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Factors Influencing the Outcome of Hematopoietic Stem Cell Transplantation in Pediatric Acute Myeloid Leukemia: Single Institution Results from Saudi Arabia

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Abstract

Medical records of 73 patients with AML who underwent HCT, 2005-2011. The OS was 51.8% and the EFS were 48%. Median follow-up time for the cohort was 50.667 ± 2.4 months (95%CI: 45.9-55.4). 39 patients were alive with a median follow-up time of 50.1 months (Min: 1.8, Max: 111.8). Sixteen patients survived for more than 5 years (Min: 65.2, Max: 111.8 months). The cumulative incidence of acute GVHD was 6.8 ± 2.9 and of chronic GVHD was 9.9 ± 3.6. Median time to ANC and platelet recovery was 16 days (range 9-37) and 29 days (range 15-180) respectively. Three patients acquired CMV infection after transplant. There was a significant impact of patient's age at diagnosis on the overall survival (Infantile: 100%, others: 45.6% ± 6.4%, P=0.016) and event free survival (Infantile: 100%, others: 40.6% ± 7.1%, P=0.013). Percentage of blasts at transplant, patients or donors gender, donor source and HLA disparity did not significantly affect OS or EFS.

Keywords: Acute myeloid leukemia; Hematopoietic cell transplantation; Factors influencing outcome

Abbreviations: AML: Acute Myeloid Leukemia; ANC: Absolute Neutrophil Count; BM: Bone Marrow; CB: Cord Blood; CR: Complete Remission; EFS: Event Free Survival; GVHD: Graft Versus Host Disease; HCT: Hematopoietic Cell Transplantation; IRB: Institutional Review Board; OS: Overall Survival; SPSS: Statistical Package for Social Sciences; VOD: Venoocclusive Disease.

Introduction

Acute Myeloid Leukemia (AML) accounts for approximately 25% of pediatric leukemia across the world [1]. There has been an enormous progress in the diagnosis, treatment and outcome of pediatric AML during the last decade with survival rates of almost 60% [2,3]. Geographic variation, ethnicity, initial response to treatment and molecular and cytogenetic aberrations affect the outcome [3,4] and in some studies, mitochondrial genome alterations have been found with an increased incidence of high risk AML in children [5]. Similarly, abnormalities of chromosome 5 & 7, presence of *FLT3/ITD* and MRD by flow cytometry, t (6; 9) (p23; q34), MLL gene rearrangement and infancy all point to higher risk AML patients [6-9]. Despite some promising results in the last few years, there are still 35% patients die of the disease and the survivors are left with long term complications [10]. Risk stratification will not only help high risk patients to get treated with modifications in treatment in a timely manner to improve their outcome, but it will also spare the low risk patients from adverse side effects by treatment de-escalation [1-11]. Currently one of the most important challenges in treating AML is the uniformity of the treatment options for different subsets of disease [12]. Various studies have highlighted the role of HCT in treating high risk patients, especially in CR-1, with encouraging Overall survival (OS) and Event free survival rates (EFS) [13-16] and HCT is being considered as a better treatment option for most children with a relapse and with secondary disease [17]. Unfortunately HCT poses some challenges as patients and parents suffer from severe emotional stress [18], growth failure and growth hormone deficiency [19], restrictive pulmonary functions [20], ocular complications [21], post-traumatic stress [22], graft versus host disease, gastrointestinal bleeding, infections [23] and hypertension [24]. With current success of HCT in treating high risk AML and a significant long term follow-up period, blood and marrow transplantation centers across the world are able to gather enough information about its efficacy versus side effects. Keeping in view of its potential success in treating high risk AML, coupled with short term and long term complications, it is very important to have a look at recent patient data with enough long term follow-up, to enable decision makers to evaluate how the use of treatment options impact the outcome of children with AML. We therefore, conducted a retrospective study at our center to evaluate the outcome of HCT in pediatric AML. Determining the factors affecting the overall outcome of HCT, evaluation of overall (OS) and disease free survival (DFS) of our patients at King Faisal Specialist Hospital and Research Center (KFSH and RC) were our primary objectives. Secondary objective was to measure the incidence of post-HCT complications.

Materials and Methods

Our study was conducted at the Department of Pediatric Hematology/Oncology, King Faisal Hospital and Research Center, Riyadh, Saudi Arabia. Children with AML, with age at diagnosis less than or equal to 14 years, and who sought treatment at our institution from January 2005 to December 2011 were included in the data set. These patients were referred to KFSH and RC from all over the Kingdom of Saudi Arabia, as well as from neighboring countries, since the hospital is the main tertiary care, referral center for pediatric HCT

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in the whole region. Seventy three patients were registered in the study. Medical record numbers were identified, after getting approval of the project from our Institution Review Board (IRB). Patient's medical charts were requested from the Medical Records Department and reviewed. The data pertaining to patients' demographics (mainly age and gender), the disease (histology and classification) and response to treatment were collected in a Case Report Form. Two qualified and trained study coordinators conducted the chart reviews and collected the data. Data items extracted included those related to clinical characteristics of the patients, treatment details and the outcome of the HCT. Outcome metrics included overall and event free survival (OS, EFS), cumulative incidence of graft versus host disease (GVHD), count recovery and post-transplant complications.

The data from the patients' medical charts was collated and maintained at the Central Data Unit, Department of Pediatric Hematology and Oncology, in accordance with KFSH&RC policy on data confidentiality, security and safety. Being a retrospective review, no consent/assent was taken from patients and/or the guardians. A waiver of informed consent/assent was sought from the IRB of the hospital. Data was entered on an in-house developed database management system namely PIMS (Patients' Information Management System) from the case report forms. Data set was prepared using IBM Statistical Package for Social Sciences (IBM-SPSS) for Windows® (Version 20). After performing QA of the dataset, descriptive statistics was calculated to describe the patient characteristics, treatment and outcomes. Chi-Square test along with Fisher's Exact Test, were used to find the relationship between dependent variables. OS and EFS were calculated using Kaplan-Meier survival analysis and compared for independent variables identified in the western literature. Cumulative incidence of GVHD was calculated using R (Ver. 3.2.1 from The R Foundation for Statistical Computing Platform).

Results

Medical records of 73 patients who came to KFSH&RC seeking treatment, between 2005 and 2011, and were transplanted for the primary indication of AML, were reviewed. There were forty six (63%) male and twenty seven (37%) female in the data set (Table 1). Six had monosomy 7 and no one had FLT3 gene. Median age at HCT was 7.9 years (range 0.6-14.2) median time to HCT after diagnosis was 6.5 months. All but one patient received myeloablative conditioning. All patients received GVHD prophylaxis. 51 patients received HCT from HLA identical related donors and 22 from other donors (1 or 2 antigens mismatch cord blood (CB) or one antigen mismatch sibling or related bone marrow (BM)). Stem cell source was BM in 55 (75.3%), CB in 17 (23.28%) and peripheral blood (PB) in 1 (1.36%). All patients were in CR at the time of HCT, 54 patients were in CR1, 18 in CR2 and 1 in CR3. The five years OS in our group of patients was 51.8% (Figure 1) and the EFS was 48% (Figure 2). The median follow-up time for the cohort was 50.667 ± 2.4 months (95%CI: 45.9-55.4). 39 patients were alive with a median follow-up time of 50.1 months (Min: 1.8, Max: 111.8). 16 patients survived for more than 5 years (Min: 65.2, Max: 111.8 months). The cumulative incidence of acute GVHD was 6.8 ± 2.9 and of chronic GVHD was 9.9 ± 3.6. Median time to ANC and platelet recovery was 16 days (range 9-37) and 29 days (range 15-180) respectively. Three patients acquired CMV infection after transplant. No one developed VOD, Haemorrhagic cystitis or other major complications. There was a significant impact of patient's age at diagnosis on the overall survival (Infantile: 100%, others: 45.6% ± 6.4%, P=0.016) and event free survival (Infantile: 100%, others: 40.6% ± 7.1%, P=0.013). Percentage of blasts at transplant, patients or donors gender, donor source and HLA disparity did not significantly affect OS or EFS. Infantile AML was associated with superior outcome.

	Number of patients	Overall Survival	P-Value	Event Free Survival	P-Value
Patient's Age at Diagnosis					
≤ 1 year	8 (11%)	100 ± 100	0.016	100 ± 100	0.013
>1 year	65 (89%)	0.456 ± 0.064		0.406 ± 0.071	
Recipient Gender					
Male	46 (63%)	0.446 ± 0.075	0.202	0.403 ± 0.075	0.218
Female	27 (37%)	0.652 ± 0.094		0.654 ± 0.093	
Disease Status at HCT					
CR1	54 (74%)	0.560 ± 0.069	0.141	0.550 ± 0.068	0.060
CR2	18 (24.6%)	0.419 ± 0.122		0.212 ± 0.161	
CR3	1 (1.37%)	0.000 ± 0.000		0.000 ± 0.000	
Donor's Gender					
Male	38 (52%)	0.501 ± 0.084	0.767	0.435 ± 0.090	0.796
Female	35 (48%)	0.540 ± 0.085		0.541 ± 0.084	
HLA Compatibility					
HLA Identical	51 (70%)	0.551 ± 0.063	0.199	0.497 ± 0.083	0.179
Other Donors	22 (30%)	0.446 ± 0.114		0.430 ± 0.104	
HCT Source					
Bone Marrow	55 (76%)	0.524 ± 0.070	0.374	0.474 ± 0.080	0.550
Cord Blood	17 (23%)	0.529 ± 0.121		0.500 ± 0.118	
PBSC	1 (1.7%)	0.000 ± 0.000		0.000 ± 0.000	
Blasts at HCT					
M1	67 (92%)	0.505 ± 0.063	0.460	0.463 ± 0.067	0.510
M2	5 (7%)	0.800 ± 0.179		0.800 ± 0.179	
M3	1 (1%)	0.000 ± 0.000		0.000 ± 0.000	
Cytogenetics at HCT					
Normal	19 (26%)	0.474 ± 0.115	0.499	0.474 ± 0.115	0.518
Abnormal	49 (58%)	0.554 ± 0.073		0.502 ± 0.078	

Table 1: Patients' Characteristics and Outcome Parameter.

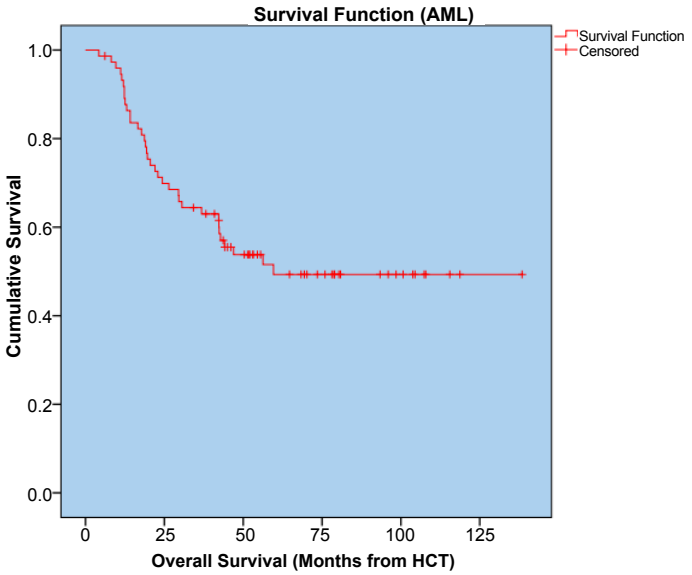

Figure 1: Overall Survival (Months from HCT).

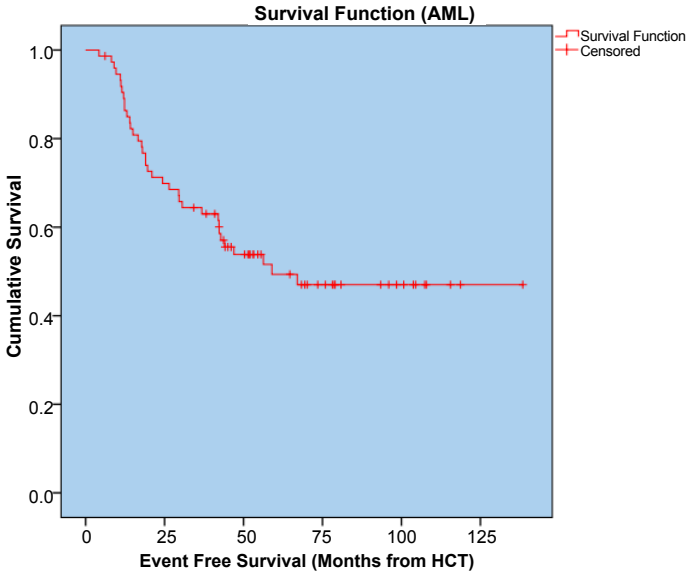

Figure 2: Event Free Survival (Months from HCT).

Discussion

Over the years, a better understanding of risk group identification and administration of risk adapted therapy has resulted in an improved but plateaued outcome [25]. Therefore, new drugs are needed to achieve further improvement [26]. With evolution of HCT in terms of transplantation techniques, donor availability, donor-recipient HLA match, conditioning therapy and other supportive measures, it is rapidly becoming a viable option for the high risk patients. The primary objective of our study was to identify the factors that may have influenced the outcome of AML patients who underwent HCT at our institution. This is because data describing outcomes after HCT for AML in children is very scarce in this part of the world. To our knowledge, this is the first comprehensive study on this topic in the region. Our results demonstrate that patient's age at diagnosis had an impact on the outcome with a better OS and EFS in the infantile group (Table 1), which endorses the improving outcome in infants [9] with HCT is considered the treatment of choice in this age group, if a matched related donor is available [27] HLA disparity did not play any significant role in the outcome in our patients. Ballen et al. also found that outcome among pediatric patients with AML after hematopoietic stem cell transplantation was not affected by donor type [28]. In fact it was shown by Godder et al. that bone marrow transplantation success can actually be increased significantly by encouraging transplants from partially mismatched related donors with good engraftment rates and low GVHD. Except for one, all our patients, at the time of first transplant, received myeloablative conditioning regimen in the form of

BU/CY/ATG, BU/CY/VP-16/ATG and BU/CY/VP-16 [29]. There was no significant impact found on the OS or EFS amongst all the groups. Similar observations were made by Holter-Chakrabarty and his team while evaluating the sequence of cyclophosphamide and myeloablative total body irradiation in hematopoietic cell transplantation for patients with acute leukemia. Recently it is shown that the use of busulfan based conditioning in very young children cause late effect such as dental problems, short stature, pulmonary dysfunction and abnormal pubertal developments [30]. European society for blood and transplantation also advocates the use of Treosulfan based conditioning as a potential substitute for TBI and Busulfan for its low toxicity and increased efficacy [31].

The whole cohort of our patients was in complete remission at the time of HCT [32]. This is a significant step in the course of our treatment as various studies have endorsed the fact that the disease status at HCT does play a crucial role in determining the outcome, and patients in CR-1, if transplanted with a matched donor, would compensate for the poor outcomes usually associated with high risk AML in children treated alone with chemotherapy [13-33]. Assessment of minimal residual disease at transplant may also influence the outcome as it helps in risk stratification and adopting a more individualized approach during HCT [13-33]. In our group of cases, 51 patients received HCT from HLA-identical related donors compared to 22 from others (1 or 2 antigens mismatch cord blood (CB) or one antigen mismatch sibling or related bone marrow(BM), but that did not affect the outcome [34]. Godder and Lee observed similar results in their studies, which revealed that for HCT conducive AML patients, in the absence of fully matched or an unrelated donor, transplantations can be performed from partially matched and unrelated donors with good outcome [29,35]. We also found no significant difference in the outcome with different sources of transplant in our patients which is comparable to other studies that advocate the use of unrelated cord blood with great effect in patients who are candidates for HCT but lack a suitable sibling donor [29,35]. Milano et al. documented in his study that especially for pre transplant minimal residual disease patients, transplantation with cord blood donor was associated with the similar overall survival as with an HLA- matched, un related donor [36,37]. Chinese also came up with a similar result and also noticed a lower incidence of chronic GVHD in cord blood donor transplant compare to unrelated donor and with a similar outcome with a suitable sibling [38]. Post-HCT toxicity is a cause of concern in most transplant centers and is highlighted in various studies [39]. In our cohort,three patients acquired CMV infection after transplant and no one developed VOD, Haemorrhagic cystitis or other major complications, which could be the due to optimally matched donors and a good post HCT nursing support [40-44].

Our study also aimed to measure the incidence of acute and chronic Graft versus host disease. All patients received GVHD prophylaxis. Fifty six were given MTX/CSA, seventeen received CSA/ Steroids and one received Steroid only. There were 17 incidences of acute and 7 of chronic GVHD but with an insignificant cumulative incidence. Acute GVHD is a major cause of morbidity and mortality in the first 3 months after transplant, although recent data has shown that one the main successes in HCT is the declining rates of acute graft versus host disease [45].

Since the five years survival rates of leukemia children have improved, the acute and long term toxicities of chronic GVHD have now major impact on organ function, quality of life and overall survival [46], and there is a great need than ever to develop novel strategies to overcome and reduce the incidence of chronic GVHD.

There is a lot of variation observed in the treatment of AML patients and different institutes adopt different strategies for considering HCT based on the clinician experience, availability of an appropriate donor, minimal residual disease, protocols being used in the institutes and the stratification of the disease. Our findings indicate that HCT is a viable option for pediatric AML patients especially for the high risk group [47]. We did not find any factor such as gender of the patient, donor's gender, source of transplant and CR status (CR1, CR2 or CR3) at HCT to significantly affect the outcome. We also appreciate the fact that the measurement of MRD is a pivotal tool for assessing the status of patient at HCT and the outcome afterwards, which our center has not been doing until recently. In most of the cases a HLA-identical sibling is available for HCT in this part of the world, but unrelated cord blood and partially mismatched related donors can also be used otherwise. Despite having good outcomes with busulfan based conditioning in our patients, in view of its long term complications, especially in young children, we strongly recommend to use Treosulfan based conditioning as a potential substitute for TBI and Busulfan for its low toxicity and increased efficacy. We also observed that complications such as GVHD, venoocclusive disease, hemorrhagic cystitis, infections and other post-HCT problems can be alleviated by a good match and nursing care.

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