RESEARCH COMMUNICATION

Overview of Chronic Myeloid Leukemia Patients in Pakistan in the Pre-Imatanib Era

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Abstract

Objectives: To study the patient characteristics of patients diagnosed with chronic myelogenous leukemia (CML) at a tertiary care cancer hospital in Pakistan. Methods and Materials: A retrospective analysis was conducted on CML patients treated between 1996 and 2004 at Shaukat Khanum Memorial Cancer Hospital & Research Center. Results: A total of 461 CML patient charts were reviewed. The mean and median ages at presentation were much younger than in the prior reports in the western literature with a quicker progression of disease. Conclusion: The advent of tyrosine kinase inhibitors will likely have more impact on the lifespan of CML patients in Pakistan when compared with patients in the western hemisphere due to younger age at diagnosis.

Key Words: chronic myelogenous leukemia - imatinib - young patients

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Introduction

Chronic myelogenous leukemia (CML) is a clonal hematopoietic disorder characterized by a balanced, reciprocal chromosomal translocation between chromosome 9 and 22 (also known as the Philadelphia chromosome). This translocation results in transcription and translation of the constitutively active BCR-ABL tyrosine kinase, which is central to CML pathogenesis (de Klein et al., 1982). The translocation occurs at the pluripotent stem cell level, therefore, the Philadelphia chromosome and BCR-ABL tyrosine kinase is also seen in erythroid, myeloid and megakaryocytic lineage cells (Deininger et al., 2002). CML has a worldwide incidence of 1.6 to 2 cases per 100,000 population per year and accounts for approximately 15% of all adult leukemias (Riel et al., 2003). In western literature, the median age at presentation is 66 years with a small male predominance [2.2(M):1.3(F)].

The introduction of imatinib, a tyrosine kinase inhibitor (TKI), in CML management has transformed the field of cancer therapeutics. Imatinib specifically targets the ATPase pocket of the BCR-ABL tyrosine kinase, thereby allowing the cells to differentiate normally. CML has moved on from being a life-threatening disease to a chronic illness in the span of a decade. Two more TKIs (Table 1) have been US-FDA approved to add to the hematologist's arsenal with more in the developmental pipeline. We wanted to evaluate the epidemiology of this disease at a tertiary care institution in Pakistan during the transitional period where imatinib had not made its way to the developing countries.

Materials and Methods

The data were collected retrospectively from the medical files of 461 patients registered at SKMCH & RC from Dec1994-September 2003. SPSS Version 10.0 was utilized for all data entry and statistical analyses.

Results

Age/Gender/Demographics: 297(64%) were males while 164(36%) were females. Mean and median age for the males was found out to be 36.5 yr. and 31yrs with a range of 18-76 years, and for females it was 39yrs, 36yrs and range of 19-72 years. At SKMCH&RC, 92% were from Punjab, 5% from NWFP, 2% from Sindh and 1% from Balochistan.

Presenting Symptoms/Signs: More than 95% patients had presented with fever, fatigue, left upper quadrant pain or a combination of the above to other hospitals where the diagnosis was suggested on CBC. Splenomegaly was present in 90% of chronic phase, in 97.5% of accelerated phase while all patients had splenomegaly in the blast phase.

Investigations: The ajority of patients were referred to clinics due to complete blood count abnormalities and symptoms (>95%) at presentation but bone marrow biopsy was done in less than 70% before being referred to SKMCH & RC. Philadelphia chromosome was checked in 112 (24%) aspirate samples and 99% of those samples (111/112) were positive. Leukocyte alkaline phosphatase (LAP) score was checked only in 49 patients and was found to be low in all cases (average ~24).

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Table 1. Tyrosine Kinase Inhibitors Available for Treatment of Chronic Myelogenous Leukemia

Inhibitor	Indications in Adults (excluding Philadelphia chromosome +ve ALL)	Recommended Dose	Administration Requirements	Main Side Effects
Imatinib (Gleevec®)	Newly diagnosed patients with Ph+ CML-CP Patients with Ph+ CML (all phases) after failure of interferon-α	CML-CP: 400 mg once daily CML-AP/-BP: 600 mg 1x daily	Doses should be taken with a meal and a large glass of water	Myelosuppression, elevated liver enzymes, edema/fluid retention, congestive heart failure/ LV dysfunction, bullous dermatologic reactions, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, fatigue, abdominal pain
Dasatinib (Sprycel®)	For the treatment of adults with any phase CML with therapy resistance or did not tolerate prior therapy (including Imatinib)	CML-CP: 100 mg once daily CML-AP/-BP: 70 mg 2x daily	None	Myelosuppression, pleural effusions, bleeding,QT prolongation, diarrhea, headache, nausea, rash, fatigue, dyspnea
Nilotinib (Tasigna®)	For the treatment of Ph+ CML-CP/-AP therapy resistance or did not tolerate prior therapy (including Imatinib)	CML-CP/-AP: 400 mg 2x daily	Avoid food 2 hours before and 1 hour After consumption	Myelosuppression, elevated liver enzymes, elevated serum lipase, electrolyte abnormalities, QT prolongation (black box warning), rash, pruritus, nausea, fatigue, head-ache, constipation, diarrhea, vomiting

Data from Bristol-Myers Squibb Company Sprycel® (dasatinib) prescribing information and Novartis Pharmaceuticals Corporation Gleevec® (imatinib) and Tasigna® (nilotinib) prescribing information; ALL, Acute lymphoblastic leukemia; CML-chronic myelogenous leukemia; CP, chronic phase; AP,accelerated phase; BP, blast phase

CML Phase at Presentation, Choice of Therapy and Response: Eight seven percent presented in chronic phase, 9% in accelerated and 4% in blast phase. Majority of the patients were treated with Hydrea at SKMCH&RC. Sixty five percent had been started on Hydrea or Busulfan while Interferon and Imatinib were used in 9% and 3 %, respectively. Palliative radiation was given to enlarged spleen to 38 patients in either accelerated or blast phases. Three hundred patients were lost to follow up. The average duration of different phases for the patients who continued to follow were chronic, 46-48 months; accelerated, 4.5-7 months; and blast phase 3-5 months.

Discussion

The data presented in the paper highlight a number of features which are unique to the CML patients in Pakistan. In our population, the median age at presentation is found to be younger than what is quoted in the western literature while the age ranges are approximately the same. A higher predilection for males is observed. The duration of chronic, accelerated and blast phases in the western literature is reported to be 48-60 months, 9-18months and 3-6months, respectively.

We noticed a trend towards shorter chronic and accelerated phases in our population. This is most likely the result of genetic / biological variation of the disease. A high failure to follow up rate did not allow for an accurate analysis of data on therapy and its effect, progression free survival and overall survival. Therapy with interferon and transplant could not be provided due to availability and financial reasons.

CML has evolved from an incurable hematologic disorder to a chronic disease for the majority of patients. The introduction of tyrosine kinase inhibitor (TKI) Imatinib, and now second generation TKIs, have not only changed the natural history of this disease but also provided a template to follow for other malignancies. This paper is a descriptive account of the salient features of CML patients presenting at Shaukat Khanum Memorial Cancer Hospital & Research Center (SKMCH & RC, Lahore, Pakistan) during 1996-2004 in the pre-TKI era. The paper highlights the younger age of presentation and presence of symptoms in our patient population, signifying the need for diagnostic vigilance and access to the TKIs for these patients in the modern era. It would be interesting to evaluate the impact of the TKIs in our younger patient population in the next few years.

References

de Klein A, van Kessel AG, Grosveld G, et al (1982). A cellular oncogene is translocated to the Philadelphia chromosome in chronic myelocytic leukaemia. *Nature*, **300**, 765.

Deininger MW, Goldman JM, Melo JV (2000). The molecular biology of chronic myeloid leukemia. *Blood*, **96**, 3343.

Ries L, Eisner M, Kosary C, et al (2003). SEER cancer statistics review, 1975–2000. Bethesda, MD: National Cancer Institute.