RESEARCH LETTER

Second allogeneic hematopoietic stem cell transplantation for relapsed acute myeloid leukemia: a retrospective single-center analysis of the outcome

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Introduction Relapse of acute leukemia after allogeneic hematopoietic stem cell transplantation (alloHSCT) is the principal cause of treatment failure and, consequently, patient death.[1,2] Prognosis for the patients who relapsed is poor, with 1-year probability of survival between 7% and 33%, and with median overall survival (OS) of about 3 months.[3,4]

Treatment options include chemotherapy, donor lymphocyte infusion, and second alloHSCT.[5] The last option seems to be the most effective but it also involves a high risk of serious, life-threatening complications.[4] A strategy of this procedure, especially optimal reinduction, choice of donor, type of conditioning and immunosuppression remain unknown. So far, no randomized controlled trial to compare second alloHSCT with other treatments has been conducted.

In this study, we evaluated the outcome in a homogenous group of patients who underwent second alloHSCT for acute myeloid leukemia (AML) only, with the main focus on the reason of treatment failure and relapse.

Patients and methods We retrospectively analyzed the outcome of second alloHSCT in 40 patients (21 women, 19 men) with AML, transplanted in our center between 2005 and 2021. We included only the patients with AML, 2 of them were transplanted for the first time due to myelodysplastic syndrome (MDS), but AML was recognized at relapse after the first alloHSCT. The patients with acute lymphoblastic leukemia were excluded from the analysis.

The first transplant took place between 2004 and 2020. Median (range) age at the first alloHSCT was 40 (19–68) years. At the first alloHSCT most patients (90%) were transplanted in complete remission (CR) of the disease; for 26 patients this was the first remission (CR1), 8 patients were in the second or subsequent remission (>CR1), and 4 patients were transplanted in active disease (nCR). Genetic risk was defined in 23 cases, and adverse cytogenetics were found in 10 patients. The most frequently used conditioning protocol was busulfan-based (77.5%; + cyclophosphamide [BuCy2], 10 patients; + fludarabine [FluBu], 21 patients). Most patients (80%) received myeloablative first conditioning. The donor at the first alloHSCT was a matched sibling in 16 patients (40%), matched / mismatched unrelated person in 23 cases (57.5%), or a haploidentical individual in 1 case (2.5%). Only 7 patients presented graft versus host disease (GvHD) symptoms after the first alloHSCT.

Median time between the first alloHSCT and relapse of the disease was 10 (3–120) months; 13 patients relapsed within 6 months after the first alloHSCT, 21 patients between 7 and 24 months, 6 patients after longer than 2 years, including 1 after 10 years.

At the relapse of the disease, all but 2 patients received reinduction chemotherapy (mostly based on cytarabine), 1 patient received donor lymphocyte infusion. At the time of the second transplant, 28 patients were in CR, and 12 were transplanted in active disease.

Median age at the time of the second transplant was 41 (20–69) years. Only 14 patients (35%) received myeloablative conditioning (busulfan- or treosulfan-based) before the second alloHSCT, usually the younger ones in good general condition; 26 patients received reduced-intensity conditioning regimen. Five patients transplanted in active disease received myeloablative prolonged conditioning based on melfalan and treosulfan.

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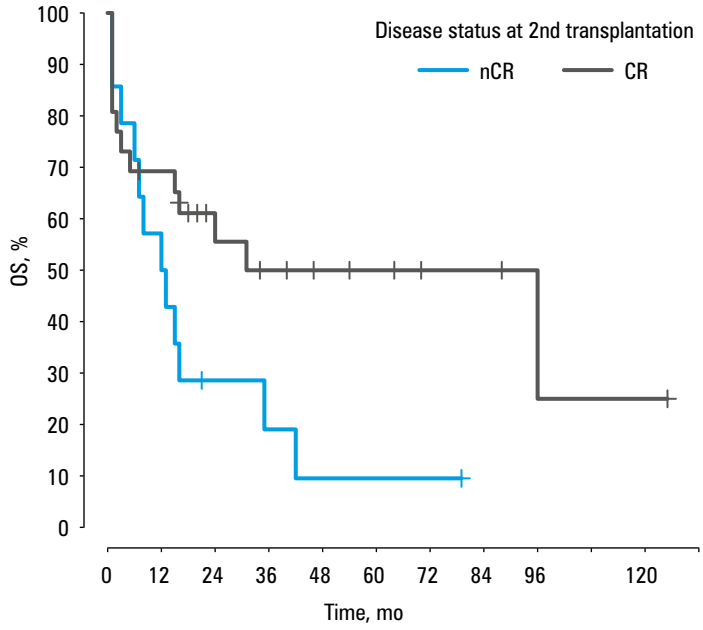

FIGURE 1 Impact of the disease status at the second allogeneic hematopoietic stem cell transplantation on overall survival (OS) (Kaplan–Meier analysis, $P = 0.04$)
Abbreviations: CR, complete remission; nCR, noncomplete remission

Stem cells from peripheral blood were used in 39 patients, and from bone marrow in 1 patient.

The donor at the second alloHSCT was a matched sibling in 11 patients (27.5%), matched / mismatched unrelated person in 13 patients (32.5%), and a haploidentical individual in 16 cases (40%). Twenty two patients received the second alloHSCT from the same donor as the first transplant, and 18 from different ones. Additional data are provided in Supplementary material, *Table S1*.

We defined OS as the time from the second alloHSCT to death or the end of the follow-up, and event-free survival (EFS) as the time from the second alloHSCT to relapse or progression or the end of the follow-up.

Statistical analysis The Kaplan–Meier curves for OS and EFS were compared with the log-rank test. For competing risks of relapse mortality, nonrelapse mortality, and relapse incidence, the Aalen–Johansen curves were used and compared with the Gray test. Significance level for all statistical tests was set to 0.05. For univariable analyses, 12-, 24- and 60-month survival rates in the compared groups were shown along with median survival time. For multivariable analyses, hazard ratios (HRs) with corresponding 95% Cl were shown. R 4.1.2. software was used for computations (R Foundation for Statistical Computing, Vienna, Austria).[6]

Results After the second alloHSCT, neutrophil engraftment was achieved in 35 patients, with median time of 22 days (IQR, 10–47). Five patients died before reconstitution due to infection.

Eight patients (20%) died within up to 100 days due to transplant-related reason (infection, multiorgan failure [MOF]), 1 patient died before 100 days due to early relapse. Three of those patients were transplanted in active disease.

Only 7 patients (17.5%) presented GvHD symptoms, 5 in an acute and 3 in a chronic form. Relapse occurred in 17 patients (42%) and was the cause of death in 15 cases. The median time between the second alloHSCT and relapse was 7 (2–30) months. After the median follow-up of 37.5 months among survivors, 15 patients (37%) remained alive, with 14 in remission of the disease.

Overall survival Median OS for the whole group was 16 months. The 1-year, 2-year, and 5-year OS was 62.31%, 45.8%, and 34.17%, respectively. Disease status at the time of the second alloHSCT, that is, CR vs nCR, significantly improved OS (FIGURE 1). The 1-year, 2-year, and 5-year OS was 69.23%, 55.53%, and 49.98% for the patients transplanted in CR, and 50%, 28.57%, and 9.52% for the patients transplanted in nCR. Median OS for the CR group was 31 months, and for the nCR group 12 months ($P = 0.04$; HR, 0.39; 95% CI, 0.17–0.89). Among the patients who were transplanted in CR, 14 (50%) remained alive at the time of the data collection, while of those who were not in CR at the second transplant only 1 was alive.

We analyzed the impact of the remission duration after the first alloHSCT on OS after the second alloHSCT. For this analysis, we divided the patients into 2 groups (relapse before or after 12 months), or into 3 groups (relapse before 6 months, between 7 and 24 months, and later than 24 months). We found no effect of time to relapse on OS. We also analyzed other factors, such as the type of conditioning, donor type, or donor change, and concluded that they did not affect OS. No difference was found between the patients who received myeloablative and those on the reduced-intensity conditioning regimen.

Event-free survival Median EFS for the whole group was 12 months. The 1-year, 2-year and 5-year EFS was 47.14%, 41.9%, and 26.19%, respectively.

Only disease status at the time of the second alloHSCT (CR vs nCR) significantly influenced EFS. The 1-year, 2-year, and 5-year EFS was 61.3%, 57.21%, and 36.62%, respectively, for the patients transplanted in CR, and 21.43%, 14.29%, and 7.14% for those transplanted in nCR. Median EFS for the CR group was 30 months, and for the nCR group it was 6 months ($P = 0.01$; HR, 0.39; 95% CI, 0.17–0.89). EFS remained unaffected by other factors, such as the time from the first transplantation to the first relapse, type of conditioning, type of donor, and donor change.

Nonrelapse mortality Ten patients (25%) died due to treatment-related mortality. In all cases an infection, mostly bacterial, was the main cause of death. Additionally, in 2 cases MOF was recognized. Eight patients died within up to 100

days after the transplant, 5 before neutrophil engraftment. One patient died 6 months following the transplant due to infectious complications, including a fungal infection, and central nervous system hemorrhage, and 1 patient died 16 months after the second transplant due to an infection in the course of severe GvHD. The last 2 patients were in remission of leukemia at the post-transplant assessment.

Cumulative incidence of nonrelapse mortality (NRM) was 22.5% at 12 months, and 25.1% at 24 and 60 months. None of such factors as disease status at the second alloHSCT, time from the first alloHSCT to relapse, donor type, donor change, and type of conditioning had any influence on NRM.

Discussion Currently, there is no standard approach to the treatment of patients with AML who relapse after alloHSCT. A majority of available published observational studies or registry-based studies include heterogenous groups with various malignancies. None randomized controlled study has been published that compares the result of the second alloHSCT and other methods of treatment, such as chemotherapy, donor lymphocyte infusion, or other new agents, for example, FLT3 inhibitor or inhibitor of anti-apoptosis factor B-cell lymphoma 2.

One of the largest registry-based, retrospective study performed on behalf of the European Group for Blood and Marrow Transplantation, in which the outcomes and predictors of the second alloHSCT were analyzed, included as many as 2632 patients, however, only 36% of the patients (n = 948) had AML. For the AML patients, the study reported a 5-year OS after the second alloHSCT of 17%, and a very high NRM of 42%.[7] Despite these poor results, cellular therapy seems to be better than classic chemotherapy alone.[4,8] Previous studies identified several different prognostic factors that corresponded to better outcomes, such as longer duration of remission, remission of disease at the time of transplantation, younger age, as well as factors associated with significant mortality, such as GvHD, infections, or ongoing immunosuppression at the time of relapse.[8-11]

In our report, only 1 factor influenced OS and EFS. The patients in remission of the disease at the time of transplantation had longer OS and EFS than those without remission. However, the analyzed group was small. The second alloHSCT should not be proposed to a patient without remission of the disease or to older patients, with high hematopoietic cell transplantation-specific comorbidity index and the Eastern Cooperative Oncology Group score above 2 due to both low efficacy and high NRM.[10,12]

Several novel molecule inhibitors and immunotherapeutic options are being investigated. Current data suggest that the response to these drugs is often short-term. Perhaps their combination with cellular therapy will improve their effectiveness.

Conclusions The second alloHSCT remains a curative option for the patients with AML relapsing after the first alloHSCT. Achievement of CR before transplantation probably increases the chance for successful treatment. The rate of transplant related mortality is high. Most patients died due to relapse of the disease.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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