RESEARCH LETTER

Allogeneic hematopoietic stem cell transplantation for relapsed B-cell acute lymphoblastic leukemia after failure of autologous hematopoietic stem cell transplantation: a retrospective single-center analysis

Marta Panz-Klapuch, Adrianna Spałek, Katarzyna Duda, Anna Kopińska, Agata Wieczorkiewicz-Kabut, Grzegorz Helbig

Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia, School of Medicine in Katowice, Katowice, Poland

Correspondence to:
Prof. Grzegorz Helbig, MD, PhD, Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia, ul. Dąbrowskiego 25, 40-032 Katowice, Poland, phone: +48 32 259 13 10, email: ghelbig@o2.pl
Received: January 7, 2022.
Revision accepted: February 17, 2022.
Published online: March 2, 2022.
Pol Arch Intern Med. 2022; 132 (3): 16220
doi:10.20452/pamw.16220

Introduction The prognosis of adult patients with relapsed acute lymphoblastic leukemia (ALL) is extremely poor, and postrelapse treatment rarely results in long-term survival. A retrospective analysis of the PETHEMA (*Programa Español de Tratamiento en Hematologia*) study group, comprising 263 phenotypically and cytogenetically different adult patients with ALL at first relapse, showed that age below 30 years and duration of the first complete remission longer than 2 years may have a favorable impact on postrelapse survival.[1] For adult, standard-risk patients with ALL, a remission consolidation therapy with autologous hematopoietic stem cell transplantation (auto-HSCT) followed by post-transplant maintenance therapy remains a valuable therapeutic option with overall survival and progression-free survival of 59% at 5 years.[2] On the other hand, it was demonstrated that auto-HSCT as consolidation therapy does not provide a substantial benefit for this patient population when compared with chemotherapy alone.[3,4] According to the treatment protocol of the Polish Adult Leukemia Group (PALG; www.palgwitaj.pl), auto-HSCT may be considered as consolidation for adult, standard-risk ALL patients with minimal residual disease (MRD) negativity after induction and consolidation treatment, and with no other risk factors. Similar criteria for auto-HSCT are used by Czech and Italian ALL National Groups. Auto-HSCT is not taken into consideration in treatment protocols of other European Study Groups.[4]

Relapse of ALL after auto-HSCT always remains a challenge, and allogeneic hematopoietic stem cell transplantation (allo-HSCT) seems to be the only curative treatment in this scenario.[4] Data on the efficacy and safety of allo-HSCT after initial auto-HSCT for ALL are scarce and based on small case series.[5]

Herein, we evaluated the feasibility and efficacy of allo-HSCT in patients who relapsed after prior auto-HSCT for Philadelphia chromosome (Ph)-negative B-cell ALL.

Patients and methods A total of 371 allo-HSCTs for ALL were performed in our center between 1992 and 2019. We identified 18 Ph-negative B-cell ALL patients who underwent allo-HSCT after failure of auto-HSCT. The patients were referred for auto-HSCT in accordance with the PALG protocol in force at that time or when a suitable donor was not identified. Relapse from hematological remission was defined as a bone marrow blast count of 5% or greater, reappearance of blasts in the blood, or development of extramedullary disease. The MRD status was assessed by flow cytometry. Late relapse was defined as a relapse occurring over 2 years after treatment completion. Engraftment was defined as a sustained blood neutrophil count of 0.5×10^9/l or greater for 3 consecutive days. Acute and chronic graft-versus-host disease (GVHD) were graded according to the standard criteria.[6,7] Post-transplant complications were assessed

TABLE 1 Characteristics of patients (n = 18) at the time of diagnosis and autologous hematopoietic stem cell transplantation

Parameter		Value
At diagnosis		
Sex	Female	11
	Male	7
Age, y		23 (16–57)
Hemoglobin, g/dl		6.8 (4.7–14.5)
Leukocyte count, $\times 10^9$/l		8.8 (0.1–379.0)
Platelet count, $\times 10^9$/l		58 (11–343)
Blasts in blood, %		46 (0–98)
Blasts in bone marrow, %		90 (20–100)
Splenomegaly		6 (33)
Hepatomegaly		7 (39)
Peripheral lymphadenopathy		5 (28)
Mediastinum enlargement		2 (11)
CNS involvement		1 (5)
Time from diagnosis to auto-HSCT, mo		9.8 (6.8–19)
At auto-HSCT		
Conditioning	Cy-TBI	14 (78)
	CAV	4 (22)
Source of stem cells	Bone marrow	14 (78)
	Peripheral blood	4 (22)
Number of transplanted $CD34^+$, $\times 10^6$/kg		2.52 (0.59–13.2)
Time to ANC $>0.5 \times 10^9$/l, d		16 (9–24)
Time to platelet count $>20 \times 10^9$/l, d		15 (10–20)

Data presented as median (range) or number (percentage).

Abbreviations: ANC, absolute neutrophil count; auto-HSCT, autologous hematopoietic stem cell transplantation; CAV, cyclophosphamide, etoposide, cytarabine; CNS, central nervous system; Cy-TBI, cyclophosphamide and total body irradiation

using the World Health Organization classification (mucositis) or the National Cancer Institute--Common Toxicity Criteria (other) (nice.org.uk; ctep.cancer.gov).

Not all data were available due to the retrospective design of the study. All patients provided an informed consent in accordance with the Declaration of Helsinki.

Details on statistics can be found in Supplementary material, *Statistical analysis* section.

Results **Patient characteristics at diagnosis and at auto-HSCT** A total of 18 patients diagnosed with B-cell ALL underwent allotransplantation after failure of auto-HSCT. At ALL presentation, median age was 23 years (range, 16–57). Median time from diagnosis to auto-HSCT was 9.8 months (range, 6.8–19.0). All patients were in complete remission before auto-HSCT. Conditioning consisted of cyclophosphamide and total body irradiation (Cy-TBI) in 4 patients, whereas 14 individuals received the CAV (cyclophosphamide, etoposide, cytarabine) regimen. In 14 cases, the source of stem cells was bone marrow. Disease relapse after auto-HSCT occurred after a median of 13.4 months (range, 2.6–41.5). Blinatumomab (n = 2) and salvage chemotherapy ([mini] FLAM, ie, fludarabine, cytarabine, mitoxantrone or (mini) hyper-CVAD, ie, cyclophosphamide, vincristine, doxorubicin, dexamethasone; n = 16) were used at relapse as a bridge to allo-HSCT. As a result, before allo-HSCT, 14 patients were in complete remission, 1 achieved partial response, 2 had active disease, and no data on the response status were available for 1 individual. The MRD status was negative, positive, and not assessed in 6 patients, respectively. Patient characteristics are shown in **TABLE 1**.

Transplant data Baseline characteristics of allotransplanted patients Median recipient age was 25 years (range, 18–59). Median time from auto-HSCT to allo-HSCT was 5.1 months (range, 2.9–19.3). Allotransplantation was performed in 4 patients after 2010. Seven patients received grafts from a matched related donor, whereas 11 were either transplanted from a 10/10 human leukocyte antigen (HLA)-matched unrelated donor (n = 7) or received 9/10 HLA-mismatched grafts (n = 4). Blood ABO mismatch was present in 10 patients and sex was matched in 6 individuals. Peripheral blood was the source of stem cells for 6 patients and 12 patients received stem cells from bone marrow. Myeloablative conditioning was administered in all but one study patients and included BuCy +/– Ara-C (busulfan, cyclophosphamide +/– cytarabine; n = 6), Cy-TBI (n = 11), and TBF (tepadine, busulfan, fludarabine; n = 1). GVHD prophylaxis included cyclosporine (n = 13), mycophenolate mofetil (n = 3), cyclosporine with mycophenolate mofetil (n = 1), or tacrolimus with mycophenolate mofetil (n = 1).

Outcome of allotransplanted patients Median time to engraftment was 20 days (range, 12–56). Complete remission with full donor chimerism was demonstrated for all tested patients at day 30 or later after allotransplantation. Acute and chronic GVHD developed in 12 (66%) and 8 (44%) patients, respectively. Acute GVHD grade II–IV occurred in 6 patients (33%).

There was no primary graft failure. In early posttransplant period (up to day 30 after the procedure), 4 patients developed life-threatening *Enterococci* bacteremia (*E. cloacae*, *E. faecium*, *E. coli*), and 4 patients presented *Staphylococcus* bacteremia (*S. epidermis*). *Klebsiella pneumoniae* bacteremia was detected in a single patient. Four patients were found to have cytomegalovirus reactivation. None of the patients developed veno-occlusive disease. Other complications were mild and included mucositis (n = 14), diarrhea (n = 1), and fever of unknown origin (n = 5). None of the patients died within the first 100 days after transplantation. Post-transplant complete remission was achieved in all transplanted patients.

Eight patients developed leukemia relapse / progression after a median of 1.82 years (range, 0.3–4.2) and received salvage regimens with no effect. Three patients underwent an unsuccessful second allo-HSCT during active

leukemia and 4 patients received donor lymphocyte infusions.

In total, 13 (72%) patients died. The causes of deaths included leukemia resistance (n = 8), infectious complications (n = 2), steroid-resistant GVHD with cytomegalovirus reactivation (n = 1), and cerebral bleeding (n = 1). A single patient died 20 years after the procedure of unknown cause (probably not related to leukemia).

Five patients (27%) were alive at last contact and all remain in complete remission with full donor chimerism. Median follow-ups from diagnosis of ALL and allo-HSCT are 7.7 years (range, 1.8–25.2) and 4.4 years (range, 0.26–20.5), respectively. Four patients transplanted after 2010 died. Transplant data are summarized in Supplementary material, *Table S1*. Cumulative incidence of relapse and nonrelapse mortality at 2 years were 22% (95% CI, 10–48) and 17% (95% CI, 4–36), respectively. The 2-year overall survival and event-free survival were 61% (95% CI, 42–88) and 55% (95% CI, 37–84), respectively (Supplementary material, *Figure S1* and *S2*). Median overall survival for survivors was 16.4 years. Details on the survivors are in presented Supplementary material, *Table S2*.

Discussion Nowadays, standard-risk ALL is a rare indication for auto-HSCT and the number of cases decreases over time, with only 66 transplants reported to the European Registry in 2019. This number constituted 0.3% of all autologous transplantations in Europe in 2019.[8] According to the current European Society for Blood and Marrow Transplantation recommendations, auto-HSCT remains a clinical option for standard-risk, MRD-negative ALL.[9] A large meta-analysis based on data from 13 countries with 2962 patients with ALL in first remission demonstrated no beneficial effect of auto-HSCT over chemotherapy.[10]

Currently, assessment of pretransplant MRD status may help identify ALL patients who may be candidates for auto-HSCT due to the lack of a suitable donor or contraindications for allogeneic transplantation. Nevertheless, the role of auto-HSCT remains controversial. Even less data are published on the efficacy and safety of allo-HSCT for relapsed ALL after prior auto-HSCT.[2,5] In one of the largest studies,[5] data on 13 patients were analyzed. Nonrelapse mortality, relapse incidence, and disease-free survival at 2 years were 54%, 23% and 23%, respectively. Nonrelapse mortality was very high and the conclusion was not to proceed with allo-HSCT after failure of auto-HSCT due to safety aspects. Other data on second allotransplantation were also unsatisfactory.[11]

Our results are much more promising, with 2-year overall survival and event-free survival of 61% and 55%, respectively. The incorporation of novel therapies before allotransplantation is of great hope. It was demonstrated that blinatumomab- or inotuzumab ozogamicin–based salvage therapy for relapsed and refractory ALL led to complete remission rates of 78% and 94%, respectively. MRD negativity was achieved in about 70% of patients and approximately 80% of patients were referred for allo-HSCT.[12] Even more hope comes with CD19 chimeric antigen receptor T cell (CAR-T) therapy for relapsed ALL. The use of subsequent consolidative allo-HSCT was found to be beneficial in terms of post-transplant outcomes when compared with non-HSCT treatment.[13]

In conclusion, the role of allo-HSCT after failure of previous auto-HSCT is difficult to define. Our report describes the largest registry published so far, but we realize that auto-HSCT for ALL is performed in only few transplant centers in the world. Our data may suggest that allo-HSCT is a worthwhile procedure, especially in patients with late relapses after auto-HSCT. Based on our small report, we conclude that allo-HSCT after ineffective auto-HSCT for ALL is a feasible procedure associated with a relatively high proportion of patients to be cured.

SUPPLEMENTARY MATERIAL

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

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

HOW TO CITE Panz-Klapuch M, Spałek A, Duda K, et al. Allogeneic hematopoietic stem cell transplantation for relapsed B-cell acute lymphoblastic leukemia after failure of autologous hematopoietic stem cell transplantation: a retrospective single-center analysis. Pol Arch Intern Med. 2022; 132: 16220. doi:10.20452/pamw.16220

REFERENCES

1 Oriol A, Vives S, Hernández-Rivas JM, et al. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. Haematologica. 2010; 95: 589-596.

2 Ding Z, Han MZ, Chen SL, et al. Outcomes of adults with acute lymphoblastic leukemia after autologous hematopoietic stem cell transplantation and the significance of pretransplantation minimal residual disease: analysis from a single center of China. Chin Med J (Engl). 2015; 128: 2065-2071.

3 Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL trial (MRC UKALLXII/ECOG E2993). Blood. 2008; 111: 1827-1833.

4 Giebel S, Marks DI, Boissel N, et al. Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2019; 54: 798-809.

5 Radich JP, Gooley T, Sanders JE, et al. Second allogeneic transplantation after failure of first autologous transplantation. Biol Blood Marrow Transplant. 2000; 6: 272-279.

6 Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation. 1974; 18: 295-304.

7 Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015; 21: 389-401.e1.

8 Passweg JR, Baldomero H, Chabannon C, et al. Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. Bone Marrow Transplant. 2021; 567: 1651-1664.

9 Duarte RF, Labopin M, Bader P, et al. Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. Bone Marrow Transplant. 2019; 54: 1525-1552.

10 Gupta V, Richards S, Rowe J. Allogeneic, but not autologous, hematopoietic cell transplantation improves survival only among young adults with acute lymphoblastic leukemia in first remission: an individual patient data meta-analysis. Blood. 2013; 212: 339-350.

11 Grullich C, Bertz H, Spyridonidis A, et al. A fludarabine, thiotepa reduced toxicity conditioning regimen designed specifically for allogeneic second haematopoietic cell transplantation after failure of previous autologous or allogeneic transplantation. Bone Marrow Transplant. 2008; 41: 845-850.

12 Stelmach P, Wethmar K, Groth C, et al. Blinatumomab or inotuzumab ozogamicin as bridge to allogeneic stem cell transplantation for relapsed or refractory B-lineage acute lymphoblastic leukemia: a retrospective single--center analysis. Clin Lymphoma Myeloma Leuk. 2020; 20: e724-e733.

13 Xu X, Chen S, Zhao Z, et al. Consolidative hematopoietic stem cell transplantation after CD19 CAR-T cell therapy for acute lymphoblastic leukemia: a systematic review and meta-analysis. Front Oncol. 2021; 11: 651944.