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Original Article

COMPARISON OF TREATMENT OUTCOME AMONG PATIENTS WITH CHRONIC MYELOID LEUKAEMIA WHO ACHIEVED COMPLETE CYTOGENETIC RESPONSE WITHIN OR AFTER ONE YEAR OF IMATINIB MESYLATE THERAPY

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Abstract. *The introduction of imatinib, as a type of targeted molecular therapy, has profoundly changed the treatment outcome of chronic myeloid leukaemia (CML). The aim of this study was to assess and compare treatment outcome among patients who achieved complete cytogenetic response (CCgR) within or after one year following initiation of imatinib therapy. A group of 42 adult patients with early chronic-phase Philadelphia-positive CML treated with imatinib mesylate therapy has been studied. In the study group CCgR has been achieved in 36/42 (85.71%) analysed patients, while in 3/42 (7.14%) patients the absence of cytogenetic response has been noted. Early CCgR has been achieved by 25/36 (69.44%) patients with response at median time of 6.9±1.9 months, while late CCgR has been achieved by 11/36 (30.56%) patients at median time of 18.75±2.4 months. Univariate analysis has identified prognostic factors for achieving early and late CCgR. Analysis of remission duration of treatment responders has shown that 21/25 (84%) patients in the group with early CCgR and 9/11 (81.81%) patients from the group with late CCgR still maintained stable remission on last cytogenetic control. The estimated 5-year survival rate was 85% for early responders and 74% for late responders. In conclusion, these results demonstrate that there are no differences in the treatment outcome, i.e. level of response, of patients with CML in relation to whether the CCgR was achieved within or after one year of imatinib therapy*.

Key words: *chronic myeloid leukaemia, imatinib, prognostic factors, treatment outcome.*

Introduction

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disease that occurs because of constitutive activation of the BCR-ABL tyrosine kinase, a result of the t(9;22) (q34;q11) translocation designated as the Philadelphia (Ph) chromosome [1]. The introduction of the tyrosine kinase inhibitors (TKIs), as a type of targeted molecular therapy, has revolutionized the management and outlook in CML [2]. The largest study up to date that provides the data on the effectiveness of imatinib in CML patients is IRIS study. It has shown that when imatinib was given as an initial treatment of patients in early chronic phase CML, complete hematologic response (CHR) after one year occurred in 95% of patients and complete cytogenetic response (CCgR) in 76%. Of CML patients who achieved a CCgR, major molecular response (MMoR) was achieved by 57%. After 5 years of treatment, the estimated rate of progression-free survival was 84%, and an estimated 93% of patients had not progressed to the accelerated phase or blast crisis [3]. Initial studies have shown the importance of early achievement of therapeutic response, not only achievement of CCgR but also MMoR and particularly within the first year of therapy, what has been predictive of durable cytogenetic remission [4, 5]. Similarly, according to achieving CCgR or not at 12 months, the 3-year event free survival rate was 98% and 67%, and overall survival was 99% and 94% [6]. However, another study [7] has shown that there was no difference between group of patients with early and late achievement of CCgR according to progression-free survival rate and an estimate 4-year overall survival (100% vs. 88% and 100% vs. 92%, respectively). Thus it has been demonstrated that it was important to achieve CCgR, and that the time of achieving this level of response was of less importance.

The aim of this study was to compare two groups of patients with early and late CCgR to determine whether there are differences in treatment outcome compared to when CCgR was achieved. To explore the difference between the two groups based on the time when patients achieved CCgR, one year was chosen as the cut-off point. This paper presents the examination of the

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connection between the characteristics of patients before treatment and the subsequent possibility of achieving early and late CCgR, in order to determine which baseline characteristics of patients lead to differences in treatment outcome. The probability of maintaining CCgR and survival in all patients and in groups with early and late CCgR has also been determined.

Material and Methods

The analysis included 42 adult patients who were treated in our institution with the diagnosis of Ph-positive CML in early chronic phase of the disease, during the period from 2006 to 2014. In this study patients with CML who achieved CCgR to imatinib therapy have been analysed. Patients were divided into two groups: the patients who achieved CCgR within 1 year (early response) and patients in whom CCgR has been achieved after 1 year from the beginning of treatment (late response). The study analyses the treatment response and survival rate of patients in these two groups in order to determine whether there are differences in relation to when CCgR was achieved.

The patients have not received prior therapy for leukaemia except hydroxyurea which has been conducted for initial leukoreduction. All patients started treatment with recommended oral dose of imatinib of 400mg once a day. Escalated doses of 600mg and 800mg were administered in case of failure of previous treatment, apropos in patients with cytogenetic relapse or cytogenetic refractoriness.

Chronic phase CML was defined according to the recommendations of the LeukaemiaNet panel [8, 9] 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. After the start of treatment haematological and cytogenetic responses have been evaluated in order to monitor the response to the treatment. Complete blood count and serum chemistry evaluations have been performed every month until the CHR was achieved, and then every 6 months or in accordance with other controls. Marrow studies, including morphologic and cytogenetic analysis have been performed every 6 months to 2 years of therapy, and then every year in terms of disclosure of additional chromosomal aberrations in case they have achieved stable CCgR. Cytogenetic response has been assessed by conventional cytogenetics with direct preparation of material from the bone marrow with optimal number of mitosis of at least 20 for assessing response. The response criteria have also been defined according to recommendations of the LeukaemiaNet panel [8, 9]: complete hematologic response (CHR) has been defined as a white blood cell count of less than 10×10^9/L, a platelet count of less than 450×10^9/L, the absence of immature cells (blasts, promyelocytes, myelocytes) in the peripheral blood, and disappearance of all signs and symptoms associated with leukaemia (including palpable splenomegaly) for at least four weeks. Cytogenetic response has been defined as: complete 0% Ph+ cells in metaphase, partial 1%-35% Ph+ cells in metaphase, minor 36%-65% Ph+ cells in metaphase, minimal 66%-95% Ph+ cells in metaphase and absent >95% Ph+ cells in metaphase. Major cytogenetic response (MCgR) included complete plus partial cytogenetic response.

The results are presented in tables and graphs, processed according to the methodology of descriptive and analytical statistics. Standard descriptive statistical methods (number, proportion, mean, range) have been used to summarize the characteristics of the patients before treatment and for monitoring the cytogenetic response to therapy. To identify potential prognostic factors associated with early and late CCgR Pearson χ^2 test has been used. The following levels of statistical significance of Pearson χ^2 test have been used: n.s. without statistical significance, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$. For the evaluation of the probability of survival Kaplan-Meier method has been used.

Results

A total of 42 adult patients with newly diagnosed Ph-positive early chronic phase CML who were treated with imatinib have been analysed. The average age of patients was 50.52 years (range, 19-73 years) and 22 patients (52.38%) were female. Significant characteristics of the patients before treatment with imatinib are presented in Table 1. Median duration of disease from diagnosis to initiation of treatment with imatinib therapy was 2.5 months (range 1-7 months). The mean follow-up of patients in this study was 48.4 months (range 32-90 months) and none of the patients were lost during follow-up.

The rate of cytogenetic response, stability and duration of CCgR during the entire study period are shown in Table 2. In the study group CCgR has been achieved in 85.71% of the analysed patients, while in 7.14% of patients the absence of cytogenetic response to imatinib after more than 1 year of treatment has been noted. Patients who achieved CCgR were divided into two groups according to the time needed to achieve this level of response. Group with early CCgR comprised 69.44% of the total number of analysed patients, with a median time of 6.9±1.9 months (range 3-12 months) needed to accomplish this response. In this group 88% of patients achieved CCgR at 6 months, while 12% of patients achieved the same response between 6 and 12 months. Group with late CCgR comprised 30.56% of the patients, and the median time from start of treatment until CCgR was accomplished was 18.75±2.4 months (range 15-24 months). In this group, 81.82% achieved CCgR at 18 months and 18.18% between 18 and 24 months of treatment with imatinib. Analysis of steadiness of CCgR has shown that 84% of the patients in the group with early CCgR and 81.81% of the patients in the group with late CCgR still maintained stable remission without elements of clonal cytogenetic progression during

the last control. These results show that there was no difference between the groups of patients with early and late response in terms of loss of already achieved CCgR.

Table 1 Clinical and laboratory characteristics of patients with chronic myeloid leukaemia before treatment with imatinib

Parameter	Mean values±SD, (range)	
Age, g	50.5±13.8	(19–73)
Time from diagnosis to imatinib, m	2.5±1.7	(1–7)
WBC count $\times 10^9$/L	114.6±73.8	(20–298)
Platelets $\times 10^9$/L	395.5±230.8	(140–1165)
Haemoglobin, g/dL	118.5±19.5	(74–145)
Peripheral blasts, %	2.0	(0–7)
Peripheral basophils, %	2.8	(0–9)
Marrow blasts, %	3.0	(0–6.5)
Marrow basophils, %	3.4	(0–10)
Splenomegaly, n (%)	29	(69.1)
Dose, mg, n (%)		
400	30	(71.4)
600	5	(11.9)
800	7	(16.7)
Sokal score, n (%)		
Low	20	(47.7)
Intermediate	19	(45.2)
High	3	(7.1)
Hasford score, n (%)		
Low	27	(64.3)
Intermediate	12	(28.6)
High	3	(7.1)

Table 2 The rate of cytogenetic response to imatinib therapy in the analysed period

	Patients	
Cytogenetic response (CgR)	Number (n)	%
Complete CgR,	36/42	85.71
Early Complete CgR,	25/36	69.44
Late Complete CgR,	11/36	30.56
Early response and maintenance Complete CgR	21/25	84.00
Late response and maintenance Complete CgR	9/11	81.81
Partial to minimal CgR	3/42	7.14
Absent CgR	3/42	7.14

Correlation between the basic characteristics of the patients and the subsequent possibility of achieving early CCgR have been analysed and presented in Table 3. According to statistical analysis out of 12 baseline variables 5 of them were identified as prognostic factors for achieving early CCgR: less than 5% of marrow blasts, less than 5% of marrow basophils, less than 4% of peripheral basophils, the absence of peripheral blasts ($p < 0.001$), as well as low Hasford risk score ($p < 0.05$).

Table 3 Prognostic factors associated with early complete cytogenetic response

Characteristics	n	Early CCgR	p	
Age (years)				
<60	31	15 (48.39)	0.114	n.s.
≥60	11	10 (90.91)		
Haemoglobin (g/dL)				
<10	16	10 (62.50)		
10–11.9	13	9 (69.23)	0.465	n.s.
≥ 12	13	6 (46.15)		
WBC count (x 10^9/L)				
<50	9	6 (66.67)		
50–99	15	7 (46.67)	0.449	n.s.
≥ 100	18	12 (66.67)		
Platelets (x 10^9/L)				
<450	21	14 (66.67)		
450–699	16	8 (50.00)	0.592	n.s.
≥ 700	5	3 (60.00)		
Peripheral blasts (%)				
0%	10	10 (100.0)		
1–2%	22	13 (59.09)	0.001	***
≥ 3 %	10	2 (20.00)		
Marrow blasts (%)				
< 5%	36	25 (69.44)	0.000	***
≥ 5%	6	0 (0.00)		
Peripheral basophils (%)				
< 4%	27	21 (77.78)	0.001	***
≥ 4%	15	4 (26.67)		
Marrow basophils (%)				
< 5%	33	25 (75.76)	0.000	***
≥ 5%	9	0 (0.00)		
Splenomegaly (bcm)				
0	13	10 (76.92)		
1–9	21	12 (57.14)	0.193	n.s.
≥ 10	8	3 (37.50)		
EUTOS score				
Low	40	25 (62.50)	0.079	n.s.
High	2	0 (0.000)		
Hasford score				
Low	27	19 (70.37)		
Intermediate	12	6 (50.00)	0.045	*
High	3	0 (0.00)		
Sokal score				
Low	20	12 (60.00)		
Intermediate	19	13 (68.42)	0.081	n.s.
High	3	0 (0.00)		

*p<0.05 **p<0.01 ***p<0.001
n.s. without statistical significance, bcm-below costal margin

Baseline characteristics of patients that are associated with the achievement of the late CCgR are shown in Table 4. Of the 12 pre-treatment characteristics only two have been identified as prognostic factors for achieving late CCgR: the presence of more than 3% of peripheral blasts and value of haemoglobin less than 10g/dL ($p < 0.05$).

Table 4 Prognostic factors associated with late complete cytogenetic response

Characteristics	n	Late CCgR	p	
Age (years)				
<60	31	11 (35.48)	0.121	n.s.
≥60	11	0 (0.00)		
Haemoglobin (g/dL)				
<10	16	1 (6.25)		
10-11.9	13	3 (23.08)	0.014	*
≥ 12	13	7 (53.85)		
WBC count (x 10^9/L)				
<50	9	2 (22.22)		
50– 99	15	7 (46.67)	0.066	n.s.
≥ 100	18	2 (11.11)		
Platelets (x 10^9/L)				
<450	21	4 (19.05)		
450–699	16	6 (37.50)	0.425	n.s.
≥ 700	5	1 (20.00)		
Peripheral blasts (%)				
0%	10	0 (0.00)		
1–2%	22	6 (27.27)	0.039	*
≥ 3 %	10	5 (50.00)		
Marrow blasts (%)				
< 5%	36	9 (25.00)	0.667	n.s.
≥ 5%	6	2 (33.33)		
Peripheral basophils (%)				
< 4%	27	5 (18.52)	0.129	n.s.
≥ 4%	15	6 (40.00)		
Marrow basophils (%)				
< 5%	33	8 (24.24)	0.582	n.s.
≥ 5%	9	3 (33.33)		
Splenomegaly (bcm)				
0	13	3 (23.08)		
1–9	21	6 (28.57)	0.936	n.s.
≥ 10	8	2 (25.00)		
EUTOS score				
Low	40	10 (25.00)	0.433	n.s.
High	2	1 (50.00)		
Hasford score				
Low	27	6 (22.22)		
Intermediate	12	4 (33.33)	0.735	n.s.
High	3	1 (33.33)		
Sokal score				
Low	20	6 (30.00)		
Intermediate	19	4 (21.05)	0.783	n.s.
High	3	1 (33.33)		

*p<0.05 **p<0.01 ***p<0.001 n.s. without statistical significance, bcm-below costal margin

Of the 42 analysed patients 36 are alive, six patients died, two in accelerated phase and four due to complications with associated diseases. In case of 30 patients stabile CCgR on the last cytogenetic control was maintained and they have been on therapy with imatinib. Twelve patients were excluded from imatinib therapy, nine were treated with second-generation of tyrosine kinase inhibitors, three were treated with interferon plus cytarabine.

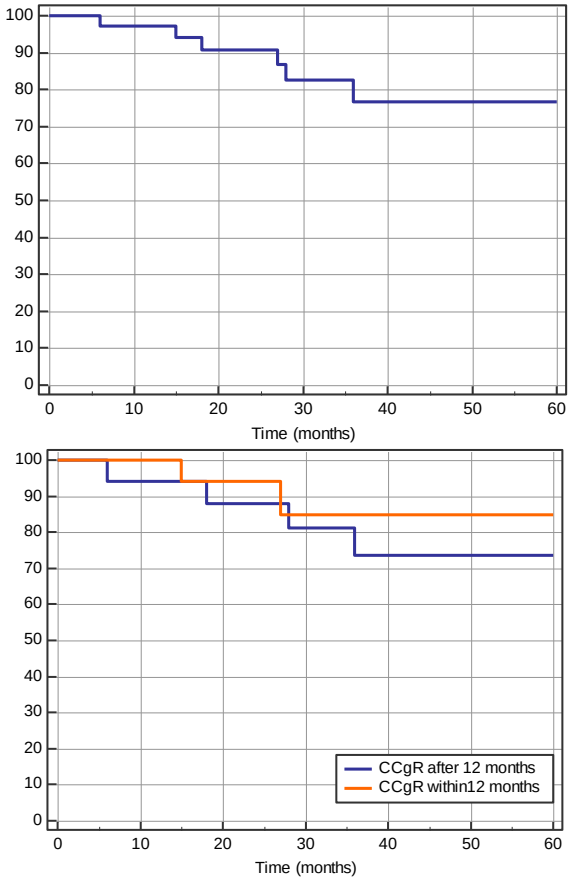

Fig. 1 Kaplan-Meier survival probability in all analysed patients (A) and in patients who have achieved complete cytogenetic response within 12 months or later during treatment with imatinib (B).

Finally, in this study the survival probability has been determined for all patients, both in groups with early and late CCgR. Figure 1 shows the estimated 5-year survival rate for all patients with CCgR (A) and (B), namely for patients who achieved this response within 1 year or later during treatment (n=25 for early response and n=11 for the late response). After 5 years of treatment, 77% of patients with CCgR were still alive (Fig. 1A). The estimated 5-year overall survival rate was 85% in patients with early response and 74% for patients with late response (Fig. 1B).

Discussion

The introduction of imatinib in CML therapy, a potent and selective inhibitor of tyrosine kinase, has led to great progress in the treatment of these diseases [10]. Most of the available data on the efficacy of imatinib in patients with CML is based on the results of the IRIS study. This study showed that after an average follow-up of 54 months, the rate of CHR was 93%, CCgR was 89%, while the rate of absence of progression was 91%. IRIS study has reported the significance of achieving cytogenetic response at 12 and 18 months, and that the early response at 3 and 6 months was also important

[11]. A six-year update of the IRIS study showed that the best cumulative rate of CCgR was 82% and the estimated overall survival rate after 6 years was 88%-95% [12]. Results of 8-year IRIS study update [13] once again confirmed long-term efficacy and safety of imatinib.

Clearly, it had been established that the depth of response to imatinib therapy was the most important prognostic factor for treatment outcome of patients with CML [14]. Initial reports suggested the importance of achieving cytogenetic response and showed that patients without cytogenetic response at 6 months and those with minimal cytogenetic response at 12 to 18 months, had a worse estimated 4-year survival rate of 70% and 79%, compared to those who had a better cytogenetic response in whom the estimated 4-year survival rate was 88% and 100% [15]. Similarly, subsequent analysis has again confirmed that the cytogenetic response to imatinib at 12 months is indicative of a prognosis. Patients who did not achieve CCgR plus PCgR at 12 months had worse estimated 3-year survival rate than the rest, 84% versus 99%. The estimated 5-year survival rate for patients achieving CCgR and PCgR at 12 months was 94% in the both cytogenetic subgroups [16]. Analysis of steadiness of CCgR in the study of Iacobucci I. et al. [7] showed that in the group of patients who achieved CCgR at 12 months, 81% of patients continued to maintain stable CCgR at 48 months of follow-up, while 19% of patients showed a loss of response in the same period. It has also been demonstrated that there was no difference between the groups of patients with early and late response in terms of CCgR loss. Similar results were also obtained in this study: in patients with early response 84% were still in stable CCgR at the last cytogenetic control, while 16% of patients showed loss of cytogenetic remission. Our data indicate that patients with late response maintained stable cytogenetic response of treatment in 81.81%, while 18.19% of patients lost CCgR during follow-up.

Considering that failure regarding achieving CCgR at 12 months of therapy was associated with a higher risk of disease progression, Cardema et al. [17] have analysed factors associated with achieving early response. Univariate analysis identified the following characteristics of patients prior to treatment to be independent poor prognostic factors for achieving early CCgR: lower haemoglobin, higher percentage of blasts in the peripheral blood and bone marrow, splenomegaly and imatinib therapy in the standard dose. In the multivariate analysis, lower haemoglobin, higher percentage of blasts in the peripheral blood and treatment with standard dose imatinib, remained as predictors of a decreased opportunities for achieving early CCgR on imatinib therapy. In this study the results of the correlation between the basic characteristics of the patients and the subsequent possibility of achieving early CCgR were to some extent different. This analysis showed that 5 variables were significant predictors of achieving early CCgR: lower marrow blasts, lower marrow basophils, lower peripheral basophils, the absence of peripheral blasts ($p<0.001$), as well as low Hasford risk score ($p<0.05$).

In this study, analysis of the estimated 5-year survival has shown that these probabilities in patients with early and late CCgR were not significantly different. These findings correlate with the results of several studies which have confirmed a cytogenetic response being important prognostic factor for long-term outcome of patients with CML. Five-year update of the IRIS study showed that progression-free survival was better for patients who achieve CCgR regardless of whether that response was achieved at 12, 18 or 24 months, which indicated that the time of achieving cytogenetic response was of the lesser importance [3]. Similarly, it has been shown that patients treated with imatinib who achieved CCgR at 12 months of treatment had progression-free survival rate and the estimated 4-year survival rate similar to those who have not achieved CCgR at 12 months [7]. It is worth mentioning that there are also reports that showed that among patients who achieved CCgR significant differences were not observed in the duration of CCgR and disease-free survival regardless of whether the CCgR has been achieved within or after 12 months of imatinib therapy. Although patients who did not achieve CCgR can improve response during continued imatinib therapy, they basically have two options: either to achieve CCgR or progress to acceleration phase [17].

Conclusion

Results presented in this paper suggest that among patients who achieved CCgR there is no significant difference in the rate and duration of CCgR regardless of whether they belong to a group with early or late response. Analysis of the estimated 5-year survival for patients with CCgR has shown similar results in early and late responders. All these results indicate that there is no difference in the treatment outcome of patients with CML in relation to whether the CCgR was achieved within or after one year of imatinib therapy.

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