RESULTS OF HEMATOPOIETIC CELL TRANSPLANTATION IN PEDIATRIC LEUKEMIA

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Abstract- Hematopoietic cell transplantation (HCT) is an accepted treatment for acute myeloid leukemia (AML) in first remission, the treatment of choice for chronic myeloid leukemia (CML) and high risk groups of ALL who relapse with conventional chemotherapy. We assessed results of HCT for pediatric leukemia in our center. A total of 92 children, 63 with diagnose of AML, 23 with ALL and 6 with CML received allogeneic transplantation from HLA full matched siblings (57.6%) and autologous transplantation (42.4%). Source of hematopoietic cells were peripheral blood 83.7%, bone marrow 15.2% and cord blood 1.6%. The median transplanted nucleated cells were 6.4 ± 4.7 $\times 10^8$ /Kg (body weight of patients) and mononuclear cells were 5.5 ± 2.9$\times 10^8$/Kg. The most common conditioning regimens were cyclophosphamide + busulfan. Prophylaxis regimen for GVHD was cyclosporin ± methotrexate. GVHD occurred in 50 (54.3%) patients. Eighty five of children had engraftment, 26 (28.6%) relapsed and 57 (62%) are alive. The most common cause of death was relapse (68.6%). Five years overall survival of patients with AML and ALL were 49% and 44% respectively and disease free survival of them were 52% and 49%. One year overall survival and disease free survival of CML was 57%. Overall survival increased with increasing age of patients at transplantation time (P = 0.06). Longer survival significantly related to earlier WBC and platelet recovery (P < 0.0001 and P = 0.006 respectively). Considering acceptable overall and disease free survival of patients after HCT, we concluded that is a good modality in treatment of leukemia of children.

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INTRODUCTION

Leukemia is the most common malignancy in children accounts about 41% of all malignancies occurs in children younger than 15 years old. Acute lymphoblastic leukemia (ALL) accounts for 77%, acute myeloid leukemia (AML) 11%, chronic myeloid leukemia (CML) 2-3%, juvenile chronic myeloid leukemia (JCML) 1-2% and remainder are variety of leukemia do not fit to classic definition for above diagnosis (1). ALL in 70-80% cases of children are cured by conventional chemotherapy except high risk groups who relapse with conventional chemotherapy. Disease free survival (DFS) rate of ALL with conventional chemotherapy is 15-65% and relapse rate is 30-70% but with hematopoietic cell transplantation (HCT) becomes 70-80% and 0-10% respectively. HCT is accepted for AML in first remission with DFS of 55-83% (2). HCT is the treatment of choice for CML. HLA identical sibling transplantation results 80% long term DFS (2).

We assessed results of HCT for pediatric leukemia in our center.

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MATERIALS AND METHODS

Ninety two children, including 53 boys (57.6%) and 39 girls (42.4%), have been transplanted from 1991 till June of 2005 in bone marrow transplantation center of Shariati Hospital consecutively. We obtained informed consent from parents of all children.

Sixty three (68.5%) patients had AML, 23 (25%) had ALL and six (6.5%) had CML. All patients were in remission. They have received allogeneic or autologous HCT from bone marrow (BMSC), peripheral blood (PBSC) or cord blood (CBSC). Conditioning regimens were cyclophosphamide + busulfan, cyclophosphamide + Cytosar + VP16, busulfan + Cytosar, busulfan + fludarabine, busulfan + idarubicin, busulfan + VP16 and cyclophosphamide + VP16.

Prophylaxis regimen for GVHD (graft versus host disease) was cyclosporin ± methotrexate. We followed them in our post BMT clinic after discharge weekly during first month, every two weeks till day +100 and there after according to condition of each patient. We have considered status of disease, primary cytogenetic, cell dose of transplanted hematopoietic cells, duration of hospitalization, frequency of GVHD and its treatment, day of neutrophil recovery (WBC > 0.5×10^9/L), day of platelet recovery (platelet > 20×10^9/L), CMV infection, day of relapse, time of death and cause of death. Data were analyzed with SPSS version 10.

RESULTS

The median age of children was 12 ± 3.8 (2.2-15) years. The median age of donors was 14 ± 7.39 (8 mo-30 y) years. Fifty three (57.6%) have received allogeneic transplantation (from 24 female donors and 29 male HLA full matched siblings) and 39 (42.4%) patients have received autologous transplantation. Source of hematopoietic cells were 77 (83.7%) from peripheral blood, 14(15.2%) from bone marrow and cord blood 1.6%. (Table 1- shows kind of transplantation and source of stem cells in each disease).

The median transplanted nucleated cells was 6.4 ± 4.7 (1- 24.5) × 10^8 /Kg body weight of patient and the median of transplanted mononuclear cells was 5.5 ± 2.9 (0.43-16) × 10^8/Kg. The most common conditioning regimens were cyclophosphamide (60 mg/Kg/day × 2) + busulfan (4 mg/Kg/day × 4) for 45 (48.9%) patients and cyclophosphamide (60 mg/Kg/day × 2) + Cytosar (1000mg/m^2/BID for 3 days) + Vp16 (500 mg/m^2/day × 3) for 25 (27.2%) patients.

Fifty six children (60.9%) had normal cytogenetic, 8 (8.7%) were positive for Philadelphia chromosome, 4 (4.4%) were hyperdiploid and remainder had other cytogenetic abnormality.

Seventy four (80.4%) patients were in first complete remission, 15 (16.3%) in second and three (3.3%) in third complete remission. GVHD occurred in 45 patients (48.9%), 51.1% acute, 46.7% acute and chronic together and 2.2% chronic alone. It was treated in 13.2% patients only with cyclosporine, 35.2% of cases with cyclosporine and prednisolone and others with cyclosporine and prednisolone in combination with mycophenolate mofetil (MMF), anti thymocyte globulin (ATG) or thalidomide .The most common clinical presentation of acute GVHD was skin-gastrointestinal involvement in 50%, skin-gastrointestinal-liver involvement in 20.5% and only gastrointestinal or skin involvement in 13.6% of patients. 16.7% had grade one, 38.1% had grade two, 33.3% had grade three and 11.9% had grade four of acute GVHD.

The most common presentation of chronic GVHD was skin involvement (66.7%). Veno-occlusive disease occurred in 3 patients.

Table 1. Kind of transplantation and source of stem cells in each disease

	Kind of transplantation			Source of cells			
	ALLO	AUTO	Total	PBSC	BMSC	CBSC	Total
AML	31(49.2%)	32(50.8%)	63(100%)	54(85.7%)	8(12.7%)	1(1.6%)	63(100%)
ALL	16(69.6%)	7(30.4%)	23(100%)	18(78.3%)	5(21.7%)		23(100%)
CML	6(100%)		6(100%)	5(83.3%)	1(16.7%)		6(100%)

Table 2. Incidence of engraftment, relapse and death in each disease

	Alive		Relapse		Engraftment	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**
AML	40 (63.5%)	23 (36.5%)	17 (27.4%)	46 (72.6%)	58 (92.1%)	5 (7.9%)
ALL	13 (56.5%)	10 (43.5%)	9 (39.1%)	14 (60.9%)	22 (95.7%)	1 (4.3%)
CML	4 (66.7%)	2 (33.3%)		6 (100%)	5 (82.3%)	1 (16.7%)

Positive microbial cultures were seen in 31 patients (33.7%). CMV antigenemia were seen in 9 patients during hospitalization or after that which have been treated with ganciclovir for 19 days.

The median time to achieve WBC > 0.5×10^9/L was 11 ± 7.18 (6-52) days after transplantation. There were not any significant differences in allogeneic or autologous HCT in this median time (P = 0.548). The median time to achieve platelet >20×10^9/L was 13 ± 8.78 (1-64) days after transplantation. It was 16.6 ± 10.46 in allogeneic HCT and 12.8 ± 4.3 in autologous HCT with significant difference (P = 0.025).

Eighty five (92.4%) of children had engraftment. Twenty six (28.6%) relapsed and 24 of them have been died. (Table 2 shows the incidence of engraftment, relapse and death in each disease).

Fifty seven (62%) are alive and 35 (38%) dead. The most common cause of death was relapse (24 patients, 68.6%) and other causes of death were GVHD, multiorgan failure, sepsis and hemorrhage.

The relation of disease with kind of transplantation, source of hematopoietic cells, engraftment, death and relapse were not significant (P > 0.001). There were not any significant differences between allogeneic and autologous BMT in terms of engraftment frequency (P = 0.45), relapse (P = 0.062) and death (P = 0.169). There were not significant differences between PBHC and BMHC for incidence of GVHD (P = 0.23), engraftment (P = 0.93), relapse (P = 0.5) and death (P = 0.46). Patients who received PBHC, 56% had acute and chronic GVHD with each other and 44% had acute GVHD alone. Patients who received BMHC 80% acute GVHD alone and 20% had both acute and chronic. The median time from diagnosis to transplantation was 10 months (4 mo-9 y). The median hospitalization period was 41 days (11 to 163 days). Hospitalization period for allogeneic transplantation was 47 days (20-163) and for autologous 16 days (11-69) (P = 0.0001). Five years overall survival was 47% and five years disease free survival was 51% in all patients. Five years overall survival of patients with AML and ALL were 49% and 44% and five years disease free survival of them were 52% and 49% respectively. One year overall survival and disease free survival of CML was 57%. One patient with ALL has been alive for 14 years. (Fig. 1).

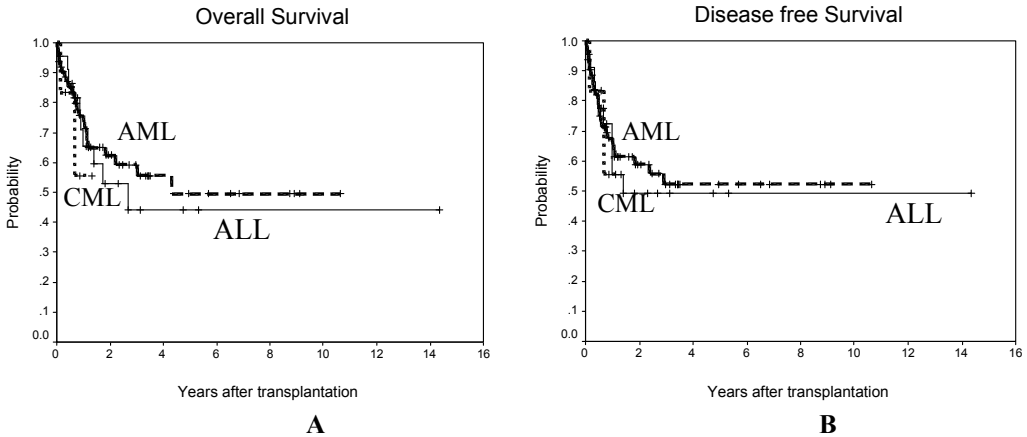

Fig. 1. Overall survival (A) and disease free survival (B) in each disease.

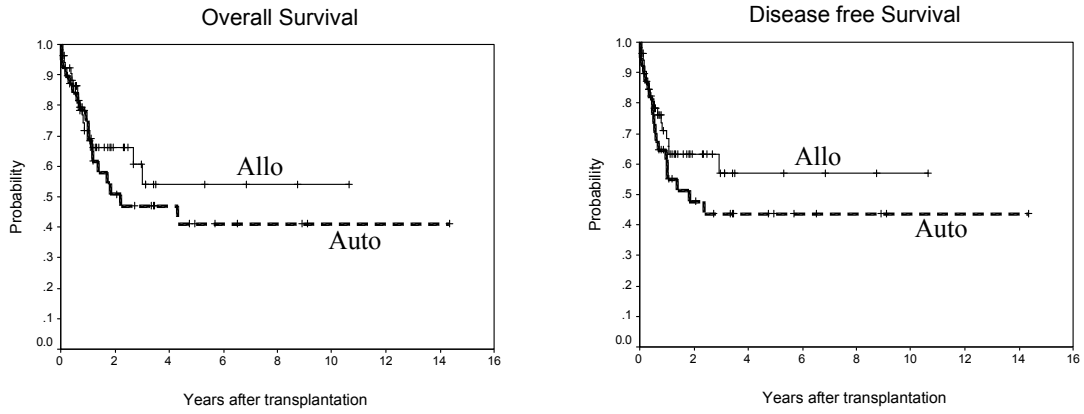

Fig. 2. Overall survival (A) and disease free survival (B) in allogeneic and autologous.

Five years overall survival of allogeneic transplantation was 54%and autologous was 41% and disease free survival of them was 57% and 44% respectively (Fig. 2)

The median time from transplantation to relapse was 6 months (1.5-35 mo) and to death was 8.5 months (7d -51.7 mo).

Overall survival and DFS had not any significant relation to sex of patients, sex and age of donors, type of disease, number of remission, kind of transplantation, source of hematopoietic cells and hematopoietic cell dose, duration of hospitalization and duration of diagnosis to time of transplantation.

Overall survival increased with increasing age of patients at transplantation time (P = 0.06 and OR = 0.923).

Longer survival significantly related to WBC and platelet recovery (WBC > 0.5×10^9/L, P < 0.0001 and OR = 1.09 and platelet > 20×10^9/L P = 0.006 and OR = 1.047).

DISCUSSION

According to our study, (68.5%) patients had AML, (25%) had ALL and (6.5%) had CML which is compatible with the prevalence and indication of SCT in leukemia. Fifty three patients (57.6%) have received allogeneic transplantation 39 (42.4%) patients have received autologous transplantation. Most of patients (80.4%) were in first complete remission**,** so the effect of number of remission can not be assessed on mentioned factors.

Fortunately, 92.4% of children have been engrafted. Most common cause of death was relapse (68.6%). GVHD occurred in 48 (48.9%) of patients which had not significant effect on their OS and DFS. Prevalence of acute GVHD in BMHC was more than PBHC. Patients with autologus HCT had platelet > 20×109/L earlier than allogeneic HCT, 12.8 ± 4.3 versus 16.6 ± 10.46.

Five year overall survival was 47% and disease free survival was 51%. Overall survival increased with increasing age of patients at transplantation time. Longer survival significantly related to earlier WBC and platelet recovery. Overall survival and disease free survival had not significant differences in AML and ALL. No significant differences were observed for overall survival and disease free survival between allogenic and autologous SCT (P = 0.42, P = 0.26).

In Taiwan 1994 to February 2003, 23 children with leukemia or myelodysplasia underwent matched-unrelated-donor bone marrow transplantation. Engraftment was achieved in 91.3% of cases. Acute graft-versus-host disease (GVHD) occurred in 18 of 21 patients who engrafted (85.7%). Event-free survival for all patients was 24.46 ± 9.24%. (3)

In Turky, 81 children with AML in first CR, 67 were biologically randomized for allogeneic (n = 31), autologous (n = 20), or peripheral stem cell transplant (n = 16) after completing consolidation treatment, with the remaining (n = 11) dropping out or receiving chemotherapy. Allogeneic trans-plantation is not superior to autologous and

autologous peripheral blood stem cell transplantation (PBSCT) (DFS in 5 years is 61%, 50%, and 75%). The 5 years DFS in the autologous PBSCT group is significantly better than in the autologous BMT group (75% vs. 50%, $P < 0.05$). (4)

219 paediatric patients in Spain with ALL in second remission received allogeneic or autologous hemopoietic cell transplantation depending on the availability of a matched sibling donor. No significant differences were observed for DFS between allogeneic and autologous SCT (5).

A retrospective study of 58 children with AML in second complete remission or with relapsed disease, median age 7.4 years, who received matched related or unrelated BMT in Research Center, University of Washington, Seattle, DFS at 5 years (95% confidence interval) for patients in CR2, with untreated first relapse and refractory disease were 58% (27-80%), 36% (11-63%) and 9% (2-21%) respectively (6).

In Children's Cancer Group (CCG) in Atlanta, patients with AML were assigned randomly to standard or intensive-timing induction chemotherapy. Patients in first complete remission (CR1) and who had a human leukocyte antigen (HLA)-identical, related donor or a donor disparate at a single class I or II locus were no randomly assigned to receive a bone marrow transplant by using oral busulfan (16 mg/kg) and cyclophosphamide (200 mg/kg). Methotrexate only was given for graft-versus-host disease (GVHD) prophylaxis. One hundred fifty patients received transplants. Grade 3 or 4 acute GVHD occurred in 9% of patients. Disease-free survival (DFS) at 6 years was 67% and 42% for recipients of intensive- and standard-timing induction therapies, respectively (7).

There are many studies in which HCT was compared with chemotherapy and in most of them overall survival and disease free survival of HCT is more than chemotherapy (8-13).

In our study we did not camper results with chemotherapy, so we suggest this comparison with match patients.

Conflict of interests

We have no competing interests.

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