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LETTERS TO THE EDITOR

Chronic myeloid leukemia patients call for quality and consistency when generics are introduced to treat their cancer

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Imatinib is a tyrosine kinase inhibitor (TKI) used in the treatment of multiple cancers, most notably chronic myeloid leukemia (CML). A patent application for imatinib was filed in Switzerland in 1992, as well as in the EU, the USA and for other countries in 1993. Companies began selling generic formulations of imatinib in India in the early 2000s, surrounded by controversial patent disputes.[1] The period for market exclusivity for imatinib has lapsed in 10 EU Member States and lapses in most countries in 2016.[2]

Various anecdotal concerns of efficacy related to generic formulations of imatinib versus the originator product have been reported in the scientific literature.[3–5] There has been confusion and uncertainty with regard to the safe administration of patented drugs, quality-controlled generics, copies of patented drugs and medicines of substandard quality.[5–8] Physicians and patient organizations have been increasingly confronted with the issue of generics and copies of patented drugs in the treatment of CML. This has raised concerns about the outcomes when patients are switched between different products for non-medical reasons.[2] At the same time, significantly lower prices of generics and copies of patented drugs have allowed more patients to afford treatment, and healthcare cost savings have been realized.[6,9] The CML Advocates Network, a patient-run network of CML patient organizations from more than 70 countries, undertook a survey to investigate some of the concerns that patients experience when an alternative, less expensive formulation of the originator TKI is prescribed for management of their cancer.

During 2013, the CML Advocates Network designed a questionnaire (see supplementary material) to survey 80 patient advocacy organizations of the worldwide CML Advocates Network as well as a physicians registered at the International CML Foundation. Questions included the availability of different TKI products, availability of certificates of quality to the public, bioequivalence and/or effectiveness of these products, duration of availability, as well as observations of unusual side effects or efficacy compared with the experience of the established original/patent-protected TKIs. There were 86 responses from 55 countries.

On the basis of the data received from the 2013 survey, representatives of CML patient organizations from 58 countries met in 2014 for their annual global advocacy meeting in Belgrade, Serbia. Joint recommendations for the optimal use of TKI generic formulations in the management of CML were discussed and agreed.

According to the results of the 2013 survey, imatinib was available in 55 countries, nilotinib in 44, dasatinib in 30, bosutinib in 6 and ponatinib in 4. Generic formulations or copies of imatinib had become available in 15 countries (Bosnia-Herzegovina, China, Colombia, Costa Rica, Egypt, Guatemala, Hong Kong, India, Lebanon, Lithuania, Nepal, Nigeria, Russia, Serbia and Uruguay) and similarly for dasatinib in three countries (Costa Rica, Guatemala and India).

At the annual CML global advocacy meeting in Belgrade during 2014, representatives of the 58-country patient organizations present determined that generic formulations or copies of imatinib and dasatinib had become available in 32 countries: Argentina, Bosnia-Herzegovina, Canada, Chile, China, Colombia, Costa Rica, Croatia, Cyprus, Dominican Republic, Guatemala, Ecuador, Egypt, Estonia, India, Kazakhstan, Lebanon, Latvia, Lithuania, Macedonia, Malta, Nepal, Philippines, Peru, Russia, Romania, Serbia, Slovenia, Slovakia, South Africa, Turkey and Uruguay.

Following intense discussion covering a number of concerns, the CML patient organizations worked towards concluding the meeting with a declaration that calls for quality and consistency when generics and copies of patented drugs are introduced on the market. In the face of more generic formulations entering the market, the group felt clearer guidance is required for demonstration of bioequivalence to the originator product, especially for drugs with a narrow therapeutic range.[2,4] In some countries, generic formulations can be authorized on the basis of *in vitro* dissolution tests without clinical evidence of bioequivalence.[7,10] There have been reports of loss of efficacy after switching to generic formulations.[6] The group supported the suggestion that manufacturers of generic formulations should not only demonstrate clinical bioequivalence but also provide comparative clinical data with appropriate treatment group sample sizes following generic drug approval.[5] Patients welcomed and acknowledged that generics may improve patient access to more affordable therapies in many countries.[9] However, patients also raised concerns about being switched between different products for non-medical reasons. Notably, what impact would alternative, less expensive products have on the management of CML when the quality, safety and efficacy of these alternative products in patients is uncertain?[5,6,8,11] CML patient groups called out to governments, health authorities and healthcare professionals to minimize the potential uncertainties and risks for patients with the following five recommendations:

1. No generic drug to treat CML should be provided to patients without reliable proof of quality as well as bioequivalence (equivalent bioavailability/pharmacokinetics) to the originator drug. Generic drugs should be approved by the appropriate authorities of the respective country or region, and a narrow therapeutic range of some cancer drugs should be considered before acceptance of bioequivalence.
2. When generic drugs are intended for the treatment of severe diseases like leukemia, further comparative clinical data should be demanded by regulatory bodies and published to ensure that the generic drug is therapeutically equivalent (same safety and efficacy) to the original product in patients.
3. A CML patient should not be switched between different products with the same active substance for non-medical reasons provided this patient already responded optimally to the current product and tolerates it well.
4. If a switch for non-medical reasons between products with the same active substance is enforced, this should not happen more frequently than once a year. Sufficient follow-up is necessary to assess safety and efficacy to estimate drug response. If a patient experiences loss of drug response or experiences a significant increase in toxicity after switching to another product containing the same active substance, the patient must have the option to return to the previous treatment or switch to another treatment, if available.

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5. After switching between products with the same active substance, more frequent molecular monitoring should be conducted to detect potential differences in effectiveness or side effects early after the switch.

There is significant uncertainty for both prescribers and patients concerning the introduction of generic formulations of CML TKIs. More data and guidance are necessary when patients are being switched to alternative, less expensive products, to ensure the procedures are equally safe and that the risk of increased toxicity and/or loss of drug response is minimized. The recommendations from the patient community may provide a basis for discussion by the expert groups for publishing treatment guidelines and recommendations for the management of CML. Previous guidelines such as the European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013 (ref. 12) serve as a valuable reference source for patients and physicians seeking to reduce the level of risk and uncertainty for safe administration of generic formulations of CML TKIs.

CONFLICT OF INTEREST

GS: patient advisor to Ariad, Novartis, BMS and Pfizer. JG: patient advisor to Ariad, Novartis, BMS and Pfizer. JC: patient advisor to Novartis and Pfizer. RP: patient advisor to Novartis. ŠN: patient advisor to Novartis and Pfizer. MR and VV: none.

AUTHOR CONTRIBUTIONS

JG designed and performed the research, collected, analysed and interpreted the data, and wrote the manuscript. GS designed and performed the research, collected, analysed and interpreted the data. JC, RP, SN, MR and VV collected the data . All authors reviewed and finalized the manuscript.

J Geissler[1,2], G Sharf[1,3], J Cugurovic[4], R Padua[5], Š Narbutas[6], M Remic[7], V Venkatesh[8] for the CML Advocates Network
[1]*Leukemia Patient Advocates Foundation, Bern, Switzerland;*
[2]*LeukaNET e.V., Riemerling, Germany;*
[3]*Israeli CML Patients Organization, Netanya, Israel;*
[4]*CML Association of Serbia, Belgrade, Serbia;*
[5]*Touched by Max, Navotas City, The Philippines;*
[6]*Lithuanian Cancer Patient Coalition, Kaunas, Lithuania;*
[7]*Slovenian Lymphoma and Leukemia Patient Association, Ljubljana, Slovenia and*
[8]*Friends of Max, Mumbai, India*
E-mail: jan@cmladvocates.net

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Anti-CD44 antibodies inhibit both mTORC1 and mTORC2: a new rationale supporting CD44-induced AML differentiation therapy

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Acute myeloid leukemia (AML) is a heterogeneous disease characterized by a blockage in the differentiation of myeloid cells at different stages of maturity and by an increase in their proliferation. Despite important advances in understanding the pathophysiology of AML, therapeutic approaches have not significantly improved patient survival with the exception of ATRA (all-trans retinoic acid) for acute promyelocytic leukemia (APL),[1] prompting scientists to search for differentiating agents that could be used in the treatment of all AML subtypes.

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