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Chapter

Consolidation: Autologous Stem Cell Transplantation in Acute Leukemia

Fatma Keklik Karadağ, Fahri Şahin and Güray Saydam

Abstract

The goal of complete remission (CR) in acute leukemias could be achieved with intensive induction chemotherapy however patients need post remission consolidation strategies such as high-dose chemotherapy, or autologous (ASCT) or allogeneic (allo-SCT) hematopoetic stem cell transplantation for durable response. However, Allo-SCT is getting more attention in last decades because of improvements of conditioning regimens and graft versus host disease (GVHD) prohylaxis strategies and alternatively available donor sources, it is not suitable for all leukemia patients. The patients who would benefit from Allo-SCT or ASCT could be defined more easily by using risk stratification systems and minimal residual disease (MRD) monitoring. ASCT is considered a treatment option even if its use is declining in the world. Herein, we tried to summarize the studies that report the outcomes of ASCT in acute myeloid leukemia (AML) and acute, lymphoblastic leukemia and describe the patients who would be good candidate for ASCT.

Keywords: autologous stem cell, transplantation, acute leukemia, adult, lymphoblastic leukemia, myeloid leukemia

1. Introduction

Standard chemotherapy regimens are the first step for the treatment of acute leukemias. However, the complete remission could be achieved with intensive chemotherapy, durable remission is not common and patients will relapse within months unless additional therapy is given. There is an extensive debate about post remission therapy. There is no consensus about intensive chemotherapy as a consolidation and/or stem cell transplantation (SCT) after first remission (CR1). Allogeneic stem cell transplantation (Allo-SCT) for acute leukemias has been increased due to the developments of allo-SCT techniques. Availability of alternative donor sources (including haploidentical, matched unrelated donors and umbilical cord blood), improvements of graft versus host disease (GVHD) prophylaxis strategies and reduced-intensity conditioning (RIC) regimens are developed in last decades and Allo-SCT has been used widely all over the world. However, lower incidence of relapse rates after allo-SCT because of graft versus leukemia effect makes allo-SCT more popular, high morbidity rates due to chronic GVHD, secondary graft failure and high treatment related mortality (TRM) rates in the patients who underwent Allo-SCT should be considered and it is not recommended for the patients with good risk. Allo-SCT is not available for elderly patients and

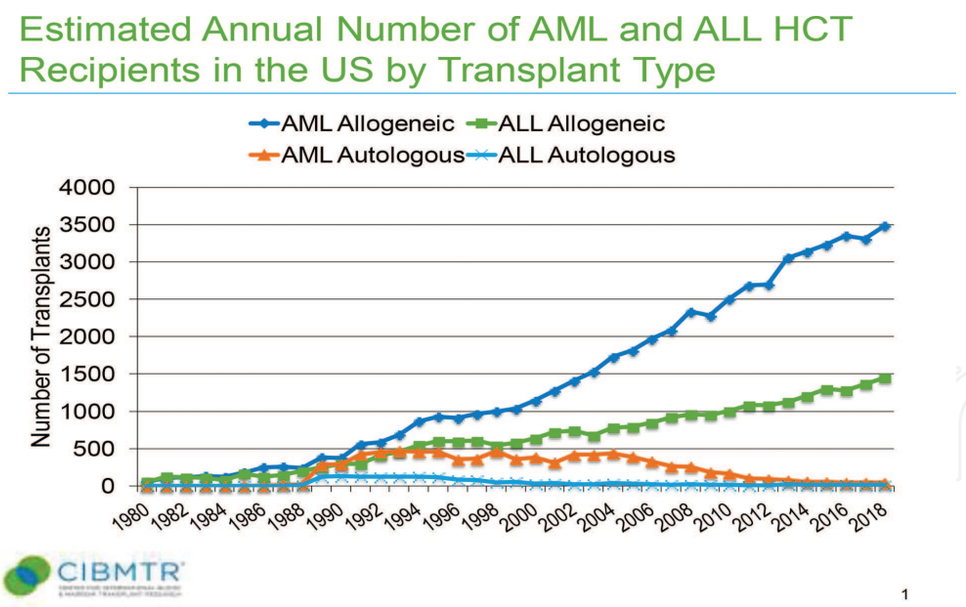

Figure 1.
The rates of autologous stem cell transplantation (ASCT) and allogeneic stem cell transplantation in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). (*Data presented in table is kindly provided by CIBMTR).*

the patients who do not have HLA-matched related or unrelated donor. Autologous stem cell transplantation (ASCT) is an alternative and valuable treatment option with acceptable long term outcomes and lower TRM rates for the patients with low and intermediate risk after CR1 and the patients who are not eligible for Allo-SCT. Center for International Blood and Marrow Transplantation Research (CIBMTR) showed the rates of ASCT and Allo-SCT in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) in the USA (**Figure 1**).

2. ASCT for acute myeloid leukemia

More than half of AML patients achieved complete remission after standard induction therapy but 60–70% of patients will relapse without consolidation therapy. ASCT, an effective therapy for AML was started to use in 1980's for consolidation in AML patients [1–5]. Since then, it is a challenge to define the patients who would benefit from ASCT. Bone marrow (BM) initially preferred source of stem cells for ASCT. After hematopoietic growth factors provided the possibility to use peripheral blood stem cells (PBSC) grafts after intensive chemotherapy courses since 1994, the treatment compliance of ASCT has improved and the treatment-related mortality (TRM) has been reduced due to accelerated hematopoietic reconstitution [6]. Mobilized PBCS have replaced bone marrow because of the main advantages of PBSCs as a stem cell source are markedly faster neutrophil and platelet recovery times than bone marrow, with consequently reduced infection, bleeding and hospitalization risks. The PBSC target dose is considered an amount of CD34+ cells $\geq 2 \times 10^6$/kg body weight. There is numerous clinical studies compare ASCT with chemotherapy or Allo-SCT in AML patients according to cytogenetic risk groups and CR1 or second remission (CR2). National Comprehensive Cancer Network (NCCN) and European leukemia network (ELN) divided patients with AML into three risk status groups: good/favorable, intermediate, and poor/adverse risk by genetic abnormality in 2017 (**Table 1**) [7]. The 'favorable' group includes patients with either inv.(16), t(16;16), t(8; 21), mutated NPM1 without FLT3

Risk category	Cytogenetic abnormality
Favorable	t(8;21)(q22;q22): *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22): *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}
	Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34): *DEK-NUP214*
	t(v;11)(v;q23): *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	−7
	Complex karyotype
	Monosomal karyotype
	Wild type *NPM1* and *FLT3*-ITD^{high}
	Mutated *RUNX1*
	Mutated *ASXL1*

Table 1.
Genetic risk stratification according to the ELN-2017.

ITD (internal tandem duplications) (NPM+/FLT3 ITD−) or mutated CEBPA. An 'adverse' group consists of patients with inv. (3) or t (3;3), t(6;9), t(v;11) either −5 or del (5q), −7, abn (17p) or ⩾3 cytogenetic abnormalities not including translocations (complex karyotype). An intermediate-1 group comprises patients with a normal karyotype (NK) and with the other genotypic combinations of NPM1 and FLT3 ITD (+/+, −/−, −/+) and an intermediate-2 group consists of patients with t (9;11) and cytogenetic abnormalities not noted above. Good-risk AML patients qualify for chemotherapeutic consolidation, but recent reports suggested favorable outcome for good-risk patients with ASCT, which provides a possible option in that category of patients [8, 9]. The survival outcomes of patients with good-risk or intermediate-risk AML who underwent ASCT as postremission therapy were favorable—probably due to the use of PBSC rather than instead of BM, which may decrease the risk of transplant-related complications—but that the survival outcomes of similarly treated poor-risk AML patients were not.

Gruppo Italiano Trapianto di Midollo Osseo (GITMO) analyzed 809 AML patients who were autografted in CR1 retrospectively [10]. Two year leukemia free survival (LFS) and Overall Survival (OS) rates were found 51% and 65%, respectively and it was reported that survival was significantly influenced by cytogenetic risk. Patients with good risk group had remarkable better outcomes in this study. The 2 year cumulative incidence of relapse was higher in poor risk patients (28 ± 7% for good risk group vs. 48 ± 8% for poor risk group, $p < 0{,}0002$). Patients with CEBPA double mutated (CEBPAdm) and nucleophosmin-1 (NPM) mutated AML have better outcome with ASCT [9, 11]. It has been already demonstrated that the subset of patients with *NPM*1^{+} mutations without fms-related tyrosine kinase 3 gene *(FLT3)* internal tandem duplications (*FLT3-ITD*) derive no survival benefit from allo-SCT [12].

Several historical randomized trials have reported that ASCT can significantly reduce the relapse rates compare with conventional chemotherapy alone. The study performed by the Dutch–Belgian Hemato-Oncology Cooperative Group/Swiss Group for Clinical Cancer Research (HOVON-SAKK) Cooperative Consortium compared the outcomes of ASCT with chemotherapy including 517 patients who were randomly recorded between 1995 and 2006 [1]. Rates of relapse after chemotherapy vs. after ASCT were 70% vs. 58%, respectively (P = .02), 5 year follow up and no significant difference in LFS of 29% vs. 38% (P = .065). OS did not differ between these two groups and was estimated to be 41% vs. 44%, respectively, at 5 years from randomization. TRM was higher in ASCT group than chemotherapy group (4% vs. 1% respectively).

A meta-analysis which included 11 studies compared survival outcomes of alloSCT from matched sibling donor (MSD) or matched unrelated donor (MUD) versus ASCT in intermediate-risk AML and demonstrated alloSCT from MSDs rather than MUDs was associated with better OS than that with ASCT [13] however recent retrospective trials reported similar survival rates for AML patients who underwent autoSCT and allo-SCT from MSDs and MUDs [3, 14, 15].

The treatment options are not well defined in older patients with leukemia. Higher incidence of AML secondary to previous myelodysplastic syndrome (MDS), adverse mutation pattern and karyotype and poor performance status are the reasons of poor outcomes in older AML patients [16–18]. They usually do not have MSD and available regimens are limited due to many of comorbidities especially cardiovasculary disease. ASCT may be used in patients up to age 70 years with an acceptable TRM of approximately 8%, which compares favorably to 17% as was observed after RIC alloHSCT.

Several reports from EBMT and CIBMTR showed long-term leukemia free survival (LFS) rates are 45–55% in patients transplanted in CR 1 and 25–35% for those transplanted in CR2 [19–21]. The patients who are not eligible for Allo-SCT ASCT may be an acceptable post-remission therapy in CR1 [14]. Allo-SCT still remains first line treatment for poor risk patients while ASCT is getting attention for good risk and especially intermediate risk patients who have favorable prognostic factors, including MRD negativity after the imitation of induction chemotherapy, a WBC count of <20,000/μL at time of the diagnosis, an FAB classification of M1–5, and ≥ 50% MPO positivity. Decision-making might benefit from taking minimal residual disease (MRD) into account [22, 23]. Real-time quantitative PCR (qPCR) and multiparameter flow cytometry (MFC) are effective techniques for monitoring MRD before and after ASCT in patients with AML, and MRD status pre-ASCT is an independent prognostic factor for both OS and LFS after ASCT [24, 25]. Whereby MRD-negative patients may be consolidated by ASCT and MRD-positive patients may proceed to allo-SCT. ASCT is generating new interest, especially in intermediate-risk patients who became MRD negative upon induction chemotherapy [26].

The traditional conditioning regimens before ASCT that are mostly myeloablative and based on busulfan; combination of busulfan/ cyclophosphamide (BUCY), busulfan/etoposide, cyclophosphamide/Total body irradiation (TBI), Busulfan/ high dose melphalan. Different regimens such as modifications of the BCNU, etoposide, cytarabine, melphalan (BEAM) regimen, busulfan/etoposide/ cytarabine, TBI/cytarabine/melphalan could be used in different centers. Three large retrospective studies showed that busulfan/high dose melphalan regimen has better outcomes than BUCY [27–29]. Although both oral and intravenous busulfan were used in various regimens, it has become clear that the intravenous administration of busulfan should be preferred because of fewer complications [30]. Favorable long-term LFS after auto-SCT using a high-dose cytarabine-containing regimen has been showed. The most common treatment related complication of ASCT is mucositis

and mucositis are usually more frequent in the patients who were treated with oral busulfan than iv busulfan.

3. ASCT for acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) accounts 10–15% of AML in adults. It is highly curable disease and remission is achieved in 90% of APL patients after anthracycline-based induction therapy plus ATRA and recently arsenic trioxide (ATO). The combination of ATRA and anthracyclines remains the gold standard for high risk patients. There is not a role for stem cell transplantation in APL in CR1, independently from any initial risk category. ELN suggested that patients who relapsed after ATRA plus chemotherapy should be treated with an ATRA plus ATO based approach as salvage therapy until achievement of MRD negativity. Despite of SCT is accepted treatment for the 10–20% patients who relapsed, the choice of ASCT vs. Allo-SCT remains controversial.

EBMT reviewed 625 APL patients transplanted ASCT or Allo-SCT, lower relapse rates and higher 5 year LFS reported in Allo-SCT group. Although TRM was higher in Allo-SCT patients, Allo-SCT was recommended in CR2 when a sibling donor was available in this study [31]. Holter et al. reported OS was better after ASCT than after chemotherapy and ATO. ASCT was the preferred therapy for patients with CR2 status, and survival outcomes were superior in patients who received ASCT compared with those who received ATO-based consolidation therapy [32]. Besides ASCT is superior than allo-SCT in relapsed APL due to low TRM and durable remission, pre-SCT bone marrow cytogenetic and molecularly evaluation is important. It was recommended allogeneic HCT if the pre-HCT marrow was cytogenetically or molecularly positive [33]. ASCT is less toxic than allo-SCT, and appears equally potent particularly when a negative *PML-RARA* status is achieved before transplantation.

4. ASCT for acute lymphocytic leukemia

ALL is divided into tumors of B cell and T cell lineage and it is the most common cause of leukemia in children however up to 20% of the cases of ALL occur in adults. Despite of the developments of induction chemotherapy regimen, relapse rates and mortality still remain high in this century. Most of studies were designed according to risk stratification and categorized patients into standard, intermediate or poor risk. Poor risk criteria are cytogenetic abnormalities t(9;22), t(4;11), or t(1;19); pro–B-cell immunophenotype; high WBC (i.e., $> 30 \times 10^9$/L in case of B-ALL; $> 100 \times 10^9$/L in case of T-cell ALL [T-ALL]) at the time of diagnosis. Although the introduction of more aggressive chemotherapy regimens has reduced the need for allo-HSCT in patients younger than 35 years of age, allo-HSCT remains the standard of care for high-risk patients and relapse after CR1. SCT is still a debate in ALL patients without poor-risk features however Allo-SCT is highly recommended in poor risk ALL patients in CR1. Allo-SCT is not certainly suggested in ALL patients without poor risk to avoid the unnecessary risks of transplantation procedure-related mortality and GVHD to patients, who may be cured with chemotherapy alone and to postpone allo-SCT to an eventual relapse. The standard risk patients rather than the high-risk patients, older patients and the patients who are not eligible for Allo-SCT may be the ones who are most likely to benefit from ASCT in first remission. MRD has emerged as a prognostic marker that can define patients to high-risk, making them candidates for Allo-SCT.

Several studies have been published about the experience of ASCT in ALL. The results of some recent trials are summarized in **Table 2**. Data from three prospective trials of the French group have failed to demonstrate any significant superiority of ASCT over chemotherapy, even in a subset of high-risk patients [39–41]. Conversely, it has been reported that ASCT may be an effective treatment for ALL patients who experienced an isolated extramedullary relapse. A recent randomized study of 433 adult standard risk ALL patients showed that LFS at 5 years was significantly better in patients who underwent allo-HSCT compared with ASCT (60% vs. 42%, $P = 0.01$). In a large study which is comparing chemotherapy and autologous transplantation in ALL patients, the LFS and OS were found superior for chemotherapy group [34]. In the LALA-87 trial, results in standard-risk ALL were similar for Allo-SCT [37] and for chemotherapy or ASCT and then the same group reported no benefit of ASCT for ALL in all risk groups [42].

The Philadelphia chromosome (Ph) translocation (9; 22) is the most common chromosomal abnormality seen in adult patients with ALL. The t(9;22) is observed

Reference	Patient number	Period	Age (years)	Study design	Outcomes
Goldstone et al. 2008 [34]	1929	1993–2006	15–59	Ph- ALL patients divided groups; with donor vs. no donor chemotherapy vs. ASCT group	5-year OS is better in donor group, 53% versus 45% (P = .01), and lower the relapse rate in donor group (P < or = .001) OS is better in Chemotherapy group than ASCT group (46% [95% CI = 39–53%] vs. 37% [95% CI = 31–44%]; *P* = .03)
Thomas et al. 2004 (LALA94 study) [35]	922	1994–2002	15–55	ASCT vs. chemotherapy	ASCT did not show superiority over chemotherapy in high-risk ALL patients.
Hunault et al. 2003 (GOELAMS) [36]	198	1994–1998	15–59	Allo-SCT vs. ASCT	OS and LFS is better in Allo-SCT (75% vs. 39% *P* = .0027 and 72% vs. 32% *P* = .0004 respectively) relapse rates higher in ASCT
Fiere et al. 1993 [37]	572	1986–1991	15–60	ASCT vs. consolidative chemotherapy	Not significantly benefit of ASCT over chemotherapy
Powles et al. 2002 [38]	77	1984–1998	16–59	All patients underwent ASCT	10-year LFS and OS rates are 50% (95% CI, 38–62%) and 53% (95% CI, 41–65%), respectively

Table 2.
Summaries of studies on autologous stem cell transplantation in ALL.

in 2 to 5% of children with ALL and 30% percent of adults. Historically, Ph-positive ALL (Ph + ALL) was considered a very high-risk subtype and Allo-SCT was highly recommended for all eligible patients. After the introduction of tyrosine kinase inhibitors (TKIs) (first TKI, imatinib; second-generation TKIs such as dasatinib or nilotinib; the third-generation TKI, ponatinib) which could be successfully used both as salvage therapy and upfront in combination with intensive chemotherapy, complete remission is achieved in 90% of Ph + ALL patients [43]. The critical role of MRD prior to ASCT was already confirmed in Ph-negative ALL and may also be important in the Ph + setting [44]. Results of ASCT for Ph + ALL improved markedly in recent years with more than half of patients being alive and leukemia-free at 2 years [43, 45, 46]. The role of biologic response modifiers such as α-interferon (α-IFN and interleukin-2) in Ph + ALL is analyzed and it was reported that combination of α-IFN with maintenance chemotherapy and ASCT improves the outcomes in Ph + ALL [47, 48].

5. Conclusion

According to NCCN guidelines; Patients with good-risk AML are recommended to undergo high-dose cytarabine-based chemotherapy. Patients with poor-risk AML are recommended to undergo allogeneic stem cell transplantation (alloSCT). However, the best post remission therapy for patients with intermediate-risk AML in first complete remission (AML/CR1) is still uncertain. ASCT would be an option in CR1 and MRD negative. ASCT is a kind of standard treatment of CR2 in APL patients. There is no benefit of ASCT in Ph negative ALL patients however ASCT is a therapeutic option for relapsed Ph + ALL. Although the main disadvantages of ASCT are the possibility of contamination of leukemic cells in the stem cell product and the absence of graft-versus-leukemia effect, which lead to a higher relapse rates than that of Allo-SCT, ASCT should be considered a standard therapy in acute leukemia patients who are not eligible Allo-SCT and MRD negative in CR1 and the patients without poor risk.

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