Highlights in Transplantation

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SUMMARY

When considering a stem cell transplantation for a patient, many factors come in to play, especially in case of an allogeneic stem cell transplantation (allo SCT). The best donor and source of stem cells should be selected, the type of conditioning must be considered and the type of underlying disease and disease status at transplant also have an impact on the outcome of the transplantation. Additionally, survival post-transplant is influenced by the occurrence of graft versus host disease (GVHD), infections, or relapsed disease. Advances in different areas of allo SCT reported at the 2017 Annual Meeting of the American Society of Hematology (ASH) will be discussed in this summary.

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SELECTING THE BEST DONOR

In the era of haplo-identical transplantation with post-transplantation cyclophosphamide, donor hierarchy might be changing. To address this question *Roni Shouval* presented data of the European group for Blood and Marrow Transplantation (EBMT) analysing over 100,000 transplants performed between 2000 and 2015. All donor types except cord blood were analysed. Outcome was correlated with donor type, disease risk and time of transplantation. Matched sibling donors (MSD) were used in 46% of the cases, 50% used an unrelated donor (UD, 8% mismatched unrelated donor) and 4% were haplo-identical donors. They found that for all donor types, survival after transplantation has increased over time and this was most obvious for haplo-identical stem cell transplantation. This is mainly due to a clear decrease of non-relapse mortality (NRM) in these patients. NRM was found to be up to 55% between 2000 and 2005 and has decreased to approximately 30% in the most recent period (2011-2015). Overall, one can conclude that, certainly in low and intermediate risk disease, a MSD is still associated with the best outcome in all time periods. In high-risk disease, there is no significant difference in overall survival (OS) after MSD or a matched UD transplant (MUD). MSD is associated with a lower NRM but a higher relapse rate, whereas MUD transplantation has a lower relapse rate. Results of haplo-identical transplantation in recent years has become competitive to MUD and might outperform mismatched unrelated donors.[1] More specifically for the identification of the best MUD, the Center for International Blood and Marrow Transplant Research (CIBMTR) performed a comprehensive analysis of over 10,000 MUD transplants. Their goal was to define donor characteristics related to outcome and subsequently develop a donor selection score. The following donor factors were examined: HLA DQB1 matching, HLA DPB1 matching, age, sex matching, parity, CMV matching, ABO matching and race matching. In the training cohort of nearly 6,000 transplants performed between 1999 and 2011, 3 factors were associated with inferior outcome: HLA DBP1 matching, older donor age and CMV mismatching for CMV+ recipients. However, in a second cohort of approximately 4,500 patients transplanted between 2012 and 2014 only donor age was correlated with outcome, with 2-year survival being 3% better when a donor was 10 years younger.[2]

WHAT IS THE OPTIMAL CONDITIONING REGIMEN?

When the best available donor is selected, the most appropriate conditioning regimen must be chosen. *Mary Eapen* reported the impact of conditioning intensity on the outcome of an allo SCT for acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). The study examined all transplants performed for these indications in the United States between 2009 and 2014. All patients received non-irradiation conditioning regimens, peripheral blood stem cells were the predominant stem cell source regardless of donor type (90%). Myeloablative conditioning (MAC) was

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Conflict of interest: The selection of the abstracts discussed here is the sole responsibility of the author and was not influenced by third parties.

TABLE 1. Checkpoint blockade can provide durable responses in a subset of patients with relapsed hematological malignancy after allo SCT.[10]

	Ipilimumab 10 mg/kg cohort	Ipilimumab 5 mg/kg cohort	Nivolumab cohorts
Number of patients	22	15	8
Histologies	• AML (n=10) • Hodgkin lymphoma (n=7) • NHL and MDS (n=2 each) • MM (n=1)	• AML (n=6) • CLL (n=3) • MM (n=2) • CMML, MDS, ALL and NHL (n=1 each)	• AML (n=4, including 2 with extramedullary disease) • MDS, CMLL, Hodgkin lymphoma, and primary mediastinal B cell lymphoma (PBMCL) (n=1 each) ALL and NHL (n=1 each)
Median age at enrollment	59 (range 22-72)	52 (range 25-73)	69 (range 38-74)
Median number of prior therapies (excluding transplant)	3 (range 2-11)	2 (range 1-7)	2 (range 1-9)
Median time from allo SCT to study enrollment	18.3 mo (range 4.8-61 mo)	24.6 mo (range 7-111 mo)	14.7 mo (range 5.9-75 mo)
Patients with prior GVHD	15/22 (68%)	10/15 (67%)	2/8 (25%)
Notable toxicities	• Liver cGVHD (n=2) • Gr 2 acute GVHD (n=1) • Gr 3 colitis with fatal pneumonities	• mild cGVHD (n=5) • acute GVHD (n=1) • acute and cGVHD (n=1) • Fatal myocardities (n=1) • Fatal sepsis (n=1)	• mild cGVHD (n=15) • Fatal sepsis with ARDS (n=1) • Fatal cerebrovascular accident (n=1)
Overall Response Rate	7/22 (32%)	3/15 (23%)	1/6 (17%)
Median OS, PFS	28.3 mo, 9.4 mo	7 mo, 3.4 mo	N/A

administered in 57% of patients, the remaining 43% were treated with reduced intensity conditioning (RIC). A fludarabine-busulfan backbone was the most frequently used conditioning regimen (64%). Regimens were compared according to intensity and according to the addition of anti-thymocyte globulin (ATG). Adding ATG to the conditioning regimen universally correlated with a decreased incidence of GVHD, but never had an impact on overall mortality, in most cases due to an increased relapse rate. The authors concluded that RIC regimens should be reserved for patients who are not able to tolerate a MAC regimen. Of the RIC regimens included in the study (Flu/Bu2 ± ATG and Flu/Mel ± ATG), Flu/Mel without ATG appears to be the optimal regimen.[3]

GVHD AND RELAPSE

One of the major complications after an allo SCT consists of GVHD. The risk of developing GVHD is highest in case of a mismatched transplant. Abatacept is a molecule that inhibits T-cell co-stimulation with CTLA4 and is being used as a disease modifying anti-rheumatic drug.[4] *Lean et al.* reported the results of the 7/8 MUD cohort of a multicentre phase II trial adding 4 doses of abatacept 10mg/kg/dose days -1, +5, +14 and +28 to standard immune suppression with calcineurin inhibition (CNI) and methotrexate (MTX). The results of this cohort were compared to CIBMTR matched controls. The median time of follow-up was 559 days and 43 patients were treated according to the protocol. The primary endpoint of the study was acute GVHD prior to day +100. There was a marked reduction of grade III-IV acute GVHD in the study cohort with only 2.3% compared to 30% in the control group. This reduction of severe acute GVHD resulted in a significant decrease of NRM at 12 months and did not correlate with an increased relapse rate. As a result, disease free survival (DFS) and overall survival (OS) rates at 12 months (81% and 85%, respectively) were significantly better than in the control group treated with CNI, MTX and ATG (63% and 68%, respectively). As such, this group is the first to show a beneficial effect of *in vivo* blockade of T-cell co-stimulation in the prevention of GVHD. However, it should be noted that the incidence of chronic GVHD in the study cohort and control are the same, the authors argue that this might be related to stopping the administration of abatacept at day +28.[5]

Notwithstanding the importance of GVHD, the major cause of death after allo SCT remains to be relapse of the primary disease. When looking at the causes of death beyond day 100 post-transplant in MSD transplants performed in 2013 and 2014 in the US, 57% of patients died of relapsed disease as opposed to 14% of patients who died from GVHD or infections.[6] This illustrates that there is still an unmet medical need to tackle disease relapse after an allo SCT.

A comprehensive screening for genetic changes in AML relapse after allo SCT was performed by *Ley et al*. They performed RNA sequencing of AML blasts at diagnosis and relapse after chemotherapy or transplantation. These analyses showed that there was a trend towards downregulation of MHC Class II and several other genes involved in MHC Class II antigen processing. There was no differential expression of MHC Class I. These data suggest that one mechanism of relapse post allo SCT and immune escape is the loss of MHC Class II.[7]

When patients do relapse after an allo SCT, this can be treated with pharmacologic agents or with adoptive cell therapy. At ASH 2017, the first results were presented of the Viola Trial. AML relapse post-transplantation was treated with a combination of azacytidine and lenalidomide. When used in monotherapy lenalidomide treatment post-transplantation leads to severe GVHD, when using this combination, there was no excess GVHD and of the 15 patients who were treated with at least 3 cycles, 6 reached a CR/CRi resulting in a significant increase in the OS to 17.3 months versus 3.2 months. The antileukemic effect of this combination appears to be independent of the PD1 pathway.[8]

Pharmacologic agents that are at the centre of many new treatment schedules are checkpoint inhibitors. These molecules might also be used to treat relapsed disease after transplantation, but might incur significant toxicities.[9] *Matthew Davids* presented the updated results of checkpoint blockade with ipilimumab 10 mg/kg for relapsed hematologic malignancies. Additionally, data from 2 new cohorts were presented: a first cohort of patients was treated with ipilimumab 5 mg/kg to minimize toxicity while maintaining efficacy, a 2nd cohort of patients was treated with nivolumab 1 mg/kg (*Table 1*). To date, the results show that a subset of patients treated with ipilimumab 10 mg/kg will attain durable responses with a median OS of 28.2 months. Dose de-escalation to 5 mg/kg does not appear to limit toxicities. In the nivolumab cohort, the incidence of GVHD has been low. However, serious immune related toxicities occurred, leading the authors to conclude that dose exploration and prospective evaluation of nivolumab post-transplant is warranted.[10]

Administration of donor lymphocyte infusion (DLI) is a method of adoptive cell therapy for relapsed disease after allo SCT. *Lulla et al*. reported the results of the first patients treated in a clinical trial with donor-derived tumor directed T-cells for AML relapse after allo SCT. In this trial patients were either included for adjuvant therapy, (i.e. to prevent relapse) or after overt relapse of AML. DLI were enriched for T-cells primed by dendritic cells for the leukaemia associated antigens WT1, PRAME, NY-ESO1 and survivin (multi LAA T-cells). These T-cell lines did not exhibit activity against recipient derived non-malignant cells. Of the 7 patients included in the adjuvant arm, 2 relapsed. Of 5 patients treated for relapse, 2 reached an objective response. Analysis of the T-cells, including deep sequencing, in a patient responding to the treatment showed sustained increase of circulating WT1 specific T-cells of multi LAA origin.[11]

CONCLUSIONS

In conclusion, we can state that haplo-identical stem cell transplantation with post-transplant cyclophosphamide has clearly improved the outcome for this donor type. The latter is mainly related to a decrease in NRM. Conditioning intensity does appear to be of importance in AML and MDS. A major challenge after allo SCT remains to be the management of relapsed disease, which is still the most important cause of mortality.

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KEY MESSAGES FOR CLINICAL PRACTICE

1. **Donor age is related to outcome after transplantation.**
2. **Post-transplant cyclophosphamide has decreased toxicity of haplo-identical stem cell transplantation, moving haplo-identical donors up in the donor hierarchy.**
3. **Abatacept is a promising drug in prevention of graft versus host disease.**
4. **Relapsed disease remains a major concern after stem cell transplantation.**
5. **Immune checkpoint inhibition after allo SCT appears to be feasible but more trials and prospective trials are needed.**

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