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Interferon alpha (IFN-α) in treatment of malignant diseases

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There are several natural varieties of IFN-α in clinical use. Although IFNs were the first cytokines in use as a new treatment modality, we still know little about their mode of action in malignancies. IFN-α can inhibit cell growth, but it has been shown only recently, on malignant cells from patients with multiple myeloma, that IFN-α can exert a direct cytotoxic effect on tumor cells. The treatment with natural leucocyte IFN-α in doses used in the early clinical trials, are still most widely used. It has been shown that through a high local concentration by local application in malignant melanoma, basalioma, pleural carcinosis, glioblastoma, total local tumor control may be achieved. It is thus not known what the optimal doses of IFN-α are, and they may vary by the tumor type, as well as from patient to patient. The neccessary duration of treatment also remains an open question. IFNs are a tool for treatment of malignant tumors. Their cytotoxic effect, however, is not strong enough and does not last. At present, there is a vast field of investigative work still open - but in the meantime it seems necessary to proceed with clinical trials of different types of IFN, the natural IFN-α again beeing the most interesting one.

Key words: neoplasms-drug therapy; interferon-alpha

Introduction

The antiviral and antitumor efficacy of interferon alpha (IFN-α) has been established in the 1960's and 1970's.[1] During the 1970's it was demonstrated that IFN-α has an affects on benign and malignant tumors in man, but the question was whether this was due to the presence of IFN-α or contaminating substances in the preparations.[2-4] By 1979, recombinant human IFN-α had been produced in an almost pure form, thus the antitumor effect of IFN-α in man could be established.[5-7]

The natural IFN-α contains several species of IFN-α. Individual IFN-α subtypes have been isolated and they have specific activities according to the cell on which they are tested. Much effort has gone into attempts to isolate and purify single subtypes of IFN-α. The natural mixture of IFN-α, however, seems to be more active than any of its components: synergistic interactions might exist among IFN-α components. Consequently, new interest was aroused in the natural IFN-α.[8]

There are several natural varieties of IFN-α in clinical use. IFNs affect the organism and the tumor in a number of ways. They may act by altering the immune response, their antitumor action may be due to the effect on oncogenes, on the growth factor responses, on proliferation and differentiation, and on their cytostatic effect. Allthough IFN-s were the first cytokines in use as a new treatment modality, we still know little about their mode of action in malignancies. It is conceivable that their major mode of action varies with the disease and even among individuals. It is likely that the antitumor effects of IFN-α are due to different effects in interaction.[2]

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Laboratory and clinical studies

It is a well established fact that IFN-α can inhibit cell growth, but it has been shown only recently, on malignant cells from patients with multiple myeloma, that IFN-α can exert a direct cytotoxic effect on tumor cells.[9]

In several patients with different tumors such as Kaposi's sarcoma, lymphoma or renal cell carcinoma there has been no statistically significant correlation between the dose of IFN-α and the effect of treatment. The treatment with natural leucocyte IFN-α in doses (3×10^6, 3 times weekly) used in the early clinical trials, are still most widely used and regarded as the optimal treatment. They were introduced mostly for practical reasons such as: they produced a mesurable antiviral effect in monkeys which lasted about 3 days. Due to side effects, no higher doses could be given.[2, 10]

On the other hand, it has been shown that high local concentration by local application in malignant melanoma, basalioma, pleural carcinosis, glioblastoma, may achieve total local tumor control.[11-15] Systemic effect has been described in breast cancer patients some 20 years ago.[7] Some doubts have been expressed that IFN-α can be effective in solid tumors systemically, but in vitro experimental models showed that IFN-α may have effect on tumor cell metastasis. Furthermore, subcutaneous injections of IFN-α in combination with surgery and radiotherapy were effective in treatment of patients with skeletal metastases from renal cell carcinoma.[16-18]

Recently it has been shown that in breast cancer IFN-α is able to reduce cell proliferation, enhance steroid hormone receptors and sensitize breast cancer cells to tamoxifen treatment. It also increases the activity of medroxyprogesteron and restores hormone sensitivity in hormone resistant cells.[19]

Clinical application

It is thus not known what the optimal doses of IFN-α are, and they may vary by the tumor type, as well as from patient to patient. The neccessary duration of treatment also remains an open question. Most tumors recur when IFN-α treatment is discontinued. The doses may also vary when IFN-α is combined with chemotherapy or radiotherapy. Side effects should be dealt with to reduce symptoms, but the most efficacious way of deverting complication has been the reduction of the dosage. Moderate temperature rises should not be treated since some of the IFN-α effects are known to be enhanced by higher temperature.[1]

IFN-α has been effective against Kaposi's sarcoma. In certain groups of patients with HIV infection, IFN-α may enhance the CD 4 + cell count.[20, 21]

IFN-α has some advantages over other treatment modalities in patients with hairy cell leukemia: there is no enhanced risk for infections, as is with chemotherapy or corticosteroids. Complete remissions have been achieved in patients with hairy cell leukemia following low doses of IFN-α.[8] With low doses of IFN-α, the Philadelphia (Ph 1) positive cell clones could be suppressed in patients with chronic myelogenous leukemia. Approximately 70 % of patients with chronic myelogenous leukemia respond to IFN-α treatment and 20 % display complete cytogenetic remission. In hairy cell leukemia with continuous treatment, additional complete remissions were achieved. Therefore it was proposed that treatment of patients with chronic myelogenous leukemia should also be prolongued.[22]

IFN-α is used for treatment of T as well as B lymphomas. There is evidence that IFNs are natural regulators of various B cell functions including the induction of blast transformation and plasmacyto differentiation in malignant B cells. IFNs also inhibit the generation and function of T suppressor cells and some of the T-cell lymphomas may respond well to IFN-α treatment. Approximately 50% of cutaneous T cell lymphomas respond to high dose treatment with IFN-α. It has been reported that some patients with adult T cell leukemia respond to interferon, impressive responses in combination with zivudine have been reported in such patients.[8, 23-25]

IFN-α has antitumor effect in multiple myeloma, with a 15% response rate. A particularly beneficial effect is noted in IgA myeloma treated with natural IFN-α. Intermittent melphalan (prednisone treatment and IFN-α) is regarded by many clinicians as the standard primary therapy for patients with multiple myeloma since there is evidence of better results of chemotherapy when combined with IFN-α.[2, 26, 27] IFN-α is used in the treatment of renal carcinoma and ovarian carcinoma alone and in combination with chemotherapy.[27] While with IFN-α in breast cancer patients, 22 to 41% response rates were reported, with recombinant IFN-α, this was not confirmed. IFN-α has been less effective in the treatment of gastrointestinal cancer and of some

other solid tumors.[8, 16] In advanced malignant melanoma the response rate of 12-22% with IFN-α alone have been reported.[2]

With IFN-α as adjuvant therapy to surgery, the disease free survival of patients with osteogenic sarcoma has been 50%.[5, 6]

Experience of the Oncological Institute of Ljubljana

At the Oncological Institute in Ljubljana, IFN-α was introduced in clinical use in 1976 for treatment of patients with pleural carcinosis from breast cancer. After intrapleural applications the malignant cells disappeared, however, no systemic effect was noted and the advanced metastatic disease progressed. IFN-α in patients with pleural carcinosis from breast cancer was continuously studied. There was evidence that IFN-α, as addition to systemic treatment, is an effective means of paliative treatment of pleural carcinosis. There were some observations that IFN-α seemed to affect the survival of patients with inflammatory breast cancer and pleural carcinosis.[29]

IFN-α has been shown to be effective in non-small lung cancer patients with pleural carcinosis. Following intrapleural applications, the effusion was cleared from cancer cells and haemorrhagic admixture in a majority of patients, it did arrest fluid accumulation with minimal side effects and probably did prolong the survival in these patients.[30] In a non randomized clinical trial of patients with non-small-cell lung cancer treated with intrapleural application of IFN-α in combination with radiation therapy it seemed that the survival of these patients was prolongued.[31] At present a randomized clinical trial is underway to study the effect on the survival of patients with non-small-cell lung cancer and pleural carcinosis, treated with radiation alone or in combination with IFN-α.

Serum interferone levels have been studied in patients with breast cancer and non-small lung cancer treated with intrapleural application of IFN-α. A correlation of the clinical effect and the levels of serum IFN-α could not be established.[32]

IFN-α has been given locally in patients with glioblastoma and malignant astrocytoma. This treatment was combined with chemotherapy and radiation. The study showed that with this combination therapy the malignant tumor could be eradicated succesfully, as confirmed by histological examination. The treatment, however, had unacceptable levels of neurotoxicity.[33]

At the Institute of Oncology in Ljubljana a prospective randomized trial study was undertaken in 1988 in patients with malignant melanoma stage IIA and B to establish the role of interferon as an adjunct to surgery. The survival of the 160 patients treated with IFN-α was significantly higher than in the 161 patients of the control group.[34] In a randomized trial (70 pts) it was further shown that patients with advanced malignant melanoma treated with IFN-α additionally to DTIC have a significantly better survival than those treated with DTIC alone.[35]

Conclusions

There is no doubt that IFNs are a tool for treatment of malignant tumors. Their cytotoxic effect, however, is not strong enough and does not last, cures of systemic malignant disease are rather exceptional with IFN alone. It seems reasonable to expect that clinical trials with IFN in combination with chemotherapy and radiotherapy will improve the results in certain groups of patients. It is possible that with a better understanding of problems, such as antagonism to IFN by some substances, antibodies to IFN, the effect of IFN on various oncogenic systems, the clinical use of IFN will yield better results. At present, there is a vast field of investigative work still open, but, in the meantime, it seems necessary to proceed with clinical trials of different types of IFN, the natural IFN-α again beeing the most interesting one.

Our experience is with IFN-α produced at the Institute of Immunology in Zagreb. In terms of low toxicity, high tolerance and the clinical effect, it concurs with that of others. In our opinion, it constitutes a promising tool for further clinical trials.

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