Failure of copy Imatib (CIPLA, India) to maintain hematologic and cytogenetic responses in chronic myeloid leukemia in chronic phase

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Abstract A 50-year-old woman presented with CML-CP and was initially treated with branded imatinib (Glivec\textsuperscript{\(	extregistered\)}) 400 mg/day. She rapidly achieved a complete hematologic response (CHR), at which point she switched therapy to a copy version of imatinib (Imatib). She received 400 mg/day of Imatib for 3 months, during which time her platelet count decreased from 250 \(\times 10^9\) to 105 \(\times 10^9\)/L and her hemoglobin count fell from 12.8 to 11 g/dL. The patient’s total leukocyte count rose rapidly from 4 \(\times 10^9\) to 70 \(\times 10^9\)/L, and the CHR was lost. At this point, therapy was switched back to Glivec at 400 mg/day, and the CHR was rapidly regained. Furthermore, the patient achieved a major cytogenetic response by 6 months after reintroduction of Glivec. This case report suggests a difference in clinical efficacy between the authorized form of imatinib (Glivec) and the copy version of the drug (Imatib). The exact reasons for the observed difference in clinical efficacy are unknown, but likely relate to the use of alternative polymorphic forms of the drug. Glivec can be obtained directly from the manufacturer (Novartis Pharmaceuticals) through a variety of patient access programs that should be fully explored when needed.

Keywords Imatinib · Imatib · Glivec · CML

The recommended first-line treatment for all patients presenting with chronic myeloid leukemia in the chronic phase (CML-CP) is imatinib mesylate (Glivec\textsuperscript{\(	extregistered\)}/Gleevec\textsuperscript{\(	extregistered\)}, Novartis Pharmaceuticals, East Hanover, NJ) [1, 2], a BCR-ABL tyrosine kinase inhibitor (TKI) that specifically targets the oncogenic fusion protein created by the Philadelphia chromosome (Ph+) translocation [3–5]. Two polymorphic forms of imatinib were identified during its early clinical development, the alfa- and beta-crystalline forms, of which the beta polymorph is the most thermodynamically stable and was chosen for further clinical development. All large-scale clinical trials conducted to date, including the pivotal phase III study that first demonstrated the superiority of imatinib over the previous standard of care, interferon-alfa plus cytarabin [6, 7] have used only the beta-crystalline polymorph.

In a number of countries, alternative, low-cost forms of imatinib are now becoming available, which often utilize the alfa-crystalline polymorph. One such example is the copy product Imatib (CIPLA, India). This product is marketed and officially accepted in some countries, including Egypt, as being comparable to imatinib. To date, little is known about the relative efficacy and pharmacokinetic profile of these alternative BCR-ABL TKIs, and their bioequivalence and pharmaceutical equivalence have not been established. For this reason, we do not yet know whether these alternative agents have similar clinical efficacy and tolerability profiles as the authorized, beta-crystalline form of imatinib, or whether their use may potentially compromise patient safety.

In December 2006, a 50-year-old woman presented with anemia and splenomegaly to 20 cm. Laboratory examination showed a moderately low hemoglobin concentration of 10.0 g/dL and an elevated total leucocytic count of 105 \(\times 10^9\) cells/L, with 1% basophils and 3% peripheral blasts. Her platelet count was normal, at 200 \(\times 10^9\)/L. A diagnosis of CML-CP was suspected, and confirmed by bone marrow examination, which revealed 55% Ph+ cells by fluorescence in situ hybridization.
The patient was treated with standard first-line therapy for CML-CP, imatinib (Gleevec®, Novartis Pharmaceuticals, East Hanover, NJ) at 400 mg/day. This initial therapy was successful, with the total leukocyte count falling to $4 \times 10^9/L$ and hemoglobin levels returning to the normal range within 2 months (Fig. 1). Shrinkage of the spleen, from 20 to 13 cm, was also observed. At this time point, the patient was deemed to have achieved a complete hematologic response (CHR); however, no molecular or cytogenetic responses were observed during this brief 2-month treatment period.

Two months into her therapy and after achieving CHR, the patient chose to switch to a copy of imatinib, Imatib, for financial reasons. This patient was switched to Imatib at a dose of 400 mg/day for 12 weeks. The dose was chosen on the assumption of having comparative effect to Glivec®. During this time, her platelet count fell by more than half, from $250 \times 10^9$ to $105 \times 10^9/L$, and her hemoglobin count was also reduced slightly, from 12.8 to 11 g/dL (Fig. 1). In addition, her total leukocyte count rose rapidly back toward pre-treatment levels, reaching $70 \times 10^9/L$ by the end of this 12-week period and a splenic size of 15 cm was recorded at the end of that period. The patient also lost her previously documented CHR. No non-hematological side effects were noted at that point following the use of Imatib. Because the International Patient Assistance Program for Glivec® (GIPAP) was not available in Egypt at the time, the patient had to sell a private asset to be able to afford switching back to the initial therapy of imatinib (Glivec®) at 400 mg/day in an attempt to regain disease control.

The patient’s total leukocyte counts recovered rapidly on reconversion to imatinib (Glivec®) falling to $10.4 \times 10^9/L$ within 2 months (Fig. 1). Hemoglobin and platelet counts also rose, reaching similar levels to those achieved during the first 2 months on imatinib with splenic size reaching 13 cm. After 2 months, switching back to the authorized form of the drug, the patient regained her CHR. This therapy was continued at 400 mg/day, as per the licensed indication, and a PCyR was achieved by 6 months after reconversion, with only 15% of cells found to be Ph+.

The European LeukemiaNet recommendations define imatinib failure in CML-CP as a loss of CHR or a loss of complete cytogenetic response at any time [1]. According to these criteria, the patient described here had achieved a CHR within 2 months with imatinib, but suffered treatment failure rapidly after switching to the copy product, Imatib. Despite this treatment failure, reconversion to the established pharmacologically active and tested form of the drug at the initial dose of 400 mg/day allowed a full and rapid recovery of her CHR, and a PCyR was also achieved within 6 months. As this patient was able to regain her CHR by reconverting to imatinib, without the need for dose escalation beyond the initial dose of 400 mg/day, treatment failure did not appear to be a result of acquired imatinib resistance, suggesting a difference in efficacy between the pharmacologically active and tested form of imatinib and the copy form.

The reasons for this potential difference in efficacy are unclear, but may relate to differences in pharmaceutical properties between the two compounds. Therapeutic equivalence requires that a generic product should show pharmaceutical equivalence and thus have the same active ingredient, dosage form, route of administration and strength or concentration as the innovator’s reference drug. In particular, differences in bioequivalence may affect the rate and extent of absorption of the active ingredient. One potentially important difference between the two compounds described here is the polymorphic form of imatinib.

Fig. 1 Hematologic response parameters over the entire course of treatment
that they contain. The pharmacologically active and tested form of imatinib consists of the beta-crystalline polymorph, while Imatib is made up of the alfa-crystalline form. During early clinical development of imatinib, the beta-crystalline form was found to be more thermodynamically stable; therefore, it is less likely to convert to a different polymorph or degrade during processing or storage. The clinical implications of this difference have not yet been explored, but pharmaceutical and biological equivalence would need to be demonstrated before any assumptions of clinical equivalence can be drawn. When choosing between pharmacologically active and tested and other forms of biologic agents that are not bioequivalent such as Imatib, consideration must also be given to patient safety, which may be impacted by product degradation and the associated generation of impurities. This is of particular concern with imatinib as the active ingredient is a mesylate salt [5, 8], and degradation byproducts such as mesylate esters of methanesulfonic acid are known to be highly genotoxic [9].

This case report suggests that switching from the pharmacologically active and tested form of imatinib (Glivec®) to a copy product may compromise efficacy and could have multiple negative impacts on long-term patient outcomes. Novartis Pharmaceuticals has established a GIPAP, which is designed to provide FDA approved products to qualified patients in countries where imatinib mesylate is approved. This program is open in at least 80 countries and should be utilized by patients who may have limited access to commercially available imatinib (Glivec®) to avoid the lack of efficacy and potential toxicity with copy imatinib products.

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