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Interferon therapy in neoplastic diseases

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Three types of interferon preparation (α, β and γ) have been used in the treatment of tumours *in vivo*. At the time of writing no information is available on IFN-γ treatment of tumour patients. Treatments with IFN-α and IFN-β have been undertaken at many clinical centres. Both types of preparation can exert side effects. Both types have also been able to cause regression of certain tumours in individual patients. At our hospital, IFN-α has been given to tumour patients over the last decade. Antitumour effects have been registered on patients with juvenile laryngeal papillomatosis, Hodgkin's disease, myelomatosis, ovarian carcinoma, hypernephroma and glioblastoma. Further study is needed on how therapy with IFN should best be undertaken and also how such treatment compares with other treatments of various tumour diseases. IFN therapy should also be combined with other such treatments.

Introduction

In 1962 a report was published showing that the growth of mouse L cells is inhibited by an interferon (IFN) preparation (Paucker *et al.* 1962). That paper was the first to show that IFN could affect the growth of tumour cells *in vitro* and it was also the first to indicate that interferon could act on cells in other ways than antiviral. In a series of animal studies Gresser and coworkers were then able to show that interferon preparations had the capacity to inhibit the appearance and growth of virus-induced and chemically induced tumours as well as transplanted and spontaneous tumours (Gresser 1977). The results from these studies and the developments of methods for the production of HuIFN in relatively large quantities (Cantell & Strander 1977) formed the basis for initiating clinical trials with IFN in human tumours.

Interferon preparations used in clinical trials

Mainly IFN-α preparations have been used so far in the treatment of human diseases. IFN-α is usually produced by exposing human peripheral leucocytes to Sendai virus in tissue culture medium. After 18 h the supernatants are harvested and the crude IFN is purified by precipitation. The final product employed at the clinic usually contains approximately 1×10^6 IFN units per milligram of protein.† This means that only about 0.5 % of the protein present in the preparations is IFN. Recently more purified material has been employed at the clinic (see Priestman, this symposium).

During the last years IFN-β preparations have also been used in clinical studies. This IFN is produced by exposing cultured fibroblasts to inducers. IFN-β is then purified to approximately the same purity as the IFN-α preparations used.

IFN-γ preparations are currently being developed in various laboratories, but so far there have been no reports on possible clinical effects with such preparations.

† Units with reference to international standard.

Clinical trials on human tumours

During the last 11 years, trials have been undertaken employing IFN in malignant diseases of man. The main problem in designing such trials is the fact that we do not know the important mechanism(s) in the antitumour action of IFN. As an example, an intramuscular (i.m.) dose of 3×10^6 units of IFN has been used in several studies in man. This is a dose that was shown in early trials to exert an antiviral effect in monkeys, as calculated on the basis of body mass. It was shown in similar experiments that the antiviral effect lasted for approximately 2–3 days. Because of these findings, IFN has been injected three times weekly in several clinical trials. It was at that time also calculated to be the approximate maximum dose, causing no serious side effects (Strander *et al.* 1973). Later on it was, however, shown that much higher doses of highly purified IFN can be given to patients without serious side effects. The results from studies of IFN therapy in patients with malignant diseases have been the subject of several recent reviews (Borden & Hawkins 1980; De Maeyer *et al.* 1981; Dunnick & Galasso 1979; Kono 1982; Munk & Kirchner 1982; Priestman 1979; Scott & Tyrrell 1980). In this paper we shall therefore focus only on some of the tumours studied and also discuss possible mechanisms behind the antitumour effects of IFN.

Benign tumours

In several countries patients with juvenile laryngeal papillomatosis today receive IFN therapy. These studies were initiated in Stockholm in 1976. Out of 10 patients treated so far at Karolinska Hospital, 7 show complete responses and 3 have partial responses with only small papillomas remaining. It should be emphasized that in the Stockholm study only patients with advanced disease have been included. The 10 patients included have been collected from the whole of Sweden. At present there are no serious problems with laryngeal papilloma in Sweden owing to IFN. We think it safe to state that juvenile laryngeal papillomatosis is the first tumour disease in which IFN has been shown to be superior to conventional treatment.

Condyloma accuminata and plantar warts in immunosuppressed patients are possibly caused by agents similar to that causing juvenile laryngeal papillomatosis (papilloma virus). It has therefore been decided to treat these patients in Sweden with IFN. The results in the treatment of these patients are so far promising (Borglund & Strander, unpublished; Einhorn & Strander, unpublished).

Osteosarcoma

Adjuvant trials in osteosarcoma patients were initiated in 1971 at the Karolinska Hospital. IFN therapy starts before surgery and continues for at least 18 months. Of the IFN-treated patients in this trial, 60% remain free of metastatic disease after 3 years of follow-up. The corresponding figure for a concurrent control group not receiving IFN therapy is 35%. It should be emphasized that this trial is not a randomized one.

Patients in the IFN trial who develop metastases have a tendency to develop subclinical and clinical virus infections during IFN therapy, but this is not true of patients not developing metastases (Ingimarsson *et al.* 1981). This finding is currently subject to further evaluation.

Osteosarcoma patients developing metastases during or after completion of therapy with IFN receive increased doses of IFN (3×10^6 IFN units daily) in combination with irradiation of both lungs (20 Gy).

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Other solid malignant tumours

In 40 patients with generalized breast carcinoma, 12 exhibited a partial response to IFN therapy. The longest duration of response has been 70 weeks. The results of systemic treatment of patients with melanoma and non-small cell cancer of the lung have shown that only approximately 1–2 % of melanoma patients respond partly to IFN, whereas in lung carcinoma no responses have been observed so far. A pilot study with the use of IFN in the treatment of ovarian carcinoma has shown that partial remissions can be obtained in this disease. These studies are continuing.

Haematological malignancies

In some patients with multiple myeloma it has been shown that the monoclonal antibody concentration and the excretion of Bence-Jones protein in the urine can be decreased by treatment with IFN. It has also been shown that in some of these patients the tumour volume can be significantly reduced. The duration of the response has in some patients been at least 3 years. A randomized trial is in progress in Stockholm in patients with IgA and Bence-Jones myeloma. IgG myelomas, on the other hand, do not seem to be good candiates for IFN therapy.

In American trials with IFN-α preparations, it has been shown that nodular lymphomas can respond to IFN therapy. Out of 13 treated patients 6 have shown complete or partial remissions.

English and American studies have shown that significant decreases in peripheral blast counts can be obtained in patients with acute leukaemias. Improvement in the bone marrow only occurred in occasional patients.

Several possible mechanisms behind the antitumour effects of IFN

Although we know that IFN preparations can affect the course of malignant diseases, little is still known about the mechanism(s) behind these effects. One possibility is that IFN acts directly on the tumour cells, causing an inhibition of cell multiplication. Another possibility is that IFN acts on the tumour cells indirectly, for instance by augmenting possible antitumour mechanisms of the immune system. Other mechanisms than these are conceivable, and IFN may also act by a combination of several mechanisms.

Direct effects of IFN on the tumour cells

IFN inhibits the multiplication of tumour cells in tissue culture (Einhorn & Strander 1978; Paucker *et al.* 1962). Also non-malignant cells can be inhibited in their multiplication by IFN. These effects may be due to a specific block of the cells in S phase, but also other phases of the cell cycle are affected by IFN. There is a large variation in the susceptibility of tumour cell lines to the inhibitory effect of IFN on cell multiplication. Some cell lines respond to IFN at less than 1 unit ml^{-1}, whereas the growth of others is not affected by IFN doses exceeding 10000 units ml^{-1}. For comparison it may be noted that the concentration of IFN in serum after an i.m. injection of 3×10^6 units of IFN to man is 30–100 units ml^{-1} of serum. Also, freshly explanted tumour cells differ considerably in their susceptibility to the inhibitory effect of IFN on cell metabolism (Ernberg *et al.* 1982). Thus the direct effects of IFN are of importance for

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antitumour actions of IFN, some resistant tumours may not respond to IFN therapy, irrespective of the IFN dose given. If the susceptibility of tumour cells to IFN could be tested in tissue culture before initiation of IFN therapy, patients who are more likely to respond to IFN could be selected for this type of treatment, whereas the others could receive other forms of therapy. Studies along these lines have been initiated with a tumour stem cell colony assay.

Effects of IFN on the immune system

Although there is so far no conclusive evidence that the immune system can affect the growth of an established tumour in man, IFN may theoretically act by stimulating the action of lymphoid cells directed against the tumour. IFN exerts a variety of effects on the immune system (Bloom 1980). It inhibits some functions of lymphoid cells, such as response to mitogens and delayed type hypersensitivity reactions, whereas it stimulates other immune functions such as natural killer cell activity and monocyte phagocytosis. Some immune functions may be either stimulated or inhibited by IFN depending on the experimental conditions used.

In tumour patients receiving IFN therapy, Natural Killer cell (NK) activity increases and remains at an enhanced level during prolonged therapy (Einhorn *et al.* 1980). In 39 myeloma patients receiving IFN therapy, NK activity was measured before and at different time points during therapy after which effects on NK activity were correlated with the clinical effects of IFN. No correlations could be found, indicating that NK activity plays little or no role in the antitumour action of IFN in multiple myeloma (Einhorn *et al.* 1982). Also, other immunological functions, such as the response of lymphocytes to mitogens and monocyte phagocytosis, have been followed during prolonged therapy with IFN. For lymphocyte response to mitogens no major effects were noted (Einhorn *et al.* 1979), whereas monocyte phagocytosis was found to decrease during therapy with IFN (Einhorn & Jarstrand 1982).

Summary and perspectives for the future

We know today that IFN can exert antitumour effects in human malignancies. One of several questions that remains to be answered is whether IFN is superior to conventional treatment for any malignant tumour. Several randomized trials have been started recently to answer this question. Today we have very little information on how to use IFN as a treatment for human tumours: Should we use as high doses of IFN as possible? Should we administer it intramuscularly, intravenously, intratumourally or by other routes? Should we combine it with other methods of treatment? and so on. To answer these questions a lot of clinical and experimental work has yet to be done, before we know how to use IFN optimally. A major drawback in interpreting results is the fact that little is known about the mechanism(s) of action of IFN in tumour patients. Further studies in this field are necessary.

Because of the recent advances in the methods of producing IFN from bacteria, we shall soon have large quantities of IFN for performing clinical trials on human tumours. It is important that these studies are performed under strict clinical control and planned carefully on the basis of previous clinical trials and also of experimental studies in animals and in tissue culture.

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Discussion

It was suggested that mice may be more susceptible than man to both the antitumour and the antiviral effects of interferon.

There was no information on the production of interferon by patients treated with interferon or on the sensitivity of host or tumour cells in patients who relapsed on treatment.

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