reasons, a promising avenue to therapy for incurable lymphoid tumours is to directly target BCL-2 and related pro-survival proteins. One approach is to mimic their physiological antagonists, the BH3-only proteins. In previous work, we had determined that cell death induced by BH3 mimetics such as ABT737 was dependent upon the pro-apoptotic proteins Bax or Bak, providing evidence of exquisite specificity of action. More recently, we have found that ABT 737 is highly active in vivo against murine lymphomas, and efficiently induces killing in vitro of primary cells from chronic lymphocytic leukaemia patients, including those refractory to fludarabine and other cytotoxic agents. Further, ABT737 synergises with conventional cytotoxic agents, both in vitro and in vivo in these preclinical settings. The orally available BH3 mimetic, ABT263, which like ABT737 inhibits the function of both BCL-2 and BCL-xL, commenced clinical trials in late 2006. While the initial Phase I studies remain ongoing, preliminary data indicate significant single agent activity (Wilson et al, ASH 2007; Roberts et al ASCO 2008) in CLL.

Meeting Room 4
ANZSBT: Transfusion Risks

1600-1730
1600

Anaphylaxis: Diagnosis and Management

Simon Brown

Emergency Medicine, Royal Perth Hospital, University of Western Australia & Centre for Clinical Research in Emergency Medicine, Western Australian Institute for Medical Research

Anaphylaxis is a systemic reaction affecting multiple organ systems characterised by vasodilation (generalized erythema), extravasation (angioedema, urticaria, airway oedema) and smooth muscle contraction (bronchospasm, cramping abdominal and pelvic pains). In severe reactions these processes cause severe upper and/or lower airway obstruction, hypoxaemia and/or hypotension due to mixed hypovolaemic-distributive (and possibly also cardiogenic) shock. Anaphylaxis may be allergic (requiring prior sensitization and initiation of a specific immune response) or non-allergic. Allergic causes may be generally classified as IgE mediated or non-IgE mediated. Anaphylaxis in childhood is caused most often by food, with bronchospasm being more common, and there is usually a background of atopy and asthma. Poorly controlled asthma is the main risk factor for death in this age group. Venom and drug-induced anaphylaxis is more common in adults, in whom hypotension is more likely to occur. Age >35 and previous severe reactions are the main risk factors for hypotension and death.

Although many episodes are easy to diagnose by the combination of characteristic skin features with other organ effects, this is not always the case and a workable clinical definition of anaphylaxis and useful biomarkers of the condition have been elusive. Diagnosis can be difficult, with skin features being absent in up to 20%. Anaphylaxis must be considered as a differential for any acute onset respiratory distress, bronchospasm, hypotension or cardiac arrest. At post-mortem, diagnostic features are present in only 50% of those diagnosed clinically as anaphylaxis. Serial measurement of mast cell tryptase is more sensitive and specific than a single measurement. Other mediator assays are available in research settings.

The cornerstones of initial management are the supine position, intramuscular adrenaline into the lateral thigh (0.01 mg/kg up to 0.5 mg), intravenous fluid resuscitation, support of the airway and ventilation, and supplementary oxygen. If response is inadequate, the next step is an intravenous infusion of adrenaline. For severe &/or refractory bronchospasm, additional bronchodilator treatment with continuous salbutamol and corticosteroids are used. Nebulised adrenaline may be a useful adjunct for upper airway obstruction. For hypotension that is refractory to treatment consider more aggressive volume resuscitation, selective vasopressors, atropine (for bradycardia), inotropes that bypass the beta adrenoreceptor, and bedside echocardiographic assessment. Observe for at least 4 hours after the resolution of all symptoms (longer/overnight for severe reactions with hypotension and/or hypoxia). Refer to an allergist to assist with diagnosis as to the most likely trigger, allergen avoidance measures, risk assessment, preparation of an action plan and education on the use of self-injectable adrenaline.

Management guidelines continue to be opinion- and consensus-based, with retrospective studies accounting for the vast majority of clinical research papers on the topic. The clinical spectrum of anaphylaxis including major disease subgroups requires clarification, and validated scoring systems and outcome measures are needed to enable good quality prospective observational studies and randomised controlled trials.

A32

Meeting Room 4
ANZSBT: Transfusion Risks

1600-1730
1625

Transfusion-related Anaphylaxis: Investigations and Management

Krishna G Badami

New Zealand Blood Service, Christchurch, New Zealand

Anaphylaxis is an IgE-mediated, severe, systemic, allergic reaction. Features include hives, facial swelling, stridor, wheeze, breathlessness, hypotension, tachycardia, nausea, abdominal cramps & diarrhoea & severe anxiety.

Following transfusion, localised, minor reactions (e.g. urticaria or wheeze) are common but anaphylactic reactions are rare (1:20000-40000 transfusions). Anaphylactic, and possibly also milder, reactions are ultimately caused by mast cell degranulation. This can result from IgE cross-linked by a re-encountered foreign plasma protein antigen on the mast cell surface as well as directly acting agents such as complement intermediates (C3a, C5a), leukotrienes and opioids.

Transfusion-related allergic reactions are more common with predominantly plasma containing components such as FFP and platelets but the specific trigger mostly remains undetermined. Exposure to IgA in IgA-deficient patients with IgE anti-IgA is a well-recognised, though infrequently-found cause. Other plasma proteins (e.g. haptoglobin in Japanese) may be responsible. In addition, non-transfusion-related drug & food allergens and the passive transfer of donor-derived IgE should be considered.

Clinical features overlap those occurring with other serious transfusion-related adverse events such as TRALI, TACO, HTR & bacterial sepsis but there are differentiating features. The diagnosis of anaphylaxis is essentially clinical. IgA (remote from transfusion), anti-IgA and paired serum mast cell tryptase measurements may be helpful. The predictive value of IgA and anti-IgA testing in the absence of previous reactions is low and while the specificity of raised mast cell tryptase is high, levels may be normal in anaphylaxis.

In addition to stopping the transfusion, prompt treatment with antihistamines, iv fluids, oxygen, bronchodilators, adrenaline, and steroids is required. To prevent future reactions, pharmacological & other non-transfusion alternatives, premedication, autologous donations, components from IgA-deficient donors or washed cellular components and low-IgA products should be considered.

Meeting Room 4
ANZSBT: Transfusion Risks

1600-1730
1700

Transfusion Transmissible Viral Infections

CR Seed

Australian Red Cross Blood Service

The Australian Red Cross Blood Service collects over one million homologous blood donations every year from voluntary non-remunerated blood donors. Each donation carries the potential to transmit a variety of blood borne viruses including Hepatitis B & C, human immunodeficiency virus (HIV), human T lymphotropic virus (HTLV), Human Cytomegalovirus (CMV) and dengue virus (DENV). The so called 'safety tripod' consisting of careful donor selection, state-of-the-art testing and pathogen inactivation minimises, but does not entirely eliminate the risk of transfusion transmission. However, the level of risk reduction achieved for the principal viruses over the past three decades has been remarkable. For example the risk of Hepatitis C, which was assessed as 1-2% in Australia in the late 1980's is currently estimated to be in excess of four orders of magnitude lower at approximately 1 in 3 million. This risk reduction has been principally driven by the initial implementation and subsequent improvement in viral screening tests, the most recent of which was the addition in 2000 of HIV and HCV RNA to the existing antibody based testing.

Despite this success there remains an ongoing threat from established, as well as emerging viruses particularly where an appropriate screening test is unavailable. An example is the threat of DENV which now appears to be transfusion transmissible and although not endemic in Australia, causes regular outbreaks in Northern Queensland. In the absence of a suitable high throughput screening test the risk to the blood supply is currently mitigated by additional donor selection measures implemented at the commencement of an outbreak. Donors who reside in, or have visited the affected area are identified by additional 'supplementary' donor questions. Those identified are temporarily restricted from donating fresh blood components although plasma for further fractionation which is subject to dedicated viral inactivation procedures shown to adequately inactivate DENV, is permissible. Although this strategy is effective in managing the risk, it results in a loss of valuable blood components.

One future option to avoid such losses in the absence of a test is the application of physicochemical pathogen reduction techniques for cellular components which offer, through chemical means the ability to inactivate a range of viral agents. Despite the potential advantages of such a 'catch all' solution there remain several hurdles to implementation including; the lack of a single method applicable to all components, lack of universality for all infectious agents, concern over toxicity of residual chemicals and a perception of a lack of cost effectiveness.

Ultimately, protecting the blood supply from transfusion transmissible viruses requires continuous vigilance and the war is far from over!

A34

Meeting Room 2/3
ASTH: How Do I Treat?

1600-1730
1600

Antiphospholipid Antibody Syndrome

Chris Ward

Northern Blood Research Centre, University of Sydney; Department of Haematology and Transfusion Medicine, Royal North Shore Hospital, St Leonards, NSW Australia

Antiphospholipid antibodies (APL) are a heterogeneous and poorly-understood class of autoreactive antibodies that prolong clotting times *in vitro*, but are associated with an increased risk of arterial and venous thromboembolism *in vivo*. Advances in basic science have shown that the major ligand for APL is beta2-glycoprotein I (GPI), and that thrombogenic APL can induce cellular and procoagulant changes by binding to membrane-associated proteins such as GPI. A wide variety of laboratory methods can be used to test for APL, but their correlation with clinical parameters, such as the risk of a first or recurrent vascular event, remains poor. The updated criteria for the APL syndrome include arterial, venous and microvascular thromboembolism, or obstetric events in the presence of a persistent APL. This diagnosis can only be made retrospectively, and there are marked differences between the cohorts in the literature with primary autoimmune disorders and those who present first with thromboembolism. APL are common in the general population, often transient in response to infection, and most of these individuals will not develop a clinical problem.

Effective anticoagulation is a mainstay of therapy, and recent studies have shown that an increased intensity of warfarin therapy (INR >3.0) is not necessary in the majority of patients. The presence of a persistent lupus anticoagulant may be an indication for prolonged or indefinite warfarin after a first venous thromboembolism. Longerterm LMWH therapy may be used in patients who develop thrombosis on warfarin, and there may be a role for antiplatelet therapy in selected cases. Catastrophic APL syndrome is a rare situation where maximal anticoagulation must be combined with strong immunosuppression, to remove the pathogenic antibody. Patients with this syndrome of multiorgan failure have a high mortality despite optimal therapy. The importance of antiphospholipid antibodies in pregnancy is still uncertain – although there is an association with miscarriage and other adverse pregnancy outcomes, there are only limited studies to guide antenatal therapies. APL remain a challenge for pathologists and clinicians alike.

Meeting Room 2/3
ASTH: How Do I Treat?

1600-1730
1630

PE in Pregnancy

1630

Claire McLintock
Auckland City Hospital, Auckland, New Zealand

Abstract not available at time of going to print

Meeting Room 2/3
ASTH: How Do I Treat?

1600-1730
1700

Venous Thrombosis in Unusual Sites

Harry Gibbs

Dept of Vascular Medicine, Princess Alexandra Hospital QLD

More than 90% of all cases of deep vein thrombosis (DVT) occur in the lower extremities. Deep vein thrombosis does however occur in other sites. DVT of the upper extremity may occur spontaneously or with indwelling vascular devices, i.e. catheters or pacemakers. The majority of spontaneous upper extremity DVT occurs due to compression of the subclavian vein at the thoracic. Upper extremity DVT is associated with pulmonary embolism in about 30% of cases, although this is less commonly fatal than with lower extremity DVT. For this reason, however, it is usual practice to use anticoagulant therapy for three months. Subsequent annual recurrence rates of about 3% are lower than for lower extremity DVT. The post-thrombotic syndrome occurs less frequently with upper extremity DVT than with lower extremity DVT and patients can be reassured that post-thrombotic of a severity that interfere with quality of life are very rare. In spite of this, it has been suggested that more aggressive approaches to management are required including catheter-directed thrombolysis, which is usually followed by first rib resection. This approach confers considerable morbidity due to a significant increase in the risk of bleeding and the potential for nerve or pulmonary complications from surgery. This aggressive approach to upper extremity DVT should not be regarded as standard therapy and should be further evaluated in appropriate clinical trials. Renal vein thrombosis occurs in patients with the nephrotic syndrome and may lead to deterioration in renal function. Renal function often subsequently improves. Anticoagulant therapy is indicated in this situation. Renal vein thrombosis may also occur in the presence of a renal cell carcinoma where there is endovascular spread. In this situation a combination of tumour and thrombus may extend into the inferior vena cava and from there to the right atrium. This should be regarded as tumour rather than thrombus and treated accordingly. Mesenteric venous thrombosis has a wide spectrum of clinical presentation from asymptomatic to rapidly fatal extensive bowel infarction. Mesenteric venous thrombosis may be spontaneous or secondary to intra-abdominal abnormality such as sepsis, surgery or neoplasia. Spontaneous mesenteric venous thrombosis is commonly associated with thrombophilic states and in particular with myeloproliferative disorders. The reason for the association between myeloproliferative disorders and mesenteric venous thrombosis is poorly understood. Anticoagulant therapy is indicated for mesenteric venous thrombosis. Cerebral sinus thrombosis usually presents as headache and may be associated with cerebral infarction. There is a high incidence of haemorrhagic transformation of cerebral infarction due to cerebral sinus thrombosis but anticoagulant therapy should nonetheless be administered. The prothrombin gene mutation is particularly associated with cerebral sinus thrombosis and the risk greatest in women receiving the combined contraceptive pill, who have the prothrombin gene mutation.

Summary

Deep vein thromboses in unusual sites are generally treated in the same fashion as for lower extremity DVT. Aetiological differences, however, are often present and differ according to the site involved.

Meeting Room 1
Nurses: Non-malignant Haematology

1600-1730
1600

Iron Deficiency Anaemia (IDA) – A Neglected Diagnosis and Common Reason for Transfusion (and Over-transfusion) in Stable Patients

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Aim

To examine the frequency of IDA in transfused patients.

Method

Retrospective audits were conducted on consecutive red cell transfusions in 6 teaching hospitals in Adelaide in May and October 2006. Data was entered into Auditmaker™ software. Iron deficiency was defined as definite if the ferritin level was <20 µg/L. If iron studies were not performed or showed a ferritin <100 µg/L and transferrin saturation <20%, then CBE and film comments were reviewed independently by 2 haematologists to determine if IDA was likely.

Results

232 transfused adult patients were reviewed (47% female, mean age 70 years, range 19-98). In 11/221 (5%) of transfusion episodes the patient had definite IDA and in 43/221 (19%) the patient was assessed as having likely IDA, with an overall rate of 24%. IDA was more frequent in transfused obstetric/gynaecology patients (5/12 -42%) than medical (29/124 -23%) and surgical patients (20/85 -24%). 191/232 (82%) patients were stable. The frequency of IDA was higher in stable (50/191 -26%) than unstable patients (4/41 -10%). Post transfusion Hb was > 100 g/L in 73% and > 110 g/L in 33% of episodes. Only 13% of iron deficient patients received a single unit transfusion.

Conclusions

Barriers to best practice need attention at a national level to ensure that iron (oral and intravenous) become the cornerstone of therapy to optimise patient outcomes, reduce inappropriate use of red cells and the associated economic costs.

No conflict of interest to disclose.

Meeting Room 1
Nurses: Non-malignant Haematology

1600-1730
1630

A Practical Approach to Haemophilia

Claire Bell

Haemophilia Centre of WA, Royal Perth Hospital, Perth, WA

The aim of the haemophilia treatment centre (HTC) nurse is to provide comprehensive care for patients with bleeding disorders. The HTC nurse is usually the first point of contact for patients with bleeding disorders. Our role is multi-dimensional and involves assisting in attaining a correct diagnosis, counselling and support, acute and peri-operative management of the bleeding disorder, assisting patients with travel arrangements and ensuring patients have an emergency treatment plan. HTC nurses are also responsible for ordering plasma/recombinant factor supplies and data entry. Education is also an important role, both staff education and community education. It is essential that HTC nurses work with the haemophilia community to ensure that the service provided meets their needs.

At the Royal Perth Hospital HTC we are constantly trying to improve the service provided. An example is our recently commenced nurse run haemophilia carrier clinic, which aims to encourage more haemophilia carriers to attend the HTC. This is the beginning of nurse run clinics at the Royal Perth Hospital HTC which are the result of the HTC nurse changing from a clinical nurse consultant to a nurse practitioner position.

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Nurses: Non-malignant Haematology

1600-1730
1650

A Practical Approach to Thrombosis

Karen Flounders

Royal Perth Hospital Perth WA Australia

The Thrombosis Unit, at Royal Perth Hospital, provides a seamless service for acute Venousthromboembolism (VTE) from initial presentation to long term management. The Unit provides assessment for the long-term management of thrombophilia, recurrent VTE and post thrombotic syndrome. The Thrombosis Unit also provides a unique service in Perioperative Ambulatory Anticoagulation. This service responds to referrals from a variety of multi-disciplinary teams to ensure the safe provision of health care in patients already taking anticoagulants who are undergoing a wide variety of surgical procedures. All patients presenting to the Emergency Department with VTE are seen in the Thrombosis Unit where their care is planned and coordinated usually without the need for an overnight stay in hospital. The Thrombosis Unit also takes part in clinical trials for new emerging anticoagulants. The role of the Clinical Nurse Consultant is to coordinate the acute and long term care of all patients with VTE so that they receive the best possible care available to us at the time. With the Clinical Nurse Consultant Role being developed into a Nurse Practitioner role it is hoped that the service provided will be even more seamless with the introduction of Nurse Prescribing and Nurse Led Clinics.

Meeting Room 1
Nurses: Non-malignant Haematology

1600-1730
1710

Establishing a Haemophilia Nursing Program

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Haemophilia is an inherited bleeding disorder with no cure. In haemophilia A clotting factor VIII is missing and in haemophilia B clotting factor IX is missing.. The disease is characterised in its severest form by spontaneous bleeding into joints, muscles and organs.

Bleeding after trauma or surgery is catastrophic and frequently fatal unless treated. Globally, 75 % of people with haemophilia have no access to treatment and die young or become severely crippled. Treatment is to replace the missing clotting factor.

In South Africa, there is sufficient replacement clotting factor but this treatment is not readily accessible to all. The Department of Health recognised that all people with haemophilia should receive treatment regardless of where they live and that to achieve this, training of registered nurses in haemophilia care needed to be prioritised.

In 2002, the first haemophilia nurses' training course was undertaken and has been run annually since. The course is run over five days and includes lectures and practical demonstrations. Course content includes overview of haemophilia and diagnosis, treatment, von Willebrand's Disorder, women and bleeding disorders and product safety. The participants meet people with haemophilia so they can collect information to use as a case history, which is presented to the rest of the group. An examination completes the course.

The course has been shown to be successful by evaluations from the participants, people with haemophilia and their families. The number of haemophilia treatment centres has increased from 4 to 8 and the number of haemophilia clinics across the nation has increased. The haemophilia database shows an increase in numbers of people with haemophilia registered, reflecting the fact that more people have access to haemophilia treatment centres. The South African Haemophilia Medical Advisory Committee strongly supports the continuation of the course.

NOTES

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