Hematologic and cytogenetic responses of Imatinib Mesylate and significance of Sokal score in chronic myeloid leukemia patients

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Abstract

Aim: The objectives of this study were to evaluate the effects of treatment with Gleevec (Imatinib mesylate) in the chronic stage of chronic myeloid leukemia (CML), to follow up the hematological and cytological remissions in patients treated in this way and to observe the significance of Sokal score in these patients.
Methods: Evaluation study of Imatinib mesylate responses in chronic phase of chronic myeloid leukemia and the significance of Sokal score was performed at the Haematological and Genetic Service in University Hospital Center ¨Mother Theresa'' in Tirana, Albania on a sample of 70 CML patient's with an average age of 48 years old (range, 18-72 years old) at the time of diagnosis. This study was conducted from April 2011 to April 2013. Hematologic and cytogenetic responses were assessed according to defined criteria. At the end of the study, responses were overall analyzed according to Sokal score.
Results: Complete hematologic responses were seen in 91% of patients while complete and major cytogenetic responses were observed in 59% and 78% of cases respectively. Responses were found to be higher in patients who had low Sokal score at the time of presentation.
Conclusions: Imatinib mesylate has a substantial activity in the chronic phase of CML. A low Sokal score predicts a higher hematologic as well as cytogenetic response in patients during chronic phase.

Keywords: chronic myeloid leukemia, cytogenetic response, hematological response, imatinib mesylate, Sokal score.

Introduction

Chronic Myeloid Leukemia (CML) is a clonal disease characterized by balanced translocation between the long arms of chromosomes 9 and 22 (Philadelphia chromosome). This translocation results in the head-to-tail fusion of the breakpoint cluster region (BCR) gene on chromosome 22 at band q11 with the Abelson (ABL) proto-oncogene on chromosome 9 at band q 34. The Ph chromosome is found in 95% of patients with CML, the remaining cases have no cytogenetically visible Ph chromosome, but are positive for the BCR-ABL fusion which is masked either as a cryptic translocation or within a complex karyotype. The resulting BCR-ABL gene is translated into a fusion protein known as p210 because it has a molecular weight of 210 kDa and has tyrosine kinase activity which stimulates cellular growth. Imatinib mesylate (Gleveec) is a specific and potent inhibitor of the BCR-ABL tyrosine kinase which gives hematologic and cytogenetic results in CML patients during the chronic phase (1).

Imatinib mesylate (Gleevec) is the most successful among a new generation of specific inhibitors of signal transduction. It inhibits the BCR/ABL tyrosine kinase activity by competing with ATP at the ATP binding site of BCR/ ABL, leading to decreased phosphorylation on the tyrosine activity (2). Imatinib is easy to administer orally, and has relatively few side effects. The drug is rapidly absorbed, reaching a maximum plasma concentration 2-4 hours after oral administration . It is metabolized by the liver, mainly via the cytochrome P 450, and primarily eleminated via feces. Response to therapy is defined as hematological and cytogenetic remissions and clinical trials of imatinib mesylate have shown promising results in chronic phase of CML. Here, we analyze the response rate of imatinib mesylate in chronic phase of chronic myeloid leukemia and the significance of Sokal score (3,4).

Methods

From April 2011 to April 2013, 70 patients were analyzed, all diagnosed at the Haematological Service and Genetic Service of University Hospital Center ¨Mother Theresa¨ with myeloid leukemia in chronic phase. Eligible patients should not have received treatment for CML before and were randomly assigned to receive imatinib as the initial therapeutic treatment ambulatory at a dose of 400 mg orally per day (5). Results were determined by clinic examination, analysis of peripheral blood and presence of Philadelphia chromosome. Patients were allowed to cross over to the other treatment group if they did not achieve either a complete hematologic response after 6 months of therapy, or a major cytogenetic response after 12 months; if they had a relapse or an increase in white cell count or could not tolerate treatment (6). All patients underwent a complete physical examination and the baseline spleen size was recorded. Complete hematological responses (CHR) were defined as normalization of the peripheral leukocyte count when $<10 \times 10^9$/ L and when platelets $< 450 \times 10^9$/L without peripheral blasts, promyelocytes and myelocytes, while cytogenetic response was based on the proportion of the Ph-positive metaphases among at least 25 metaphases. Responses were defined as complete cytogenetic response CCR (0% Ph-positive metaphases), partial cytogenetic response PCR (Ph-positive 1-35%), minor cytogenetic response MCR (35-65% Ph-positive) and the rest of the other responses were merged in a single category named no-cytogenetic response (> 65% Ph positive metaphases). Major cytogenetic response was characterized as combination of both complete and partial cytogenetic responses. Cytogenetic response was not assessed in patients with overt hematologic progression (7). Sokal score was applied in patients for risk stratification at the beginning of the study by using four clinical variables: age, size of spleen, percentage of blast cells and platelet count. The hazard ratio (Sokal score) was calculated by entering data in the following equation:

$$\text{Exp}\,[0.116\,(\text{age} - 43.4)] + 0.0345\,(\text{spleen size} - 7.51) + 0.188\,[(\text{platelets}/\,700)^2 - 0.563] + 0.0887\,(\text{blast \%} - 2.10)$$

This classification divides patients into three groups: low risk group (Sokal score <0.8), intermediate risk (Sokal 0.8-1.2) and high risk group in which Sokal score was >1.2 (8).

All statistical analysis was computed with SPSS statistical software (version 13.0.1). Data was presented as mean or median values and percentages. Response rate was checked overall and according to Sokal scoring system.

Results

A total of 70 patients were registered over a period of two years. The average age at the beginning of the study was 48 years old (range, 18-72 years old); among these 41 were males and 29 were females. Patients were classified into prognostic groups using the Sokal formula at the time of diagnosis. 51 (72%) of patients had Sokal score < 0,8 which means they were in the low risk group. The intermediate risk group was comprised of 13 (18 %) patients (Sokal score 0,8-1,2) and 6 (8 %) were high risk (Sokal score > 1,2). 64 patients (91%) of 70 who were started on imatinib mesylate achieved complete hematological response. The overall response rate of imatinib mesylate in chronic phase is described in table1.

Table 1. Response rate of imatinib mesylate in chronic phase of chronic myeloid leukemia

Response	Number	Percentage
Complete hematological response (CHR)	64/70	91
Cytogenetic response		
Complete (CCR)	38/64	59
Partial (PCR)	12/64	18
Minor	10/64	15
No response	4/64	6
Major (CCR+PCR)	50/64	78

Among 51 valuable cases with low Sokal score, complete hematological response was observed in 50 cases, 29 patients had complete cytogenetic response and 39 had major cytogenetic response. The other responses are described in table 2 and analysis of Sokal score, age and achievement of major cytogenetic response are described in table 3.

Table 2. Response of Imatinib mesylate according to Sokal risk group

Risk group	CHR	CCR	PCR	Not valuable
Low – 51(72%)	50	2 9	10	1
Intermediate – 13 (18%)	11	8	1	2
High – 6 (8%)	3	1	1	1

Table 3. Analysis of Sokal score, age and achievement of major cytogenetic response

Variable	Evaluation patients (number)	Major cytogenetic response n (%)
Age, years		
<40 years	16	11 (68%)
≥40 years	54	39 (72%)
Sokal risk group		
Low	50	39 (78%)
Intermediate	11	9 (81%)
High	3	2 (66%)

There were significant differences in the rates of cytogenetic response according to the scoring system devised which divides patients with CML into low-risk, intermediate-risk, and high-risk groups. In patients who were deemed to be at low risk on the Sokal scoring system, the rate of major cytogenetic response was 78%; the rate among patients at intermediate risk was 81%, and for those at high risk the rate was 66%. However, the risk of relapse in patients who had a cytogenetic response was not associated with the Sokal score. Imatinib mesylate has changed the current approach to the management of chronic myeloid leukemia. With this therapy the prognostic significance of some clinical variables is changing and few variables have been identified to have an impact on survival. We examined the response rate of imatinib mesylate in chronic phase of chronic myeloid leukemia and tried to find out any correlation between the response and age.

Discussion

This is the first report from Albania compiling response of Imatinib in CML patients. Regarding the results obtained in this study it is important to point out that: Imatinib mesylate is safe and effective first line therapy for chronic phase in the management of CML with tolerable side and adverse effects. The introduction of imatinib in the treatment of CML has brought a high frequency of complete hematological and cytogenetic responses. Although response rate in our series is less than in most studies, however in the current scenario of other available treatment modalities (interferon and bone marrow transplant) it seems to be the most effective treatment option. However, new tyrosine kinase inhibitors are the emerging modalities and should be utilized in the resistant cases.

Zhao et al. retrospectively investigated 116 Chinese patients with chronic-phase CML who had been treated with imatinib (9). The complete hematologic response rate was 94.1%and the complete cytogenetic response rate was 69.6%. Yusuf Bilen investigated 31 turkish patients with chronic- phase CML who had been treated with imatinib, the complete hematologic response rate was 100% and the complete cytogenetic response rate was 71% (10). The consistent value of the Sokal scoring system in different clinical situations suggests that it measures, at least in part, factors that are intrinsic in leukemia and does not merely reflect the point in its evolution at which the leukemia is diagnosed.

Classical prognostic indicators such as the Sokal score have been used to estimate the relative risk of outcome in chronic phase of chronic myeloid leukemia patients, based on age, spleen status, platelet count and the proportion of blood myeloblasts noted at diagnoses. A low Sokal score predicts a higher hematologic as well as cytogenetic response in patients during chronic phase. We found that substantial numbers of patients in our series were in intermediate or high risk groups; this might be because of late diagnosis. In our study lower response rate in early chronic phase and even in young ages, is probably due to small sample size or because substantial number of patients were in high o intermediate risk group according to Sokal score. Prognostic relevance is also attributed to cytogenetic abnormalities and the degree and timing of hematologic and cytogenetic responses to treatment. Although the introduction of imatinib has to some extent attenuated the predictive value of these indices, the Sokal score remain the only validated predictores of response in newly diagnosed patients. Ongoing assessments allow patients who are not responding optimally to be considered for alternative treatment strategies.

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