Update in Haematology
volume 1
2018
Sri Lanka College of Haematologists
No 6 Wijerama House, Wijerama Mawatha
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President's Message

Dear Members

It is with great pleasure that we launch volume 1 of Haematology update 2018. Aim of the 'Haematology Update' is to bring latest knowledge in Haematology extracted from international publications during the each quarter of the year to the members in a concise and easily readable format. On behalf of the council of the SLCH my heartiest thanks go to the editorial board for their untiring efforts to publish the first Haematology update for the year 2018.

Enjoy going through the concise pages of this update and you will realize that this is the easiest and most tireless way of updating yourself. I invite you to make the maximum use of the update. I believe it will help you to refresh as well as sharpen your knowledge on the haematological problems that you deal with during the day to day practice. The wider topics included hopefully would help give better care for our patients.

Best wishes,

Dr Vishaka P Gunawardena
President SLCH 2018

Mild antithrombin deficiency and risk of recurrent venous thromboembolism : results from the MEGA follow-up study

J . Sokol, J. F. Timp, S . Le cessie, A. Van Hylckama-Vlieg, F. R. Rosendaal, P. Kubisz, S . C. Cannegieter and W. M. Lijfering
J Thromb Haemost 2018; 16:680–8.

Mild antithrombin deficiency (previously defined as antithrombin activity below 70% or 80%) has been associated with a 2.4–3.5-fold increased risk of recurrent venous thromboembolism (VTE). The duration of antithrombotic therapy in VTE patients with mild antithrombin deficiency may be influenced by this finding. In a population-based cohort study, patients with a first VTE (n = 2357) were stratified according to percentile cut-off antithrombin levels (< 5th[< 87%], 5–10th [87–92%], > 10th percentile [> 92%]) and functional antithrombin levels (< 70%, 70–80%, > 80%). During a median follow-up of 7.4 years, 361 recurrent events occurred (incidence rate, 2.5/100 patient-years). There was an increased risk of recurrent VTE in the lowest antithrombin activity category (< 5th percentile; < 87%) as compared with antithrombin activity that was > 10th percentile (> 92%). Mild antithrombin deficiency was able to predict recurrent VTE over at least 8 years of follow-up and the association remained when the population was stratified to the presence or absence of thrombosis risk factors.

Compiled by Dr Chandima Kulathilake

Recombinant Human Thrombopoietin promotes platelet engraftment and improves prognosis of patients with MDS and Aplastic Anemia after Allo-HSCT

Hong Wang et al.
Biology of blood and marrow transplantation

October 2017, Volume 23, issue10, p1678–1684

Thrombocytopenia is a problematic complication following allo-HSCT. Good platelet Graft function (GPGF) was defined as persistent platelet count ≥50,000/μL without transfusions on or after day 90. Poor platelet graft function (PPGF) may be primary or secondary.
A prospective study was done on patients who underwent first allo HSCT for various haematological conditions to see the prognostic value of platelet graft function after allo- HSCT and to evaluate the clinical effects of Recombinant Human Thrombopoeitin (rhTPO).
Results: The OS after 3 years, patients with GPGF was significantly higher than patients with PPGF. Similarly, the prognosis of MDS and AA who were treated with rhTPO was significantly better than patients who did not. However, no advantage in prognosis was seen in patients with other conditions(acute leukaemia, PNH, MPN and lymphoma).
In conclusion, PPGF was associated with a poor prognosis after allo-HSCT. Administration of rhTPO could lead to GPGF and significant improvement of prognosis in MDS and AA.

Compiled by Dr Manel Ratnayake
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Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma (DLBCL)
Schmitz R, Write GW, Huang DW et al.
New England Journal of Medicine 2018 387:1396-407

DLBCLs are phenotypically and genetically heterogeneous. Gene-expression profiling identified 4 subgroups of DLBCL. 574 biopsy samples were analysed using exome and transcriptome sequencing, array based DNA copy number analysis and targeted amplicon reseqnencing of 372 genes to identify genes with recurrent aberrations. The 4 subtypes are –
1. MCD – co occurrence of *MYD88*^{L265P} and *CD79B* mutations,
2. BN2 – occurrence of *BCL6* fusions and *NOTCH2* mutations,
3. N1- occurrence of *NOTCH1* mutations,
4. EZV – occurrence of *EZH2* mutations and *BCL2* translocations.
These subtypes have different phenotypes as well as differences in response to immuno chemotherapy. BN2 and EZB subtypes have favourable survival than the other subtypes.

MCD and BN2 DLBCLs are categorized as “chronic active” B cell receptor signaling and respond to therapeutic inhibition.

Compiled by Dr Senani Williams
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Minimal factor XIII activity level to prevent major spontaneous bleeds
M. Menegatti, R. Palla, M. Boscarino, P . Bucciarelli, L. Muszbek, E. Katona, M. Makris, and F. Peyvandi

J Thromb Haemost 2017; 15: 1728–36.

Congenital factor XIII (FXIII) deficiency is a rare bleeding disorder associated with significant bleeding manifestations. The European Network of Rare Bleeding Disorders (EN-RBD) study, from 2007 to 2010, showed a strong association between bleeding severity and FXIII activity in plasma of patients with FXIII deficiency. Among these

patients, variable levels of FXIII activity, from undetectable to 30%, were associated with a wide range of severity of bleeding. The present cross sectional study, the PRO-RBDD project, a prospective cohort study, analyzed data of 64 patients with FXIII deficiency and different types of clinical and laboratory severity. The results of this analysis confirmed that FXIII coagulant activity in plasma is well associated with clinical severity of patients. In addition15 IU/dL of FXIII activity was identified to be the level under which the probability of spontaneous major bleeding sharply increases. The PRO-RBDD study suggests a FXIII coagulant activity level of 15 IU/dL as a target to start prophylaxis in order to prevent major bleeding, such as central nervous system or gastrointestinal tract hemorrhage.

Compiled by Dr Chandima Kulathilake
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Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma
Facon T et al.
(Blood. 2018;131(3):301-310)

Lenalidomide and low-dose dexamethasone (Rd) and melphalan plus prednisone and thalidomide (MPT) are 2 treatment options for patients with newly diagnosed multiple myeloma (NDMM) ineligible for autologous stem cell transplant. These regimens
were investigated in phase 3 FIRST (Frontline Investigation of Revlimid Plus Dexamethasone Versus Standard Thalidomide) trial. This trial compared efficacy and safety of Rd until disease progression (Rd continuous), Rd for 72 weeks (18 cycles; Rd18), and MPT for 72 weeks (12 cycles) in patients not eligible for transplant with NDMM.
Primary end point was Progression free survival (PFS) in Rd continuous vs MPT. Secondary endpoints included; PFS between Rd continuous vs Rd18 arms and MPT vs Rd18 arms , overall survival (OS), overall response rate (ORR) ; ≥ partial response [PR]), time to next antimyeloma treatment (TTNT; which censors deaths), and safety, including second primary malignancies.
1623 patients were randomized to receive Rd continuous (n= 535), Rd18 (n =541), or MPT (n =547
Rd continuous significantly improved PFS compared to MPT (hazard ratio [HR], 0.69; 95%. Confidence interval [CI], 0.59-0.79; P < 00001 . Rd continuous also reduced the risk of progression or death compared with Rd18 (HR, 0.70; 95% CI, 0.60-0.81). The median PFS was 26.0 months with Rd continuous, 21.0 months with Rd18, and 21.9 months with MPT. In addition, the 4-year PFS rate more than doubled with Rd continuous (32.6%) compared with Rd18 (14.3%) and MPT (13.6%). PFS of Rd continuous was better over MPT in the majority of subgroups analyzed.
Median OS was 10 months longer with Rd continuous vs MPT (59.1 vs 49.1 months; HR, 0.78; 95% CI, 0.67-0.92; P 5 .0023), and similar with Rd18 (62.3 months).
Median TTNT was longer with Rd continuous (36.7 months) than with MPT (26.7 months) or Rd18 (28.5 months) In patients achieving complete or very good partial responses, Rd continuous had 30-month longer median time to next treatment vs Rd18 (69.5 vs 39.9 months).
Higher-quality responses (ie, ≥VGPR) were more frequent with

bortezomib as second-line treatment following Rd continuous and Rd18 than following MPT.

There were no new safety concerns compared with earlier analyses. Similar to results of previous analyses, hematologic secondary primary malignancy (SPM) was more frequent with MPT (3%) than with Rd continuous (1%) or Rd18 (,1%).The incidence of solid tumor SPM was similar across treatment arms.

Compiled by Dr Durga Moratuwagama

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The effect of recanalization on long-term neurological outcome after cerebral venous thrombosis(CVT)

E . Rezoagli, I . Martinelli, D. Poli, U. Scoditti, S.M. Passamonti, P. Bucciarelli , W. Ageno and F . Dentali

J Thromb Haemost 2018; 16: 718–24

The neurological outcome after a first episode of CVT is good, but the role of recanalization on neurological dependence is still debated. In a retrospective observational multicenter cohort study, five-hundred and eight patients with an acute first episode of CVT with at least one available imaging test during follow-up were enrolled. Patency status of the vessels was categorized as complete, partial or not recanalized. Neurological outcome was defined using the modified Rankin scale (mRS) as good(mRS = 0–1) or poor (mRS = 2–6). Complete or partial recanalization was not differently represented in patients undergoing scans at different periods of time (from 28-day to 3 month-period up to a 1–3 year-period). mRS at the time of follow-up imaging was available in 483 patients; 92.8% of them had a mRS of 0-1. CVT recanalization was positively associated, whereas cancer , and personal history of venous thromboembolism (VTE) were negatively associated as independent predictors of favorable (mRS = 0–1) outcome at follow-up. The study concluded that most patients with a first CVT had complete or partial recanalization at follow-up. Recanalization was independently associated with a favorable neurological outcome.

Compiled by Dr Chandima Kulathilaka

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Early detection of differentiation syndrome (DS) by chest ultra-sound in acute promyelocytic leukaemia

Karunakaran P, Yanamandra U, Nampoothiri R V, Khadwal A, Prakash G, Lad D, Sinha A, Naseem S, Varma N, Varma S, Malhotra P
BJH 2018

DS is a life-threatening complication in APML. It's diagnosed with at least 3 features in the absence of other causes – fever, weight gain of 5 kg, lung infiltrates, respiratory distress, pleural & pericardial effusion, hypotension and renal failure. These are also seen in sepsis or heart failure. As treatment is high dose dexamethasone, diagnosis on clinical criteria alone is dangerous. An earliest sign of DS is pulmonary oedema. Chest ultrasonography detects DS by a mismatch in impedance between fluid-filled interstitium and air-filled alveoli. This leads to a comet tail sign on chest ultrasound - a positive comet tail sign would be suggestive of DS.

35 newly diagnosed patients with APML underwent daily chest

ultrasounds for 14 days. All were treated with arsenic trioxide (ATO) and All-trans retinoic acid (ATRA). Hydroxycarbamide was used to reduce leucocyte count when the total leucocyte count rose above 5.9 10^9/l. ATO and ATRA were continued until haematological recovery.

All were commenced on DS prophylaxis, oral prednisolone (1 mg/kg/day). Those who developed DS received dexamethasone (10 mg twice daily).

Point-of-care chest ultrasound was performed on each hemi- thorax divided into 4 quadrants – upper, and lower anterior and upper and lower lateral quadrants divided transversely by the 2nd intercostal space. A comet-tail image was defined as a hyper-echogenic, coherent bundle with narrow basis arising from the pleural line and extending to the edge of the screen. Comet tail sign was positive if: (i) At least three comet tails per scan, (ii) diffusely positive with more than one positive scan per side and (iii) bilateral presence of comet tails.

3 patients had DS by clinical criteria. Chest ultrasound confirmed comet tails in all 3. Comet tail sign was detected 12 h prior to onset of symptoms. Comet tail signs resolved in responding patients.

No comet tails were detected in those who didn't develop DS. Transient comet tail detected for 2 days in 2 patients, was attributed to fluid overload. The chest ultrasound had 100% sensitivity and 90.9% specificity in detection of DS. [Fisher's exact test (two tail): P = 0 0087].

Chest ultrasound had 100% sensitivity and 100% negative predictive value in detection of DS. Ultrasonography is operator dependent with individual variation in interpretation of results. The comet tail sign on chest ultrasound is a good bedside tool for early identification of DS.

Compiled by Dr Senani Williams

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Preoperative platelet transfusions to reverse antiplatelet therapy for urgent non-cardiac surgery: an observational cohort study

M. Baschin, S. Selleng, A. Hummel, S . Diedrich, H. W. Schroeder, T . Kohlmann, A. Westphal, A. Greinacher and T. Thiele

J Thromb Haemost 2018; 16:709–17.

Patients receiving antiplatelet therapy (APT) have an increased risk of perioperative bleeding and cardiac adverse events (CAE). Preoperative platelet transfusions may reduce the bleeding risk but may also increase the risk of CAE, particularly coronary thrombosis in patients after recent stent implantation. This study analyzed the incidence of perioperative CAE and bleeding in patients undergoing non-cardiac surgery using a standardized management of transfusing two platelet concentrates preoperatively and restart of APT within 24–72 h after surgery.A cohort of consecutive patients on APT treated with two platelet concentrates before non-cardiac surgery between January 2012 and December 2014 was retrospectively identified.
Patients were stratified by the risk of major adverse cardiac and cerebrovascular events (MACCE). The primary objective was the incidence of CAE (myocardial

infarction, acute heart failure and cardiac troponine T increase). Secondary objectives were incidences of other thromboembolic events, bleedings, transfusions and mortality.

Among 181 patients, 88 received aspirin, 21 clopidogrel and 72 dual APT. MACCE risk was high in 63, moderate in 103 and low in 15 patients; 67 had cardiac stents. Ten patients (5.5%) developed a CAE (three myocardial infarctions, four cardiac failures and three troponin T increases). None was caused by coronary thrombosis. Surgery-related bleeding occurred in 22 patients (12.2%) ,making 12 re-interventions necessary. Conclusion was that preoperative platelet transfusions and early restart of APT allowed urgent surgery and did not cause coronary thromboses, but non-thrombotic CAEs and re-bleeding occurred. Randomized trials are needed to test platelet transfusion against other management strategies.

Compiled by Dr Chandima Kulathilake

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Frailty and the management of hematologic malignancies

Gregory A. Abel1 and Heidi D. Klepin2
Blood. 2018;131(5):515-524

In spite of advances in treatment of hematological malignancies, there is scarcity of evidence regarding management of elderly as they are under represented in clinical trials. Assessment of frailty is important in applying current evidence to older patients.

Frailty is a vulnerable state that arises from “decreased reserves in multiple organ systems, which are initiated by disease, lack of activity, inadequate nutritional intake, stress, and or the physiological changes of aging”.

Its associated with poor therapeutic response, increased toxicity, and lower survival rates in patients with blood cancers.

Evidence for effect of frailty:

1. AML & MDS

Prospective study of 50 patients - > 50% with cognitive impairment had ECOG performance status of 0 or 1 indicating patients with good performance status could be impaired.

Retrospective study of 101 patients with AML, ≥ 65 years, in addition to increased comorbidity, difficulty with strenuous activity (hazard ratio [HR] 5 2.2 [1.2, 4.0] and reports of pain (HR 5 2.2 [1.2, 4.0]) were independent prognostic factors.

In another prospective study of patients with AML, impaired cognition and physical function were independently associated with worse survival.

An European study of 195 older patients both pretreatment impairment in routine daily activities (HR 5 2.60 [1.37, 5.46]) and poor quality of life/fatigue (HR 5 1.82 [1.02, 3.23]) were associated with worse survival.

2. Lymphoma & CLL

In 44 patients ≥ 70 years, most with diffuse large B-cell lymphoma (91%) abnormal Groningen Frailty Indicator was associated with early termination of chemotherapy (odds ratio [OR] 5 9.2 [1.5, 55.8]), as well as worse overall survival (HR 5 2.6 [1.1, 6.1]).

In 143 patients in Germany with lymphoma, advanced age, poor performance status, dependence in activities of daily living, dependence in instrumental activities of daily living, and presence of severe comorbidity were all associated with shorter survival.

As some aggressive lymphomas are potentially curable, it is important to determine whether aim of treatment is “curative”.
Geriatric assessment could identify a group of (“unfit”) patients who are not robust, but still fit enough to have treatment with curative intent. Treatment with curative intent improved overall survival in unfit (75% vs 45%) but not frail (44% vs 39%) patients,
Frailty results from the CLL9 trial showed that poor performance was associated with lower survival rates (P5.005 and .007, respectively). Authors concluded that frailty should be integrated into future trials, and routine management of CLL.

3. Multiple Myeloma

IMWG frailty score predicted survival and risk for toxicity. 3-year overall survival was 84% among the fit, 76% among the intermediate-fit, and 57% among the frail. Cumulative incidence of grade 3 or more non-hematologic adverse events at 1 year in these groups was 22%, 26%, and 34%, respectively.
Several tools are available for measurement of frailty and is feasible in routine clinical setting.
Furthermore, meaningful functional and/or patient-reported measures should be evaluated as end-points, in addition to survival.

Compiled by Dr Durga Moratuawagama

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Progressive telomere shortening is part of the natural history of chronic lymphocytic leukaemia and impacts clinical outcome: evidences from long term follow-up

Ghio P et al BJH 2017

Many biological markers are used to predict outcome of CLL, shorter telomere lengths at diagnosis are associated with poor outcome. Unmutated IGHV, High levels of CD38, CD49d, and ZAP70 also carry a poor outcome. A study of 401 patients of CLL showed that short TL <5000 bp at diagnosis is an independent predictor of shorter overall survival, treatment free survival and progression to Richter syndrome.

90 patients were evaluated with telomere loss over time calculated in terms of absolute loss, defined as loss of telomeric DNA in base pairs, adjusted for time as yearly loss. Yearly loss = absolute loss(bp)/ Time(months). 2nd telomere length was analysed on peripheral blood mononuclear cells. TL was determined by Southern blot. The first TL was assessted at early stage of the disease. The second follow up wasn’t uniform in all patients. Telomeres were shorter at follow up than baseline, specially in IGHV mutated patients. Those with longer telomeres had deeper erosion than those with shorter telomeres. Only 4 biomarkers were associated with shorter TFS – unmutated IGHV, ZAP70 positivity, TL,5000 bp and %YL>6%. In a multivariate analysis all except ZAP70 were independently associated with poor TFS, while ZAP70 lost statistical significance.

This identified a highly favourable group of patients with TL >5000 BP and % YL,6%. This study shows a progressive telomere erosion occurs as part of the natural history of CLL.

Compiled by Dr Senani Williams

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Prognostic significance of additional chromosomal

abnormalities at the time of diagnosis in patients with chronic myeloid leukemia treated with frontline tyrosine kinase inhibitors

Ahmad Alhuraiji, Hagop Kantarjian, Prajwal Boddu, Farhad Ravandi, Gautam Borthakur, Courtney DiNardo, Naval Daver, Tapan Kadia, Naveen Pemmaraju, Sherry Pierce, Guillermo Garcia-Manero, William Wierda, Srdan Verstovsek ,Elias Jabbour, Jorge Cortes

Am J Hematol. 2018;93:84–90.

Additional clonal cytogenetic abnormalities (ACA), also known as cytogenetic clonal evolution is a reflection of genomic instability and a sign of progression of disease. Frequency of abnormalities increases as disease progresses. 5-10 % at diagnosis in chronic phase and nearly 80% in blast phase. These abnormalities predict an inferior outcome in advanced stages. Impact of these changes at diagnosis in chronic phase is not well described. ACA are divided into two groups; major route and minor route. Major route abnormalities are ; Trisomy 8 , a second Ph chromosome, chromosome 17, +der(22). Minor route abnormalities are - trisomy 21 , t(3;12), t(4;6),t(2;6) and t(1;21).

The objective of this study was to analyze the impact of ACAs at the time of diagnosis on outcome of patients with CML-CP receiving frontline TKI therapy. 603 patients with CML on 4 different TKIs were enrolled and divided in to 2 groups based on the presence or absence of ACAs. Karyotyping with G banding and RT-PCR were done at diagnosis and every 3 months till 12 months and every 6 months thereafter.
29 patients (5.2%) had ACA at diagnosis. Major route abnormalities were seen in 12. 5.4% who didn't have ACAs at diagnosis developed it during the study period. Those who had ACAs at diagnosis did not develop further abnormalities. Long-term survival outcomes were similar between the two groups. There was a non-significant trend for an inferior failure-free and overall survival for patients with ACA, with no difference in event-free and transformation-free survival.
According to this study, the presence of ACAs alone is not a sign of worse prognosis. The type of abnormality doesn't seem to have a major impact on the outcome. However the highest risk abnormalities were not detected at diagnosis in this study. Therefore diagnostic value of cytogenetic evaluation at diagnosis remains questionable.

Compiled by Dr Durga Moratuwagama

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