

**EBMT 2018 Report**

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44th Annual Meeting of EBMT was held from 18 – 21 March 2018 in Lisbon Portugal. Lisbon, being the capital of Portugal, is a charming city with quaint architecture and beautiful old trams.

This was the first time I attended EBMT. Thanks to MSH for giving me the opportunity. Below is the summary of the important learning points:

**How I treat session – Approach Differential Diagnosis of Post-transplant Complications**

Most of the post-allogeneic transplant complications arise from the basic of endothelial injury. There are multiple factors that result in tissue injury, namely conditioning chemotherapy, engraftment itself, complement activation, calcineurin inhibitors, infections/sepsis, cytokines, and GVHD. Damage to the endothelium from HSCT leads to a number of early vascular complicaitons (VOD/SOS, IPS, DAH, TAM, capillary leak syndrome) - which is termed vascular endothelial cell syndrome, and subsequently leads to multiorgan dysfunction. These complications contribute to high mortality rate in post-transplant patients, reaching about 60-80% mortality.

In terms of VOD, it is important for us to identify the risk factors (pre-existing hepatic disease, transplant factors, and patient factors). Besides Baltimore’s and Seattle’s criteria, EBMT has come out with its own VOD Diagnostic Criteria which is not only facilitate the diagnosis of late-onset VOD, but also to help treating physician to grade the severity of VOD and act accordingly. The EBMT severity grading criteria can also be used for suspected VOD before patients fulfil the diagnostic criteria.

Speaker did mentioned that liver biopsy to prove the existent of VOD histologically, is not a mandatory procedure. It is only reserved for patients in whom the diagnosis is unclear and should be undertaken using the transjugalar approach. After all, VOD remains a clinical diagnosis.

The standard of care of VOD is treatment with defibrotide and meticulous supportive care.

One important point to be borne in mind: many of the early post-transplant complications share the same clinical pictures. In facts, risks factors for such complications are overlapping, e.g. some risks factors for VOD are overlapping with risks factors for aGVHD ( MAC, MUD, second AlloSCT, old age, etc).

**AML in 2018**

There is newly added entity in the session of “AML with recurrent genetic abnormalities” in the new 2016 WHO Classification of Myeoid Neoplasm and Acute Leukaemia. ELN 2017 Risk Classification divides AML risk into 3 risk group, i.e. favourable, intermediate, and adverse). FLT3-ITD risk stratification according to allelic ratio (high/low). There are new molecular markers are included in the high risk group, which are AML with mutated RUNX1, ASXL1, and TP53. CBF with C-Kit mutation is not mentioned in ELN Risk Stratification, but speaker do agree that CBF with c-kit mutation is considered high risk AML (as stated in NCCN guideline).

A phase III clinical trial AMLSG 21-13 evaluating standard induction therapy (daunorubicin and cytarabine, and consolidation therapy (high-dose cytarabine [HDAC]) with or without dasatinib in adult patients with newly diagnosed CBF-AML has yet to complete.

Speaker did emphasize about the importance of Next Generation Sequencing (NGS) to map out the comprehensive molecular characterization in AML

Speaker did emphasize about the importance of NGS, which can give us a comprehensive information about the genetic profile of AML, which, combining the clinical presentation of patient, we may be able to predict the disease outcome and hence therapeutic decision.

AlloSCT in AML – For patients with FLT3-ITD mutant/wildtype ratio of >0.51, AlloSCT is proven to improve OS significantly compared to those without transplant. Whereas for low allele burden (ratio <0.51), there was no different in terms of OS between transplant and non-transplant group. ELN 2017 recommendation: Younger patients (18 – 60/65yo) with Intermediate and High Risk AML, AlloSCT from MSD or MUD is recommended. AutoSCT for intermediate risk group is acceptable if there is no Allo option.

For older patients (>60/65yo), consider AlloSCT only in those patients with low HCT-Comorbidity Index.

Based on the recent published papers, speaker recommended that MSD and 10/10 MUD may be stilled preferred type of AlloSCT in AML, in view of a better leukaemic-free survival and lower cumulative incidence of relapse.

Choosing between MAC and RIC has to be taken into account risk of relapse and non-relapse mortality. Patients received MAC has higher NRM whereas RIC has higher relapse incidence.

There are various strategies to prevent relapse after allograting: (1) minimize pre-transplant disease burden (2) optimize cytotoxic properties of the conditioning regimen (3) target leukemic specific antigen post-transplant. MRD monitoring is important. It is a major risk factor of relapse after AlloSCT.

CAR-T Cells in AML – Unlike B-ALL/B-NHL, choosing a targeted antigen in AML is really challenging. Tumour antigen considered as targets for CAR-T therapy are mostly expressed by myeloid progenitors (CMP, MEP, GMP), and mature granulocytes and monocytes. Targeting these antigens (e.g. CD33, CD123, CD44) may inhibit or delay myeloid recovery. There are few proposed strategies to mitigate safety risks in AML CAR-T therapy, e.g targeting NKG2D-L, controlled CAR expression, CAR-T depletion by alemtuzumab, safety switch, etc.

**Multidislinary Approach to the Management of CAR T-cell Therapy**

CAR T-cell therapy is a rapidly emerging immunotherapy in haematological malignancy. It received FDA approval recently in the treatment of relapsed refractory B-ALL (rates of CR/CRi ranged from 67 to 93%) and DLBCL (ORR 52-86%). CD19 antigen is an ideal tumour target in B-Cell malignancies as its expression is generally restricted to B-cell and B-cell precursors. CD19 CAR has evolved into 3rd generation in which it incorporated costimulatory domains (4-1BB/CD28). Combined Flu-Cy lymphodepletion chemotherapy prior to CAR T-cell infusion is proven to improved CAR T-cell expansion and persistence. However, this advent therapy is not without side effects. Toxicities of CAR T-cell therapy includes anaphylaxis/allergy, CRS, CRES, HLH/MAS, “on-target, off-tumour” toxicities. 3 fundamental steps to assess and to manage acute toxicities are (1) Determine the types of toxicities (?CRS ?CRES ?HLH) (2) Grade the severity (3) Management according to the grading.

There are several trials targeting other antigens in patients with lymphoma and myeloma (e.g. CD20 CAR, kappa light chain, CD30 in Hodgkin Lymphoma, BCMA in myeloma). Long term efficacy and safety of CAR T-cell therapy is still unknown.

Practical consideration – Few important issues pointed out by speaker are (1) Apharesis and manufacturing. CAR T-cell therapy can be successful despite low CD3 counts and leucocytosis/blasts in the periphery blood. Nonetheless, manufacturing failure does occur. (2) Bridging therapy. Disease control may be necessary before CAR T-cell therapy, and it should be individualized. CR is desired but not required. Balance between bridging therapy and complication form such therapy must be taken into consideration. (3) Lympohdepletion by Flu-Cy (4) Infusion. Avoid steroid, cytostatics, and immunosuppressors. (5) Complications/Toxicities. (6) Monitoring. Persistence of CAR T-cell, recurrence of disease, B-cell aplasia, viral vector reactivation, infectious complications. (7) Quality of life.

**Controversies in Haploidentical SCT (HaploSCT)**

HaploSCT transplantation is on the raising trend throughout the world. While “CD34 selection” represents the historical backbone of HaploSCT, there are now strategies to improve the outcome of HaploSCT by means of (1) T-deplete strategy (e.g. TCRαẞ-CD19-depletion, suicide approach-transferring of suicide gene HSVtk, and photodepletion of alloreactive T-cell). (2) T-replete strategy (post-cyclophosphamide, T-replete BM plus immunosuppression)

Donor T-cells are important for post-transplant anti-leukaemic and anti-infection role. Unfortunately, they are also the culprit in the development of GVHD. Prolonged risk of infection in T-deplete HaploSCT is always a major concern. There are several strategies mentioned by the speaker to decrease infection by improving post-transplant immunological reconstitution, one of it is by adding back mature donor T cells with a broad repertoire, and by innovative procedures for graft processing - which is TCRαẞ+ cell depletion while maintaining stem cells and facilitating cells (NK cells, TCRγɗ T-cells) in the allograft. Besides, photodynamic therapy to eliminate alloreactive donor T-cells (Phase II Clinical Trial ATIR101-Allodepleted T-Cell Immunotherapy) is another potential effective strategy. T-cell depleted HaploSCT + infusion of ATIR101 at D+28 – D+32 days without the need of GVHD prophylaxis is a safe and effective immunosuppressant-free regimen in HaploSCT. This Phase II study showed that photodepleted strategy reduced TRM and improved OS significantly, and did not cause grade III/IV GVHD

Post-transplant cyclophosphamide is one of the well-known T-replete strategy to improve the outcome of HaploSCT. Speaker had shared numerous retrospective studies and mata-analysis comparing Haplo PTCy vs MUD, Haplo PTCy has comparable outcomes with MUD transplant. PTCy has improved safety and outcome of HaploSCT.

HATCY study: A Phase III, multicenter, randomized controlled study to compare safety and efficacy of a haploidentical HSCT and adjunctive treatment with ATIR101 with post-transplant cyclophosphamide in patients with hematologic malignancies is currently still on-going.

**Updates in Management of Transplant Complications**

Immunotherapy for Viral Infection – Future direction of the management of post-transplant viral infection will be focusing on adoptive cellular therapy and redirecting T-cell strategies.

Transfer of virus specific T-cell (CD4+ and CD8+), for example CMV, EBV, and ADV virus specific T-cell to the recipient may help to reduce the infection risk. Researchers have also inventing CAR-modified virus-specific T-Cells – one stone kill two birds: virus-specific T-cells engineered to co-express tumour-specific receptors.

Management of Invasive Fungal Infection – Speaker recommended ECIL 5 guideline as a guide to adopt antifungal prophylaxis in high risk AML/MDS. Posaconazole (oral solution 200mg TDS OR Tab 300mg BD for 1 day followed by 300mg daily) has grade A1 recommendation in this context, whereas against the usage of Amphotericin B desoxycholate has grade AII recommendation. In AlloSCT, antifungal prophylaxis is generally divided into 3 groups: pre-engraftment with low risk of moulds (Fluconazole, AI), pre-engraftment with high risk of moulds ( Itraconazole BII, Voriconazol BI), GVHD (Posaconazole A1). Serum galactomanannan remain an important asset to diagnose aspergillosis in persistently febrile symptomatic patients.

Treatment for candidaemia: ECIL-6 Grade AII recommendation in haematologic patients: Micafungin, Anidulafungin, Caspofungin, liposomal amphotericin B.

Treatment for invasive aspergillosis: ECIL-6 Grade AI recommendation are Voriconazole and Isavuconazole.

Treatment for invasive mucormycosis: Control of underlying condition and surgical intervention (Grade AII). None of the antifungal drugs receive grade A recommendation. Amphotericin B (liposomal and lipid complex) is Grade BII recommendation.

Chronic GVHD Novel Therapies – Increasing understanding of the pathophysiological mechanism of cGVHD facilitate the invention of new compounds against cGVHD, opening new therapeutic opportunities. Novel therapies mentioned in the speaker’s talk include interleukin-2, bortezomib, Ruxolitinib, TKI, and Ibrutinib.

**Immunotherapy before and after Transplantation**

Adoptive T-cell Therapy and Stem Cell Transplantation – There are various adoptive T-cell therapies, from the basic DLI, to multiantigen-specific T-Cell, TCR transduced T-cells, and CAR-T. Various methods are used to incorporate T-cell therapy into SCT. From EBMT DLI’s experience, there are several strategies to improve DLI outcome, namely ex vivo CD3/CD28 activation of effector, and incubation with IFN-γ, IL-2, anti-CD3.

**Transplant in Specific Myeloma Situation**

With kidney dysfunction – As we know, CKD is staged from I to V based on GFR value. Renal failure in MM is associated with shortened survival. Approximately 20-25% of MM patients suffer from CKD, and about 10% of patients require dialysis at the time of diagnosis. There are various causes of renal impairment in MM, including light chain disease, hypercalcaemia, nephrocalcinosis, obstructive uropathy due to kidney stone disease, fluid depletion, and nephrotoxic drugs, amyloidosis, and cast nephropathy.

Speaker showed few studies of AutoSCT in MM with CKD, with Melphalan dose of 140/200mg/m2, TRM ranged between 6 to 29%! Significant comorbidities which may arise in this group of patients is attributed by arrhythmias, pulmonary complications, sepsis, severe mucositis, encephalopathy.

Bortezomib/Dex +/- Doxorubicin or cyclophosphamide had proven in several tudies to be effective in treating MM patients with CKD, in which high respond rate, improvement in renal function, becoming dialysis independent, and predictable toxicity profile.

Dose adjustment of conventional drugs according to CrCl: (1) CrCl 30-59ml/min: Oral Melphalan reduced by 25%, (2) CrCl 15-29ml/min: Oral Melphalan reduced by 25%. (3) CrCl <15ml/min: Melphalan reduced by 50%. High dose Melphalan for conditioning regimen was kept at 140mg/m2 across these 3 groups. Dexamethasone, Doxorubicin and Cyclophosphamide do not need dose adjustment.

Speaker mentioned about AutoSCT in patient with MM with established ESRD. Recommended practice is depends on the remission status of MM. (1) If non-CR after induction, to performed AutoSCT first. If attain CR after AutoSCT, then to follow by kidney transplant. (2) If in CR after induction, to perform kidney transplant followed by AutoSCT. \*\* Stem cell harvest before kidney transplant as collection will likely be impaired by post-kidney transplant immunosuppression.

AutoSCT for relapsed/progressive disease – Speaker mentioned about feasibility of second AutoSCT in patient relapsed post AutoSCT. Timing of relapsed post-AutoSCT is a strong determinant of the prognosis. He shared about a randomized trial by G, Cook et al, patients who relapsed at least 18 months after prior AutoSCT were treated with PAD (Bortezomib, Doxorubicin, Dexamethasone) for 2-4 cycles, followed by PBSC collection and then were randomized into 2 arms. 1 arm was HDM followed by 2nd AlloSCT; the other arm was Oral Cyclophosphamide 400mg/m2/week x 12. After median follow-up of 31 months, 2nd AutoSCT resulted in longer median PFS (19 months vs 11 months).

AlloSCT in MM – While AlloSCT maybe the only “curative treatment” for MM, it carries high TRM and complications/morbidities (e,g ,GVHD, infection). Speaker did not recommend upfront AlloSCT in MM. Only those patients who are young and fit, with high risk myeloma, with matched donor, and willing to take the risks of AlloSCT, or those who relapsed after AutoSCT, may consider AlloSCT.

