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Autologous hematopoietic stem cell transplantation in adult acute lymphoblastic leukemia: still not out of fashion

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Abstract The role of autologous hematopoietic stem cell transplantation (autoHSCT) in adult acute lymphoblastic leukemia (ALL) is still unclear. We retrospectively analyzed the results of the autoHSCT and maintenance therapy, with oral 6-mercaptopurine and methotrexate, in comparison to conventional-dose chemotherapy in the consolidation treatment of adult ALL and lymphoblastic lymphoma (LBL). The patients, with HLA identical sibling donor, underwent allogeneic transplantation, while the others were treated with autoHSCT and maintenance therapy with oral 6-mercaptopurine and methotrexate, or by conventional-dose chemotherapy (patient's decision, no autologous hematopoietic stem cells harvest). Sixty consecutive adult patients (median age 35.2 years; range 17.3 to 70.7) with ALL ($n=52$), LBL ($n=7$), and acute biphenotypic leukemia ($n=1$) were treated in our center from 1997 to 2007. Patients treated with chemotherapy alone ($n=35$) had a shorter median progression-free survival (PFS) compared to patients who underwent autoHSCT plus maintenance therapy ($n=18$), 8.4 and 46.8 months, respectively ($p=0.017$). Patients treated with chemotherapy alone had also a shorter median overall survival (OS) compared to patients treated with autoHSCT: 13.0 vs. 46.8 months ($p=0.046$). The differences remained statistically significant even after excluding patients with Ph positivity. We can conclude that,

in our case, autoHSCT followed by maintenance chemotherapy is a good option for adult patients with ALL and, in standard-risk and high-risk patients, provides more favorable OS and PFS rates compared to patients treated by chemotherapy alone. However, we are aware of the fact that our analysis may have been distorted by the fact that the analysis is retrospective, that treatment with autoHSCT was based on patient's decision, and that chemotherapy may have been administered to negatively selected patients.

Keywords Acute lymphoblastic leukemia · Adults · Allogeneic stem cells transplantation · Autologous stem cells transplantation

Introduction

Postremission treatment in adult acute lymphoblastic leukemia (ALL) is still controversial, especially concerning autologous hematopoietic stem cell transplantation (autoHSCT) [1]. Even though autoHSCT has been used for treatment of adult ALL patients for many years, it is still unclear if it has any positive contribution for those afflicted with ALL. Studies from the early 1990s revealed encouraging results for autoHSCT among ALL patients in first complete remission (leukemia-free survival rates 40–60% at 3 years). However, these studies involved small numbers of patients, many of whom were children [2–6]. In later years, larger studies were performed comparing autoHSCT with allogeneic transplantation or with chemotherapy [7–11]. Nevertheless, the question remains open. It is not clear whether the performance of allogeneic transplantation in ALL patients with a HLA-identical sibling in first complete remission (CR) is generally better than conventional-dose chemotherapy or autoHSCT [7, 8]. It might be expected

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that greater success would result from allogeneic transplantation [9, 10]. As for patients without HLA-identical sibling, in intention-to-treat analyses, no significant differences have been demonstrated for autoHSCT compared with conventional-dose chemotherapy [7, 8, 11]. Even in the International ALL Trial (MRC UKALL XII/ECOG E2993), the administration of a single autoHSCT instead of consolidation treatment resulted in decreased leukemia-free survival (LFS) [10]. On the other hand, the French group revealed that autoHSCT was associated with a lower relapse rate and improved LFS compared to the chemotherapy consolidation [12]. The retrospective analysis of the European Working Group for ALL showed surprisingly good results for autoHSCT among adult ALL patients, if prior to transplantation, the level of minimal residual disease (MRD) is below 0.1% [13].

At our institution, we have been performing autoHSCT in adult ALL patients for over 10 years. Our consolidation treatment of patients with standard-risk or high-risk ALL in first complete remission is as follows: patients with a HLA-identical sibling were consolidated with alloHSCT, and patients without a HLA-identical sibling were directed toward autoHSCT, with follow-up maintenance therapy or consolidated using conventional-dose chemotherapy (patient's decision, no autologous hematopoietic stem cells harvest).

With respect to the previously unclear opinion regarding postremission treatment in adult ALL, we decided to make our own contribution to this issue with the presentation of our results for consolidation therapy.

Materials and methods

We retrospectively analyzed data of all the consecutive ALL patients treated in our department according to our treatment protocol in the years 1997 to 2007.

The protocol scheme is displayed in Fig. 1. Our protocol is derived from the works published by Attal et al. [9] and by Powles et al. [14]. Treatment was started through the first and second phase of induction. The first phase of induction was composed of prednisone (p.o.; 60 mg/m²; days 1–28; tapered until day 38), vincristine (i.v.; 1.5 mg/m² [max. 2 mg]; days 1, 8, 15, 22), daunorubicin (i.v.; 45 mg/m²; days 1, 8, 15, 22), and L-asparaginase (i.v.; 10,000 U/m²; days 10, 13, 16, 19, 21, 24). The second phase of induction was composed of cyclophosphamide (i.v.; 1 g/m²; days 29 and 50), cytarabine (i.v.; 75 mg/m²; days 31–34, 38–41, and 45–48), and 6-mercaptopurine (p.o.; 30 mg/m²; days 29–50). The central nervous system prophylaxis consisted of methotrexate (i.t.; 10 mg/m²; days 1, 15, 31, 45). The induction treatment was followed by two (patients with HLA-identical sibling) or three (patients without HLA-identical sibling) consolidations with high-dose methotrexate (3 g/m²; day 1) plus high-dose cytarabine (4 g/m²; day 1). In some patients, the last consolidation was simultaneously a mobilization regimen. It was followed by the application of filgrastim (s.c.; 10 µg/kg/day; from day 2 until HSC harvest). In other patients, the last consolidation was followed by bone marrow collection. For patients with a HLA-identical sibling, autoHSC was used as a backup, and for those directed toward autoHSCT, autoHSC was used as a graft. The exception was for patients with Philadelphia chromosome (Ph) positive ALL, for whom an attempt was always made to perform allogeneic HSCT in the first CR. In the event that patients with Ph-positive ALL lacked a HLA-identical sibling and were relatively young, an unrelated donor was sought for them. All transplanted patients received conditioning regimen of total body irradiation (TBI; 12 Gy; days –6 to –4) and cyclophosphamide (60 mg/kg; days –3 and –2). In allogeneic HSCT, graft-versus-host prophylaxis consisted of cyclosporine A and methotrexate. Maintenance therapy with 6-mercaptopurine (p.o.; 30 mg/m²/day) and

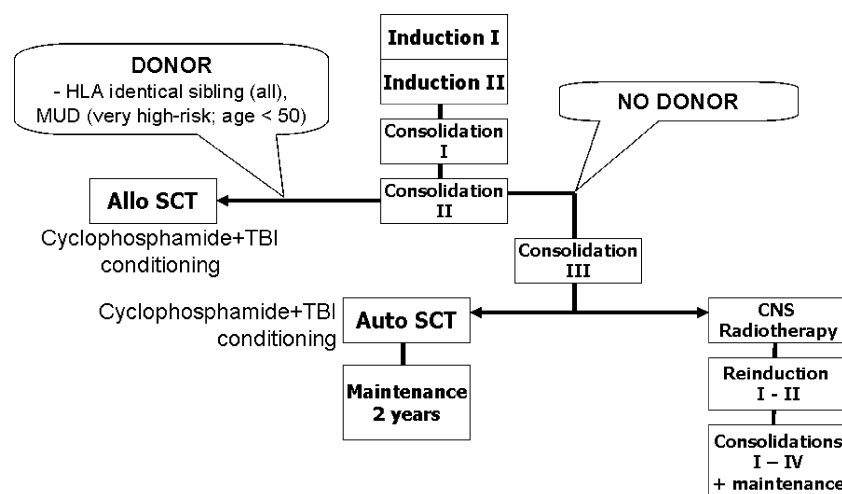


Fig. 1 Flowchart of the protocol for the treatment of adult acute lymphoblastic leukemia and lymphoblastic lymphoma

methotrexate (p.o.; 20 mg/m²/week) followed after autoHSCT for 2 years [14]. If transplantation was not performed, the patients underwent CNS irradiation (24 Gy) and subsequent conventional-dose reinduction and maintenance therapy (according to GMALL 05/93 protocol). Imatinib was not yet given to the majority of Ph-positive ALL patients. MRD monitoring was not regularly performed. Standard prophylactic measures were used.

Risk stratification of patients (standard-risk, high-risk, and very high-risk) was based on the criteria adopted from the German ALL protocols. Standard-risk (SR): B-precursor ALL (CR after induction 1, WBC < 30,000/μL, no proB ALL, no Ph positive ALL, no t(4;11) ALL), and thymic T-ALL. High-risk (HR): B-precursor ALL (CR after induction 2, or WBC > 30,000/μL, or proB ALL, or t(4;11) ALL), and early or mature T-ALL. Very high-risk (VHR): Ph positive ALL [15].

The data were analyzed for achieving CR, progression-free survival (PFS), overall survival (OS), relapse rate, and causes of death. PFS and OS were calculated from the date of diagnosis, as well as from the date of achieving CR following induction. Data on PFS and OS calculated from the date of achieving CR, i.e., exclusively from patients who achieved CR and who underwent all three cycles of the consolidation therapy, were used to compare autoHSCT with allogeneic transplantation or with chemotherapy. Calculation of OS and PFS was carried out according to the Kaplan–Meier method. Wilcoxon test was used for calculation of the statistical significance of differences in analyzed groups of patients. Probability values of less than 0.05 were considered as significant.

Results

The data for 60 patients was analyzed. There were 35 males and 25 females, with a median age of 35.2 years at the time of diagnosis (range 17.3 to 70.7). Fifty-two (87%) patients had ALL, seven (12%) lymphoblastic lymphoma (LBL; six patients had T LBL), and one (2%) acute biphenotypic leukemia. Eighteen of 52 (34%) patients with ALL showed T lineage and 34 (65%) B lineage markers. Nine (17%) patients were found Ph positive.

Seven (12%) patients were consolidated with allogeneic HSCT (one patient with Ph positive ALL), 18 (30%) patients with autoHSCT plus maintenance therapy (all patients who underwent autoHSCT subsequently received maintenance therapy), and 35 patients (58%) with chemotherapy.

Out of the total number of 60 patients, 49 (82%) achieved CR after induction chemotherapy (CR1); 44 of 52 (85%) with ALL and four of seven (57%) with LBL.

Mobilization of HSC was carried out in 30 patients. Autologous peripheral blood hematopoietic stem cells

harvest was successful in 29 (97%) of these patients. Median number of harvested C34+ cells was 6.28×10^9 /kg of recipient weight (2.61–20.74).

The median OS was 14.8 months in all patients and 39.6 months in patients in CR after induction. The median PFS was 11.7 months in all patients and 21.1 months in patients in CR after induction. Patients treated with chemotherapy alone had a shorter median PFS than patients who underwent autoHSCT and maintenance therapy (8.4 vs. 46.8 months in patients in CR after induction; $p=0.019$). Patients treated with chemotherapy alone had also a shorter median OS than patients after autoHSCT or alloHSCT (13.0 vs. 46.8 vs. 44.3 months in patients in CR1; $p=0.046$). The differences remained statistically significant even after excluding Ph positive patients ($p=0.04$).

The probabilities of PFS at 5 years were as follows for SR and HR patients in the CR after induction: alloHSCT 67% ($n=6$), autoHSCT + maintenance 62% ($n=17$), and chemotherapy 46% ($n=28$), respectively (chemotherapy vs. autoHSCT + maintenance: $p=0.076$). The probabilities of OS at 5 years were as follows for SR and HR patients in the CR after induction: alloHSCT 67% ($n=6$), autoHSCT + maintenance 66% ($n=17$), and chemotherapy 49% ($n=28$), respectively (chemotherapy vs. autoHSCT + maintenance: $p=0.04$). This analysis only includes patients reaching all three consolidation cycles. In the total patient cohort, the probability of OS at 5 years is 41%.

There was no significant difference between PFS and OS in patients with B-ALL and T-ALL. We found no difference in the survival rates for the groups of patients with standard and high-risk levels. The representations for both groups of patients in individual treatment arms were equal (Table 1). Of the total number of patients in CR1 after induction, relapse was observed in 26 (43%). For 13 patients, it occurred even during the process of treatment. Relapse of the disease was treated by chemotherapy with or without stem cell transplantation in 24 out of 26 cases, but only seven (29%) patients achieved second complete remission. Most common causes of death in the total group of patients were infection (41%), disease progression (24%), and bleeding (12%). Of patients following autoHSCT, none died from toxicity of the conditioning regimen, and for the patients following alloHSCT, the treatment-related mortality until day +100 was 29% (two out of seven). All deaths in those patients who underwent autoHSCT or were treated with conventional-dose maintenance chemotherapy were caused by the progressing disease. Peripheral blood count recovery was observed in all patients with autoHSCT.

Results of the analysis are summarized in Table 1 and Figs. 2 and 3.

Table 1 Summary of the treatment results

	Number of patients	CR after induction (%)	PFS 5 years (patients in CR after induction; %)	OS 5 years (patients in CR after induction; %)	p value
All patients	60	82	46	49	—
Type of disease					
B lineage	34	82	41	44	PFS (B lineage vs. T lineage): <i>p</i> =NS OS (B lineage vs. T lineage): <i>p</i> =NS
T lineage	18	94	50	50	
Risk groups					
Standard-risk (SR)	22	91	59	64	—
High-risk (HR)	21	81	57	62	
Very high-risk (VHR)	9	78	0	0	
Consolidations (Ph-positive ALL patients are excluded; all patients in CR after induction)					
AlloHSCT	6	—	67	67	PFS (chemotherapy vs. autoHSCT): <i>p</i> =0.076; OS (chemotherapy vs. autoHSCT): <i>p</i> =0.04
	Risk groups: SR: <i>n</i> =3, HR: <i>n</i> =3. Median age: 33.0 years (19.0 – 50.1) Male/female: 2/4				
AutoHSCT + maintenance	17	—	62	66	
	Risk groups: SR: <i>n</i> =7, HR: <i>n</i> =6, ABL: <i>n</i> =1, LBL: <i>n</i> =3. Median age: 29.2 years (17.8–53.5) Male/female: 16/1				
Chemotherapy	28	—	46	49	
	Risk groups: SR: <i>n</i> =13, HR: <i>n</i> =11, LBL: <i>n</i> =4. Median age: 42.1 years (17.3–70.7) Male/female: 14/14				

ABL acute biphenotypic leukemia, *ALL* acute lymphoblastic leukemia, *alloHSCT* allogeneic hematopoietic stem cell transplantation, *autoHSCT* autologous hematopoietic stem cell transplantation, *CR* complete remission, *LBL* lymphoblastic lymphoma, *HR* high-risk, *OS* overall survival, *PFS* progression-free survival, *SR* standard-risk, *VHR* very high-risk

Discussion

AutoHSCT offers a chance to administer myeloablative treatment with a low risk of transplant-related mortality. On the other hand, as no graft-versus-leukemia reaction is present after autoHSCT, and there is a risk of graft contamination with leukemic cells, relapses are the major reason for failure [16]. In adult ALL, the majority of previously published large-scale studies that compared autoHSCT with alloHSCT or conventional-dose chemotherapy in consolidation therapy did not show any significant advantage in using autoHSCT [7, 8, 10, 11, 17]. The use of purged marrow only brought about an improvement for ALL results with autoHSCT in a few cases [18] and is not

used significantly today in ALL treatment. Several of the working groups that focus on ALL treatment do not recommend autoHSCT [17, 19]. On the other hand, though, there are several studies which reveal that autoHSCT can improve the outlook for ALL patients, particularly if performed on patients with a low MRD level prior to the autoHSCT [12, 13, 20]. AutoHSCT performed in accordance with MRD-based risk stratification [21] could lead to further improvements in the results of this treatment.

Although we are well aware that the results of our analysis need to be interpreted with caution (retrospective analysis, smaller number of patients, MRD analysis performed only in a few cases, maintenance chemotherapy may have been administered to negatively selected

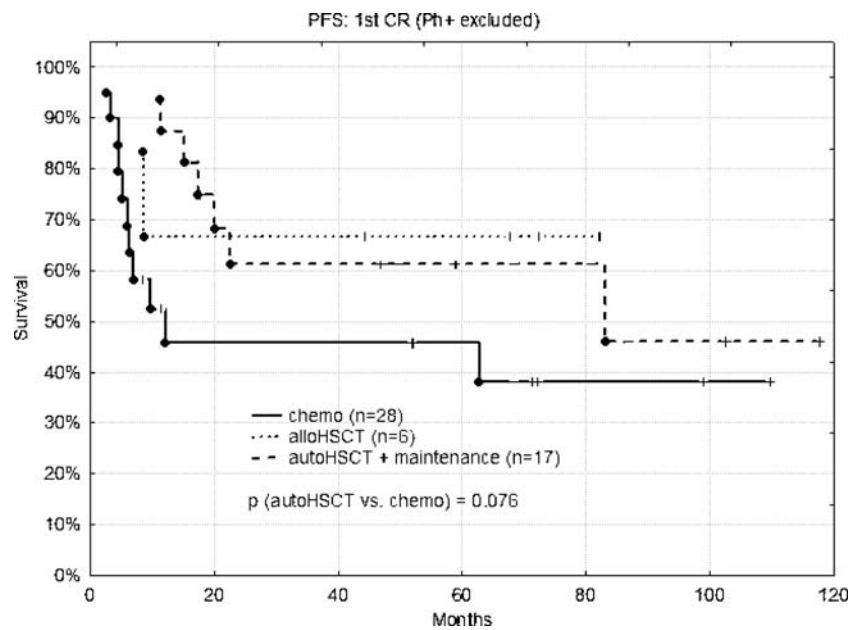


Fig. 2 Progression-free survival (PFS) of patients in complete remission (CR) after induction according to the type of consolidation therapy. Ph-positive (Ph+) acute lymphoblastic leukemia patients are excluded. The probability of PFS at 5 years: alloHSCt 67%,

autoHSCt 62%, and chemotherapy 46%, respectively. *AlloHSCt* allogeneic hematopoietic stem cell transplantation, *autoHSCt* autologous hematopoietic stem cell transplantation, *chemo* conventional-dose chemotherapy

patients), we hold the view that the success rate we have presented for consolidation treatment using autoHSCt plus maintenance therapy is significant, supporting the idea of a re-evaluation of the role of autoHSCt for certain types of ALL. For our patients, autoHSCt coupled with mainte-

nance therapy not only shortened the intensive therapy duration, but above all revealed better PFS and OS in comparison with standard-dose chemotherapy. Nonetheless, we would like to once again point out that difference may have been influenced by negative selection of patients

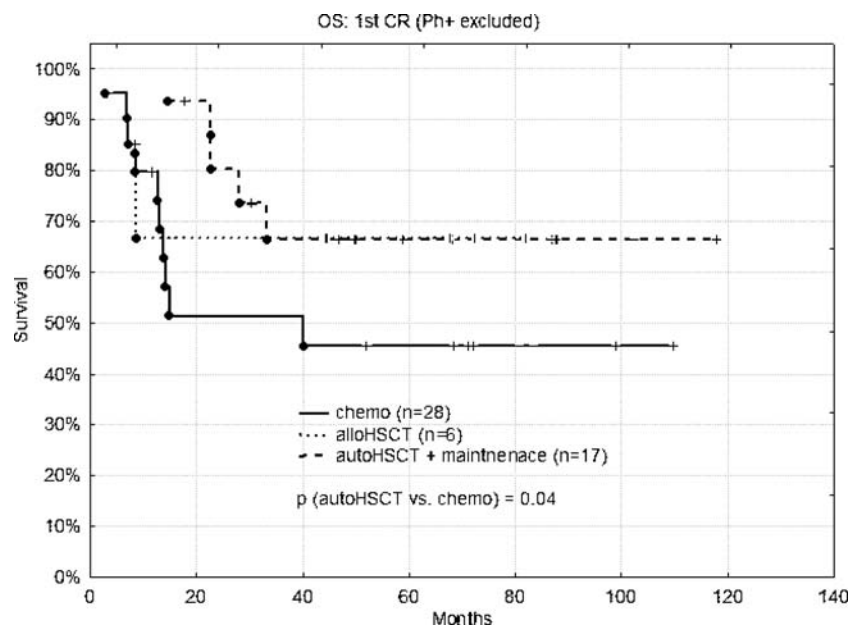


Fig. 3 Overall survival (OS) of patients in complete remission (CR) after induction according to the type of consolidation therapy. Ph-positive (Ph+) acute lymphoblastic leukemia patients are excluded. The probability of OS at 5 years: alloHSCt 67%, autoHSCt 66%,

and chemotherapy 49%, respectively. *AlloHSCt* allogeneic hematopoietic stem cell transplantation, *autoHSCt* autologous hematopoietic stem cell transplantation, *chemo* conventional-dose chemotherapy

treated with maintenance chemotherapy and the slightly higher age of these patients compared to those included in the group treated with autoHSCT + maintenance (median age 29.2 vs. 42.1 years; Table 1). AutoHSCT should not perhaps have the final say in the treatment of both standard- and high-risk adult ALL. For patients with very high-risk ALL, it is likely that, in this time of tyrosin-kinase inhibitors, the autoHSCT is not a suitable method, or at best, theoretically, autoHSCT could be advantageous only in combination with these inhibitors.

It is likely that a significant part of our good results with autoHSCT is also due to the following maintenance therapy. Maintenance, in general, is still standard for ALL patients, since all attempts to omit it have led to inferior long-term outcome with LFS rates of 18–28% [1]. It can be assumed that our results for autoHSCT would be worse without maintenance therapy, a view that concurs with the data published by Sotomayor et al. [22] and Mehta et al. [23]. The question still remains, though, whether to further increase the dose of maintenance would lead to even better results [24].

In conclusion, according to our analysis, autoHSCT coupled with maintenance chemotherapy is still an option in adult ALL and provides favorable OS and PFS rates. There may be a group of patients for whom autoHSCT in first remission is a reasonable and perhaps superior treatment choice. Our view is that this method, supplemented with MRD-based risk stratification particularly before performing the transplantation, should be taken into account.

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