Interferon α in the treatment of polycythemia vera

Abstract Interferon z (IFN) inhibits the growth of the abnormal clone in patients with myeloproliferative disorders, leading to a reduction of the clinical and laboratory signs of the pathologic myeloproliferation. The therapeutic efficacy of IFN in polycythemia vera (PV) is demonstrated by the summarized treatment results of 279 patients participating in 16 prospective nonrandomized studies and in three case reports. The initial IFN dose ranged from 3 to 35 million IU/week. In 82% of the patients the frequency of phlebotomies was reduced. In 50% a complete remission was achieved, defined as a stable hematocrit of 45% without concomitant phlebotomies. Reduction of splenomegaly was seen in 77% and control of pruritus in 81% of the patients. The median observation time of the studies was 13 months (ranging from 3 to 84 months). Individual cases were followed for up to 126 months. In 21% of the patients IFN was terminated, owing mostly to side effects. The selective suppression of the malignant clone by IFN was demonstrated by the induction of cytogenetic remissions in sporadic cases with a chromosomal marker and by the observation of unmaintained remissions that lasted up to 4.8 years. IFN has no known mutagenic or teratogenic effects. The data presently available demonstrate that IFN is an effective alternative to the present forms of treatment in PV. Controlled prospective studies are essential to clarify whether the favorable biologic properties are also reflected by a benefit in clinical course and survival, and whether IFN may reduce the rates of acute leukemia and myelofibrosis.

Introduction

Polycythemia vera is a clonal stem cell disorder with predominant involvement of the erythroid cell line [1]. The clinical course is characterized by thromboembolic complications in about 40% of the patients, transition to acute leukemia in 5–20%, and myelofibrosis in up to 25% [21, 24]. The median age at diagnosis is approximately 60 years [21]. Higher age is associated with a higher frequency of thromboembolic complications [21]. It is difficult to estimate the prognosis of the individual patient on the basis of presently available data due to large differences between various reports [24]. If the hematologic parameters are controlled, life expectancy in PV may be similar to that of the normal population, in particular in patients with late onset of the disease [40]. However, an increased risk of death due to severe vascular complications was observed in young individuals with PV [24, 32]. The main goals of treatment are the improvement of clinical symptoms caused by the erythrocytosis and the reduction of the rates of thrombohemorrhagic complications, of myelofibrosis, and of acute leukemia.

Of the presently available cytoreductive substances, radiophosphorus and alkylating agents have been abandoned in first-line therapy owing to the increased rate of acute leukemia as compared with phlebotomy alone [2]. Hydroxyurea (HU) and pipobroman can control the clinical and laboratory signs of the pathologic myeloproliferation. However, a leukemogenic potential of these drugs is discussed [16, 34, 35, 47, 51]. Phlebotomy alone is associated with a higher risk of vascular complications during the first 3 years when compared with cytoreductive therapy, and in only a minority of patients was long-term treatment with phlebotomy alone practicable [2,33]. Higher doses of acetylsalicylic acid (ASA) are associated with an...
increased risk of bleeding complications, and the benefit of low doses of ASA is uncertain [46]. Hence, none of these forms of treatment seems to be optimal in PV, and all are only palliative.

By acting on the level of the pluripotent stem cell, interferon \( \alpha \) (IFN) inhibits the growth of the malignant clone in patients with myeloproliferative disorders (MPD) [6, 7, 10, 20]. In patients with PV, IFN is able to control the clinical and laboratory signs of the increased myeloproliferation by a selective suppression of the abnormal clone, and it might delay or avoid the transition to myelofibrosis or acute leukemia [42]. IFN has no known leukemogenic or teratogenic effects. This paper gives an overview of the treatment results as well as the advantages and disadvantages of IFN in PV on the basis of the literature presently available.

**Biological effects**

In normal hematopoiesis, IFN inhibits the in vitro proliferation of the immature multilineage hematopoietic progenitor cell and of the committed stem cell [4, 36]. The exact mechanism of the therapeutic action of IFN has not been clearly defined. A direct inhibition by IFN as well as cytokine-mediated secondary effects may be responsible for the suppression of growth of the hematologic progenitors, and probably the combination of several biologic effects causes the therapeutic efficacy in MPD. In PV and other MPDs, a suppression of the colony growth of erythroid, myeloid, and megakaryocytic progenitors is induced by IFN [7, 12, 20]. These in vitro observations correspond well to the clinical results in patients with PV [42]. Furthermore, in vitro results and clinical data suggest that the clonal hematopoiesis has a higher sensibility to IFN than the normal progenitor cells. In vitro, clonal BFU-E of PV patients showed a greater growth inhibition by IFN as compared with normal BFU-E [7, 12]. In vivo, the selective effect of IFN on the malignant clone is supported by the fact that a cytogenetic remission has been documented in some cases of PV which had a chromosomal marker [26, 28, 30, 41]. However, in the majority of PV patients no marker of the malignant clone is available, and the response to IFN can be assessed only by the clinical course.

The development of myelofibrosis in PV, as in the other MPDs, seems to be associated with the pathologic megakaryopoiesis. The release of transforming growth factor \( \beta \) and platelet-derived growth factor (PDGF) from the abnormal megakaryocytes might be responsible for bone marrow fibrosis [39, 52]. IFN inhibits the growth of the megakaryocytic progenitors [6, 17]. This suggests that IFN might reduce or delay the development of myelofibrosis in patients with PV and other MPDs.

**Treatment results with IFN in PV**

**Induction therapy**

IFN was first described in 1983 to lower high platelet counts in patients with CML [44]. Later, the platelet-reducing effect and the reduction of all signs of increased myeloproliferation was also shown in Philadelphia chromosome-negative MPDs, including PV [19, 45]. In order to obtain an overview on the present state of IFN treatment in this disease, a Medline search of the key words “polycythemia” and “interferon” was done in June 1999. Nineteen studies or case reports were suitable for analysis, defining the response criteria satisfactorily [5, 7–9, 11, 13, 14, 18, 25, 26, 30, 31, 37, 38, 41–43, 48, 50]. The results of these reports, comprising a total number of 279 patients, are summarized in Table 1. The studies were performed mainly with the intention to assess the practicability of IFN therapy in PV, its therapeutic efficacy, and its side effects. The median observation time of all reports is 13 months. The range of the median is 3–84 months. Individual cases were followed up to 126 months. All reports address the period of the induction therapy, lasting from a few months up to 1 year.

The inclusion criteria are not uniform, leading to a heterogeneity of the patients. Altogether, cases in the early and later stages of the disease as well as newly diagnosed and previously treated patients who had received cytotoxic drugs were included. In all studies, the reduction of the phlebotomy rate was the main parameter to assess the response to IFN. The decrease of erythrocytosis was associated mostly with a reduction of leuko- and thrombocytosis and of splenomegaly. Patients with a stable hematocrit of 45% without the requirement of phlebotomies were classified as complete responders, even if the other signs of increased myeloproliferation had not completely normalized.

Despite the study differences, some general information is given. The initial IFN dose ranged from 3 to 35 million IU/week. As shown in Table 1, in 82% of patients the frequency of phlebotomies was reduced, and in 50% a complete response was achieved. Elevated WBC and platelet counts were also reduced simultaneously, but detailed information on the peripheral blood counts are not available in all studies. The hematologic response was achieved mostly within 1–3 months after the start of therapy. A complete response was often reached later and sometimes did not occur until the second year of treatment [42]. The decrease of the peripheral blood counts corresponded to a reduction of the respective cell rows in the bone marrow in some patients, but the increased cell content also persisted in some cases [15, 31, 38, 41, 42].

Reduction of splenomegaly was found in 77% of the patients. Control of pruritus was seen in 81%,