OPTIMIZATION OF TIMING FOR HEMATOPOIETIC STEM CELL TRANSPLANTATIONS IN PATIENTS WITH MYELOID LEUKEMIA

OPTIMIZACIJA VREMENA ZA TRANSPLANTACIJU HEMATOPOEZNIH MATIČNIH ĆELIJA KOD PACIJENATA SA MIJELOIDNIM LEUKEMIJA

Stevan L. POPOVIĆ

Summary
Hematopoietic stem cells transplantations, allogeneic and autologous are forms of treating acute myeloid leukemia, chronic myeloid leukemia and other forms of malignant hematological diseases. Autologous stem cells transplantations is the most intense form of chemotherapy with myeloablative doses of cytostatic agents and with the aim of destroying “each and every” leukemic cell in the patient’s body. In order for patients to survive myeloablation, infusion of their own stem cells which renew their own hematopoiesis is carried out. Thanks to myeloablative and submyeloablative conditioning regimen and the biological graft-versus-leukemia effect, allogeneic transplantations is the only form of therapy which can lead to curing patients with malignant hemopathies. How ever, the same or similar mechanisms, which are basically GvL, are responsible for the similar reaction of the graft versus host (GvHD) and cause serious deadly illnesses, which is why allo-hematopoietic stem cells transplantations is a risky form of treatment in terms of ethics. Lower mortality of patients makes auto-SCT safer ethical-wise, but its anti-leukemic effect is weaker.

Key words: Transplantation, Autologous; Hematopoietic Stem Cell Transplantation; Precision Medicine; Leukemia, Myeloid; Antineoplastic Agents; Myeloblastic Agonists

Introduction
Hematopoietic stem cells transplantations (HCT), allogeneic (allo-SCT) and autologous (auto-SCT) are forms of treating acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and other forms of malignant hematological diseases. Auto-SCT is the most intense form of chemotherapy with myeloablative doses of cytostatic agents and with the aim of destroying “each and every” leukemic cell in the patient’s body. In order for patients to survive myeloablation, infusion of their own stem cells which renew their own hematopoiesis is carried out. Thanks to myeloablative and submyeloablative conditioning regimen and the biological graft-versus-leukemia effect (GvL), allo-SCT has the best anti-leukemic effect and is considered the only form of therapy which can lead to curing patients with malignant hemopathies. However, the same or similar mechanisms, which are basically GvL, are responsible for the similar reaction of the graft versus host (GvHD) and cause serious deadly illnesses, which is why allo-SCT is a risky form of treatment in terms of ethics [1–3]. Lower mortality of patients makes auto-SCT safer ethical-wise, but its anti-leukemic effect is weaker [3].

The positioning of SCT in treating AML, CML and other malignant hemopathies depends on the results and development, transplant, pace of progress and toxic profile of competitive forms of treatment, quality of clinical studies in which these forms of treatment were compared, and indications for selective application of SCT in optimal time. During the last decades of the previous century, fascination with the anti-leukemic effect of SCT and disappointment with the moderate effects of the competitive forms
Over the last few decades, major breakthroughs have been made in the development of allo-SCT, while auto-SCT has gradually been outplaced from treating CML and AML. Introduction of reduced intensity conditioning regimens (RIC), better HLA-matching and choice of donor, and more efficient control of GvHD have expanded the indications for application of transplant in older patients and patients without an HLA-identical related donor, and with better quality supportive care, patient mortality has decreased [10].

According to data of EBMT group [11], per 2628 patients two-year survival, mortality and relapse frequency after allo-SCT from HLA-identical related donors in the first chronic stage of CML were 54%, 37% and 11% in the period 1980-1990, 70%, 25% and 12% in the period from 1991-1999 and 74%, 22%, 18% in the period from 2000-2003. Thanks to reduced transplant-related mortality, chances for curing patients have been increased, while the anti-leukemic effect, measured by risk of relapse has been stagnating. Ethical risk related to transplants in the analysed periods, inversely proportional to the cure/mortality ratio [3], has gone down from 1.46 to 3.36. Two-year survival and mortality of patients after allo-SCT from an unrelated donor in the specified periods are 38% and 10%, 56% and 12%, 63% and 19% with a considerable reduction of ethical risk and anti-leukemic effect similar to transplant effect from a related donor. Results of SCT from a haplidential donor, RICT, SC transplant and transplant of cells from umbilical blood have also been continuously improving. According to the release of the German CML Group and SAKK [12], three-year survival of patients after allo-SCT from an HLA-identical related donor is about 90% in the first chronic stage of CML and 56% in advanced stages of the disease with transplant-related mortality of 8%. Results of developing allo-SCT in CML are significantly lower treatment-related mortality of patients, better chances for curing and lower ethical risk attached to its application.

Trends in developing allo-SCT in AML are similar. According to the analysis of clinical studies, chances for curing patients after allo-SCT in first remission, relapse and secondary remission of AML are 48%, 15% and 26% with risk of transplant-related death of 31%, 28% and 26% and a high ethical risk of 1.5, 0.9 and 1.0 [3]. Clinical studies, from the start of this century, have shown significantly better results of SCT and lower ethical risk. Event free survival (EFS) and early mortality rate (ERM) of patients after allo-SCT in first remission of AML are 55-65% and 7-10%, in secondary remission 30-40% and 10-20%, and in resistant disease 15-20% and 30-40% [13]. Ethical risk related to applying allo-SCT is 3-4 times lower in first and nearly two times lower in second remission of AML. Improvement of results of allo-SCT in childhood AML is impressive, EFS grew from 22.9% in the period from 1980-1990 to 62.4% after 2002 [14].

Allogeneic SCT and competitive forms of treatment

Position of SCT in treating malignant hematological diseases depends, primarily, from the poten-
tial and toxicity of competitive forms of treatment. Reduction of ethical risk with the preservation of the anti-tumor effect enabled allo-SCT to resist new molecule drugs and save its place in treating most hematological diseases. The only exception are tyrosine-kinase inhibitors which have pushed allo-SCT out of the forefront when it comes to chronic stage of CML with the remark of the authors that such a standpoint requires new and better quality clinical evidence [15]. Early analysis of the results of the IRIS study [16] showed that imatinib mesylate has a better effect than interferon, that it changes the course of CML and gives a real chance for operative treatment [17] with acceptable toxicity. Analysis of treatment results in 1569 patients with CML treated since 1965 has shown an increase of eight-year survival in patients in the first chronic stage with less than 15% in the period up to 1983, to 42-65% in the period 1983-2000 and to 87% in the era of imatinib, after 2001 [18]. Nilotinib, dasatinib and ponatinib have proved efficient in CML resistant to imatinib mesylate. Tyrosine-kinase inhibitors have drastically changed the position of allo-SCT in treating CML despite its improved results. In the era of imatinib, CML was the most frequent indication for allo-SCT, while now its share is down to 2%. Absolute trust in allo-SCT in CML has been replaced by almost absolute trust in treatment with tyrosine-kinase inhibitors.

Development of competitive forms of treatment in AML was less dynamic. Results of induction treatment have slightly improved, mostly thanks to the development of supportive care which reduced the patient mortality [19]. Intensifying of induction therapy [20] and consolidation of remission with high-doses of cytosine-arabinoside improved the prognosis only in certain patient categories [21]. Insufficient development of chemotherapy and transition to selective and early application of allo-SCT, which improved its results, made AML the most frequent indication for allo-SCT.

Analysis of clinical studies

Medicine based on evidence assumes the existence of quality clinical studies which justify the position and ranking of some forms of treatment. What are the clinical evidence on which the place of allo-SCT in treating CML and AML rested in the past and on which it rests today?

Busulfan and hydroxyurea had moderate effects in the chronic stage of CML, very poor effects in the advanced stages of the disease [22], and the fact that this drug could cause molecule remission in a smaller number of patients was not accompanied by clinical evidence that it can lead to curing the patient. The advantage of allo-SCT over chemotherapy and interferon has not been proven in any prospective clinical study or meta-analysis. However, convincing results of transplants are sufficient for the leading authorities to conclude that allo-SCT is the treatment of choice in CML and that it should be applied within the first year following diagnosis [23, 24]. Retrospective comparison of data from the International Bone Marrow Transplant Registry for 548 patients with CML under 55 years of age who underwent allo-SCT from HLA-identical donors in the period from 1983-1991 against treatment results for 196 patients of the German CML Study Group treated with hydroxyurea and interferon revealed inconsistencies: transplant patients were six years younger, they had lower percentage of blasts and were more often without splenomegaly [25]. Though seven-year survival is significantly higher after allo-SCT than in the group of non-transplant patients (58% vs 32%), in the first four years following diagnosis, non-transplant patients survive longer, and after 5.5 years, transplant patients survive longer [25]. Results of the IRIS study were sufficient to confirm the undoubted advantage of imatinib mesylate over interferon alfa [16] and sufficient to oust allo-SCT from the first treatment line [26] with the occurrence of new tyrosine-kinase inhibitors. Comparison of allo-SCT and drug therapy was done in only three prospective studies: German CML Group and SAKK who had different conclusions [27, 28, 29]. In the first study [27], allo-SCT from HLA-identical related donor and best drug treatment (43% of pts treated with imatinib) were compared over a period from 1995 to 2001. Drug treatment induced longer survival of patients than allo-SCT in the first eight years from diagnosis, the difference was the biggest in the first three years and maintained the longest in the low-risk group according to Euro Score. Complete cytogenetic remission and large molecule response was achieved in 91% and 81% of transplant pts and 48% and 45% of pts treated with competitive therapy. Conclusion of the study is that contemporary medicament care should replace allo-SCT in the first treatment line [27]. Conclusion of another study [28], in which allo-SCT (all pts were administered imatinib prior to transplant) was compared to treatment with imatinib, is that both treatments achieve equal survival in patients and that allo-SCT should be applied only in pts resistant to imatinib. Two years after allo-SCT, 79% of pts is in complete molecule remission. The last study [12] compared allo-SCT and drug therapy (84% treated with tyrosine-kinase inhibitors) and showed that the effect of therapy depends on the combination of prognostic risks according to the EBMT score in the transplant group and according to Euro score in non-transplant pts. In a Mexican study, the choice between allo-SCT and treatment with imatinib depended on non-medical, financial reasons [29]. Six-year survival is equal after allo-SCT and imatinib treatment (77% vs 84%) with equal risk of acceleration and blast transformation.

The position of auto-SCT in treating myeloid leukemia is not clearly defined. Meta-analysis of
studies with comparison of auto-SCT and interferon treatment in the chronic stage of CML did not show any difference in survival, but authors leave the possibility of applying auto-SCT in patients resistant to drug treatment [30]. Prospective comparisons of auto-SCT with imatinib mesylate or allo-SCT in the chronic stage of CML have not been made.

Conclusion from reviewing the above named studies could be that the attitude of absolute trust toward allo-SCT in the era of imatinib and conversion of positions into almost absolute trust toward tyrosine-kinase inhibitors were not founded on clear and solid clinical evidence.

Comparison of allo-SCT from HLA-identical related donor and consolidation chemotherapy in the first remission of AML was done in a larger number of prospective clinical studies and a few meta-analyses [31, 32]. Our analysis of older studies with non-selective application of allo-SCT in first remission of AML showed that they are encumbered with statistical and other irregularities [3]. Patients envisaged for allo-SCT who died or went through early relapse during consolidation chemotherapy were included in the chemotherapy group, which improved results of allo-SCT and disrupted results of the competitive treatment. Though the upper age limit was equally set for both groups of subjects, transplant pts were, on average, five years younger than pts treated with chemotherapy which points to “preselectivity” of the allo-SCT group. Application of allo-SCT after consolidation chemotherapy bears the risk of transplanting in patients in whom leukemia may have been eradicated and who are potentially healthy. Result of irregularity in studies of allo-SCT versus chemotherapy is such that over 35% of pts have an HLA-identical donor which does not correspond to the demographic reality. In more recent studies, donor and no-donor groups were compared in first remission of AML regardless of whether the donor group underwent allo-SCT or not. Analysis of data of three HOVON/SACK studies, designed in this way, revealed “preselectivity” of the group of transplant patients because DFS (disease free survival) in no-donor group (37%) is significantly higher than in non-transplant pts in the donor group (22%).

Controlled clinical studies and meta-analysis defined the place of selective application of allo-SCT in the first remission of AML: it is not recommended to apply it in the cytogenetic group of good risk, and in high-risk group transplant of HLA-identical related donor and unrelated donor is recommended, while the place of allo-SCT in consolidation of first remission in the group of intermediate risk is not uniquely defined [33–35]. Auto-SCT is a competitive form of treatment for both consolidation chemotherapy and allo-SCT in first remission of AML. Meta-analyses of clinical studies have not proven the advantage of auto-SCT over consolidation chemotherapy or over allo-SCT in first remission of AML [36–38]. Current indication for applying auto-SCT is second remission of acute promyelocytic leukemia where it gives better results than allo-SCT [39]. Data on high frequency of secondary primary neoplasm in late post-transplant period contributed to the replacement of auto-SCT in AML treatment [40, 41], which has not been confirmed in other studies which showed that the life expectancy of transplant patients is no different than the life expectancy of the general population [40, 42]. Maybe it is time to expand indication for applying auto-SCT in first remission of AML in some categories of pts who do not have an adequate donor for allo-SCT [39, 43].

**Optimal timing of transplantation in CML**

SCT from HLA-identical related donor was, in the era prior to imatinib, the treatment of choice in the first chronic stage of CML with the lowest mortality rate and the best results in the first year following diagnosis [25]. At the time of absolute trust in allo-SCT, the biggest issue was to make waiting lists for transplantation according to medical criteria. According to our cumulative risk models [44–46], allo-SCT from HLA-identical related donor should be applied no later than the second, third and fourth year following diagnosis in low-, intermediate- and high-risk groups according to the Sokal score. Through similar modelling of CML treatment results with interferon, we found that in low-risk patients according to the Euro score, allo-SCT from an HLA-identical donor may be delayed until year nine of the disease, and that allo-SCT from an unrelated donor should not be applied [46]. Our models suggest that treatment with interferon in a group of low-risk may replace allo-SCT and perhaps lead to cure. Such possibility has been confirmed by later clinical studies and it is believed that interferon may induce long-term molecule remissions. Analysis of survival curves in transplant CML patients and patients treated with hydroxyurea and interferon revealed that seven-year survival is significantly different (58% vs. 32%) and that allo-SCT is gaining an advantage over the competitive therapy after 5.5 years from diagnosis [25]. In a low-risk group, the difference in seven-year survival is not as high, 58% vs. 49% and allo-SCT takes the lead only after eight years. However, the specified study does not deny the advantage of applying allo-SCT in the first year of the disease and in low-risk patients. An important conclusion of this study is that prognosis of risk groups affect the results of drug treatment of CML, but it does not affect the results of allo-SCT which may be basis for individual optimization of timings for applying transplantation.

Tyrosine-kinase inhibitors (TKI) have been replacing allo-SCT at the chronic stage of CML and absolute trust in allo-SCT has been replaced with absolute trust in contemporary drug treatment. Today, allo-SCT is recommended in patients resistant or intolerant to at least one TKI of the second generation in advanced stages of the disease [26]. The German CML Study IIIA [12] showed that there is no difference in ten-year survival between allo-SCT and the “best drug treatment” (84% pts treated with...
According to ELN recommendations [33] in patients with normal karyotype, i.e. patients with good and bad prognosis, but they have not provided basis for a clear position in the group of intermediate risk, i.e. patients with normal karyotype. According to ELN recommendations [33] in patients with high cytogenetic risk, therapy of choice in first remission is allo-SCT from an HLA-identical related or unrelated donor, but it is not applied in the group with good prognosis, except maybe in patients with present c-KIT mutation or measurable minimal residual disease (MRD) with low risk of transplant-related mortality. Patients with acute promyelocytic leukemia are not candidates for allo-SCT, and auto-SCT is recommended in second remission of the disease. In patients with normal karyotype, genetic mutations may be good basis for deciding on treatment [54, 55]. The best known prognostic significance is the mutation of three genes, FLT3-ITD, NPM1 and double CEBPA mutation and their combinations [56]. FLT3-ITD is the bearer of bad prognosis after chemotherapy, but also allo-SCT and is candidate for transplant in first remission [56]. Presence of minimal residual disease (MRD) is a sign of bad prognosis in any stage of remission of AML and for each form of post-induction therapy [57, 58]. Lack of this prognostic parameter is insufficient precision of measurement, indefinite limit values and still, limited prognostic significance because in about one third of MRD-negative remissions, relapse develops, and in one third of MRD-positive remissions the patient is cured without therapy. Because of this measurement of MRD in remission of AML before allo-SCT, risk of transplanting potentially healthy persons is not eliminated. Contrary to this, presence of MRD in remission of AML is considered a counter indication for applying auto-SCT [35]. Speed of inducing remission has a considerable impact on the effects of all forms of post-induction therapy because it correlates with the depth of remission and MRD, initial WBC count and cytogenetic anomalies [59]. Acute promyelocytic leukemia, remission induced by the first therapy and initial count of leukocytes are predictors of other remissions in our patients treated with standard induction in our programs for individualized therapy ANLL-NS [7, 8, 60] acute promyelocytic leukemia and remission caused by first induction treatment are criteria for giving up on allo-SCT in first remission of AML. Prognostic significance of speed of inducing remission in the decision about applying SCT in first remission of AML has changed the therapeutic regimes which assess the effect of first induction therapy one week after its completion in order to prevent resistance by quickly applying other induction therapies. Comparison of remissions caused in first and second line of treatment in such therapeutic regimes has proven that they are of equal duration and quality [61]. Since such therapeutic protocols are applied in a large number of American and European facilities, with the inclusion of their data in the clinical studies about predictors of SCT outcomes, speed of induction has lost its place in the decision-making about the selective application of transplantation in the first remission of AML. Advantages of therapeutic protocols with the assessment of early effects of the first induction treatment give good basis for preemptive application of allo-SCT immediately after the first unsuccessful induction treatment and this

Optimal timing for transplantation in AML

Over the last couple of decades of the last century, at a time of absolute trust, allo-SCT was applied non-selectively in first remission of AML after finishing consolidation chemotherapy, with high risk of applying transplantation in potentially healthy persons in whom leukemia had been eradicated with previous therapy. First mathematical analysis of clinical data [50] showed that cumulative results of allo-SCT applied non-selectively in first remission of AML are identical to the results of non-selective transplants delayed until the second remission. The specified mathematical conclusions implied the possibility that SCT in first remission of AML should be applied selectively, only in patients with whom the competitive forms of therapy do not provide chance of curing patients, and in other patients, it should be delayed for possible relapse or secondary remission. Our calculations [3, 51–53] are also among the pioneer papers. They show that selectively applied allo-SCT in first AML remission significantly increases chances of curing patients (61% vs. 48%, p<.01), reduces the mortality risk in patients (22.7% vs 31%, p<.01) and reduces the ethical risk of applying transplantation measured by the cure/death ratio by nearly two times. Similar calculations have proven the advantages of selective application of auto-SCT in first remission of AML [3, 52]. Nowadays, selective application of allo-SCT is the official position in treating AML.

The issue with selective application of SCT in first remission is good prognosis of cure chances, i.e. relapse risk. Candidates for the position of best predictor are the cytogenetic changes (chromosome anomalies and gene mutations), minimal residual disease and speed of inducing remission. Results of meta-analysis of clinical studies have provided good basis for selective transplantation in cytogenetic groups with good and bad prognosis, but they have not provided basis for a clear position in the group of intermediate risk, i.e. patients with normal karyotype. According to ELN recommendations [33] in patients
gives better results from applying allo-SCT as salvage therapy in resistant AML.

According to last ELN recommendations, allo-SCT needs to be done in refractory AML and in first remission in patients with high cytogenetic risk, and auto-SCT in MDR- negative remission. In other patients, the decision on applying SCT needs to be tailor-made based on the dynamic prognosis and assessment of risk of relapse and risk of transplant-related mortality.

The biggest ethical risk which accompanies SCT is the risk of its application in potentially healthy persons in whom leukemia has been eradicated with prior treatment. Such a risk is the highest in non-selective application of SCT after finishing consolidation chemotherapy. Some thirty years ago, the EBMT group [62] published data that LFS, patient mortality and risk of relapse are 23%, 13% and 64% if auto-SCT is applied in the first three months of first remission of AML, and that the same parameters are 48%, 6% and 46% if auto-SCT is applied after six months of remission. The specified results were the basis for recommendations that auto-SCT and allo-SCT should be applied in later stages of remission. If we exclude patients who die or relapse during consolidation chemotherapy which “artificially” improves results of auto-SCT, the assumption that transplant patients include patients in whom leukemia has been eradicated with the previous therapy is realistic. Using a mathematical model of cumulative risks, we calculated that pure anti-leukemic effect of auto-SCT is 23% in all stages of remission, that late transplant “re-cures” 22.6% of patients and that 1.4% patients who die after auto-SCT have been cured with previous treatment. Such risks would be considerably higher today when modern consolidation potentially cures twice as many patients, and especially in late application of allo-SCT. Fortunately, today, allo-SCT is usually applied after first consolidation treatment, rarely after second or immediately after induction therapy considerably decreasing the risk of transplanting potentially healthy persons.

Mathematics is farsighted and accurate. Through mathematical processing of results from renowned clinical studies which we did a quarter of a century ago, we proved that SCT in AML should be applied selectively and in early stages of remission, as well as that AML should be individualized based on the dynamic prognosis, and not protocol type and equally for all patients. Back then this was heresy, today selective early application of SCT is standard clinical practice, and personalized medicine is a very current term and a wide field for further research and progress.

References


