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The efficacy of generic imatinib in patients with chronic myeloid leukemia – a single center experience

Efikasnost generičkog imatiniba u lečenju bolesnika sa hroničnom mijeloidnom leukemijom – rezultati jednog centra

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Abstract

Background/Aim. The treatment of chronic myeloid leukemia (CML) has changed dramatically with the advent of targeted therapies. This study aimed to assess the efficacy of generic imatinib in CML patients treated in our center. **Methods.** The study was retrospective. It included 101 patients diagnosed with CML – chronic phase (CP). The patients were divided into two groups. Group 1 included 55 patients initially treated with branded imatinib and then switched to generic imatinib. Group 2 consisted of 46 newly diagnosed patients who received only generic imatinib from the beginning of therapy. **Results.** The patients were treated with branded imatinib for the mean of 42 months (range 6–132 months) before switching to generic imatinib. Treatment with generic imatinib lasted for 25 months on average (range 3–66 months). A quarter of the patients from the group 1 lost their cytogenetic response after being switched to generic imatinib, but without signs of transformation to acute leukemia. The patients treated with branded imatinib had a significantly longer event-free survival (EFS) and failure-free survival (FFS) (log-rank $p = 0.01$ and $p = 0.03$, respectively). These results could have been influenced by frequent changes of the brand and dosage formulation of generic imatinib. **Conclusions.** Our study showed a significantly longer EFS and FFS in the patients who were initially treated with branded imatinib, compared to those treated with generic imatinib only. These results provide useful information, but have to be interpreted within the context of the crossover study.

Key words:
leukemia, myeloid, chronic-phase; imatinib mesylate; drugs, generic; survival.

Apstrakt

Uvod/Cilj. Ciljna terapija je značajno izmenila uspeh lečenja bolesnika sa hroničnom mijeloidnom leukemijom (CML). Cilj rada je bio da se proceni efikasnost lečenja obolelih od CML generičkim imatinibom u našem centru. **Metode.** Istraživanje je bilo retrospektivno. Obuhvatilo je 101 obolelog od CML u hroničnj fazi. Bolesnici su bili podeljeni u dve grupe. Prvu grupu je činilo 55 bolesnika koji su inicijalno lečeni originalnim imatinibom i koji su kasnije tokom lečenja prevedeni na terapiju gneričkim imatinibom. Drugu grupu činilo je 46 novodijagnostikovanih bolesnika koji su od početka lečeni generičkim imatinibom. **Rezultati.** Bolesnici su originalnim imatinibom bili lečeni u proseku 42 meseca (od 6 do 132 meseca) nakon čega su prevedeni na generički imatinib. Lečenje generičkim imatinibom je u proseku trajalo 25 meseci (od 3 do 66 meseci). Četvrtina bolesnika prve grupe izgubila je citogenetski odgovor nakon prevođenja na generički imatinib. Nije bilo znakova za transformaciju u akutnu leukemiju. Bolesnici lečeni originalnim imatinibom imali su statistički značajno duže preživljavanje bez događaja koje podrazumeva smrtni ishod (*event-free survival* – EFS) i preživljavanje bez neuspeha terapije (failure-free survival – FFS) (log-rank $p = 0{,}01$ i $p = 0{,}03$, redom). Na ovakve rezultate mogla je da utiče učestala promena dozne formulacije i proizvođača generičkog imatiniba. **Zaključak.** Naše istraživanje ukazalo je na značajno duže EFS i FFS kod bolesnika koji su lečenje započeli originalnim imatinibom u odnosu na bolesnike koji su sve vreme lečeni generičkim imatinibom. Navedeni rezultati pružaju korisnu informaciju, ali se moraju tumačiti u kontekstu studije po tipu unakrsnog izajna.

Ključne reči:
leukemija, mijeloidna, hronična; imatinib mesilat; lekovi, generički; preživljavanje.

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Introduction

The treatment of chronic myeloid leukemia (CML) has changed dramatically with the advent of targeted therapies [1]. Imatinib mesylate is a highly selective inhibitor of tyrosine kinase used in the treatment of CML. It has shown long-term efficacy and safety in published randomized clinical trials [2]. Results from the landmark International Randomized Study of Interferon and STI571 (IRIS) comparing interferon alpha (IFNα) plus low-dose cytarabine (LDAC) with imatinib for the clinical management of CML patients led to the adoption of the first targeted therapy (ie. imatinib) as standard first-line treatment [3]. Overall survival at eight years was 85%; for only CML-related deaths and those before stem cell transplantation, the survival was 93% [4]. The IRIS trial also showed that imatinib provided significant advantages regarding health-related quality of life (HRQOL) over IFNα + LDAC [4].

On the other hand, the high cost of tyrosine kinase inhibitors (TKI) developed for CML is a significant concern for health care payers in countries with restricted resources. It is true that generics lead to considerable cost savings, but also give rise to questions associated with their efficacy, safety, and quality [5].

In Serbia, as in most countries, for the registration of generics, official regulations only require evidence of pharmaceutical and biological equivalence, but no evidence of efficacy and safety. Generic imatinib was approved by the Medicines and Medical Devices Agency of Serbia in January 2012. In July 2012, The National Health Insurance Fund of Serbia introduced this drug in the positive list.

This study aimed to assess the efficacy of generic imatinib in CML patients treated in our center.

Methods

Since the introduction of TKI in Serbia, all CML patients on TKI from the region of Vojvodina, Serbia, have been treated at the Clinic of Hematology, Clinical Center of Vojvodina, Novi Sad, Serbia. During August and September 2012, all CML patients treated at the Clinic of Hematology, Clinical Center of Vojvodina, Novi Sad, Serbia, were switched from branded imatinib to generic imatinib. All newly diagnosed CML patients' treatment started with generic imatinib.

Subjects

This retrospective study was performed at the Clinic of Hematology, Clinical Center of Vojvodina, Novi Sad. It included 101 patients diagnosed with CML – chronic phase (CP). All patients included in the study received treatment with TKI, and they represented all CML patients on TKI in the region of Vojvodina, Serbia, in the period from June 2006 to August 2017. The patients were divided into two groups. The group 1 included 55 patients initially treated with branded imatinib and then switched to generic imatinib. The group 2 consisted of 46 newly diagnosed patients who received only generic imatinib from the start of therapy. Four commercial generics of imatinib have been available in Serbia since 2012. The dose formulation and type of generic drug were changed frequently, depending on the availability, without the influence of the treating physician.

CML patients that were not treated with TKI were not included in the study.

Methods

All data [patient's age and sex, whole blood count, cytogenetic results, results of polymerase chain reaction (PCR) for bcr/abl testing, date of the diagnosis, date of TKI treatment initiation, duration of treatment with branded imatinib, duration of treatment with generic imatinib, date of the loss of response to treatment, event-free survival (EFS – intolerance and death) and failure-free survival (FFS – failure to treatment) were collected from the medical documentation]. Hematologic and cytogenetic responses were monitored according to the recommendations of the European Leukemia Network (ELN) [6]. Molecular monitoring was performed by GeneXpert® from 2013.

Statistical analysis

Descriptive statistical analysis was performed determining patients' demographic characteristics, scores for calculating the relative risk concerning CML patients (Sokal, Hasford and EUTOS score — European Treatment and Outcome Study), mean values for treatment duration with generic and branded imatinib, rate of hematological, cytogenetic and molecular response, and rate of treatment failure in patients treated with generic imatinib. The efficacy of TKI treatment was compared in the two groups using a log-rank test by StatSoft, Inc. STATISTICA, version 10.0. Statistical significance was set at $p < 0.05$.

Results

Patients' characteristics

Medical records for a total of 101 CML-CP patients treated with imatinib were reviewed. The group 1 consisted of 55 patients (30 male and 25 female). Characteristics of the patients in the group 1 are summed up in Table 1. Upon diagnosis, most patients in the group 1 were stratified as high risk according to Sokal score (low 23.1%, intermediate 30.7%, high 46.2%) and low risk according to EUTOS score (low 61.5%, high 38.5%). The patients were treated with branded imatinib for the mean of 42 months (range 6–132 months) before switching to generic imatinib. Treatment with generic imatinib lasted for 25 months on average (range 3–66 months) until the end of the follow-up period. A quarter of the patients from the group 1 lost their cytogenetic response after being switched to generic imatinib but without signs of transformation to acute leukemia. Distribution of patients who lost cytogenetic response according to Sokal and EUTOS scores is shown in Table 2.

Table 1

Characteristics of patients treated with branded imatinib

Parameters	Mean	Min	Max
Age (years)	28.5	21	77
WBC (10^9/L)	107	12	411
Hemoglobin (g/L)	112	64	139
Platelets (10^9/L)	429.5	131	3795
Blasts (%)	2.5	1	8
Promyelocytes (%)	4	2	9
Eosinophls (%)	3	1	6
Basophils (%)	2	1	8

WBC – white blood cells.

Table 2

Distribution of patients who lost their complete cytogentc response (CCgR) after being switched to generic imatinib according to Sokal and Eutos scores

Group	Patients (%)	
	Sokal score	Eutos score
Low	23.1	53.8
Intermediate	23.1	
High	53.8	46.2

The group 2 consisted of 46 patients (26 male and 20 female) with newly diagnosed CML, treated only with generic imatinib. Characteristics of the patients in the group 2 are summed up in Table 3. Unlike the group 1, most of the patients were classified as low and intermediate risk according to Sokal score (low 41.3%, intermediate 43.5%, high 15.2%). As in the group 1, patients in the group 2 were also mostly low risk according to EUTOS (low 71.7%, high 28.3%).

Table 3

Characteristics of newly diagnosed patients treated with generic imatinib (n = 46)

Parameters	Mean	Min	Max
Age (years)	56.5	20	83
WBC (10^9/L)	127.7	16.2	367.8
Hemoglobin (g/L)	118	75	157
Platelets (10^9/L)	444.5	123	1280
Blasts (%)	4	1	7
Promyelocyte (%)	5	2	8
Eosinophyls (%)	2.5	1	4
Basophils (%)	3	1	4

WBC – white blood cells.

Ninety percent of patients treated only with generic imatinib achieved complete hematologic response (CHR) after a mean of 3 months. As shown in Figure 1, half of the patients (50%) in the group 2 had a complete cytogenetic response (CCgR) at six months after the beginning of treatment. At twelve months, 66.6% of patients were in CCgR. A molecular response with less than 1% of bcr/abl transcript was achieved by 28.6% of patients in the group 2 after six months (Figure 2). By 12 months, 28.6% of patients achieved a major molecular response (MMR) defined as less than 0.1% bcr/abl transcript (Figure 3). The patients who had treatment failure after 12 months of treatment with generic imatinib (28.6% of patients) were switched to the second generation of TKI (nilotinib).

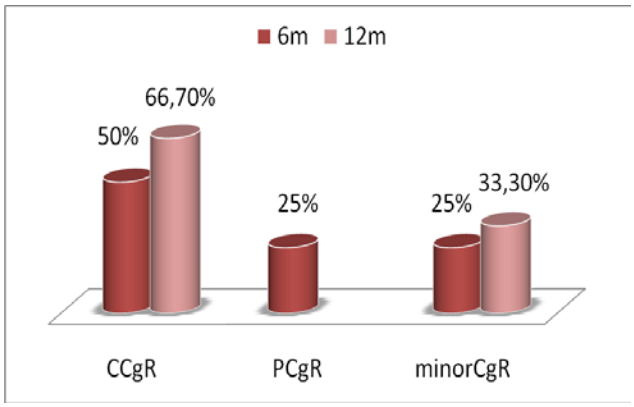


Fig. 1 – Cytogenetic response of patients treated with generic imatinib. CCgR – complete cytogentic response; PCgR – partial cytogenetic response.

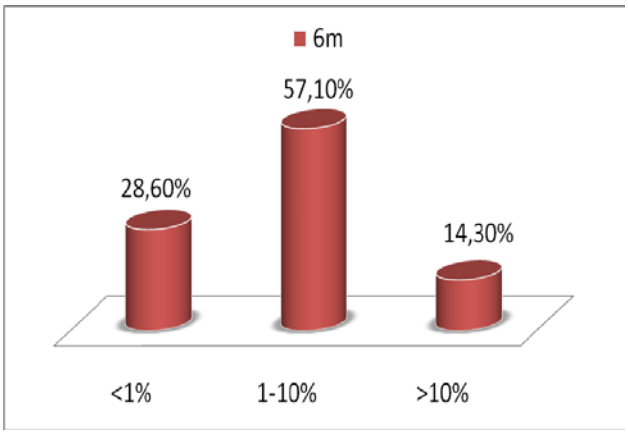


Fig. 2 – Molecular response at 6 months for patients treated with generic imatinib.

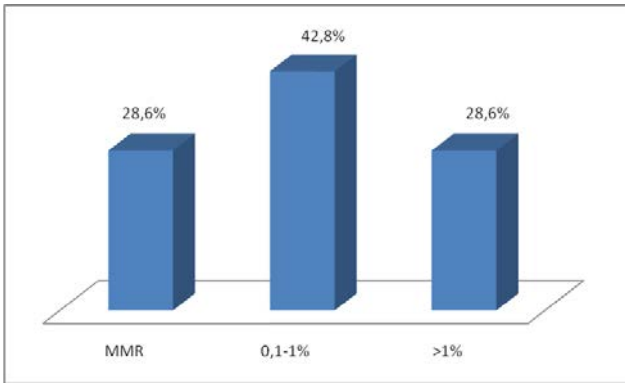


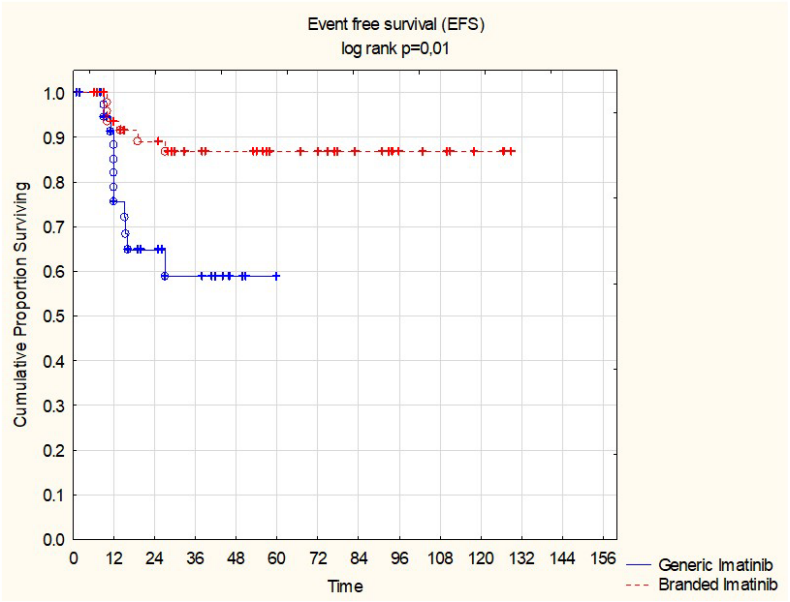
Fig. 3 – Molecular response at 12 months for patients treated with generic imatinib.

Comparisson of event-free survival (EFS) and failure-free survival (FFS)

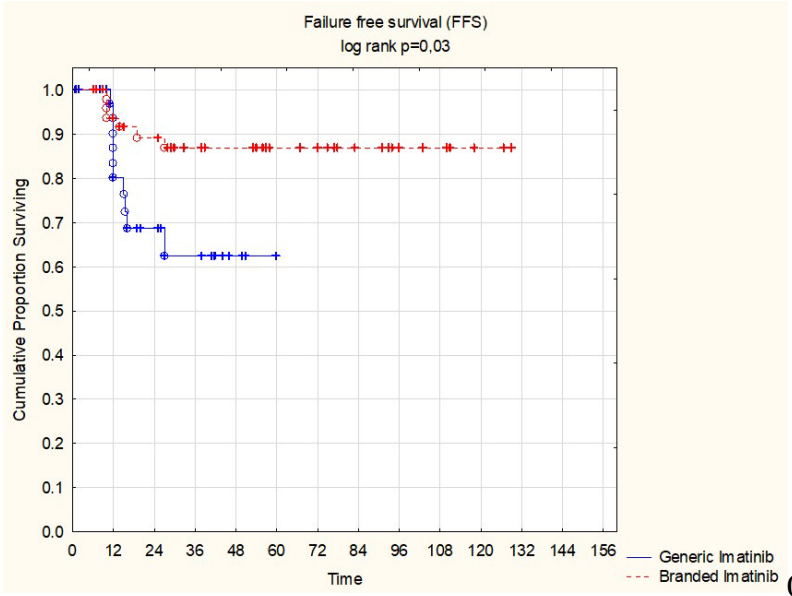
Five-year EFS and FFS were significantly different between the two groups of patients (87% vs. 59%, and 87% vs. 62%, respectively), meaning that the patients started on a therapy with branded imatinib had a significantly better EFS

(p = 0.01) and FFS (p = 0.03) compared with the patients treated with the generic drug (Figures 4a and 4b). It is important to note, as pointed out above, that it was a crossover study design.

Our results showed that 25% of patients initially treated with branded imatinib lost their cytogenetic response when switched to generic imatinib. Around half of the patients were classified as high risk according to Sokal and EUTOS



(a)



(b)

Fig. 4 – Kaplan Meier curve of event-free (a) and failure-free (b) survival.

Discussion

In published randomized clinical trials, imatinib has shown long-term efficacy and safety improving the 10-year survival rate from 20% to 85% [1]. However, the high cost of treatment led to the approval of generic formulations of imatinib.

Generally, generics are approved after a bioequivalent trial without long-term safety and efficacy data [5]. There has been confusion and uncertainty concerning the safe administration of patented drugs, quality-controlled generics, and copies of patented drugs and medicines of substandard quality [5].

scores (53.8% and 46.2%, respectively). In concordance with our study, four case reports showed that switching to a generic imatinib product was associated with a loss of CHR achieved while on branded imatinib [6–10].

In our study, 90% of patients treated initially with generic imatinib achieved CHR at three months. In international studies involving generic imatinib, rates of CHR were 96%–100% from 3 to 28 months [10–12]. On the other hand, a larger prospective study conducted by Alwan et al. [13] has shown that 33% of patients lost a hematologic response in 6 months.

Patients treated with generic imatinib reported by Eddou et al. [14] achieved 77% of major cytogenetic response (MCgR). In our group of patients, 50% achieved CCgR at six months, and 66.6% achieved CCgR at 12 months, which is slightly less than Eddou et al [14] reported.

Rates of MMR from 8–47% in 6 to 18 months have been reported in patients treated with generic imatinib [11, 12, 14]. The other two observational studies have shown interesting results. One of them is a study conducted by colleagues from Turkey involving 145 patients with CML [15]. There were two groups: one included patients receiving branded imatinib (Glivec®), and the other comprised patients who initially received Glivec® and then switched to the generic drug. MMR rate was quite similar between these two groups [15]. The other study from India included 213 patients with CML: 64% of patients were on Gippar Glivec®, while 36% were on generic imatinib [16]. It may be noted that cytogenetic and molecular responses were better in the group of patients treated with generic imatinib. These results could be explained by the fact that molecular responses were not documented in 42% of patients in the Glivec® group because of economic reasons [16].

In the ENESTnd study of 283 patients receiving branded imatinib, 22% reached MMR after 12 months of therapy and 53% after 36 months [17, 18]. In our study, molecular response with the level of bcr/abl transcript less than 1% at six months in patients treated only with generic imatinib was 28.6%. The same percentage of these patients achieved MMR at 12 months.

Five-year EFS and FFS were significantly better in patients treated with branded imatinib as shown in Figures 4a and 4b (log-rank $p = 0.01$ and $p = 0.03$, respectively). These results could have been influenced by frequent changes in the brand and dosage formulation of generic imatinib.

There are reliable data on CML patients in Europe using generic imatinib forms. Results from Bosnia and Herzegovina show that generic imatinib as first-line treatment was less efficient when compared to branded imatinib, but it did not influence the outcome of treatment when used as second-line treatment [19]. Another study involving 24 patients from Croatia shows adequate efficacy of generic imatinib alongside a decreased cost of treatment [20].

However, our results cannot be compared to the results achieved in patients taking the original imatinib due to the crossover study design, but they provide an informative view of patients initially treated with branded imatinib compared to those initially treated with the generic drug.

Conclusion

Our study showed a significantly longer EFS and FFS in the patients who were initially treated with branded imatinib, compared to those treated with generic imatinib only. These results provide useful information, but have to be interpreted within the context of the crossover study.

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