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Original Article

Adult Philadelphia-Positive Acute Lymphoblastic Leukemia: A Single-Institution Experience in Limited-Resource Setting

Rudresha Haleshappa Antapura[1] Amale Baburao Vaibhav[1] Lokanatha Dasappa[1] Linu Abraham Jacob[1] Mallekavu Channappa Sureshbabu[1] Kadabur Nagendrappa Lokesh[1] Lakkavalli Krishnappa Rajeev[1] Smitha C. Saldanha[1] Tirumala Venkatesh[1]

[1] Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

Address for correspondence L. K. Rajeev, DM (medical oncology), Kidwai Memorial Institute of Oncology, Karnataka 560029, India (e-mail: lkrajeev@gmail.com).

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Abstract

L. K. Rajeev

Background Adult Philadelphia-positive (Ph +) acute lymphoblastic leukemia (ALL) is a distinct entity with poor prognosis. Treatment with tyrosine kinase inhibitors improved responses but still with poor outcomes. We evaluated treatment outcomes in these patients treated in limited-resource settings in the absence of availability of allogeneic stem cell transplantation (ASCT).

Materials and Methods We studied case record files of the adult patients diagnosed with Ph+ ALL.

Results A total of 18 patients were evaluated retrospectively. The median age of presentation was 28 years. Male-to-female ratio was 1:1. Patients presented with fever and fatigue. Six patients (33.33%) presented with cervical lymphadenopathy. Clinical splenomegaly was present in 16 (88.88%) patients on palpation, whereas on ultrasonographic evaluation, all 18 patients had splenomegaly. The median size of the spleen was 15 cm. Hepatomegaly was seen in 5 (27%) patients. All 18 patients had anemia at the time of presentation. Leukocytosis was seen in 17 (94.44%) patients, whereas 1 (5.56%) patient presented with low total leukocyte count. The median platelet count at the time of presentation was 30,000/mm.^{3} On peripheral smear, median number of blast cells was 55%, and on bone marrow aspiration samples, median blast percentage seen was 70%. Conventional cytogenetics was done in all the patients on bone marrow aspiration samples. Ten patients (55.55%) had t(9;22) – Ph chromosome. One patient (5.56%) on cytogenetics showed double Ph chromosome. The median value of breakpoint cluster region-ABL1 transcript in IS% was 13%. Seventeen (94.44%) received ALL protocol (BFM95) along with tyrosine kinase inhibitor (imatinib). One (5.56%) patient refused aggressive cytotoxic chemotherapy. No patient underwent ASCT. The median duration of follow-up was 7.5 months, ranging from 3 to 16 months. Median overall survival (OS) was 7.5 months and 2-year OS was 33.33%.

Conclusion Poor prognosis of this disease, especially in the absence of ASCT, remains a major challenge in the treatment.

Keywords

- adult
- breakpoint cluster region-ABL1
- Philadelphia-positive acute lymphoblastic leukemia

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Introduction

B-lymphoblastic leukemia/lymphoma with t(9;22) (q34.1; q11.2); breakpoint cluster region (BCR)-ABL1 is a distinct entity classified in the 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia.[1] Acute lymphoblastic leukemia (ALL) with t(9;22), that is, the Philadelphia (Ph) chromosome is recognized as the ALL subtype with poor outcome historically.[2] About 20 to 30% of adult ALL patients have Ph-positive (Ph+) ALL, and its incidence increases with age.[3] The use of tyrosine kinase inhibitors (TKIs) in the treatment has induced higher remission rates and better survival.[4] Here, we present our experience in the treatment of adult patients with this subtype of ALL using chemotherapy plus TKIs, without allogeneic stem cell transplantation (ASCT). Poor prognosis of this disease, especially in the absence of ASCT, remains a major challenge in the treatment.

Materials and Methods

We retrospectively evaluated case record files of patients with adult ALL presented to our department between January 2017 and December 2018. Ph+ ALL patients were selected on the basis of conventional cytogenetics or the presence of BCR protein on polymerase chain reaction (PCR)-based test. Total patients diagnosed with ALL were 160 during this period. A total of 18 patients were found to have Ph+ ALL. Patients were treated with BFM-95 protocol with the addition of TKI; imatinib. Response assessment was made at the end of induction. Complete remission (CR) is defined as the recovery of a peripheral blood absolute neutrophil count of >1,000/mL, and a platelet count of >1,000,000/mL, and bone marrow aspirate showing <5% blasts. Follow-up data were collected.

Results

A total of 18 patients were evaluated retrospectively. The median age of presentation was 28 years, ranging from 16 to 44 years. Male-to-female ratio was 1:1. Out of 18, 17 (94.44%) patients presented with fever with a median duration of 2 months. One patient presented with the fatigue of 2 months' duration. Six patients (33.33%) presented with cervical lymphadenopathy. Clinical splenomegaly was present in 16 (88.88%) patients on palpation, whereas on ultrasonographic evaluation, all 18 patients had splenomegaly. The median size of the spleen was 15 cm. Hepatomegaly was seen in five (27%) patients. All 18 patients had anemia at the time of presentation with median hemoglobin value of 8.7 g/dL. Leukocytosis was seen in 17 (94.44%) patients, whereas one (5.56%) patient presented with low total leukocyte count. Median platelet count at the time of presentation was 30,000/mm.^{3} On peripheral smear, median number of blast cells was 55%, and on bone marrow aspiration samples, median blast percentage seen was 70%.

Conventional cytogenetics was done in all the patients on bone marrow aspiration samples. Ten patients (55.55%) had t (9;22) – Ph chromosome. Cytogenetics failed in 5 (27.77%) patients due to poor metaphase yield. Two (11.11%) patients had normal karyotype. One patient (5.56%) on cytogenetics showed double Ph chromosome with additional abnormalities (47,XX, t(9;22)(q34;q11.2), add(19)(p13), der(22)t(9;22)(q34;q11,2)(3)/46,XX(3) (►Fig. 1 and ►Table 1).

PCR-based qualitative and quantitative analysis was done for transcript protein. In total, 12 (66.66%) patients had P190 protein transcript, and 5 (27.77%) patients had P210 transcript. The median value of BCR-ABL1 transcript in IS% was 13%.

All 18 patients received treatment. Seventeen (94.44%) received ALL protocol (BFM95) along with TKI (imatinib). One (5.56%) patient refused aggressive cytotoxic chemotherapy and was prescribed metronomic 6-mercaptopurine, methotrexate, and prednisolone with imatinib. Day 8 blast clearance was recorded in 17 (94.44%) patients with one patient on metronomic regimen lost to follow-up immediately after starting treatment. Induction mortality was seen in 2 (11.76%) patients out of 17 patients. In the rest of 15 (88.23%) patients, remission was documented at the end of induction. The median duration of follow-up was 7.5 months, ranging from 3 to 16 months. Median overall survival (OS) was 7.5 months, and 2-year OS was 33.33%. Out of 17 patients, 7 (41.17%) patients relapsed, bone marrow being the most common site of relapse. After relapse, patients were given metronomic chemotherapy with 6-mercaptopurine, methotrexate, and prednisolone. None of our patients underwent ASCT.

Discussion

In preimatinib era, the treatment of Ph+ ALL with chemotherapy alone achieved CR rates of 45 to 90%, but associated with early relapses with median event-free survival ranging

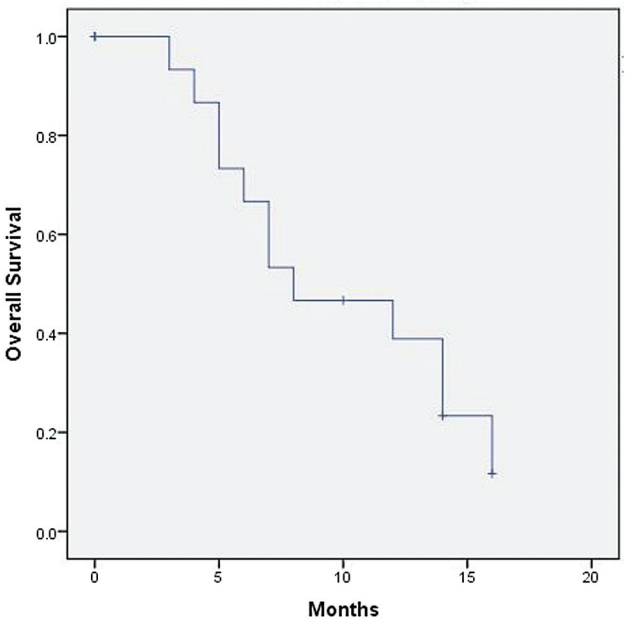

Fig. 1 Median overall survival Kaplan–Meier graph.

Table 1 Clinical characteristics

Parameters	Observations
Number of patients	18
Median age (y)	28 (16–44)
Males	9
Females	9
Male:female ratio	1:1
Presenting complaint (%)	
Fever	17 (94.44)
Fatigue	1 (5.56)
Median duration of symptoms	2 months
Lymphadenopathy (%)	
Cervical	6 (33.33)
Splenomegaly (%)	
Palpable	16 (88.88)
On imaging (USG)	18 (100)
Median size of spleen (cm)	15
Hepatomegaly (%)	5 (27)
Median Hb at presentation (gm/dL)	8.7
Total leucocyte count (%)	
Leukocytosis	17 (94.44)
Leukopenia	1 (5.56)
Median platelet count	30,000
Median blast (%)	
Peripheral smear	55
Bone marrow	70
Conventional cytogenetics (%)	
t(9;22)	10 (55.55)
Failed	5 (27.77)
Normal	2 (11.11)
Double Ph+	1 (5.55)
BCR-ABL1 (%)	
P190	12 (66.66)
P210	5 (27.77)
Not available	1 (5.56)
Median BCR-ABL1 IS (%)	13

Abbreviations: BCR, breakpoint cluster region protein; Hb, hemoglobin; USG, ultrasonographic.

from 5 months to 13 months in various trials, and median OS was also not satisfactory ranging from 8 to 16 months.[5] The addition of imatinib to the standard chemotherapy is beneficial, as demonstrated by Fielding et al.[6] However, the use of TKI still failed to achieve long-term cure with or without allogeneic transplantation with 5-year OS around 40 to 50%.[7]

In our study, we found that 11.25% of ALL patients had a Ph+ phenotype. In literature, in adults with ALL, Ph+ phenotype is seen in 20 to 30% patients. In studies from India, Ph+ ALL is seen in various studies ranging from 5.9[8] to 22.6%.[9] Low percentage of Ph+ patients in our study may be due to the fact that we perform BCR-ABL1 PCR test only in patients having t(9;22), failed conventional cytogenetics, and normal karyotype. It was not performed in all the patients of ALL.

BCR-ABL1 transcripts seen in our studies are p190 (66.66%) and p210 (27.77%). Other studies by Lim et al found similar results with p190 (77%) and p210 (20%). Median IS% of BCR-ABL1 in our study was 13%. Lim et al reported the median value were 2.01% (0.005–79.6%).[10]

Clinically, majority of the patients had splenomegaly either palpable or on imaging study. Hepatomegaly was less common. Most patients had high white cell count on presentation, and thrombocytopenia was more common. The mean platelet count was 30,000/mm^3. Median blast percentage in peripheral blood was 55%, and in bone marrow, it was 70%. These findings are comparable with various studies in the literature.

In our study, 15 patients who received intensive treatment with BFM-95-positive imatinib, all patients achieved remission. It is as per the literature, showing around 90% of patients' remission at the end of induction.[5,10] Induction mortality was seen in two (11.76%) patients, which were comparable with other studies.

A poor outcome of this disease was observed in our study. Median OS was 7.5 months and 2-year OS was 33.33%. Bone marrow was the most common site of relapse. It was comparable by Danthala et al study.[8] In another study by Jain et al, the high-risk group which includes Ph+ ALL; 5-year OS was 27.2% ± 4.2%.[9] Lim et al reported 5-year OS of 33.4%, it was seen similarly in other historical studies also.[5,10] Majority of the studies include patients who underwent ASCT. None of our patients underwent ASCT due to limited resources, which reflects the poor prognosis.

The limitation of our study is short follow-up. The second limitation is the number of patients is low to draw any firm conclusions, and the third limitation is none of our patients underwent ASCT. Although allogeneic transplant has not shown impressive results, it is an only curative option in these patients. The use of newer TKIs such as dasatinib and nilotinib which show better responses need to be studied extensively.

Conclusion

Adult Ph positive ALL has poor prognosis, especially in the absence of ASCT, remains a major therapeutic challenge.

Funding

None.

Conflict of Interest

None declared.

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