INTERFERON TREATMENT OF HUMAN MALIGNANCIES – A SHORT REVIEW

STEFAN EINHORN and HANS STRANDER
Department of Oncology, Radiumhemmet, Karolinska Hospital, S-104 01 Stockholm, Sweden
(First submitted 5 February 1993; accepted 8 February 1993)

Interferon (IFN) therapy can induce remissions in human malignancies and has been established as a treatment of choice in several diseases. The clinical effects of IFNs are especially obvious in the treatment of hematological malignancies and virus-associated tumor diseases. Most other types of malignant solid tumors are less likely to respond to IFN as monotherapy and optimal therapeutic schedules are yet to be developed. It is of special interest that combinations of IFNs with other treatment modalities have yielded an increased response rate in several diseases. Several studies on the use of IFN as adjuvant therapy are under way.

It is possible, if not likely, that the antitumor effects of IFNs are mediated by different cellular effects in cooperation. These may differ between different malignancies. Mainly based on studies comparing in vitro sensitivity of malignant cells to clinical effects on the same tumor, we suggest that the direct effects of IFNs on the malignant cell are of major importance for the antitumor action of IFN. A deepened insight into the cellular aspects of the antitumor action of these cytokines is a prerequisite for the optimal use of IFNs in the treatment of tumors in man.

INTRODUCTION

α-, β- and γ-interferons (-IFNs) have all been used in the treatment of tumors in man. All of them are produced in vivo during the course of viral infections and malignant diseases and it is a well-grounded hypothesis that they are part of the bodily defence against these diseases. The clinical IFN field has expanded immensely during the last few years and there are some 15 indications for which IFNs have been registered as drugs in various countries.

It is still under discussion by what means the IFNs exert their action in responding cases. It is conceivable that their major mode of action varies with the disease being treated and even between individuals. This article provides a summary of the clinical antitumor effects obtained so far and discusses some of the possible mechanisms underlying the antitumoral effects of IFN.

CLINICAL EFFECTS OF IFN

IFN in virus-associated tumors

After the original demonstration of an effect on human warts IFNs have been used extensively for the treatment of virus associated tumors. Especially IFN-α has been shown to exert an effect on papilloma virus- (condylomata acuminate, juvenile laryngeal papillomatosis), EBV- (nasopharyngeal carcinoma) and HIV-associated diseases (Kaposi’s sarcoma and cutaneous lymphoma). IFNs have been tested against several of these diseases by using different doses, various schedules, local and generalized treatments and combination therapy with other types of antiviral drugs. In no case, however, has a distinct therapeutic schedule been worked out which can be considered optimal. These areas are still under close investigation.

Over the past five years several investigations have been performed on the use of IFN treatment in different types of chronic hepatitis. Especially in hepatitis B and C it is an established fact that IFNs, and especially α-IFNs, have an important role in therapy. It is a distinct possibility that patients with hepatitis C may have a reduced risk of developing the cirrhosis that predisposes to malignancy if they are treated with IFN. Thus, these diseases serve as models to evaluate whether IFN can work as a prophylaxis against malignant transformation.

IFN in hematological malignancies

IFNs have been used extensively for the treatment of various forms of leukemia. All the main studies have been done with α-IFNs, although IFN-γ has been shown to be effective at least in chronic myeloid leukemia (CML). Approximately 70 % of CML patients respond to IFN-α therapy and 20 % of the patients display complete cytogenetic remissions. The duration of the latter responses seem to be longer than in patients showing no cytogenetic response. A recent randomized trial indicates that IFN-α prolongs life in patients with CML. A definite survival
benefit for IFN therapy has to be established in large scale phase III studies, however. It has been proposed that IFN treatment should be used for extremely long periods in CML patients. This is based on the fact that continuous treatment of hairy cell leukemia patients yields additional complete responders as the years go by, providing the treatment is continued (Braide, personal communication).

IFN exerts a strong antitumor effect in hairy cell leukemia. On the other hand alternative treatments have recently become available for patients with this particular disease.

In acute leukemias the response rate with IFN therapy has been reported to be low. However, in exceptional cases long-lasting remissions during prolonged IFN-α therapy have been reported in patients with acute lymphocytic leukemia that are refractory to chemotherapy.

Several types of malignant lymphomas, including both non-Hodgkin’s and Hodgkin’s lymphomas respond to IFN therapy. High response rates have only been achieved in low grade lymphomas and especially cutaneous T-cell lymphomas. It has recently been shown that combined treatment with IFN-α and high-dose chemotherapy prolongs life in patients with low/intermediate-grade non-Hodgkin’s lymphoma.

In myelomatosis IFN-α clearly has an effect by itself while this is more questionable when employing γ- and β-IFN. As an induction regimen IFN-α has been used together with chemotherapy to the advantage of the patients. The recent studies employing the combination of IFN and chemotherapy have given rise to increased survival in particular groups of patients with myeloma. IFN-α has also been used as maintenance treatment, causing prolonged remission periods. IFNs clearly have a role in the future treatment of this disease.

**IFN in solid tumors**

IFNs have been tested extensively in solid tumors. In advanced melanoma the response rate with IFN alone has been reported to be 12–22% in various trials. Studies are being conducted on a large scale to see whether IFN-α given adjuvantly or in combination with other drugs can affect the survival of melanoma patients. Interim analyses of a large scale adjuvant trial in the US seem to indicate a difference between the IFN-treated patients and the groups not receiving such therapy (Kirkwood J, personal communication).

In renal cell carcinoma it is well known that metastatic disease is fairly resistant to cytostatic treatment. α-IFN alone or combined with chemotherapeutic drugs can induce remissions in a proportion of these patients, especially in those with pulmonary metastases. In bladder carcinoma IFNs have been used for intravesical treatment and IFNs also seem to exert effects on the bladder epithelium in high-risk patients.

In osteosarcoma the ongoing study at the Karolinska Hospital has a 5-year survival rate of 70% and this tallies exactly with the results obtained with high-dose chemotherapy in the Scandinavian Sarcoma Study (Strander H, unpublished data). In these studies IFN is being given after surgery, as an adjuvant treatment.

Results have also been encouraging in meningiomas and in patients with neuroendocrine tumors. In the latter case the results strongly suggest that the survival of these patients is prolonged by IFN therapy.

IFNs are also being evaluated in different squamous cell carcinoma patients, and particularly in head and neck tumors together with chemotherapy. They are also used together with irradiation and chemotherapy in patients with various types of lung tumors. A combination treatment that has yielded some very promising data is the use of IFN in combination with 13-cis-retinoic acid in squamous cell carcinoma.

Recent results in the treatment of solid tumors are encouraging and the interest in IFN treatment of these diseases has increased with time. Still it is crucial, however, to find out how IFNs are able to exert their antitumor effects whenever they are efficacious.

**ON THE MECHANISM BEHIND THE ANTITUMOR EFFECTS OF IFN**

It is today a well established fact the IFNs can induce lasting remissions in human malignancies. The mechanism(s) behind these antitumor effects is, however, to a large extent unknown. The object of this part of the review is to give some background on possible effector mechanisms of IFNs and to speculate on which of these are of importance for the antitumor action of IFNs.

**IFNs - pleiotropic proteins**

Although IFNs were originally defined as antiviral substances it has been shown that these proteins can exert a variety of other effects on cells. One aspect of IFN’s cellular effects is the inhibition of cell proliferation, occurring in malignant as well as in non-malignant cells. Other aspects of the cellular action of IFN include inhibitory and stimulatory effects on the immune system. A majority of immunological functions known to man have been shown to be influenced by IFNs, either in a positive or in a negative way. Some of these effects are exclusively performed by γ-IFN, whereas others are also exerted by α- and β-IFNs. Induction of cell surface changes is another aspect of the cellular repertoire of IFNs. Finally, the IFNs can influence the production of various substances, including other cytokines and prostaglandins. Also these