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ORIGINAL ARTICLE

Outcome of Philadelphia Positive Acute Lymphoblastic Leukemia With or Without Allogeneic Stem Cell Transplantation in a Retrospective Study

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Abstract Philadelphia positive ALL (Ph + ALL) is an aggressive leukemia associated with lower remission rates and poor survival. Current treatment approach for Ph + ALL is chemotherapy along with TKI and CNS directed therapy followed by Allogeneic stem cell transplantation (Allo-SCT). To analyze outcome of Ph + ALL with or without Allo-SCT in the era of universal TKI uses. Retrospectively reviewed medical records of 267 patients who were diagnosed and treated for ALL during study period at our centre. Fifty-one Ph + ALL patients (males = 31, females = 20) out of a total of 267 ALL patients were eligible for the study. Post induction 48 patients achieved complete remission while 1 died during induction. Forty-six patients received further treatment with TKI + CNS directed therapy and thereafter the consolidation therapy with Allo-SCT (n = 16) or chemotherapy + TKI (n = 30).Overall mortality was 7/51 (13.9%) (6/16 transplant related mortalities due to GVHD and infections and 1 induction death). Fifteen out of 46 patients (32.6%) had relapse (1/10 relapse after Allo-SCT vs. 14/24 after chemotherapy) on or after consolidation therapy. At a median follow-up of 17.5 months (2–58 months) of cohort, the median EFS was 22 months (95% CI 10.4–33.5 months). The estimated 4 year EFS and PFS in Allo-SCT versus chemotherapy only group was 36.0 ± 17.9 versus 27.3 ± 9.1% (p = 0.21) and 75 ± 21.7 versus 34.1 ± 10.9% (p = 0.02) respectively. Allo-SCT groups has a better progression free survival than chemotherapy group only. Preventing treatment related mortality can further improve outcome after Allo-SCT Ph + ALL.

Keywords Philadelphia positive ALL · Allogeneic stem cell transplant · Chemotherapy with TKI

Introduction

Philadelphia positive ALL (Ph^+ALL) is an aggressive leukemia associated with lower remission rates and poor survival with 5 year event-free survival (EFS) of less than 20% [1].

Proportion of Ph^+ALL increases with age as from 3 to 5% of pediatric ALL to 25% of adult ALL and nearly 50% of elderly patients above 60 years of age [2–4].

Success of BCR-ABL tyrosine kinase inhibitors(TKI) in chronic myeloid leukemia (CML) patients led to its use in Ph^+ALL patients. Addition of TKI to standard chemotherapy not only improved the remission rates but also improved the depth of remission in these patients which translated into improved survival from 10–20 to 40–50% [5–7].

Current treatment approach for Ph^+ALL is chemotherapy along with TKI and CNS directed therapy followed by Allogeneic stem cell transplantation (Allo-SCT) which still offers survival rates but with associated morbidity and mortality [8].

Here, we are presenting retrospective study of Ph^+ALL patients who received chemotherapy and a TKI followed by consolidation therapy with chemotherapy or Allo-SCT from 1st January 2011 to 30th June 2016 at Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India.

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The aim of the study is to analyse outcome of Ph^+ALL with or without Allo-SCT in the era of universal TKI uses.

Materials and Methods

We retrospectively reviewed medical records of 267 patients who were diagnosed and treated for ALL during study period at our centre and 63 (23.6%) patients were Philadelphia chromosome/BCR-ABL positive. Fifty-one patients were started on treatment thus eligible for the study. The study was approved by the Institutional Review Board.

Ph^+ALL was defined as ALL carrying the t(9; 22) translocation on standard karyotype and/or positivity for BCR-ABL fusion transcript detected by real-time polymerase chain reaction (RT-PCR) analysis.

Treatment Protocol

Induction

The treatment included 4 weeks induction chemotherapy with vincristine, daunorubicin, steroid as per COG0232 or UK-ALL protocols. TKI was given in all patients. Imatinib 400 mg OD was used till February 2012 and thereafter the dasatinib 140 mg daily was used in all Ph^+ALL patients. Post induction assessment included a bone marrow examination and a quantitative BCR-ABL transcript evaluation by PCR. Patients refractory to induction chemotherapy were considered for salvage chemotherapy with Hyper-CVAD regimen. Patient who received all 4 doses (vincristine/daunorubicin) with at least 2 weeks of steroids during induction and 28 days of TKI exposure were considered to have received a mean intensity of 100% of chemotherapy and TKI respectively.

Patients in complete morphological remission further received high dose Methotrexate based (HDMtx) CNS directed therapy with high dose methotrexate @2–5 g/m^2 or Hyper-CVAD-B (high dose methotrexate and high dose Ara-C) for 2–4 cycles.

Consolidation

All patients were considered for Hematopoietic Stem Cell Transplantation (HSCT) after 2 cycles of HDMtx based therapy. Few patients received up to 4 cycles in case of delays in Allo-SCT. Patients eligible for transplant received Matched Related Donor (MRD)or Haplo-identical allogeneic stem cell transplant (HaSCT) as per donor availability. A bone marrow examination and a quantitative BCR-ABL were done for all patients before transplant. Post transplant monitoring included, chimerism analysis at day 30 and day 100, quantitative PCR for BCR-ABL once every 2–3 months, acute and chronic GVHD, Cytomegalovirus (CMV) PCR quantitative assay once every 2 weeks in matched related stem cell transplantation and once every week in HaSCT till day 100.

Patients who were not eligible or those who were not willing for Allo-SCT were continued on consolidation chemotherapy as per COG0232/UK-ALL or Hyper-CVAD regimen based therapy with continuous TKI and monitored for minimal residual disease with quantitative PCR for BCR-ABL every 3–6 months. The follow-up was censored at the 30-Sep-2017.

Definitions

Complete remission(CR) was defined as blasts $< 5\%$ with Absolute Neutrophil Count(ANC) $> 1000/\mu L$ and platelet $> 100{,}000/\mu L$. Relapse was defined a presence of blasts($> 5\%$) in bone marrow or in any extra-medullary site after a previous documented CR. CNS1: no detectable leukaemia cells in the CSF; CNS2: less than 5 white blood cells/microliter and a positive "cytospin" for blasts; CNS 3: more than 5 white blood cells/microliter and a positive cytospin for blasts.

Complete molecular response (CMR) was defined as the absence of a detectable BCR-ABL 1 transcript with a sensitivity of 0.01%. Major molecular response (MMR) was defined as a BCR-ABL1:ABL1 ratio $< 0.1\%$ on the International Scale but not meeting criteria for CMR [9].

Statistical Analysis

Primary study endpoints were EFS defined as the time from diagnosis with ALL until the time of progression of disease, death and lost from follow-up. Secondary endpoint was progression free survival (PFS) defined as the length of time till relapse and overall survival (OS) defined as the length of time from diagnosis till death or last follow up. Patients were censored at the time of transplant/treatment related mortality (TRM) or those who were lost to follow up (LFU) without completing their intensive phase of consolidation chemotherapy and were excluded from PFS calculation. Categorical variables were reported as total number (n) and percentages. Continuous variables were reported as median and inter-quartile range. A two-tailed $p = 0.05$ indicated statistical significance. Survival curves for OS and EFS were plotted according to the Kaplan–Meier method and compared using log rank method. All statistical analyses were performed using SPSS 21.0 statistical software (SPSS 21, IBM SPSS Statistics for Windows, version 21.0; IBM Corp., Armonk, NY, USA).

Results

Out of a 51 eligible patients, 31 (60.7%) were males and 20 (39.2%) were females, with a median age of 35 years (14–76 years). Median WBC count was 49.6 × 10^3/mm^3 (0.7–432.4 × 10^3/mm^3), 6 patients were CNS-3 while rest were CNS-1. Cytogenetic information was available for 42 patients out of whom 16 patients had only Philadelphia chromosome positive, 17 patients had Philadelphia chromosome with additional cytogenetic abnormality, 7 patients had normal cytogenetics while 2 patients had failed cytogenetics study (Table 1). BCR-ABL 1 transcript type was available for 48/51 patients. Transcript type p190 and p210 were found in 13 and 35 patients respectively.

The overall mean intensity of chemotherapy and TKI received during induction in our patients was 82 and 80% respectively. TKI were initiated at a median day 8 (2–39 day) from initiation of induction chemotherapy. Forty-two patients received dasatinib at a median dose of 70 mg/day (50–140 mg) and 9 patients received imatinib at a median dose of 400 mg/day.

Post induction 48 (94%) patients achieved CR while 2 patients were induction failure and lost to follow up. One patient died during induction due to fungal pneumonia. Forty-six (46) patients received further treatment with TKI and CNS directed therapy and thereafter the consolidation therapy with Allo-SCT(n = 16) or chemotherapy + TKI (n = 30) (Fig. 1). Pre-consolidation BCR-ABL assessment by RT PCR was better than MMR in 28 patients (60.8%) and less than MMR in 18 (39%) patients. Seventeen (36.9%) patients achieved CMR while 11 (23.9%) were able to achieve MMR.

Table 1 Demographics of eligible patients

Patient characteristic	N (range)
Age (n)	35 (14–76)
≤ 40 years	31 (60.7%)
> 40 years	20 (39.2%)
Gender	–
Male	31 (60.7%)
Female	20 (39.2%)
WBCs	49,600 (700–4,32,400)
≤ 100,000 (/cumm)	35 (68.6%)
> 100,000 (/cumm)	16 (31.3%)
Hb (gm/dl)	8.9 (4.2–15.2)
Platelets (/cumm)	45,000 (3000–4,41,000)
BM Blasts (%)	88 (8–100)
Peripheral Blasts (%)	62 (0–95)
CNS involved (CNS 3)	6 (11.7%)
Additional Cytogenetics abnormalities	17 (33.3%)
Ph chromosome only	16 (31.3%)
Failed test	2 (6.5%)
Normal karyotype	7 (13.7%)

Chemotherapy related complications: A total of 32 episodes of febrile neutropenia were recorded. Thirty-three bacterial cultures were positive (gram positive bacteria n = 16, gram negative bacteria n = 17) out of which 19 were blood stream infections, 12 were urinary tract infections and 2 positive sputum cultures. Eleven patients were treated for possible invasive fungal infection while 1 patient developed pulmonary tuberculosis. Three patients developed pseudo membranous colitis. Other than infectious complications, 4 patients developed dasatinib induced pleural effusion. The dasatinib was stopped temporarily in all 4 patients which was started later on again in reduced doses. Fifteen patients developed vincristine induced neuropathy (grade 1–2), managed with temporary dose modifications. There were no treatment related deaths in chemotherapy consolidation group.

Stem cell transplant: For MRD transplants (n = 12), conditioning regimens were myeloablative in 9 patients and RIC in 3 patients. For Haplo-identical transplants(n = 4), the conditioning regimens used were non-myeloablative in 3 patients and RIC in one patient (details in Table 2). All patients received post transplant TKI till 2 years. Median day of initiation of TKI was 108 days (55–232 days), 12/16patients received dasatinib at a median dose of 70 mg (50–140 mg); 4 patients did not receive TKI because of early deaths.

Transplant related complications: Post transplant all (n = 16) patients had febrile neutropenia. Eleven culture positive bacterial infections (n = 11, gram negative) were detected out of which blood and urine infections were 2 and 9 respectively. Among other infections seen in post transplant patients 1 patient each developed pulmonary tuberculosis, oesophageal tuberculosis, and herpes-zoster and B K virus infection. Six patients had probable fungal pneumonia. A total of 10 episodes of CMV reactivations were seen (Table 2).

Two patients had grade 4 acute GVHD while 2 patients each had grade 3 and grade 2 acute GVHD. Chronic extensive GVHD was found in 1 patient and 6 patients had chronic limited GVHD. Six patients (37.5%) died in post transplant period owing to transplant related complications with GVHD and infections in 3 patients each.

Relapse: Forty-six patients were eligible for assessment of outcome after consolidation therapy. Overall 15/46 patients (32.6%) had relapse. Six (20%) patients out of 30 patients from chemotherapy only group were lost to follow-up during consolidation, only 24 patients were on follow-up hence incidence of relapse in patients with chemotherapy consolidation was 14/24 (58.3%) patients. In

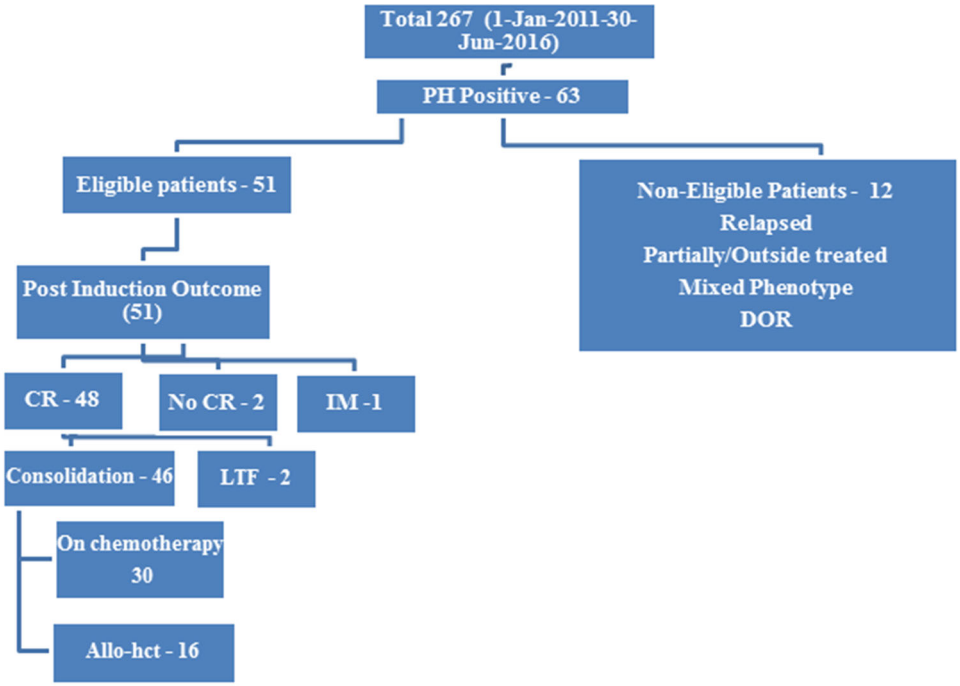

Fig. 1 Flow diagram showing treatment outcomes

Table 2 Allogeneic stem cell transplant characteristics

Variable	No (%)
Donor used	
MRD	12 (75%)
Haploidentical	4 (25%)
Conditioning-MRD (n = 12)	
Myeloablative (n = 9)	
Cy-TBI-12 Gy	5
Bu 12.8/kg-Flu	1
Flu-TBI-12 Gy-PTCy	3
RIC (n = 3)	
Flu-TBI-8Gy-PTCy	2
Bu 6.4/kg-Flu-rATG	1
Conditioning-Haplo (n = 4)	
RIC (Flu-TBI-8Gy-PTCy)	1
NMA (Flu-Cy-TBI-2Gy-PTCy)	3
Acute GVHD	
Grade 2	2 (14%)
Grade 3	2 (14%)
Grade 4	2 (14%)
Cumulative episodes of CMV reactivation	10
Chronic GVHD	n = 7 (50%)
Limited	6 (43%)
Extensive	1 (7%)

Allo-SCT consolidation group 6 patients died out of 16 with transplant related complications and the incidence of relapse 1/10 (10%).

Outcome: Median follow-up of entire cohort was 17.5 months (2–58 months) with 17 months (2–58 months) for Allo-SCT group and 17.5 months (3–55 months) for chemotherapy group. The median EFS was 22 months (95% CI 10.4–33.5 months) (Fig. 2a). The estimated 4 year EFS in Allo-SCT versus chemotherapy only group was 36.0 ± 17.9 versus $27.3 \pm 9.1\%$ ($p = 0.21$) (Fig. 2b). The estimated 4 year PFS was 75 ± 21.7 versus $34.1 \pm 10.9\%$ after Allo-SCT versus chemotherapy consolidations respectively ($p = 0.02$) (Fig. 2c). The median OS was 40.5 months (95% CI 33.2–47.9 months) of entire cohort (Fig. 2d). The estimated 4 years OS (n = 46) in Allo-SCT versus chemotherapy only group was $36.4 \pm 18.1\%$ versus 53.4 ± 17.8 ($p = 0.15$) (Fig. 2e). The EFS, PFS and OS were not found to be significantly associated with age, initial WBC count, presence or absence of additional cytogenetic abnormalities and pre-consolidation MMR (Table 3). Overall 7 patients (15.2%) died during treatment or follow up which includes induction mortality (n = 1) and TRM [n = 6; (GVHD = 3, Infection = 3)].

Discussion

Addition of TKI to standard chemotherapy in induction has improved both haematological response as well as OS in Ph^+ALL. Initial studies used imatinib in these patients showed significant improvement in haematological response and survival in both adults [10–14] and in

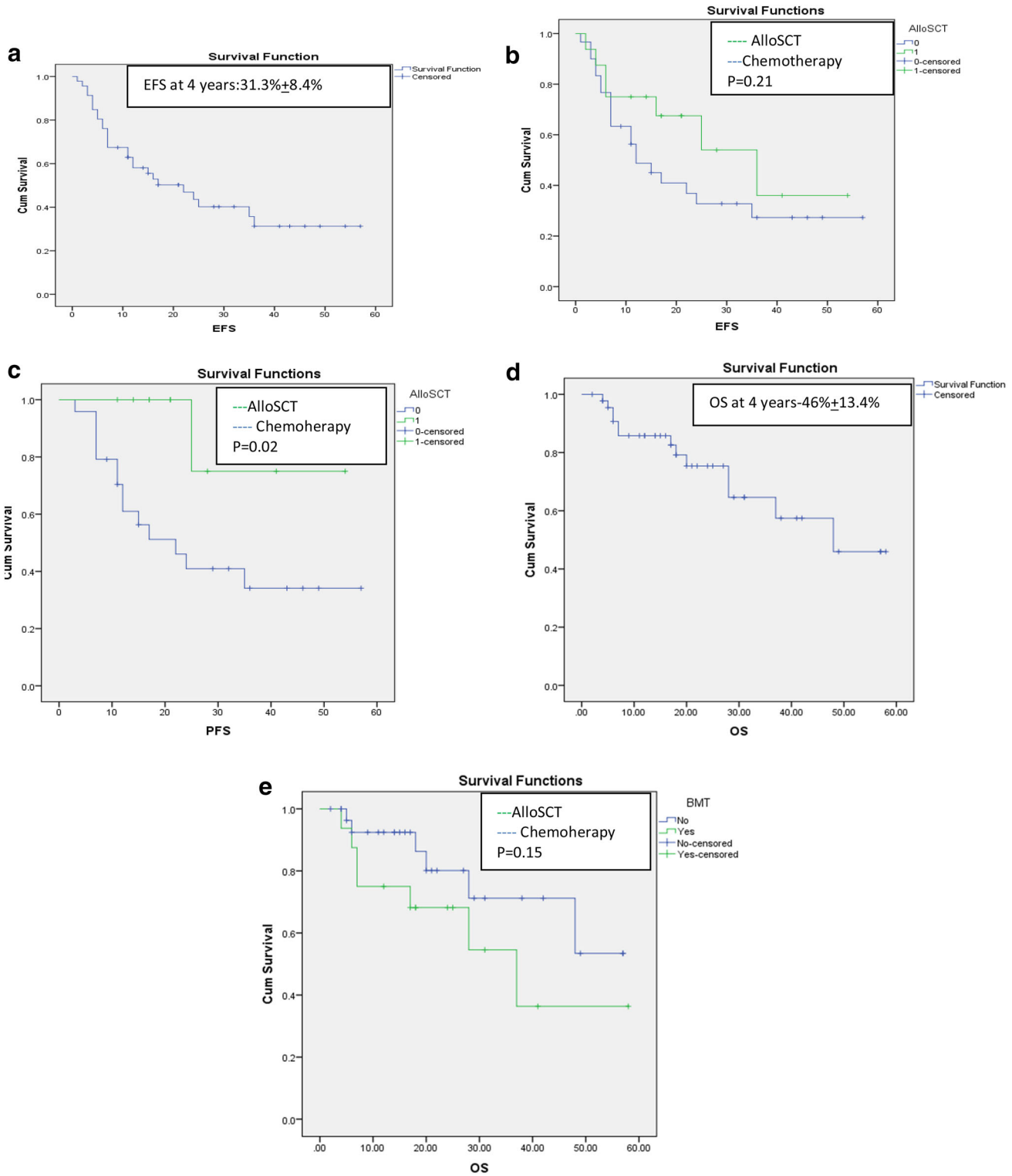

Fig. 2 **a** Kaplan–Meier curve depicting event free survival of cohort. **b** Kaplan–Meier curve depicting event free survival with Allo-SCT group and chemotherapy only group. **c** Kaplan–Meier curve depicting progression free survival with Allo-SCT group and chemotherapy only group. **d** Kaplan–Meier curve depicting overall survival of cohort. **e** Kaplan–Meier curve depicting overall survival with Allo-SCT group and chemotherapy only group

children [15, 16]. As the development of imatinib-resistant mutations and increased activity of other kinase pathways such as *src* kinases are the significant cause of loss of response in these patients, a significant interest has been

Table 3 Factors determining event free survival, progression free survival and overall survival

Variables	EFS (n)	Estimated percentages of EFS at 4 years (%)	*p* value	PFS (n)	Estimated percentages of PFS at 4 years (%)	*p* value	OS (n)	Estimated percentages of OS at 4 years (%)	*p* value
Allo-SCT versus chemotherapy only group			0.21			**0.02**			0.15
Allo-SCT	09/16	36 ± 17.9		09/10	75 ± 21.7		09/16	36.4 ± 18.1	
Chemotherapy only	10/30	27.3 ± 9.1		10/24	34.1 ± 10.9		24/30	53.4 ± 17.8	
Age			0.96			0.58			0.49
≤ 40 years	11/28	30.3 ± 10.5		11/21	45.4 ± 12.4		19/28	44.4 ± 14.2	
> 40 years	08/18	33.7 ± 13.8		08/13	46.6 ± 17.8		14/18	54.6 ± 23.2	
WBC count			0.90			0.50			0.59
≤ 1,00,000/cumm	16/34	41.2 ± 9.6		16/25	57.1 ± 11.7		26/34	63.2 ± 11.7	
> 1,00,000/cumm	03/12	20.8 ± 12.6		03/09	29.6 ± 16.4		07/12	25.8 ± 20.5	
CNS disease			0.55			0.34			0.28
CNS-1	17/41	31.8 ± 8.7		17/30	45.9 ± 11		28/41	44 ± 13.2	
CNS-3	02/05	40 ± 21.9		02/04	50 ± 25		05/05	100	
Pre consolidation MMR			0.93			0.84			0.33
≤ 0.1%	12/30	35.3 ± 9.4		12/23	46.6 + 11.4		23/30	61.1 ± 12.3	
> 0.1%	07/16	18.2 ± 15.5		07/11	35.1 ± 25.9		10/16	24.6 ± 20.4	
Cytogenetics			0.60			0.67			0.35
Without additional cytogenetics	07/22	20.8 ± 10.1		07/14	35.7 ± 15.3		13/22	30 ± 15.7	
With additional cytogenetics	07/15	40 ± 15.1		07/11	54.5 ± 18.7		12/15	64.3 ± 19.8	

Statistically significant value in bold

raised in the utilization of 2nd and 3rd generation TKIs which have increased activity against the ABL kinase as well as other kinases [17–19] and a better CNS penetration with dasatinib [23] which we used in most of our patients. Recently reported studies demonstrate the efficacy as well as feasibility of combining 2nd or 3rd generation TKI with cytotoxic chemotherapy regimens [20–22]. In our patients the TKI was started as soon as BCR-ABL1 results available. Cytopenias were initially managed by temporarily holding or modifying chemotherapy doses. However in case of persistent cytopenias TKI was stopped.

The incidence of Ph^{+}ALL increases with age, with more than 50% of cases being detected after the fifth decade of life [2, 3]. A very high number of these patients were not able to tolerate the intensive chemotherapy regimens used before TKI era. Several groups studied low intensity chemotherapy with TKI and demonstrated efficacy of this approach in achieving a CR. [23–26]

Most of our patients received a moderate intensity chemotherapy protocol based on UK-ALL or COG protocols along with 2nd line TKI. A low threshold was kept for chemotherapy modification but TKI was withheld only during severe neutropenia or in a TKI specific toxicity. The complete haematological remission rate achieved post induction was 94.1% with one death during induction.

Minimal residual disease levels at various time points in CR, especially at the end of induction therapy, are considered an important prognostic factor in ALL [27]. Effect of MRD negativity in Ph + ALL still remains to be determined. Yanada et al. [28] performed prospective

monitoring of BCR-ABL1 transcript levels in patients with Ph + ALL undergoing imatinib-combined chemotherapy reported that the RFS rate for the patients with negative MRD at the end of induction therapy was similar to that for patients with positive MRD. Ravandi et al. [29] reported that achieving a negative MRD by multi-parameter flow cytometry and MMR by RT-PCR at 3 months (and beyond) from starting treatment were associated with a decreased likelihood of relapse and with a longer OS. Our study did not show a correlation between molecular remission and EFS.

The estimated EFS at 4 years was 31.3% ± 8.4% while the OS for the whole group was 46% ± 13.4%. These survival figures are comparable to other centres in the world. The Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) published their study of 268 adults (median age, 47 years) with Ph + ALL treated with reduced intensity chemotherapy/HYPER CVAD + TKI ± Allo-SCT. At a median follow-up of 4.8 years, 5-year EFS and OS rates were estimated at 37.1 and 45.6%. [30] Similarly in the UKALLXII/ECOG2993 among patient that were treated with imatinib along with chemotherapy ± Allo-SCT, at 4 years, the EFS was 33% (95% CI 5 26–40%) while the OS was 38% (95% CI 5 31–45%) [10].

The long-term results of regimens combining chemotherapy with TKIs suggest the possibility of long-term survival in these patients without Allo-SCT. In a recent trial conducted at MD Anderson, CMR was found to be the most important prognostic factor in patients that did not undergo Allo-SCT. It also led to the debate that Allo-SCT may not be required in first remission for patients who achieve a CMR and who continue on indefinite TKI therapy [6] in our study on comparing the patients who received Allo-SCT to those who were treated with only chemotherapy, the Allo-SCT group shows a better PFS which is statistically significant. However this advantage has not converted into an improved OS due to a high treatment related mortality in a small cohort. Small number of patients in both groups and retrospective nature of study also limits our ability to make any conclusive deduction. However in the absence of other evidence in support of this theory and lack of long term follow-up supporting this hypothesis Allo-SCT still remains the best treatment modality for these patients.

Small number of patients, higher drop outs in chemotherapy group of patients, high TRM prevented us from drawing a strong conclusion of superiority of one over other approach Apart from that retrospective nature of the study and non-comparability of the two groups are other limitations of our study.

In conclusion, Allo-SCT was associated with better progression free survival as compared to chemotherapy with similar EFS and OS.

Compliance with Ethical Standards

Conflict of interest Narendra Agrawal, Priyanka Verma, Neha Yadav, Rayaz Ahmed, Pallavi Mehta, Priyanka Soni, Shinto Francis, Dinesh Bhurani declare that they have no conflict of interest.

Ethical Approval The study was approved by our Institutional Review Board.

Human and Animal Rights Statement All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent This is a retrospective study hence for this type of study formal consent is not required.

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