ARTICLE - Cell Therapy & Immunotherapy

Lower overall survival in male patients with advanced disease undergoing allogeneic hematopoietic stem cell transplantation is associated with *CYP1B1* Leu432Val polymorphism

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Received: June 1, 2023.
Accepted: September 18, 2023.
Early view: September 28, 2023.

https://doi.org/10.3324/haematol.2023.283649

Supplement - Stute N and Koldehoff M

Supplementary Methods

Additional laboratory information

Pre-transplant histocompatibility testing of patients and donors was performed at low-resolution human leukocyte antigen (HLA)-A, -B, -C and high-resolution HLA-DRB1, -DQB1 level DNA-based typing according to standard methods.[37] Additional information was available for 198 (of 382) patients: maximum levels of bilirubin and creatinine, and engraftment data. This was an unselected group.

Conditioning regimen

The myeloablative conditioning regimen consisted of intravenous cyclophosphamide in combination with fractioned total body irradiation (TBI) or oral busulfan (BU), in combination with cyclophosphamide, or treosulfan in combination with cyclophosphamide or fludarabine as published earlier.[38] Patients who underwent transplantation of highly enriched CD34+ cells received a conditioning regimen with fractioned TBI, cyclophosphamide and thiotepa as published earlier.[39] Patients scheduled for stem cell transplantation with reduced intensity conditioning received BU (1 mg/kg of body weight every 6 h over 2 days), in combination with fludarabine (30 mg/m2 of body surface area over 5 days). GvHD prophylaxis consisted of methotrexate (MTX) and cyclosporine (CSA) in patients who received an unmanipulated graft. In the patients who underwent a CD34+ PBSCT, no further GvHD prophylaxis was given. In vivo T-cell depletion was performed using Campath-1H (alemtuzumab 10 or 20 mg for 5 days) in combination with CSA or rabbit anti T-lymphocyte globulin (ATG-S, Fresenius, Bad Homburg, Germany) (10 mg/kg of body weight for 3 days) in combination with CSA and MTX. All patients were isolated in reverse isolation rooms equipped with high-efficiency particular filtration systems. They received prophylactic oral metronidazole 400 mg three times daily, ciprofloxacin 500 mg twice daily, and fluconazole 200 mg once daily.

Clinical study endpoints

Overall survival (OS) was defined as time between transplantation and death from any cause or last follow-up for patients alive (censored). Non-relapse mortality (NRM) was defined as death due to any cause after SCT without ever experiencing prior relapse. Only patients surviving for more than 30 days were included in the analysis of acute GvHD. Acute GvHD was graded according to standard criteria (Glucksberg).[40,41] Chronic GvHD was assessed in patients alive after 100 days.[42]

Covariates in multivariate analysis

The following covariates were analyzed: *CYP1B1* C432G genotype in patients: CC vs. CG vs. GG, patient age at transplant (⩽40 vs. >40 years or ⩽50 vs. >50), patient gender, donor gender (or patient-donor gender constellation), disease stage at transplant (advanced vs. early disease), conditioning intensity: myeloablative (MAC) vs. reduced intensity (RIC), TBI based (yes vs. no), donor type (sibling vs. unrelated), HLA-constellation between patient and donor (identical vs. mismatch), stem cell source (PBSC vs. bone marrow), and *in vivo* T-cell depletion (ATG and other, yes vs. no).

Statistics Software

Statistical analyses were performed using the SPSS software, version 29 (SPSS Inc. / IBM, Armonk, NY, USA) and R, version 4.2.2 (R Development Core Team, Vienna, Austria) software packages ‘survfit’, ‘cmprsk’, ‘prodlim’ and RStudio version 2022.07.2 (Boston, MA).[47,49]

Supplementary Results

The role of gender mismatch on outcome

Gender mismatch plays no role for male patients with advanced disease in multivariate analysis (see Table 4). This is the case for OS, Relapse and NRM.
It does not matter whether R SNP is included in multivariate analysis or not. The same holds true for all patients and for male patients. In multivariate analysis gender mismatch plays no role in severe acute GvHD and in chronic GvHD both limited and extended. As expected, T-cell depletion plays a major role in GvHD as does mismatch donor in chronic GvHD.

In univariate analysis, findings revealed that in male patients with advanced disease, overall survival and NRM are both similar with gender mismatch, but death occurs earlier (not significant). Relapse is identical with gender mismatch. Severe acute GvHD is higher with gender mismatch (not significant), and there is no evidence of more chronic GvHD. The same holds true for all patients and for male patients.