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Hematologic Relapse after 2 Years on a Non-Authorized Copy Version of Imatinib in a Patient with Chronic Myeloid Leukemia in Chronic Phase: A Case Report

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Key Words
Chronic myeloid leukemia · Imatinib · Imatinib-COPER

Abstract
Imatinib (Gleevec®/Glivec®) has demonstrated high and durable hematologic and cytogenetic response rates, favorable safety and toxicity profiles, and prolonged survival when used for the treatment of chronic myeloid leukemia (CML). Imatinib copy drugs are currently available in some countries; however, the safety and efficacy of these compounds have not been widely assessed. We present a patient who received the copy drug imatinib-COPER, lost hematologic response while on therapy, and was subsequently treated with branded Glivec. This report, and other published cases, suggests that imatinib copy drugs may not be equivalent to branded Glivec in pharmacology, safety, and efficacy. The case was a 42-year-old Moroccan male with CML. Initial therapy with hydroxyurea alone followed by hydroxyurea in combination with interferon-α resulted in durable complete hematologic remission (CHR). Due to adverse effects, the patient was switched to imatinib-COPER at 400 mg/day. Despite compliance with therapy, he lost his CHR after 2 years and presented with aplasia requiring a blood transfusion. Administration of Glivec in combination with hydroxyurea resulted in re-achievement of complete hematologic remission that was stable at last follow-up. Data from large-scale trials demonstrating high and durable responses and favorable safety have resulted in Glivec being considered as standard frontline therapy for patients with CML. Such trials have not been conducted for imatinib copy drugs. In the absence of clinical trial data, information from individual cases is critical to assessing the utility of copy drugs. This report suggests that initial treatment with an imatinib copy drug may compromise efficacy.

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Introduction

Imatinib mesylate (Glivec®/Gleevec®; Novartis Pharmaceuticals Corporation), an inhibitor of the constitutively active oncogenic fusion protein tyrosine kinase BCR-ABL [1, 2], is the recommended frontline treatment for all patients with chronic myeloid leukemia (CML) [3, 4]. The International Randomized Study of Interferon and STI571 (IRIS) trial demonstrated improved safety and efficacy over the previous standard of care, interferon-α plus cytarabine [5]. Long-term follow-up from the IRIS trial at 7 years demonstrated a cumulative best complete cytogenetic response (CCyR) rate of 82% in patients randomized to imatinib [6]. At 7 years, 93% of patients had freedom from progression to accelerated phase/blast crisis, and the event-free and overall survival rates were 81 and 86%, respectively.

Although Glivec has been clinically proven to induce durable responses [5–8], to prolong survival [6–8], and to have a favorable long-term safety profile [6–8], some patients look for substitutes due to cost or lack of access. In several countries, alternative, lower-cost 'copies' of Glivec are available. While these products are marketed as being comparable to Glivec, little is known about the relative efficacy or safety of these products. Bio- and pharmaceutical equivalence to Glivec has not been established, and these agents have not been evaluated in randomized clinical trials. Thus, the question of whether use of Glivec 'copies' may result in compromised patient safety and treatment outcomes remains unanswered.

Here, we report a case of a patient diagnosed with CML in chronic phase (CML-CP) treated in Morocco, who was originally treated with hydroxyurea/interferon-α and subsequently with the Glivec copy 'imatinib-COPER,' then switched to branded Glivec after experiencing hematologic relapse on the copy drug.

Case Presentation

In May 2002, a 42-year-old male was diagnosed with CML during a routine checkup. He exhibited no splenomegaly, but had ganglions and adenopathies of the lateroinguinal and cervical lymph nodes of a few millimeters. The patient was otherwise healthy and had no significant medical or surgical history. Initial laboratory assessment revealed a total leukocyte count of 207,000/mm^3, hemoglobin concentration of 10.7 g/dl, and 18% blast cells in the peripheral blood smear (**table 1**). A diagnosis of CML-CP was confirmed by fluorescence in situ hybridization (FISH) analysis of a peripheral blood specimen, which revealed 100% Philadelphia chromosome-positive (Ph+) cells.

The patient was treated with hydroxyurea at 3 g/day for 2 months. In July 2002, his total leukocyte count had dropped to 3,000/mm^3 and he had achieved complete hematologic response (CHR). He was then switched to hydroxyurea at 2 g/day supplemented with subcutaneous interferon-α at a daily target dose of 3 million U/m^2 5 days a week until October 2002. At this time, interferon was stopped. One month after stopping interferon, the patient remained in CHR. The patient continued on hydroxyurea at 2 g/day until April 2004. In June 2005, the patient, who remained in CHR, presented with algic mouth ulcers, which led to discontinuation of treatment with hydroxyurea.

In September 2006, the patient was started on a copy of imatinib called imatinib-COPER at 400 mg/day. In January 2007, the patient showed a reduction in mouth ulcers, was generally feeling better, and was in hematologic remission. In December 2008, after 2 years on therapy, the patient began to feel ill and presented with aplasia requiring an urgent blood transfusion. Prior to transfusion, he had a decreased hemoglobin level (7.4 g/dl) and lost his CHR (total leukocyte count, 90,960/mm^3). Karyotyping of 20 metaphase cells revealed clonal evolution in 2 cells. One Ph+ clone also had trisomy 8; one clone had a double Ph chromosome and trisomy 8. Imatinib-COPER treatment was immediately stopped. The patient reported compliance with daily imatinib-COPER therapy throughout treatment (2 years and 3 months total).

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At this time, the patient was switched to branded Glivec at 400 mg/day in combination with low-dose (1 g/day) hydroxyurea. The patient achieved complete hematologic remission within 1 month of starting Glivec (table 1). After 2 months, he stopped hydroxyurea and remains on Glivec at 400 mg/day. His last checkup was September 2009, at which time he had gained weight, returned to work, and remained in CHR.

Conclusion

The patient described herein achieved CHR on hydroxyurea, but had to end treatment due to unmanageable side effects. Two years after switching to the Glivec copy drug imatinib-COPER, he lost his hematologic response, and clonal evolution was revealed. The patient reported compliance to therapy, and reasons for failure are unknown. Within 1 month of initiating branded Glivec at 400 mg/day, the patient regained CHR. Thus, failure on imatinib-COPER did not result from acquired imatinib resistance. These data suggest that imatinib-COPER may be a very different molecular entity from Glivec and has substantially different pharmacokinetic and pharmacodynamic characteristics. This is likely to result in differences in safety and efficacy between imatinib-COPER and Glivec, as was demonstrated in this case.

While the copy product used to treat this patient was intended to be comparable to Glivec, there is no published clinical evidence to support the claim of comparable safety or efficacy. In contrast, long-term follow-up from the IRIS trial demonstrates durable hematologic, cytogenetic, and molecular responses in the majority of patients treated with Glivec [6–8]. At 12 months on therapy, the estimated rates of CHR, major cytogenetic response, and CCyR were 96, 85, and 85%, respectively, in patients randomized to imatinib, increasing to 98, 92, and 87% at 5 years [7]. Hematologic relapse, as was seen in this case, was highly uncommon among patients treated with frontline imatinib on IRIS.

This case report suggests that initial therapy with an imatinib copy drug may compromise efficacy and detrimentally impact long-term outcomes in patients with CML. Further studies are needed to confirm this finding. Switching to a copy drug in a patient responding to Glivec may similarly compromise outcomes. Major guidelines recommend indefinite continuation of imatinib therapy unless loss of response or intolerance occurs [3, 4].

In an interim analysis of the Stop Imatinib (STIM) discontinuation study, in which Glivec was discontinued in patients sustaining complete molecular response for at least 2 years, 36 of 70 patients (51%) experienced molecular relapse [9]. Other case series have shown a similar risk of relapse upon discontinuation of Glivec [10–12]. The impact of switching to a copy drug in a similar patient population is unknown. In the absence of clinical trials comparing safety and efficacy of Glivec with copies, patients administered Glivec copies require careful monitoring and follow-up.

In cases where medical insurance is limited, treatment cost may be a major factor in the decision to prescribe a Glivec copy. To ensure access to the agent currently approved throughout the world as frontline therapy for CML, Novartis Pharmaceuticals Corporation has established the Glivec International Patent Assistance Program (GIPAP). This program, available in more than 80 countries worldwide, is designed to provide FDA-approved imatinib to qualified patients. Maintaining daily medication with the approved drug and careful monitoring of response and adverse events are crucial for ensuring optimal long-term outcomes in patients with CML.

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Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Table 1. Hematologic parameters at baseline and following treatment changes

	Baseline	Hydroxyurea	Hydroxyurea/interferon	On copy drug (imatinib-COPER)		At discontinuation of copy drug	After starting imatinib (Glivec)		
	May 2002	July 2002 (2 months on hydroxyurea)	Nov 2002 (4 months on hydroxyurea/IFN)	Sept 13, 2006 (day before starting treatment)	Nov 21, 2006 (2 months after treatment)	Dec 2008	Dec 20, 2008	Mar 23, 2009	May 6, 2009
Red blood cell count, $\times 10^6$ n/mm^3	3.51	3.90	3.91	2.95	4.01	3.25	3.42	3.41	3.61
Monocytes, %	10.7	12.4	12.4	12.4	13.8	11.1	11.7	11.9	13.2
Total leukocyte count, n/mm^3	207,000	3,000	11,000	13,500	8,000	90,690	54,000	6,980	7,530
Neutrophils, %	56	52	70	62	69	45	58	64	54
Eosinophils, %	1	2	2	2	4	1	1	7	1
Basophils, %	1	0	0	0	0	0	1	4	0
Lymphocytes, %	8	45	23	15	26	4	7	1.6	41
Monocytes, %	2	1	5	2	1	3	0	8	4
Platelet count, n/mm^3	unknown	87,000	53,000	239,000	172,000	175,000	162,000	85,000	85,000
Myelemy	42%					4%			
Myeloblasts	18%	100% –		100% –		47%	100% –		
Myelocytes	17%	no more myelemy		no more myelemy		8%	no more myelemy		
Metamyelocytes	7%					11%			

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