Interferon α induces a good molecular response in a patient with chronic eosinophilic leukemia (CEL) carrying the JAK2V617F point mutation

The JAK2 V617F point mutation is very rare in hypereosinophilic syndome and/or chronic eosinophilic leukemia. Here we report on a patient with chronic eosinophilic leukemia and detectable JAK2 mutant clone, who achieved a good molecular response to interferon α-2a after 4 months of treatment. The molecular response correlated with only moderate haematological improvement

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The diagnosis of chronic eosinophilic leukemia (CEL) requires the presence of persistent eosinophilia at least 1.5x10^9/L with increased peripheral blood or marrow blasts (<20%) or the demonstration of cytogenetic/molecular evidence of clonality.[1] Idiopathic hypereosinophilic syndrome (HES) is a condition of unknown cause with sustained eosinophilia and organ damage.[2]

The JAK2V617F point mutation leads to constitutive tyrosine phosphorylation and cytokine hypersensitivity. It occurs in a substantial proportion of patients (pts) with polycythemia vera, essential thrombocythemia and idiopathic myeolofibrosis, but is very rare in hypereosinophilic syndrome.[3]

We report here, a good molecular response to interferon α after 4 months therapy in a patient with CEL and JAK2V617F mutant clone.

A 64-year old male was presented to our institution in 2003 with unexplained and persistent hypereosinophilia. He showed moderate hepatosplenomegaly at presentation: spleen was palpable 4 cm below the left costal margin and liver 2cm below the right costal margin. Echocardiography was normal with an ejection fraction of 56%. Haematology revealed an increased white blood cell (WBC) count (12x10^9/L) with marked hypereosinophilia (7.9x10^9/L). There was also slighty increased platelet count (515x10^9/L). Serum B12 level was 846 pg/mL (range 157-1057) and IgE level was 168 IU/mL (range <100). Serum tryptase level was not measured. Histological examination of the biopsied bone marrow (BM) showed hypercellularity in the myeloid lineage (90%) with fibrosis of grade 1. There was predominance of eosinophils (70%). Mast cells occupied 1-2% of the BM, blast cells were absent. Normal karyotype was revealed on cytogenetic studies; BCR-ABL and FIP1L1-PDGFRA fusion transcripts were negative by RT-PCR. The KIT genotyping was not performed. Patient was diagnosed as having myeloproliferative variant of HES and hydroxyurea (HU) was initiated. Two years later while still on HU, he developed marked thrombocythemia (platelet count >1500x10^9/L) and hypereosinophilia was also present. The combined treatment with anagrelide (1.5mg daily) and imatinib (200mg/day) was started, but it was ineffective and discontinued. The further therapeutic options included mercaptopurine, cytarabine and busulphan with no success. In December 2006, patient was readmitted because of progressive weakness. Test showed moderate anaemia (Hgb-8.5 g/dL) and thrombocytopaenia (38x10^9/L). WBC count was 4.0x10^9/L with 1.5x10^9/L of eosinophils and 7% of myeloblasts in peripheral blood. A repeat marrow exam revealed the cellularity of 80% with fibrosis of grade 1 and 2. The BM was infiltrated by eosinophils in 60%. There was 15% of myeloblasts. Mast cells occupied less than 1% of BM. The chronic eosinophilic leukemia was diagnosed. The cytogenetic study was normal, but JAK2V617F point mutation on marrow cells was detected by melting curve assay PCR as described by McClure *et al.*[4] This method has a reported sensitivity of ~5%. Initially, patient was administered 2 cycles of low-dose cytarabine, but myeloblasts were still present. Interferon α (IFN)-2a (Roferon, Roche) was commenced at dose of 3x10^6 U 3 times a week with a rapid eosinophils and myeloblasts clearence from peripheral blood. An increase in haemoglobin concentration and platelet count was also observed. Patient became transfusion independent. A repeat marrow biopsy showed the cellularity of 70-80% with fibrosis of grade 1 and 2. Eosinopils were still present, but occupied less than 40% of BM and myeloblasts were <10%. JAK2V617F point mutation was not more detectable after 4 months of IFN treatment.

Our report is unique in one main aspect: we proved that IFN-α-2a even at moderate doses may induce a good molecular response in a patient with JAK2V617F point mutation and this response does not necessarily correlate with haematological remission.

To our knowledge, JAK2V617F was identified only in 2 patients with CEL so far.[3] IFN-α has proven to be effective agent for HES and CEL,[5] but its efficacy in patients with JAK2V617F is limited. Jones *et al.* showed that patients with polycythemia vera (PV) who received IFN-α, remained positive for JAK2V617F, but the median percentage of mutant allele was significantly reduced if compare to control groups. The lower level of JAK2V617F correlated with better haematologic response.[6] The similar results, but after administration of pegylated IFN α-2b, were obtained by Samuelsson *et al.*[7] One another study showed that pegylated IFN-α-2a may decrease the mutated JAK2 cells in 89% of PV patients with one molecular remission reported after 12 months.[8]

To date, due to small number of CEL/HES pts with detectable V617F mutation, the pathogenic role of this mutation in such population has not been determined and it is unclear whether this mutation contributes to a specific phenotype. To find out if this mutant clone was already present at the time of HES, we extracted DNA from original bone marrow obtained at two time points: 1) at the onset of the disease (2003) and 2) during the disease course (2005). We revealed that JAK2 mutant clone was detectable in both analysed time points, so CEL should be identified from the beginning. We did not detect any other eosinophilia-associated mutations

which could be responsible for blast progression: the studies for the presence of PDGFRA, PDGFRB, ETV6 were negative and the karyotype remained normal. Other screened oncogens such FLT3-ITD and WT1 were also negative in this case.

At blast progression the JAK2V617F point mutation had been detected before cytarabine was commenced, but it is unlikely that cytarabine induced molecular response, or participated somehow in this response. The total dose of cytarabine administered during two 5-days cycles was as high as 600mg with no haematological response (blast cells and eosinophils still circulated in blood after therapy). The second evidence against its potential role in the induction of the molecular response is that this agent has already been used in this patient, in HES phase and mutant clone did not disappear. There are also no data in the literature that cytarabine may eradicate JAK2 or influenced JAK2 mutational status.

It should be emphasized that molecular response was rapid and achieved with moderate IFN doses, but in fact it correlated with only moderate haematologic response observed mainly as the improvement of peripheral blood tests, whereas minimal disease regression was seen on bone marrow biopsy. The longer follow-up and larger patient population are needed to confirm whether disappearance of JAK2 mutation reflects disease resolution.

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