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Alpha Interferon: The Potential Drug of Adjuvant Therapy: Past Achievements and Future Challenges

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This paper aims to summarize current experience with alpha interferon and provide direction for future study. There are four areas in which alpha interferon has proven or potential activity: antiviral, premalignant, adjuvant and advanced disease settings. The three main viral diseases in which interferon alfa-2b has been shown to have activity are chronic viral hepatitis, acquired immunodeficiency syndrome, and human papilloma virus infections. *In vitro* studies suggest that alpha interferon may inhibit transformation of some premalignant conditions into malignant disease; e.g., vaginal intraepithelial neoplasia. In the adjuvant setting, it is possible that a biological response modifier, such as alpha interferon, may have a role in helping the immune system to destroy residual tumour cells following tumour bulk reduction with radiation or chemotherapy. A higher response rate has been seen in patients with small tumour bulk compared to those with large tumour bulk (e.g., malignant melanoma, ovarian carcinoma), and in patients with early, rather than late, disease (e.g., chronic myelogenous leukaemia, hairy cell leukaemia, multiple myeloma, non-Hodgkin's lymphoma). This may be due to efficacy in a small tumour bulk setting or due to an immunoadjuvant role. In advanced disease, the question is how best to exploit the possible synergistic effects between alpha interferon and other therapeutic modalities. The optimum dose, schedule and patient populations for combined treatment have yet to be determined. The major objective of this paper is to determine how best to capitalize upon the current state of knowledge to build for future trials of alpha interferon, and to determine whether the existing data suggest an adjuvant role for interferon after initial tumour regression.
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INTRODUCTION

THE PURPOSE of this paper is to review in summary form the uses of alpha interferon over the past 10 years, and to provide the foundation and direction for future efforts. In order to accomplish this, one must first ask why a compound with pleiotropic biological effects can be utilized both as an antiviral therapy and as an antineoplastic drug. A model of carcinogenesis may help to explain this (Fig. 1).

If one accepts the premise that a neoplasm proceeds through various stages, then a proposed role for alpha interferon is demonstrated in Fig. 2. In this model of tumour progression, those conditions to the left are disease states in which alpha interferon either has an established active role or preliminary evidence is highly suggestive of activity. Those diseases to the

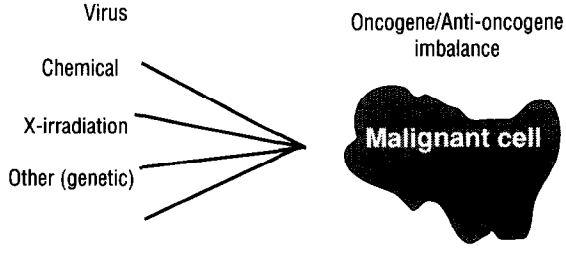

Fig. 1. Model of carcinogenesis.

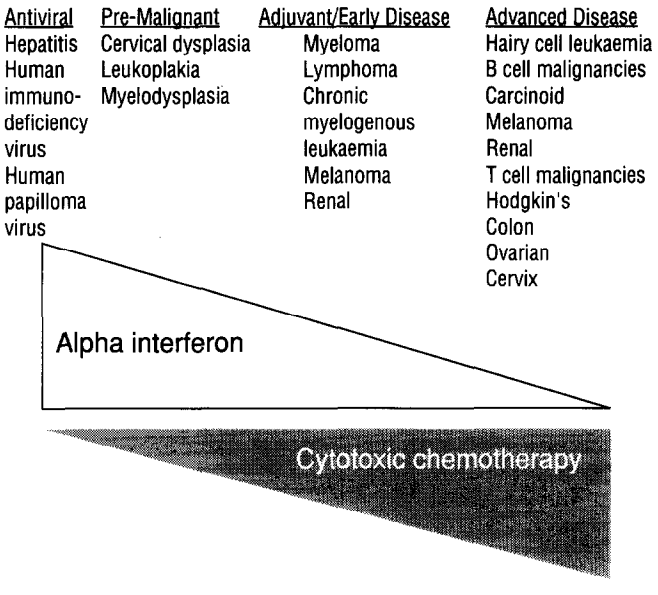

Fig. 2. Role of alpha interferon in a model of tumour progression.

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right of the figure are conditions in which interferon has activity, albeit low in some cases. Cytotoxic chemotherapy and/or other antineoplastic modalities such as radiation or surgery form an interface with alpha interferon on the right side of Fig. 2.

Is this model speculative or is there evidence to support it? This paper will examine all four areas: antiviral, premalignant, adjuvant and advanced disease settings.

ANTIVIRAL INDICATIONS

The three main viral diseases in which alpha interferon has been shown to have activity are chronic viral hepatitis, acquired immunodeficiency syndrome (AIDS), and human papilloma virus (HPV) infections.

In several trials investigating the efficacy of interferon alfa-2b for lowering serum alanine aminotransferase (ALT) levels in patients with chronic non-A, non-B (NANB) hepatitis, the overall response rate was 54% with 3 million units (MU), 32% with 1 MU, and 11% in untreated or placebo controls (3 MU versus control, $P < 0.001$) [1]. These data are quite encouraging and it will require the test of time to determine whether this improvement in chronic hepatitis will translate into a lower frequency of malignant transformation to hepatocellular carcinoma.

Another virus under intense study is the human immunodeficiency virus (HIV). *In vitro* work by Berman *et al.* [2] has demonstrated that a 95% viral inhibition required 0.11 μmol/L of azidothymidine (AZT) or 1060 U/mL of alpha interferon, a dose that is clinically unachievable because of the resulting toxicity. When alpha interferon was combined with AZT, however, there was a nine-fold reduction in the amount of AZT and a 56-fold reduction in the interferon dose required to achieve 95% viral inhibition. This brought the interferon dose down to 19 U/mL, a clinically achievable amount. The synergy observed in this instance suggests that alpha interferon may have additive or synergistic effects when combined with other cytotoxic agents [2]. Similar *in vivo* models have been published [3]. In a manner analogous to the cancer model, alpha interferon is now being studied in advanced states of AIDS, such as Kaposi's sarcoma (KS), or earlier states, such as HIV positivity but without the full complex of AIDS. In KS, for example, late-stage patients or those with a severe defect in the immune system have a lower response rate than those with earlier-stage disease or those with relatively intact (T4 cells > 200 cells/mm^2) immune systems [4]. Recent work by Lane *et al.* suggests that early intervention after seroconversion will lead to loss of p24 antigenaemia and possibly prevention of progression to full blown AIDS [5]. While encouraging, these data require further follow up and additional confirmation.

Finally, another viral infection worthy of discussion is the human papilloma virus (HPV), most notably because of its association with cervical dysplasia and cervical carcinoma. Work has been published on the use of alpha interferon in the treatment of genital infections with HPV types 6/11 and 16/18 [6]. Out of 18 patients, 17 responded to treatment with alpha interferon 10 MU/day for 6-12 weeks.

In another trial [7], patients with vaginal intraepithelial neoplasia or condyloma were randomized to receive either laser therapy alone, or laser plus 5-fluorouracil (5-FU), or laser plus alpha interferon. Only two of 34 patients receiving laser plus alpha interferon were treatment failures, compared to nine of 34 on laser alone and nine of 35 on laser plus 5-FU [7]. Long-term study will be required, however, to determine whether or not prevention of this premalignant lesion will prevent the occurrence of vaginal/cervical carcinoma.

The activity of other alpha interferons in cervical carcinoma has not been well studied. Preliminary reports with small numbers of patients suggest moderate antineoplastic activity [8-10].

PREMALIGNANT INDICATIONS

Studies comparing the *in vitro* effects of alpha, beta and gamma interferons on the differentiation of various cell lines have demonstrated that alpha interferon increased differentiation in three of the four haematopoietic and non-haematopoietic cell lines tested. In addition, in two systems looking at the C-Ha-*ras* oncogene, alpha interferon has been observed to inhibit the RT4 cell line, and beta interferon to inhibit 3T3 cells. There are also several reports in the literature on the ability of various interferons to inhibit c-*myc* oncogene expression. This effect appears to occur independently of interferon's ability to inhibit cell proliferation. Is it possible, therefore, that interferon might inhibit transformation of a premalignant condition into a malignant disease? The example of vaginal intraepithelial neoplasia has been mentioned previously, and a number of other studies have been carried out to investigate the clinical activity of various interferons in such conditions. Beta interferon, for example, has been shown to be active in oral leukoplakia, and alpha interferon in actinic keratosis, and possibly myelodysplastic syndromes [11-19]. This entire area remains unexplored and much work needs to be performed.

ADJUVANT TREATMENT

In addition to the above evidence, there is a mathematical reason why alpha interferon might have activity in early malignancy. According to the classic textbook model of malignant growth, a tumour of 1 or 2 cm diameter at diagnosis already has 10^9 cells. A tumour that doubles in size only three or four times reaches 1 kg in weight and most patients will not survive. Chemotherapy and radiation therapy seem to act by log kill and it is suggested that once the tumour is largely eradicated, the immune system is then activated to destroy any residual tumour cells. One could therefore speculate that there is a potential role for various biological response modifiers, such as GM-CSF, interleukins or alpha interferon in the adjuvant setting, once the tumour bulk has been reduced.

Early evidence for such a role emerged from a trial of interferon alfa-2b in malignant melanoma, in which it was observed that patients with small (≤ 1.5 cm) tumour bulk, i.e., dermal or soft tissue metastases, had a higher response rate (8/26; 31%) than patients with large (≥ 3.5 cm) tumour bulk (1/18; 6%) [20]. A second trial was then carried out using intraperitoneal interferon alfa-2b in patients with ovarian carcinoma [21]. Again, it was observed that three out of five patients with microscopic disease had a complete response, compared to no responses among four patients with tumour bulk greater than 5 mm.

Additional evidence came from the trial by Talpaz *et al.* in which alpha interferon was used for the treatment of patients

with chronic myelogenous leukaemia (CML)[22]. When patients were divided into low-, intermediate- and high-risk categories, the response rates were, respectively, 59%, 44%, and 0%. When responses were analyzed in relation to time from diagnosis, the best responses were again seen in early disease. Looking at the results with alpha interferon in a range of malignant diseases, the response rates are uniformly better in early than in advanced disease (Table 1)[4,23-39], reinforcing the potential for alpha interferon as adjuvant therapy.

Table 1. Approximate response rates (%) to alpha interferon in relation to disease stage.

Disease	Early	Advanced
Hairy cell leukaemia [23,24]	80	50-70
Multiple myeloma [25-27]	50	20-40
CML [28-32]	70	40
Non-Hodgkin's lymphoma [33-35]	50	30
Kaposi's sarcoma [4,36,37]	40	20
Renal cell carcinoma [38,39]	—	20

One of the first studies to investigate this idea further was a randomized trial comparing the effect of maintenance therapy after remissions in patients with small cell lung cancer [40]. Patients received alpha interferon versus CAP (cyclophosphamide/doxorubicin/platinum) or no treatment. At the 1-year survival point, 55% of interferon-treated patients were alive, compared to 45% on CAP and 19% on no treatment. Two years later, however, the difference in survival did not achieve statistical significance. The Southwest Oncology Group has also undertaken a trial to try and establish whether or not there is a role for interferon as adjuvant therapy in small cell lung carcinoma patients after achievement of response.

Another trial has been performed evaluating the potential of alpha interferon for the prevention of cytomegalovirus (CMV) infection in allogeneic bone marrow transplantation for acute leukemia. In this study, CMV infection was slightly but not significantly lower in the interferon-treated group (21/39 patients) than in the control group (28/40 patients). The most interesting aspect of the trial, however, was the very low probability of relapse observed in the interferon group compared to control patients ($P = 0.008$) [41]. This, again, is consistent with the possibility that alpha interferon would work in an adjuvant setting after initial treatment.

A recent study on interferon as adjuvant therapy in multiple myeloma has also shown prolonged response and increased survival [42]. Similarly, fewer relapses have been observed in non-Hodgkin's lymphoma patients who received alpha interferon as maintenance therapy following remission induction with chemotherapy [43].

These preliminary data in diseases as diverse as CML, acute leukaemia, myeloma, and small cell lung cancer are most suggestive of an adjuvant role for alpha interferon in a variety of settings. This information has been seized upon by the medical community and, at present, there are no fewer than 10 different clinical trials in myeloma, lymphoma, melanoma, CML, renal cell carcinoma, head/neck carcinoma and ovarian carcinoma, which explore the potential usefulness of interferon alfa-2b as an adjunct after primary treatment.

ADVANCED DISEASE

While the aforementioned uses of alpha interferon are encouraging, most patients, unfortunately, present with advanced disease. The question then is how best to combine alpha interferon with other therapeutic modalities which have a more established role. The possibility of synergy between agents first emerged from a xenograft model of P-388 leukaemia implanted into mice [44]. Post implant, mice received alpha interferon alone, cisplatin alone or a combination of the two agents; it was demonstrated that survival was prolonged in comparison to the control untreated group. The most significant survival was in those mice receiving both agents [44]. In another study in a xenograft model of breast carcinoma, a combination of interferon plus cyclophosphamide completely eradicated the tumour [45]. A similar finding has been observed with irradiation and interferon [46]; in some studies the combination achieved additive effects and in others there was synergy.

There are several ways in which alpha interferon might interact with a cytotoxic agent. Firstly, interferon inhibits P450 and might therefore alter the metabolism of the cytotoxic agent. Secondly, alpha interferon affects cell cycling and this may have an impact upon the schedule of administration with the cytotoxic agent. Thirdly, interferon itself can affect various metabolic enzymes (e.g. thymidilate synthetase). Interferon can augment immune effector cells, which may in some way interact with cytotoxic agents. Finally, membrane transport of drugs is critical and alpha interferon clearly affects membrane antigen expression and possibly p glycoprotein levels.

The literature is now full of *in vitro* and *in vivo* information on such synergy and the reader is referred elsewhere for a more comprehensive review [47, 48].

Trials have been done with 5-FU, cyclophosphamide, cisplatin, etoposide, melphalan, doxorubicin, radiation and others. Are there any principles that can be evolved in terms of how to combine these agents? First, the dose-limiting toxicity has almost always been flu, fatigue and leucopenia, regardless of the agent being used. Importantly, the toxicities that are seen when alpha interferon is combined with any cytotoxic agent are similar to what would be expected with either agent alone; that is, the toxicities are additive and not synergistic. Second, the doses of interferon have been kept relatively low (1-10 MU/day).

One of the more interesting combinations to receive attention recently is alpha interferon and 5-FU. Clinical trials have been undertaken to explore this combination in patients with gastrointestinal malignancy. All of these trials have illustrated the two principles elucidated above, i.e., low dose of interferon and no alteration of toxicity [49-54]. In previously treated patients, response values ranged from 14-17%, and in previously untreated patients from 30-76%. The overall response rate is 33% (Table 2).

This is consistent with prior sections of this discussion in which alpha interferon's greatest potential appears to exist in early disease states. Yet to be determined are the optimum

Table 2. Studies of alpha interferon plus 5-fluorouracil (5-FU) in patients with colorectal carcinoma

Investigator	IFN dose (MU)	5-FU dose (mg/m^2)	*n*	CR	PR	% responding	Prior treatment: Yes	Prior treatment: No
Clark *et al.* [49]	5-20 t.i.w.	250-500 bolus x 5	14	0	2	14	X	
Kreuser *et al.* [50]	2 t.i.w.	700 bolus b.i.w.	6	0	1	17	X	
Wadler *et al.* [51]	9 t.i.w.	750 x 5 CIV	17	1	12	76		X
Kemeny [52]	9 t.i.w.	750 x 5 CIV	34	0	9	26		X
Huberman *et al.* [53]	9 t.i.w.	750 x 5 CIV	8	0	3	38		X
Pazdur *et al.* [54]	9 t.i.w.	750 x 5 CIV	22	1	6	32		X
Total			101	2	33	33		

IFN = interferon; CR = complete response; PR = partial response; t.i.w. = three times weekly, b.i.w. = twice weekly; CIV = continuous intravenous infusion

dose, schedule and population of patients in which this combination of agents may be of use.

SUMMARY AND FUTURE CHALLENGES

It has been the purpose of this discussion to lay the foundation for the presentations that follow in this supplement. In so doing, there are certain challenges which remain. The first major challenge for interferon alfa-2b in the coming years is to establish in which disease states and to what extent the agent has a role in the *adjuvant* treatment of malignancy. There is certainly preliminary encouraging evidence in myeloma and possibly lymphoma; it remains to be seen whether these results are generally applicable to other malignancies.

The second challenge is a more difficult one to define, and one question inevitably leads to many others. Why, for instance, would an antiviral compound have antineoplastic activity? If synergy between interferon and one cyclic nucleotide (AZT) can occur, can such synergy, which is clearly demonstrable with other antineoplastic agents *in vitro,* be carried into the clinic for patients with advanced disease?

Finally, the potential of interferon alfa-2b in AIDS has not been fully explored. It has activity in Kaposi's sarcoma. However, in approaching AIDS, the model used in malignancy should be applicable, i.e., clinical trials in advanced disease, in newly diagnosed patients, or in an adjuvant setting should all be undertaken in order to explore this agent's full potential.

In the papers that follow, the reader should try to ascertain where the data presented fit into the model proposed Fig. 2. Hopefully, this will permit the reader to build a foundation upon which to conceptualize the data.

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