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Article *in* The Hematology Journal · February 2003

DOI: 10.1038/sj.thj.6200294 · Source: PubMed

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The Hematology Journal (2003) 4, 410–412

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Effective treatment of hypereosinophilic syndrome with imatinib mesylate

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Imatinib mesylate treatment is highly effective in chronic myeloid leukaemia and recent data have suggested that imatinib mesylate is also effective in the treatment of idiopathic hypereosinophilic syndrome (HES). Six patients with HES were treated daily with 100 mg imatinib mesylate. Five patients had normal karyotype and one showed trisomy 8. RT-PCR was negative for ETV6-PDGFRB and BCR-ABL fusion mRNAs. All patients rapidly achieved complete haematological remission. One patient remained in remission for more than 6 weeks after discontinuing treatment. No significant side effect was noted. Imatinib mesylate should be considered in the first-line therapy of idiopathic HES.
The Hematology Journal (2003) **4,** 410–412. doi:10.1038/sj.thj.6200294

Keywords: imatinib mesylate; hypereosinophilic syndrome; eosinophilia; leukaemia

Introduction

Imatinib mesylate is a tyrosine kinase inhibitor that specifically inhibits the activity of ABL, platelet-derived growth factor receptor (PDGFR) and KIT kinases. Imatinib mesylate induces a high rate of haematological, cytogenetic and molecular remissions in BCR-ABL-positive chronic myeloid leukaemia, representing one of the first examples of oncogene-targeted treatments. Recently, imatinib mesylate at 400 mg/day was shown to induce durable responses in four patients with chronic myeloproliferative diseases associated with hypereosinophilia and chromosomal translocations involving 5q33 with rearrangement and activation of PDGFRB.[1]

Idiopathic hypereosinophilic syndrome (HES) is a heterogeneous haematological disorder characterized by persistent eosinophilia with severe organ involvement.[2] Treatment options include corticosteroids, hydroxyurea, acute-leukaemia-type chemotherapy and interferon-α. Recently, a rapid response to imatinib mesylate at 100 mg/day was described in six patients with HES.[3–5] We describe here six additional patients with HES who showed dramatic responses to imatinib mesylate.

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Received 21 January 2003; accepted 28 March 2003

Patients and methods

Patients' characteristics

Six patients with idiopathic HES received imatinib mesylate (Glivec™, Novartis) at 100 mg p.o. daily. Patients' characteristics are listed in Table 1. All patients suffered from symptomatic HES with fever, dyspnoea, fatigue, hepatosplenomegaly and/or lymphadenopathies. Known causes of reactive eosinophilia were excluded in each instance. A thorough history was taken regarding allergies and drug intake. Parasitic infestation was excluded by means of repeated stool microscopy, urine analysis, hydatid disease serology. CT scans of chest, abdomen and pelvis were performed to exclude the presence of occult neoplasms or infestations. CBC at diagnosis showed leucocytosis (median = 28×10^9/l; range 11.3–66.8) and significant eosinophilia (median = 12×10^9/l; range 2.8–41.2). Three patients had moderate anaemia and two patients had moderate thrombocytopenia. Bone marrow aspirate and trephine biopsy showed normal morphology and differentials except for increased numbers of mature eosinophils. Bone marrow karyotype was normal in five patients and showed isolated trisomy 8 in one patient. All patients received other therapies prior to imatinib mesylate: patients 1 and 5 received corticosteroids alone, patients 3 and 6 received corticosteroids and hydroxyurea while patients 2 and 4 received corticosteroids, hydroxyurea, interferon-α and cytarabine. All patients achieved partial response to these initial therapies. The median

Table 1 Patients characteristics

	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*
Age at diagnosis (years)	63	29	62	27	11	53
Sex	Male	Male	Male	Male	Male	Male
Clinical presentation	Dyspnoea Hepatomegaly Splenomegaly	Fever Dyspnoea Splenomegaly	Dyspnoea Deep vein thrombosis	Generalized pain Splenomegaly	Fever Lymph adenopathies	Dyspnoea Fatigue Weight loss
WBC $\times 10^9$/l	11.3	19.0	32	28.4	60.7	66.8
Neutrophils $\times 10^9$/l	6.6	3.6	11.8	5.9	12.1	42.1
Eosinophils $\times 10^9$/l	2.8	12.5	13.1	17.6	41.2	12
Haemoglobin (g/l)	118	136	160	118	112	165
Platelets $\times 10^9$/l	151	96	172	131	92	155
Karyotype	Normal	Trisomy 8	Normal	Normal	Normal	Normal
Prior treatments	Steroids	Steroids Hydroxyurea Interferon-α Cytarabine	Steroids Hydroxyurea	Steroids Hydroxyurea Interferon-α Cytarabine	Steroids	Steroids Hydroxyurea
Response to previous treatments	Partial	Partial	Partial	Partial	Transient	Partial
Maximal WBC $\times 10^9$/l	170	29.8	32	87.4	90.9	66.8
Maximal eosinophils $\times 10^9$/l	28.9	20.2	14.8	34.9	43.6	12
Time from diagnosis-imatinib mesylate (months)	7	50	5	23	2	48
Time from imatinib mesylate to molecular analysis (weeks)	12	6	19	19	12	12
RT-PCR t(5;12)	Negative	Negative	Negative	Negative	Negative	Negative
RT-PCR t(9;22)	Negative	Negative	Negative	Negative	Negative	Negative

time from diagnosis to imatinib mesylate was 7 months (range 2–50 months).

Molecular analysis

Molecular analysis was performed while patients were already on imatinib mesylate. The time from initiation of imatinib mesylate to molecular analysis is listed in Table 1 (median = 12 weeks; range 6–19 weeks). Total RNA was extracted using the TRIzol LS Reagent (Gibco BRL, USA). ETV6-PDGFRB fusion mRNA was reverse transcribed into cDNA using the PDGFRB gene specific primer PD-F (5′–TTGACGGCCACTTTCATCGT). Amplification of the ETV6-PDGFRB fusion was then performed with the PDGFRB gene specific primer PD-Cs (5′-GGCTTCTTCTGCCAAAGCAT) and the ETV6 gene specific primer, ETV6-JS (5′- GTCATACTGCAT CAGAACCATGAA) using real-time PCR on the Light Cycler (Roche Diagnostics). For fusion product detection, PDGFRB gene specific fluorescent probes PDGFR FL (5′-CCATCCTGGCCCTGGTGGTGCTC) and PDGFR LC (5′-LC Red640- CCATCATCTCCCTTAT CATCCTCATCAT) were used. Probes and primers were designed by TIB MOLBIOL (Germany). RT-PCR amplification control reactions of all samples were carried out using PDGFRB specific primers and probes. For BCR/ABL fusion transcript detection, we used the Light Cycler-T(9;22) quantification kit (Roche Diagnostics). Glucose 6-phosphate dehydrogenase (G6PDH) was amplified using the same cDNA that was used for t(9;22). Products of this reaction serve both as control for RT-PCR performance and as reference for relative quantification.

Results

Overall, the treatment was well tolerated with no significant side effect. CBC at initiation of imatinib mesylate treatment showed a median WBC count of = 6.4×10^9/l (range 3.2–46.8) and a median eosinophil count of 1.5×10^9/l (range 0.9–36). A dramatic decrease in the absolute eosinophil count was rapidly observed within days after initiation of treatment, reaching a median of 0.4×10^9/l (range 0–12) after 1 week (Figure 1). Complete haematological remission (CR) defined by the absence of clinical symptoms, normal CBC and normal eosinophil count was achieved in all patients. RT-PCR analysis showed no evidence of ETV-PDGF transcript that results from t(5;12)(q33;p13) or BCR-ABL transcript that results from t(9;22)(q34;q11).

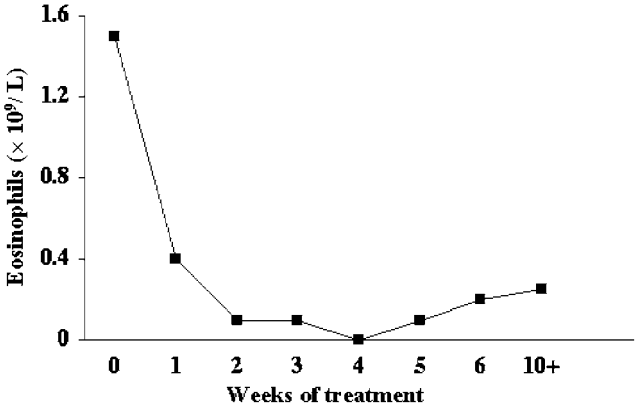

Figure 1 Median eosinophil count before and weekly after treatment with imatinib mesylate.

The most dramatic response was observed in patient 5, an 11-year-old boy who rapidly relapsed after discontinuing corticosteroids. Imatinib mesylate was started in this patient while off treatment with an absolute eosinophil count of 36×10^9/l. A rapid and progressive decrease in eosinophil count was observed with the achievement of haematological remission after 6 weeks. Treatment was maintained in all patients except in patient 6, where imatinib mesylate was interrupted after 4 months. Interestingly, 6 weeks after the end of treatment, patient 6 remains in CR. None of the six patients has relapsed so far (Figure 1).

Discussion

Here, we report six patients with idiopathic HES who rapidly achieved CR after imatinib mesylate treatment. A normal eosinophil count was promptly achieved within 2 weeks in all patients except one who required 6 weeks of treatment. Interestingly, this patient had a very elevated pretreatment eosinophil count. One patient (patient 6) remains in CR 6 weeks after interruption of treatment, suggesting that continuous therapy may not be required to maintain remission.

The mechanism of action of imatinib mesylate in the treatment of idiopathic HES remains unknown. Imatinib mesylate specifically inhibits the tyrosine kinase activity of ABL, PDGFR and KIT kinases. Efficacy of imatinib mesylate was recently reported in four patients with chronic myeloproliferative diseases associated with hypereosinophilia and chromosomal translocations involving 5q33, usually caused by a t(5;12)(q33;p13) translocation resulting in ETV6-PDGFRB fusion gene. None of our six patients presented rearrangement of 5q33 or Philadelphia chromosome. Indeed, pretreatment bone marrow karyotype was normal in five patients and showed isolated trisomy 8 in patient 2. Moreover, RT-PCR was negative for ETV6-PDGFRB and BCR-ABL fusion mRNAs. Although molecular analysis was performed during imatinib mesylate treatment, it is unlikely that a median of 12 weeks of treatment results in the disappearance of pre-existing fusion transcripts.

Idiopathic HES remains an aggressive disease with severe organ involvement, sometimes life-threatening.[2] Classical treatment options such as corticosteroids, hydroxyurea, aggressive chemotherapy and interferon-α are frequently associated with serious side effects and result in partial response only. Based on the rapid and dramatic response of idiopathic HES to low-dose imatinib mesylate and the absence of side effects to this treatment, we recommend that imatinib mesylate should be considered in the first-line therapy of idiopathic HES.

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