

Comparable Outcome of Allogeneic versus Autologous Hematopoietic Peripheral Blood Stem Cell Transplantation in Acute Myeloid Leukemia Patients with Normal Karyotype and FLT3-ITD Negative

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Abstract

Introduction: Optimal post-remission treatment for acute myeloid leukemia patients with normal karyotype (AML-NK) in first complete remission (CR1) who lacks an HLA identical donor is still not well-defined.

Aim of the Work: To compare the outcome of allogeneic versus autologous peripheral blood stem cell transplantation (PBSCT) in adult AML patients regarding toxicities of transplant procedure, transplant-related mortality (TRM), disease free survival (DFS) and overall survival (OS).

Patients and Methods: 43 AML patients were included; 34 patients (with a median age 28 years) received myeloablative allogeneic PBSCT from a matched sibling donor while 9 patients (with a median age 36 years) received PBSC autograft. All patients had a normal karyotype (NK), FMS-like tyrosine kinase 3 internal tandem duplication (FLT3 ITD) negative and were in CR1.

Results: After a median follow up of 21.5 months (0.3- 46.5), the cumulative 2-year OS and DFS in the allogeneic group were 73.5% and 70.6% respectively, compared to 74.1% and 64.8%, respectively in the autologous group ($p=0.690$ and 0.768). Increasing number of consolidation cycles (>3) and lower CD34 stem cell dose were associated with lower relapse rates and higher DFS in the autologous group.

Conclusion: Preliminary data show a comparable outcome of autologous compared to allogeneic PBSCT in patients with AML-NK and FLT3 ITD negative in CR1. In absence of matched sibling donor, autologous PBSCT may provide an acceptable post remission therapy for patients with low risk molecular profile.

Keywords: AML; Autologous PBSCT; Normal karyotype; FLT3-ITD

Introduction

Despite high complete remission rates with anthracycline/cytarabine-based induction therapy in de-novo acute myeloid leukemia (AML), most patients relapse. Given the heterogeneity of outcomes among AML patients after conventional chemotherapy, establishing an optimum role for auto-transplantation especially for patients lacking a suitable HLA matched donor has been challenging [1].

AML patients with normal karyotype (AML-NK) represent an intermediate-risk cytogenetic category and are the most heterogeneous group in clinical outcome [2]. Whether autologous transplantation should be applied for AML NK in CR1 is still debatable as this strategy was initially developed for patients lacking a matched sibling donor [3]. Therefore, AML patients without a suitable allogeneic donor might be considered potential candidates for auto-transplantation taking into consideration a number of biological factors that can affect the

outcome of auto-transplantation, mainly karyotype and high risk molecular markers as FLT3-ITD status [3,4].

Although patients receiving an allogeneic transplant had a lower relapse rate compared to autologous and chemotherapy arms, allogeneic transplantation is usually associated with higher TRM and some studies found that there was no difference in OS at 4 years between allo- and auto-transplantation in AML [5]. On the other hand, results of autograft for AML showed a reduction of non-relapse mortality (NRM), probably due to better supportive therapy. In most studies, leukemia-free survival ranges from 40 to 50% at 3 years. These results are encouraging, especially considering that autologous HSCT can be now offered to AML patients up to 65 years and beyond [6]. Novel molecular and cytogenetic stratification methods allowed the transfer to auto-transplantation AML patients who could benefit from this procedure as a post-remission therapy [7].

The current study aims to compare the outcome of allogeneic versus autologous peripheral blood stem cell transplantation (PBSCT) in adult AML-NK patients and FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) negative status in first complete

remission (CR1) regarding toxicities of transplant procedure, transplant related mortality (TRM), disease free survival (DFS) and overall survival (OS) after a uniform conditioning regimen in both groups.

Patients and Methods

Between 2012 and 2015, 43 AML- NK patients, FLT3 ITD negative underwent PBSCT in CR1 at National Cancer Institute (NCI) and Nasser Institute of Health (NIH), Cairo, Egypt. Patients with t (8; 21), inv (16) or t (15; 17), age <15 yrs, patients with biphenotypic leukemia and those with history of antecedent hematologic neoplasia or cytotoxic chemotherapy were excluded. Eligible patients were genetically randomized according to the availability of HLA-matched sibling donor into 2 categories: 34 patients in the allo-PBSCT group and 9 patients in the autologous PBSCT group. All research protocols were approved by Institutional Review board. All patients gave informed consent for the transplant.

Pre-transplant remission status was confirmed by morphological analysis of bone marrow and flow cytometry analysis for minimal residual disease (MRD) status of leukemia associated immunophenotype. Patients were considered MRD negative if <0.1%. Patients were admitted in transplant Unit to start pre-medications then high dose chemotherapy and stem cell infusion till complete neutrophil and platelet recovery.

Treatment

Before PBSCT, all patients received (3+7) Induction therapy consisting of 100 mg/m² Ara-C as continuous infusion for 7 days and Idarubicin 12 mg/m² IV for 3 days (days 3-5) and varying cycles of consolidation chemotherapy consisting of high dose Ara-C 1500 mg/m² IV infusion/12 hrs for 3 days or high dose Ara-C and mitoxantrone (HAM regimen) (Table 1).

Graft	No of Induction cycles (regimen)		No of Consolidation cycles (regimen)		
	1	2	2	3	4
Allo (n=34)	20 (3+7)	12 (3+7)	15 (HDAC) 2 (HAM)	10 (HDAC)	7(HDAC)
Auto (n=9)	7 (3+7)	2 (3+7)	2 (HDAC)	2 (HDAC)	5 (HDAC)

3+7: Ara-C + Idarubicin, HDAC: High dose Ara-C, HAM: High dose Ara-C + mitoxantrone

Table 1: Number of induction and consolidation cycles prior to transplantation

Conditioning regimen

In allogeneic group, Flu/BU regimen was given to 11 patients (median age 39 years), while 23 patients received BU/Cy regimen (median age 26 years). In autologous group, all patients received BU/Cy regimen (median age 31 years). Flu/BU regimen consisted of Fludarabine 30 mg/m² for 5 days (-10 to -9), then days (-4 to -2) and Busalphan 4 mg/kg/6 hrs/day PO for 4 days (-8 to -5). Bu/Cy regimen consisted of Busalphan 4 mg/kg/6 hrs/day PO for 4 days (-7 to -4) and cyclophosphamide 60 mg/kg/day every 2 hrs IV infusion for 2 days (-3 to -2).

Allo-HSCT

DNA typing for human leukocyte antigens (HLA) class I (A, B, C) and class-II (DRB1, DQB1) was performed by polymerase chain reaction sequence specific oligonucleotide probes (PCR-SSO) [8]. All donors were 6/6 HLA matched siblings. Prior to mobilization, donors were injected with G-CSF (filgrastim, 5 ug/kg SC daily for 5 days). Donors stem cell collection was performed with COBE Spectra cell separator (Gambro, Lakewood, CO, USA) using Spin-Nebraska protocol [9]. CD34 stem cells were counted using a monoclonal antibody CD34 Class III, BIRMA-K3 (DAKO) by Flow cytometry (Coulter EPICS, Coulter electronics, Hialeah, FL, USA) using ESHAGE protocol. Minimum stem cell dose collected was 3×10⁶ viable CD34+ cells/kg recipient's body weight. All patients received apheresis product on day 0.

Auto PBSC harvest

Cyclophosphamide 1.5 gm/m² IV infusion over 2 hours and 10 ug/kg filgrastim was used for mobilization on days 6 to 9. Stem cells were harvested on days 9 ± 10 ± 11. PBSCs were cryopreserved till patients received conditioning regimen then were re-infused to patients 48 hrs after the last day of high dose chemotherapy (day 0).

GVHD prophylaxis

All allografted patients received cyclosporine-A (CSA) at a dose of 3 mg/kg/day IV from day 1 until oral intake was possible then shifted to oral dose 3-5 mg/kg/day divided on two daily doses to keep a CSA trough level between 150-200 mg and maintained till day 180 then gradually tapered off. Methotrexate was given at a dose of 15 mg/m² IV on day +1, then 10 mg/m² on days +3, +6, and +11.

Supportive care

All patients were treated in protective isolation rooms with positive pressure ventilation. All patients received prophylactic antibacterial (levofloxacin), anti-fungal (fluconazole), anti-herpes (acyclovir), and anti-pneumocystis jiroveci therapy (trimethoprim/sulfamethoxazole) starting from 2 days before conditioning regimen till end of immunosuppression. Febrile neutropenia was treated with piperacillin/tazobactam and amikacin and in case of persistent fever switched to imipenem (or meropenem) with or without the addition of amphotericin-B or voriconazole. Packed RBCs and platelet transfusions were given to maintain Hb >8 gm/dl and platelets >10×10⁹/L, respectively. Blood products were irradiated and filtered for leukocyte depletion.

Hematopoietic recovery Post-transplant

Neutrophil and platelet engraftment were defined as three successive days with absolute neutrophilic count (ANC) 0.5×10⁹ /L and platelet count 20×10⁹/L without transfusion.

Outcome definitions

TRM was defined as mortality from any cause directly related to conditioning regimen or due to graft rejection. Relapse was defined as clinical or hematological leukemia recurrence. OS was calculated from time of transplant till death from any cause. DFS was calculated from time of obtaining a clinically documented CR till the time of first evidence of relapsed disease.

Chromosomal banding analysis

Chromosomal banding analysis was performed by G banding techniques according to standards methods [10]. Unstimulated BM blast cells were cultured for 24 hours in RPMI 1640 with L-Glutamine and 25 mM HEPES (Cambrex Bioproducts, Belgium) supplemented with 15% FCS (Cambrex Bioproducts, Belgium) and penicillin/streptomycin mixture 1000 U Pen/10000 ug Strept (Cambrex Bioproducts, Belgium) (complete medium). On the second day, metaphases were stopped with colcemid for 30 min and treated with hypotonic 0.075 M potassium chloride (KCl) solution for 30 min at 37°C. Cells were then fixed in methanol: acetic acid (3:1). At least twenty metaphase cells were analysed using Cytovision Software (Applied Biosystem) for each sample after trypsinization and staining slides with Giemsa. Karyotypes were described according to International system for Human Cytogenetic nomenclature [11].

FLT3-ITD detection

All samples were analyzed for FLT 3 gene ITD exon 11 after extraction of genomic DNA from MNC using a PCR method. The use of exon 11 specific primers allowed covering the whole JM and the first part of TK – 1 domain where most of the reported mutations are located. Fifty to 100 ng of genomic DNA was amplified in a 50 ul-reaction containing a master mix 10 mM Tris HCl (PH 8.3), 50 mM KCl, 1.5 mM MgCl₂, 200 uM of each deoxyribonucleotide triphosphate (dNTPs), 2.5 units Taq DNA polymerase, 40 pmol of each primer, 6% dimethylsulphoxide (DMSO) and DW till a total volume of 50 µl. PCR Amplification process consisted of 40 cycles of denaturation at 94°C for 30 sec, annealing at 50°C for 45 sec and extension at 72°C for 1 min. Final extension (one cycle) at 72°C for 7 min. Sequence of primers used: Sense 5'-CAATTTAGGTATGAAAGCC-3' and Antisense 5'-CAAACCTCTAAATTTTCTCT-3'. Ten ul of the PCR product were electrophoresed on 2% agarose gel stained with ethidium bromide for 40 min and photographed. Size marker ø x 174 Hae III was used [12].

Statistical analysis

All analyses were performed using the statistical package for social sciences (SPSS) software version 20. Comparison between groups was performed using independent samples t-tests for quantitative variables and p-values<0.05 were considered statistically significant. Survival analyses were calculated using Kaplan Meier test and survivals of the 2 groups were compared by Log-rank (Mantel-Cox) test [13]. Probability of relapse and treatment related mortality was calculated using cumulative incidence curves [14].

Results

Forty three patients underwent PBSCT. Allogeneic group included 34 patients: 16 males and 18 females with a median age of 28 years (16-49). Autologous group included 9 patients; 2 males and 7 females with a median age of 36 years (20-50).

Leukapheresis

In allogeneic group, median number of leukapheresis days was one day (1-2). Median Total CD34 count was 6×10⁶/Kg (3–14×10⁶). In autologous group, median number of leukapheresis day was one (1-4 days) and median CD34 count was 3×10⁶ /Kg (2.4–4.1×10⁶).

Haematopoietic reconstitution

Time needed till hematopoietic recovery was longer in allogeneic compared to autologous group. Mean duration of hospital stay was 39.7 days in allogeneic group and 37.6 days in the autologous group (Table 2).

	Mean days for TLC>500×10 ⁹ /L	Mean days for TLC>1000×10 ⁹ /L	Mean days for PLT>25000×10 ⁹ /L
Allogeneic group	10.8	12.2	9.4
Autologous group	9.2	10.2	6.8
P value	<0.001	0.034	0.001

TLC: Total Leukocytic Count ; PLT: Platelets

Table 2: Haematopoietic reconstitution of AML patients

Graft versus host disease (GVHD)

aGVHD occurred in 14/34 (41%) allotransplanted patients; 4 patients were grade I (11.8%) while the remaining 10 patients (29.4%) were grade II-IV aGVHD. Grade III-IV aGVHD occurred in 6 patients (17.6%). Chronic GVHD occurred in 19 (55.8%) patients; 2(5.8%) had limited form while 17(50%) developed extensive cGVHD, mainly related to use of PBSC as a graft source (Table 3).

	Allo (n:34)	Auto (n:9)
Febrile neutropenia	34 (100%)	9 (100%)
Bacterial pneumonia	5 (14.7%)	3 (33.3%)
Fungal pneumonia	4 (11.7%)	1 (11.1%)
Herpes zoster infection	4 (11.7%)	0 (0%)
Sinusitis	3 (8.82%)	1 (11.1%)
Skin infection	1 (2.9%)	0 (0%)
Eye infection	1 (2.9%)	0 (0%)
Septic shock	4 (11.8%)	1 (11%)

Table 3: Infectious complications

In allo group, oral mucositis occurred in 16 patients (47.1%), hemorrhagic cystitis in 5(14.7%), hepatic toxicity in 16(47.1%), renal toxicity in 4(11.8%), osteoporosis in 3(8.8%), DVT in 0 (0%), thrombotic thrombocytopenic purpura (TTP) in 1(2.9%), Internal Jugular vein (IJV) thrombosis in 1(2.9%) and cerebral haemorrhage in 1(2.9%). In autograft group, same complications occurred in 4(44.4%), 3(33.3%), 4(44.4%), 1(11.1%), 0(0%), 1(11.1%), 0(0%), 0(0%) and 0(0%), respectively.

TRM

Occurred in 2 allografted patients (5.9%) while none (0%) of autografted patients died during transplant procedure. Both deaths in the allo-group were due to refractory infection caused by profound neutropenia.

DFS

Median follow-up period was 21.5 months (0.3 - 46.5). At the last follow up, 23/34 (68%) patients in the allogeneic group were free of disease versus 6/9 (66%) patients in the autologous group (Table 4). Cumulative risk of relapse was 32% in allografted versus 33% in autografted patients. The cumulative DFS at 24 months was 70.6% in the allogeneic group and 64.8% in the autologous group ($p=0.768$) (Table 4 and Figure 1).

	No.	Cumulative survival at 24 months	p-value
OS			
Allo.	34	73.5%	0.690
Auto.	9	74.1%	
DFS			
Allo.	34	70.6%	0.768
Auto.	9	64.8%	

Table 4: Cumulative OS and DFS at 24 months.

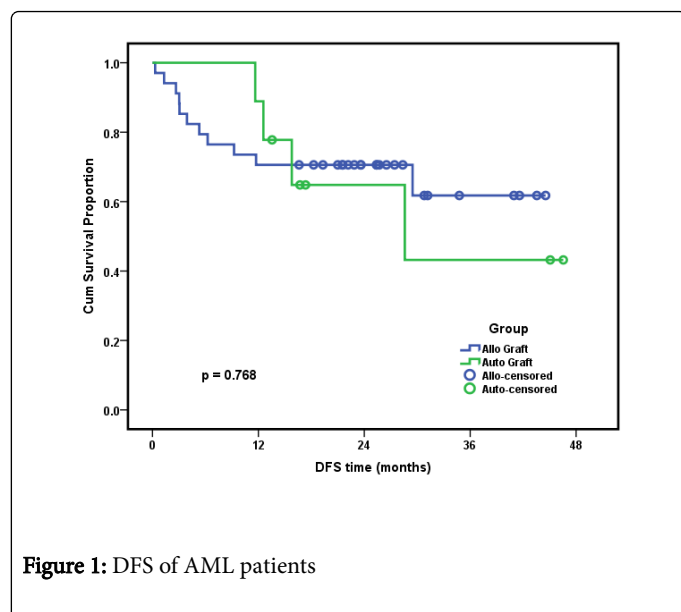


Figure 1: DFS of AML patients

OS

At last follow up, 25/34 patients (73.5%) were alive in the allogeneic group versus 7/9 (78%) patients in the autologous group (Table 4). The cumulative OS at 24 months was 73.5% in the allogeneic group versus 74.1% in the autologous group ($p=0.690$), (Table 4 and Figure 2).

Causes of death

9/ 34 (26.5%) patients died in the allogeneic group. Death was due to septic shock in 2 patients from febrile neutropenia after conditioning. Two other patients died due to cerebral haemorrhage and haemoptysis following severe thrombocytopenia. Two deaths were due to relapse. Three patients died due to extensive complicated

cGVHD, bacterial pneumonia and TTP, respectively. In the autologous group, 2/9 patients (22.2%) died due to relapse.

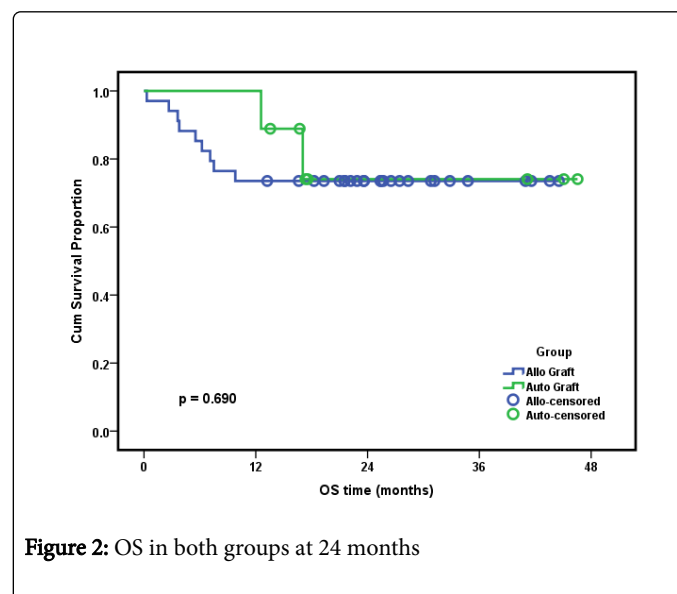


Figure 2: OS in both groups at 24 months

Discussion

Ultimate post-remission strategies for AML-NK in CR1 who lacks an HLA identical donor is still not well defined. Autologous PBSCT is potentially curative for many patients and could be a valid option for patients who lack a suitable donor especially if they are negative for high risk molecular markers as FLT3-ITD [5].

Controlled prospective trials comparing consolidation chemotherapy with autologous BM transplantation and biological randomization to myeloablative allogeneic HSCT from an HLA-identical matched sibling donor conducted in the mid-1990s favoured allogeneic BM strategy because of a lower probability of relapse, despite the high incidence of TRM of up to 30% [15-18]. Autotransplantation during this period was performed with a BM graft and led to lower TRM rates of 8-20%. Recently, TRM was found to be significantly lower after autologous PBSCT and the reported TRM in many series was less than 5% [19-21]. Here we report a TRM of 0% as no patients died during the autograft procedure. We were interested in determining the effect of the lower TRM rate obtained with PB autografts and whether this benefit translated into better outcomes compared with those of allogeneic PB transplantation. We reported a similar survival between both groups (74% vs 73%, $p=0.690$), respectively. We could assume in our study that this was due to lower contamination with leukemic cells in PB than BM grafts.

We also found but in a different way than others that intensity of pre-transplant therapy, measured by number of cycles of consolidation had an impact on the outcome of autografted AML patients [22]. Consolidation chemotherapy is essential because autografted patients without prior consolidation relapse. In our study, patients who received four cycles of consolidation had better outcome than others. Two patients in the autograft group received only 2 cycles of HDAC as consolidation relapsed. A third patient received 3 cycles of consolidation also relapsed. None of the 5 patients who received 4 cycles relapsed. So specifying only two cycles of consolidation chemotherapy prior to collection of cells is questionable for our

patients, especially that the induction dose of AraC in our regimens is only 100 mg/m² and 1500 mg/m²/12 hrs in consolidation doses.

Despite the many prospective trials of post-remission treatment for AML in CR1, a definitive role for autologous transplantation remains uncertain. Several systematic reviews suggest an advantage of matched sibling donor HSCT for patients in CR1 with high risk and, possibly, intermediate risk AML at diagnosis [5]. More recent studies have compared patients treated on the basis of whether they do or do not have a donor, as we did, which has the advantage of avoiding the bias of eliminating higher risk patients who relapse before assignment to autotransplantation or to consolidation chemotherapy.

The role of autologous transplantation in AML in CR1 as a post-remission therapy is still under evaluation despite the many prospective trials in this field. Most studies favour allogeneic HSCT for high and intermediate risk at diagnosis [5]. More recent works compare and categorize patients' outcome on basis of donor availability to eliminate the bias of patient's referral to autotransplantation. The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and the Swiss Group for Clinical Cancer Research Collaborative Group (SAKK), proved a lower TRM and relapse rate for PB autotransplantation (4%) in comparison with consolidation chemotherapy (58% versus 70%, respectively; P=0.02) [15]. However, a higher risk of relapse was seen in PB autografts versus allogeneic HSCT, especially in patients over 40 years [16,18,22]. In our autografted patients, we found that those who received 4 cycles of consolidation chemotherapy had the lower CD34 cell dose and consequently the lower risk of relapse. This finding may suggest that PB grafts with higher CD34 count may include mobilized leukemic cells resulting in greater graft contamination and risk of relapse [23,24].

Our preliminary data suggest that given similar OS at 2 years between allo- and auto-PBSCT (73% versus 74%), post-remission strategies for AML in CR1 lacking a matched sibling donor should include consideration of autologous PBSCT with appropriate stratification of patients according to molecular prognostic markers. In recent years, therapeutic options for AML patients lacking an HLA identical donor are becoming challenging, especially after the introduction of haplo-identical donor transplantation. This procedure can facilitate allografting for almost every patient. However, given equivalent results between auto- and allogeneic group, we think that as a post-remission strategy, autologous PBSCT can be addressed to AML-NK, FLT3-ITD negative patients in CR1 who lacks an HLA matched donor. This should include as a priority older age patients and those with comorbidities unfit for haplo-identical transplantation. In addition, treating AML patients adequately with a higher number of consolidation cycles initially, affect the outcome of auto-transplantation and reduces relapse rate. The 5 years follow-up period with more recruitment of AML patients candidate for autograft will prove the benefit of this procedure.

Conflict of Interest

The authors have declared no conflict of interest.

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