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SHORT COMMUNICATION

Isolated molecular relapse in FIP1L1-PDGFRα hypereosinophilic syndrome after discontinuation and single weekly dose of imatinib: need of quantitative molecular procedures to modulate imatinib dose

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Abstract Imatinib is the treatment of choice for FIP1L1-PDGFRα (F/P+) positive myeloproliferative neoplasms, but little is known about optimal dose and duration of treatment to maintain complete molecular remission once achieved. We describe a case of F/P+ patients who started imatinib and reached a molecular remission, but did relapse after 15 months of therapy for poor adherence to therapy, and re-obtained remission only with standard dose of 400 mg/day. We reviewed the literature and highlights the need of quantitative molecular procedures to modulate imatinib dose.

Keywords Imatinib · Hypereosinophilic syndrome · FIPL1-PDGFR-alpha · Molecular remission

Introduction

Hypereosinophilic syndrome (HES) is a rare disorder recognized as an unexplained production of eosinophil cells (>1.5 × 10^9/l), with possible organ damage that persisted for over 6 months [1]. A small proportion of patients were identified as clonal HES for the detection of a small interstitial deletion in chromosome 4 q12 that generates a fusion gene, FIP1L1-PDGFRα (F/P+) [2]. The F/P+ patients are extremely sensitive to imatinib and those with this mutation respond dramatically to therapy with clinical, haematological and molecular remission documented in nearly all treated patients [3]. From the first observation in 2001 [4], more than 47 patients treated with imatinib were described, with a rate of complete haematological (CHR) and clinical remission of about 95% [5]. Recently, the results of a prospective multicenter study of primary HES treated with imatinib were reported: all the 27 F/P+ patients reached CHR in a median of 1 month, and complete molecular remission (CMR) in a median of 3 months. Three out of these 27 patients relapsed after drug discontinuation [5].

It was referred that the majority of F/P+ patients continued imatinib at a dose of 100–200 mg/day with responses being sustained [5, 6], but the question relating optimal dose and treatment duration have not been completely defined.

We report here a case of F/P+ HES, which lost CMR after discontinuation of imatinib at 400 mg/day. Re-starting dose of 100–200 mg/week did not allow CMR, which was only regained after resumption of the initial standard dose of 400 mg/day. We reviewed the literature concerning optimal dose required to maintain CMR in F/P+ HES patients, and highlights the predictive role of WT1 monitoring and the need of quantitative molecular tools to assess transcript level and modulate the dose of imatinib.

Case report

A 27-year old male was admitted to our Department for weakness: a complete blood count revealed Hb 9.4 gr/dl,

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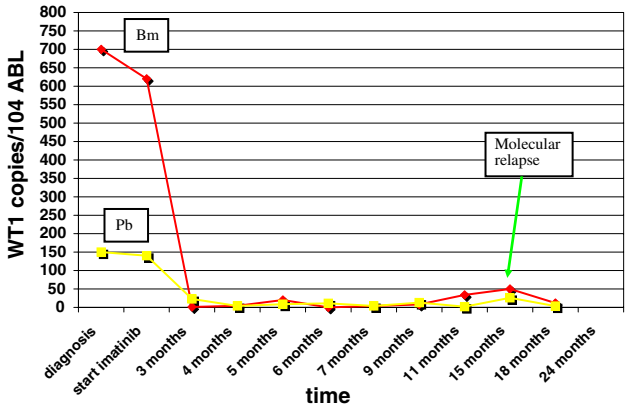

Fig. 1 WT1 monitoring during imatinib treatment

WBC 19 × 10^9/l, platelets 94 × 10^9/l. A peripheral blood (PB) examination showed 57% eosinophils; a bone marrow (BM) examination revealed 65% of eosinophil infiltration. At clinical examination, epatosplenomegaly was revealed (4 and 7 cm from costal margin, respectively); cardiologic examination showed 60% EF with normal cardiac function at echocardiography. Molecular biology by RT-PCR detected FIP1L1-PDGFRα rearrangement (F/P+) and a diagnosis of clonal HES was made (F/P+ HES). At diagnosis, WT1 gene expression was tested both in bone marrow (700 copies/10^4 ABL copies) and peripheral blood (150 copies/10^4 ABL copies, Fig. 1) [7]. Patient was started on imatinib at the dose of 100 mg/day, with eosinophil count being 8 × 10^9/l. After 7 days of imatinib therapy, WBC count dropped to 2.1 × 10^9/l, with eosinophil count being 0.2 × 10^9/l, PMN count 0.3 × 10^9/l and absence of palpable splenomegaly. Imatinib was discontinued for 15 days due to haematological toxicity; then imatinib was resumed at 200 mg/day and dose gradually increased to 400 mg/day at the fourth week. After 1 month of therapy, BM examination showed a complete morphologic response while RT-PCR revealed the persistence of FIP1L1-PDGFRα; WT1 gene decreased to 55 copies/10^4 ABL copies in the BM and 4 copies/10^4 ABL copies in the PB. At the second month of therapy, RT-PCR showed complete molecular remission, with no more detectable FIP1L1-PDGFRα rearrangement. Molecular monitoring was performed in the subsequent 12 months, which confirmed a stable complete molecular remission. At 15 months from initiation of imatinib, RT-PCR displayed molecular relapse in the absence of signs of haematological relapse (eosinophil count 0.1 × 10^9/l). At that time, WT1 expression increased to 102 copies/10^4 ABL copies in the BM and 40 copies/10^4 ABL copies in the PB. We discovered that molecular relapse was likely due to reduced compliance and adherence to therapy by the patient: in fact he confessed that during the 13th month on his own initiative he had not assumed imatinib and from the 14^{th} month he had assumed 100–200 mg/week.

Imatinib was restarted at the standard dose of 400 mg/day and complete molecular remission was re-obtained after 3 months. At the present time, patient is in good clinical condition, in complete molecular response, under imatinib therapy at the standard dosage.

Discussion

Hypereosinophilic syndromes (HES) are a heterogeneous group of disorders characterized by marked blood and tissue eosinophilia, resulting in a wide variety of organ manifestations [2]. According to the definition of Chusid et al. [1], the diagnostic criteria for HES are: absence of an underlying cause of eosinophilia, blood eosinophilia >1500/mmc, presence of organ damage or dysfunction related to eosinophilia. Recently WHO revised classification of 2008, included HES and CEL/NOC (chronic eosinophilic leukaemia/not otherwise categorized) in the category of myeloproliferative neoplasms, whereas molecular abnormalities of PDGFRα, PDGFRb and FGFR1 identify a distinct disease subset [8]. This latter is reclassified as clonal eosinophilia, for the presence of FIP1L1-PDGFRα fusion transcript. In 2003, Cools et al. [9] identified an interstitial deletion of chromosome 4q12, undetectable by conventional cytogenetic analysis, which resulted in the fusion of FIP1L1 with PDGFRα and which characterised a disease responsive to imatinib. This drug had an inhibitory concentration (IC50) value of 3.2 nM, significantly lower than the value obtained in BCR-ABL expressing cell lines [10]. Since 2001, imatinib was used in the clonal forms of HES and rapid clinical responses with symptoms disappearance, complete molecular remission in a median of 3 months of treatment, were observed [11]. Clinical remission and normalization of eosinophil count was reported in patients treated with imatinib at doses as low as 100 mg daily: however, some patients continued to have molecular disease evidence of the mutation at this dose [6]. Baccarani et al. [5] reported the results of a multicenter trial with escalating dose of imatinib ranging from 100 to 400 mg in 4 weeks: the majority of patients continued treatment at a daily dose of 100 or 200 mg. Since imatinib inhibits PDGFRα at nanomolar concentration, an imatinib dose of 100 mg or 200 mg is likely to be sufficient to obtain and maintain the response. In fact, Pardanani et al. [10] and Helbig et al. [6] reported cases in which response was maintained with 100 mg every second day and even once a week. In 2007, Klion et al. [12] reported a de-escalation study in 5 patients in CMR who gradually reduced and suspended imatinib: all patients relapsed without any clinical signs or symptoms of disease recurrence and re-obtained CMR after imatinib resumption. In two patients the need of increased imatinib dose was referred. The kinetics of molecular relapse and the

rapid re-induction of remission with resumption of imatinib are consistent with a suppressive effect of the drug rather than a complete eradication of the clonal cell population.

Which is the optimal dose to induce and maintain CMR in F/P+ HES/CEL patients is still a matter of debate. Recently, Helbig et al. [13] reported 7 cases in which, after achievement of molecular remission with imatinib dose of 100–200 mg/day, 100 mg/week were able to maintain CMR. Although 100 mg daily appears to be sufficient to maintain CMR in most patients, some patients nevertheless seem to require higher doses.

In our observation, for unsatisfactory compliance the patient suspended imatinib for 1 month and then resumed the drug at the dose of 100–200 mg/week, without re-obtaining CMR. Although the low prevalence of the disorder, the utility of quantitative PCR monitoring, as recommended in CML, remains to be determined. An alternative tool may be the quantitative assessment of WT1 gene measurement as a powerful marker capable of distinguishing between clonal HES/CEL and reactive eosinophilia [7]. In our case, WT1 measurement showed a progressive reduction in expression levels, which paralleled the specific FIP1L1-PDGFRα transcript. Only at the moment of molecular relapse the mean value of WT1 increased, thus confirming that a longitudinal monitoring of WT1 may represent a good marker of disease progression in this subset of patients.

In conclusion, our observation suggests the need of new quantitative procedures for the assessment of FIP1L1-PDGFRa level before and during treatment with imatinib, which can allow to optimize the drug dose to maintain CMR.

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