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A Retrospective Analysis of Autologous Stem Cell Transplantation Outcomes in Adult Philadelphia Chromosome Positive-Acute Lymphoblastic Leukemia

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Abstract

Introduction Philadelphia chromosome positivity (Ph +) is a poor prognostic feature in adult acute lymphoblastic leukemia (ALL). Allogenic hematopoietic stem cell transplantation in first complete remission (CR1) is recommended. There is limited literature on the role of consolidation autologous stem cell transplantation (ASCT). This study was undertaken to assess the potential of consolidation ASCT in CR1 in adults with Ph + ALL.

Objectives The aim of this study was to analyze the safety and efficacy of ASCT in CR1 in adults with Ph + ALL.

Materials and Methods Adult patients diagnosed with Ph + ALL who underwent ASCT in CR1 after modified ALL-BFM95 protocol from 2015 to 2017 were included. Patients who achieved major molecular response or better were considered for ASCT with cyclophosphamide-total body irradiation regimen and peripheral blood stem cells infused on day 0. Toxicities as per Common Terminology Criteria for Adverse Event v4.0, disease-free survival (DFS), and overall survival (OS) were assessed. Inclusion criteria: Following patients were included—patients aged 18 years and above diagnosed with Ph + ALL; patients receiving BFM-95 induction chemotherapy protocol; patients who achieved CR after induction therapy; nonavailability of human leukocyte antigen match from a matched sibling donor or matched unrelated donor. Exclusion criteria: Patients not willing or unfit for ASCT and patients planned for allogenic hematopoietic stem cell transplantation were excluded.

Results Six adult patients with Ph + ALL underwent ASCT in CR1 (median age: 23 [range: 19–36] years, five patients were males [83%]). Imatinib was started at a median of 11 days from the start of induction IA (range: 10–21). Five patients achieved

Keywords
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morphological CR after induction 1A and, one patient at the end of induction 1B. The median time to ASCT (from diagnosis) was 8 months (range: 6.4–13). All the six patients had disease relapse and died due to progressive ALL. The median DFS and OS were 19.2 months and 23.3 months, respectively.

Conclusion Consolidation ASCT yielded poor outcomes in this study. There was a significant delay from diagnosis to ASCT, which might have impacted the results.

Introduction

The most common cytogenetic abnormality associated with adult acute lymphoblastic leukemia (ALL) is the Philadelphia chromosome, and it is seen in 20 to 30% of all adult ALL.[1,2] Philadelphia chromosome is due to the reciprocal translocation between long arms of chromosome 9 and 22: the Abelson (*ABL1*) oncogene on chromosome 9 translocate to the breakpoint cluster region (*BCR*) oncogene on chromosome 22, resulting in a fusion oncoprotein with constitutive tyrosine kinase activity leading to excessive proliferation of leukemic cells.[3]

Ph + ALL carries a poor prognosis in adult patients. However, the incorporation of tyrosine kinase inhibitors (TKIs) with standard chemotherapy has significantly improved outcomes.[4] The treatment of choice remains allogeneic hematopoietic stem cell transplantation (allo-HSCT) at first complete remission (CR1).[4] However, in patients who lack a human leukocyte antigen (HLA) match or in older patients, several reports suggest the advantage of consolidation autologous stem cell transplantation (ASCT) in Ph + ALL.[5–7] The absence of the graft-versus-leukemia effect is a major drawback with ASCT.

Data on adult Ph + ALL outcomes from India are scarce. In a multicenter study by the Indian Acute Leukemia Research Database (INwARD) of the Hematology Cancer Consortium, Ph + ALL was diagnosed in 17% of all adolescent and young adult (AYA) ALL patients (15–29 years).[10] The 2-year event-free survival among patients with Ph + ALL was 48 versus 59% for patients with Ph-ALL ($p = 0.01$).[8]

The present study was undertaken to analyze the real-world outcomes of ASCT in CR1 in adult patients with Ph + ALL due to the lower uptake of consolidation allo-HCT in India due to various socio-economic factors.

Materials and Methods

In 2015, based on the GRAALL study,[5] after obtaining a written informed consent, we started offering ASCT in adult patients with Ph + ALL in CR1. Ph + ALL was confirmed by the demonstration of *BCR-ABL* by qualitative reverse transcriptase-polymerase chain reaction (RT-PCR) in peripheral blood. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Ethics Committee Approval

As this study was a retrospective analysis of patients with Ph + ALL who underwent ASCT between 2015 and 2017, Institutional Ethics Committee approval (IEC) was not required. However, an IEC waiver was obtained: IEC Waiver form- Ref No-IEC/2021/Dec01. The patients received standard chemotherapy as per the modified Berlin-Frankfurt-Munster-95 (ALL-BFM95) protocol.[9] Imatinib was incorporated along with standard chemotherapy as soon as *BCR-ABL* by qualitative RT-PCR was positive.

Inclusion Criteria

Following patients were included for the study: Patients aged between 18 and 50 years and above diagnosed with Ph + ALL; patients receiving ALL-BFM95 induction chemotherapy protocol; patients who achieved CR after induction therapy; nonavailability of HLA match from a matched sibling donor or matched unrelated donor.

Exclusion Criteria

Patients not willing or unfit for ASCT and patients planned for allo-HSCT were excluded.

Induction IA consisted of prednisolone (60 mg/m^2, D1–D28), vincristine (1.5 mg/m^2, D8, D15, D22, D29), without daunorubicin and L-asparaginase and three doses of intrathecal (IT) methotrexate; IT was started after clearance of blasts in peripheral blood. Bone marrow studies were performed after the end of IA.

The second induction (IB) from day 34 to day 61 comprised of tablet 6-mercaptopurine (60 mg/m^2, D34- D61), injection cyclophosphamide (1gm/m^2 D34, D61), injection cytarabine arabinoside (75 mg/m^2, 4 blocks) and two more doses of IT methotrexate. *BCR- ABL* by quantitative RT-PCR was done at the end of IB. Morphological CR was defined as less than 5% blasts in the bone marrow aspirate smear with an absence of blasts in the peripheral smear with no extramedullary disease and transfusion independence. If the patient was not in CR after the end of IA, bone marrow studies were repeated at the end of IB. Bone marrow was not assessed for minimal residual disease (MRD) as it was not available at our center during the study period.

Major molecular response (MMR) was defined as *BCR-ABL* transcripts less than or equal to 0.1% by quantitative RT-PCR. Eligible patients were then consolidated with ASCT in CR1.

Cyclophosphamide-total body irradiation (Cy-TBI): cyclophosphamide 60 mg/kg for 2 days and TBI 2Gy twice daily for 3 days were used as a conditioning regimen. Cy-TBI conditioning was chosen because of its myeloablative and adequate immunosuppressive properties ensuring an adequate antileukemic effect, also ensuring homogenous dose distribution to the whole body, including sanctuary sites such as the central nervous system (CNS) and testicles.[5,7]

Stem cells were mobilized from the peripheral blood after priming with granulocyte colony stimulating factor (G-CSF) 10 µg/kg daily for 5 days. Plerixafor 0.24 mg/kg was given 10 to 12 hours before the apheresis. The apheresis was performed on day 5 of G-CSF. Engraftment was defined as peripheral blood neutrophil count more than 500/mm^3 for 3 consecutive days and platelet count more than 20,000/mm^3 for at least 7 days independent from platelet transfusion. All the patients were restarted on imatinib post-transplant upon engraftment.

Statistical Analysis

ASCT with Cy-TBI conditioning-related toxicities, disease-free survival (DFS), and overall survival (OS) were assessed. Toxicities were assessed as per Common Terminology Criteria for Adverse Event v4.0.[10] DFS was defined as the time to relapse of leukemia or death from the date of morphological CR. OS was defined as the time from diagnosis to death. OS after relapse was calculated as the time from disease relapse to death. Data were retrieved from electronic case records or case files, compiled, and analyzed using Microsoft Excel 2016.

Results

Seven patients were screened for the study, and six were included (refused ASCT-1). Six adult patients with Ph + ALL underwent ASCT in CR1 between 2015 and 2017 (►**Table 1**). The median age of the study group was 23 years (range: 19–36); five out of six were males (83%). p190 *BCR-ABL* transcript

Table 1 Patient details

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Day of starting imatinib during IA	D + 11	D + 21	D + 10	D + 12	D + 11	D + 11
Initial dose of imatinib	400 mg o.d. escalated to 600 mg o.d.	400 mg o.d. escalated to 800 mg o.d.	400 mg o.d.	400 mg o.d.	400 mg o.d. escalated to 600 mg o.d.	400 mg o.d. escalated to 600 mg o.d.
End of induction (IA) BM status	CR	Not in CR (CR achieved after IB)	CR	CR	CR	CR
BM prior to ASCT	CR	CR	CR	CR	CR	CR
Quantitative *BCR-ABL* prior to ASCT	0.03%	Undetectable	Undetectable	Undetectable	Undetectable	0.06%
Phase of treatment during which ASCT was performed	Consolidation	2nd maintenance	Consolidation	Consolidation	Consolidation	Consolidation
Time to ASCT from diagnosis (mo)	6.4	13	8.5	8.4	5.9	8
Day of starting imatinib post-transplant and dose	D + 32 600 mg o.d.	D + 33 400 mg o.d. escalated to 600mg o.d.	D + 42 400 mg o.d.	D + 36 600 mg o.d.	D + 33 600 mg o.d.	D + 34 600 mg o.d.
Quantitative *BCR-ABL* post-ASCT	N/D	N/D	Undetectable (+8 mo)	Undetectable (+9 mo)	Undetectable (+8 mo)	N/D
DFS (in mo)	8.9	20.5	59.1	23.2	17.9	10.3
Type of relapse	Medullary	Isolated CNS	Isolated CNS	Medullary	Medullary	Medullary
2nd line TKI and dose at relapse	Nil	Dasatinib 50 mg o.d.	Dasatinib 50 mg o.d.	Dasatinib 50 mg o.d.	Nil	Dasatinib 50 mg o.d.
OS (in mo)	13.2	32.8	68.8	44.4	20.3	14.8
OS after relapse (in mo)	3	11	8.5	5	1.3	3.4

Abbreviations: BM, bone marrow; CNS, central nervous system; CR, complete remission; DFS, disease-free survival; N/D, not done; o.d., once daily; OS, overall survival; TKI, tyrosine kinase inhibitor.

Table 2 Toxicities as per CTCAE v4.0

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Febrile neutropenia	Grade 3	Grade 3	Grade 3	Grade 3	Grade 3	Grade 3
Infections	Nil	CLABSI-Coagulase-negative staphylococcus aureus	Nil	H1N1 bronchopneumonia (not requiring oxygen or ventilatory support)	Acute suppurative otitis media (organism not grown)	Nil
Chemotherapy-induced nausea and vomiting	Grade 3	Grade 2	Grade 3	Grade 3	Grade 2	Grade 2
Mucositis oral	Grade 3	Grade 2	Grade 2	Grade 2	Grade 2	Grade 2
Diarrhea	Nil	Grade 2	Nil	Grade 2	Grade 2	Grade 2

Abbreviation: CLABSI, Central line-associated blood stream infection.

by qualitative RT-PCR was detected in all the six patients. Conventional cytogenetics revealed t(9;22) in two patients (33%) and normal karyotype in the other four patients. CSF study was performed on day 8 after clearance of peripheral blood blasts. None of the patients had CNS disease. The median duration of starting imatinib was D + 11 of IA (range: 10–21). All the patients were compliant with imatinib. Five patients achieved morphological CR after IA and one patient at the end of IB. All the patients achieved MMR or better before ASCT. Among the six patients, five underwent ASCT during consolidation and one during second maintenance. Delay in ASCT was due to prolonged transplant waiting period due to immediate bed nonavailability.

The median time to consolidation ASCT from the start of induction chemotherapy was 8 months (range: 6.4–13). The median stem cell dose was 8.3×10^6 cells/kg (range: 4.6–10.6). The median time to neutrophil engraftment was day 13 (range: 12–22), and platelet engraftment was day 16 (range: 15–32). All patients had grade 2 to 3 nausea and vomiting, grade 2 to 3 mucositis, and grade 3 febrile neutropenia requiring intravenous antibiotics (►**Table 2**). There was no treatment-related mortality. All the patients were restarted on maintenance imatinib between D + 32 and D + 42 post-ASCT and were compliant. Six doses of monthly IT methotrexate were given post-transplant. There were no other imatinib-related toxicities. All six patients relapsed (100%); four patients-medullary relapse and two CNS relapse. Four patients (67%) received dasatinib 50 mg daily at relapse. Dasatinib-related toxicities were not observed; compliance with dasatinib was good.

All six patients died. The median follow-up was 23 months. The median DFS was 19.2 months (range: 8.9–59.1). The median OS was 23.3 months (range: 13.2–68.8). The median survival after relapse was 4.2 months (range: 1.3–11; ►**Table 1).**

Discussion

ASCT in CR1 for Ph + ALL has shown promising results in a few prospective and retrospective studies, including the CALGB study 10001(Alliance), registry data from Acute Leukaemia Working Party (ALWP) of the European Group of Blood and Marrow Transplantation (EBMT), and the GRAAPH 2003 study; the study characteristics are highlighted in ►**Table 3**.[5–7] The GRAAPH 2003 study showed a 4-year DFS of 50% and 4-year OS of 80% in Ph + ALL patients who underwent ASCT in CR1. The

Table 3 Comparison of ASCT outcomes in Ph + ALL with other studies

Variable	GRAAPH 2003 (5)	CALGB 10001(Alliance) (6)	EBMT (7)	Present study
Sample size	10	19	67	6
Conditioning regimen	Cy-TBI	Ara-c/VP 16-TBI	TBI based- 64% Cy-TBI Flu-TBI Chemotherapy-based-(34%) Bu-Cy Bu-Flu Bu-Mel	Cy-TBI
TRM	0	1(5%)	1(1.49%)	0
MRD assessment	Yes	Yes	Variable	No

Abbreviations: ASCT, autologous stem cell transplantation; CALGB, Cancer and Leukemia Group B; Cy-TBI, cyclophosphamide-total body irradiation; EBMT, European Group of Blood and Marrow Transplantation; MRD, minimal residual disease; Ph + ALL, Philadelphia chromosome positivity acute lymphoblastic leukemia; TRM, treatment-related mortality.

CALGB study 10001(Alliance) reported a 5-year OS of 51%, and the data is similar to a large retrospective registry cohort reported by EBMT. Given the favorable outcomes, we adopted this strategy in a real-world setting. While allo-HCT is recommended for adult Ph + ALL patients in CR1, the uptake is far lower in India due to various socioeconomic and psychological factors: the reasons are procedure refusal, lower availability of allo-HCT, including a long wait time at high-volume transplant centers, noncompliance to treatment, and cost; some of these factors have been highlighted already in other studies from the region.[8,11]

In our study, all six patients relapsed and died due to disease. The median DFS was 19 months and the median OS was 23 months. The results of the present study indicate that the outcomes of ASCT were poor. Due to early relapses, the lack of effective salvage chemotherapy options, and financial constraints for further treatment, patients were advised to continue palliative care. All the patients who started dasatinib at relapse had short-term disease remissions. The median survival after relapse was only 4.2 months (range: 1.3–11). The major limitations of the study are the small sample size and being retrospective in nature. In the GRAAPH-2003 study, patients underwent consolidation ASCT after completing a 28-day induction and consolidation chemotherapy protocol.[5] However, in our study, consolidation ASCT was performed at a median of 8 months after initiating induction chemotherapy. This delay could have contributed to the poor outcomes observed in our study. Bone marrow MRD was not assessed post-induction or prior to ASCT during the study period. In the GRAAPH 2003 study, outcomes in patients who underwent post-consolidation ASCT were best in those patients with low or negative MRD levels. MRD assessment was not available at our center during the study period. The lack of MRD assessment in the present study could have contributed to the poor outcomes in our study cohort. There was no treatment-related mortality. Treatment for these patients was supported by the State Health Insurance scheme. Therefore, imatinib was used as a first-line TKI due to the high cost of dasatinib and the nonavailability of generic versions of dasatinib during the study period. After the initial experience with these six patients, the practice was abandoned at our center because it was not practically possible to offer ASCT at our center immediately after initial induction and consolidation therapy as in the GRAAPH 2003 study. These numbers are very small to make definite conclusions against the role of ASCT in CR1 in Ph+ ALL. However, if this must be put into practice, we must ensure that the ASCT is timed early in the course as per published data. Even in the GRAAPH 2003 study, patients who received more than 1 course of high-dose methotrexate prior to ASCT (indicating delay) had worse outcomes.

Conclusion

Consolidation ASCT in patients with Ph + ALL yielded poor outcomes in this study. There was a significant delay from diagnosis to ASCT, which might have impacted the results. In patients who are not willing or unfit for allo-HCT, prospective studies can be undertaken to assess the outcome of ASCT in CR1 after dasatinib-based induction chemotherapy regimens with available data on the MRD status prior to and following ASCT.

Author's Contributions

All co-authors have reviewed the manuscript and have contributed substantially to the present study.

Ethics Approval

As this study was a retrospective analysis of patients with Ph + ALL who underwent ASCT between 2015 and 2017, IEC approval was not required per institutional policy. An IEC waiver form was obtained for the same.

Consent

Informed consent was obtained from all individual participants included in the study.

Funding

None.

Conflicts of Interest

None declared.

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