Allogeneic stem cell transplant for chronic myeloid leukemia as a still promising option in the era of the new target therapy

Alogena transplantacija matičnih ćelija u lečenju hronične granulocitne leukemije kao još uvek prihvatljiv pristup u eri nove ciljne terapije


Military Medical Academy, *Clinic of Hematology, †Institute of Transfuziology, §Institute of Pathology, Belgrade, Serbia; ‡Clinical Center of Serbia, Clinic for Hematology, Belgrade, Serbia

Abstract

Uvod/Cilj. Inhibitori tirozin-kinaze (TTK) u osnovi su izmenili pristup lečenja, jasno poboljšavajući efikasnost lečenja hronične granulocitne leukemije (HGL). Mesto i uloga allogene transplantacije matičnih ćelija hematopoete (TMCH), kao do sada jedine metode mogućeg izlečenja HGL, danas su kontroverzni. Cilj ove retrospektivne studije bio je procena rezultata dobijenih lečenjem bolesnika sa HGL, sa posebnim osvrtom na parametre od značaja za po- voljan klinički ishod i dugotrajno preživljavanje posle alogene TMCH. Metode. Kod ukupno 32 bolesnika sa HGL (27 u hroničnoj, a pet u uznapredovanoj fazi bolesti), 11 ženskog i 21 muškog pola, starosti od devet do 54 (prosečno 37) meseci do transplanta articulated days, with female/male ratio 11/21, aged from 9 to 54 (32 in average) years, underwent allogeneic SCTs (1993 to 2009). The initial treatment for 25 patients was interferon alpha (IFN–α) with or without ARA–C, and additional 7 patients with no response to imatinib mesylate (IM). The objective of this retrospective study was to evaluate the results obtained in the treatment of CML patients, with a particular attempt to determine parameters critical for clinical benefit and superior overall outcome following allogeneic SCT. Methods. A total of 32 CML patients (27 in chronic phase and 5 with advanced disease), with female/male ratio 11/21, aged from 9 to 54 (32 in average) years, underwent allogeneic SCTs (1993 to 2009). The initial treatment for 25 patients was interferon alpha (IFN–α) with or without ARA–C, and additional 7 patients with no response to imatinib mesylate (IM). The time from diagnosis to SCT was approximately 12 (range 3–37) months. The patient were categorized according to the risk for the disease, transplant-related mortality (TRM) scoring system, and stem cell (SC) source. The basic conditioning regimen was a combination of busulphan and cyclophosphamide (BuCy–2). Graft-versus-host disease (GvHD) was typically prevented with cyclosporine–A (CsA) and methotrexate (MTX). Results. Engraftment was observed in 26 (84.4%) patients, with polymorphonuclear (PMNs) and platelet (Pt) recovery on the 15th (range 10–22) and 19th (range 11–29) posttransplant days, respectively. Acute GvHD (aGvHD) had 13/26 (50%), and chronic GvHD (cGvHD) 10/21 (47.1%) patients. The incidence of overall TRM was 46.8% (15/32), while early death was noticed in 4 (12.5%) patients. A cause of death in 9 (28.1%) patients was infection, and in 3 (9.35%) cases disease–relapse was occurred. Fourteen (43.7%) of the patients are still alive, 9 from the low-risk group for TRM, with long-term survival from 1 to 16 years. Patients who received SCs from peripheral blood (PB) vs bone marrow (BM) had significantly faster engraftment (p < 0.05), lower oropharageal mucositis rate (25% vs 70%; p < 0.05), but more frequent cGvHD (83.3% vs 30.3%; p < 0.05). A significantly improved (log–rank = 2.39; p < 0.01) overall survival (OS) was obtained in BM-setting. Conclusion. The results obtained in this study are in accordance with data from analogous clinical trials. Exactly, in the era of the new target therapy (TKI application), allogeneic SCT can be still a convenient therapeutic approach for well-selected CML-patients, especially for those with initial high-risk disease and lower probability of TRM.

Key words: leukaemia, myelogenous, chronic, bcr-abl positive; stem cells; transplantation, homologous; treatment outcome.

Correspondence to: Dragana Stamatović, Military Medical Academy, Clinic of Hematology, Crnoavcanske 17, 11 000 Belgrade, Serbia.
E-mail: stamatovicm@sbb.rs
bolesnika bio je interferon alfa (IFN–α), a sedam bolesnika je bilo rezistentno na imatinib mesilat (IM). Period od postavljanja dijagnoze do TM bio je prosečno 12 (opsseg 3–37) meseci. Bolesnici su bili svrstani u grupu prema parametrima rizika bolesti, skorine sistema za smrtni ishod uzrokovani transplantacijom (transplant related mortality – TRM) i izvoru matičnih celija hematopoeeze (MCH). Osnovni kondenzi režim bio je protokol sa busulfanom i ciklofosfamidom (BuCy-2). Predviđenje bolesti kalem protiv domaćina (graft-versus-host disease – GVHD) sprovođena je ciklosporinom A (CsA) i metotrexatom (MTX). Rezultati. Prihvatanje kala je bilo rezistentno (p < 0,05) i manji stepen orofaringealnog mukozitisa (25% vs 70%, p < 0,05), a češći hGvHD (83,3% vs 30,3%, p < 0,05). Značajno bolje ukupno preživljavanje (overall survival – OS) (log-rang = 2,39, p < 0,01) imali su bolesnici sa izvorom MCH iz KS. Zaključak. Rezultati ove studije u saglasnosti su sa izveštajima drugih autora. U cem ITK, alogena TMCH još uvek može biti terapijska opcija za određenu grupu bolesnika sa HGL, i to sa inicijalnom bolesću visokog rizika i malom verovatnoću TRM.

Ključne reči: leukemia, granulocitna, hronična, bcr-abl pozitivna; matične čeliće; transplatacija, homologna; lećenje, ishod.

Introduction

Chronic myeloid leukemia (CML) is a clonal disease of hematopoietic stem cells (SCs) with specific chromosome translocation t(9; 22) – i.e. Philadelphia chromosome (Ph). It is generally accepted that CML is associated with bcr–abl fusion gene and consecutive abnormal tyrosine kinase activity and malignant transformation of SCs. The disease starts with chronic phase when myeloid precursors and derived cells are collected in blood and hematopoietic tissue. Transformation into acute leukemia happens after 3 to 4 years usually with a phase of acceleration before .

Induction treatment of CML with splenectomy and afterwards with busulphan and hydroxurea represents a good palliative therapy but without important influence on the course of the disease and usual survival is 3 to 5 years. Since 1982, the application of interferon-alpha (IFN–α) has lead to cytogenetic response with the prolongation of chronic phase of the disease in the small cohort of patients and thus, for a long period of time that was a therapy of choice for those potential donor for allogeneic stem cell transplant (SCT). The first syngeneic SCT in a patient with CML was done back in the 1970s. Twenty years latter, the standard proposal for the treatment of newly diagnosed CML patients younger than 50 years was allogeneic SCT from HLA sibling (family) donor. During two decades of transplant activity in CML numerous progresses were done: precise risk parameters for posttransplant complications and peritransplant mortality were defined; current techniques for HLA typing and complete supportive therapy have arisen numerous transplantations from unrelated donors; reduced-intensity conditioning (RIC) has allowed transplantations for older patient; efficacy of different sources of SCs has been defined like the methods for the subsequent minimal residual disease (MRD) after transplant and donor-lymphocyte infusion (DLI) has shown success in prevention and treatment of relapses after transplantation .

Since 1998, we have been witnessing clinical use of imatinib mesylat (IM), tyrosine kinase inhibitor (TKI), meaning inhibitor of enzyme activity of bcr–abl oncprotein. Investigations performed from 2000 until nowadays, undoubtedly recommend IM as the first-line therapy for chronic phase of CML with very good tolerance and high-level of long-term clinical, hematological, cytogenetic and even molecular disease remission. Approved efficacy of the first and second generation of TKIs in the treatment of CML have bought into the focus numerous questions about the place and importance of allogeneic SCT in this particular indication. Is allogeneic SCT at all, and in what patients, indicated as the first line treatment? Is allogeneic SCT an option in the cases of failure to IM, or second generation of TKI and should it be applied in such cases? Does previous treatment with TKI have impact on the results of allogeneic SCT? If we choose allogeneic SCT, which SC source and which conditioning regimen should be used? Therefore, the results obtained in the treatment of our CML patients, as well as the parameters important for clinical benefit and superior overall outcome following allogeneic SCT were retrospectively analyzed.

Methods

We analyzed 32 patients with CML, median age 32 (range 9–54) years, 11 females (F) and 21 males (M), who underwent allogeneic SCT from a HLA sibling donor in our center from 1993 to 2009 (Table 1).

Median time from the diagnosis to the transplant was 12 (range 3–37) months. Induction treatment in 25 patients was IFN–α (with or without ARA–C). In 7 patients, IM was given as initial treatment. At the time of transplantation, 27 patients were in chronic phase of CML, 3 of them in the acceleration phase and 2 had blast transformation. According to the Stanford prognostic scoring system, 21 patients had "high" risk and 11 patients "intermediate" risk for the disease. Concerning the European Group for Bone Marrow and Blood Transplan-

tation (EBMT) scoring system for the transplant-related mortality (TRM) 8, 10 patients were in the "low"; 16 in the "intermediate" and 6 in the "high" risk group. In 30 patients the donor was a HLA identical sibling while in two recipient–donor pairs the difference in two HLA loci was present.

The source of SCs was the bone marrow (BM) for 20 patients; cells were collected by multiple aspirations from the iliac bone (up to 15 mL/kg bm). In additional 12 patients, SCs were harvested from peripheral blood (PB) by a Cobe–Spectra (Caridian–BCT, USA) using one procedure of "Large Volume Leukapheresis" after rHuG–CSF (5–12 µg/kgbm/day, 5 days) mobilization.

Mostly used conditioning (27 patients) was a combination of busulphan and cyclophosphamide (BuCy–2). Five additional patients received RIC. Prophylaxis of the graft–versus-host disease (GvHD) was realized using cyclosporine A (CsA) and metothrexate (MTX) 19. In the posttransplant period, each patient received antimicrobial, antiviral and antifungal prevention, in a combination with intravenous immunoglobulins. All blood products transfused during the supportive treatment of patients were leukodepleted (by filtration) and irradiated.

Engraftment was defined as arising of polymorphonuclear (PMN) count above 0.5 × 109/L and platelet (Plt) number above 20 × 109/L in three consecutive days. Bone marrow was analyzed on days +14th and +28th and chimerism was estimated from the day +28th by sex chromosome, cytogenetic marker of disease, red blood cells phenotype or by DNA isolation and afterwards in a 3-month period. For the control of MRD we used the PCR method in a 3-month period after the transplant. Grading of acute GvHD (aGvHD) was up to "consensus" recommendations 20 and all patients that lived at least 3 months after the transplant with adequate engraftment were enrolled for the analyses of chronic GvHD (cGvHD). TRM is defined as death after transplantation while relapse was excluded as a potential cause. Early TRM represents death in the first 100 days after SCT.

The existence of some group variables was checked by using the χ2 test. The Kaplan Meier method was used to analyse overall survival (OS).

Results

All the transplanted patients (n = 32) received optimal number of mononuclear cells (MNCs), on average 3.7 ± 1.56 × 108/kg bm (range: 1.9 × 108/kg bm to 12.6 × 108/kg bm) MNCs (Table 2).

A successful engraftment was observed in 26 (84.4%) of the patients, with PMN recovery on the 15th (range 10–22) day and Plt recovery on the 19th (range 11–29) day following SCT. Oropharangeal mucositis grade 3/4 was observed in 17 (53%) patients, aGvHD had 13/26 patients who engrafted (50%), while cGvHD was observed in 10/21 (47.1%) patients who lived at least 3 months after the transplantation. Overall TRM in our cohort of patients was 46.8% (15/32). Extensive form of cGvHD was a cause of death in 9 (28.1%) patients and 2 (6.25%) patients died due to infection. Relapse was registered in 3 (9.35%) patients after 3, 30 and 37 months from the allogeneic SCT. Fourteen (43.75%) patients are still alive (9 patients from the low risk group for TRM) in complete clinical, hematological, cytogenetic and molecular remission, with survival from 1 to 16 years.

Table 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, ¯ (range), (years)</td>
<td>32 (9–54)</td>
</tr>
<tr>
<td>Gender (M/F) (n)</td>
<td>21/11</td>
</tr>
<tr>
<td>Phase of the disease (n)</td>
<td>chronic 27; acceleration/blast transformation 3/2</td>
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<tr>
<td>Previous therapy (n)</td>
<td>TKI 7; other (IFN–α ± ARA–C) 25</td>
</tr>
<tr>
<td>Hasford score (n)</td>
<td>high 21; intermediate 11</td>
</tr>
<tr>
<td>EBMT score (n)</td>
<td>low 10; intermediate 16; high 6</td>
</tr>
<tr>
<td>Time from diagnosis to transplant, ¯ (range) (months)</td>
<td>12 (3–37)</td>
</tr>
<tr>
<td>SC source: PB/BM (n)</td>
<td>12/20</td>
</tr>
<tr>
<td>Conditioning (n)</td>
<td>BuCy-2 27; Other (RIC) 5</td>
</tr>
<tr>
<td>GvHD prophylaxis (n)</td>
<td>CsA+MTX 27; Other</td>
</tr>
</tbody>
</table>

TKI – tyrosine kinase inhibitor; SC – stem cell; EBMT – European Group for Bone Marrow and Blood Transplantation; MTX – Methotrexate; PB – peripheral blood; BM – bone marrow; BuCy – busulphan and cyclophosphamide; GvHD – graft versus host disease; CsA – cyclosporine A
The MNC yield in peripheral blood (PB) vs bone marrow (BM) setting was significantly higher (10.2 ± 7.07 × 10⁸/kg bm vs 2.4 ± 0.75 × 10⁸/kg bm; p < 0.05). Consequently, PMN engraftment (12th vs 17th day) and Plt recovery (13th vs 21th day) were significantly (p < 0.05) superior in PB setting. The incidence of oropharyngeal mucositis was lower (25% vs 70%; p < 0.05) in the patients treated by PB–SCT. Contrary, the rate of overall cGvHD (83.3% vs 30.3%), as well as the incidence of extensive cGvHD (66.6% vs 20%) was significantly higher (p < 0.05) in PB setting. There was no significant difference (BM vs PB: 40.66% vs 54.5%) in the occurrence of aGvHD (Table 3).

Finally, the OS was significantly better in patients treated with BM derived SCs (log–rank test = 2.39; p < 0.01) (Figure 1).

### Discussion

Numerous clinicians and other investigators have been focused on chronic myeloid leukemia as an entity for many years. Following knowledge about this disease over the past 50 years, therapy approach has been changed. Historical irradiation of spleen, and the subsequent use of busulphan and hydroxurea, did not influence the course of the disease leading to undoubted progression, but represents an excellent palliative therapy 21, 22. Clinical use of IFN–α, for the first time gave a new quality response in the treatment of CML patients by achieving cytogenetic remission with better overall survival 5, 21. Thanks to the first experience with IFN–α,
recommendation for the estimation of cytogenic response in CML were defined. IFN-α, as monotherapy, or in a combination with other cytoreductive agents, for twenty years have been on first-line therapeutic option for patients with no HLA identical donor for allogeneic SCT. Until 2000 CML has most frequent been indicated for allogeneic SCT, with constant arising of transplanted patients number every year, with a peak in 1999. In our series, out of 32 patients, in 25 patients allogeneic SCT was done before 2000. Experiences obtained in a 20-year period of performing allogeneic SCT in the treatment of CML allow objective analysis of efficacy of this treatment modality through retrospective studies. Precise prognostic parameters were defined and up to them the EBMT established a scoring system with a strict prediction of TRM. Well-defined parameters for the outcome after allogeneic SCT are: patient age, time from the diagnosis until SCT, phase of the disease, gender combination of recipient and donor and level of HLA compatibility. Concerning the mentioned parameters, three groups of risk are formed: the group of low, intermediate and high risk with probability for lethal outcome after SCT from 15% to 70%. Retrospective analysis by Gratwohl et al. on behalf of EBMT showed that a 5–year survival in the low-risk group for TRM is 60–80%, while in the high-risk group, TRM is up to 30%. Furthermore, in the low-risk group for TRM, probability of relapse after a 5-year follow-up is significantly smaller with the majority of patients with a great opportunity for a long-term OS and even being cured. In our series, we performed stratification of the patients up to disease risk parameters (Hasford) and risk for lethal outcome (EBMT) but due to a small cohort of patients, it was impossible to do valid statistical analysis. Out of the whole group (n = 32), 14 (43.75%) patients are still alive with a follow-up period from 1 to 16 years. In the low-risk group up to EBMT scoring system, 9/10 (90%) patients are alive with long-term survival and that correlates with other study groups. Transplant related mortality in our series is 46.8% (15/32). Early TRM occurred in 4 (12.5%) patients with initially advanced disease (acceleration phase in 2 and blast transformation in 2) which is also similar to results from other study groups.

Peripheral blood as a source of SCs is used more often than BM in everyday practice as a result of several advantages. Above other, faster engraftment is observed with much less immediate complications that correlates with marrow aplasia. But, it is clearly showed that cGvHD is significantly more frequent in the cases when PB is a source of SCs. In our series, even 9 (28.1%) patients – the majority with SCs originated from PB – died with extensive form of cGvHD, which is also observed by other authors. In CML patients, BM is used more often as a source of SCs with the possibility of long-term OS, the same as we found. Relapse was noticed in 3 (9.37%) patients and that also correlates with literature data.

We used mostly myeloablative conditioning up to BuCy–2 regimen, similar to other authors recommending. RIC regimen is used in older patients with comorbid diseases or in the cases of secondary allogeneic SCT.

Tyrosine kinase inhibitors have made enormous advance in the treatment of CML since 2000. Numerous clinical results emphasize high level of hematological, cytogenetic and even molecular remissions with the possibility of long-term OS. After a 5-year follow-up, IRIS study objecthematological remissions in 98% of patients, whitest 87% of complete cytogenetic remissions with a high level of molecular response and 4% of disease progression with IM therapy found. Despite encouraging results achieved with the first, second and other generations of TKIs, current knowledge could not predict the possibility of curing patients with CML that we prepared with allogeneic SCT. Well tolerance of TKIs and high level of responses are basic facts to propose this particular group of medicines as the first-line treatment option for CML patients. Despite such advances, in some cases allogeneic SCT is still recommended as the first-line treatment: in children due to its curative potential; in cases of initial advanced phase of disease; in poor-standard countries due to cost of TKI therapy.

Former treatment with TKIs does not have a significant impact on the results of allogeneic SCT and that was almost impossible to assess in our small cohort of 7 patients.

**Conclusion**

Clinical results obtained in our retrospective study are in accordance with data from other clinical trials. Although allogeneic SCT can be associated with posttransplant complications, its application could be still appropriate therapeutic approach for well-selected CML patients, particularly for those with initial high-risk disease and lower probability of TRM.

**REFERENCE**


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