ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPANTATION AT THE CLINICAL CENTER OF VOJVODINA

Uvod. Allogene transplantacija matičnih ćelija hematopoze je metoda izbora za lečenje raznih urođenih i stečenih poremećaja hematopoetnog sistema, kao i raznih hematoloških maligniteta.

Materijal i metode. Retrospektivna studija, koja je obuhvatila 35 pacijenata lečenih alogenom transplantacijom matičnih ćelija hematopoze. Od ukupno 35 pacijenata, medijane životnog doba od 33 godine, 3 pacijentca je bolovao od akutne mijeloidne leukemije, jedan od akutne limfoblastne leukemije, detet od hronične mijeloidne leukemije, pet od aplastične anemije, pet od mijeloidoplastičnog sindroma, jedan od duploj mijeloidni sindrom i jedan je bolovao od Juicngovog sarkoma (Sarcoma Ewing). Devet bolesnika (26%) imalo je uznapredovalo, rezistentnu bolest u vreme transplantacije. Većina bolesnika je imala transplantaciju od podudarnog srodnog davaoca 89% (31/35); kod tri bolesnika sprovedena je singenja transplantacija i kod jednog haploidentična transplantacija. Od 35 pacijenata, 16 (45,7%) su živi.

Sažetak

Uvod. Allogene hematopoietic stem cell transplantation is the best therapeutic option for the treatment of some inherited and acquired diseases of the hematopoietic system as well as various hematological malignancies. Material and Methods. The study was conducted as a retrospective analysis of 35 patients who underwent allogene hematopoietic stem cell transplantation at the Clinical Center of Vojvodina. Results. In a group of 35 patients with median age 33 years, 13 patients had acute myeloid leukemia, one patient had acute lymphoblastic leukemia, nine had chronic myeloid leukemia, five had aplastic anemia, five myelodysplastic syndrome, one had multiple myeloma and one had Ewing sarcoma. Nine patients (26%) had an advanced, resistant disease at the time of transplantation. The majority of patients had a matched related transplantation - 89% (31/35) - three patients had syngeneic transplantation, and one patient had a haploidentical transplantation. Out of 35 patients, 16 (45.7%) are alive. The European Bone Marrow Transplantation score ≥3 and the presence of advanced disease at the time of transplant were unfavourable prognostic factors for survival (p<0.01). If we exclude the cases with advanced, resistant disease at the time of transplantation, the probability of 5-year survival rate was as follows: 100% in patients with aplastic anemia, 75% in patients with acute leukemia, 34% in myelodysplastic syndrome, and 14% in chronic myeloid leukemia patients. Conclusion. The outcome of allogene hematopoietic stem cells transplantation in our patients is generally comparable with previously reported results. The main prognostic factors for survival were European Bone Marrow Transplantation risk score and disease status at the time of transplantation.

Key words: Hematopoietic Stem Cell Transplantation; Survival Rate; Graft vs Host Disease; Treatment Outcome

Introduction

Over the last half-century, allogene hematopoietic stem cell transplantation (AHSCCT) has evolved from an idea to a well-established therapy used in the treatment of tens of thousands of individuals annually [1]. AHSCCT is still the best therapeutic option for the treatment of inherited and some acquired diseases of the hematopoietic system as well as various hematological malignancies [2]. AHSCCT requires the harvest of an adequate number of hematopoietic stem cells (HSC) from a histocompatible donor and their infusion into a patient following a conditioning regimen [3]. HSC could be collected from the bone marrow (BM), peripheral blood (PB) after chemotherapy and/or recombinant hematopoietic growth factors, as well as various hematological malignancies [2]. AHSCCT requires the harvest of an adequate number of hematopoietic stem cells (HSC) from a histocompatible donor and their infusion into a patient following a conditioning regimen [3].
well as from the umbilical cord blood [2]. In the past two decades, peripheral blood AHSC replaced the BM as a HSC source due to faster engraftment and practicability. As transplant indications and conditioning regimens continue to change, whether the choice of the stem cell source has an impact on transplant outcomes remains to be determined [4]. The AHSC is multi-staged and begins with identifying the HSC donor. The donor can be a Human leukocyte antigen (HLA)-matched relative (most often a brother or a sister), HLA-matched unrelated donor, HLA miss-matched family member (haploidentical donor) or HSC from unrelated umbilical cord blood [5]. Then an adequate conditioning regimen needs to be applied. The conditioning regimens have been classified as high-dose (myeloablative), reduced-intensity and non-myeloablative. The conditioning regimens are administered as part of the procedure to achieve two goals: provide sufficient immunoablation to prevent graft rejection and reduce the tumor burden. The intensity of conditioning regimens can vary substantially, and when selecting the optimal conditioning regimen for any given patient, disease-related factors such as diagnosis and remission status, as well as patient-related factors including age, donor availability, and presence of comorbid conditions, need to be considered [6]. HSCT performed in the early phases of the disease and in young patients offers more than a 50% cure rate. The transplant-related mortality still represents the greatest obstacle, ranging from 20–30%, despite the less toxic conditioning regimens, high-resolution HLA typing, and better supportive care. Graft versus host disease (GvHD) and infections remain the main causes of morbidity and mortality. As for disease relapse, it correlates with the disease status at the time of transplantation [3].

The aim of this study was to analyze the medical data, prognostic factors, survival rate and transplant-related complications of 35 patients who underwent AHSC at the Clinic of hematology, Clinical Center of Vojvodina.

Table 1. Clinical and transplant characteristics of the study patients

<table>
<thead>
<tr>
<th>Variable/Varijabla</th>
<th>Values/Vrednosti</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Medin, min-max, years/Životno doba, Medijana, min-maks, godine</td>
<td>33, 15-56</td>
</tr>
<tr>
<td>Sex Male/Female, N (%)</td>
<td>15 (43)/20 (57)</td>
</tr>
<tr>
<td>EBMT score &lt; 3 / ≥ 3 N (%)</td>
<td>22 (63)/13 (37)</td>
</tr>
<tr>
<td>HCT-CI score &lt; 2 / ≥ 2 N (%)</td>
<td>30 (86)/5 (14)</td>
</tr>
<tr>
<td>Donor sister to brother Yes/No N(%)</td>
<td>7 (20)/28(80)</td>
</tr>
<tr>
<td>Time from diagnosis to transplant, Median, min-max, months</td>
<td>10, 2-146</td>
</tr>
<tr>
<td>Vreme od dijagnoze to transplantacije, Medijana, min-max, meseci</td>
<td></td>
</tr>
<tr>
<td>Stem cell source BM/ PB N(%)/Izvor matičnih ćelija periferna krv/koštana srž N (%)</td>
<td>16 (45.7)/19 (54.3)</td>
</tr>
<tr>
<td>Major ABO incompatibility* N(%)/Major ABO inkompatibilija* N (%)</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Minor ABO incompatibility* N(%)/Minor ABO inkompatibilija* N (%)</td>
<td>8 (23)</td>
</tr>
<tr>
<td>MNCx10^8/kg BW - Median, min-max/Mononuklearne ćelije x10^8/kg TM – Medijana, min-maks</td>
<td>6.1, 3.2-12</td>
</tr>
<tr>
<td>CD34+ cells x10^6/kg BW - Median, min-max/CD34+ ćelije x10^6/kgTM – Medijana, min-maks</td>
<td>6.23, 2.21-11.7</td>
</tr>
<tr>
<td>Time to engraftment - Median, min-max, days/Vreme do engraftmenta – Medijana, min-maks, dani</td>
<td>12, 8-21</td>
</tr>
<tr>
<td>Acute GvHD N(%)/Akutni GvHD N (%)</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>GvHD chr. N(%)/Hronični GvHD N (%)</td>
<td>(grade 3/4 6%)</td>
</tr>
<tr>
<td>Relapse N(#)/#Relaps N(#)</td>
<td>11 (31%)</td>
</tr>
<tr>
<td>Non-relapse mortality N(%)#Mortalitet koji nije u vezi sa relapsom N(%)</td>
<td>9 (26%)</td>
</tr>
</tbody>
</table>

*In one case both major and minor ABO incompatibility was present

*U jednom slučaju bila je prisutna i major i minor ABO inkompatibilija
Material and Methods

We retrospectively analysed 35 patients who underwent transplants at the Clinical Center of Vojvodina in Novi Sad, Serbia. The study was conducted in accordance with the Helsinki Declaration.

Data on clinical outcome (death, survival, relapse) and other clinical and laboratory characteristics were collected from patients’ medical files.

The following parameters were assessed: age, sex, time from diagnosis to transplantation, transplantation date, diagnosis, European Bone Marrow Transplantation-EBMT score [7], Hematopoietic cell transplantation-specific comorbidity index - HCT-CI [8], the presence and grade of acute and chronic GvHD, HSC source (PB vs BM), the number of apheresis, number of mononuclear cells per kg/bodyweight (BW) of the recipient, the number of CD34+ cells per kg/BW of the recipient, the type of transplantation (matched related, syngeneic, haploidentical), the conditioning regimen, the presence of ABO incompatibility, the presence of graft failure, survival and relapse status. We defined the advanced disease similar to definition of the late disease in EBMT score [7]: AL not in complete remission (CR), chronic myeloid leukaemia (CML) in blast crisis, myelodysplastic syndrome (MDS) not in CR or partial remission (PR) previously treated with more than 10% of blasts, lymphoma and multiple myeloma (MM) not in CR, PR nor in stable state, previously treated. Staging was not applicable for aplastic anemia.

Numerical variables are presented in median values and ranges. Categorical variables are shown as counts and relative frequencies. Overall survival was determined as the time between the date of transplantation and the date of death or last follow-up for censored patients. The survival was analyzed using Kaplan–Meier plots. The survival curves were compared using the log-rank test. A p-value of less than 0.05 was considered to be statistically significant. Analyses were performed using Stata 12 (Stata Corp LP, College Station, USA).

Results

The first transplantation was syngeneic and performed in 1977 in a patient with AA. The patient recovered after second transplantation. The second transplantation was done in 1980 in a patient with resistant acute myeloid leukemia (AML) but without success. From 1990 to 1999 eighteen transplantations were performed (four AA, three AML, nine CML, one MDS, one MM and one Ewing sarcoma-ES). From 2004 to 2017 fifteen transplantations were done, predominantly in patients with AL (ten AML, four MDS, one AA).

Out of 35 patients, 20 (57%) were female and 15 (43%) male. The median age of the patients was 33. Table 1 shows the clinical and transplantation characteristics of the study patients.

In relation to the diagnosis of the underlying disease, the distribution of the patients was as follows: acute leukemia in 40% of the patients (13 patients had AML - including 3 cases of secondary AML not in CR nor PR, one patient had acute lymphoblastic leukaemia), CML in 26% (9 patients, two were in resistant, blast transformation phase, two in acceleration phase), AA in 14% (five patients), MDS in 14% (five patients), MM in one patient as well as one case of Ewing sarcoma (ES).

Nine patients (26%) had an advanced, resistant disease at the time of transplantation.

The majority of patients had a matched related transplantation, 89% (31/35), three patients with AA had syngeneic transplantation, and only one patient with ES had a haploidentical transplantation.

The conditioning regimes were as follows: cyclophosphamide in four patients with AA, ATG only in hepatitis associated AA in the case of syngeneic transplantation, cyclophosphamide + busulphan in 23 patients, busulphan + fludarabine in three cases with reduced conditioning, busulphan + cyclophosphamide + ATG in one patient, busulphan + cy-
clophosphamide + etoposide in one patient, fludarabine + melphalan in one case, and TBI in one patient.

Thirteen patients (37%) had an EBMT score ≥3 while five patients (14%) had a HCT-CI score ≥2. In 7 (20%) cases, the donor was female (sister) to a male recipient (brother). The GvHD prophylaxis was cyclosporine A + methyl-prednisolone in 19 patients (18/19 were transplanted before 2000), cyclosporine A + methotrexate in 11 patients and cyclosporine A + mycophenolate mofetil in three patients (all patients transplanted after 2004), and methotrexate and corticosteroids in two patients transplanted till 1980.

The acute GvHD was present in 37% of patients, chronic GvHD in 31% of patients (Table 1).

Relapse occurred in nine (26%) of patients. Non-relapse mortality was present in 10 (28.6%) of patients. Out of 35 patients, 16 (45.7%) are alive. The median follow-up time of censored patients was 49 months (range from 3 to 480 months). The median survival rate was 18 months (range from 1 to 480 months). Survival of all patients is presented in Graph 1.

Graph 3. Survival of patients according to disease status at time of transplantation

Figure 3. Preživljavanje bolesnika prema statusu bolesti u vreme transplantacije

Discussion

We presented the results of allogeneic hematopoietic stem cell transplantation from our institution. The study group is very heterogeneous considering the time of transplantation, diagnosis, conditioning regimens, and GvHD prophylaxis. In the period before 2000, the main indications for AHSCT were CML and AA. After 2000, the majority of patients had AL or MDS. The outcome of transplantation in AA patients was excellent. All patients had engraftment with long-term survival of 100%. These results are in concordance with published reports with long-term survival in more than 80% of patients younger than 40 years old [9, 10].

However, the long-term results of transplantation in CML patients were not satisfactory. These transplants were all performed in pre-tyrosine-kinase inhibitor (TKI) era and without real time PCR monitoring which could have had an impact on the outcome. Almost half of the CML patients were in blast transformation or acceleration phase of the disease, both phases known as prognostically unfavorable [11]. According to EBMT results, the probability of survival at 20 years was 34% for transplanted CML patients which is higher than in our group [7] but still seems to be not very satisfactory. These results have a historical value considering the fact that the indications for transplantation in CML in TKI era is restricted to patients who didn’t respond to at least two lines of TKI treatment [12].

The outcome of transplantation in AL and MDS is in correlation with the published results. The probability of five-year survival in AML patients transplanted in any remission is 75% which is similar to the published results [13, 14]. The projected five-year survival rate in MDS patients after AHSSCT is 34% if we exclude the patients with advanced, late disease. Published results reported long-term survival in MDS at the level of 30 to 40% for a similar group of patients [15, 16].
In our study, considering the limited number of transplanted patients our primary aim was to present the main results of AHSCT, and not to conduct a detailed prognostic analysis. However, we found the EBMT risk score and disease status have a strong prognostic value which is in concordance with the published results [11, 17].

**Conclusion**

The outcome of allogeneic HSC transplantation in our patients is generally comparable with the previously reported results. The main prognostic factors for survival were European Bone Marrow Transplantation risk score and disease status at the time of transplantation.

**References**


Rad je primljen 15. IX 2017.