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Research Article

Factors Determining Outcome of Hematopoietic Cell Transplantation in Patients with Chronic Myeloid Leukaemiaat King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

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Abstract

Medical records of 13 CML patients who underwent 14 HCTs, 2005-2011. Ten patients were male (71.4%). Median age at HCT was 10.1 years (range 6.1-13.9), median time to HCT after diagnosis was 11.4 months (range 3.5-44.1). 12 patients were in chronic phase 1 (85.7%) at the time of HCT. OS and EFS in our group of patients were 91.7% and 68.8% respectively. Median follow-up time was 77.8±19.3 months (95%CI: 40-115.6). Median time to ANC and platelet recovery was 18 days (range 14-30) and 27.5 days (range 17-37) respectively. Two patients developed CMV infection (14.3%), one developed new malignancy (7.1%) and 4 developed relapse (28.6%). No one developed GVHD, VOD, or haemorrhagic cystitis. There was a trend toward superior OS and EFS in (female patients, patients with female donors, patients who were transplanted > one year after diagnosis, and recipient of TKI post-transplant) but did not reach statistical significance. Relapsed patients were males, one received TKI post-transplant and one transplanted > one year after diagnosis. Female patients or donors, patients transplanted > one year after diagnosis, and recipient of TKI post-transplant were associated with trend of better outcome.

Introduction

Chronic Myeloid Leukaemia (CML) is accounted around 2% of newly diagnosed leukaemia in paediatric population younger than 15 years and 9% in 15-19 years of age [1]. With incidence of 1per million children and adolescents less than 20 years of age [1]. It is rarely affected young children less than 2 years of age [2]. Presentation of the disease in the children almost same compared to adult patients. However, it is noticed that the paediatric population have more aggressive features [3].

Although the treatment of CML was changed dramatically 15 years ago, since introduction of Tyrosine Kinase Inhibitors (TKI) [4], Stem Cell Transplant (SCT) is still considered the curative option for the paediatric patients to eliminate the lifelong TKI requirement [5]. There are limited publications regarding stem cell transplant in paediatric CML and most data regarding the prognostic factors for stem cell transplant in children with chronic myeloid leukaemia comes from studies in adult patients, in this study we review the factors that affect outcome of Hematopoietic Cell Transplantation (HCT) for Chronic Myelogenous Leukaemia (CML) in retrospective analysis.

Materials and Methods

Our study was conducted at the Department of Pediatric He-

matology/Oncology, King Faisal Hospital and Research Center, Riyadh, Saudi Arabia. Children with the diagnosis of CML, with age at diagnosis less than or equal to 14 years at the time of acceptance, 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&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 in the whole region.

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 were collected 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. Primary measures were to review the outcome of management in terms of disease status and with reference to OS and EFS, treatment related toxicities and outcome of disease with respect to the use of CB vs BM. Secondary measure was to measure the incidence of acute and chronic GVHD. 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

Ten patients were male (71.4%). Median age at HCT was 10.1 years (range 6.1-13.9), median time to HCT after diagnosis was 11.4 months (range 3.5-44.1). All patients were more than one year of age at diagnosis. All patients were in haematological, cytogenics, and molecular remission at the time of HCT.12 patients were in chronic phase 1 (85.7%) at the time of HCT. 12 patients (85.7%) received HCT from HLA-identical related donors and 2 (14.3%) from a one antigen mismatched sibling. Stem cell source was BM in all. All patients were given myeloablative conditioning regimen (Busulfan and Cyclophosphamide). OS and EFS in our group of patients were 91.7% and 68.8% respectively. Median follow-up time was 77.8±19.3 months (95%CI: 40-115.6). Median time to ANC and platelet recovery was 18 days (range 14-30) and 27.5 days (range 17-37) respectively. Two patients developed CMV infection (14.3%), one developed new malignancy (7.1%) and 4 developed relapse (28.6%). No one developed GVHD, VOD, haemorrhagic cystitis, seizures, encephalopathy, hypertension or other complication. There was a trend toward superior OS and EFS in (female patients, patients with female donors, patients who were transplanted > one year after diagnosis, and recipient of TKI 6 months' post-transplant but did not reach statistical significance. Relapsed patients were males, one received TKI post-transplant and one transplanted > one year after diagnosis. There was no statistically difference in the mean dose of CD34 between the two groups.

Discussion

Huge strides in the management and classification of Acute Myeloid Leukaemia (AML),One of the most important challenges faced, is the uniformity of the chemotherapy protocols used, as with the exception of APL, AML has been treated as a homogenous disease and hence a protocol for a disease subtype has not been evolved. Many studies have highlighted the role of Stem Cell Transplant (SCT) in treating high risk patients, especially in CR-1, with encouraging Overall Survival (OS) and Event Free Survival Rates (EFS). SCT is also considered a superior treatment option for most children with a relapse and with secondary disease. In the other hand, it is still a significant challenge to paediatric oncologists in choosing the appropriate treatment options for paediatric patients with CML.

Chronic myeloid leukaemia is myeloproliferative disease characterized by proliferation of granulocytes without loss of differentiation. It is accounted around 2% of newly diagnosed leukaemia in paediatric population younger than 15 years and 9% in 15-19 year of age[1]. It is rarely affected young children less than 2 years of age [2]. There is no noticeable different in presentation of the disease between them in comparison to adult population. However, it is noticed that they have more aggressive clinical features and this could be related to the difference in CML biology in children which affect the presentation, progression and response to treatment [3]. Most of the patients presented with fatigability,

splenomegaly and other symptoms and signs of bone marrow infiltration like anaemia and thrombocytosis. Hyperleukocytosis symptoms could be seen in advanced cases.

The introduction of molecular target therapy as tyrosine kinase inhibitors 15 years ago, has revolutionized the management and change the treatment methods dramatically [4]. Prognostic scores which used in adults, is difficult to be applied in paediatric patients [6]. There was high discrepancy between the Sokal (age, spleen size,platelet and blast count) [6,7], Hasford [6,8], EUTOS (splenic size and basophilic percentage) [6,9] and modified sokal young score when it was applied by Suttorp et al in 90 children (1-18 years) [10].

Millot et al tried to validate the significance of early molecular and cytogenetic response in 40 treated children with imatinab and the results were compatible when compared with adult CML patients as the early response considered as prognostic factors for long term survival. The patients with < 10 % BCR/ABL1/ABL after 3 months of imatinab had high cytogenetic and molecular response at 12 months compared to others [11]. NCCN and ELN guidelines consider 3, 6, and 12 months TKI response as important factor to detect treatment failure and to decide change of the treatment if required [12]. The prognostic factor of TKI response in paediatric patients with CML need further studies and evaluation.

Prognostic factors: determination the phase of the disease at transplant is the most significant factor in OS post BMT. The OS fall from 50-90 % in the chronic phase to 40-50 % in CML patients in accelerated phase and to 10-20 % in blasticphase[13,14]. Younger patients at transplant is one of the good prognostic factor for survival rate [15]and it is considered as 0 score for less than 20 years in EGBMT risk assessment score [16]. The IBMTR reported that the 5 years OS is 70 % in patients under age of 50 years including paediatric group who underwent transplant in the first year of diagnosis and 60% in 1391 patients who were transplanted more than 1 year after diagnosis of CML(IBMTER,http://wwwibmtrorg2002).

Most of the CML patients presented with splenomegaly and it has no effect on the outcome [17,18] other than refractory cytopenia in massive splenomegaly which can be reduced dramatically with low dose of radiation [19,20]. Since it is difficult to categorize paediatric CML patients using adult score and treat them based on adult guidelines, allogenic stem cell transplant is considering the only curative option for lifelong survival and elimination of long term using of TKI [21]. Median time to ANC and platelet recovery was 18 days (range 14-30) and 27.5 days (range 17-37) respectively.

Transplant Related Mortality (TRM) rate was 7% for allogenic SCT in the CML IV study with median age of patients is 37 years [22] compared to 0% after 52 months follow up of 12 patients in Italian experience done by Giona et al [23] and the same results in 100 day follow up for allogenic SCT in CR1 and less than 21 years of age as reported by Health Resources And Services Administration (HRSA) .In our study two patients developed CMV infection (14.3%), one developed new malignancy (7.1%). No one developed GVHD, VOD, haemorrhagic cystitis, seizures, encephalopathy, hypertension or other complication.

The relapse rate in our institution is 28.6 % during median follow-up time 77.8±19.3 months. CIBMTR cohort analysis estimate the relapse rate of CML patients and it was 11% at 1 year, 18 % at 3 years and 21% at 5 years post SCT which is close to the relapse rate in our study (5) . OS and EFS in our group of patients were 91.7% and 68.8% respectively. Although the number of the patients is still small, it can be deduced that the there was a trend toward superior OS and EFS in (female patients, patients with female donors, patients who were transplanted > one year after diagnosis, and recipient of TKI post-transplant) but did not reach statistical significance and could be related to the small population and There was no statistically difference in the mean dose of CD34 between the two groups.

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