Fatal bone marrow aplasia during interferon-α(α-IFN) treatment in chronic myelogenous leukemia

Sir,

We describe the occurrence of fatal bone marrow aplasia in a patient with chronic myelogenous leukemia (CML) during IFN-α treatment.

At diagnosis the patient’s leukocyte count was $233 \times 10^9/L$ (N 77, L 15, B 1, Mo 2, Eo 3, myelo- and metamyelocytes 2), hemoglobin 10.9 g/dL and platelet count 462 x 10^10/L. No HLA identical donor was available. He was treated with hydroxyurea for one month followed by 9 X 10^6 U of IFN-α daily. A stable hematologic response (HR) was obtained after 4 months of IFN-α. At six months 100% Ph+ metaphases were present in the BM.

After 10 months of therapy, pancytopenia developed, with a leukocyte count of 2.4 X 10^9/L (N 70%), platelet count of 2 X 10^9/L and hemoglobin of 9.4 g/dL. IFN-α was promptly discontinued.

BM biopsy showed a rich cellularity, granulocytic hyperplasia constituted by metamyelocytes and granulocytes. Blasts and megakaryocytes were absent. Erythroid precursors were disorganized with a left shift. Some aspects of dyserythropoiesis and an increased amount of reticulin fibers were present. The autoantibody pattern and serology for hepatitis B, C, EBV and CMV were negative. Abdominal ultrasound showed marked hepatosplenomegaly.

Karyotype analysis was impossible because of the absence of metaphases, but molecular analysis showed the persistence of Ph1. Despite discontinuation of IFN-α, the peripheral blood count progressively worsened. A further BM biopsy showed complete disappearance of hematopoietic precursors, the presence of isolated plasma cells and lymphoid aggregates. No blasts were observed. G-CSF did not improve the polymorphonuclear cell count.

The patient soon became febrile. Despite broad spectrum antibiotics and antifungal treatment he remained aplastic and died from disseminated aspergillus infection.

IFN-α induces HR in a large portion of patients with Ph1 CML in chronic phase; 20-40% of patients may achieve disappearance or major reduction in Ph1 metaphases in BM. Severe cytopenias associated with IFN-α in CML were described by Talpaz and Shephard in eight patients who sequentially received busulphan or hydroxyurea and IFN-α. Three patients died from severe BM aplasia and related infection.

Talpaz suggested that IFN-α has a myelosuppressive effect on both normal and Ph1 progenitor cells but that these have different recovery capacities, the normal cells having a better capacity to protect themselves. In CML patients developing severe BM aplasia the normal progenitor cells compartment loses the ability to adapt and the BM reservoir is severely compromised. In our case the patient received hydroxyurea for only 4 weeks and developed severe aplasia ten months later. Therefore in our case IFN-α played a pivotal role in the development of BM aplasia. Interestingly in our patient bcr/abl was still present despite no sign of BM function. Blastic crisis could never be documented and fibrosis by itself was not responsible for BM suppression. BM aplasia did not revert following discontinuation of the IFN-α, was unresponsive to G-CSF and finally proceeded to complete BM failure and death.

In CML patients lacking a normal stem cell reservoir IFN-α may induce hematologic response but irreversible severe aplasia can be expected. Follow-up should be rigorous also when a stable HR is achieved since patients developing BM aplasia are at high risk of treatment-related death.

Key words: CML, IFN-α treatment, aplasia.

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References:


Does interferon-α(α-IFN) exert an anti-leukemic effect by enhancing cell mediated immunity in chronic myeloid leukemia?

Three patients with chronic myeloid leukemia (CML) in complete cytogenetic remission under interferon-α(IFN-α) therapy displayed a relevant lymphocytosis (20-25%) on their bone marrow biopsy. The immunohistochemistry characterization revealed a polyclonal B and T-cell component with moderate increase of CD8+ lymphocytes. These findings support the hypothesis that IFN-α elicits an autologous cellular mediated immunity against CML cells.
SIR,

Interferons have several effects on cell mediated immunity, including inhibition of lymphocyte proliferation and DNA synthesis after activation by lectins, antigens and allogenic cells. On the other hand, interferons enhance target-specific T-cell cytotoxicity and spontaneous and natural killer activity both in vitro and in vivo, in murine and in human systems. Interferon-α (IFN-α) induces cytogenetic remissions in patients with chronic myeloid leukemia (CML) and prolongs survival. One of the mechanisms by which IFN-α restores, at least in part, normal hemopoietic function relates to the adhesion defect of CML cells. IFN-α, by restoring normal β1-integrin inhibitory effect on CML hemopoietic progenitors induces the adhesion of malignant hemopoietic progenitors, to the marrow microenvironment and also causes microenvironmental inhibition of CML progenitor proliferation. However, the mechanisms underlying the defect in β1-integrin and how this latter's effect is restored after IFN-α treatment remain elusive and it is conceivable that other unrecognized mechanisms may also be relevant in the recovery of normal hematopoiesis in CML.

IFN-α treatment restores lymphokine activated killer (LAK) cytotoxicity against CML cells. It was recently found that autologous IL-2 activated natural killer (ANL) cells suppress malignant hematopoiesis in CML. Interestingly, IFN-α enhances the terminal differentiation of dendritic cells which appear to be efficient antigen presenting cells capable of inducing a T-cell-mediated cytotoxicity against the leukemic cells. Taken together these studies indicate that IFN-α may directly or indirectly cause cell-mediated cytotoxicity against CML cells. We found that three patients, aged 43, 46, 53 years, with CML in continuous complete cytogenetic response (100% Ph1 negativity) who had receiving IFN-α therapy (3 to 9 MIU daily) for 1 to 5 years, displayed unexpected lymphocytosis (20-25%) in their bone marrow biopsy (Figure 1). Examination of the initial marrow biopsy before starting IFN-α treatment did not reveal any lymphoid nodules. The immunohistochemical characterization of the lymphocytes revealed polyclonal B- and T-cell components with a moderate increase in CD8 cells. These findings may further support the hypothesis that IFN-α elicits an autologous cell-mediated immunity against CML cells.

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Key words
CML, IFN-α, cell mediated immunity.

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