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LETTER TO THE EDITOR

Long-term efficacy and safety of nilotinib therapy after imatinib failure in eosinophilic myeloproliferative neoplasm and ETV6-ABL rearrangement

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Dear Editor,

The ETV6 gene, previously known as TEL, is a member of the ETS family of transcription factors located at 12p13. Its role in leukemogenesis was initially estabilished as a fusion partner to the PDGFR-beta gene in a case of chronic myelomonocytic leukemia with t (5;12)(q33;p13) [1]. The ETV6-ABL gene product has been demonstrated to have tyrosine kinase activity remarkably similar to that of BCR-ABL, despite the fusion partners for ABL being completely different [2]. Several studies proved the efficacy of imatinib for patients with hypereosinophilic syndrome (HES) and chronic eosinophilic leukemia (CEL), especially in those who express the FIP1L1-PDGFRα fusion gene [3–5]. As development of resistance or intollerance to Imatinib in these patients may parallel that seen in chronic myeloid leukemia (CML), the evaluation of second-generation tyrosine kinase inhibitors (TKIs), such as nilotinib, has been reported [6]. However, to date, little is known on long-term efficacy and safety of second-generation TKIs after imatinib failure in patients with eosinophilic neoplasms.

A 65-year-old male was found to have hemoglobin 13.0 g/dL, platelets $302\times10^3/\mu L$, leukocytes $16.7\times10^3/\mu L$, with 65 % neutrophilis, 3 % metamyelocytes, 3 % myelocytes, 10 % eosinophils, 8 % basophils, 8 % lymphocytes, and 3 % monocytes. The physical exam was negative. Bone marrow biopsy and aspirate were consistent with a chronic phase myeloproliferative neoplasm (MPN). Karyotype was 46,XY,t(9;12)(q34;p12); molecular analysis was negative for BCR/ABL and for rearrangements involving PDGFRα and β and FIP1L1 gene, while showing a fusion between ETV6 and ABL genes.

The patient was enrolled in a protocol testing imatinib for HES, starting in May 2005 at a dose of 100 mg daily, with weekly dose escalation up to 400 mg/day. The patient attained a complete hematologic response (CHR) at 1 month and a complete cytogenetic response (CCyR) at 6 months. In January 2006, the patient complained an olfactory dysfunction (dysosmia). An ear, nose, and throat (ENT) visit and central nervous system RMN scan were negative; so supposing a possible imatinib toxicity, the drug was stopped with a slight improvement of olfactory function. There was a progressive increase in eosinophil count; so in June 2006, imatinib was restarted at 100 mg daily and progressively increased up to 400 mg, at which dose dysosmia recurred. In December 2006, while receiving imatinib 400 mg, despite persistent olfactory dysfunction, the patient lost CHR. To investigate imatinib resistance, a mutational study of ABL kinase domain was performed, without evidence of any mutation. In October 2007, the patient started nilotinib 400 mg twice a day. The patient attained CHR within 2 weeks and regained CCyR and molecular remission at 6 months that were confirmed at the 12 months of therapy and at all the molecular testing performed thereafter. Five years after initiation of nilotinib, the patient developed signs of peripheral arterial occlusive disease (PAOD) of the lower limbs that required angioplasty and surgical treatment of the skin lesions. Nilotinib was reduced to 400 mg/day. In June 2014, almost 7 years from nilotinib start; and while in confirmed complete molecular remission, the patient complained of abdominal pain and weight loss. An abdominal CT scan revealed a pancreatic carcinoma that caused the patient's death in September 2014.

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The chronic MPNs with associated eosinophilia are largely linked to constitutively active cellular TKs that drive the clonal cell proliferation. The clinical significance of the identification of such mutant kinases is their susceptibility to molecularly targeted small-molecule inhibitors, which frequently constitute a very effective treatment for these patients [3, 4]. We describe the case of a patient with atypical MPN with ins(9;12)(q34;p13p13), producing an ETV6-ABL gene rearrangement. ETV6 is the only non-BCR fusion partner for ABL reported to date, and it is thought to have TK activity similar to BCR/ABL. In the last years, few case reports focused on the efficacy of imatinib in chronic-phase MPNs and ETV6-ABL rearrangement, with cytogenetic and molecular remissions but short follow-up [5, 7]. Our patient had an excellent response to imatinib though complicated by an unusual olfactory toxicity (dysosmia) that, to the best of our knowledge, has never been reported with imatinib. However, after about 14 months of therapy, our patient experienced hematologic and cytogenetic relapse, suggesting that TK inhibitory effect of imatinib is therapeutically useful but not enough to induce a long-term complete remission. As we did not document any ABL TK domain mutation, like in other cases reported to date, mechanism of imatinib resistance remains unknown.

Only Nand et al. reported on a patient with ETV6-ABL-positive MPN in chronic phase achieving CCyR on imatinib, experiencing after 17 months cytogenetic relapse and attaining with nilotinib a second CCyR, lasting 11 months at the time of writing [6]. Our case displayed early (i.e., within 6 months) complete cytogenetic and molecular responses that lasted for more than 6 years. Albeit its efficacy, nilotinib is known to be associated with higher incidence of pancreatic and metabolic abnormalities [8, 9] and, more recently, with a significant incidence of progressive PAOD [10]. In line with this, after 5 years of nilotinib, our patient progressively develops signs of PAOD that required revascularization and dose reduction. Of note, at the time of nilotinib start, the patients had no current risk factors for PAOD except for age (68 years); during nilotinib therapy, the patient developed a mild diabetes mellitus treated with metformin with excellent glycemic control.

In summary, ETV6-ABL-positive eosinophilic MPN is a rare clinical entity that, in chronic phase, often displays a transient response to imatinib. Nilotinib therapy seems effective, also granting deep and durable response, but several issues remain on drug's long-term safety. Similar cases deserve to be reported to allow further understanding of their molecular basis, disease history, and response to TKI therapy.

Conflict of interest M. Tiribelli acted as a consultant and received honoraria from Novartis, BMS, and Ariad. All other authors declare no competing financial interests.

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