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Safety and efficacy of switching from branded to generic imatinib in chronic phase chronic myeloid leukemia patients treated in Italy

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ABSTRACT

The use of generic drugs after patent expiration of their originators is a relative novelty in the treatment of chronic cancer patients in Western countries. In this observational study we analyzed a cohort of 294 Italian chronic phase chronic myeloid leukemia patients treated frontline with branded imatinib (Glivec®) for at least 6 months and then uniformly switched to generic imatinib upon requirement of health authorities in early 2017.

Median age at diagnosis was 57 years (range 19–87). Sokal risk was low/intermediate/high in 55%, 32% and 8% of cases, respectively. Median duration of branded imatinib treatment was 7.4 years (range 0.5–16.7). At a median follow-up of 7.5 months after switch to generic imatinib, 17% of patients reported new or worsening side effects, but grade 3–4 non-hematological adverse events were rare. Six patients switched back to branded imatinib, with improvement in the side effect profile, and 4 pts moved to bosutinib or nilotinib for resistance/intolerance. The majority of patients were in major (26%) or deep molecular response (66%) at the time of switch. Molecular responses remained stable, improved or worsened in 61%, 25% and 14% of patients, respectively.

We conclude that switch to generic imatinib for patients who have been receiving branded imatinib appears to be effective and safe. Molecular responses may continue to improve over time. Some patients experienced new or worsened side effects but less than 5% of the whole cohort needed to switch back to branded imatinib or move to other treatments. Savings were around 3 million Euros.

1. Introduction

Imatinib is the most commonly used drug in chronic myeloid leukemia (CML) patients worldwide [1]. Frontline treatment of newly diagnosed patients with imatinib 400 mg daily determined a 10-year survival rate around 82–83% [2], close to that of the general population [3]. In early 2017 a generic formulation of imatinib was introduced in the Italian market and patients switched from branded (i.e. Glivec®, Novartis) to the generic one upon requirement by regional health authorities.

The use of generic drugs after patent expiration of their originators aims at reducing financial costs, an issue of increasing relevance also in

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developed countries [4]. However, switching from innovator to generic drugs in cancer patients represents a relative novelty and some concerns exist both from the perspective of clinicians and patient advocacies [5].

In some earlier studies the transition from branded to generic imatinib resulted detrimental in terms of efficacy and safety [6] or determined a higher rate of subsequent switch to 2nd generation (2 G) tyrosine kinase inhibitors (TKI) [7,8]. However, the majority of later reports showed similar efficacy between branded and generic imatinib: these studies indirectly compared distinct cohorts of patients treated before or after the availability of generic drugs on regional markets [9] or reported about a mix of patients treated with generic imatinib as frontline therapy or after switching [10–12]. A Turkish report showed that early molecular response at 3 and 6 months was similar in two cohorts of patients receiving either upfront branded or generic imatinib, and the attainment of molecular endpoints was clearly associated with similarly favorable long-term outcome [13]. Very few data are available about longitudinal cohorts of patients treated for a prolonged time with branded imatinib and then switched to the generic formulation. A study from Latvia evaluated 25 patients treated for at least 2 years with branded imatinib and followed for other 2 years after switching to the generic drug: all these patients maintained a stable MMR, but side effects were not detailed [14].

To address this issue we analyzed the outcome of an Italian CML population to assess changes in adverse event (AE) profile or efficacy after switching from branded to generic imatinib.

2. Patients and methods

In this observational study we analyzed 294 chronic phase CML patients treated at 10 hematological centers of Triveneto region (Northeastern Italy) with branded imatinib for at least 6 consecutive months before switching to a generic formulation (Imatinib Sandoz). The generic product was determined with a regional contract, and was the same for all patients throughout the entire period of observation. Patients were switched upon requirement of health authorities for the purpose of public resource savings and they did not receive any direct financial incentive. Full data about diagnosis, cytogenetic and molecular response and AE experienced on branded imatinib were available through an electronic database. After switching, RT-Q-PCR and biochemical exams were performed at least every 3 months and AE were continuously assessed. Molecular analyses were performed in standardized laboratories and responses were defined according to the ELN2013 and European Treatment and Outcome Study (EUTOS) for CML recommendations [15,16]. Major molecular response (MMR or MR^3) was defined as $BCR\text{-}ABL^{IS}$ ratio < 0.1%. Deep molecular response (DMR) was defined as $BCR\text{-}ABL^{IS}$ ratio ≤0.01% or undetectable disease with ≥10,000 ABL copies (i.e. MR^4) plus $BCR\text{-}ABL^{IS}$ ratio ≤0.0032% or undetectable disease with ≥32,000 ABL copies (i.e. $MR^{4.5}$). The rate and severity of hematologic and non-hematologic AE were assessed according to the CTCAE 4.0 scale. All data were analyzed for descriptive purposes. All patients provided written informed consent for participation in this retrospective and prospective observational study, which was reviewed and approved by the Internal Review Board of the participating institutions, and performed in accordance with the Declaration of Helsinki.

3. Results

3.1. Patient characteristics

Characteristics of patients at CML diagnosis are summarized in Table 1. Median age was 57 years (range 19–87 years). The majority of cases (55%) had a low Sokal risk. Branded imatinib was the first TKI treatment for all patients, but 32 of them (11%) had received interferon alpha as frontline treatment, before the availability of imatinib.

Table 1
Characteristics of patients at diagnosis.

Characteristics	Patients, n (%)
Gender: male	148 (50)
female	146 (50)
BCR-ABL transcript type: b_2a_2	74 (25)
b_3a_2	167 (57)
b_2a_2 / b_3a_2	28 (10)
other/unknown	25 (8)
Sokal risk: low	162 (55)
intermediate	93 (32)
high	24 (8)
not evaluable	15 (5)

Median duration of branded imatinib treatment was 7.4 years (range 0.5–16.7 years). Imatinib dose at switch was 400 mg, less than 400 mg and more than 400 mg daily in 71%, 27%, and 2% of patients, respectively. Imatinib dose and administration schedule were not changed upon switching. At the time of switch, molecular responses were as follows: less than MR^3 in 25 (8%), MR^3 in 75 (26%), MR^4 in 87 (30%) and $MR^{4.5}$ or better in 107 (36%) patients, respectively.

3.2. Safety of switching from branded to generic imatinib

The majority of patients (171/294, 58%) had experienced at least one AE while on branded imatinib, most commonly muscle cramps, fluid retention, diarrhea and anemia (Table 2). Grade 3–4 non-hematological AE were uncommon and included infections (n = 4), arrhythmia (n = 2) ischemic stroke (n = 1) and cardiac failure (n = 1). Of note, 9 patients had a secondary neoplasm diagnosed while on branded imatinib.

At a median follow-up of 7.5 months after switch to generic imatinib (range 0–12.2 months), 49 patients (17%) reported new or worsening AE (Table 2), most commonly nausea, diarrhea and muscle cramps, and 64 patients (22%) maintained low-grade persistent AE, with unchanged severity upon transition from branded to generic imatinib. The majority of new AE occurred within the first 3 months after switch. Grade 3–4 non-hematological AE of new occurrence included increase of lipase (n = 3), infections (n = 2), vomiting (n = 1), muscle pain (n = 1), and severe allergic reaction at the first intake of generic imatinib (n = 1). Twelve patients (4%) interrupted generic imatinib for > 30 days and 20 patients (7%) had the dose permanently reduced, most commonly to 200 mg daily.

Table 2
Frequency of adverse events upon treatment with branded and generic imatinib.

Adverse event term	Branded imatinib	Generic imatinib *persistent AE (severity unchanged from branded imatinib)*	Generic imatinib *new or worsened AE (severity increased from branded imatinib)*
Fluid retention	58 (19.7%)	8 (2.7%)	5 (1.7%)
Muscle cramps	71 (24.1%)	23 (7.8%)	9 (3.1%)
Arthralgia	28 (9.5%)	8 (2.7%)	6 (2.0%)
Ocular symptoms	31 (10.5%)	6 (2.0%)	6 (2.0%)
Skin rash / pruritus	24 (8.2%)	6 (2.0%)	3 (1.0%)
Nausea / vomiting	24 (8.2%)	5 (1.7%)	7 (2.4%)
Diarrhea	46 (15.6%)	5 (1.7%)	10 (3.4%)
Increased creatinine	10 (3.8%)	7 (2.4%)	1 (0.3%)
Anemia	37 (12.6%)	14 (4.8%)	4 (1.3%)
Leukopenia	18 (6.1%)	5 (1.7%)	3 (1.0%)
Thrombocytopenia	25 (8.5%)	7 (2.4%)	1 (0.3%)
Overall*	**171 (58.2%)**	**64 (21.8%)**	**49 (16.7%)**

* this value is not the sum of the column since a patient may have experienced more than one AE.