Guest Editorial*

Interferons as Antitumor Agents

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Introduction

Interferons are a group of proteins the amino acid sequences of some of which are defined (Derynck et al. 1980; Taniguchi et al. 1980). Other interferons, in particular the interferon gamma (IFNγ, formerly called immune interferon) are – at least presently – less well characterized. Interferons have many biologic effects (pleiotropic molecules) and, similarly to hormones, they are of great biologic activity, i.e., only minute amounts of interferon are required to cause most of the biologic effects caused by interferon. Among the latter are immunoregulatory effects, antiviral effects, and a host of effects on cellular metabolism and on cell membranes. It is therefore obvious that interferons are molecules that carry an enormous potential in many specialized areas of research.

Interferons appear to have antitumoral effects, at least in animal models (Gresser 1978). Two effects of interferon, in particular, are noteworthy in regard to its antitumoral effects: Interferons have a direct antiproliferative effect on tumor cells in vitro and they activate, both in vitro and in vivo, certain effector cells that have a known capacity to destroy tumor cells, i.e. macrophages and natural killer (NK) cells (Huang et al. 1971; Gidlund et al. 1978). Two additional effects of interferon are noteworthy. Recently, it has been shown that the expression of cell surface antigens is increased by treatment of the cells with interferon (e.g., Heron et al. 1978). The same may be true for “tumor antigens”, thus making the cells more vulnerable to the attack of killer cells. Furthermore, prolonged treatment of cells by interferon has been shown to partially reverse the malignant phenotype (Brouty-Boyé and Gresser 1981).

Thus, there are good reasons to test the effects of interferon in cancer patients. Interferons are proteins that naturally occur in the human body and have very high

biologic activity. They have proven activity in experimental animal tumors and they may act by several principles involving both direct effects on tumor cells and stimulatory effects on the defense systems of the body.

However, there have been two serious shortcomings for clinical application: (1) There has not been enough interferon of any type and (2) there has not been any preparation sufficiently pure to either rule in or out a beneficial effect of interferon on tumors in man.

Clinical Studies

Clinical studies on the effects of interferons as antitumor agents in man are few, and most of them are not completed. The most recent progress reports have been given at two International Meetings and will be published shortly (DeMaeyer et al. 1981; Munk and Kirchner 1982) – (see also Newmark 1981). It is my opinion that it is absolutely premature to specifically evaluate any of these studies, at this point of time. However, I believe it is very important to present a concept about the future trials with interferon since, owing to great investments of the pharmaceutical industries, one may anticipate that in the near future certain interferons will be available in quantities high enough for reasonably large clinical trials. It goes without saying that randomized controlled trials will be those to receive the majority of the materials available. It also goes without saying that these trials have to be backed up by careful investigations in the clinical laboratories to learn as much as possible about the effects of interferons, e.g., on the immune system as one of its prime targets.

As rightly pointed out by Lindenmann (1981), the clinical trials will have to be evaluated with the greatest care possible since after great investments of the pharmaceutical industries have been made there certainly is a danger of being biased for success.

Overall Status of the Human Cancer Trials

It is now quite clear that interferons have not led to miraculous cures of cancer. However, there have been a few totally unexplained individual cases in which interferon therapy was of clinical benefit and there have been objective, measurable responses in certain tumor patients (see the clinical reports in DeMaeyer et al. 1981 and Munk and Kirchner 1982). To make this very clear, these latter types of responses have not been of much benefit to the patients, and they were of less magnitude than one could obtain with other forms of therapy (this latter point is important and should be pointed out to the patients urging their physicians to receive interferon therapy).

However, the above mentioned studies do show that there are therapeutic effects of interferons. This is in fact surprising if one considers the lack of purity of the interferons used and the present lack of knowledge in all aspects where one ought to have knowledge in pharmacotherapy (dosage, schedule, pharmacokinetics, etc). One also does not know which interferons to use in therapy and which tumor types to select for interferon therapy and whether one should give interferon alone or in conjunction with other therapeutic agents. Thus, the fact that objective responses – albeit of relative little benefit to the patient – have been measured are surprising indeed.