

## Comparison of post-remission strategies in acute myeloid leukemia: Autologous hematopoietic stem cell transplantation versus consolidation chemotherapy

Zeynep Arzu Yegin, Asena Dikyar, Lale Aydın Kaynar, Ferda Can, Zübeyde Nur Özkurt, Münici Yağcı  
Department of Hematology, Gazi University School of Medicine, Ankara, Turkey

### Abstract

Autologous Hematopoietic Stem Cell Transplantation (auto-HSCT) has become a therapeutic option for first-line consolidation in Acute Myeloid Leukemia (AML) patients with favorable and intermediate risk features. A total of 101 AML patients in first complete remission, who were not eligible for allogeneic HSCT, were randomized to receive intensive cytarabine-based chemotherapy or to undergo auto-HSCT. The probability of LFS was significantly better in auto-HSCT recipients compared to chemotherapy arm (43% vs 4.8%,  $p=0.008$ ). At the end of 915 (30-4470) days of follow-up, the probability of overall survival was better in auto-HSCT group compared to chemotherapy, without statistical significance (79.2% vs 38.8%,  $p=0.054$ ). Multivariate analysis revealed a significant predictive impact of cytogenetic risk status on OS ( $p=0.002$ , HR: 2.824, 95% CI: 1.445-5.521). Auto-HSCT is considered as an effective consolidation approach in favorable and intermediate risk AML patients.

### Introduction

Maintenance of remission is considered as a major concern in the primary treatment of Acute Myeloid Leukemia (AML) despite favorable remission rates after induction treatment. Complete Remission (CR) rates are approximately 70-80% for adult patients with AML, however 60% of these patients experience relapse in their first CR on intensive chemotherapy with cytarabine based regimens.<sup>1</sup> As a result of progressive efforts to improve Leukemia Free Survival (LFS) in AML patients, distinct therapeutic approaches for post-remission consolidation have been developed. Treatment decision is mainly based on cytogenetic risk profile,

quality and intensity of remission including Minimal Residual Disease (MRD) determination and patient related factors to optimize potential options for salvage therapy.<sup>2</sup>

Currently available consolidation strategies for AML patients in CR1 are intensive chemotherapy, autologous (auto) and allogeneic (allo) Hematopoietic Stem Cell Transplantations (HSCT). Although allo-HSCT is the most effective treatment to prevent leukemia relapse, high Non Relapse Mortality (NRM) rate, which is mainly associated with Graft versus Host Disease (GvHD), remains to be the major obstacle in allo-HSCT recipients. In this perspective, auto-HSCT has become a therapeutic option for first-line consolidation in AML patients with favorable and intermediate risk features as it prolongs LFS with a tolerable toxicity profile compared to allo-HSCT.<sup>3-5</sup> Nevertheless, lack of Graft versus Leukemia (GvL) effect and possibility of graft contamination may increase post-transplant relapse incidence. Minimal residual disease eradication at the time of transplant may help to improve prognosis in this group of patients.<sup>3,6-8</sup>

This retrospective study was planned to compare the efficacy of auto-HSCT with respect to conventional cytarabine based chemotherapy in a relatively elderly population of AML patients in CR1.

### Materials and Methods

A total of 101 AML patients in CR1 [median age: 47(19-79); male/female: 51/50], who were not eligible for allo-HSCT and did not have an HLA compatible donor, were randomized to receive intensive cytarabine-based chemotherapy or to undergo auto-HSCT after high dose cyclophosphamide and busulfan as conditioning regimen. Only one patient received TEAM (thiotepa, etoposide, cytarabine, melphalan) conditioning regimen due to neurotoxicity secondary to central nervous system leukemia. Diagnosis and risk stratification were based on French-American-British classification and European Leukemia Net 2017 guidelines.<sup>9</sup> Patient characteristics are summarized in Table 1.

Continuous variables were compared using T-test, Mann Whitney U and Kruskal Wallis tests while Chi-square test was used for categorical variables. Correlation analysis was performed using Pearson and Spearman tests. Kaplan Meier and log rank tests were used for survival analysis. Risk factors for survival were determined by Cox

Correspondence: Zeynep Arzu Yegin, Gazi University School of Medicine, Department of Hematology, Beşevler, Ankara, Turkey.  
Tel.: +90.3122025579 - Fax: +90.3122236714.  
E-mail: zeyneparzu yegin@gmail.com

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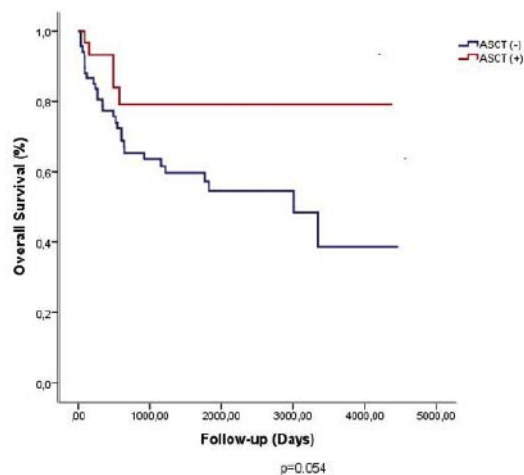
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regression test. SPSS 22.0 (SPSS Inc, Chicago, IL, USA) programme was used for statistical analysis and  $p<0.05$  was considered as statistically significant. The study was approved by the local ethical committee of Gazi Medical School.

### Results and Discussion

Leukemia relapse was demonstrated in 22 patients (31.4%) in the chemotherapy arm at median 330 (60-2190) days of follow-up. In this group, allo-HSCT was performed in

4 patients (18.2%) as salvage treatment for post auto-HSCT relapse. Among auto-HSCT recipients, leukemia relapse was observed in 14 patients (45.2%) at median 225 (60-395) days of follow-up. Allo-HSCT was performed in a total of 12 patients (85.7%) who had experienced relapse after auto-HSCT. Five-year relapse incidence was found to be 65% and 46%, in chemotherapy and auto-HSCT groups respectively ( $p>0.05$ ). A total of 52 patients were analysed for LFS. The probability of LFS was significantly better in auto-HSCT recipients compared to chemotherapy arm (43% vs 4.8%,  $p=0.008$ ). One-year Non Relapse Mortality (NRM) rate was 27% in chemotherapy and 22% in auto-HSCT groups ( $p>0.05$ ). At the end of 915(30-4470) days of follow-up, the probability of Overall Survival (OS) was better in auto-HSCT group compared to chemotherapy, without statistical significance (79.2% vs 38.8%,  $p=0.054$ ) (Figure 1). Univariate and multivariate analysis revealed a significant predictive impact of cytogenetic risk status on OS ( $p=0.002$ , HR: 2.824, 95% CI: 1.445-5.521). This retrospective study yielded comparable results with the previous reports, which evaluate consolidation strategies in AML patients. Although leukemia relapse was seen more frequent in auto-HSCT recipients in short-term follow-up, 5-year relapse probability was found to be higher in chemotherapy arm without statistical significance. In addition, LFS was significantly longer in auto-HSCT patients with similar NRM rates in both groups. However, better OS in auto-HSCT arm did not reach statistical significance, which may be due to small sample size and short follow-up. Several studies have investigated the role of auto-HSCT in AML consolidation therapy. In a study by Vellenga *et al.*, auto-HSCT group represented a reduced relapse rate and better relapse-free survival compared to conventional chemotherapy. However, NRM was found to be higher in auto-HSCT group. Statistical insignificance in terms of OS was primarily based on different post-transplant salvage strategies including allo-HSCT.<sup>10</sup> In a retrospective analysis of European Society for Blood and Marrow Transplantation (EBMT) in 3567 AML patients who underwent auto-HSCT, the probability of relapse at 10 years was 16% which was markedly lower compared to our study. Similarly, a lower NRM rate (8%) and a better LFS (76%) were reported in the same study. Use of mobilized blood and older age were found to be associated with increased risk of relapse and decreased probability of LFS.<sup>3</sup> Leukemia relapse, which affects approximately 40-50% of auto-HSCT recipients with AML in CR1 and



**Figure 1.** The probability of overall survival was better in auto-HSCT group compared to chemotherapy group, without statistical significance (79.2% vs 38.8%,  $p=0.054$ ).

**Table 1. Patient characteristics.**

Characteristic	N.
All patients, n (%)	101 (100)
Consolidation chemotherapy	70 (69.3)
Autologous hematopoietic stem cell transplantation	31 (30.7)
Median follow-up, median (range) days	915 (30-4470)
Age, median (range) years	47 (19-79)
Gender, n (male/female)	51/50
AML subtype (FAB classification), n(%)	
M0	8 (7.9)
M1	13 (12.9)
M2	18 (17.8)
M4	31 (30.7)
M5	9 (8.9)
Unclassified	22 (21.8)
Cytogenetic risk group, n(%)	
Low	12 (11.9)
Intermediate	45 (44.5)
High	44 (43.6)
Extramedullary disease, n(%)	5 (4.9)
CNS involvement, n(%)	3 (2.9)
Time from diagnosis to transplant, median (range) days	95 (57-187)
Pre-transplant performance status (ECOG), median (range)	0 (0-1)
Pre-transplant comorbidity index (Sorrer's), median (range)	0 (0-2)
Mobilization regimen, n(%)	
HDAC	22 (71)
IDAC	7 (22.6)
Cy-Etoposid	1 (3.2)
G-CSF	1 (3.2)
Conditioning regimen, n(%)	
Cy Bu	30 (96.8)
TEAM	1 (3.2)
Stem cell source, n(%)	
Bone marrow	0
Peripheral blood	31 (100)
Number of infused CD34+ cells, median (range, 10 <sup>6</sup> /kg)	4.47 (2.2-5.86)
Neutrophil engraftment, median (range) days	12 (9-27)
Platelet engraftment, median (range) (days)	13 (10-202)
Sinusoidal obstruction syndrome, n(%)	1 (3.2)
Mucositis grade, median(range)	1 (1-3)

AML: Acute Myeloid Leukemia; FAB: French-American-British; CNS: Central Nervous System; ECOG: Eastern Cooperative Oncology Group; HDAC: High-Dose Cytarabine; IDAC: Intermediate-Dose Cytarabine; Cy: Cyclophosphamide; G-CSF: Granulocyte Colony Stimulating Factor; Bu: Busulfan (intravenous); TEAM: Thiotepa, Etoposide, Cytarabine, Melphalan; CD: Cluster of Differentiation.

70% in CR2, is the major cause of treatment failure after auto-HSCT in the first 2 years. Post-transplant tumor control measures such as maintenance therapy with hypomethylating agents may be considered to overcome early relapses within the first 2 years after HSCT. Our results are compatible with the previous studies which demonstrated an advantage for auto-HSCT compared to conventional chemotherapy in terms of improved LFS with no significant impact on OS.<sup>2,3,5,7,11,12</sup> In our study, the follow-up period of auto-HSCT recipients was relatively shorter than chemotherapy arm, which may be an explanation for the higher early relapse rates. We did not perform MRD analysis at the time of transplant, therefore the potential impact of MRD status on relapse incidence should also be taken into account. Similarly, higher NRM rates in our study may be associated with the higher number of elderly patients in our study population, as older age may have an adverse prognostic impact despite contradictory reports which underline the safety and efficacy of auto-HSCT in AML patients above 65 years.<sup>3,4,6,13</sup>

Allogeneic HSCT has favorable outcomes in AML-CR1 patients with intermediate or poor cytogenetic risk profile. Intermediate risk AML patients who underwent matched sibling donor (MSD) allo-HSCT in CR1, represented best outcomes in terms of LFS and OS compared to auto-HSCT and chemotherapy arms. Nevertheless, in intermediate risk patients lacking a MSD, auto-HSCT should be considered as a valid option as better survival appears to be provided by auto-HSCT compared to mismatched unrelated transplants.<sup>1,8,14-17</sup> The main disadvantages of auto-HSCT are the possibility of contamination of leukemic cells in the stem cell product and lack of GvL effect, which causes a lower curative potential compared to allo-HSCT.<sup>1</sup>

The role of allo-HSCT as salvage treatment should be considered in AML patients who experience leukemia relapse after auto-HSCT. Approximately 20% of autografted patients have received a second allo-HSCT with a LFS of 30% at 3 years. Younger age, late relapse, and the absence of total body irradiation in the auto-HSCT conditioning regimen have been indicated as favorable prognostic factors. Disease status at the time of allo-HSCT is considered as the most significant prognostic factor.<sup>12,18</sup> Relatively higher incidence of salvage allo-HSCT may have positively affected the long term outcomes of auto-HSCT survivors in our study.

## Conclusions

In conclusion, auto-HSCT is considered as an effective consolidation approach in favorable and intermediate risk AML patients. Salvage allo-HSCT for leukemia relapse in autografted patients remains to be a feasible treatment option which prolongs LFS and reduces relapse rates. Pre-transplant MRD negativity is critical in order to minimize graft contamination with leukemic stem cells. Post-transplant maintenance strategies may have a role in preventing relapse and improving long term outcomes of auto-HSCT.

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