

Outcomes of Allogeneic Stem Cell Transplant in Chronic Myeloid Leukaemia - A Single-Centre Experience from Pakistan

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ABSTRACT

Objective: To determine indications and outcomes of stem cell transplant in Chronic Myeloid Leukemia in a tertiary care centre in Pakistan.

Study Design: Retrospective longitudinal study

Place and Duration of Study: Armed Forces Bone Marrow Transplant Center, Rawalpindi Pakistan, from Jan 2002 to Jan 2019.

Methodology: Retrospective analysis of all the patients who had undergone transplants for chronic myeloid leukaemia at our centre from 2002 to 2019 was done. Cases enrolled included patients of both genders and any age for whom data related to disease status and follow-up post-transplant was available. Patients with incomplete records and follow-ups were excluded from the study.

Results: Out of 73 patients, data from 53 patients was analyzed. At a median follow-up of 40 months, overall survival was 72%. Survival in patients <40 years was better (78%) compared to the >40 years (50%). Among the three conditioning regimens, Bu16Cy120 was the most commonly used (n=35, 66%) and had better overall survival (n=29, 83%) though statistical significance could not be established ($p=0.172$).

Conclusion: In addition to the established indications of resistance or intolerance to tyrosine kinase inhibitors for bone marrow transplant in CML, the non-availability/ affordability, young age, and lack of access to novel drugs can be included in underdeveloped countries like Pakistan.

Keywords: Bone marrow transplantation, Chronic myeloid leukaemia (CML), Conditioning regimen, Survival analysis.

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INTRODUCTION

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder of stem cells. It is characterized by the rapid proliferation of clonal myeloid precursors in bone marrow, leading to a rise in total leucocyte count in blood, a proportion comprising immature myeloid cells.¹ Many patients are asymptomatic, with incidental findings of leukocytosis or splenomegaly heralding the diagnosis.²

Tyrosine kinase inhibitors (TKIs) are the standard of care in treating CML.^{3,4} Imatinib was the first TKI approved for the treatment of CML in 2001, followed by second (Nilotinib, Dasatinib) and third generation (Ponatinib). Survival for patients diagnosed with CP undergoing treatment with TKI exceeds 90%.⁵

The tremendous efficacy of TKIs has relegated hematopoietic stem cell transplant (HSCT) to second place.⁶ About 400 patients in Europe have undergone HSCT for CML annually since 2007, with ~150 of these patients in the chronic phase without relapse (CP1).⁷

The current paradigm of CML treatment involves the indefinite use of a TKI with regular monitoring. The possibility of stopping treatment in patients who achieve deep molecular response and maintaining it for (3-5) years has been proposed.^{8,9} This idea of treatment-free remission applies to a small subset of carefully selected patients. Long-term TKIs use is associated with toxicities besides financial cost. Considering these challenges, the indications for transplant often differ in our setup from those of advanced countries. The relatively young age of CML patients and sibling donor availability make HSCT an alternative option. However, more local data must be needed to influence clinical decisions on this aspect. For this reason, we analyzed records of CML patients who underwent HSCT regarding demographics, indications, and transplant outcomes in our centre, Armed Forces Bone Marrow Transplant Center Rawalpindi, Pakistan.

METHODOLOGY

The retrospective longitudinal study was conducted safter taking approval from the Hospital Ethical Committee (IRB/013/AFBMT/Approval/

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2022), non-probability consecutive sampling was done by scrutinizing hospital records for CML patients who underwent allogeneic HSCT at AFBMTC, Rawalpindi, between 2002 and 2019.

Inclusion Criteria: Cases included patients of both genders and any age for whom adequate information related to disease, donor, conditioning chemotherapy and follow-up outcome data was available.

Exclusion Criteria: Patients with incomplete records were excluded from the data analysis.

Variables recorded included basic demographic, disease phase at the time of HSCT, conditioning regimen and source of stem cells. Data for survival, disease remission, relapse and graft vs. host disease (GvHD) were analyzed.

Statistical Package for Social Sciences (SPSS) version 24.0 was used for the data analysis. The outcomes measured include overall survival (OS) and GvHD-free relapse-free survival (GRFS) concerning gender, source of stem cells and conditioning regimen. Survival curves were plotted using the Kaplan-Meier estimates.

RESULTS

A total of 53 patients were included in the final analysis. All patients had undergone matched sibling donor transplants. Conventional cytogenetics were positive for Ph chromosome t(8:21) and qPCR positive for BCR-ABL1 transcript encoding (p210). In risk stratification, 39(73%) patients had an EBMT risk score of 2 or less, 9(17%) had a risk score of 3, and 5 patients had an EBMT risk score of 4. The treatment modalities used before the transplant included Hydroxyurea and TKIs. Thirty-three (60%) received TKIs. The remaining 22(40%) had no access to TKIs.

Out of 33 Patients on TKI, 20(71%) achieved a complete hematologic response, two achieved a complete cytogenetic response, and three failed to respond. Since lifelong treatment with a TKI for them was deemed impractical because of cost and availability. In the remaining, n=12 (23%) had refractory disease to TKIs (first and second generation). All patients received a myeloablative condition regimen. Three subgroups of patients were defined based on conditioning chemotherapy used (1) Bu16Cy120, used in n=35 (66%) (2) Bu16Cy200 in 7(13%) patients and (3) Bu16Cy120 + Etoposide in 6(11%). The record was lacking for the remaining five patients. No ABO mismatch was present in 34(64%) of cases; in 6 (11.3%) cases, there was a bidirectional mismatch; significant ABO mismatch was

in 7(13.2%) cases. The remaining (n=6, 11.3%) candidates had minor ABO mismatches.

Intravenous Methotrexate and oral Cyclosporin for GvHD prophylaxis were continued for three months post-transplant. GvHD, febrile neutropenia, and mucositis were the most common post-transplant complications. Grade-1 acute GvHD occurred in n=21 (39%) of patients, 5(9.4%) had GvHD of Grade II or higher. Two patients (3.7%) developed grade III skin GvHD, while 3(5.6%) had grade IV GvHD. Chronic GvHD occurred in 7(13%) of patients. Oral mucositis was documented in 19(35%) patients.

At a median follow-up of 40 months (range 3-204 months), the overall survival (OS) was 38(72%), while GvHD-free, relapse-free survival (GRFS) was n=36 (68%). Younger patients (<40 years) had a significantly better outcome, with OS of 32/41(78%) compared to n=6/12 (50%) for those ≥ 40 years (Figure-1). Overall survival in patients who had received bone marrow harvested stem cells alone was n=19/22 (86.4%) compared to n=18/23 (78%) for PBSC (Figure-2).

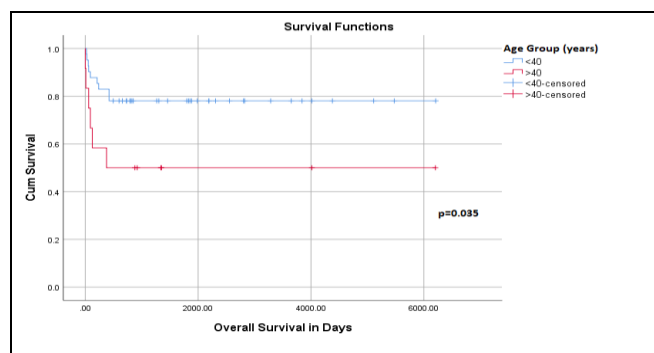


Figure-1: Overall Survival (OS) in relation to Age of patient (n=56)

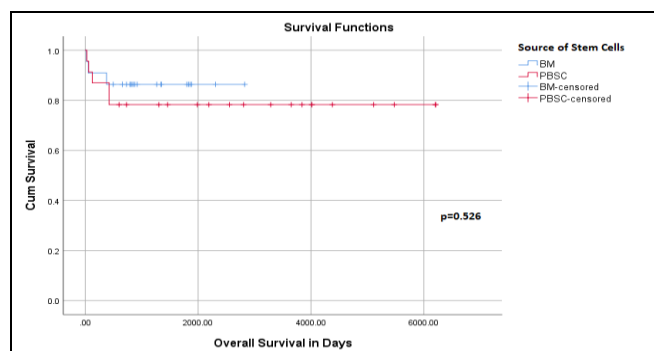


Figure-2: Overall Survival (OS) in relation to Stem Cell Source (n=56)

Regarding the conditioning regimen, data was available for 48 patients. Bu16Cy120 had superior OS

n=29/35 (83%), compared to Bu16Cy200 4/7 (57%) and Bu16Cy120 Etoposide 4/6 (66%) (Figure-3).

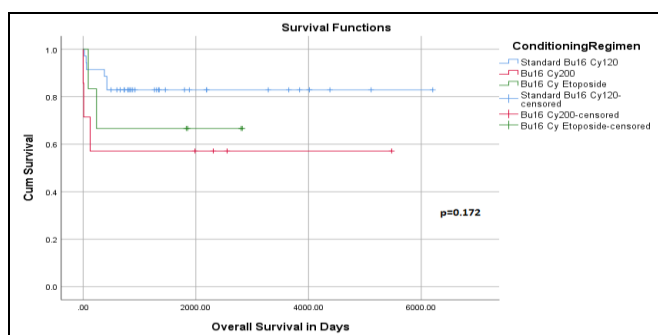


Figure-3: Overall Survival (OS) in relation to Conditioning Regimen (n=56)

DISCUSSION

This study aimed to establish a third-world perspective on bone marrow transplantation in CML patients. Outcome indication HSCT for CML varies from region to region based on highly effective targeted therapy availability. In developed countries, the CML treatment paradigm has dramatically changed with the advent of TKIs. With it, the indications for transplant have been narrowed down to TKIs intolerance or resistant disease.^{9,10} Imatinib achieves a complete cytogenetic response (CCyR) rate of 92% and a major molecular response (MMR) rate of 83% in treatment naïve patients.^{11,12}

In resource-constrained countries, in addition to the established indications, the treatment choice is often influenced by the financial impact of a particular therapy.^{13,14} In Pakistan, the monthly cost of Imatinib is around 140,000 Pakistani Rupees. The average monthly income of a household is estimated to be about PKR 35,000.¹⁵ With no universal health insurance system in place, this makes lifelong TKI therapy impractical for most patients. Non-availability of third and fourth-generation TKI is yet another problem for those who can afford it. So only, the first and second-gen (Imatinib and Nilotinib) are available. Therefore, in a country like Pakistan, stem cell transplant is still in second place for all those patients who are non-affording and resistant to treatment or those who cannot afford lifelong TKIs.

These challenges of the third world necessitate treatment guidelines tailored to the needs and resources. Disease dynamics, especially relatively young patients in our country compared to the developed world, is another aspect influencing therapeutic strategy. However, data from first-hand experience in

Pakistan needs to be included to guide such decisions. Our hospital-based retrospective study from Pakistan revealed the demographics of CML patients,¹⁶ having a median age of patients (n=461) was 36 years, compared to around 50 years internationally. In our study, the median age of patients when taken for transplant was 29 years. Younger age at presentation, availability of sibling donor, poor long-term close monitoring of treatment with TKIs and non-affordability makes HSCT a viable option.

The Swedish CML registry reported data on 118 patients transplanted between 2002 to 2017. TKI resistance was the most common transplant indication, 62.5% in patients diagnosed with CML in CP at <65 years of age, and the cumulative probability of undergoing allogeneic-HSCT within five years was 9.7%. Overall, 5-year survival was 96.2%, 70.1% and 36.9% for BMT in the first CP, second or later CP, and accelerated phase or blast crisis, respectively.¹⁷ In our study, overall survival, irrespective of disease phase, was 72%. Patients in the advanced phase of the disease had very good GRFS (87%); the effect was, however, most likely due to refinement in conditioning regimen and younger age of patients. Disease phase-dependent BMT outcomes with the current standard of care conditioning regimen and advancement of post-transplant disease monitoring and strategies like donor lymphocyte infusion (DLI) needs to be validated by multivariate analysis on larger cohorts. In our study, survival outcome in the two genders was significantly skewed, with better survival in females (93.8%) than males (62.3%). The difference was not statistically significant, and the effect of confounding factors like age, disease phase, and conditioning regimen needs to be considered, which is not currently the aim of this study. Another important observation was the effect of the conditioning regimen on overall survival. Conditioning with Bu16Cy120 had the best outcome in terms of GRFS. The difference failed to translate to statistical significance; however, was in line with international data.¹⁸

LIMITATIONS OF STUDY

The limitations of the study, include its retrospective nature, relatively small sample size, and a proportion of data that came from the early 2000s, a time when TKIs were not available in Pakistan. However, considering this data coming from the largest of countries' registries having experience with BMT carries its importance; it provides valuable information regarding the role of transplant in CML from the perspective of an underdeveloped country and would help physicians managing patients with CML.

CONCLUSION

Despite the effectiveness of TKIs, HSCT holds an important place in treating CML in patients with TKIs resistance or intolerance. In underdeveloped countries, these indications may be extended to the non-affordability of TKIs, in young patients with sibling donors available. However, extensive, multi-centre studies are the way forward.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

JR: & FH: Conception, study design, drafting the manuscript, approval of the final version to be published.

QNC: & SKM: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

MAK & NS: Data data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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