Response of a KIT-Positive Extra-Abdominal Fibromatosis to Imatinib Mesylate and KIT Genetic Analysis

Fibromatosis is a rare nonmalignant neoplasm that is often sporadic or associated with familial adenomatous polyposis. It arises from deep musculoaponeurotic structures, and its etiology is poorly understood. Aggressiveness is locoregional, and optimal treatment requires complete surgical removal, which is sometimes difficult or mutilating, according to the location and extension (1). Irradiation is used after incomplete resection or in unresectable disease but can induce clinically significant toxicity. In advanced or recurrent disease, hormonal manipulation, nonsteroidal anti-inflammatory drugs, and conventional chemotherapy induce responses (2,3). Imatinib mesylate (Gleevec; Novartis, Basel, Switzerland) is a tyrosine kinase inhibitor targeting BCR-ABL protein in chronic myelogenous leukemia, as well as in KIT-positive gastrointestinal stromal tumors and are associated with imatinib resistance. We report on a patient with KIT-positive fibromatosis who had a germline KIT alteration and whose disease was very sensitive to imatinib.

A 33-year-old female with a progressive cervicothoracic fibromatosis was referred to our institution in November 2004. The patient, a professional violinist, had no personal or familial history of desmoid tumor or polyposis. At diagnosis in 1996, the tumor was near vascularous cervicobrachial structures and expressed progesterone receptor. Patient first received tamoxifen without tumor response and then underwent complete surgical removal of the tumor in April 1997. A cervicomedial recurrence occurred in August 1998, and a subtotal resection was performed. Complementary radiotherapy was considered to be potentially highly toxic in terms of functional sequel, and luteinizing hormone–releasing hormone antagonists were given until November 2004, when a computed tomography scan detected cervicothoracic progression. Because KIT (CD117) expression had been identified by immunohistochemistry, we delivered imatinib at 400 mg/day. After 10 weeks of treatment, the disease progressed (Fig. 1, A), and the dose was increased to 600 mg/day. After 10 additional weeks, a minimal response was observed (~31%, World Health Organization criteria) that improved 20 weeks later to reach an objective partial response (~55%). The response was still ongoing (~66%) after 34 weeks of imatinib at 600 mg/day (Fig. 1, A).

After obtaining written informed consent and approval from the local institutional review board, we analyzed a frozen sample of the tumor removed in 1997 for mutations in KIT and PDGFRα genes. Direct sequencing of genomic DNA for KIT exons 9–13 and 17 and for PDGFRα exons 10–21 detected no proven deleterious mutation, but a heterozygote variant in KIT exon 10 (an A→C point mutation at position 1621, resulting in the amino acid substitution of methionine for leucine at position 541 [Met541→Leu]). Its RNA expression was confirmed in the tumor by reverse transcription–polymerase chain reaction and cDNA sequencing of KIT exon 10 (Fig. 1, B). This allelic variation was also present in peripheral blood cells, indicating its germline origin.

Two cases of refractory fibromatosis benefiting from imatinib at 800 mg/day (one response and one stabilization) have been reported previously (4). Tumors expressed KIT and PDGFRα, but no genetic analysis was performed. Our report presents, to our knowledge, the first mutational analysis of a KIT-positive fibromatosis. The tumor was sensitive to imatinib and harbored a germline allelic KIT variant in exon 10 (Met541→Leu). This variant has been reported by others and had a poorly understood clinical significance. Some authors have considered it as a polymorphism identified in 1.5%–9% of healthy subjects (5,6), whereas others described it as a potential somatic event in human tumors, including chronic myelogenous leukemia (6), liposarcoma (7), and mastocytosis (P. Dubreuil, unpublished results). Our data confirm the clinical activity of imatinib in KIT-positive fibromatosis and highlight a potential role for the Met541→Leu KIT variant in disease and sensitivity to imatinib. More analyses are required to further explore these results.

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**NOTES**

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