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RISK FACTORS FOR ALLOGENEIC STEM CELL TRANSPLANTATION IN PATIENTS WITH MYELOFIBROSIS WITH MYELOID METAPLASIA

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Objective: We sought to determine risk factors for allogeneic stem cell transplantation in myelofibrosis with myeloid metaplasia (MMM) by retrospective analysis within the German Cooperative Transplant Group. **Patients:** Between 1999 and 2006 97 patients (pts) from 15 German centers with an median (md) age of 51 (19–66) years were grafted from 41 related and 56 unrelated donors. 74 pts had chronic idiopathic myelofibrosis, 13 and 10 pts MMM secondary to ET and PV, respectively (resp.). 32 pts were Dupriez score 0, 37 score 1 and 28 score 2 at transplant, 49 needed red cell transfusions. Chromosomal and molecular analysis was available from 75 and 51 pts resp.: 51 pts had favourable, 24 pts unfavourable cytogenetics, 31 pts were JAK2 mutated. Conditioning was of standard, intermediate and reduced intensity in 27, 57 and 13 cases. 28 pts received bone marrow, 69 PBSC. Cellular immunotherapy (5 boosts, 16 donor lymphocytes) was given in 19 cases for 16 relapses, 2 incomplete chimerisms and one graft failure. **Results:** At a md follow up of 975 (100–2630) days probability of overall and relapse free survival (OS and RFS) was 62 and 39%. Neither time from diagnosis to transplant, age, B-symptoms, marrow fibrosis, splenomegaly, JAK2, hemoglobin <10 g/dl, platelets <100/nl, LDH, comorbidity (CCI or HCT-CI), conditioning, type of donor nor graft source were discriminative for survival. Log rank test showed a trend towards lower survival in cases with Dupriez score ≥1 ($p = 0.07$) and transfusion dependence ($p = 0.1$). Solely pretransplant new Mayo PSS ($p = 0.019$), circulating blasts >1% ($p = 0.016$), monocytes >1/nl ($p = 0.008$) and cytogenetics ($p = 0.009$) were predictive for survival after allogeneic transplant. Cox regression analysis within pretransplant variables revealed cytogenetics as the only independent factor for OS and RFS ($p = 0.023$). Following transplant acute GvHD°≤II was associated with better RFS than aGvHD°III-IV (49 versus 19%, $p < 0.0001$). Limited chronic GvHD led to an identical OS and RFS of 84 and 81% as opposed to 43% RFS for no and 20% RFS for extensive cGvHD, resp. ($p = 0.018$). 7 pts treated with cellular immunotherapy had a partial and 7 a complete response. **Conclusions:** Pretransplant disease characteristics like cytogenetics are the most important outcome variables for allogeneic stem cell transplantation in MMM. Evidence for a potent graft-versus-myelofibrosis-effect suggests exploitation of adjuvant donor lymphocyte infusions to improve these results.

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LONG-TERM FOLLOW-UP OF ADMINISTRATION OF DONOR-DERIVED EBV-SPECIFIC CTLS TO PREVENT AND TREAT EBV LYMPHOMA AFTER HEMOPOIETIC STEM CELL TRANSPLANT

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Since 1993 we have administered polyclonal donor-derived EBV-specific CTLs to high-risk recipients after HSCT. A total of 73 patients have received CTLs, 66 as prophylaxis and 7 as therapy. 11 patients had underlying primary immunodeficiencies (6 XLP, 1 WAS, 2 undefined CID, 2 CAEBV), and 5 had developed EBV-associated LPD or HLH which was controlled prior to HSCT. None of the patients on the prophylaxis study had any acute toxicity and only 2 patients developed exacerbations of previously existing GVHD month after infusion. Local inflammation during a therapeutic response was seen in 3 patients who had high EBV DNA and likely had undiagnosed LPD prior to receiving CTLs. All recovered with no active intervention and had no long term sequelae. 6 patients have been treated for established EBV lymphoma, with complete responses seen in 5, accompanied by accumulation of gene-marked CTL at sites of disease. In 1 patient with extensive disease significant inflammation was seen at sites of disease after CTL administration illustrating the benefits of treating patients with early disease. The patient who failed treatment was found to have a mutation resulting in deletion of the two 2 immunodominant HLA11 restricted epitopes in EBNA 3B, recognized by the donor CTL line. In the first 26 patients CTLs were marked with the neomycin resistance gene to track their fate and persistence and 17 of these 26 patients are alive from 11 to 14 years post CTLs with the remaining 9 patients dying from relapse (n = 6) infection (n = 2) and a motor vehicle accident (n = 1). No RCR has been detected and no patient has developed any new malignancies although 1 patient had recurrence of a pre-existing non hematologic malignancy which was negative for the marker gene by PCR analysis. Analysis of DNA using a real time PCR assay has shown detection of the marker gene for up to 85 months with intermittent detection in peripheral blood T-cells. The gene-modified EBV-CTL population expanded in vivo directly after infusion and also at later times in response to EBV-reactivation, contracting when the antigenic stimulus subsided. Integration site analysis performed on peripheral blood samples has shown polyclonal cell populations with no gene or genomic locus appearing to be preferentially selected by retroviral integration. EBV-specific CTLs can therefore restore anti-viral immunity and mediate antitumor effects with an excellent safety profile on long term follow up.

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A MULTICENTRIC COMPARATIVE ANALYSIS OF OUTCOMES OF HLA IDENTICAL RELATED CORD BLOOD AND BONE MARROW TRANSPLANTATION IN PATIENTS WITH BETA-THALASSEMIA OR SICKLE CELL DISEASE

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Most patients with beta thalassemia major (TM) or sickle cell disease (SCD) can be cured by hematopoietic stem cell transplantation (HSCT) from either cord blood (CB) or bone marrow (BM). One advantage of CB is the absence of risk associated with donation. In order to compare outcomes after HSCT with CB or BM, we studied 402 patients with TM or SCD who received HLA identical sibling CB (n = 72) or BM (n = 330) allografts between 1994 and 2005. In order to avoid center and period effect, only centers that performed both types of HSCT during the same period were