Occasional Review

Does interferon cure cancer?

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Interferon has recently been given wide publicity as a potential anticancer agent. Many patients with cancer are wondering why they are not receiving the drug. There are even local appeals to collect money to buy interferon for individual patients. I hope that this brief attempt to put current clinical results into perspective will help in dealing with questions from patients and their relatives.

Historical perspective

Since their discovery in 1957 the interferons have been extensively studied by virologists and molecular biologists. Their clinical use in preventing and treating viral disease has been recently reviewed in this journal.[1] Shortly after their discovery it was noted that certain tumour cell lines grew more slowly in tissue culture in the presence of interferon.[2] This was followed by the demonstration that interferon could decrease tumour growth in mice bearing experimental tumours.[3] The comparison between mouse and human systems has continually been hampered by the apparent species specificity of interferon and by the different growth kinetics of experimental and human neoplasms. Interferon was first used against human cancer in France in 1963.[4] Eleven patients with acute myeloid leukaemia were treated with a relatively impure leucocyte interferon preparation. A partial antitumour effect was noted in one of these patients. In the same year Dr Kari Cantell of the Central Public Health Laboratory in Helsinki began the large-scale purification of interferon from buffy coat leucocytes collected from blood for transfusion.[5] The scale of production and the purity of the product have increased over the years. Most of the clinical pharmacokinetic, antiviral, and antitumour studies have been carried out with this product. In 1971 the first large-scale clinical trial of interferon in cancer was begun.[6] It was given as adjuvant treatment to patients who had had limbs amputated for osteosarcoma. The initial results were promising, but, as will be shown, the absence of a randomised, concurrent control group makes their interpretation difficult.

In 1974 the National Cancer Institute in Washington began trials with synthesised interferon inducers.[7] Various compounds that stimulate the production of endogenous interferon are available. Toxicity limits the dose that can be administered and thus the serum concentrations of interferon achieved. Some 30 patients with various tumours were treated with polyriboinosinic-polyribocytidylic acid. Although interferon was successfully induced in some of these patients, no tumour responses were seen.

Stimulated by the apparent success in osteosarcoma, several groups became interested in the use of leucocyte interferon in other solid tumours. This interest coincided with increased production by Cantell's group and the collection of considerable data on the pharmacokinetics of interferon from its use in treating viral diseases. In 1977 three patients with end-stage diffuse histiocytic lymphoma treated with leucocyte interferon at Stanford University Hospital in California failed to show any tumour response.[8] The same group, however, were able to obtain dramatic responses in three patients with nodular lymphoma. At the M D Anderson Hospital at Houston Dr Jordan Gutterman also showed that interferon was effective in nodular lymphoma. After showing a tumour-reducing effect in patients with metastatic breast cancer and myeloma he wrote a proposal, in June 1978, to the American Cancer Society requesting $2m to purchase adequate leucocyte interferon to extend the trial to 150 patients. The American Cancer Society agreed to purchase the interferon but set up the trials at several different cancer centres within the United States.[9] This led to the blaze of publicity that has surrounded the drug ever since.

Interferon has now been given with therapeutic intent to some 200 patients with cancer. The results have generated considerable interest through being widely reported by the media. Most of the clinical data are as yet unpublished or available only in abstract form. This has led to an over-optimistic view in the minds of the general public and indeed of many physicians as to the efficacy of current interferon preparations.

Assessment of tumour response

The measurement of tumour size before and after treatment has so far formed the basis on which the therapeutic effects of interferon have been judged. Such measurements are not always simple. Tumours are composed of dividing cells, their non-dividing progeny, and various non-malignant cells such as fibroblasts, lymphocytes, and macrophages. Both malignant and non-malignant cells may export products such as collagen and mucin, which contribute to tumour bulk. Growth rate is determined by the rate of cell proliferation, the fraction of cells not dividing, and the rate of cell loss. These factors may all be affected by local physiological variables including blood flow, hypoxia, and the availability of nutrients.

Because of these many factors we may easily be misled by apparent short-term changes in tumour size. Three categories of response are traditionally used by oncologists: complete response, when no evidence of residual tumour can be seen after treatment; partial response, when some measure of tumour load is reduced to half of its pretreatment value; and no response, when there is no change in tumour size. A fourth category of "less than partial response" has been added, denoting a reduction in tumour burden but not reaching the 50% level. These latter responses are subject to considerable inter-observer variation. The response obtained also depends on how clinical measurements are used to compute an index of tumour load. If the volume of a tumour mass is calculated then a linear change of 1·25:1 would result in a partial response. Many of the interferon-induced responses are in this category. We know that a high

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percentage of partial or less than partial responses can be obtained by using available chemotherapeutic agents in patients with most of the common solid tumours. There is no evidence, however, that this prolongs their survival.[10] It is now apparent that only the complete eradication of tumour can result in realistic improvement in survival. Such responses have been rare with interferon.

OSTEOSARCOMA

In 1971 Dr Hans Strander at the Karolinska Hospital in Stockholm began to use leucocyte interferon as adjuvant treatment in patients with operable osteogenic sarcoma. After amputation patients were treated with a daily dose of 3×10^6 units intramuscularly for one month. For the next 18 months they received the same dose three times a week. Thirty-three patients were treated in this way and followed up. Initially their disease-free survival two years after presentation was compared with that of a historical control group of patients with osteosarcoma who had had their amputation before 1971.[11] Unfortunately, although the difference in results is startling, a change in the overall behaviour of the disease took place in the period between the treatment of the controls and those patients given interferon. This difference was noted in many other centres but is clearest in data reported from the Mayo Clinic[12] (table I). Better diagnostic tests, such as whole lung tomography and isotopic bone scanning, have contributed to this apparent improvement by screening out those patients with metastatic disease before amputation. Thus the survival of the amputees has improved. Strander then compared his data to a concurrent control group from other Swedish hospitals and still showed an advantage in the patients treated with interferon.[6] Such comparisons may often be misleading, as subtle differences in referral pathways can lead to the selection of patients with different prognoses arriving for treatment at different centres. It is only by randomly selecting patients to receive interferon or no treatment that the true efficacy of interferon as an adjuvant can be assessed. Such a trial is now under way in Vienna, and the results are eagerly awaited.

Interferon has also been used in an attempt to reduce measurable tumour masses in patients with metastatic osteosarcoma. Little change in tumour size has been observed.[13]

TABLE I—*Two-year disease-free survival in patients with osteosarcoma*

Karolinska Hospital—interferon treated	(1971–)	61%
Karolinska Hospital—historical controls	(1952–71)	14%
Concurrent controls	(1971–4)	37%
Mayo clinic—no adjuvant treatment	(1963–5)	18%
	(1966–8)	28%
	(1969–71)	41%
	(1972–4)	51%

NON-HODGKIN'S LYMPHOMA

Over the past two decades we have come to recognise that the non-Hodgkin's lymphomas comprise a range of diseases of widely differing natural history. At one end is the relatively benign nodular lymphocytic lymphoma (five-year survival with conventional treatment 85%) and at the other a group of aggressive, rapidly fatal, undifferentiated lymphocytic or lymphoblastic neoplasms with a five-year survival of less than 20% in most reported series. Interferon has so far been singularly unsuccessful in treating this latter group of malignancies (table II). In nodular lymphoma, however, dramatic reductions of tumour have been observed. The clearest evidence of response comes from the Stanford series.[8] Here, patients with the disease were followed for up to one year without any treatment. Tumour load, as measured by lymph node diameter on lymphangiography, was assessed frequently during this period. No significant fluctuation in node size was seen. The administration of 10^7 units daily of interferon resulted in considerable reduction in lymph node size in three out of six patients. Similar results were obtained by other groups.[14] Unfortunately, such responses have not been seen in patients who have uncontrolled disease after failing to respond to conventional radiation or chemotherapy.[21]

MYELOMA

Serial determinations of abnormal serum immunoglobulins have been used to assess response in this disease. In addition, measurement of Bence-Jones protein excretion can provide a useful index of disease activity. Interferon has complex effects on the immune system. There is some evidence that it may reduce the rate of immunoglobulin synthesis by normal and

TABLE II—*Overall results of interferon in cancer*

	Type	Daily dose (units)	Treatment duration (days)	Response					
				Total	NR	LPR	PR	CR	CR+PR
Nodular lymphocytic lymphoma									
Merigan *et al*[8]	LEU	10^7	30	8	5	0	2	1	20%
Gutterman *et al*[14]	LEU	$3–9 \times 10^6$	>28	6	1	2	1	2	
Diffuse histiocytic lymphoma									
Merigan *et al*[8]	LEU	10^7	30	3	3	0	0	0	0%
Gutterman *et al*[14]	LEU	$3–9 \times 10^6$	>28	1	0	1	0	0	
Hill *et al*[15]	LEU	5×10^6	>14	2	2	0	0	0	
Priestman[16]	LB	3×10^6	30	1	1	0	0	0	
Myeloma									
Priestman[16]	LB	4×10^6	30	1	1	0	0	0	33%
Osserman *et al*[17]	LEU	$3–6 \times 10^6$	>30	11	8	0	3	0	
Mellstedt *et al*[18]	LEU	3×10^6	30	4	0	0	2	2	
Gutterman *et al*[14]	LEU	6×10^6	30	10	4	3	2	1	
Hill *et al*[15]	LEU	5×10^6	>14	4	3	0	1	0	
Breast cancer									
Priestman[16]	LB	4×10^6	30	1	1	0	0	0	29%
Gutterman *et al*[14]	LEU	$3–9 \times 10^6$	>28	17	10	1	6	0	
Hill *et al*[15]	LEU	5×10^6	>14	4	4	0	0	0	
Borden *et al*[19]	LEU	$3–9 \times 10^6$	>42	16	9	2	5		
Lung cancer									
Krown *et al*[20]	LEU	3×10^6	30	12	12	0	0	0	0%
Melanoma									
Hill *et al*[15]	LEU	5×10^6	>14	2	2	0	0	0	25%
Priestman[16]	LB	4×10^6	30	2	0	0	1	0	

NR = No response. LPR = Less than partial response. PR = Partial response. CR = Complete response. LB = Lymphoblastoid. LEU = Leucocyte.

neoplastic B lymphocytes.[22] There is, however, other evidence of tumour regression in some of the treated patients. Reduction in bone pain, disappearance of hypercalcaemia, and a decrease in plasma cell infiltration in bone marrow aspirates have been observed after administration of interferon.[18] The overall response rates compare unfavourably with those obtained with standard chemotherapy (table II).

BREAST CANCER

All patients with breast cancer treated with interferon had metastatic disease. Many received extensive prior treatment. Although responses were seen, none was complete, and there is as yet no evidence that interferon has cured any patient (table II). Some interesting correlations have been noted.[14] Patients who responded to interferon were more likely to have responded to previous hormone or chemotherapy. In addition interferon was more effective in patients with predominantly soft-tissue metastatic disease rather than those with bone or visceral involvement. Intralesional injections of interferon have also been attempted.[23] Five patients with metastatic disease and two with primary breast cancer were given 3×10^6 units by daily injection for several weeks. Some regression was seen in the patients with metastatic disease. The assessment of intralesional treatment is difficult as the injection of any foreign proteins into a tumour will stimulate an immune response in which tumour cells may die as "innocent bystanders."

LEUKAEMIA

A total of 26 patients with acute leukaemia are reported to have received interferon with therapeutic intent.[4 11 24] Transient changes in peripheral blood and bone marrow counts have been observed, but there is scanty evidence that complete remission of any duration has been obtained. There is no doubt that interferon has a profound effect on the number of circulating granulocytes and lymphocytes in non-leukaemic patients. Within three days of its administration there is a rapid fall in the number of circulating granulocytes—a phenomenon explicable by sequestration or maturation arrest rather than by decreased stem cell turnover. A similar effect may result in changes in the numbers of circulating blast cells in the acute leukaemias, without affecting the course of the disease.

Interferon has also been used in chronic lymphocytic leukaemia. Again transient reductions in circulating abnormal cells have been noted, but the number of circulating lymphocytes returned to the untreated value shortly after cessation of treatment (T C Merigan *et al*, unpublished observations).

MELANOMA

Responses of any treatment for this tumour are notoriously difficult to assess. Tumour size often fluctuates without treatment and even complete tumour regression has been observed without treatment. Of four patients with metastatic melanoma treated with systemic leucocyte interferon, only one showed a short-lived partial response.[15 16] At Roswell Park Memorial Institute in Buffalo workers attempted intralesional injection of interferon. Histological changes were noted, but no dramatic tumour resolution was seen.

LUNG CANCER

At Memorial Hospital in New York, Oettgen *et al* used 3×10^6 units daily of leucocyte interferon over 30 days to assess response in 12 patients with non-small-cell lung cancer.[20] All patients had disease clearly assessable by chest radiography. No responses were seen.

OTHER NEOPLASMS

Interferon has been used to treat several other neoplasms. In many cases the numbers treated are extremely small and overall response rates difficult to assess. Indeed the duration of response is often very short, suggesting that interferon has not appreciably prolonged survival in these patients. Several patients with juvenile laryngeal papillomatosis have shown complete tumour regression when given interferon (H Strander, unpublisheddata). This rare disease occurs in children and adolescents and can cause life-threatening airway obstruction. Regression of venereal warts (condyloma acuminata) by intralesional injection of human fibroblast interferon has also been shown.[25] Claims of tumour regression after interferon treatment have been made for carcinoma of the stomach,[16] Hodgkin's disease,[26] and rhabdomyosarcoma (Independent Television News, London, 15 July 1980). In all of these the duration of remission was short.

SIDE EFFECTS

Currently available interferon preparations have a specific activity of 10^6 reference units per milligram of protein, which may be compared with the currently estimated specific activity of pure interferon of $>10^9$. It is therefore impossible to dissociate which side effects are due to impurities and which are due to interferon itself. Reported side effects have included fever, granulocytopenia, thrombocytopenia, malaise, fatigue, alopecia, and joint pains. No deleterious effects on hepatic, renal, or cardiac function have been observed.

MECHANISM OF ACTION

Clearly, from the results presented above, interferon as currently used does not cure cancer. It does, however, affect tumour growth in man. There are several possible mechanisms for this. Interferon has antiviral activity. There is evidence that interferon can stop the replication of DNA and RNA tumour viruses. For example, in SV 40 virus-infected cells the accumulation of early viral messenger RNA is inhibited, while for the murine leukaemia virus, defective virus with reduced infectivity is produced by cells in the presence of interferon.[27] Although there are hints that viruses may be implicated in the aetiology of human cancer, there are no assay systems available in which to determine the effects of interferon on putative human tumour viruses.

A direct growth inhibitory effect of interferon has been observed on a wide range of cell lines. Interferon binds to surface receptors on tumour cells and seems to trigger signals that can alter the kinetics of the cell cycle. The intracellular mediators may well be small cyclic nucleotides. This mechanism is clearly different from that of the conventionally used cytotoxic drugs and provides an exciting avenue for further research.

A third possible site for interferon's antitumour effect is the immune system. Interferon has been shown to have a wide range of effects on the complex network of the immune system. Interferon can increase phagocytosis and also killing by natural-killer cells, both of which could lead to increased tumour cell destruction. Its inhibitory effects on antibody production may result in a decreased level of blocking (tumour protecting) antibodies, thus allowing the immune system to deal more effectively with the tumour.

The future

At present no patient with cancer need feel deprived if he is not receiving interferon. The media have exaggerated the therapeutic potential of current interferon preparations. The results are certainly no better than those obtained with conventional radiation or chemotherapy.

Undoubtedly, however, interferon is an exciting substance

for the oncologist. It is remarkable that a physiological product can have an effect on the growth rate of cancer. The interferons are a group of related molecules that may well have different individual effects. We need a more purified product for use in clinical trials, and there are recent suggestions that this will soon be on the way. We must also investigate the molecular mechanisms responsible for its anticancer effects. By doing this we may uncover more information about cell control systems and how to tamper with them pharmacologically.

We can reassure our patients with cancer that the doctors carrying out clinical trials with interferon are not like Sir Colenso Ridgeon in Bernard Shaw's *The Doctor's Dilemma*, busy selecting patients, on their personal merits, to receive a rare and expensive cure. The only similarity is that interferon might work by stimulating the phagocytes.

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Two years ago a woman of 77 did not need glasses for distance but since taking disopyramide (Rythmodan) 100 mg thrice daily (she has been treated with sotalol hydrochloride for moderate hypertension) her usual acuity has diminished and she now needs glasses for distance and a stronger lens for reading. Could there be any association?

Blurred vision is a common side effect of disopyramide owing to its anticholinergic properties like those of atropine. Anticholinergic drugs produce dilatation of the pupil and reduce accommodation. Visual disturbance with beta-adrenergic blocking agents, such as sotalol hydrochloride, may occasionally occur but is usually transitory and unimportant. Disopyramide interacts with beta-adrenergic blocking drugs, and therefore in sensitive individuals the side effects of both the drugs could be augmented when used together. Anticholinergic drugs should not be used in elderly patients with potential angle-closure glaucoma having a shallow anterior chamber and a very narrow anterior chamber angle, since these drugs can cause pupillary dilatation. But the basis for this precautionary measure is observations of the effects of these drugs applied topically to the eye in high concentration, and there are only few clinical case reports linking acute angle-closure glaucoma with the systemic administration of anticholinergic drugs. As to this particular patient the most likely cause for the change in visual acuity and refraction would be lens changes, since the accommodative power of the eye is virtually reduced to nii in most patients over the age of 70, and their vision is unlikely to be affected by the systemic administration of anticholinergic and beta-adrenergic blocking agents.

This answer was first published on 24 May (p 1258), and we regret that it was incomplete.

Promethazine hydrochloride (Phenergan) is often used to counteract some of the side effects of pethidine in labour. Does it affect the baby in any way?

Promethazine is a phenothiazine with antihistamine properties; it is also a sedative, and its effectiveness as an antiemetic is due to a direct action on the vomiting centre. When promethazine hydrochloride is given in labour to counteract the emetic effect of pethidine, both drugs reach the baby; probably the sedative effect of the pethidine will be much greater than that of the promethazine, but there have been no studies on how the baby is affected by promethazine alone in labour. Most other antiemetics also have sedative effects. Two recent reports have some relevance. The administration of promethazine syrup to babies in the early months of life may possibly exacerbate a tendency to apnoeic attacks,[1] but in rhesus isoimmunisation prolonged treatment with promethazine hydrochloride (150 mg/day for up to 24 weeks) has been used in mid and late pregnancy without apparent ill effects on the baby.[2] Promethazine theoclate (Avomine) has been used for over 20 years to treat vomiting in early pregnancy. There is no evidence of unwanted side effects such as teratogenesis. In one study of patients who had taken phenothiazines a slightly increased incidence of congenital abnormalities was detected, but this has not been confirmed in a larger series and promethazine was not one of the phenothiazines under suspicion.[3] The drug appears to be safe, although—as with all drugs—its use in pregnancy should be kept to a minimum.

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