Soft tissue and skeletal involvement in fip1l1-pdgfr-α positive chronic eosinophilic leukemia: imatinib mesylate may induce complete molecular and imaging remission

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Chronic Eosinophilic Leukemia (CEL) is a chronic myeloproliferative disorder characterized by a persistent hypereosinophilia eventually associated with organ dysfunction. Recently, a fusion gene, FIP1-like 1 (FIP1L1)-PDGFR-alpha, has been found to be involved in some patients with CEL responsive to imatinib. We report a case of FIP1L1-PDGFR-alpha positive CEL, with soft tissue and skeletal involvement, where a complete molecular and imaging response to imatinib was documented.

In October 2003, a 47 years old male with no significant past medical history, presented in the first aid department of San Marino hospital with signs and symptoms of anaphylactic shock, which was responsive to a single dose of corticosteroids (methyl prednisone 80 mg i.v.). Leukocytosis with eosinophilia and an abnormal mass in the left temporal/parietal area were also found. A complete blood count showed leukocytosis of $24x10^9$ /L with 42% eosinophils. Hemoglobin level and platelet count were within normal ranges. Some causes of secondary eosinophilia (parasitic infection, atopy, hypersensitivity reactions, collagen vascular disease or tumors) were excluded.[1] A surgical biopsy of the temporal/parietal mass was performed. The diagnosis was extramedullary myeloid tumor. A bone marrow aspirate and biopsy with a complete cytogenetic and molecular analysis was performed. The bone marrow analysis showed an hypercellular marrow with significant infiltration by eosinophils and the diagnosis was CEL. The karytotype was normal (46,XY). No BCR-ABL rearrangement was found. FIP1L1-PDGFR-alpha rearrangement was found. The presence of this fusion transcript was searched as previously described.[2] The lumbar puncture was performed: there was no evidence of cells in the cerebral fluid. A complete cerebral magnetic scan, a skeletal scintigraphy with ^{99m}Tc and a total body Positron Emission Tomography (PET) with ^{18}F-Fluor-Deossi-Glucose were also performed. As shown in Figure 2a the radiologist describes a left temporal/parietal extracranial mass, extended to the cranial bone, together with a diffuse skeletal enhancement.

Based on prior reports on the efficacy of imatinib in CEL,[3-7] treatment with imatinib was begun in November 2003. A dose escalation was adopted: 100 mg/day for the first week, with a dose increasing of 100 mg/day/week, until the maximum dose of 400 mg/day. Seven days after starting treatment with imatinib, the white blood cell count and eosinophils were dramatically reduced and maintained constantly within normal ranges after 120 days of observation. Molecular response was documented 80 days after the beginning of the therapy (Figure 1). Neither a significant hematological nor a non hematological toxicity was observed. Concomitantly the temporal/parietal mass reduced. After 1 month of treatment with imatinib a complete cerebral magnetic scan, a skeletal scintigraphy with 99mTc and a total body Positron Emission Tomography (PET) with ^{18}F-Fluor-Deossi-Glucose were performed to evaluate the response to therapy. As shown in Figure 2b all these examinations showed no evidence of disease. These data were also confirmed 120 days after the beginning of imatinib therapy.

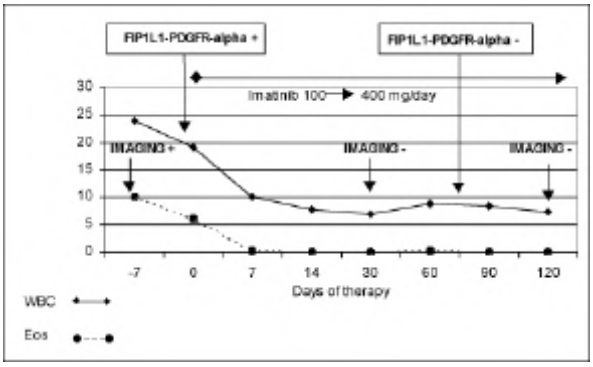

Figure 1. Represent some clinical and biological characteristics of the patient UPN07 with CEL.

Figure 2. Represent radiological images of the patient UPN07 with CEL. a) Complete cerebral magnetic scan and total body Positron Emission Tomography (PET) with 18F-Fluor-Deossi-Glucose at diagnosis. b) Complete cerebral magnetic scan and total body Positron Emission Tomography (PET) with 18F-Fluor-Deossi-Glucose after 1 month of therapy with imatinib.

In this CEL case the temporal/parietal tumor was likely to be an extramedullary localization of the myeloid underlying disease. Eosinophils carry the FIP1L1-PDGFR-alpha fusion gene. A hematological response was obtained rapidly within the first 3 weeks of therapy with imatinib. Imaging response was documented one month after the beginning of the therapy. No significant clinical and laboratory toxicities were observed. A complete molecular remission (CMR) was demonstrated 80 days after the beginning of imatinib therapy. Frickhofen et al obtained a similar result in a 33-year old man with CEL and clinically significant CNS involvement.[8] In our patient imatinib resulted active in extramedullary tumor (skeletal and soft tissue), as well as in bone marrow. The value of the molecular remission has not been defined yet. A better definition of molecular response could be obtained with quantification of minimal residual disease with Taqman RT-PCR, in order to understand if imatinib can really eradicate the neoplastic clone. Moreover two aspects need to be better defined: how long imatinib therapy should be administered in this type of patients

and whether resistance to imatinib develops as described for chronic myeloid leukemia.[9]

This case report confirms that imatinib is highly effective in cases of CEL, carrying the rearrangements of FIP1L1-PDGFR-alpha. Assessing the long term benefit of the treatment and the possibility of eradicating the mutated clone will require a much longer follow up.

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