Prognostic Factors Associated with Complete Cytogenetic Response in Patients with Chronic Myelogenous Leukemia on Imatinib Mesylate Therapy

Irena Ćojbašić, Lana Mačukanović-Golubović

Clinical Centre, Clinic of Haematology and Clinical Immunology, Niš, Serbia

SUMMARY

Introduction Imatinib mesylate, a selective Bcr-Abl tyrosine kinase inhibitor, has proved to be most effective therapy of Philadelphia chromosome-positive chronic myelogenous leukemia. Imatinib induces complete haematological and cytogenetic response in high percentage of patients.

Objective The aim of this study was to identify potential prognostic factors before beginning treatment with imatinib associated with complete cytogenetic response.

Methods We analyzed 20 patients with newly diagnosed Philadelphia positive chronic myelogenous leukemia treated at our institution from June 2006 until May 2009. These patients were treated with imatinib mesylate in oral dose of 400 to 800 mg daily. Complete blood counts were performed every month, while serum chemistry evaluations and bone marrow evaluations including morphology and cytogenetics were performed every 6 months.

Results Of the 20 patients analyzed in this study, 19 (95%) achieved complete haematologic response within three months. In all patients cytogenetic analyses were done and all have achieved absolute cytogenetic response. The best cytogenetic response rate at any time during study treatment among 20 patients was: complete cytogenetic response in 15, partial cytogenetic response in three and minor cytogenetic response in two patients. Among 11 observed base-line patients' characteristics five were independent predictors of a high rate of complete cytogenetic response; the absence of blasts and basophils in peripheral blood, the presence of less than 5 percent of bone marrow blasts, white blood cell count less than $10x10^9$/L and the absence of splenomegaly ($p<0.01$).

Conclusion Our results showed that some pre-treatment characteristics of patients might be the cause of differences in treatment outcome. On the basis of this analysis, we identified several pre-treatment patients' characteristics to be independent prognostic factors for achievement of complete cytogenetic response.

Keywords: chronic myelogenous leukemia; treatment; imatinib mesylate; prognostic factors

INTRODUCTION

Chronic myelogenous leukemia (CML) is a clonal haematopoietic stem cell disorder characterized by a specific chromosomal translocation t(9;22). Philadelphia chromosome (Ph)-positive CML evolves through three different phases: chronic, accelerated and blastic. The molecular consequence of Ph chromosome is the production of activated Bcr-Abl tyrosine kinase [1].

Imatinib mesylate is a selective Bcr-Abl protein tyrosine kinase inhibitor. Imatinib has shown significant activity in all phases of Ph chromosome positive chronic myeloid leukemia [2]. The benefit of imatinib was definitively shown in the International Randomized Study of Interferon and imatinib mesylate (IRIS) trial; by comparison of effectiveness of imatinib with interferon and cytarabine combination in 1106 newly diagnosed patients [3]. In this trial, the estimated rates of complete cytogenetic response after 18 months of treatment were 76% for patients in the imatinib group and 14% for those in the interferon–cytarabine group. The rate of freedom from progression to the accelerated phase was 97%, and to the blastic phase it was 92%. After a 5-year follow-up, the overall rate of complete cytogenetic response was 78%, progression-free survival was 83%, and overall survival was 89% in the imatinib group [4].

Imatinib treatment is associated with a variety of adverse effects, most of which are mild to moderate in intensity and thinning after the first few months of treatment. Most patients do not require dose reduction or interruption of therapy [3].

Now it is generally accepted recommendation that imatinib is used as the first-line treatment for patients with newly diagnosed CML [5].

OBJECTIVE

In this paper we analyzed the pre-treatment characteristic of patients with chronic-phase CML treated with imatinib mesylate that correlate with probability to achieve complete cytogenetic response.

METHODS

We analyzed 20 patients with Ph-positive CML in the chronic phases that were treated with imatinib mesylate at our institution from June 2006 until May 2009. Cytogenetic response was

Correspondence to:
Irena ĆOJBAŠIĆ
Orlovića Pavla 20a
18000 Niš, Serbia
icojbasic@gmail.com

evaluated. All patients started treatment with recommended dose of 400 mg daily. The dose of the drug was increased to 600/800mg daily in cases of previous therapy failure, i.e. in patients with cytogenetic refractoriness or cytogenetic relapse. As a part of routine follow-up, complete blood counts were controlled each month, while serum chemistry evaluations and bone marrow evaluations including morphologic and metaphase cytogenetic were performed every 6 months.

Chronic-phase CML was defined as the presence in the peripheral blood of blasts less than 15%, basophils less than 20%, blasts together with promyelocytes less than 30%, and platelets more than 100×10^9/L. As chronic-phase and response criteria were defined according to the recommendations of LeukemiaNet 2006 panel [5]: complete haematologic response (CHR) was defined as a white blood cell count of less than 10×10^9/L, a platelet count of less than 450×10^9/L, no immature cells (blasts, promyelocytes, myelocytes) in the peripheral blood, and disappearance of all signs and symptoms related to leukemia (including palpable splenomegaly) lasting for at least four weeks. Cytogenetic response was evaluated using standard cytogenetic analysis by direct preparation of material from the bone marrow. Cytogenetic responses, based on metaphase analysis of at least 20 cells, were defined as: complete Ph-positive 0%, partial Ph-positive 1% to 35%, minor Ph-positive 36% to 95%, and absent Ph-positive >95%. Major cytogenetic response assumed the sum of complete and partial cytogenetic responses.

Descriptive statistic (number, proportion, median, range) were used to summarize the pre-treatment characteristics of the patients and response to imatinib mesylate therapy. Multivariate analyses was performed to identify potential prognostic factors associated with complete cytogenetic response.

RESULTS

Significant pre-treatment characteristics of the patients are shown in Table 1.

The median duration of the disease from the diagnosis to start of imatinib mesylate therapy was 2.9 months (range 1-7 months). The median follow-up time for the patients in the study was 17.75 months (range: 6-34 months). Of 20 analyzed patients, 19 (95%) achieved complete haematologic response (CHR) within 3 months and all patients within 6 months from the start of the treatment.

Response to the treatment was evaluated in 20 patients after 6 months of therapy; complete cytogenetic response was achieved in 6 patients, partial cytogenetic response in 7, minor cytogenetic response in 6, while no response was observed in 1 patient.

Response to the treatment was evaluated in 14 patients after 12 months of therapy; complete cytogenetic response was achieved in 6 patients, partial cytogenetic response in 6, minor cytogenetic response in 1 and no response was shown in 1 patient.

Response to the treatment evaluated in 10 patients after 18 months of therapy; complete cytogenetic response was achieved in 9 patients, while minor cytogenetic response in 1 patient. Best cytogenetic response rate during imatinib mesylate treatment is shown in Table 2.

Table 1. Baseline characteristics of patients treated with imatinib mesylate

Variable		Value
Age	Median (years)	49.5
	Range (years)	19-68
	≥60 (n)	3 (14.3%)
Sex (n)	Male	13 (65%)
	Female	7 (35%)
Splenomegaly (n)	Yes	16 (80%)
	No	4 (20%)
White blood cells count ($\times10^9$/L)	Median value	28.4
	Range	3.5-90.2
Platelets count ($\times10^9$/L)	Median value	382.5
	Range	140-863
Haemoglobin (g/L)	Median value	122.8
	Range	87-145
Basophils (%)	Median value	2.54
	Range	0-10
Time since diagnosis (months)	Median value	20.4
	Range	6-66

n – number of patients

Table 2. Best cytogenetic response rate during imatinib mesylate therapy

Cytogenetic response	Number of patients
Major (Complete+Partial)	18 (90%)
Complete	15 (75%)
Partial	3 (15%)
Minor	2 (10%)

In 8 of the 20 patients, imatinib mesylate dose was escalated for unsatisfactory response after a median duration of 17.25 months (range: 6-24 months). Dose was escalated to 800 mg daily (n=3) or to 600 mg daily (n=5). In 3 patients the dose of the drug was escalated for cytogenetic relapse, and they improved their cytogenetic response to complete after three months. In 5 patients the dose was escalated for cytogenetic refractoriness, and they improved their cytogenetic response to complete after three months. No patients progressed to accelerated or blastic phase.

Association between pre-treatment characteristics and later probability of achievement of complete cytogenetic response during treatment is shown in Table 3. According to the multivariate analyses, among 11 base-line variables five independently predicted a high rate of complete cytogenetic response; the absence of blasts and basophils in peripheral blood, the presence of less than 5 % blasts in bone marrow, white blood cell count less than 10×10^9/L and the absence of splenomegaly ($p<0.01$).

DISCUSSION

Imatinib mesylate, a selective Bcr-Abl tyrosine kinase inhibitor has improved the treatment of Ph-chromosome-positive CML and has become the standard first line treatment for this disease. Imatinib mesylate induces complete haematological response in 80% to 90% of patients with newly diag-

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Table 3. Prognostic factors associated with complete cytogenetic response (CCR)

Parameter		Total number of patients	Number of patients with CCR	p
Age (years)	<60	17	13 (76%)	0.18
	≥60	3	2 (67%)	
Splenomegaly (cm BCM)	None	4	3 (75%)	<0.01
	1-9	11	8 (73%)	
	≥10	5	4 (80%)	
Haemoglobin (g/dL)	<10	4	2 (50%)	0.22
	≥10	16	13 (81%)	
White blood cells count ($\times 10^9$/L)	<10	10	9 (90%)	<0.01
	10-49	6	4 (67%)	
	≥50	4	2 (50%)	
Platelets count ($\times 10^9$/L)	≤450	13	10 (77%)	0.03
	>450	7	5 (71%)	
Peripheral blasts	None	12	11 (91%)	<0.01
	Any %	8	4 (50%)	
Peripheral blood basophils	None	12	10 (83%)	<0.01
	Any %	8	5 (63%)	
Bone marrow blasts (%)	<5	18	14 (78%)	<0.01
	≥5	2	1 (50%)	
Bone marrow basophils (%)	<5	17	14 (82%)	0.05
	≥5	3	1 (33%)	
Sokal risk group	Low	10	8 (80%)	0.02
	Intermediate	8	6 (75%)	
	High	2	1 (50%)	
CML duration (months)	<12	6	4 (67%)	0.11
	12-24	9	7 (785)	
	≥24	5	4 (80%)	

BCM – below costal margin

nosed chronic-phase CML, a complete cytogenetic response in 70% to 80% of patients, and a major molecular response in 40% of patients [6].

In the study of Goldman et al. [7], the highest number of patients achieved normal blood counts within three months, and more than 90% of them achieved complete haematological response within 6 months from the beginning of treatment. Approximately 40% of previously untreated patients achieved major cytogenetic response after 6 months, and 65% achieved a complete cytogenetic response after one year of therapy. In contrast to a study of Goldman et al., the results of our analysis show that complete haematological response was achieved in all patients within 6 months from the start of the imatinib mesylate treatment. Major cytogenetic response was achieved in 65% of patients after 6 months and complete cytogenetic response was achieved in 42.9% of patients after one year of therapy. A small minority of the patients who achieved complete cytogenetic response subsequently regained evidence of marrow Ph positivity and in our analysis it was 15% of analyzed patients. However, after drug dose escalation all achieved a complete cytogenetic response after three months.

In this study we tried to detect base-line factors associated with achieving complete cytogenetic response in patients with chronic-phase CML treated with imatinib mesylate. Based on the analysis, we identified five basic factors: the absence of blasts and basophils in peripheral blood, the presence of less than 5% of blasts in the bone marrow, white blood cell count less than 10×10^9/L and the absence of splenomegaly ($p<0.01$).

Our results are similar to those identified in previous studies about factors associated with a high rate of major and complete cytogenetic response. The base-line variables that independently predict a high rate of major cytogenetic response in the study of Cortes et al. [8] were: the absence of blasts in peripheral blood, peripheral basophils less than 7%, the presence of less than 5% blasts and the presence of less than 5% basophils in the bone marrow, white blood cell count less than 10×10^9/L and the absence of splenomegaly. The pre-treatment characteristics of patients associated with achieving complete cytogenetic response in the study of Kantarijan et al. [9] were: the absence of blasts and basophils in peripheral blood, the presence of less than 5% blasts in bone marrow, white blood cell count less than 10×10^9/L and platelet count less than 450×10^9/L.

The use of imatinib has greatly improved the outcome of patients with CML. The efficiency of imatinib was definitively established in IRIS trial. The group of patients treated with imatinib had a rate of complete cytogenetic response of approximately 80% and an overall survival of nearly 90% after 5 years [4]. For patients who experience treatment failure with imatinib, recommendation is to use higher dose of imatinib or second-generation tyrosine kinase inhibitors (TKIs) dasatinib and nilotinib which have induced treatment response in more than 90% of patients, and may lead to an improved event–free and transformation-free survival [10].

CONCLUSION

By the analysis of our results, we identified characteristics of patients before treatment, which are independent prognostic factors for achieving complete cytogenetic response: the absence of blasts and basophils in peripheral blood, the presence of less than 5% blasts in the bone marrow, white blood cell count less than 10×10^9/L and the absence of splenomegaly ($p<0.01$). Our results showed that some pre-treatment characteristics of the patients could be the cause of differences in treatment outcomes. Our results are consistent with the literature data, although they are obtained by analyzing a relatively small number of patients.

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Прогностички фактори удружени с потпуним цитогенетским одговором болесника с хроничном мијелоидном леукемијом који се лече иматиниб-месилатом

Ирена Ћојбашић, Лана Мачукановић-Голубовић

Клиника за хематологију и клиничку имунологију, Клинички центар, Ниш, Србија

КРАТАК САДРЖАЈ

Увод Иматиниб-месилат, селективни инхибитор *Bcr-Abl* тирозин-киназе, показао се као најефикаснија терапија Филаделфија хромозом-позитивне хроничне мијелоидне леукемије. Иматиниб индукује потпуни хематолошки и цитогенетски одговор код великог броја болесника.

Циљ рада Циљ рада је био да се утврде потенцијални прогностички фактори пре лечења иматинибом који су удружени с потпуним цитогенетским одговором.

Методе рада Испитано је 20 болесника с Филаделфија хромозом-позитивном хроничном мијелоидном леукемијом који су лечени у Клиници за хематологију и клиничку имунологију Клиничког центра у Нишу од јуна 2006. до маја 2009. године. Сви су орално примали иматиниб-месилат у дози 400-800 *mg* дневно. Крвна слика је контролисана сваког месеца, док су биохемијска и испитивања коштане сржи, укључујући морфологију и цитогенетику, вршена сваких шест месеци.

Резултати Од 20 испитаника, код 19 (95%) је постигнут потпуни хематолошки одговор током три месеца, док је одређени цитогенетски одговор постигнут код свих. Најбоља стопа цитогенетског одговора током испитиваног периода била је: потпуни цитогенетски одговор, постигнут код 15 болесника, делимични, постигнут код три, и мали, забележен код два испитаника. Међу 11 основних одлика, пет су биле независни предсказатељи високе стопе потпуног цитогенетског одговора: одсуство бласта и базофила у крвној слици, присуство мање од 5% бласта у коштаној сржи, број леукоцита мањи од 10×10^9/l и изостанак спленомегалије ($p<0,01$).

Закључак Резултати истраживања су показали да неке одлике болесника пре лечења могу бити узрок разлика у исходу лечења. На основу ове анализе препознали смо неколико независних прогностичких фактора за постизање потпуног цитогенетског одговора.

Кључне речи: хронична мијелоидна леукемија; лечење; иматиниб-месилат; прогностички фактори

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