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Philadelphia chromosome-positive acute lymphoblastic leukemia: 8 years' experience from a tertiary care center in India

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Abstract

Introduction: The Philadelphia chromosome (Ph) is the most common cytogenetic abnormality associated with adult acute lymphoblastic leukemia (ALL) occurring in 20% to 40% of patients. It is also detected in 2% to 5% of children with ALL. Historically, patients with Ph-positive ALL carried a dismal prognosis, with poor response to most chemotherapy combinations, short remission durations, and long-term disease-free survival rates of 10% to 20%. The advent of tyrosine kinase inhibitors (TKIs) has revolutionized therapy of Ph-positive ALL. **Materials and Methods:** This retrospective and descriptive single center study was carried out based on data retrieved of 508 patients treated for ALL from 2007 to 2014. Of these thirty patients were Ph-positive ALL and were available for analysis, and these patients were included in the study. Ph-positive ALL was defined as ALL carrying the t(9;22) translocation on standard karyotype and/or fluorescent in situ hybridization analysis and/or positivity for BCR-ABL fusion transcript detection by real-time quantitative polymerase chain reaction (RQ-PCR) analysis. Patients were treated with combination chemotherapy and oral TKIs and responses were classified as either CR defined by the absence of circulating blasts and <5% marrow blasts on a bone marrow examination done at the end of induction chemotherapy or failure, including persistent disease and early death. **Results:** There were 30 (5.9%) cases of Ph-positive ALL out of a total of 508 cases of ALL with a median age of 27.5 years (range: 7-55). The choice of first line TKI was Imatinib in 25 (83.3 %) patients and Dasatinib in 1 (3.3 %) patient. Fourteen patients (46.6 %) had a CR, 3 (10 %) had a partial response (PR), 8 (26.6 %) had persistence of disease at the end of induction chemotherapy. The overall survival in those who received sequential chemotherapy followed by TKI (n = 4) was 28.5 months (95% CI 10.78 to 46.21 months) compared with 13.98 months (95% CI 6.04 to 21.97 months) for patients who received concurrent chemotherapy and TKI (n = 20); log rank (Mantel Cox) $X^2 = 8.33$, $P = 0.040$), however limited sample precluded meaningful subgroup analysis. **Conclusion:** The results of our study showed that we still have a long way to go to match outcomes of western published series, even when the same treatment protocol is used, probably due to the underutilization of Allogeneic SCT as an option in first CR.

Key words: Acute lymphoblastic leukemia, chemotherapy, overall survival, Philadelphia chromosome

Introduction

The Philadelphia chromosome (Ph) is the most common cytogenetic abnormality associated with adult acute lymphoblastic leukemia (ALL) occurring in 20% to 40% of patients.[1] It is also detected in 2% to 5% of children with ALL.[2] The Ph chromosome results from a reciprocal translocation (t) between chromosomes 9 and 22 (t[9;22][q34;q11]) and produces a fusion gene on chromosome 22, namely the breakpoint cluster region-Abelson leukemia viral proto-oncogene (BCR-ABL).

Historically, patients with Ph-positive ALL carried a dismal prognosis, with poor response to most chemotherapy combinations, short remission durations, and long-term disease-free survival rates of 10% to 20%.[3,4] The advent of tyrosine kinase inhibitors (TKIs) has revolutionized therapy of Ph-positive ALL. We performed a retrospective analysis of patients with Ph-positive ALL during the period 2007–2014 at the Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.

Materials and Methods

This retrospective and descriptive single center study was carried out based on data retrieved of 508 patients treated for ALL from 2007 to 2014. Of these thirty (5.9%) patients were Ph-positive ALL and were available for analysis, and these patients were included in the study. Patient consent was taken and the study was approved by the Institutional Review Board. Ph-positive ALL was defined as ALL carrying the t(9;22) translocation on standard karyotype and/or fluorescent *in situ* hybridization analysis and/or positivity for BCR-ABL fusion transcript detection by real-time quantitative polymerase chain reaction (RQ-PCR) analysis. The regimens were chosen based on age, performance status, comorbidities, and financial status as the majority were completely dependent on state-sponsored health schemes which had a capping of the amount that could be sanctioned for the entire course of therapy. Patients diagnosed with Ph-positive ALL were enrolled in a support program for free supply of imatinib (Glivec International Patient Assistance Program, Max Foundation, Novartis Oncology Access, active since 2002 in India). A verification and approval process followed, which was the sole determinant of which phase/day of treatment the patient could be started on TKI, in those who could not afford it. Combination chemotherapy backbone was started in the meantime, with either a course of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), MCP 841, BFM-95, or Siebel protocol. The use of oral TKIs plus steroids alone without additional chemotherapy has induced complete remissions (CRs) and prolonged survival in studies on elderly Ph-positive ALL; a similar strategy was adopted for patients who fit the criteria. Responses were classified as either CR defined by the absence of circulating blasts and <5% marrow blasts on a bone marrow examination done at the end of induction chemotherapy or failure, including persistent disease and early death.

Statistics

Data were analyzed using SPSS for Windows, Version 16.0. Chicago, SPSS Inc.. Categorical variables were denoted and

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frequency distribution was performed using the Chi-square test. Cox regression analysis (or proportional hazards regression) using the backward elimination method was used to assess the effect of risk factors on response at the end of induction therapy. The probability of survival was estimated with the use of the product limit method of Kaplan and Meier and compared by the log-rank test.

Results

Patient baseline characteristics and treatment details are summarized in Table 1.

Response at the end of induction therapy

We found a CR in 66.6% of patients treated with imatinib plus combination chemotherapy during induction, versus 52.9% in those who received combination chemotherapy alone. Cox regression analysis revealed age (P = 0.006) as the only predictive factor for a complete response to induction therapy.

Complications during induction chemotherapy

Bacteria were isolated in at least one blood culture in two patients. The organisms isolated were *Escherichia coli* and *Pseudomonas aeruginosa*. Three patients had evidence of possible invasive aspergillosis. The noninfectious complications during induction chemotherapy were steroid related-diabetes (n = 3) and myopathy (n = 1), acute pancreatitis (n = 1), azotemia (n = 1), acute fulminant hepatic failure (n = 1), and lower limb deep venous thrombosis (n = 1). One patient died of acute coronary syndrome 20 days after induction chemotherapy.

Table 1: Patient characteristics at diagnosis and treatment details

Characteristic	Value, *n* (%)/mean (±SD)
Age (years)	27.5 (7-55)
Gender	
Male	19 (63.3)
Female	11 (36.6)
Height (cm)	156.8 (15.28)
Weight (kg)	53.7 (18.05)
Body surface area (m^2)	1.49 (0.32)
Hepatomegaly	7 (23.3)
Splenomegaly	12 (40)
CNS disease	2 (6.7)
Initial hemoglobin (g/dl)	8.76 (3.12)
White blood cell count (cells/cumm)	73,205 (79,398.1)
Platelet count (cells/cumm)	106,600 (99,269.2)
Peripheral blood blast percentage	58.7 (29.04)
Bone marrow blast percentage	85.2 (11)
Additional cytogenetic abnormalities	
Present	3 (10)
Absent	27 (90)
Phase of chemotherapy TKI started in concurrent strategy	
Induction	11 (36.6)
Consolidation	8 (30)
Maintenance	1 (3.3)
First line TKI	
Imatinib	25 (83.3)
Dasatinib	1 (3.3)
Nilotinib	0 (0)
None	4 (13.3)
Second line TKI	
Dasatinib	3 (10)
Nilotinib	1 (3.3)
Third line TKI	
Dasatinib	0 (0)
Nilotinib	1 (3.3)

TKI=Tyrosine kinase inhibitor, SD=Standard deviation, CNS=Central nervous system

Induction deaths

Of the thirty patients in whom induction therapy was initiated there were three (10%) induction deaths. Two patients succumbed to infectious complications, one was documented by culture positivity with *E. coli*, and the other was culture negative. One patient died of bacterial meningitis. The median time to induction death was 20 days (range: 10–34).

Survival analysis

An additional 14 (51.8%) patients died postinduction, during the period of study, after a median follow-up of 4 months (range: 1–57 months). Of these, the majority 8 (57.1%) deaths were due to disease relapse and two were due to persistence of disease. Two patients died in remission during subsequent treatment due to neutropenia (infections), one patient died of acute respiratory distress syndrome, and one patient died of acute coronary syndrome 20 days after induction. Relapse percentage was 34% in the present study. Nine (15.2%) patients were lost to follow-up. The median overall survival (OS) in patients who received oral TKI with chemotherapy was 5.5 months (95% confidence interval [95% CI] 1.89–15.96 months) compared with 1 month (95% CI 0.062–0.52 months) in those that did not receive oral TKI (log-rank Mantel–Cox χ^2 5.88, P = 0.01). The median OS in patients who received sequential chemotherapy followed by TKI (n = 4) was 36 months (95% CI 8.057–160.9 months) compared with 5.5 months (95% CI 0.31–5.95 months) for patients who received concurrent chemotherapy and TKI (n = 20), 4 months (95% CI 0.16–3.14 months) for sequential TKI followed by chemotherapy (n = 2), and 1 month (95% CI 0.006–0.12 months) for patients who received chemotherapy alone (n = 4); log-rank (Mantel–Cox) χ^2 = 8.33, P = 0.03). Kaplan–Meier estimates of OS for Ph-positive ALL patients, with and without TKI in treatment protocol, and according to phase at which TKI was introduced are represented in Figures 1 and 2.

Discussion

The incidence of Ph-positive ALL in the current study which included both pediatric and adult patients was 5.9% (30 out of 508 patients).

Outcomes of treatment of patients with Ph-positive ALL, with conventional chemotherapy regimens alone during

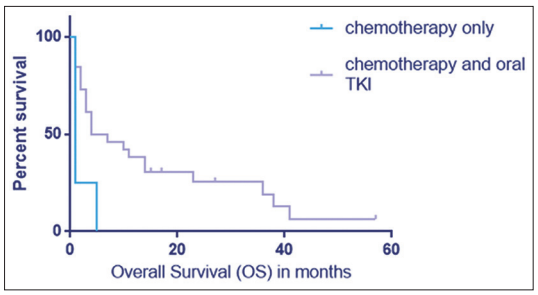

Figure 1: Kaplan–Meier curves showing overall survival with and without oral tyrosine kinase inhibitor in treatment protocol

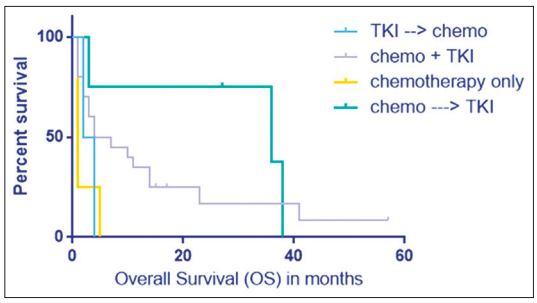

Figure 2: Kaplan–Meier curves showing overall survival stratified according to phase at which tyrosine kinase inhibitors were introduced into treatment protocol

induction are abysmal, with remission rates ranging from 46% to 60%.[5] Remission rates improve and approach 80–90% in patients treated with oral TKI plus combination chemotherapy.[6] We found a CR in 66.6% of patients treated with imatinib plus combination chemotherapy during induction, versus 52.9% in those who received combination chemotherapy alone, and this correlated well with results of previous studies.

Overall 3-year survival rates in those who receive traditional combination chemotherapy alone are <10%, and median survival of 6 months.[5] The median OS for the four patients who received chemotherapy alone was 1 month in the present study. Of these, two succumbed during induction due to treatment-related complications and two were lost to follow-up after induction. Hence, meaningful analysis of outcome in this group was not possible.

Overall 3-year survival rates of patients who receive oral TKIs in addition to combination chemotherapy are up to 30%, and median survival of 9–11 months.[5] The median OS in patients who received oral TKI with chemotherapy was 5.5 months in the present study. Subgroup analysis demonstrated the best median OS of 36 months, for those who received sequential chemotherapy followed by oral TKI. The conclusion of trials conducted to establish the best strategy of incorporating imatinib into ALL therapy was that the concurrent regimen had a greater antileukemia efficacy but did not translate to improvements in EFS and OS.[7] However, of the four patients who received treatment by the sequential strategy, two were detected to be Ph-positive only after they relapsed while on the maintenance phase of chemotherapy. One patient was detected to be Ph-positive and started on oral TKI, only after induction chemotherapy with hyper-CVAD and repeat induction with mitoxantrone plus etoposide failed to achieve remission.

Limitations

A limitation of our study was the retrospective design. However, Ph-positive ALLs are rare in the general population, making a prospective study with an adequately sized sample extremely difficult. Our sample size was fairly small at thirty patients, which limited the number of patients in certain subgroup analysis of OS.

Options to improve treatment

Limiting the variations in the design of imatinib administration (time of onset, sequential versus continuous administration, daily dosage), adopting a definite protocol with regards to the number of days imatinib is to be administered during intensive chemotherapy and assessment of early response to chemotherapy and TKIs with documentation of molecular response to risk stratify patients and intensify treatment strategy to consider the possibility of an allogeneic stem cell transplantation (SCT).

Conclusion

The results of our study showed that treatment employing an integrative chemotherapeutic regimen using concurrent or sequential strategies with TKIs improved response rates, and better long-term outcomes compared to chemotherapy alone in Ph-positive ALL. However, we still have a long way to go to match the outcomes of Western published series, even when the same treatment protocol is used, probably due to the underutilization of allogeneic SCT as an option in the first CR.

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Conflicts of interest

There are no conflicts of interest.

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