Hypereosinophilic Syndrome in the Tyrosine Kinase Inhibitor Era

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Hypereosinophilic syndrome (HES) is a rare disorder characterized by persistent hypereosinophilia (HE) and organ dysfunction that occurs as a result of high levels of tissue eosinophil infiltration and/or extensive deposition of eosinophil-derived proteins. Because it is often difficult to make the differential diagnosis of HES despite conducting a careful evaluation, identifying particular patients with HES who exhibit clonal markers would facilitate the treatment of HES.

Dr. Danijela Lekovic and colleagues reported the case of a man with a myeloid neoplasm, eosinophilia and an abnormality in the platelet-derived growth factor receptor alpha gene (PDGFRA). The authors treated the patient with a tyrosine kinase inhibitor (TKI), imatinib mesylate, and subsequently achieved a complete cytogenetic response after six months (1). In this case report, the authors emphasized the importance of properly characterizing eosinophilia, as successful treatment depends on the underlying etiology.

The 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tissue includes a special category for myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of PDGFRA, platelet-derived growth factor receptor beta (PDGFRB) or fibroblast growth factor receptor 1 (FGFR1) (2). The most frequently observed chromosomal abnormality in patients with myeloproliferative neoplasm (MPN) with eosinophilia is the FIP1L1-PDGFRA fusion gene, which results from a cryptic del(4)(q12) mutation. The FIP1L1-PDGFRA fusion gene codes for a constitutively activated PDGFRA protein, which has been reported to be associated with primary HE. This fusion gene can be detected with fluorescence in situ hybridization (FISH) using a probe for the CHIC2 gene. Arefi et al. reported that, in their study, 19 of 78 HE patients (24%) met the criteria for HES and eight patients were found to have the FIP1L1-PDGFRA fusion gene on a FISH analysis (3). On the other hand, some HE patients with MPN features have other rare genetic abnormalities of PDGFRB or FGFR1, which can be detected using conventional cytogenetic analyses, such as t(5;12)(q31-q33;p12) or a variant translocation and t(8;13)(p11;q12) or a variant translocation, respectively. The incidence of MPN associated with PDGFRB rearrangement has been reported to be low (10 cases among 556 patients with MPN, 1.8%), and all previously reported patients with abnormalities in PDGFRB have shown moderate to severe eosinophilia (4).

Imatinib has become the standard treatment for Philadelphia (Ph) chromosome-positive chronic myeloid leukemia (CML) due to its significant clinical efficacy, producing a durable response with a prolonged survival period (5, 6). Imatinib also potently inhibits other target kinases, including c-Kit, PDGFRA and PDGFRB. The FIP1L1-PDGFR fusion gene plays an important role in the pathogenesis of primary HE, and PDGFRB is a direct therapeutic target of imatinib (7). Furthermore, numerous studies have confirmed that imatinib induces complete remission in most patients with HE who carry this fusion gene, and patients with HE associated with FIP1L1-PDGFR fusion gene rapidly respond to a lower dose of imatinib than that used to treat CML and display a sustained response to treatment (8). However, discontinuing imatinib therapy can lead to relapse, which indicates that the administration of a low dose of imatinib does not eliminate the FIP1L1-PDGFR1 clone (8). Patients with PDGFRB rearrangement have also been reported to respond to treatment with a standard dose of imatinib (400 mg) and show a sustained response under treatment (4). On the other hand, patients with FGFR1 rearrangement are resistant to imatinib and exhibit a poor prognosis, with progression to acute myeloid leukemia. Therefore, the application of intensive chemotherapy followed by early allogeneic transplantation is recommended in such cases (9).
In conclusion, because HES associated with PDGFRA or PDGFRB can be controlled with treatment with a TKI that specifically blocks the intracellular ATP-binding sites of PDGFRA or PDGFRB, it is important to identify the primary HE using an etiological and hematological work-up, including cytogenetic analyses and/or molecular testing.

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References