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Special Article

Interferons in Oncology: Current Status and Future Directions*

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Abstract—*The European School of Oncology has formed a study group to consider the present status of interferons in oncology. This position paper summarizes the discussions and conclusions of the first meeting of this study group.*§§

CLINICAL TRIALS

REVIEWING the results of clinical trials performed to date it is clear that the majority of data pertain to the use of interferon alphas with only very recent data on the use of interferons beta and gamma. The current status of interferon alpha activity in a variety of malignant diseases can be grouped into three categories as summarized in Table 1. For a number of those, for instance hairy cell leukaemia and certain non-Hodgkin's lymphomas, there is now clear evidence of activity when interferons have been administered systemically. Interferon alpha may also have activity against bladder cancer and ovarian cancer when applied locally by the intravesical or intraperitoneal route. On its own interferon alpha is clearly inactive for several diseases, such as breast cancer and colon cancer, whereas for diseases such as renal carcinoma, melanoma and small cell lung carcinoma the data are as yet inconclusive and further studies are required.

Table 1. *Activity of alpha-interferon against various malignancies in phase II studies*

Active	Hairy cell leukaemia
	Chronic myelogenous leukaemia
	Non-Hodgkin's lymphoma
	Cutaneous T-cell lymphomas
	Kaposi's sarcoma
	Multiple myeloma
	Malignant melanoma
	Bladder cancer (intravesical)
	Ovarian cancer (intraperitoneal)
Inactive	Breast cancer
	Colon cancer
	Non-small cell lung cancer
	Prostate cancer
	Acute myelogenous leukaemia
Further study required	Chronic lymphocytic leukaemia
	Acute lymphocytic leukaemia
	Hodgkin's disease
	Osteogenic sarcoma
	Astrocytoma
	Renal cell cancer
	Small cell lung cancer

In phase II studies of interferon alphas, a wide variety of doses, schedules and routes of administration have been used. The optimum method of administration remains unresolved but some preliminary conclusions appear warranted. Pharmacokinetic studies show clear differences in

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the peak plasma concentrations and areas under the curve between different routes of administration (intravenous, intramuscular, subcutaneous). Following a short intravenous infusion, peak serum levels of interferon alpha are achieved with 15–30 min with a subsequent 2 hr half-life, serum levels returning to normal by 4 hr. Following subcutaneous or intramuscular injection, peak levels are attained with in 3–4 hr with detectable levels preserved for 8–12 hr following administration.

In clinical studies of myeloma and melanoma it has been observed that the time to reach clinical response is long in comparison with the time to response to conventional cytotoxic drugs. In hairy cell and chronic myelogenous leukaemia at least 6 months of therapy appear to be necessary to obtain maximum effects on bone marrow improvement. It is also clear that toxicity is partly dose- and schedule-related. This applies both to the common "flu-like" symptoms of fever and malaise but most particularly to the neurotoxicity seen.

Whereas toxicity is partly dose-related, the relationship between tumour response and administered dose is less clear. A dose–response relationship has been suggested in Kaposi's sarcoma and possibly renal cell cancer. The available data concerning route of administration, dose and schedule suggest that the subcutaneous administration of alpha-interferon three times a week at doses < 10 million units/m^2 is to be recommended.

MECHANISM OF ANTI-TUMOUR ACTION

While it is clear that interferons can have anticancer activity in man, the mechanism(s) of this activity is as yet unknown. Interferons can alter a variety of biological responses in both the host and the tumour. For instance in experimental models and in man, interferon alphas enhance host NK cell and macrophage activity but there is no direct evidence to suggest that such enhancement results in a therapeutic effect. The major experimental evidence for a host role in the anticancer activity of interferons comes from studies with transplantable murine tumurs which are insensitive to direct effects of interferons *in vitro*. As the *in vivo* growth of such cells can be inhibited by the same interferons, a host role is suggested. However several experimental studies have failed to identify the nature of this host-mediated response and it is possible that a non-immune mechanism, such as depletion of local growth factors, could be responsible.

Interferons can have many direct effects on tumour cells that may be of importance in their anticancer activity. Following binding to specific cell surface receptors, interferons alter the synthesis of a variety of proteins in the cells. The production of some is induced *de novo* or enhanced; the production of others is inhibited. Of particular relevance is inhibition by interferons of the "competence" proteins cmyc and ornithine decarboxylase. These proteins are switched on by growth factors during G1 phase of the cell cycle. Other oncogenes, for instance ras, can be inhibited by interferons.

Enhancement of major histocompatability products and tumour-associated antigens may serve to increase host response to a tumour cell. Moreover long term *in vitro* therapy with interferons can induce differentiation and cause reversion from a transformed phenotype. Interferons can directly inhibit tumour cell growth both *in vitro*, as shown in tumour stem cell assays, or *in vivo* as shown with human tumour xenografts in nude mice.

Thus there is a wealth of experimental data to suggest that interferons can have direct effects on human tumour cells. Therefore we would emphasize the relevance of exploring clinical strategies involving localized treatment of tumours with interferons.

FUTURE CLINICAL STRATEGY

In addition to further exploration of regional therapy of interferons where applicable, we believe that there is potential for the adjuvant use of interferon alpha in melanoma, ovarian and renal cell carcinoma, and possibly small cell carcinoma of the bronchus. Preclinical data suggest that the efficacy of interferons is inversely related to tumour burden, and studies with hairy cell leukaemia have shown that long-term administration of low doses of interferon alpha is well tolerated.

Another area of interest is combination of interferons with cytotoxic drugs or other biological therapies. Experiments *in vivo* with experimental murine tumours and with human tumour xenografts have shown positive interactions between interferon alpha and chemotherapy. In human tumour xenograft studies, combinations of doxorubicin and interferon alpha have shown increased therapeutic activity against carcinomas of the breast and ovary; cyclophosphamide and interferon interacted synergistically against a breast carcinoma, and *cis*-platinum and interferon alphas showed synergistic activity against human lung cancer xenografts. The translation of these animal model data to the clinic, with appropriate dosage levels and scheduling of agents, will be of considerable interest. Concerning the direction of future research, experiments both *in vitro* and in experimental tumour models are necessary to work out the mechanisms of interaction between interferons and chemotherapy. In particular it is important to find out why interferons potentiate the activity of only some classes of cytotoxic drug.

Strong synergistic interactions have been seen between interferons and tumour necrosis factor *in*

vitro. Preliminary data from animal models, both murine and human tumour xenografts, indicate that this synergy may also be seen *in vivo*. When phase I/II testing of TNF is complete, combination trials of TNF and interferons in man should be considered.

There is also preclinical data on synergy between different interferons, and clinical trials are envisaged as more data become available on the clinical application of interferons beta and gamma. Important work should now be done in experimental models to look at mechanisms of these synergies and their dependence on schedule of exposure.

As regards the multiplicity of possible mechanisms of action, it will be important in future studies to attempt to correlate measurable *in vitro* effects with the results of clinical trials, for example to assess whether the presence of interferon receptors predicts for response clinically. This may be especially relevant in tumours such as melanoma where the results of interferon therapy are particularly heterogeneous. Related to the multiple mechanisms of actions, further work is required to try and identify why clinical responses (when they occur) tend to occur late in comparison with the effects of ionizing radiation or cytotoxic drugs. This type of response may indicate mechanisms of action of particular relevance to the biological activity of interferons against specific cancers.

In summary the study group consider that there are clear indications for the activity of interferons against a limited number of human tumours and inactivity against several of the common cancers. Further work is required on osteogenic sarcoma, astrocytoma and some of the lymphomas. It is now possible to recommend routes of administration and schedules but the complex genetic and biochemical events consequent upon exposure to interferons render it difficult at the present time to define which mechanism(s) is most relevant to the anticancer activity of interferons againt any specific tumours. The strong weight of evidence favouring direct antiproliferative effects does however emphasize the importance of exploring clinical strategies which intensify the local exposure of tumours to interferons. Future studies should concern themselves with regional treatments, with the assessment of adjuvant interferon therapy for refractory cancers such as melanoma and renal cell cancer, and with combinations of interferons with cytotoxic drugs or biological agents particularly against carcinoma of the ovary and carcinoma of the lung.