Original Research Article

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

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Abstract

Introduction: Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with an incidence of 1–2 cases per 100 000 adults. It accounts for approximately 15% of newly diagnosed cases of leukemia in adults. Chronic myeloid leukaemia arises from genetic aberration in precursor haematopoietic stem cells 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 5thor 6thdecade and forms around 15 to 20 % of all adult leukaemias.
Materials and Methods:A total of 194 patients were found, among whom 176 were in chronic phase at the time of diagnosis. Among them 14 patients who did not receive continuous treatment or lost for follow up were excluded and hence 162 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.**Results:**Out of 194 patients 90.7 % (177 patients) presented in chronic phase. Among them 162 patients who were started on imatinib mesylate were analysed in this manuscript. Median age of patient (n=162) was 44 years (range 31-71 years). Since our department deals with adult patient's paediatric CML were not registered. 98 (60.5 %) were male and 64 (39.5 %) were female. Table 1 shows number of patients in each age-group and majority of patients were in their 4th decade (42.59%).**Conclusion:**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.

Keywords: Chronic myeloid leukemia, Sokal index, TKI, Imatinib, AP, BC

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with an incidence of 1–2 cases per 100 000 adults. It accounts for approximately 15% of newly diagnosed cases of leukemia in adults[1].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[2].There is a slight male predominance of disease. Ionizing radiation has been found to be a risk factor.It belongs to the myeloproliferative group of disorder[3]. 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[4]. The BCR-ABL1 fusion gene forms BCR-ABL1 fusion product called protein 210 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[5].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[6].In 2002, the introduction of imatinib in the market for treatment of CML made a tremendous impact. and the number of bone marrow transplants done upfront for this disease came down dramatically. Imatinib is a tyrosine kinase inhibitor in ABL protooncogene[7].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 BC.

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Materials and Methods

Study design: This is a descriptive study.

Study Duration: Patients diagnosed with CML from January 2020 to December 2020 were searched from our medical records.

Study location: Department of Radiotherapy, Govt Medical College, Jammu,India.

A total of 194 patients were found, among whom 177 were in chronic phase at the time of diagnosis. Among them 15patients who did not receive continuous treatment or lost for follow up were excluded and hence 162 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 194 patients 90.7 % (177 patients) presented in chronic phase. Among them 162 patients who were started on Imatinibmesylate were analysed in this manuscript. Median age of patient (n=162) was 44 years (range 31-71 years). Since our department deals with adult patient's paediatric CML were not registered. 98 (60.5 %) were male and 64 (39.5 %) were female. Table 1 shows number of patients in each age-group and majority of patients were in their 4thdecade (42.59%) . 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 = 30) of patients were diagnosed incidentally. Splenomegaly was present in 86.4 % (n = 140) of patients while massive splenomegaly was present in 49.4 % (n= 80) of patients. 32.1 % (n = 52) patients had fever, 7.4 % (n = 12) patients had hepatomegaly ,39.5 % (n = 64) patients had pallor while bleeding was very rare at presentation.

Most of the patients tolerated Imatinib well with side effects occuringin 20-40% cases.Haematological toxicities were more common than non-haematological. Most common toxicity was anaemia seen in 39.5% (64 patients) with only 10% requiring blood transfusion. Thrombocytopenia was seen in 30.9 % (50 patients) and most of them recovered within 1-2 weeks after withholding the drug. Neutropenia was present in 18.5 % (30 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 = 36) 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 18 patients (11.1 %) and no one developed more than five times the upper limit of liver enzymes.

Table 1: Age Distribution

S.No	Age in years	Number (%) n=162
1	<30 years	5 (3.08%)
2	30-40 years	20 (12.34%)
3	40-50 years	69 (42.59%)
4	50-60 years	48 (29.62%)
5	60-70 years	14 (8.64%)
6	>70 years	6 (3.70%)

Table 2: Presentation

S.No	Symptom	Number	Percentage
1	Asymptomatic	30	18.5%
2	Fatigue	130	80.2%
3	Left hypochondrial Pain/Fullness	136	6.5%
4	Fever	52	0.5%
5	Splenomegaly	140	86.4%
	<5 cm	22	13.5%
	5-8 cm	38	23.5%
	>8 cm	80	49.4%
6	Hepatomegaly	12	7.4%
7	Pallor	64	39.5%
8	Bleeding	2	1.2%
9	Lymphadenopathy	8	4.9%

Table 3: Lab Parameters of Patients

Lab Parameter	Number (%) N=162
WBC count (cells/ul)	162 (100)
<50,000	16(9.9)
50,000-100000	28 (17.3)
>1,00,000	118(72.8)
Haemoglobin (gm/dl)	
<8	47(29.01)
8-10	53(32.71)
10-12	62 (38.27)
Platelet (lakh cells/ul)	
4.5-6	65(40.12)
>6	97 (59.87)
Basophilia (>200 cells/ul)	158(97.5)
Blast % in PS or Marrow	
<2	136(83.9)
2-5	18(11.1)
5-10	8(4.9)
Philadelphia Chromosome	
Conventional Cytogenetics	156(96.3)
FISH	6(3.7)

Table 4: Adverse effects

S.No	Adverse effects	Number (%)
1	Anaemia	64 (39.5%)
2	Neutropenia	30 (18.5%)
3	Thrombocytopenia	50 (30.9%)
4	Skin changes	38 (23.5%)
5	Pedal Oedema	42 (25.9%)
6	Musculoskeletal pain	36 (22.2%)
7	Diarrhoea	18 (11.1%)

Discussion

In our study, increased number of patients presented in chronic phase of CML (90.7 %) compared to that given in literature (around 85 %). Median age of the patients was also early (44 years) but in West and European countries it is usually between 50-70 years. The reason behind early age of presentation is not known and will need special attention. Male predominance was also seen in our study population[8].Majority of the patients were symptomatic (80%) while in other studies it was less than 50% 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[9].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. Splenomegaly also is very high compared to that given in Western literature 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 a troublesome issue during presentation since 39.5 % of patients had severe anaemia requiring blood transfusion. Anaemia can be due to various reasons that includes nutritional deficiency, splenomegaly and disease[10].Side effect profile is favorable and most of them had hematological 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[10]

Conclusion

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 BC. 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.

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