

Clinical Profile and Response to First Line Treatment in Chronic Phase of Chronic Myeloid Leukaemia

Sivasubramaniam K.¹, Latha K. V.S.², Abhishek R.³, Niranjana V.⁴,
Tintu M.V.⁵, Jyothis P. Jose⁶, Rahul T.S.⁷, Senthilkumar E.⁸

^{1, 2, 4, 5, 6, 7, 8} Department of Medical Oncology, Madras Medical College, Chennai, Tamilnadu, India.

³Department of Haematology, Madras Medical College, Chennai, Tamilnadu, India.

ABSTRACT

BACKGROUND

Chronic Myeloid Leukaemia (CML) usually occurs in the elderly population and its incidence is higher in India. Chronic Phase (CP) is treated with tyrosine kinase inhibitors (TKI) as first line until progression. Stem cell transplant is usually not done in chronic phase and it is reserved for accelerated phase and blast crisis. The exact incidence and treatment data from various institutions in India is lacking.

METHODS

81 patients diagnosed with chronic phase CML in our institute over a period of 5 years were analysed from the master case records. Their clinical profile, lab parameters, response to treatment with Imatinib and side effects of treatment were analysed. Data was analysed using SPSS version 23.

RESULTS

Median age of patient (n = 81) was 44 years (range 31 - 71 years). Majority of patients presented in the 5th decade (43.2 %). Left hypochondrial pain was the most common complaint (84 %) followed by fatigue (80.2 %). 72.8 % patients had WBC count of more than a lakh, and thrombocytosis in present in 63 %. Median blast count was 1.8 %. 18 (22.2 %), 52 (64.2 %) and 11 (13.6 %) patients (n = 81) had low, intermediate and high Sokal index respectively. CHR was achieved in 87.7 % of patients (n = 71) at 3 months. 92.6 % (74 patients) achieved CHR at 6 months. Median time to achieve CHR was 39 days. 2.5 year Progression free Survival (PFS) was 67.9 % and 2.5 year Overall Survival (OS) was 72.8 % combining all 3 risk categories in Sokal index. Most common toxicity was anaemia and its seen in 39.5 % (32 patients) followed by Thrombocytopenia seen in 30.9 % (25 patients).

CONCLUSIONS

Imatinib showed good response with manageable side effects in chronic phase CML in our institute. It is cost effective especially in the low socioeconomic group.

KEY WORDS

Chronic Myeloid Leukaemia, CML, Imatinib, Side Effects, First Line Treatment, Complete Hematologic Response, Progression Free Survival, Overall Survival

Corresponding Author:

*Dr. Latha K.V.S.,
Madras Medical College,
Park Town, Chennai – 600006,
Tamilnadu, India.
E-mail: kvslatha63@gmail.com*

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BACKGROUND

Chronic myeloid leukaemia arises from genetic aberration in precursor haematopoietic stem cell leading to uncontrolled proliferation of myeloid cells. In initial phase, more number of differentiated myeloid cells are formed and hence disease looks quiescent. It usually affects people in their 5th or 6th decade and forms around 15 to 20 % of all adult leukaemia.¹ There is a slight male predominance of disease.² Ionizing radiation has been found to be a risk factor.³ It belongs to the myeloproliferative group of disorder. The disease is caused due to fusion of two genes namely BCR gene located on chromosome 22 and ABL1 gene located on chromosome 9. The reciprocal translocation of these two genes form t(9;22)(q34;q11) known as Philadelphia chromosome. The BCR-ABL1 fusion gene forms BCR-ABL1 fusion product that has tyrosine kinase catalytic activity thereby forming unregulated production of myeloid cells. Apart from neutrophils, other myeloid lineages namely basophils and eosinophils are also usually elevated in this disease. CML was the first cancer to be consistently associated with a known and specific translocation. Ionizing radiation exposure is the only known risk factor so far. Familial predisposition though rare can be seen in some cases usually due to Philadelphia chromosome or JAK2 mutation that is transmitted in an autosomal dominant fashion. Though rare three phases of disease have been noted namely Chronic Phase (CP), Accelerated Phase (AP) and Blast Phase (BP) and around 90 - 95 % of patients present in chronic phase at presentation. As the disease progresses from chronic phase to accelerated or blast crisis there is block in formation of differentiated cells and more number of blasts start circulating. There is rapid decline in platelet count also. Most of the patients (30 - 50 %) are diagnosed incidentally during evaluation for other conditions.⁴ Other presenting complaints can be fatigue, weight loss, fever, malaise, abdominal fullness due to splenomegaly, inappropriate sweating, etc.⁴ Diagnosis is by peripheral smear and bone marrow aspiration or biopsy and demonstration of Philadelphia chromosome by either conventional karyotyping (90 %) or FISH (Fluorescence In Situ Hybridization) or RT-PCR (Real-Time Reverse Transcription Polymerase) methods.⁵ Prognosis of CML patients depends upon age of the patient, initial spleen size, percentage of blast cells and platelet counts as described by Sokal Index and ELTS scoring system. Hasford score includes eosinophil and basophil count along with the other parameters used in Sokal and ELTS system. These scoring systems guide the clinicians to choose the specific generation of tyrosine kinase inhibitors based on the previous trials. In early days chemotherapeutic drugs like busulfan, hydroxyurea, and splenic irradiation were used as treatment with minimal response. Stem cell transplant was also used but with a lot of morbidity and mortality. In 2002, the introduction of imatinib in the market for treatment of CML made a tremendous impact.⁶ and the number of bone marrow transplants done upfront for this disease came down dramatically. Imatinib is a tyrosine kinase inhibitor in ABL protooncogene. With the usage of imatinib more treatment response guides came into practice like Complete Haematologic Response (CHR), Cytogenetic Response (CR) and Molecular Response (MR). Problem during drug therapy is

side effects of imatinib and drug compliance and most of the patients will ultimately progress to AP or BP.⁷

METHODS

This is a descriptive study. Patients diagnosed with CML from January 2013 to December 2017 were searched from our medical records. A total of 97 patients were found, among whom 88 were in chronic phase at the time of diagnosis. Among them 7 patients who did not receive continuous treatment or lost for follow up were excluded and hence 81 patients were analysed. Details including age, sex, presenting complaints, their duration, clinical examination findings, lab results, Sokal index, general condition of patient and comorbidities were noted down and analysed.

Statistical Analysis

SPSS version 23 software was used for statistical analysis including descriptive study, response rate to imatinib, and side effect profile with imatinib. Mean, median, mode, range, percentages, response rate are all calculated using the software.

RESULTS

Out of 97 patients 90.7 % (88 patients) presented in chronic phase. Among them 81 patients who were started on imatinib mesylate were analysed in this manuscript. Median age of patient (n = 81) was 44 years (range 31 - 71 years). Since our department deals with adult patient's paediatric CML were not registered. 49 (60.5 %) were male and 32 (39.5 %) were female. Table 1 shows number of patients in each age-group and majority of patients were in their 5th decade (43.2 %) and 16 % of patients presented in their 4th decade. Nearly 80 % of patients were symptomatic at the time of presentation with fatigue and left hypochondrial pain being the most common presentation with a median duration of 7.5 months (range 6.5 - 8.5) combined for both these symptoms. (Table 2). Only 18.5 % (n = 15) of patients were diagnosed incidentally. Splenomegaly was present in 86.4 % (n = 70) of patients while massive splenomegaly was present in 49.4 % (n = 40) of patients. 32.1 % (n = 26) patients had fever, 7.4 % (n = 6) patients had hepatomegaly 39.5 % (n = 32) patients had pallor and bleeding was very rare at presentation.

Lab parameters of all the patients are listed in Table 3. White Blood Cells (WBC) count was more than a lakh in 72.8 % (n = 59) of patients. Mild anaemia was present in 22.2 % (n = 18) of patients and moderate anaemia in 16 % of patients. Most of them were normocytic and normochromic. Thrombocytosis was present in 63 % of patients and more than 6 lakh cells was present in 46.9 % of patients (n = 38). Basophilia was present in more than 95 % of patients. Myeloblast count was less than 2 % in 83.9 % (n = 68) of patients with a median blast count of 1.8 % (range 0.5 - 8 %). Initial diagnosis was done by karyotyping in majority of the patients (96.3 %) and remaining were diagnosed by Fluorescent in situ hybridization. After diagnosis patients were classified according to Sokal index score as low (< 0.8),

intermediate (0.8 - 1.2) and high risk (> 1.2) to know the prognosis of the patient. 18 (22.2 %), 52 (64.2 %) and 11 (13.6 %) patients (n = 81) had low, intermediate and high Sokal index respectively. All of them were started on imatinib 400 mg according to institutional protocol based on its long-term result from IRIS study.⁸

Monthly history and physical examination, complete blood count and spleen size were noted. Adherence to imatinib therapy was strictly monitored. Complete Haematological Response (CHR) was aimed after treatment initiation which includes disappearance of symptoms, normal spleen size, disappearance of blasts in peripheral smear, normal basophil count and platelet count less than 4.5 lakhs. CHR was achieved in 87.7 % of patients (n = 71) at 3 months. Among 10 patients (12.3 %) who did not achieve CHR, 4 patients (4.9 %) were found to have poor drug compliance in spite of initial counselling. They were again counselled and 3 patients achieved CHR in a month and the other one after 2 months. 92.6 % (74 patients) achieved CHR at 6 months. Cytogenic and molecular response assessment were done if patients are affordable at 6 months or whenever there is haematological failure. Median time to achieve CHR was 39 days. 2.5-year Progression Free Survival (PFS) was 67.9 % and 2.5-year Overall Survival (OS) was 72.8 % combining all 3 risk categories in Sokal index.

Most of the patients tolerated imatinib well with side effects ranging from 20 - 40 %. Haematological toxicities were more common than non-haematological. Most common toxicity was anaemia which is seen in 39.5 % (32 patients) with only 10 % requiring blood transfusion. Thrombocytopenia was seen in 30.9 % (25 patients) and most of them recovered within 1 - 2 weeks after withholding the drug. Neutropenia was present in 18.5 % (15 patients). Pedal oedema was the most common non haematological toxicity seen in 25.9 % patients followed by skin changes in the form of hypo or hyperpigmentation in 23.5 % of patients. Musculoskeletal pain was present in 22.2 % of patients (n = 18) and diarrhoea usually grade 1 - 2 in 11.1 % of patients at some point of time and managed conservatively. Elevated Liver Function Test (LFT) was present in 9 patients (11.1 %) and no one developed more than five times the upper limit of liver enzymes.

Age in Years	Number (%) n = 81
< 30	-
30 - 40	13 (16)
40 - 50	35 (43.2)
50 - 60	24 (29.2)
60 - 70	7 (8.6)
> 70	2 (2.5)

Table 1. Age Distribution

Symptom / Sign	Number (%)	Median Duration in Months
Asymptomatic	15 (18.5)	-
Fatigue	65 (80.2)	8.5
Left hypochondrial Pain / Fullness	68 (84)	6.5
Fever	26 (32.1)	0.5
Splenomegaly	70 (86.4)	-
< 5 cm	11 (13.5)	-
5 - 8 cm	19(23.5)	-
> 8 cm	40(49.4)	-
Hepatomegaly	6 (7.4)	-
Pallor	32 (39.5)	-
Bleeding	1 (1.2)	0.3
Lymphadenopathy	4 (4.9)	-

Table 2. Presentation

Lab Parameter	Number (%) n = 81
WBC Count (cells / µl)	81 (100)
< 50,000	8 (9.9)
50,000 - 1,00,000	14 (17.3)
> 1,00,000	59 (72.8)
Haemoglobin (gm / dl)	
< 8	7 (8.6)
8 - 10	13 (16)
10 - 12	18 (22.2)
Platelet (Lakhs Cells / µl)	
4.5 - 6	13 (16.04)
> 6	38 (46.9)
Basophilia (> 200 cells / µl)	79 (97.5)
Blast % in PS or Marrow	
< 2	68 (83.9)
2 - 5	9 (11.1)
5 - 10	4 (4.9)
Philadelphia Chromosome	
Conventional Cytogenetics	78 (96.3)
FISH	3 (3.7)

Table 3. Lab Parameters of Patients

Adverse Effects	Number (%)
Anaemia	32 (39.5)
Neutropenia	15 (18.5)
Thrombocytopenia	25 (30.9)
Skin Changes	19 (23.5)
Pedal Oedema	21 (25.9)
Abnormal LFT	11 (13.6)
musculoskeletal Pain	18 (22.2)
Diarrhoea	9 (11.1)

Table 4. Adverse Effects

DISCUSSION

There was slightly increase in number of patients presented in chronic phase of CML (90.7 %) compared to that given in literature (around 85 %).³ Median age of the patient was also earlier (44 years) but in West and European countries it is usually between 50 - 70 years.⁹⁻¹¹ The reason behind early age of presentation is not known and will need special attention. Male predominance was also seen in our study population. Majority of the patients were symptomatic (80 %) while in other studies it was less than 50 %⁴ which can be correlated with ignorance of patients. More patients had fatigue (80.2 %) and left hypochondrial pain (84 %) which reflects advanced disease load and in turn reflects poor treatment outcome. The median duration of these symptoms is 7.5 months and it tells us the need for these patients to be suspected and referred early from primary and secondary care centres who initially see the bulk of the patients presenting here. Most of the times early symptoms which are nonspecific are neglected both by the patient and the initial treating physician. Patients diagnosed in asymptomatic stage are very less (18.5 %) whereas its 20 - 50 % in western literature.^{3,4} Splenomegaly also is very high compared to that given in Western literature⁴ and patient experiencing any form of discomfort due to splenomegaly like early satiety, dull aching hypochondrial pain, and abdominal distention which is the trigger to visit hospital in many patients. Anaemia was not a troublesome issue during presentation since only 8.6 % of patients had severe anaemia requiring blood transfusion. Anaemia can be due to various reasons that includes nutritional deficiency, splenomegaly and disease. 72.8 % of patients were having WBCs more than a lakh at the time of presentation which makes us to treat initially with xanthine oxidase inhibitors and hydroxyurea in some patients due to the fear of tumour lysis

syndrome although it is not done universally. Most of the patients (83.9 %) had less than 2 % blasts in peripheral smear and bone marrow and thereby give better response to TKI although other factors increase the overall Sokal index of the patient. Most of our patients (64.2 %) had intermediate Sokal index and 13.6 % of them had high risk score which suggests advanced disease. Imatinib was the first TKI used in CML patients and it has a very long term follow up results. Other advantage of imatinib is that it is less cost than second generation TKIs. Due to this various advantages imatinib is used in front line setting for all risk categories in our patients unless contraindicated or poorly tolerated. Complete Haematological Response (CHR) denotes disappearance of blasts in peripheral smear, basophils and WBC count normalizes and spleen becomes normal size. 87.7 % of patients had CHR which gives symptom relief to patients especially fatigue, hypochondrial pain and dullness. Oral formulation of the drug also makes it patient friendly and easy to administer. Due to financial constraints to conduct molecular and cytogenetic response tests, they are done less frequently than recommended in our set up and it is reserved for conditions like response failure or whenever drug resistance is suspected along with imatinib resistance mutation analysis. 67.9 % patients had PFS and 72.8 % patients had OS at the end of 2.5 year follow up which gives a reasonable result and avoids the burden of haematopoietic stem cell transplant in these patients. Long term results of IRIS study showed 10 year OS of 83.3 % and 82.8 % of patients had complete cytogenetic response.⁸ Dose of imatinib is given as 400 mg based on the previous results from studies that used 600 mg and 800 mg strengths that did not increase overall survival but produced more toxicity with higher doses.¹²⁻¹⁴ Side effect profile is favorable and most of them had haematological toxicity especially anaemia (39.5 %) and thrombocytopenia (30.9 %) which can be managed by withholding drug for 1 to 2 weeks. Skin changes, pedal oedema, myalgia and GI (Gastro-Intestinal) disturbances were present in less than 25 % of patients and were not a worrying issue. LFT though deranges in 13.6 % of patients most of them had elevated liver enzymes less than 3 - 5 times that of normal upper limit and recovered after withholding the drug and reducing the dose to 300 mg.

CONCLUSIONS

The milestones achieved in treatment of CML are numerous, but the worrisome part is that most of the patients will ultimately land up in AP or BP. Since India is a developing country, most of the centres use first generation TKI namely Imatinib, and second line TKIs are reserved for treatment failure and resistance to Imatinib.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

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