Autologous hematopoietic stem cell transplantation for acute myeloid leukemia – single center experience

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We aimed to determine the effect of autologous hematopoietic stem cell transplantation (auto-HSCT) on acute myeloid leukemia (AML) patients as a valid alternative therapeutic option for patients without HLA-compatible donor. This retrospective single center study included 79 patients with AML older than 18 years. In this report, we describe the patient characteristics, engraftment, toxicity of treatment, complications, overall survival, and relapse incidence of 79 patients treated chemotherapy and followed by auto-HSCT. The descriptive statistics was used, and the method of Kaplan and Meier was applied to calculate the actuarial rate of overall survival. The patients achieved an absolute neutrophile count (ANC) of ≥ 0.5 x109/l in between 10 to 40 days; median was 14 days after auto-HSCT. The patients achieved platelet count ≥ 20 x109/l in between 10 to 209 days; median was 19 days after auto-HSCT. Hundred-day mortality after autologous transplant was 6.57% (5/76). The relapse rate was 39.5% (32 patients) and 7 patients (8.6%) were lost from follow-up. On the date of evaluation (April 30, 2016), 48 patients (60.8%) were alive, including 7 (8.6%) patients who are lost from follow-up (not responding to check-up request). The 5-year overall survival (OS) was 60.8%; median overall survival was not reached. The present clinical study has demonstrated safety and efficacy of myeloablative chemotherapy followed by auto-HSCT in the treatment of AML in first remission.

Key words: acute myeloid leukemia, autologous hematopoietic stem cell transplantation, overall survival, post remission therapy

Hematopoietic stem cell transplantation (HSCT) still remains as the most efficient therapy for patients with acute leukemia. For older patients and those lacking a related HLA-compatible donor, autologous hematopoietic stem cell transplantation is a valid alternative therapeutic option [1]. Post-remission therapy in patients with acute myeloid leukemia (AML) may consist of continued chemotherapy only or transplantation using either autologous or allogeneic stem cells. Although allogeneic HSCT (allo-HSCT) is considered the preferred type of post-remission therapy in poor risk AML, the place of allo-HSCT in intermediate-risk AML is being debated and autologous HSCT is considered a valuable alternative that may be preferred in patients without minimal residual disease after induction chemotherapy [2]. We review post remission transplantation strategies using autologous stem cell transplantation. The use of auto-HSCT as consolidation therapy for adult patients with acute leukemia has declined over time. However, multiple randomized studies in the past have reported lower relapse rates after au-

tologous transplantation compared with chemotherapy and lower non-relapse mortality rates compared with allogeneic transplantation. In addition, quality of life of long-term survivors is better after autologous transplantation than after allogeneic transplantation [3]. Further, recent developments may improve outcomes of autograft recipients. These include the use of intravenous busulfan and busulfan-melphalan combination, better detection of minimal residual disease (MRD) with molecular biology techniques, the introduction of targeted therapies, and post-transplant maintenance therapy. Therefore, auto-HSCT may nowadays be reconsidered for consolidation in the following patients if and when they reach a MRD-negative status: standard and at least intermediate risk acute myeloid leukemia in first CR, acute promyeloid leukemia in second CR, Ph-positive acute lymphoblastic leukemia. Conversely, patients with MRD-positive status or high-risk leukemia should not be considered for consolidation with auto-HSCT [4]. Intensive chemotherapy for acute myeloid leukemia (AML) achieves a complete hema-

tologic remission in the majority of patients. However, despite high complete remission rates and continued antileukemic treatment as well, the majority of patients still relapse with their underlying disease. The duration of response is usually short and most of the patients will experience a leukemia relapse. Allogeneic stem cell transplantation is a therapeutic option that is curative in a significant proportion of patients, but is associated with morbidity and mortality resulting from graft-versus-host disease and opportunistic infections. Moreover, not every patient has a fully matched histocompatible sibling donor or matched unrelated donor. Autologous stem cell transplantation (auto-HSCT) is an alternative approach, which was initially designed to consolidate remission in AML patients lacking a sibling donor or unfit for allo-HSCT [5]. Auto-HSCT holds several advantages including low non-relapse mortality rates, absence of graft-vs-host disease (GVHD) risk, lower incidence of late effects and better quality of life for survivors compared to allo-HSCT; concerns include high relapse rate, due to the absence of graft-vs-leukemia (GVL) effect and the theoretic possibility of graft contamination by leukemic cells [2]. Autologous stem cell transplantation has been used for the therapy of AML with disease-free survival rates ranging from 18% to 67% depending on the phase of disease, the preparative regimen, follow-up time, whether purging was used (and the method of purging) and time from achieving complete remission to transplantation. In an attempt to improve antitumor efficacy of the preparative regimen, we used the combination of busulfan and melphalan. In this report, we describe the patient characteristics, engraftment, toxicity, complications and overall survival, and relapse incidence of 79 patients treated with this regimen, followed by autologous bone marrow (BM) or (and) peripheral blood (PB) stem cell transplantation.

Patients and methods

The study was set as a retrospective single center study. All patients affected by AML older than 18 at the time of diagnosis, who received auto-HSCT between December 1994 and May 2016 were included. The total number 79 patients received first auto-HSCT during this 22-year period, median of annual number of auto-SCT performed for AML at our department was 3, ranged from 0 to 8 (Figure1). Thirty eight patients (48%) were transplanted in the first 10 years and 41 patients (52%) in the last 13 years.

Patient characteristics are described in Table 1. The median age was 44 years, with a range from 20 to 67 years. There were 44 males and 35 females. French-American-British (FAB) classification showed M0: 3, M1: 7, M2: 35, M4: 20 and M5: 7, 6 patients were classified as secondary AML after myelodysplasion syndrome and 1 patient with as bifenotypic leukemia. The white blood cell (WBC) count at diagnosis ranged from 0.78 to 393 x 10^9/l with average of 42.18 x 10^9/l and median is 14.75 x 10^9/l. Cytogenetic analysis was without abnormalities in 34 patients, 38 patients had a variety of different
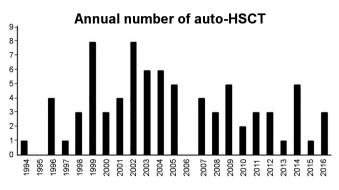

Figure 1. Annual numbers of autologous hematopoietic stem cell transplantation.

translocations and analysis was not performed in 7 patients. The patients were divided in three groups according to their risk status (Table 2).

Induction and consolidation treatment before autologous transplantation. A majority of the patients received similar remission inductions based on combination of cytarabine and anthracycline. A standard protocol, which we have been using for the last 8 years, is cytarabine 100-200 mg/m^2 continuous intravenous infusion for 7 days plus daunorubicin 45-90 mg/m^2/day for 3 days (dosage depends on age and comorbidities). Before this protocol we used other protocols, for example protocol EORTC AML 12 (induction treatment containing daunorubicin, etoposide and either standard-dose cytarabine 100 mg/m^2 per day by continuous infusion for 10 days or high-dose cytarabine 3g/m^2 every 12 hours by 3-hour infusion on days 1, 3, 5, and 7) or other protocols including combination of cytarabine, anthracycline and inhibitors of topoisomerase. Six patients received two inductions. 35 patients received one consolidation therapy (protocol DIA – or Mayer – High-dose cytarabine 3 g/m^2 over 3h every 12h on days 1, 3, and 5), followed with auto-HSCT. 32 patients received two consolidation therapies (multiple protocols; mostly based on combination of high dose cytarabine, anthracycline and inhibitors of topoisomerase), followed with auto-HSCT. Other patients either received more consolidations (3-5), or after the first or second consolidation developed relapse and received reinduction protocols. In the first complete remis-

Table 1. Patient characteristics at the time of diagnosis

No. of patients	79	
Age (years)	Range 20-67	Median 44
Sex (male/ female)	Male 44	Female 35
FAB classification	M1 – 7	M2 – 35
	M4 – 20	M5 – 7
	After MDS 6	biphenotypic 1
First WBC (x10⁹/l)	Range 0.78 to 393	Median 14.75

Table 2. Prognostic subgroups of AML based on cytogenetic and genetic lesions [6]

Risk status	Cytogenetic	Molecular abnormalities	No. of patients
Standard	– t(8;21)(q22;q22) – inv(16)(o13.q22), – t(16;16)(p13.q22) – t(15;17)	Normal cytogenetic with NPM1 mutation or CEBPA mutation in absence of FLT3-TD	9
Intermediate	– Normal – +8 – t(3;5) – t(9;11)(p22q23) – Other non-defined	c-KIT mutation with: t(8;21)(q22.q22), or inv(16)(p13.q22), t(16;16)(p13.q22)	50
Poor	– Complex karyotype (>3 abnormalities) – MK+ – -5, 5q- – -7, 7q- – other 11qp23 abnl [non t(9;11)] – inv (3)(q21q26.2), – t(3;3)(q21q26.2) – t(6;9), t(9;22) – abnl(17p)	High EVl1 expression (with or without 3q26 cytogenetic lesion) Normal cytogenetics with FLT3-ITD in absence of NPM1 mutation	13

sion (CR1) we transplanted 66 patients (83.5%), 12 patients (15.25%) were in the second complete remission (CR2), one patient (1.25%) was in the first relapse, and one patient (1.25%) was in progression of disease. The time from first date of diagnosis to auto-HSCT varied from 74 days to 1791 days with median 175 days.

Peripheral blood stem cell mobilization and collection. Mobilization was carried out after or during regeneration from last chemotherapy. Human recombinant G-CSF was used as the priming agent subcutaneously. The administration of G-CSF began at least 5 days before apheresis. G-CSF administration was continued daily until peripheral blood stem cell collection was completed and did not have to be withdrawn from any patients because of adverse effects. Apheresis was started and performed on consecutive days using a continuous flow blood cell separator COBE Spectra (COBE Laboratories, Lakewood, CO, USA), Spectra OPTIA apheresis system 61000 (Lakewood, CO, USA) or CS-3000 Plus (Fenwall, Round Lake, IL, USA). In all cases a pre-apheresis hemoglobin level >100g/l, a polymorphonuclear cell count >1.5 x 10^9/l and a platelet count 100 x 10^9/l were registered. Apheresis was performed until the total number of mononuclear cells (MNC) collected reached 4 x10^8 per kilogram of body weight until January 1995, from which

time the procedure was performed until an amount of 3x10^6 CD34+ cells/kg were collected. The collected cell suspension was immediately frozen in a controlled-rate freezer after each apheresis using DMSO 10% v/v as cryoprotectant and stored at -196 °C in liquid nitrogen until use.

Bone marrow collection and processing. Minimum of 2x10^8 nucleated marrow cells per kilogram of body weight were collected from the posterior iliac crest. The bags of bone marrow were frozen using DMSO as cryoprotectant in a controlled-rate freezer (Cryomed, New Baltimore, MI) at -1°C per minute to a temperature of -50 °C and at -10 °C per minute to a temperature of -70 °C and then transferred to the liquid phase of a liquid-nitrogen freezer.

Transplantation. Risks and benefits were explained to each patient in detail during at least two outpatient visits and again on the day of admission. Thereafter, written consent was obtained from the patients and in one case from the parent of patient, who lacks legal capacity to act of her own behalf because of mental disability (age for legal action in Slovakia is 18 years). Five patients received unmanipulated bone marrow. Sixty seven patients received peripheral blood stem cells (PNSC) and 7 patients received combination of PBSC plus bone marrow due to a low total stem cells number harvested from peripheral blood. A median of 2.72x10^6 (range 0.52 to 32.5) CD34+ cells were infused to the patients.

Preparative regimen. Seventy (88.6%) patients received preparative regimen consisting of busulfan 1mg/kg body weight orally, four times daily for 4 days, total dose 16 mg/kg administered on day -6 through day -3, and melphalan 100-150mg/m^2 intravenous over 4 hours on day -2. Busulfan with cyclophosphamide (BuCy2) conventional myeloablative conditioning was given to 4 (5%) patients, BuCy2 plus etoposide to 2 (2.5%) patients, busulfan monotherapy to 2 (2.5%) patients, and one (1.26%) patient received busulfan plus etoposide

Table 3. Conditioning regimen

Conditioning regimen (n)	Number
Busulfan + cyclophosphamide	4
Busulfan + melphalan	70
Busulfan + cyclophosphamide + etoposide	2
Busulfan + etoposide	1
Busulfan	2

(Table 3.). The graft was infused on day 0 in all patients. At the time of autologous marrow or PBSCs administration, each bag with graft was thawed rapidly in a 37 °C water bath and infused through a central venous catheter over 5 to 10 minutes.

Supportive care. The patients were housed in the single or double bed rooms. Reverse isolation techniques with masks and gowns were used when neutrophil counts decreased to less than 0.5 x10^9/l. When fever exceeded 38 °C, broad-spectrum antibiotics were instituted. Intravenous antifungals (voriconazole or echinocandin or amphotericin B) were given when fever persisted for more than 3-5 days despite appropriate antibacterial treatment. Transfusions were given to maintain hemoglobin above 90g/l and platelet count above 10 x 10^9/l. All blood products were irradiated with 25 Gy before transfusion to avoid the risk of transfusion-related acute graft-versus-host disease induction.

Statistical analysis. The descriptive statistics was used, and the method of Kaplan and Meier was applied to calculate the actuarial rate of overall survival.
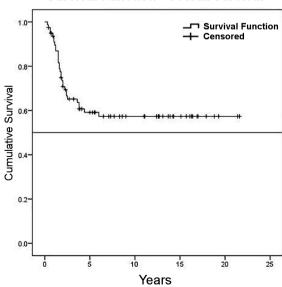
Results

Engraftment. Patients achieved an absolute neutrophil count (ANC) of ≥ 0.5 x10^9/l in between 10 and 40 days, median was 14 days, average was 15 days, only one patient died before achieving an absolute neutrophil count of 0.5 x10^9/l. Patients achieved ANC 1x10^9/l in 9 to 39 days, median was 13 days, average was 15 days, only one patient died early, before blood count recovery. Patients achieved not transfused platelet count ≥ 20 x10^9/l in between 10 to 209 days; median was 19 days, 10 patients didn't achieve platelets count above 20x10^9/l. Median of patients' discharge

from hospital was 19 days (range from 13 to 44 days) since graft administration.

Toxicity. The combination of busulfan and melphalan was associated with the expected bone marrow aplasia in all patients. Moderate to severe mucositis was observed in a majority of patients requiring opioids analgesics for pain control. Most of the patients had at least one episode of fever. Five patients died before day 100 from auto-HSCT, 3 due to infectious complications, one patient due to hemorrhage, and one because of disease progression. Hundred-day mortality after autologous transplant was 6.57% (5/76). Three patients were not evaluable because they had not yet achieved day 100.

Relapse and survival. The relapse rate was 39.5% (32/79). On the date of evaluation (April 30, 2016), 48 patients (60.8%) were alive, including 7 (8.6%) patients who are lost from follow-up (not responding to check-up request), but are alive according to health insurance database and actual report. The 5-year overall survival (OS) is 60.8%; median overall survival was not reached (Figure 2). Follow-up period of the surviving patients ranged from 115 days to 7898 days, median follow up was 1424 days and after auto-HSCT ranged from 9 to 7394 days, median follow up was of 991 days.

We also analyzed overall survival probability in 72 patients (cytogenetic analysis was not performed in 7 patients) divided in three different subgroups of patients according to cytogenetic risk status. The 5-years overall survival probability for poor risk patients (OS) was 30.8%; median overall survival is 2 years (Figure 3). The 5-years overall survival probability in standard risk patients was 66.7%; median overall survival not reached (Figure 4). The 5-years overall survival probability in intermediate risk patients (OS) was 68 %; median overall survival not reached (Figure 5).

Figure 2. Overall survival.

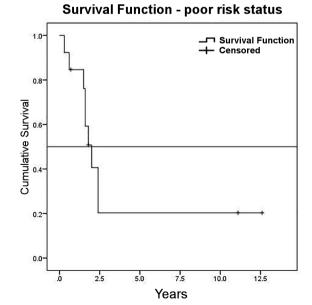**Figure 3. Overall survival of patients with poor risk cytogenetic.**

Survival Function - standard risk status

Figure 4. Overall survival of patients with standard risk cytogenetic.

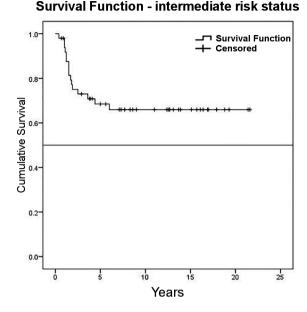### Survival Function - intermediate risk status

Figure 5. Overall survival of patients with intermediate risk cytogenetic.

Cause of failure. Thirty-one patients (39.2%) were dead at the time of evaluation. Twenty-tree patients (29.1%) died because of relapse disease, 1 patient died due to allogeneic transplantation complication (graft versus host disease of liver) after relapse of disease, 1 patient died due to generalized CMV infectious and encephalitis (day 656 after auto-HSCT), 3 patients (5.1%) died due to infectious complications after auto-HSCT (last one in 2007), 1 patient died due to progression of disease right after auto-HSCT, 1 patient due to hemorrhage related to auto-HSCT and we do not have information about cause of dead of 1 patient.

Discussion

The best post-remission therapy for acute myeloid leukemia is still being discussed. The strategy depends on risk stratification, age, having HLA matched siblings or unrelated donor [7]. Several randomized trials have shown significantly better LFS for auto-HSCT compared to chemotherapy as consolidation strategy of remission in AML [8-11]. In a prospective study, Vellenga et al. [10] observed the reduced relapse rate following auto-HSCT in comparison with chemotherapy consolidation. This group reported better survival following auto-HSCT in intermediate-risk AML. Our team has studied auto-HSCT in AML using a two-step approach model based on the concept of *in vivo* purging [12]. We treated patients with an intensive consolidation therapy using cytarabine in combination with anthracycline and/or inhibitor of topoisomerase. Hematopoietic stem-cells were collected during hematologic recovery stimulated with G-CSF.

Consolidation chemotherapy containing intermediate-dose cytarabine in the present study may be responsible for in vivo purging. The timing of PBSC collection may be important for preventing relapse. It was demonstrated that minimal residual disease in marrow and PBSC harvests could be reduced with repeated cycles of chemotherapy [13]. Based on this data, we did not collect PBSC after induction chemotherapy, but during the recovery phase after consolidation. This strategy of in vivo purging has been used to reduce the leukemic burden in the setting of auto-HSCT and has led to an improved DFS [14, 15]. Adequate consolidation of remission before auto-HSCT is the most important factor associated with continuing remission after auto-HSCT [15].

Today, peripheral blood is preferable to bone marrow as a source of stem cells. However, initial data about auto-HSCT indicated that relapse rates are as high as 60% for AML and early relapse is rather frequent when the source of cells is not bone marrow [15, 16, 17, 18, 19]. This may occur because the ratio of leukemic clonogenic progenitors to normal stem cells is higher in PBSC harvests than in marrow or because a large number of malignant cells are reinfused since the cell dose is higher in stem cells than in bone marrow [15, 19]. The initial concern that the use of auto-HSCT might lead to higher relapse rates than auto-HBMT had been largely answered by larger studies, where the use of PBSC was not associated with an increased risk of relapse [15-17]. Moreover, auto-HSCT has some advantages over autologous bone marrow transplantation: auto-HSCT leads to faster hematopoietic recovery, rapid engraftment, reduced transplant related mortality, and to satisfactory outcome.

Our study confirmed rapid granulocyte recovery in patients with AML treated with myeloablative chemotherapy and auto-HCST. Engraftment after transplantation was quick with patients reaching ANC > 0.5×10^9/l at median day +14 resulting in a duration of neutropenia (ANC< 0.5×10^9/l) of 10 days. Platelets recovered to >20×10^9/l by day +19.

Despite a markedly accelerated granulocyte recovery, side effects that were noticed probably related to intensive chemotherapy and resulting in a treatment-related mortality of 6.57%. However, it is similar to published data, and most studies have reported 5-10% transplant related mortality [16, 17, 14]. Conditioning regimen was based on busulfan plus melphalan, and a median cell dose of 2.72x10^6/kg of body weight (range 0.52 to 32.5) CD34+ was administered. Gorin et al. reported a 2-year LFS of 61 % with auto-HSCT following the same busulfan plus -melphalan conditioning [20]. In our study the 5-year overall survival probability is 60.8%, and median overall survival was not reached (see Figure 2). Possible explanation include low rate of transplant-related mortality. As in other studies, cytogenetic risk status was the major determinant of outcome. OS in patients with standard and intermediate risk was significantly better than in poor risk subgroup (68%, 66% and 30% respectively). It confirms that cytogenetic abnormality at diagnosis has prognostic significance. The encouraging results warrant additional prospective studies to evaluate the use of auto-HSCT in the treatment of AML.

Conclusion

The present clinical study has demonstrated safety and efficacy of myeloablative chemotherapy followed by auto-HSCT in the treatment of AML in first remission. Auto-HSCT is a suitable therapeutic option for patients without HLA-compatible donor and opens transplantation treatment for older patients with comorbidities as well. Based on current understanding of AML heterogeneity it is necessary to emphasize the risk-adapted approach to the AML treatment, including auto-HSCT.

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