T-cell-replete HLA-haploidentical transplantation using post-transplantation high-dose cyclophosphamide in high risk and advanced ALL: feasibility and early outcome

Anna-Katharina Zoellner, Susanne Fritsch, Dusan Prevalsek, Thomas Köhnke, Max Hubmann, Stephanie Lippl, Stephan Kruger, Johannes Hellmuth, Friederike Mumm, Georg Ledderose, Sophie Barlow, Marion Subklewe, Karsten Spiekermann, Wolfgang Hiddemann, Michael H. Albert, Christoph Schmid, Andreas Hausmann, Johanna Tischer

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Disease Risk Index (DRI) and Conditioning Regimen Based Risk Stratification of Outcome Among Adults with Acute Myeloid Leukemia Receiving Allogeneic Hematopoietic Cell Transplantation

Alexander Yip [1], *Bee Choo Tai*[2], *Yeh Ching Linn* [3], *Lip Kun Tan* [1], *Michelle Limei Poon* [1], *Ziyi Lim* [1], *Belinda Tan*[1], *Yelly Lim*[1], *Teck-Guan Soh* [4], *Davanaliz R. Del Rosario*[1], *William Y.K. Hwang*[3], *Liang Piu Koh* [1]. [1] *Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore;* [2] *Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore;* [3] *Department of Hematology, Singapore General Hospital, Singapore, Singapore;* [4] *Stem Cell Laboratory, National University Cancer Institute, Singapore, Singapore*

Background: Although allogeneic hematopoietic cell transplant (HCT) offers the most effective anti-leukemic therapy for acute myeloid leukemia (AML), the benefit on overall survival (OS) can be compromised by non-relapse mortality (NRM). Identification of disease-specific and transplant-related prognostic factors that are predictive of post-transplant outcome is imperative as it allows us to identify patients who will benefit from this aggressive post remission therapy.

Methods: We studied 225 patients undergoing first allogeneic HCT for AML at National University Cancer Institute, Singapore and Singapore General Hospital between January 2005 and December 2014. The patients received transplantation using matched related donor (MRD, n=135), matched unrelated donor (MUD, n=57) or 4-6/6 HLA matched umbilical cord blood (n=33) graft, after myeloablative (MAC, n=166) or reduced intensity conditioning (RIC, N=59) regimen.

Results: The 5-year OS for the entire cohort was 50%, and 59% for patients who were transplanted in first complete remission (CR1). In multivariate analysis, improved OS was seen in patients with low or intermediate risk group according to the disease risk index (DRI) (HR 0.46, 95% CI 0.28-0.74; $p<0.001$) and those who received MAC (HR 0.38, 95% CI 0.46-0.46; p=0.04). Similarly, lower relapse was seen in patients with low or intermediate DRI (HR 0.38, 95% CI 0.46 -2.78; $p<0.001$) and those received MAC (HR 0.60, 95% CI 0.38-2.08; p=0.05). On the basis of this findings, we stratified all patients into four risk groups incorporating the impacts of DRI and conditioning regimens: (1) DRI low/intermediate risk plus MAC (group I); (2) DRI low/intermediate risk plus RIC (group II); (3) DRI High/ very high risk plus MAC (group III); High/ very high risk plus RIC (group IV). Patients in group I had the best outcome with highest 5 year OS of 63%, as compared to group II (31%), III (32%) and IV (13%) ($p < 0.001$), and the lowest 3 year cumulative incidence of relapse (29%), as compared to group II (43%), III (60%) and IV (78%) ($p<0.001$). There was no difference in NRM among the four groups.

Conclusions: Our results show that best outcome was seen when allogeneic HCT was performed in patients with low risk/ intermediate risk DRI following MAC. We have shown that a simple risk stratification model which combines DRI and conditioning regimen, can be used as a dynamic risk assessment tool in predicting HCT outcome for AML patients. Novel anti-tumour agents combined with novel transplant approaches should be explored among patients with high or very risk DRI.

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T-Cell-Replete HLA-Haploidentical Transplantation Using Post-Transplantation High-Dose Cyclophosphamide in High Risk and Advanced ALL: Feasibility and Early Outcome

Anna-Katharina Zoellner[1], *Susanne Fritsch*[1], *Dusan Prevalsek*[1], *Thomas Köhnke*[1], *Max Hubmann*[1], *Stephanie Lippl*[1], *Stephan Kruger*[1], *Johannes Hellmuth*[1], *Friederike Mumm*[1], *Georg Ledderose*[1], *Sophie Barlow*[1], *Marion Subklewe*[1], *Karsten Spiekermann*[1], *Wolfgang Hiddemann*[1], *Michael H. Albert*[2], *Christoph Schmid*[3], *Andreas Hausmann*[4], *Johanna Tischer*[1]. [1] *Department III of Internal Medicine, Hematopoietic Stem Cell Transplantation, Ludwig-Maximilians-University Hospital of Munich-Grosshadern, Munich, Germany;* [2] *Pediatric Hematology/ Oncology, Dr. von Hauner University Children's Hospital, Muenchen, Germany;* [3] *Department of Hematology and Oncology, Klinikum Augsburg, Ludwig-Maximilians-University, Munich, Germany;* [4] *Department I of Internal Medicine, Klinikum München-Schwabing, Munich, Germany*

Haematopoietic stem cell transplantation (allo-HSCT) is a potential curative treatment option for patients suffering from high-risk ALL, but less true for patients with advanced disease. However, not in all of our patients a suitable HLA-matched donor could be identified in time. To evaluate the outcome of T-cell-replete (TCR) HLA-haploidentical haematopoietic stem cell transplantation (haplo-HSCT) utilizing high-dose cyclophosphamide post-transplantation in the context of intensification of conditioning in patients with high-risk, relapsed and refractory ALL, we retrospectively analysed the course of 25 patients (B-ALL n=23, T-ALL n=2) transplanted between 2010 and 2015 in four German transplant centres. Disease was advanced in 19 patients, including 11 patients with relapse after a first allo-HSCT. Conditioning was TBI-based in 14 patients and consisted of fludarabine and cyclophosphamide (CY) plus either 12 Gy TBI in all remission patients or 8 Gy TBI in all patients being older than 55 years; all infants (n=3) received 12 Gy TBI plus etoposide. In adults with relapse after a first allogeneic transplantation conditioning was drug-based: fludarabine, CY plus treosulfan (3 x 10-12g/m^2) and etoposide. Post-grafting immunosuppression was high-dose CY, tacrolimus and MMF in all patients. 23/25 patients engrafted, 2 patients died early in aplasia. No primary graft rejection was observed. Acute GvHD grade II-IV occurred in 5 patients (20%), while 6 patients (24%) suffered from mostly mild to moderate chronic GvHD. Severe toxicity (grade III-IV) was observed in 11 patients (44%); most commonly mucositis (36%), transient elevation of transaminases (32%) and diarrhoea (32%). Kidney failure requiring haemodialysis occurred in 3 patients. CMV reactivated in 8 patients and EBV in 3 patients while no patient developed CMV disease or PTLD. Proven invasive aspergillosis was diagnosed in 2 patients. One-year non-relapse mortality was 12%. After a median follow up of 16.6 months, estimated one-year overall survival and relapse-free survival was 74% and 48%, respectively. In summary, intensification of conditioning in the setting of TCR haplo-HSCT using PTCY is well tolerated with low NRM in patients with high-risk and relapsed ALL, while providing an effective anti-leukemic activity in advanced disease. Thus, we suggest that donor availability can be expanded in patients with high-risk and advanced ALL who lack a conventional donor or suffer from aggressive disease.