Update in Haematology
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Sri Lanka College of Haematologists
No 6 Wijerama House, Wijerama Mawatha
Colombo 7

President's Message

Dear Members

The Update in Haematology 2017 brings new knowledge, and experiences to keep us abreast with the rest of the world. New knowledge is essential to provide the best of care to our patients. Planning for the future, reviewing existing processes and needs regular update. It is not yet a mandatory process in Sri Lanka. However, when you are not uptodate, you fail to to work abreast of all the other colleagues and you may lag behind.

Gaining new knowledge is not an easy task. An importance hindrance is the availability and the cost. It may not be affordable to many of us. However, dissemination of such information needs endless effort, dedication and understanding on what is actually important.

The Update in Haematology has come back after a lapse of several years! It carries several haematology articles in a summary format, which is easy to read. The Update is for a better tomorrow.

We know where we are. We know what we have to do and where we have to be! I hope this issue of the Update in Haematology will guide you through some of the latest and best to know articles for haematologists. I invite all my colleagues - just walk through the update! Enjoy the reading!

It is what you do and how you do that will truly reflect your professional qualities.

Dr K.A.C.Wickremaratne
President SLCH 2017

TP53 Mutations in MCL: more therapy is not better

Michael E. Williams, MD, ScM Eskelund CW et al.
Blood 2017 130:1876-1877

Standard care for younger and medically fit patients with previously untreated mantle cell lymphoma (MCL) is with high-dose cytarabine and rituximab followed by autologous stem cell transplantation (ASCT).

Eight genes, which are recurrently mutated in MCL, were analysed in 183 MCL patients in two Nordic clinical trials. Results were compared with MCL International Prognostic Index (MIPI) score, blastoid morphology, and expression of Ki67 proliferation marker in >30% of tumor cells.

TP53 mutations were present in 11%, deletions in 16%, *NOTCH1* mutations in 4%, and *CDKN2A* deletions in 20%. At a median follow-up of 9.2 years, patients with these mutations had poorer outcomes than those lacking the mutations. On multivariate analysis, only patients with *TP53* mutations had poorer overall survival than those lacking *TP53* mutations (hazard ratio, 6.2; $P<0.0001$). These were strongly associated with blastoid morphology, high Ki67, MIPI high-risk, and a higher frequency of failure to achieve complete remission after induction therapy and consolidative ASCT. It is suggested that TP53 mutations are identified at diagnosis and B-cell receptor pathway inhibitors, lenalidomide or proteasome inhibitors are used in frontline therapy.

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Stabilizing the Mixed Lineage leukaemia protein

Jolanta Grembecka, Ph.D., and Tomasz Cierpicki, Ph.D.
NEJM – Clinical Implications of Basic Research 2017:376 (17) 1688-1689

Chromosomal translocations encoding mixed lineage leukemia (MLL) protein are recurrent genetic abnormalities found in AML and ALL, are especially common in infant leukemias. Fusion of MLL (KMT2A) is an enzyme that changes methylation of histones – changing gene transcription and expression. Leukemic cells with MLL translocations express both wild-type MLL and MLL fusion protein.

The fusion protein binds to a subset of the target genes and alters the level of their transcription. Expression of MLL fusion proteins leads to aggressive acute leukemias that respond poorly to treatment.

Liang and colleagues reported that expression of MLL fusion proteins is more abundant than wild-type MLL protein in leukemic cells. Ubiquitin ligase, interacts with wild-type MLL and induces degradation of the MLL protein — but not with MLL fusion proteins. Interleukin-1 signaling pathway is involved in the regulation of MLL protein stability. A kinase called IRAK4, is activated by signaling from the interleukin-1 receptor, phosphorylates UBE2O, leading to enhanced MLL–UBE2O interaction and subsequent degradation of the MLL protein. This process could be blocked with a small molecule inhibitor of IRAK4 and IRAK1 with reduced interaction between UBE2O and MLL and increased stability of the wild-type MLL protein. The relative increase in the level of wild-type MLL led to displacement of the MLL fusion protein from target genes.

Therapeutic potential of wild type MLL stabilization through IRAK inhibition, both compounds selectively blocked proliferation in the MLL-rearranged leukemia cells. Treatment with IRAK inhibitors substantially delayed progression of disease.

Outcome of Lower-Risk Patients With Myelodysplastic Syndromes Without 5q Deletion After Failure of Erythropoiesis-Stimulating Agents

Sophie Park, Jean-François Hamel, Andrea Toma, Charikleia Kelaidi, Sylvain Thépot, Maria Diez Campelo
Journal of Clinical Oncology Vol. 35, No. 14, May 10, 2017

Most anemic patients with non-deleted 5q lower-risk myelodysplastic syndromes (MDS) are treated with erythropoiesis-stimulating agents (ESAs), and second line with hypomethylating agents(HMA), lenalidomide (LEN) and investigational drugs.

1,698 patients with non-del(5q) lower-risk MDS treated with ESAs were retrospectively analysed. Erythroid response to ESAs was 61.5% with a response duration of 17 months. 67.5% had an ESA failure. 38% experienced primary failure and was associated with a higher risk of progression to AML. 494 experienced relapse after a response. 39% received second line therapy 194 - HMAs, 148 - LEN while 108 received other treatments (MISC). 697 received RBC transfusions only. Five-year AML cumulative incidence was 20.3%, 20.3%, and 11.3% for those receiving HMAs, LEN, and MISC, respectively (P = .05). Five-year OS for patients receiving HMA, LEN, and MISC was 36.5%, 41.7%, and 51%, respectively (P = .21). In a multivariable analysis adjusted for age, sex, revised International Prognostic Scoring System score, and progression at ESA failure, there was no significant OS difference among the three groups.

None of the second-line treatments HMA and LEN significantly improved OS.

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Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial

Hannah Cohen, Beverley J Hunt, Maria Efthymiou, Deepa R J Arachchillage, Ian J Mackie, Simon Clawson, Yvonne Sylvestre, Samuel J Machin, Maria L Bertolaccini, Maria Ruiz-Castellano, Nicola Muirhead, Caroline J Doré, Munther Khamashta, David AIsenberg
The Lancet Hematology Vol 3 No 9 Sept 2016

A randomised, controlled, open-label, phase 2/3, non-inferiority trial, was carried out in 2 UK hospitals, on 116 patients with antiphospholipid syndrome who were on warfarin for previous venous thromboembolism, with a target INR of 2·5. Patients were randomized 1:1 to continue warfarin or receive 20 mg rivaroxaban daily. Primary outcome was percentage change in endogenous thrombin potential (ETP) from randomisation to day 42, with non-inferiority set at less than 20% difference from warfarin in mean percentage change. Analysis was by modified intention to treat. Other thrombin generation parameters, thrombosis, and bleeding were also assessed. Treatment effect was measured as ratio of rivaroxaban to warfarin for thrombin generation.
At day 42, ETP was higher in the rovaroxaban group, peak thrombin generation was lower in the rivaroxaban group. No major thrombosis or bleeding occurred in either arms. EQ-5D-5L visual analogue scores, was significantly better in the rivaroxaban group than in the warfarin group, probably due to absence of INR monitoring as for warfarin.
No range of therapeutic rivaroxaban concentrations have been defined for clinical use. Population pharmacokinetics indicate that peak rivaroxaban concentrations are in the range 160–360 µg/L.
However, larger numbers are needed with both arterial and venous thrombosis as well as longer follow up period to study effects of rivaroxoban.

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Should any one with Philadelphia chromosome positive ALL who is negative for minimal residual disease receive a haemopoietic stem cell transplant in first remission?

Mark R Litzow
Best Practice & Research Clinical Haematology 29 (2016) 345-350

Outcome of patients with Ph +ve ALL prior to the imatinib era has been poor, if they didn't receive an allogeneic HSCT. This led to the recommendation that all with Ph+ve all should be transplanted. Once imatinib was introduced the outcomes changed dramatically.
Southwest Oncology Group (SWOG) trial studied 94 patients receiving dasatanib as a TKI. Survival curve for non transplanted was inferior to transplanted but the P value was not significant (P =0.088)
Italian GIMEMA IAL 1509 study evaluated 60 patients treated with dasatanib and steroids. 19% achieved complete molecular remission by day 85 and could have an allo HSCT if eligible.
Korean society of hematology adult ALL working party studied 82 patients receiving Nilotinib 400mg twice daily. 57 patients received an allogeneic transplant.
MD Anderson studied 37 patients using ponatinib as a TKI. No difference was noted between those who received transplant vs those who received chemotherapy alone.
Chemotherapy is necessary and should include CNS prophylaxis. Those who achieve MRD negativity at first remission do not require an allogeneic transplant. However,

cytogenetics, and molecular markers should be considered.

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Comparison of the direct antiglobulin test and the eluate technique for diagnosing haemolytic disease of the newborn

H.van Rossum, Nelly de Kraa, Melanie Thomas Cas A.G. Holleboom, Ad Castel, André P. van Rossum
Practical Laboratory Medicine 3 (2015) 17–22

The direct antiglobulin test (DAT) identifies sensitized erythrocytes. The diagnostic properties and optimal use of the DAT were studied in 317 consecutive deliveries and jaundice was observed 4 – 6 days after delivery. 21 neonates had positive DAT tests with 61 neonates had positive eluate screening. Only 4 neonates had HDN. The positive predictive value of DAT for HDN was 10% while eluate of cord blood was 93%. The DAT missed 2 cases of HDN. DAT may detect clinically irrelevant ABO immunization. A negative DAT doesn't rule out HDN while an eluate should be added when a negative DAT is seen in the presence of a HDN.

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Comparison Effect of cold storage on platelets quality stored in small containers : Implications for paediatric transfusion

Eman NasrEldin
Pediatric Hematology Oncology Journal 2 (2017) 29-34

According to current recommendations, platelets should be stored in gas permeable bags at 22^{o}C for a maximum of 5 days, with agitation.
A previous practice was to keep them at 4^{o}C. This study re-evaluated the efficacy and feasibility of this practice. It assessed the effect storing platelets at either 22^{o}C or 4^{o}C had on their quality (including their functional, metabolic and activation markers status).

Platelet Quality Parameter	Storage Method	
	Platelets stored at 22^{o}C	Platelets stored at 4^{o}C
Metabolic Rate	*Increase*	*Decrease (P<0.05)*
Lactate production	*Greater Increase*	*Increase (P<0.05)*
Glucose consumption	*Increase*	*No Increase*
PCO_2 level	*Greater Increase*	*Increase (P<0.05)*
Aggregation	*Worse*	*Better*
Expression of activation markers	*Lower*	*Higher*
Platelet Count	*Higher*	*Lower*

No differences were detected between agitated and non-agitated cold-stored platelets.

Conclusions

- Cold-storage of platelets is superior to RT-storage, especially considering the greater functionality of those platelets.
- The quality of cold-stored platelets is not improved by agitation.
- As per this evidence, it is advisable that the cold-storage of platelets be reconsidered, especially considering that cold-stored platelets may improve outcomes for acutely bleeding casualties.

Compiled by Dr Durga Moratuwagama

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The Impact of Hepatitis B Virus Infection and Vaccination on the Development of Non-hodgkin Lymphoma

C.-E. Huang; Y.-H. Yang; Y.-Y. Chen; J.-J. Chang; K.-J. Chen; C.-H. Lu; K.-D. Lee; P.-C. Chen; C.-C. Chen
J Viral Hepat. 2017;24(10):885-894.

Hepatitis B virus (HBV) infection has been documented as a risk factor for non-Hodgkin lymphoma (NHL). Only a few large cohorts have been studied for the impact of HBV vaccination. The Taiwan National Health Insurance Research Database was studied from 1997–2013, where the incidence and risk of developing NHL and $CD20^+$aggressive lymphoma between HBV and non-HBV populations were compared. The hazard ratios (HR) were analyzed of populations before and after introduction of hepatitis B immunization.
One million persons were analyzed. Of 38 628 with HBV infection,
110 (0.28%) had aggressive NHL. In the non HBV cohort 52 had aggressive NHL (0.02%). Cirrhosis, diabetes mellitus, tuberculosis, systemic lupus erythematosus and rheumatoid arthritis were also common amongst those with HBV and lymphoma. Interferon, adefovir, entecavir, lamivudine, telbivudine or tenofovir were also included in the anti lymphoma therapy of these patients.

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First in 30 Years: Improved Front Line in Hodgkin's Lymphoma

ASH 2017 Abstract Dec 11 2017
Alexander M. Castellino, PhD

According to ECHELON – 1 study presented at ASH 2017, Brentuximab vedotin can be used as frontline in advanced HL. Patients with stage III or IV HL received brentuximab vedotin instead of bleomycin in the ABVD regime.
ABVD cures 75% of patients with HL. This study has been able to significantly reduce the rate of treatment failures and avoid pulmonary toxicity caused by bleomycin. Currently, patients with HL have a PET scan after 2 cycles of ABVD. 80% will be negative and will then continue to receive AVD, without bleomycin for 4 more cycles. The RATHL trial (Response-Adapted Therapy for Advanced Hodgkin Lymphoma), confirmed that patients retained clinical benefits with reduced toxicity of the same regime.
Brentuximab + AVD is considered as second line or salvage therapy or a bridge therapy before transplantation. If this is used as first line therapy, what could a patient be offered next? The Progression free survival was significantly higher in the Brentuximab arm. Overall survival, and complete response rate was not different in the two arms. Neutropenia and peripheral neuropathy was higher in the brentuximab arm. Cost comparison - ABVD $4000, vs Brentuximab +AVD = $100,000.
The following must be considered when comparing a new regime over another - overall survival, duration of follow-up, toxicity, and cost, which includes not only the cost of the drug but also the cost of all the supportive care that is needed.

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The Use of Anagrelide in Myeloproliferative Neoplasms, with Focus on Essential Thrombocythemia

Current Haematology Malignant Reports
vol2 (4) 2016
Gunnar Birgegård

Anagrelide (ANA) reduces platelet production by inhibiting megakaryocyte (MK) colony development. GATA 1 is essential for maturation and differentiation of MK, and is upregulated in bone marrow

cells in essential thrombocythemia (ET). ANA represses GATA-1 and FOG-1 expression.

2 formulations are registered as second-line drugs in ET in Europe and as first-line in some countries. In USA it is licensed for thrombocythemia in myeloproliferative neoplasms (MPN). Platelet reduction is mainly through RL 603. Thromboreductin – an anagrelide hydrochloride has a slower uptake, a lower Cmax, and lower rate of side effects.

American Anagrelide Study group with 577 patients reported ≥50 % reduction in platelets in 93% of patients. In 1997 - a study with 900 patients achieved 70% CR. Platelet lowering effect was faster than for interferon. 2 small studies have shown that ANA may be more effective in JAK2-positive patients than in CALR-positive patients, but needs further study.

In the PT1-RCT HC and ANA HC treated patients had significantly lower number of arterial thrombosis, haemorrhage but higher risk of venous thrombosis in the HC arm. The anahydret study there was no difference in the arterial or venous thrombosis or haemorrhage in the two arms.

If ANA is used as second line therapy, with pre treatment reticulin fibrosis of grade 2 or more, surveillance with bone marrow for MF should be offered.

Side Effects – seen by inhibition of phospho di esterase III causing, tachycardia, headache dizziness, also loose stools.

Dosing – 0.5mg b.d. can be increased to 0.5mg per day/wk. ANA is registered second-line therapy in Europe. However, ANA is used as first-line therapy in young patients.

treatment goal in ET is to reduce thrombosis, haemorrhage, symptoms and normalize platelet counts.

Compiled by Dr Durga Moratuwagama

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Monoclonal Gammopathies: Electronic Subspecialty Consultation

Nicholas Burwick,Jacob Stein, David A. Garcia, Virginia C. Broudy, Robert E. Richard

European journal of Haematology
27th Dec 2017 online

Electronic consultation (e-consult) is an important part of care for patients who need sub-specialty consultation but not urgent evaluation. Monoclonal gammopathy of undetermined significance (MGUS) is a common cause for e-consult. MGUS needs careful evaluation and surveillance over time as 1% of them progress to MM.

A retrospective analysis was performed and 152 patients were identified who were suitable to be triaged for e consult. Criteria for e consult were those with a Hb >10g/dl, serum creatinine <2.0. Median time to complete the e consult was 2 days.

The median time to completion of an e-consult was 2 days. Ninety-six percent of MGUS e-consults had a hemoglobin >10 g/dL and 90% had a creatinine <2 mg/dL. Only 6 patients progressed over 44 months of follow up, representing a mean rate of 1% per year. E consult is a helpful mechanism to evaluate outpatient appointments reducing need for outpatient appointments. However, timely and strict risk stratification is critical.

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Infectious complications of CD19-targeted chimeric antigen receptor–modified T-cell immunotherapy

Joshua A. Hill,1,2 Daniel Li,3 Kevin A. Hay,4,5 Margaret L. Green,1,2 Sindhu Cherian,6 Xueyan Chen,6 Stanley R. Riddell,1,4 David G. Maloney,1,4 Michael Boeckh,1,2 and Cameron J. Turtle1,4

Blood, Jan 2018, vol 131, No 1 121

TCAR-T)-cell immunotherapy is a novel treatment for refractory or relapsed B-cell malignancies.133 patients who were treated with CD19 CAR–T-cell immunotherapy were evaluated for risk of infections. The cohort was made up of 47 ALL, 24 CLL, and 62 non Hodgkins. Most patients who present for CD19 CAR–T-cell immunotherapy have poor immune function due to both the effects of their
malignancy and prior cytotoxic treatments. The lymphodepletion chemotherapy administered immediately before CAR–
T-cell infusion also causes cytopenias and may impair mucosal barrier
The infection risk was similar to other salvage chemo immunotherapy regimes. Infection was more common in ALL prior to anti tumour therapy and higher with Cart T cell dose
or greater Cytokine Release Syndrome (CRS) and neuropathy. This may require steroids and tocilizumab a humanized IL6 monoclonal antibody - both increase infection risks. CAR - T cells also deplete normal CD 19 B cells contributing to a hypogamma globulinaemia. These patients routinely required GCSF, valcylovir, levofloxacin, flucanozole, trimethoprim, and sulfamethoxazole as anti viral, anti fungal and anti pneomocystis prophylaxis. 24 infection events in 22 patients - 12 bacterial infections with gram -ve organisms, 13 viral infections, 9% had bacterial infections - with 10 having RSV, 6 with invasive fungal infections. 28 having CRS. CAR–T-cell dose of 2 3 107 cells per kg were associated with a significantly increased infection as well as those who received more intensive anti tumor therapy.

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A cure for Haemophilia within Reach

H Marijke van den Berg
NEJM Dec 2017 377 2592 – 2593

10 patients with Haemophilia B were treated with single injection of adeno associated viral vector containing hyperfunctional factor IX variant gene (Padua) along with sequences optimizing expression and targeting the liver. These participants sustained IX levels to 33.7 ± 18.5 of normal and reduced bleeding dramatically. Haemophilia A gene therapy is not as feasible as packaging capacity is of AAV capsid is twice as large as factor IX. However B domain deleted factor VIII has been studied in 9 patients with promising results. Though impressive these results have been obtained in patients with AAV negative, patients without active hepatitis, inhibitor negative patients. Thus most patients may not yet be able to benefit from gene therapy. Platelets derived from haemopoietic stem cells could deliver factor VIII or IX directly to the circulation. Patients with hemophilia B benefit from extended half life products with approximately 20 infusions per year. If gene therapy could be perfected, these children could live a life without bleeding and other sequelae of the disease.

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Risk of Hematologic Malignancies After Radioiodine Treatment of Well-Differentiated Thyroid Cancer

RemcoJ Molenaar, Surbhi Sidana, Tomas Radivoyevitch, Anjali S. Advani, Aaron T. Gerds, Hetty E. Caraway
Journal of Clinical Oncology Dec 2017

Of 148,215 patients with well differentiated thyroid carcinoma (WDTC) 53% received surgery alone, while 47% received radioactive iodine therapy. 783 patients developed a second haematological malignancy after 6.5 years diagnosis of WDTC. RAI treatment was associated with

increased risk of developing AML with a hazard ratio of 1.79, CML with a hazard ratio of 3.44. The risk of AML and CML after RAI was seen even in low and intermediate risk of WDTC tumours. Development of AML trended an inferior survival compared to matched controls with de novo AML.

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Monitor GCSF DLBCL subanalysis: Treatment patterns/ outcomes with biosimilar filgrastim for chemotherapy-induced/febrile neutropenia prophylaxis

Pere Gascon, Andry Krendyukov, Nadja Hobel, Matti Aapro
European Journal of Haematology Dec 2017

245 patients at the age of >65 to 70 years with stage 3 or 4 DLBCL receiving chemotherapy and GCSF with biosimilar filgrastim for prophylaxis were monitored for side effects. Outcomes of interest included incidence of chemotherapy induced neutropenia and febrile neutropenia. The most frequently reported adverse event was bone pain followed by arthralgia and back pain. The biosimilar was similar in efficacy to the original product. The age and the stage of the disease of the patients may and the may have a role to play in the symptoms expressed by the patients.

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Pretransplant Vitamin D deficiency Is associated with Higher Relapse Rates in Patients Allografted for Myeloid Malignancies

Aleksandar Radujkovic, Lambros Kordelas, Julia Krzykalla, Dietrich W. Beelen, Axel Benner, Nicola Lehners
*Journal of Clinical **Oncology** Aug 2017*

492 patients were analysed pre transplant for Vitamin D status from 2002 to 2013. Serum levels of 25 hydroxyvitamin D3 <20ng/ml equivalent to <50 nM before allo SCT was assessed in an accredited laboratory by standard chemiluminescent immunoassay. 80% had vitamin D deficiency and was associated with inferior overall survival in a multivariable analysis with higher risk of relapse. A pretransplant vitamin D deficiency was seen only in myeloid diseases and not lymphoid diseases. A prospective study is warranted.

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Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation

Hugh Calkins, Stephen Willems, Edward P. Gerstenfield, Atul Verma, Richard Schilling, Stefan H. Hohnloser, Ken Okumura, Harvey Serota, Matias Nordaby, Kelly Guiver, Branislav Biss, Marc A Brouwer, Massimo Grimaldi
NEJM 2017 March 376:1627-36
Catheter ablation of atrial fibrillation is performed with uninterrupted anticoagulation with warfarin or interrupted non vitamin K antagonists oral anticoagulants. 704 patients were studied in an open labelled controlled blinded trial with catheter ablation for patients withatrial fibrillation to receive dabigatran 150 mg twice daily or warfarin with a target INR of 2 – 3. Ablation was performed during and after 8 weeks of anticoagulation. There was fewer periprocedural bleeding with Dabigatran. One thromboembolic event occurred with warfarin. No difference was seen otherwise between the two anticoagulants.

Compiled by Dr Senani Williams