

the 5'-flanking region of the IL-6 and IL-8 genes do not act independently of one another but as part of an extended promoter haplotype.¹⁰ In summary, our data demonstrate that the assessment of IL-6 and IL-8 levels in febrile neutropenic children is of limited diagnostic value and is not improved by genotyping for promoter polymorphisms.

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Key words: children, febrile neutropenia, chemotherapy, interleukin, polymorphisms.

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Chronic Myeloproliferative Disorders

Imatinib mesylate can induce complete molecular remission in FIP1L1-PDGFR-α positive idiopathic hypereosinophilic syndrome

Recently, a fusion gene, FIP1-like 1 (FIP1L1)-PDGFR-α, has been found to be involved in some patients with idiopathic hypereosinophilic syndrome (HES) responsive to imatinib therapy. We report a new case of a patient with FIP1L1-PDGFR-α positive HES, treated with imatinib mesylate for more than 17 months, who obtained a complete molecular response.

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Idiopathic hypereosinophilic syndrome (HES) is a currently incurable chronic myeloproliferative disorder characterized by persistent hypereosinophilia. Imatinib mesylate (Gleevec)[®] - a tyrosine kinase inhibitor specifically directed against abl, bcr-abl, c-kit and platelet-derived growth factor receptors (PDGFR) - has recently shown therapeutic effects¹⁻² in patients carrying the FIP1-like 1 (FIP1L1)-PDGFR-α fusion gene.²⁻³ We report the first case of FIP1L1-PDGFR-α⁺ HES with a documented complete molecular response to imatinib.

In December 2001, a 65-year old male with no significant past medical history presented with persistent leukocytosis (76×10⁹/L) with eosinophilia (42%). Molecular analysis did not detect BCR-ABL, FGFR1-BCR, or the PDGFα-TEL rearrangement. After 21 days of imatinib (600 mg/day), the white cell and eosinophil counts fell dramatically and have

since remained normal over 17 months of continuing treatment (Figure 1). No significant hematologic toxicity has been observed.

In March 2003, following informed consent, retrospective reverse transcriptase polymerase chain reaction (RT-PCR) analysis of FIP1L1-PDGFR-α was performed as reported elsewhere.² A new type of the FIP1L1-PDGFR-α fusion transcript was detected (in peripheral blood and bone marrow) both at diagnosis and after 9 months of treatment, but not at 17 months (Figures 1A and B). Mixing serially diluted total FIP1L1-PDGFR-α⁺ RNA (diagnostic sample) with the HL60 cell line, we were able to amplify the transcript up to a 1:10⁴ dilution. Sequence analysis confirmed that the breakpoints in PDGFR-α occurred in exons 12 and 8 of FIP1L1. The different bands represent splice variants (Figure 1B). It should be noted that while the hematologic response occurred rapidly within the first 3 weeks of imatinib therapy, most likely as a result of FIP1L1-PDGFR-α inhibition, as reported also by other authors,^{1,4} complete molecular response seems to have occurred much later, at some time between 9 and 17 months.

Although we do not know the exact clinical significance (or prognostic value) of the complete molecular response recorded in our patient, it seems reasonable to assume that eradication of minimal residual disease is superior to complete morphologic response. It is also unclear how long imatinib therapy should be administered to a patient affected by FIP1L1-PDGFR-α⁺ hematologic diseases (HES and systemic mastocytosis)⁵ following a complete clinical or molecular response: for the present we have preferred to continue treatment. Nevertheless, we believe that imatinib treatment might be curative.

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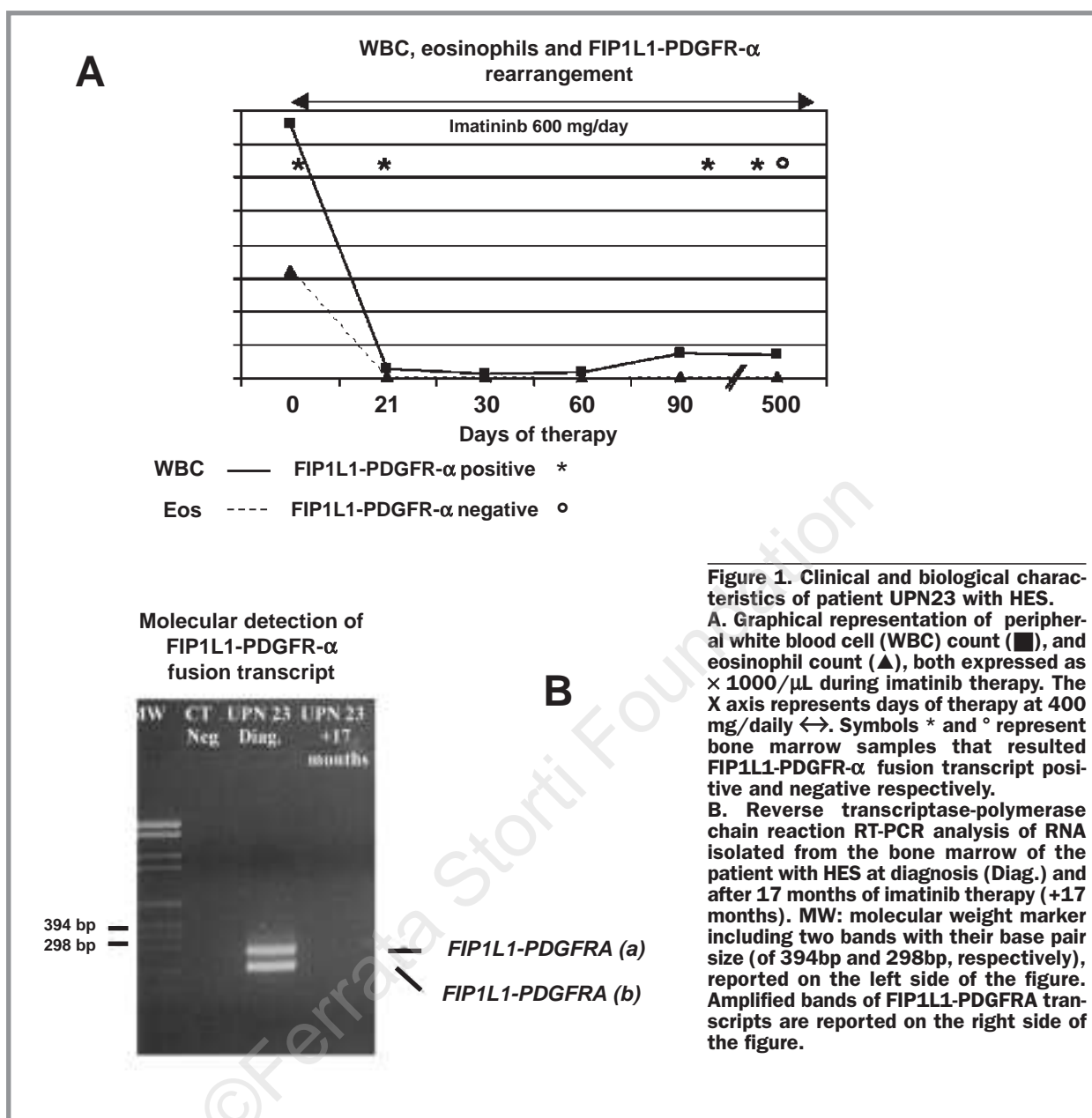


Figure 1. Clinical and biological characteristics of patient UPN23 with HES.

A. Graphical representation of peripheral white blood cell (WBC) count (■), and eosinophil count (▲), both expressed as $\times 1000/\mu\text{L}$ during imatinib therapy. The X axis represents days of therapy at 400 mg/daily \leftrightarrow . Symbols * and \circ represent bone marrow samples that resulted FIP1L1-PDGFR- α fusion transcript positive and negative respectively.

B. Reverse transcriptase-polymerase chain reaction RT-PCR analysis of RNA isolated from the bone marrow of the patient with HES at diagnosis (Diag.) and after 17 months of imatinib therapy (+17 months). MW: molecular weight marker including two bands with their base pair size (of 394bp and 298bp, respectively), reported on the left side of the figure. Amplified bands of FIP1L1-PDGFR- α transcripts are reported on the right side of the figure.

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