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Comparison of branded and generics imatinib plasma concentrations in patients with chronic myelogenous leukemia – unicentric study

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Conflict of Interest Page

Authors declare no conflict of interests.

MicroAbstract

Imatinib has been the standard of care in chronic myelogenous leukemia for fifteen years. Its optimal plasma concentration correlates with optimal disease response. We compared plasma concentrations in patients who switched from branded to generic imatinib. No statistical difference in achieved imatinib plasma concentrations was found, and the treatment response was maintained.

Abstract

Introduction: For over a decade, imatinib has been the first-line treatment of Philadelphia chromosome-positive chronic myeloid leukemia (CML). Doubts on the bioequivalence and bioavailability of emerging generic compounds have been expressed. Adequate imatinib plasma concentration (IPC ≥1000 μmol/L) is associated with a better chance of optimal treatment response in CML. In this study we compared the achieved IPCs between the branded compound and its two generic forms. **Patients and methods:** IPCs were compared in 24 consecutive CML patients in first chronic phase who changed from branded to generic imatinib. The median age was 49 (22–76) years. Fifteen of them were male. Six patients were switched to Neopax, 13 to Imakrebin, and 5 patients received both generics consecutively. All compounds were used in an equivalent dose of 400 mg per os once daily for at least one month before plasma concentrations were measured. High-performance liquid chromatography was used to determine imatinib plasma concentration from a specimen collected 21–24 hours after the last dose. **Results**: Median IPC achieved with branded imatinib was 1454 μmol/L (range 485-2707) with 18 patients (75%) having IPC ≥ 1000 μmol/L. For Neopax and Imakrebin, median IPCs were 1717 (1249-3630) and 1458 (707-880) respectively with 11/11 (100%) and 16/18 (89%) patients having IPC ≥ 1000 μmol/L. No significant difference in measured IPCs between all three compounds was found ($p>0.257$). **Conclusion:** When taken at equivalent doses, imatinib generics are bioequivalent and comparable in clinical efficacy and have the potential for substantial savings in CML treatment cost.

Keywords: imatinib mesylate, chronic myelogenous leukemia, therapeutic drug monitoring, generics

Introduction

Since 2001, imatinib improved prognosis in chronic myelogenous leukemia (CML)[1] and is the standard of care worldwide. Recently, imatinib generics became available. Some case reports/series[2–6] raised concerns about its efficacy but refer to generics with questionable bioequivalence.[7] To date, there is no evidence that imatinib generics approved in North America and the European Union (EU) lack efficacy compared to the branded drug, even when comparing different imatinib crystal forms.[7]

Several studies correlated imatinib plasma concentrations (IPC) with adequate treatment response.[8–10] Recommended therapeutic imatinib plasma concentration (IPC) is between 1000 µmol/L and 3000 µmol/L. Small intra-patient variations, greater inter-patient variation, proportional dose-exposure relationship, and therapeutic concentration interval are basic imatinib properties making it suitable for therapeutic drug monitoring (TDM).[11] Our institution standard operating protocol does not require regular screening IPC monitoring except in cases of unmet optimal treatment goal at respective time points according to ELN criteria.[12]

After the branded imatinib patent had expired in March 2013 (before Croatia was admitted to the EU), Neopax (later on marketed as Meaxin, Krka d.d., Slovenia) and Imakrebin (Alvogen IPCo S.ar.l., Luxembourg) became available on the Croatian market as the first two generics. According to the Croatian Institute for Health Insurance reimbursement policy, generics were instituted as the first line of treatment in newly diagnosed and those already using branded imatinib (Glivec, Novartis AG, Switzerland). Motivated by controversies on the efficacy of imatinib generics, we've conducted a trial in measuring IPCs in patients changing from branded to a generic drug. Results of comparison of IPCs achieved with branded and generic imatinibs are presented here as a unicentric experience.

Patients and Methods

Study design

IPC was measured in 24 consecutive CML patients in their first chronic phase running out their last branded imatinib prescription. Their prescriptions were refilled with one of the available generics by our institution pharmacy. Afterward, branded imatinib was changed to one of the available generics or both consecutively. IPCs were measured every time the change in prescription was made. All drugs were used in an equivalent dose of 400 mg po qd for at least one month before IPCs were measured. Patients were interviewed for adherence to regular imatinib use. During the study, no relevant changes in other chronic therapy were recorded.

Blood sampling and analytical methods

High-performance liquid chromatography (HPLC) was used to determine imatinib plasma concentration from a peripheral blood specimen collected 21–24 hours after the last dose. The test was performed without delay or pooling the samples. Imatinib was extracted from plasma with methanol. Clozapine was used as an internal standard. The sample was fractionated on a column MN EC Nucleosil 100-5-C-18 EC 250 x 4.6 mm with a mobile system consisting of ammonium acetate buffer, methanol, and acetonitrile (40:40:20). The flow rate was 0.75 ml min-1. Quantitation was performed by measurement of UV detector at the wavelength of 265 nm.

The bcr-abl1 level in peripheral blood was quantified after at least one month of the use of a different drug compound. A quantitative real-time polymerase chain reaction was performed using a commercial Ipsogen BCR-ABL1 Mbcr kit (Qiagen, Germany). Reporting was done on an international scale, according to ELN standards.[13]

Statistical methods

Descriptive statistics (mean, median, range, and proportions) were calculated to provide group characteristics. A paired samples t-test was done to test the significance of the means between two groups, Kruskal-Wallis's test was used to compare continuous non-parametric variables, and Fisher's exact test was used in comparing the proportions between the

groups. A two-tailed p-value of <0.05 was considered as statistically significant. All analyzes were performed using IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY).

Results

Study population characteristics

Twenty-four patients who changed from branded imatinib to generics with a median age of 49 years (range 22–76) were enrolled in the trial. Fifteen of them (63%) were male. Branded imatinib was changed to Neopax (11 patients), or Imakrebin, either from Glivec or Neopax, at some time point (18 patients). There were no statistical differences between the patients using corresponding imatinib when grouped by gender (p=0.935), age (p=0.698), or adherence (p=0.166). The analysis was also done for the IPCs in the same patients while on corresponding compounds, grouped based on the following compound changes: Glivec to Neopax (6 patients), Glivec to Imakrebin (13 patients), and Glivec to Neopax to Imakrebin, consecutively (5 patients). The groups were comparable by gender (p=0.546) and age (p=0.701). Five patients in the group whose prescriptions were refilled only with Imakrebin reported suboptimal adherence. Nevertheless, the difference did not reach statistical significance (p=0.059). Table 1 summarizes the patient's demographics and adherence characteristics.

Imatinib plasma concentrations and treatment response

The baseline median IPC achieved with branded imatinib was 1454 µmol/L (range 485-2706) with 21 and 3 patients achieving major molecular response (MMR) and complete cytogenetic response (CCyR), respectively. Eighteen patients (75%) had IPC ≥ 1000 µmol/L. Suboptimal IPCs were measured in 5 patients with poor adherence. Later on, they improved compliance (see Table 2). Patient no. 12, who reported good adherence, had suboptimal IPCs regardless of the drug he was using. Since he did not meet optimal treatment goals at the recommended time point, imatinib dose was increased to 600 mg due to his enormous body

surface area. After six months, he achieved major molecular response (MMR). Eleven patients (10 with MMR and 1 with CCyR) were using Neopax and achieved with it median IPC of 1716 (1249-3630) μmol/L. All of them maintained optimal disease response while using Neopax. Eighteen patients, while using Imakrebin at some time point after Glivec or Neopax, had a median IPC 1458 (707-2880) μmol/L and maintained optimal disease response. Of all 24 patients, 16 (89%) had IPC ≥ 1000 μmol/L while using any of three compounds.

Univariate analysis

Achieved median IPCs with all three compounds were compared in univariate analysis. Although median IPC achieved with Neopax was higher, and greater inter-patient difference of IPCs was observed, it was statistically insignificant ($p>0.257$, Figure 1). Suboptimal IPCs were measured in 33% of patients while using Glivec, 13% of patients while using Imakrebin, and none while using Neopax ($p=0.161$, Figure 2). Suboptimal adherence was associated with suboptimal IPCs while using Glivec ($p=0.006$). The same association was not observed in patients while using Imakrebin ($p=0.490$) or Neopax (no observed suboptimal adherence nor IPCs).

Six patients changed from Glivec to Neopax had a median IPC of 1821 and 1572 μmol/L, respectively, and no statistical difference was found ($p=0.786$). Comparable IPCs were observed in 13 patients that changed from Glivec to Imakrebin (medians 1152 vs. 1230 μmol/L, $p=0.362$) and in 5 patients changing from Glivec to Neopax to Imakrebin consecutively (medians 1814 vs. 1717 vs. 1783 μmol/L, $p>0.148$).

Discussion

In our study, both imatinib generics in equivalent doses achieved adequate IPCs in most of the enrolled patients (100% and 89%). All patients maintained a good therapeutic response achieved with the branded drug. Both generics were well tolerated, and there was no

recorded discontinuation due to adverse effects. These results suggest comparable efficacy and a safety profile of examined generics to branded imatinib. Moreover, the presented data demonstrate interchangeability of different imatinib generics. As expected, adherence stays an important issue in treatment with imatinib.

For CML patients in Croatia, imatinib is in total reimbursed by the Croatian Health Insurance Fund. The cost of 400 mg qd dosage of branded imatinib after generics became available, is now maintained between $37,200 and $31,200 per year, depending on US Dollar/Croatian Kuna (HRK) currency. Since the price of the first approved generic cannot cross the limit set at 80% of the price of the branded drug, and the price of all other generics is limited to 90% of the price of the first generic, by default, all generic drugs should be cheaper than the patented predecessor.[14] The introduction of several new imatinib generics resulted in continuous price reductions making treatment costs as low as $12,000 annually. In the public health system, prescriptions for imatinib are only renewed in public hospital pharmacies that are supplied with it in the process of public procurement. Competing for their interests, pharmaceutical companies offer discounts that, in turn, lead to additional cost reductions. Because of that, the cost of imatinib generic can be more than five times cheaper than the branded imatinib. Availability of generic imatinib is expected to reduce treatment costs worldwide. However, its price is subject to the healthcare system organization, geopolitical and socioeconomic conditions of the particular country or region.[15]

Conclusion

Approved imatinib generics are comparable in bioavailability and efficacy with a patented one. Pharmacoeconomic indices are showing substantial cost reductions with significant savings that could be redirected to the research of new treatment modalities or treatment of other diseases of particular interest. All said, imatinib generics are a reasonable frontline therapy in CML.

Clinical Practice Points

- Optimal imatinib plasma concentration (IPC ≥1000 μmol/L) correlates with a greater chance for optimal treatment response
- Approved imatinib generic forms achieve comparable IPCs with branded imatinib
- Treatment response achieved with patented imatinib was maintained while using its generic forms
- Imatinib generics approved by competitive authorities are valid frontline therapy in CML and result in substantial treatment cost reduction

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Figures

Figure 1 Comparison of imatinib plasma concentrations between branded and generics compounds

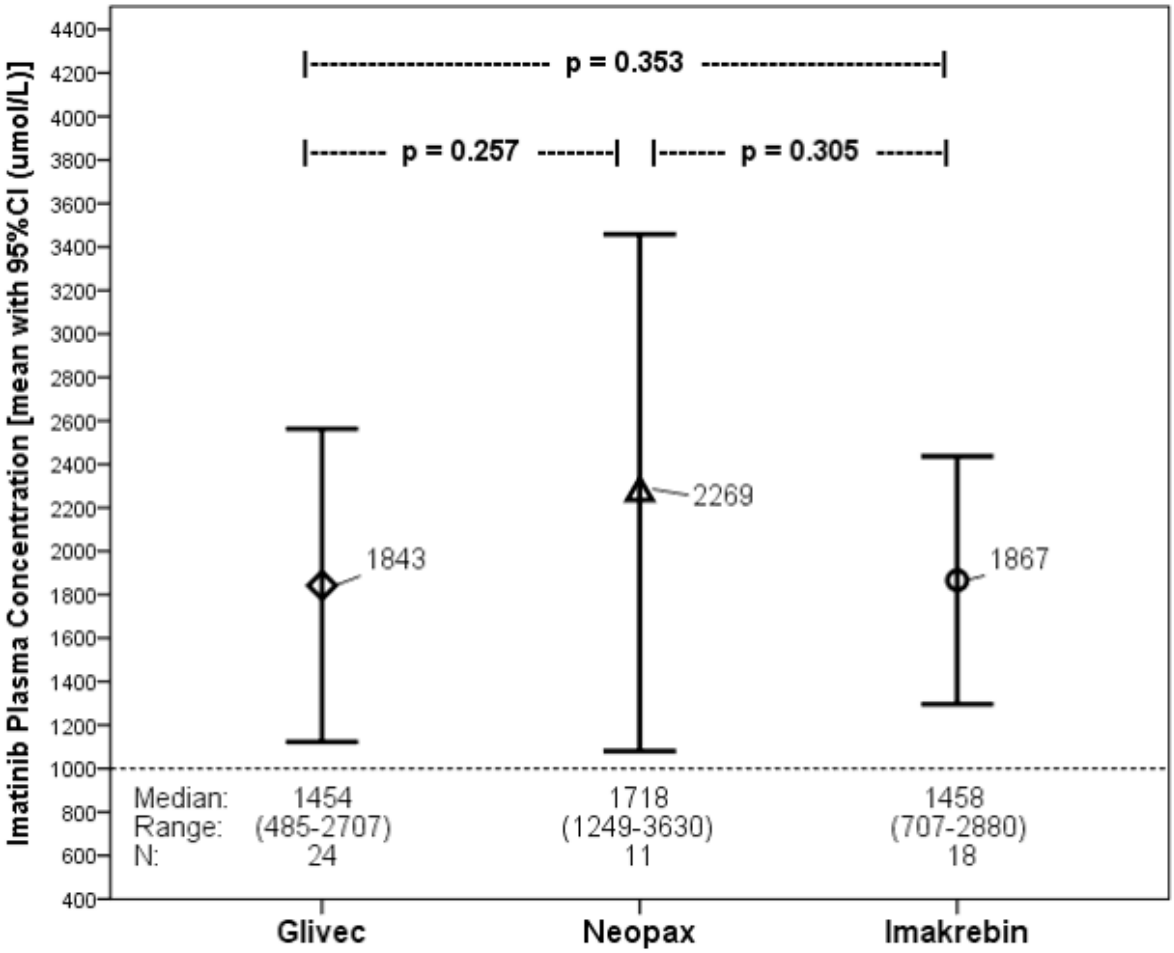
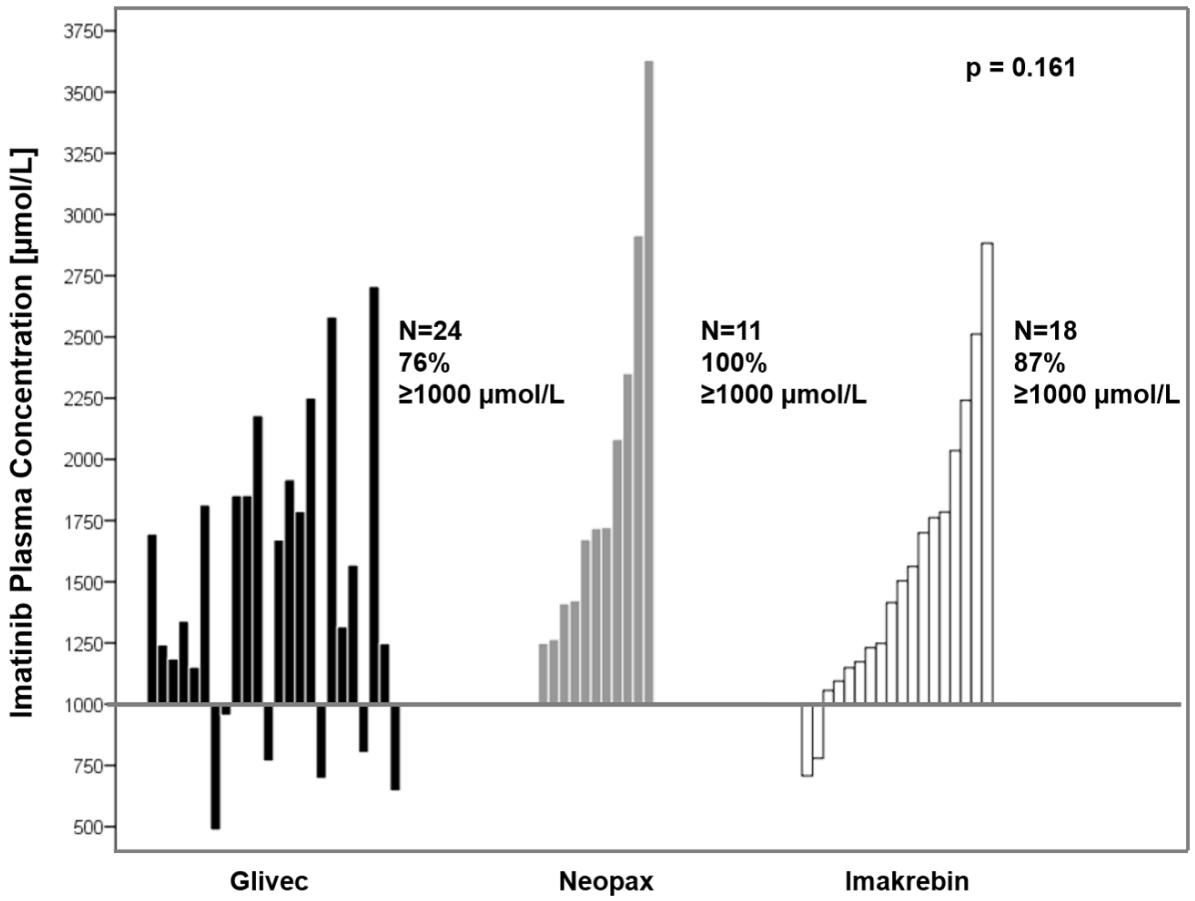


Figure 2 Optimal imatinib plasma concentrations achieved with corresponding imatinib compound



Tables

Table 1 Patient Demographics and Adherence Characteristics

Parameter	Glivec/All Patients	Neopax	Imakrebin	*P*
Patients While on Corresponding Imatinib				
Total				
n (%)	24 (100)	11 (46)	18 (75)	
Gender				
Male, n (%)	15 (63)	6 (55)	11 (61)	.935
Age				
Median, years (range)	49 (22-76)	49 (22-76)	55 (30-72)	.698
Adherence				
Optimal n (%)	19 (79)	11 (100)	17 (94)	.166
Suboptimal n (%)	5 (21)	0 (0)	1 (6)	

Parameter	Glivec to Neopax	Glivec to Imakrebin	Glivec to Neopax then to Imakrebin	*P*
Patients Grouped According to Consecutive Generic Use				
Total				
n (%)	6 (25)	13 (54)	5 (21)	
Gender				
Male, n (%)	4 (67)	9 (69)	2 (40)	.546
Age				
Median, years (range)	51 (30-67)	47 (22-76)	57 (36-72)	.701
Adherence				.059
Optimal n (%)	6 (100)	8 (62)	5 (100)	
Suboptimal n (%)	0 (0)	5 (39)	0 (0)	

Table 2

List of Patients With Imatinib Plasma Concentrations While on Corresponding Compound and Disease Response

	Gender/Age	IPC (μmol/L) and Level of Disease Response While on Corresponding Imatinib					
		Glivec		Neopax		Imakrebin	
1	M/40	1696	MR [3]	–		1230	MR [3]
2	M/67	1243	MR [4.5]	1263	MR [4.5]	–	
3	M/29	1187	MR [4]	–		706	MR [4]
4	M/46	1339	MR [3]	1249	MR [3]	–	
5	M/53	1152	MR [5]	–		1698	MR [5]
6	F/40	1814	MR [2]	1410	MR [2]	2034	MR [2]
7	F/50	485	MR [4.5]	–		1561	MR [4.5]
8	M/44	954	MR [5]	–		1096	MR [5]
9	M/55	1853	MR [4]	1423	MR [4]	–	
10	F/22	1853	MR [4]	–		1502	MR [4.5]
11	F/67	2179	MR [4]	2082	MR [4.5]	–	
12	M/62	767	CcyR	–		778	CCyR
13	M/64	1672	MR [5]	–		1148	MR [5]
14	M/30	1918	MR [4.5]	1722	MR [4.5]	–	
15	F/33	1788	CCyR	2351	CcyR	–	
16	F/72	2252	MR [5]	2915	MR [5]	1738	MR [5]
17	M/47	696	MR [4]	–		1414	MR [4.5]
18	F/36	2583	MR [4.5]	3630	MR [4.5]	2509	MR [4.5]

	Gender/Age	IPC (µmol/L) and Level of Disease Response While on Corresponding Imatinib					
		Glivec		Neopax		Imakrebin	
19	M/57	1317	MR $^{4.5}$	1717	MR $^{4.5}$	1247	MR $^{4.5}$
20	M/39	1569	MR ^{3}	–		1055	MR $^{4.5}$
21	M/58	802	MR ^{2}	–		1172	MR ^{2}
22	F/76	2707	MR ^{4}	–		2880	MR ^{4}
23	M/65	1248	MR ^{4}	1673	MR ^{4}	1760	MR ^{5}
24	F/34	645	CCyR	–		2239	MR ^{3}

Abbreviations: CCyR = Complete cytogenetic response; IPC = imatinib plasma concentration; MR = molecular response (as BCR-ABL1% to ABL1 on the International scale, where 10%, 1%, 0.1%, 0.01%, 0.0032%, and 0.001% correspond to a decrease of 1, 2, 3, 4, 4.5, and 5 logs, respectively).