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Response to imatinib mesylate in childhood chronic myeloid leukemia in chronic phase

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Abstract

Introduction: Childhood chronic myeloid leukemia (CML) accounts for less than 3% of all childhood leukemias, hence, data on imatinib (IM) in adult CML patients has been largely extrapolated to children. We have analyzed our data to add to the existing literature. **Aims:** Primary objective is to assess the progression-free survival (PFS). Secondary objective are cytogenetic response, overall survival (OS), and toxicities. **Settings and Design:** This is a retrospective analysis from the case records from a single institution. **Materials and Methods:** Institutional ethics committee approval was obtained. All the children diagnosed CML in chronic phase (CML-CP) aged less than 18 years registered between 2000 and 2009 were enrolled. All the patients were started on IM at 260 mg/m^2. **Statistical Analysis:** Kaplan-Meier curves were used to calculate the PFS and OS. **Results:** There were 64 children with median age of 13 years (range, 1-18) with male predominance (male:female (M: F) - 1.85:1). Sixty-one patients (95.4%) achieved complete hematological response (CHR) at median of 8 weeks. Thirty-seven (57.8%) patients had evaluation of cytogenetic response and were subjects for outcome analysis. The median time to best cytogenetic response evaluation was 13 months (range, 4-52). Twenty-nine patients (78.3%) achieved complete cytogenetic response (CCyR). At a median follow-up of 36 months (range 5-75), 21 (56.8%) remained progression free and 35 (94.5%) are alive. Adverse events were tolerable. **Conclusions:** PFS at a median follow-up of 36 months is 56.8% and OS 94.5%.

Key words: Childhood chronic myeloid leukemia, cytogenetic responses, imatinib mesylate, survival

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the expansion of a clone of hematopoietic cells that carries the Philadelphia chromosome (Ph) t (9;22)(q34;q11) resulting in a novel fusion gene, BCR-ABL, which encodes a constitutively active tyrosine kinase. Imatinib (IM) is a relatively specific inhibitor of the BCR-ABL tyrosine kinase which revolutionized the treatment of CML resulting better outcomes than with traditional chemotherapy/interferon.[1]

CML in children is rare as it accounts less than 3% of childhood leukemias with an annual incidence of one case per 1 million children in western countries; hence, data on IM in adult CML patients has been largely extrapolated to children. In recent time, there are reports on growth and endocrine abnormalities with IM in children.[2] The aim of this study was to look for the outcomes of pediatric CML patients on IM and its tolerability.

Materials and Methods

Children less than 18 years with CML-CP, registered in Department of Medical Oncology from a period of 2000 to 2009 year were enrolled. Their hospital records were analyzed for duration of symptoms, size of spleen, complete blood picture, bone marrow aspiration, and cytogenetics or BCR-ABL quantitative PCR (real-time PCR) at the time of diagnosis. The criteria for diagnosis of CML-CP is documentation of t(9;22) or the BCR-ABL fusion gene, bone marrow blast <10%, and does not meet the criteria of accelerated phase or blast crisis.[1]

Institutional review board approval was taken and individual patient's/parent's/guardian's informed and written consent was taken before initiation of treatment. All the children were started on IM at a dose of 260 mg/m^2.[3] All children had their hemograms done fortnightly till complete hematological response (CHR) was obtained and thereafter monthly. Karyotyping is ordered at the time of diagnosis and percentages of Ph positive cells are noted. Marrow cytogenetic testing was repeated at 6, 12, and 18 months after the initiation of therapy. Once complete cytogenetic response (CCyR) is achieved then karyotyping is requested annually.[4] Molecular response was assessed by reverse transcription PCR (RQ-PCR) whenever feasible.

For the patients who had suboptimal response to treatment, we requested for further investigations as per standard guidelines.[1] None of the patients in our study could afford for mutational analysis, second-line tyrosine kinase inhibitors (TKIs), transplant, only option left was increasing to 340 mg/m^2. After dose hike, the response is assessed with hemogram fortnightly till CHR and cytogenetic every 6 months till CCyR.[1,4]

End points

The primary end point was progression-free survival (PFS), which was referred as the time from the start of IM to the following events: Death from any cause during treatment, progression to the accelerated phase or blast crisis of CML, or loss of a complete hematologic or cytogenetic response.

Secondary end points were response to treatment (attainment of CHR and CCyR), overall survival (OS), and side effects to IM treatment. The CHR is defined as a leukocyte count <10 × 10^9/l, a platelet count of <450 × 10^9/l, <5% myelocytes plus metamyelocytes, no blasts or promyelocytes, no extramedullary involvement, and no signs of the accelerated phase or blast crisis of CML; a cytogenetic response in marrow cells, categorized as CCyR (no Ph-positive metaphases), partial (1-35% Ph-positive metaphases), major (complete plus partial responses), minor (36-65% Ph-positive metaphases), minimal (66-95% Ph-positive metaphases), and no response (100% Ph-positive metaphases) on the basis of G-banding in at least 20 cells in metaphase per sample.

Statistical methods

Patient characteristics were summarized using descriptive statistics. Inferential statistics using Kaplan-Meier curves were used for PFS and OS using GraphPad Prism software for Windows, Version 4, 2003.

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Results

A total of 64 children were enrolled in the present study, 42 (65.6%) were boys and 22 (34.4%) were girls. Median age at presentation was 13 years (range 1-18 years). Fifty-three (83%) children were in early chronic phase (CP) and 11 (17%) were in late CP. The median hemoglobin was 9.3 g/dl (range 5.1-13.8), median leukocyte count was 158 × 10^9/l (range 5.9-539) and median platelet count was 380 × 10^9/l (range 80-11,400), median basophil % was 3 (range 0-15), median eosinophil % was 2 (range 0-15), median blast % was 3 (range 0-10), and mean spleen size at presentation was 9 cm (range 0-20). Twenty-eight (43.7%), 32 (50%), and four (6.3%) children belonged to the low, intermediate, and high Hasford risk groups, respectively; while 34 (53.1%), 23 (35.9%), and seven (10.9%) belonged to the low, intermediate, and high Sokal groups.

Sixty-one patients (95.4%) achieved CHR with a median duration of 8 weeks (range, 4-16). Twenty-seven patient did not have their evaluations as per the standard guideline, 6/27 patients were in less than 6 months of follow-up, 4/27 patients were between 6 and 15 months of follow-up and not yet completed the karyotyping at the time of analysis, one was not evaluated due to prolonged hematological toxicity, 3/27 had early hematological progression and were not evaluable, and 13/27 were irregular and lost to follow-up.

Thirty-seven (57.8%) patients had evaluation of cytogenetic response and their results were analyzed. The median time to best cytogenetic response evaluation was 13 months (range 4-52). Twenty-nine patients (78.3%) achieved CCyR; five (13.5%) had minor cytogenetic response; and one (2.7%) each had minimal, partial, and no response.

At a median follow-up of 36 months (range 5-75), 21 (56.8%) remained progression free and 35 (94.5%) are alive [Figure 1]. Of the 16 who progressed, five (31.2%) had loss of cytogenetic response only, six (37.5%) had hematologic progression, two (12.5%) had molecular progression, and three (18.7%) had both hematologic and cytogenetic progression.

Of the 16 who progressed, five (31.2%) had loss of cytogenetic response, six (37.5%) had hematologic progression, two (12.5%) had molecular progression, and three (18.7%) had both hematologic and cytogenetic progression. Children who progressed on IM 260 mg/m^2 , the dose was hiked to 340 mg/m^2 as they could not afford second line TKI. Out of 16, 12 (75%) achieved CHR with dose hike of IM.

Only four patients of 37 had at some point of time molecular analysis, three of them were in major molecular remission (MMR), of which two had molecular progression.

Adverse events are not infrequent. Non-hematological side effects were hypo/hyperpigmentation of skin (54%), edema/weight gain (39%), muscle cramps/musculoskeletal pain (30%), growth retardation (29%), fatigue (23%), asthenia (15%), skin rash (15%), diarrhea (9%), oral ulcers (9%), dyspepsia (7.8%), constipation (4.5%), and liver function test abnormalities (3%). Hematological side effects were anemia (65%), neutropenia (28%), and thrombocytopenia (17%). The Z-scores for height and age were lower compared to the baseline, more so in the prepubertal age group.[5]

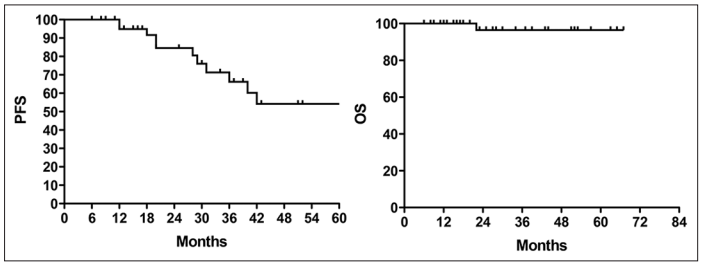

Figure 1: Progression-free survival (PFS) and overall survival (OS) of evaluable patients

Discussion

Millot *et al*., reported 40 cases of CML with 38 cases of CP and one each of accelerated phase (AP) and blast phase (BP).[6] In children very few studies are available to date, Phase I study of Children's Oncology Group (COG) reported that 12 children who were previously treated with interferon-α10 had CCyR and one patient had partial cytogenetic response.[7] A case series from Memorial Sloan Kettering Cancer Center (MSKCC) reported that two children in early phase and two children in late CP achieved CCyR.[8] Millot *et al*., reported 12 out of 20 children in CP failed Interferon (INF) attained CCyR.[9] In the present study, out of total 64 children, 61 (95.4%) achieved CHR with a median duration of 8 weeks. In the present analysis due to parental apprehension and logistic reasons, all children did not undergo cytogenetic evaluation as per schedule. Only 37 children (57.8%) had evaluation of cytogenetic response. Among them mean time to attain best cytogenetic response was 13 months, 29 patients (78.3%) achieved CCyR. Ghadyalpatil *et al*., reported 89.5% CCyR at median time of 10 months (range 3-31 months) in pediatric CML.[10] These results were comparable with the COG, European, and French pediatric CML studies' data.[1]

At a median follow up of 36 months (range 5-75), 21 (56.8%) remained progression free (PFS) and 35 (94.5%) are alive. Ghadyalpatil *et al*., reported event-free survival (EFS) and OS was 74.1 and 100%, respectively in pediatric CML patients at a median follow-up of 29 months.[10] Lakshmaiah *et al*., reported EFS and OS at 43 months as 92.8 and 100%, respectively.[11] Biswajit *et al*., reported 3-year disease-free survival (DFS) and OS as 86.2 and 89.5%, respectively, in young CML patients.[12]

Present study results were comparable with that of previous study results in pediatric CML from India in terms of response, but the PFS and OS were lower when compared with Ghadyalpatil *et al*.,[10] Biswajit *et al*.,[12] and Lakshmaiah *et al*.,[11] studies [Table 1]. The reasons for such results could be due to poor adherence to the treatment, which accounted for 25% in our center and our center caters mostly for lower socioeconomic group population.

Of the 16 who progressed, five (31.2%) had loss of cytogenetic response, six (37.5%) had hematologic progression, two (12.5%) had molecular progression, and three (18.7%) had both hematologic and cytogenetic progression. Children who progressed on IM 260 mg/m^2, the dose was hiked to 340 mg/m^2 as they could not afford second line TKI. Out of 16, 12 (75%) achieved CHR with dose hike of IM.

Adverse events are not infrequent in this study, anemia (65%), pigmentation changes (54%), and weight gain (39%) are the most common manifestation. Ghadyalpatil *et al*., reported hematological toxicity (Grade 4 thrombocytopenia)

Table 1: Survival and cytogenetic response across different studies

Study (references)	Number, *N*	Complete cytogenetic response (%)	Partial/major cytogenetic response (%)	Event-free survival (%)	Progression-free survival (%)	Overall survival (%)
Senthil *et al.*[13] (adults, early CP)	201	56	23	-	77	94
Agarwal *et al.*[14] (adult and children CML-CP)	576	62	-	72	-	87
O'Brien *et al.*[15] (adults, early CP)	553	82	7	81	93	86
Present study (children, early, and late CP)	37	78.3	2.7	-	56.8	94.5
Lakshmaiah *et al.*[11] (children, CML-CP)	43	58.1	41.9	92.8	100	100
Millot *et al.*[3] (children CML-CP)	44	61	31	-	98	98
Ghadyalpatil *et al.*[10] (children CP+AP)	48	89.5	-	74.1	-	100

CML-CP=Chronic myeloid leukemia in chronic phase, AP=Accelerated phase

in 14% and hypopigmentation in 50% as common toxicities in pediatric CML patients.[10] Biswajit *et al.*, reported hypo- or hyperpigmentation (60.0%) as the most common side effect in young CML patients and Grade 3/4 hematological toxicity accounted only 7%.[12] Rajappa *et al.*, reported similar side effect profile in adult CML patients from our center with pigmentation changes (70%), anemia (65%), and weight gain (50%) from our center.[13] The high occurrence of anemia during follow-up in the present study might be due to low mean hemoglobin level at the time of diagnosis due to low socioeconomic group. Rest of side effect profile was similar to that of western data.[1] In the present study, the Z-scores for height and age were lower to the baseline after starting on IM; we have reported it earlier from the same Institute[5] and there are reports on growth retardation on IM from other centers.[2] The influence of malnutrition cannot be ruled out totally, but to our understanding the sudden decline in the growth rate after starting IM has major influence.

We conclude that in children with CML-CP, IM showed better cytogenetic response with the minimal toxicity, which ultimately results in prolonged OS if they are adherent to the treatment. Our survival outcome is comparable to that reported from various western populations. They should be monitored for disease response with both cytogenetic and molecular techniques as well as side effects with IM. Treatment adherence should be checked in case of suboptimal response. The healthcare provider can address most of the reasons for nonadherence with adequate counseling on the importance of adherence. More prospective studies are necessary in children to determine long-term outcomes with IM.

Limitation

It is a retrospective study, with small numbers, evaluation time points not according to guidelines, and dose intensity unknown.

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