Original Article

A Retrospective Study of Clinical Profile and Long Term Outcome to Imatinib Mesylate Alone in Childhood Chronic Myeloid Leukemia in Chronic Phase

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Abstract

Objective: Chronic myeloid leukemia (CML) is relatively rare malignancy in childhood. There are limited studies of use of Imatinib Mesylate (IM) alone in management of CML in this age group.

Method: We retrospectively analyzed the outcome of 30 consecutive children with CML chronic phase treated with IM alone.

Results: The median age at the time of diagnosis was 11 years with male preponderance. Asthenia and abdominal discomfort due to splenomegaly were the most common presenting features and splenomegaly a dominant sign. At time of starting IM, 19 children were in early CP while 11 were in late CP. Complete hematological remission was achieved in 90% with a median time to achieve CHR was 60 days. Among evaluable children, 83.3% achieved cytogenetic response (CyGR). Those who achieved complete CyGR were in major molecular remission at the time of last follow up. At 3 years, progression–free survival was 81.5% and overall survival was 100%. At 10 years, 12 (40%) children failed on IM therapy of which 3(10%) children developed primary IM resistance while 9 (30%) developed secondary IM resistance. IM was well tolerated and severe (grade III–IV) events were infrequent. Non–haematological toxicities were uncommon except hypopigmentation of skin which was seen in 60% of the cohort.

Conclusion: Presenting features of CML–CP in children is comparable to other Indian and international studies. IM is very effective and safe drug for the first line treatment of CML–CP in children. It is very effective in inducing CHR. Adherence to treatment is very important for achieving CyGR and long term survival. This data will be useful for financially deprived children in developing countries where allogeneic stem cell transplant (SCT) or second line tyrosine kinase inhibitors (TKIs) is not an affordable option.

Keywords: Pediatric hematologic malignancies, Chronic Myeloid leukemia, Cytogenetics, Imatinib Mesylate

Introduction

Chronic myeloid leukemia (CML) in children is rare. The incidence of CML in children is 1–2% of all childhood cancer cases with an annual incidence of 1 case in 1 million children in western countries [1] or around 5–10 cases per 1 million population per year as defined by the Delhi cancer registry [2]. In pre Imatinib Mesylate (IM) era, the prognosis of CML was bleak. IM has revolutionized the treatment of CML resulting in better outcome than with traditional chemotherapy and /or interferon [3, 4]. The objective of this article is to report long term outcome of childhood CML–chronic phase (CP) treated with IM alone especially when they could not afford expensive allogeneic SCT or second line TKIs.

Material and Methods

This retrospective analysis was carried out at a single centre in western India. Children < 14 years with CML–CP registered in the department of medical and paediatric oncology from January 1996 to December 2005 (over 10

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years with 10 years of follow up) were included. Their hospital case records were analyzed for symptoms, size of spleen, complete blood picture, bone marrow aspiration, cytogenetics (conventional or FISH) or BCR–ABL quantitative polymerase chain reaction (real–time PCR) at the time of diagnosis. The criteria for diagnosis of CML–CP was documentation of Philadelphia chromosome or BCR–ABL fusion gene, bone marrow blast <10%, and not meeting the criteria of accelerated phase /blast phase (AP/BP) [4, 5]. After diagnosis, all children started with hydroxyurea and continued the same till the availability of IM. Since 2003–04, IM was approved in children [6] and had replaced hydroxyurea in the treatment of Philadelphia chromosome positive CML–CP [7, 8, 9, 10]. The starting dose of IM was 260 mg/m^2 [7, 11]. The response assessments, monitoring and follow–up were done as per the European LeukemiaNet guidelines [12].Toxicity grading and evaluations were done according to the American National Cancer Institute common toxicity criteria manual version 2. For the children who had suboptimal response to treatment, further investigations as per standard guidelines were requested [12]. None of the children in current study could afford mutational analysis, allogeneic SCT or second–line TKIs, so the dose of IM was increased to 340 mg/m^2 [13]. After dose hike, the response was assessed with hemogram till complete hematologic response (CHR) and cytogenetic every 6 months till complete cytogenetic response (CyGR). Primary end points were attainment of cytogenetic or molecular response and tolerance to IM therapy. The secondary end points were progression free survival (PFS) and overall survival (OS). PFS was referred as the time from the start of treatment to hematologic progression (i.e. loss of CHR) or progression to AP/BP or death from any cause during treatment. In analysis of OS, total duration of treatment with hydroxyurea and IM were included. Patient characteristics were summarized using descriptive statistics.

Results

A total of 30 children with CML–CP were analyzed, 25 (83.3%) were boys and 5 (16.7%) were girls with male to female ratio of 5:1. Median age at time of diagnosis was 11 years (range, 4–14 years). Twenty–three (76.6%) children were 10–14 years of age group. Asthenia and abdominal discomfort due to splenomegaly were the most common presenting features. Splenomegaly was present in 28 (93.3%) children, 20 (66.6%) children had moderate to massive while 8 (26.6%) children had mild splenomegaly. Only 9 (30%) children had hepatomegaly. Nineteen (63.3%) children were in early CP and 11 (36.7%) were in late CP. Clinical and parameters are described in Table 1. All children were treated with hydroxyurea before starting IM. Median duration of hydroxyurea treatment was 4 months (range, 5–91months). Nineteen children had received hydroxyurea for less than 1 year, while 11 children for more than 1 year. In 19 children, IM was started in early CP (< 1 year of diagnosis) and 11 were in late CP (> 1 year of diagnosis).

Parameters	Results
Age (years)	
Median(range)	11 (4-14)
Gender	
Boys	25
Girls	05
Ratio (M:F)	5:1
Duration of symptoms (days)	
Median(range)	90 (3-365)
Haemoglobin (gram %)	
≥12	27
< 12	03
Median(range)	9.0 (5.9-14.4)
White cell counts (x10^9 /L)	
≥ 50	23
< 50	07
Median(range)	15 (5.7-825)
Platelet counts (x10^9 /L)	
≥ 450	17
< 450	12
Median (range)	464 (96-1200)

Table 1. Clinical and hematologic parameters at the time of diagnosis

Responses:

Twenty–seven (90%) children achieved CHR with median time to achieve CHR being 60 days (range, 25–90 days). Among 3 children who did not achieve CHR, dose was escalated but 1 subsequently progressed to BP, another had persistent thrombocytopenia and 1 child was subsequently lost to follow up. Only 18 (60%) children had evaluation for CyGR. Among evaluable children, 15 (83.3%) children achieved CyGR of them 11 (61.1%) have complete and 4 (22.2%) children have partial CyGR, while 3 (16.6%) children have minimal or no CyGR. Among 11 children with complete CyGR, all (100%) children were in major molecular remission (MMR) at time of last follow up. At median follow up of 10.5 years (range, 120–240months), 12 (40%) children failed on IM therapy of which 3 (10%) children developed primary IM resistance while 9 (30%) children developed secondary IM resistance (4 had hematological progression and 5 children progressed to AP/BP). Median time to progression was 2.5 years (range, 1–11years). Among children who developed BP, 3 were on regular IM treatment. Time to develop AP/BP was at 36, 36 and 120 months of IM treatment. Two children were lost to follow up and not on any treatment and then presented with BP, one of them died and 1child is

on follow up after crisis. Among 27 eligible children, at 3 years follow up, 22 (81.5%) remained progression free and all children (100%) were alive. At 7 years of follow up 12 (44.4%) children remained progression free and 7 were lost to follow up, while at 10 years 9 children are on treatment and progression free. One child progressed to BP at 10 years of follow up. One child has completed 20 years of treatment.

Toxicity:

Overall IM was well tolerated. IM related severe toxicity (grade III–IV) were infrequent. One child developed grade IV febrile neutropenia and 2 children developed severe thrombocytopenia requiring interruption of treatment and subsequent dose reduction. Non haematological toxicities were uncommon except hypopigmentation of skin which was seen in 60% of the cohort. None of the children developed overt cardiotoxicity. There was no treatment related death. Findings of toxicity are summarized in Table 2.

Discussion

The data on the clinical and laboratory parameters, safety and efficacy of IM and long term outcome of CML–CP treated with IM alone in children are scanty. CML in children is a rare disease. A phase I study from the children's oncology group included 31 children from 23 centers, indicative of the rarity of CML in children [7]. In an analysis of French group [14] from 16 paediatric units over 12–year period, only 40 children were included. A comparison between IM and allogeneic SCT, as the therapy for childhood CML, included 30 children in the IM arm and 18 children in the allogeneic SCT arm [15]. Current study of 30 children is one of the largest (and longest median follow up of 10.5 years) study from a single tertiary care centre, catering to children from the lower socioeconomic strata. CML–CP in children affects older boys. In current study, median age at time of diagnosis was 11 years (range, 4–14years). Twenty three (76.6%) children were 10–14 years of age group. In Egypt, a study by Mohsen et al [15] reported median age of 11 years in IM arm. Median age at time of diagnosis was 12 and 13 years in study by Vijay Gandhi et al [16] and Ghadayalpatil et al [17] respectively from India. In another study from India by Lalit Raut et al [18], 61% of the children belonged to the age group of 15–17 years. In an analysis from the French group [19] the significant (47%) number of children belonged to the 10–14 year age group. As found in the analysis from the French group, boys predominated in numbers in current study [19]. Boys to girls' ratio were 5:1 in current study which is consistent with many other studies [16–19]. This high gender ratio could be explained due to referral bias or since this is a hospital based registry.

Toxicity	Number (%)
Hypopigmentation of skin	18 (60)
Fatigue	3 (10)
Anaemia	3 (10)
Thrombocytopenia	2 (6.6)
Oedema or weight gain	2 (6.6)
Skin rash	2 (6.6)
Liver function abnormality	1 (3.3)
Diarrhea	1 (3.3)
Muscle cramps	1 (3.3)
Neutropenia	1 (3.3)

Table 2. Toxicity profile

Asthenia and abdominal discomfort due to splenomegaly were the predominant symptoms and splenomegaly was the predominant sign in current study. These findings are similar to other studies in CML in children [16–19]. The median haemoglobin, white blood cell counts, and platelet counts in current study are very similar to the analysis by Mohsen S. et al [15] and Lalit et al [18] but lower than the French analysis [19] (shown in Table 3). The small sample size and different patient population may have contributed to this variation.

IM is very effective in inducing high hematologic response. In current study, 27 out of 30 (90%) children achieved CHR. High CHR observed is comparable to other Indian and International studies. In the Egyptian study by Mohsen et al [15], CHR was observed in 29 out of 30 (97%) children. In Indian study by Vijay Gandhi et al [16] 61 of 64 (95.4%) children achieved CHR. Another study by Lalit Raut et al [18], CHR was documented in 11 out of 12 (91%) children. In French study [19] 43 out of 44 (98%) achieved CHR. Cytogenetic response with IM is variable in various studies. In study by Vijay Gandhi et al [16], only 37 (57.8%) children had evaluation of CyGR with mean time to attain best cytogenetic response was 13 months, 29 (78.3%) patients achieved complete CyGR, 5 (13.5%) had minor CyGR; and 1 (2.7%) each had minimal, partial, and no response. In study by Lalit Raut et al [18], a complete CyGR was seen in 3 of 4 (75%) patients. Ghadyalpatil et al [17] , reported 89.5% complete CyGR at median time of 10 months (range 3–31 months) in childhood CML. Phase I study of Children's Oncology Group by Champagne et al [7,13] reported that 12 children who were previously treated

Parameters	Current study (N=30)	Mohsen et al [15] (N=48)	Lalit Raut et al [18] (N=13)	Millot et al [19] (N=40)
Median haemoglobin (g/dl)	9	8	9.5	11.1
Median white cell count ($x10^9$/L)	15	13.9	6.5	24.2
Median platelet count (x 10^9 /L)	464	223	462	622

Table 3. Comparison of hematologic parameters among various studies [15, 18, and 19]

with interferon–α 10 had complete CyGR and 1 patient had partial CyGR. A case series from Memorial Sloan Kettering Cancer Centre [20] reported that 2 children in early phase and 2 children in late CP achieved complete CyGR. In adult CML, in International Randomized study of Interferon versus STI 571(IRIS) data of 8 years of follow up, complete CyGR was 69% at 1 year and 87% at 5 years [21]. In the current study, 18 (60%) children had evaluation for CyGR. Among evaluable children, 15 (83.3%) achieved CyGR (complete 61.1%: and partial 22.2%). Those who achieved complete CyGR were in MMR at time of last follow up. In current study, large majority of children (11 out of 30) received IM late in the course of their disease. All children were treated with hydroxyurea for median of 4 months (range, 5–91months).

The dose of IM used was 260–340mg/m2. For the children who had suboptimal response to 260mg/m^2, the dose of IM was hiked to 340 mg/m^2. Champagne et al [13] studied children on IM at doses ranging from 260 to 570 mg/m^2. Doses ranging from 260–340 mg/m^2 provided systemic exposure similar to those for adult patients who were treated with daily doses of 400–600 mg/m^2 respectively. In current study, severe (grade III–IV) events were infrequent except 1 child with grade IV febrile neutropenia. Overall IM shows good toxicity profile and frequency of side effects is comparable to other Indian study by Ghadyalpatil et al [17], Francis J et al [22] and Biswajit et al [23]. Hypopigmentation was the only dominant side effect reported in current study. There was no treatment related death in current study.

Data on long term survival of childhood CML–CP is limited. In a prospective study by Mohsen et al [15], 6 years EFS and OS was 66% and 87% respectively. A study from India by Vijay Gandhi et al [16], reported at median follow up of 36 months (range 5–75), 21 (56.8%) remained progression free and 35 (94.5%) were alive. Ghadyalpatil et al [17] reported event–free survival (EFS) and OS 74.1 and 100%, respectively at a median follow–up of 29 months. In a study by Lalit Raut et al [18], the estimated OS and PFS was 84% and 100% respectively after median follow–up of 21 months. Biswajit et al [23] reported 3–year EFS and OS as 86.2 and 89.5%, respectively in young CML patients. Lakshmaiah et al [24] reported EFS and OS at 43 months as 92.8 and 100%, respectively. In current study, median follow up was 10.5 years (range, 120–240months) and median time to progression was 2.5 years (range, 1–11years). Majority of progression occurred within first 5 years of diagnosis. At 3 years PFS was 84.5% and OS 100%. At 7 years PFS was 44.4%. At 10 years, 12 (40%) children failed on IM therapy of which 3 (10%) children developed primary IM resistance while 9 (30%) children developed secondary IM resistance. Due to high dropout rate the long term survival of all children is not available. In current study, adherence to treatment was not formally assessed. In IRIS study [21] at the 8 year data cut–off, 304 (55%) patients remained on IM study treatment and 45% discontinued treatment due to variety of reasons. In a study by Amar Ibrahim et al [25] and Martin D et al [26] poor adherence is the principal factor contributing to treatment failure in patients on long–term therapy. In another Indian study by Prasanth G et al [27] reported compromise on EFS with non–adherence of therapy in CML. IM being lifelong and oral treatment; adherence to treatment is challenging especially when child is under remission. It is assumed by the parent that he or she is cured. There is significant dropout rate of almost 25% over the median follow up of 10.5 years. The reasons could be due to our centre caters children mostly from lower socioeconomic group with low literacy rate. Late presentation, prior treatment with hydroxyurea, lack of adherence to treatment, high dropout and poor economics may have influenced the overall long term outcome of treatment.

With the help of patient assistance programme, government run health schemes and subsequent availability of generic brand of IM, it was possible to treat all children with IM. The current study may not reflect the state of the art management of CML–CP but it shows the real picture of patient care at a tertiary care centre in a developing country.

Study Limitations

Major limitations of our study are the following: it is a retrospective study with small sample size, treated with IM alone and poor compliance with high dropout rate. Major challenges faced in management of CML–CP are late presentation, poor socioeconomic condition, low literacy rate, irregular follow up and lack of understanding compliance.

Conclusion

Presenting features of CML–CP in children is identical to other Indian and international studies. IM is very effective and safe drug for the first line treatment of CML–CP in children. It is very effective in inducing CHR. As this is lifelong and oral treatment, adherence to treatment and regular follow up is very challenging. Study of effect of allogeneic SCT or second line TKIs are needed to assess the better outcome. Collaborative efforts from different centres and well–designed prospective study are necessary in CML–CP in children to determine long–term outcome with IM.

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