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The present status of clinical studies with interferons in cancer in Britain

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Although the evaluation of cloned interferons is now under way, the only clinical results currently available from U.K. studies in cancer come from trials using the (Wellcome) lymphoblastoid preparation.

Dose toxicity studies for intravenous and intramuscular administration are now complete and show that on a daily schedule the maximum tolerated dose intramuscularly is 12×10^6 units (12 Mu) whereas by 24 h intravenous infusion doses of up to 300 Mu may be given without undue toxicity. A programme of studies has been initiated to assess the efficacy of lymphoblastoid interferon in a variety of tumours. A number of therapeutic responses have been seen but only one study, in malignant melanoma, has completed patient entry. In this series of 16 patients who had metastatic disease and had failed on conventional cytotoxic therapy one patient experienced a remission for 8 months as a result of interferon administration.

In another study the combination of interferon with conventional cytotoxics is being evaluated in advanced breast cancer. Preliminary results indicate that the combination is well tolerated but it is too early to detect any therapeutic advantage from combining the two modalities.

Introduction

Clinical studies in the U.K. with interferons in cancer are still at an early stage of development. This report records the studies that are currently in progress and discusses their objectives; it does not provide data upon which to base a definitive judgement on the value of interferons in the treatment of malignant disease.

There have been no formal studies in cancer, in Britain, with IFN-β's. Two centres are at present investigating recombinant interferons. Professor Crowther's unit in Manchester is assessing the toxicity of escalating doses of an IFN-α given by intramuscular injection, material being provided by Schering-Plough. Dr Sikora's group in Cambridge is monitoring the efficacy and safety of an IFN-α given to patients with advanced breast cancer. Two different dose schedules are being used, 50 Mu† daily or 86 Mu three times each week, all by intramuscular injection. The material for this study has been provided by Hoffmann-La Roche. Both these assessments are at a very early stage and as yet there are no results to report from them.

The human lymphoblastoid preparation, provided by the Wellcome Research Laboratories, has been the interferon most extensively evaluated in this country to date. Details of its production and purification have been given elsewhere (Finter & Fantes 1980). In brief, the material is prepared from Namalwa cells stimulated by Sendai virus. After purification the final preparation contains a mixture of at least eight different IFN-α's (Allen & Fantes 1980) and has a purity of greater than 80 % as estimated by both biological assays and G-75 Sephadex profile (N. B. Finter, personal communication). Studies in progress with this agent include assessments of dose and toxicity (phase 1) and evaluations of efficacy (phase II), in a range of tumour types.

† Units with reference to MRC 69/19 standard.

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Phase I studies

The initial evaluation of lymphoblastoid interferon was designed to determine a safe dose regimen for intramuscular injection, and the results of this study have been published previously (Priestman 1980). Although this trial was primarily concerned with monitoring toxicity, evidence of therapeutic response was noted in two of nine patients who received from 4 to 12 Mu daily for a period of 30 days. In one case a patient with lymph node metastases from a malignant melanoma experienced a greater than 50 % reduction of all measurable disease having previously relapsed on conventional cytotoxic drug therapy. The regression was sustained for a period of 6 weeks after the cessation of his interferon therapy. The second patient had a haemorrhagic gastric carcinoma resistant to chemotherapy. Interferon administration resulted in a 30 % shrinkage in the size of the tumour and arrest of the bleeding, as monitored by serial gastroscopy. This minimal response was, however, short-lived, lasting for only 2 weeks after completion of his 30 day course. A third patient is worthy of comment. He was a young man with advanced Hodgkin's disease who was failing to respond to cytotoxic drug therapy with cyclophosphamide and bleomycin (having previously relapsed on more conventional régimes). He received a 30 day course of interferon and at the end of that time there was no change in his disease. Two weeks later he recommenced cyclophosphamide and bleomycin, at similar doses to those given previously, and promptly went into a complete clinical remission which was sustained for a period of 12 months.

In parallel with the study of intramuscular administration an assessment of toxicity after intravenous injection was carried out at the Imperial Cancer Research Fund unit at St Bartholomew's Hospital (Rohatiner *et al.* 1981). The first two patients in this series were given intravenous bolus doses of the Wellcome preparation of 5 Mu m^{-2} body surface area and experienced marked toxicity. As a result of this subsequent doses were given by intravenous infusion over a 24 h period. When given in this way, although minor side-effects were noted, dose-limiting toxicity (comprising convulsions, hypocalcaemia and hyperkalaemia) was not reached until more than 300 Mu per day was infused. This contrasted with the maximum tolerated dose of approximately 12 Mu per day in the intramuscular study. The infusions were given mainly to patients with haematological malignancy, treatment being continued for 5–10 days. Six patients with acute leukaemia showed a decrease in the number of circulating leukaemic blast cells and in one patient with acute myeloid leukaemia the degree of bone marrow infiltration was also reduced from 99 % blasts to less than 5 %, this remission being sustained for approximately 2 months (A. Z. S. Rohatiner, personal communication). These results do not provide any evidence that high-dose intravenous therapy is any more effective than low-dose intramuscular administration but they do suggest a degree of activity for interferons in acute myeloid leukaemia and further studies are planned at the I.C.R.F. unit to define precisely the role of interferons in the management of this condition.

Intravenous infusion over a 24 h period is a relatively inconvenient procedure for routine use. We have recently explored the possibility of shorter infusion times with the cooperation of a patient with advanced breast cancer. Table 1 shows the dose schedules used. When the infusion time was reduced below 3 h, toxicity, in the form of rigors and transient hypotension, became unacceptable. This anecdotal observation suggests that infusion times of less than 24 h may be practical. Whether such infusions would be as effective, given that high blood levels of interferon would be achieved intermittently rather than sustained continuously,

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remains to be demonstrated. Certainly the patient we treated had no obvious benefit from her infusions.

Phase II studies

Table 2 lists the studies currently in progress and the results so far. I am grateful to the investigators listed for their permission to quote their unpublished results. The tumour types were selected for evaluation either because there had been evidence from studies elsewhere, with other preparations, that interferons might have activity or because there was no recognized systemic therapy for the condition and any evidence of a response to treatment would be of interest or, finally, because there were highly sensitive markers of disease that would accurately reflect even minimal tumour destruction resulting from interferon administration.

Table 1. Intravenous infusion of short duration in one patient

date	total dose/Mu	infusion duration/h planned	actual
7. i. 82	20	12	12
13. i. 82	25	6	6
20. i. 82	30	3	3
27. i. 82	35	1½	3
3. ii. 82	20	3	3

Table 2. Summary of phase II studies in cancer in the U.K.

tumour type	investigator and centre	prior chemotherapy	patient numbers entered	evaluable	responses
kidney, adenocarcinoma	Retsas, Westminster	no	8	6	(2)
stomach, adenocarcinoma	Priestman, Birmingham	no	1	0	—
lung, oat-cell carcinoma	Bleehen, Cambridge	no	6	5	0
melanoma	Retsas, Westminster	yes	16	16	1
myeloma	Galton, Hammersmith	yes	5	4	0
ovary, adenocarcinoma	Kirby, Cardiff	yes	2	2	0
testis, teratoma	Newlands, Charing Cross	yes	3	3	1
choriocarcinoma	Newlands, Charing Cross	yes	4	4	0

With the exception of oat-cell carcinoma, in those conditions where cytotoxic or hormonal treatment was known to be of value, patients were only considered for entry into the studies when they had failed to respond to, or relapsed on, these more conventional forms of treatment. This meant that either by virtue of the type of tumour treated, or the stage of disease, or both, the interferon was being asked to succeed where all other forms of treatment had failed. This fact should be borne in mind in considering the results of the studies so far.

In all the trials, apart from the oat-cell carcinoma series, the dose regimen was 4 Mu per day, by intramuscular injection, for a period of 30 days, followed by Mu three times each week until there was evidence of relapse. In the oat-cell study patients were given 50 Mu m^{-2} by 24 h intravenous infusion for 2 days and, if this was well tolerated, the dose was increased to 100 Mu m^{-2} for a further 3 days. This was then followed by intramuscular maintenance therapy with injections of 4 Mu three times each week.

So far only the melanoma study has completed patient entry and some of the early results have already been reported (Priestman *et al.* 1981). Sixteen patients were entered into the trial, ten males and six females, with a median age of 50 years (range 19–79). All but one had

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received prior cytotoxic therapy with imidazole carboxamide, vindesine and other agents. Three patients had soft tissue (skin or lymph node) metastases only, the remainder all had visceral disease. The only responder was a woman of 49 with multiple cutaneous in transit metastases on the right leg. The tumour nodules resolved completely leaving only a grey pigment stain on the skin and the remission was sustained for 8 months before new cutaneous lesions appeared. It was only at this stage that the pigment stains at the site of the earlier nodules were biopsied and the sections showed residual tumour cells. Similar results have been reported in a study with Finnish leucocyte interferon in malignant melanoma where only one of 35 patients responded, that patient also had only cutaneous disease (Krown *et al.* 1981). In the light of these results it seems reasonable to conclude that interferons appear to have minimal activity in advanced malignant melanoma but their therapeutic efficacy is no greater than that of conventional agents. In addition all the responses seen have been in soft tissue disease and there has been no evidence of activity in the more serious visceral metastases.

Three points should be made about the remaining phase II studies at this time. Firstly, the results of the oat-cell series are, so far, disappointing in that they fail to show any benefit from high-dose interferon therapy used as first-line treatment in a tumour that is particularly chemosensitive, about 50 % of patients gaining a remission with conventional cytotoxics. By contrast, in the renal cell carcinoma study, two patients who have been on treatment for less than 2 months are showing evidence of response although this has not yet reached the stage of 50 % regression of tumour necessary to claim a true partial response. If these patients, both of whom have lung involvement, do achieve a remission then that would represent a significant result for interferon in view of the virtual absence of any effective therapy for this tumour once it has metastasized. The final point is that two patients in these series had unexpectedly good results with cytotoxic therapy after the failure of interferon. This observation, coupled with the patient noted in the initial series, who had Hodgkin's disease and subsequently responded to the same drugs on which he had previously been deteriorating, raises the possibility that administration of interferon might alter the sensitivity of tumours to conventional drugs. Although one could argue that the period during which the patient is not receiving chemotherapy allows changes to take place in the chemosensitivity of the tumour cells that would have occurred whether or not interferon was given, the possibility that interferons might play an active role in modifying the response to cytotoxic agents is still worth exploring.

Combined modality study

There have been several reports of animal studies where the combination of interferons with conventional cytotoxics has given better results than either modality alone (Chirigos & Pearson 1973; Gresser *et al.* 1978; Slater *et al.* 1981). The final study considered in this report was designed to establish whether lymphoblastoid interferon could safely be given in combination with an established cytotoxic drug regimen and whether there was any therapeutic benefit in combining the two forms of treatment. In view of the responses seen with leucocyte interferon in advanced breast cancer (Gutterman *et al.* 1980) it was decided to use this as the target tumour. The drug schedule is outlined in table 3, the regimen being based on a schedule which gave responses in about 50–60 % of women (Edelstyn *et al.* 1975). Patients enter the study when they fail to respond to, or relapse on, conventional endocrine therapy. They are then stratified according to menopausal status and extent of disease (localized; confined to the chest wall or

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TABLE 3. TREATMENT REGIMEN IN COMBINED MODALITY STUDY IN BREAST CANCER

day 1	day 8
cyclophosphamide, 500 mg	cyclophosphamide 500 mg
5-fluorouracil 1 g	methotrexate 50 mg
vincristine 1 mg	vincristine 1 mg
hydrocortisone 100 mg	hydrocortisone 100 mg

All drugs given intravenously, cycles repeated every 28 days, with or without lymphoblastoid interferon, 4 Mu daily by intramuscular injection for 30 days, followed by 4 Mu three times each week thereafter.

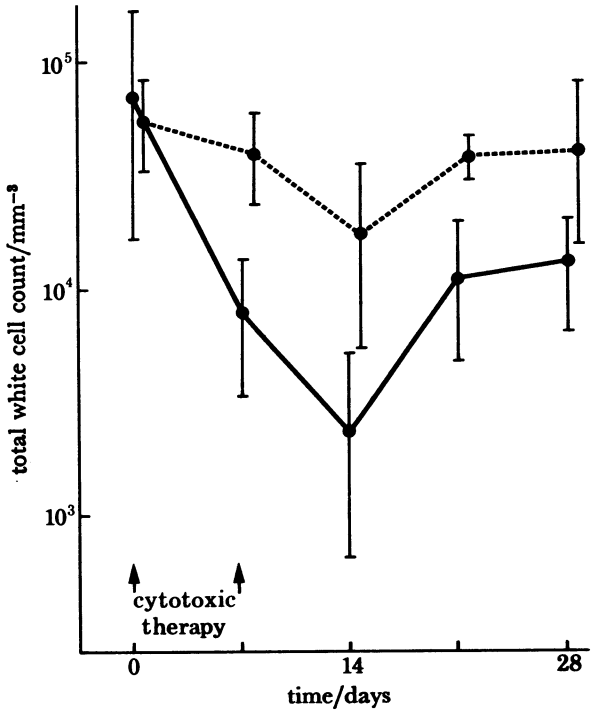

FIGURE 1. Total white blood cell counts (means and standard deviations) of patients receiving cytotoxic drugs alone (- - -, $n = 5$) or cytotoxic drugs plus lymphoblastoid interferon (——, $n = 6$).

local lymph nodes, generalized; involvement of bone, brain, lung or liver) and randomized to receive either cytotoxic drugs alone or cytotoxics plus interferon. This trial is being co-ordinated by Dr Richard Ashford at the Westminster Hospital in London. To date only eleven patients have completed more than 1 month of treatment. There has been no excessive subjective toxicity in the group receiving interferon but there have been differences in haematological tolerance between the two treatment arms. The means and standard deviations for the total white cell counts of the two groups are shown in figure 1. Although the numbers are too small for any formal analysis there is a suggestion that bone marrow suppression is, not surprisingly, greater in the combined treatment arm. In two instances this necessitated an interruption in interferon administration for a few days in the fourth week of treatment and a reduction in the cytotoxic dose at the time of the second course. The very early data, however, suggest that once the patient progresses to three times weekly injections of interferon there is no further haematological problem. In terms of therapeutic response there have been no

remissions in patients receiving cytotoxics alone, whereas in the combined treatment group two patients have already achieved a partial response and a third is showing evidence of regression although this is too early to assess formally. These results are probably best interpreted as showing that there is no obvious deleterious effect from combining interferon with conventional cytotoxics, rather than suggesting that there is an actual therapeutic advantage.

Interim observations

The word conclusions has been deliberately avoided because at this time the studies to determine the efficacy of interferons in cancer are still at a very early stage in this country. The following statements summarize our present findings.

1. Low-dose intramuscular administration has resulted in isolated responses but there is no evidence to suggest that the results will be any better than with conventional agents.
2. High-dose intravenous therapy with infusions of 100 Mu m^{-2} is possible but it remains to be demonstrated whether the higher blood levels of interferon achieved will be reflected in increased response rates.
3. Lymphoblastoid interferon may be combined with conventional cytotoxics without undue toxicity.
4. The possibility that prior therapy with interferons may alter the response of tumours to cytotoxic drugs deserves further exploration.

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Discussion

In discussion it was pointed out that high doses of interferon may impair the immune response and it may be important to choose dosages separately for trials in which it is planned to reduce cell populations acutely and those in which the object is long-term immune suppression of the tumour.

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