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**LETTER TO THE EDITOR**

# Safety and efficacy of nilotinib in chronic phase chronic myeloid leukemia in a patient with Wolf-Parkinson-White disease and hematological resistance after suboptimal response to imatinib at six months

LAURA CANNELLA, MASSIMO BRECCIA, GIUSEPPINA LOGLISCI, VINCENZO FEDERICO, MICHELINA SANTOPIETRO & GIULIANA ALIMENA

*Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome, Italy*

Despite the impressive results achieved with imatinib for treatment of CML, the emergence of resistance to the drug has become a significant problem [1]. Several strategies have been developed to overcome this phenomenon, including dose escalation of imatinib, combination treatments or novel tyrosine kinase inhibitors (TKI). Careful cardiac monitoring and assessment by a cardiologist throughout the course of treatment with TKIs that exert cardiac toxic effect is of primary importance, as recently suggested [2]. Nilotinib is 30-fold more potent than imatinib, active against a wide range of mutant clones, except T315I [3]. One of the major side effects initially reported with nilotinib treatment was the prolongation of QTcF interval (QT interval corrected using Fridericia's formula) [3]. We here describe a patient affected by Wolf-Parkinson-White (WPW) disease, who was safely treated, without any cardiac toxicity, with nilotinib at the standard dose of 400 mgBID, following disease recurrence at six months of imatinib therapy.

A 39-year-old male, due to weight loss, night sweats and fatigue, in June 2007 performed routine blood analysis, which revealed a severe leukocytosis ($334 \times 10^9$/l) and mild anemia (9 gr/dl). A peripheral blood and bone marrow morphological examination were consistent with the chronic phase of a myeloproliferative disorder. The presence of Philadelphia chromosome was revealed by both conventional cytogenetic (CBA) and FISH analyses. RT-PCR detected a b3a2 type of transcript and RQ-PCR revealed a BCR-ABL/ABL ratio of 75%. The patient was thus diagnosed as having CP-CML, intermediate Sokal risk. A cardiologic examination confirmed a prior finding of WPW disease and identified no contraindications to TKI treatment. After an initial cytoreduction with hydroxyurea, the patient was started on standard dose imatinib (400 mg/day). No side effects were recorded during the first weeks of treatment and QT interval was similar to the baseline evaluation (460 ms). The patient achieved a complete hematologic remission (CHR) after four weeks of treatment, while FISH analysis revealed only a minor cytogenetic response at three months; at six months a partial cytogenetic response was not achieved (Ph+ cells 40%) and the patient was considered as a suboptimal responder, according to EuropeanLeukemia Net (ELN) criteria [1]. For this reason a mutational test with denaturing high performance liquid chromatography (DHPLC) was performed, that did not reveal any BCR-ABL kinase domain mutations. A blood level testing (BLT) revealed a concentration of 1 200 ng/ml. Imatinib was then escalated to 600 mg/day. After a total of 10 months of imatinib (four months of dose escalation), the patient suddenly lost CHR (WBC $12 \times 10^9$/L): bone marrow morphological analysis showed persistence of CP, but at CBA three normal methaphases, three Ph+ methaphases and eight methaphases with duplication of Ph+ chromosome and acquisition of trisomy 8, were detected. Once again, DHPLC analysis did not reveal mutations. Patient was thus switched to nilotinib 400 mg BID

Correspondence: Massimo Breccia, Department of Cellular Biotechnologies and Hematology, Via Benevento 6, 00161 Rome, Italy. Tel. +39 06 857951. Fax +39 06 44241984. E-mail: breccia@bce.uniroma1.it

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for imatinib resistance: after two weeks he reached again CHR and after three months he achieved CCR (0% Ph+ cells, with disappearance of additional abnormalities), as documented at CBA and FISH analyses. During nilotinib treatment, electrocardiographic monitoring did not reveal particular alterations, with QTc interval ranging between 450 and 468 ms, similar to baseline QTc before imatinib. At the present time, the patient is in CCR, while in treatment without problems.

The retrospective application of ELN criteria to a large cohort of CP-CML patients showed that suboptimal response criteria at six and 12 months overlapped with the failure criteria [4] with similar event-free survival (EFS) and transformation-free survival (TFS) to those of failure patients, as considered at the same time point [5]. Dose optimization of imatinib or early switch to second-generation TKI, are strongly encouraged in this subset of patients [4,5].

We performed a measurement of plasma through imatinib concentration, as indicated, for lack of efficacy [6]. As suggested, in the absence of prospective available data relating to the adjustment of imatinib dose, also in case of BLT $>$ 1 000 ng/ml and in the absence of other proved mechanisms of resistance, a dose escalation of the drug should not be excluded [6]. However, despite this therapeutic strategy in our case, the patient developed hematologic resistance with evidence of clonal evolution, which required the switch to a second generation TKI.

During nilotinib phase II trials only eight patients experienced electrocardiographic QTcF prolongation greater than 60 ms from baseline [7]. Also in a recent update of a phase IIIb study (ENACT) a low frequency of QTc interval prolongation $>$ 500 ms was observed [8]. In conclusion, for patients with suboptimal response at six months an early switch to second-generation TKI is suggested; nilotinib can be safe also in patients with electrocardiographic pre-existing alterations.

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