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The Role of Interferons in the Treatment of Malignant Neoplasms

JOHN R. MURREN, M.D.,[a] AND ANTONIO C. BUZAID, M.D.[b]

[a]*Fellow, Medical Oncology,* [b]*Assistant Professor of Medicine, Section of Medical Oncology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut*

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Interferons (IFNs) are proteins with a wide range of biological effects. IFNs have antiviral and antiproliferative properties. They modulate both the immune system and the expression of cell phenotype. In the past decade, the IFNs have received intense clinical scrutiny. Alpha IFN is the best studied and displays activity in many neoplastic diseases; it has shown the most promise in the hematological cancers although several solid tumors, including epidemic Kaposi's sarcoma, renal cell carcinoma, and melanoma, respond. No neoplastic disease, however, has been cured by the IFNs. IFN seems to be most active in the setting of minimal residual disease, and clinical studies evaluating its role in the adjuvant setting are under way. Other areas of research include trials combining IFN with cytotoxic drugs or other biological response modifiers, and maintenance IFN to prolong remissions following successful induction therapy.

INTRODUCTION

Researchers recognized in 1957 that cultured cells exposed to heat-inactivated virus produced a substance that conferred cellular resistance to subsequent lytic viral infection [1]. This substance was named interferon (IFN) and was later shown to be a group of related protein cytokines produced by many different cells in response to viruses, ds RNA, and other agents. IFNs inhibit viral replication, modulate immune function, and have a direct antiproliferative effect on tumor cells. They are classified according to antigenic and physicochemical properties into three major types: alpha (leukocyte), beta (fibroblast), and gamma (immune) IFNs [2]. Many subtypes of alpha IFN have been characterized; these subtypes share a 75 percent homology in amino acid sequence and show some differences in biological activity [3].

Only one protein species has been identified for beta IFN; this protein shares a 29 percent homology of amino acid sequence with alpha IFN [4]. Beta IFN was originally obtained from stimulated fibroblasts, but, like alpha IFN, it can be produced by virtually any cell under the proper stimulus. Alpha and beta IFNs have been termed

Abbreviations: Ab: antibody ADCC: antibody-dependent cellular cytotoxicity BCG: bacillus Calmette-Guerin CIS: carcinoma in situ CLL: chronic lymphocytic leukemia CML: chronic myeloid leukemia CR: complete response CSF: cerebrospinal fluid CTCL: cutaneous T-cell lymphoma EKS: epidemic Kaposi's sarcoma HCL: hairy cell leukemia IFN: interferon IP: intraperitoneal LGNHL: low-grade non-Hodgkin's lymphoma M CARC: malignant carcinoid MEL: melanoma ME PANC: malignant endocrine pancreatic tumor MHC: major histocompatibility complex MM: multiple myeloma NK: natural killer NON-MEL SC: non-melanomatous skin cancer Ph^1: Philadelphia chromosome PR: partial response RCC: renal cell carcinoma TCC: transitional cell carcinoma

Address reprint requests to: John R. Murren, M.D., Dept. of Internal Medicine, Section of Medical Oncology, NSB-294, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06510

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type I IFNs because of their stability at low pH [4]. These IFNs bind to the same cell surface receptor [5].

Gamma IFN, produced by activated T lymphocytes, is labile in an acid environment and is called a type II IFN. The degree of homology between alpha and gamma IFN may be about 12 percent but is currently debated [6]. Gamma IFN has a cellular receptor distinct from the type I IFNs [7].

The first clinical trials of IFN involved a partially purified polyclonal mixture of alpha IFN produced by leukocytes obtained from banked transfusion blood [8]. In terms of IFN protein, this preparation was about 0.5 percent pure, extremely expensive, and available only in minute quantities. In 1975, Finter introduced a method for obtaining large amounts of natural alpha IFN from stimulated lymphoblastoid cells. This product contained many different subtypes of alpha IFN and has been marketed as IFN-a-nl [9]. Production of a single subtype of α IFN subsequently became possible through recombinant DNA technology. Two recombinant products, IFN-a-2a and IFN-a-2b have been marketed in the U.S.A. These IFNs differ in composition by only one amino acid and probably represent allelic variants of the same subtype [10]. The U.S. FDA recently approved the use of these two recombinant IFNs for the treatment of hairy cell leukemia (HCL) and Kaposi's sarcoma.

BIOLOGICAL ACTIVITY

Alpha IFN has numerous biologic effects which can be grouped into four major categories: antiviral [11], antiproliferative [2,12], immunomodulatory [13–15], and alteration of cell phenotype (including expression of tumor-associated antigens and oncogenes) [16–18]. These effects are mediated via specific cell surface receptors. The antiviral activity of IFN depends, at least in part, on the activation of endonuclease. This enzyme inhibits protein synthesis by cleaving viral and host RNA [19–23]. Other mechanisms proposed from cell culture data include impairment of 5'-methylation of newly synthesized RNA, inhibition of phosphodiesterase, and inhibition of virus maturation and budding [19,24].

The direct antiproliferative activity of IFN has been established both in cell culture and in immunodeficient nude mice. The mechanism for this effect has not yet been determined. Cell cycle changes prolonging each phase of the cell cycle and the overall cell generation time have been described [3] and result in cytostatic and possibly cytotoxic effects [25]. Some studies suggest that changes in cell cycle phases may result from DNA polymerase inhibition, from a loss of coordination between DNA replication and subsequent cell division [19], or from inhibition of the polyamine synthesis pathway [26]. Alternatively, IFNs may affect proliferation and differentiation via modification of oncogene expression. This modulation appears to play an important role in the normalization of cell growth and the disappearance of malignant characteristics [16,17,27–31].

Alteration of immune function includes effects on monocyte, neutrophil, natural killer (NK) activity, T-cell cytotoxicity, and B-cell immunoglobulin production. Various studies have yielded conflicting results as to the type of effect IFN has on these immune cells. The differences are due in part to a lack of standardization of assays used to measure immune function. Great disparity exists in how immune cells are collected, separated, stimulated, and cellular function measured [31]. Certain trends, however, are apparent in most studies, and these effects are listed in Table 1. IFN frequently inhibits immune cell function, and this effect may be related to its

TABLE 1
In Vivo Immunomodulatory Effects of Alpha IFN

Immune Component	Effect	Reference
B lymphocyte	Decrease in immunoglobulin production	[32,33]
T lymphocyte	Decreased proliferative response to mitogens and mixed lymphocyte culture	[31,32]
Monocyte	Increased Fc receptor-mediated phagocytosis	[31]
NK cell	Short-term increase usually followed by a decline in activity	[31–33] [34,35]
Antibody-dependent cellular cytotoxicity (ADCC)	Variable effect	[31,35]
MHC phenotype	Increased expression of class I and II antigens	[13]
Oncogene expression	Variable effect	[16–18,27–31,40–42]

ADCC, antibody-dependent cellular cytotoxicity; MHC, major histocompatibility complex

antiproliferative activity. IFN produces a decline in total lymphocyte count and suppresses immunoglobulin production [32,33]. NK cell activity falls within hours of an injection of IFN and then rebounds to levels above baseline one to three days after the first dose [34,35]. Repeated IFN administration, however, results in diminished NK activity in many, but not all, patients [31–33,34,35]. Future studies must clarify which immunological mechanisms are involved in the antitumor effect so that the dose and administration schedule of IFN can be optimized. Since many cancer patients have selective defects in immune function, it will also be of interest to determine if IFN can reverse these defects and if reversal produces a clinical response. In addition, it must be determined why chronic IFN exposure frequently produces hyporesponsive NK cells and whether secondary malignancies or other clinical sequelae result from this chronic immunosuppression.

The primary mechanisms of IFN antitumor action may be multifactorial and dependent on the tumor type [36]. In viral-associated tumors such as laryngeal papillomatosis and condyloma acuminatum, the antiviral effect of IFN may be involved [37]. Clonogenic assays and immunodeficient nude mice models support a direct antiproliferative effect rather than immunomodulation [38,39]. Inhibition of oncogene expression may be important in some malignancies such as HCL and chronic myeloid leukemia (CML) [40–42].

Beta and gamma IFNs share most of the biological effects of the alpha IFNs [43]. One important difference, however, relates to the expression of antigens of the major histocompatibility complex (MHC). Although all the IFNs increase expression of MHC antigens, gamma IFN is significantly more potent than the other IFNs in modulating the class II antigens [13]. Other important immunomodulatory effects of gamma IFN include stimulation of monocyte function [3] and promotion of microbicidal killing via superoxide generation [44].

DISTRIBUTION AND TOXICITY

IFNs are small protein molecules with molecular weights ranging from approximately 20,000 daltons for alpha and beta IFN to about 70,000 daltons for gamma

IFN. The pharmacokinetics of recombinant and natural alpha IFN are comparable [45–47]. Alpha IFN passes freely between the blood and extravascular pools. Cerebrospinal fluid (CSF) penetration is poor, with serum-to-CSF ratio varying from 67:1 to 1,100:1 [48–51]. Animal studies indicate that alpha IFNs are rapidly filtered by the glomeruli and catabolized in the renal tubules. Although alpha IFN is non-dialyzable, low-dose therapy in hemodialysis patients has not led to drug accumulation [52–54].

Intravenous administration of all three classes of IFN results in high peak concentrations followed by a rapid decline from the serum. Lower peak serum concentrations and longer serum half-lives can be obtained by using the intramuscular or subcutaneous routes. Using equivalent doses, intramuscular injection of alpha IFN results in peak serum levels that are only about 10 percent of the maximal levels observed after intravenous administration [55].

Most side effects of IFN are dose-dependent, more conspicuous in the elderly, and are reversible when treatment is stopped [56–58]. At the dose range recommended for HCL (3×10^6 U three times a week or less), side effects from IFN are usually mild. Studies evaluating high-dose IFN, with daily doses greater than 20×10^6 U, frequently result in severe toxicity requiring dose modification. Except for minor quantitative differences, it appears that the toxicities of beta and gamma IFN are similar to that of alpha IFN [59–63]. The most common adverse effect is an acute influenza-like syndrome seen in more than 95 percent of the patients [56–58]. In patients receiving IFN at least three times weekly, these symptoms usually decrease in intensity and dissipate within seven to ten days of continued therapy. They can recur though, if therapy is interrupted [58].

The other side effects of IFN are subacute or chronic. Common neurological effects include fatigue, weakness, anorexia, and an inability to concentrate. Large systemic doses ($>100{,}000 \times 10^6$ U daily) produce psychoses, confusion, seizures, and psychomotor retardation [64–66]. These effects have been the dose-limiting toxicities in the majority of clinical trials and do not tend to decrease with time [56–58].

Hematologic toxicity can be seen in all cell lines but is most pronounced in white cells. Leukopenia occurs consistently within hours after administration. A decrease of approximately 50 percent in the leukocyte count is frequently observed after the first week of treatment, but the count rapidly recovers once treatment is discontinued. This result and bone marrow studies suggest that IFN causes redistribution of the white cell population rather than myelosuppression [56–58,67]. Anemia due to IFN therapy is dose-related. When it occurs, it is usually normochromic, normocytic, and may require weeks to months for recovery [56–58]. Rare cases of Coombs' positive hemolytic anemia have been reported [58,68]. Interferon-induced thrombocytopenia is rare in patients with solid tumors but has been reported in 25–50 percent of patients with chronic lymphocytic leukemia and multiple myeloma [58]. A few cases of immune-mediated thrombocytopenia and coagulopathy induced by IFN have also been described [69–71].

Cardiovascular toxicities, such as tachycardia and hypotension, are usually related to the flu-like syndrome [58]. Effects on the gastrointestinal system (including nausea, vomiting, and diarrhea) are generally mild and occur in approximately one-third of patients. Elevation of hepatic transaminases is frequently seen but is rarely clinically significant. The most common renal toxicity is mild proteinuria [56–58], although rare cases of acute renal failure and nephrotic syndrome have been described [72,73]. The

most prominent dermatologic reactions are mild alopecia and transient skin rashes. The paradoxic profuse growth of eyelashes has also been seen [74].

Other rare side effects include autoimmune thyroid disease (hyperthyroidism and hypothyroidism), parotitis, epididymitis, pernicious anemia, and systemic lupus erythematosus [75–79]. IFN has also been shown to depress the drug-metabolizing hepatic cytochrome P-450 system and could potentially predispose to drug interactions [80]. Although this effect has not been of major clinical significance thus far, enhanced phenobarbital toxicity was reported in one case [81]. With the incorporation of interferon into multi-drug regimens, it will be important to remain vigilant for other potential drug interactions.

Since alpha IFN currently represents primarily a palliative treatment modality, special attention must be directed toward minimizing toxicity while not compromising efficacy. Administration of IFN at bedtime, preceded by acetaminophen and a benzodiazepine, improves patient tolerance by minimizing fever and chills and allowing patients to "sleep through" other potential side effects which often occur during the first week of therapy.

IFN NEUTRALIZING ANTIBODIES

Both natural and recombinant human alpha and beta IFNs can be antigenic in man [58]. The antigenic potential of gamma IFN is currently being evaluated but appears to be low. Factors affecting antibody (Ab) formation include the dose and schedule of IFN and the type of malignancy. Peak Ab titers occur five days following cessation of IFN therapy. Depending on the type of assay used, Abs are detectable in 2.5–25 percent of patients. Controversy exists as to the relative antigenicity of the two approved recombinant IFN preparations. Differences determined in some studies may simply reflect differences in the sensitivities of the Ab assay employed [57,82,83]. Some Abs induced by one recombinant IFN cross-react with the other recombinant preparation. *In vitro* studies, however, show no cross-reactivity of recombinant IFN Abs with partially purified natural IFN [24].

The clinical relevance of neutralizing antibodies remains unclear. Reports of patients whose response was potentially shortened due to antibody formation, however, are increasing in the literature [58,83–85]. Steis et al. [24] recently reported on 51 hairy cell leukemia patients treated with recombinant alpha IFN. Of the 16 patients who developed neutralizing antibodies in this series, six also became clinically resistant to IFN. This result suggests that in some cases clinical resistance to IFN may be through the development of IFN-neutralizing antibodies. Other mechanisms for resistance must also occur, however, since the presence of antibodies does not necessarily signal the end of a clinical response.

CLINICAL APPLICATIONS IN ONCOLOGY

Although alpha IFNs have been extensively used in the clinic, the experience with the other IFNs has been restricted to a relatively few phase I and phase II trials. Thus far, neither beta nor gamma IFN has shown more activity than alpha IFN. Figures 1 through 3 summarize the results reported for malignancies in which IFN has been extensively evaluated. For solid tumors and lymphomas, responses are defined in the standard fashion: a complete response (CR) indicates disappearance of all evaluable tumor, and a partial response (PR) means more than a 50 percent reduction in measurable disease. The response criteria for the hematologic malignancies is defined

in the text. These figures should be interpreted with caution since they aggregate data from many studies which used alpha IFN in different dosage schemas and had a different patient mix.

EXPERIENCE IN HEMATOLOGIC MALIGNANCIES

Hairy Cell Leukemia

Hairy cell leukemia (HCL) is a rare lymphoproliferative disorder which is relatively refractory to standard cytotoxic agents. Since the first promising report by Quesada et al. [86] in 1984, a number of clinical trials have been published in the treatment of HCL with alpha IFN [85–97]. In these trials, a CR has usually been defined as a peripheral hematologic remission with 5 percent or less hairy cells in the marrow and a PR as a peripheral hematologic remission with 50 percent or greater reduction in leukemic infiltration of the marrow. Most clinical trials have used IFN doses in the range of 3×10^6 U subcutaneously or intramuscularly three times a week for approximately one year. Lower doses have been evaluated, and although they result in less fatigue, they are probably less efficacious [98,99]. Extending treatment an additional six months after a year of therapy has not improved the CR rate nor prolonged the interval until disease progression [100]. The CR rate is low with IFN, as illustrated in Fig. 1; however, 70–90 percent of patients experience marked symptomatic and hematologic improvement. There does not appear to be a significant difference in response between splenectomized and non-splenectomized patients. Hematologic improvement is gradual, with normalization of the platelet count usually occurring within two months, and normalization of the hemoglobin and granulocyte count within four to six months. Following discontinuation of IFN, the percentage of hairy cells increases gradually in the marrow, with 45 percent of the patients requiring retreatment at a median of 25.4 months because of progressive cytopenias [100,101]. Remissions can be re-induced with alpha IFN in most patients [85,95,96,100]. In contrast to alpha IFN, gamma IFN appears to be inactive in HCL, a result which correlates with different intracellular effects on hairy cells by the two types of IFN [102].

Recently, a cytotoxic drug pentostatin (2′-deoxycoformycin) has been shown to have marked activity in HCL. The drug is well tolerated and produces a CR in >80 percent of the patients treated. It is too early to assess late sequelae or determine if pentostatin can cure hairy cell leukemia [103]. A multi-institutional trial comparing pentostatin to alpha IFN is currently under way.

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a hyperproliferative disorder of multipotential stem cells. The Philadelphia chromosome (Ph^1), present in 90 percent of these patients, represents a reciprocal translocation (t9,22) involving the proto-oncogene c-abl. Based on *in vitro* data showing that alpha IFN can inhibit proliferation of both leukemic and normal myeloid colony formation and downregulate oncogene expression [104], Talpaz et al. [105,106] investigated the effect of human leukocyte IFN in controlling myeloid proliferation in chronic myeloid leukemia (CML). They employed doses of alpha IFN ranging from 3 to 9×10^6 U daily until hematologic remission was obtained, followed by slightly lower doses for remission maintenance. Complete remission was defined as normalization of white cell and platelet count and disappearance of

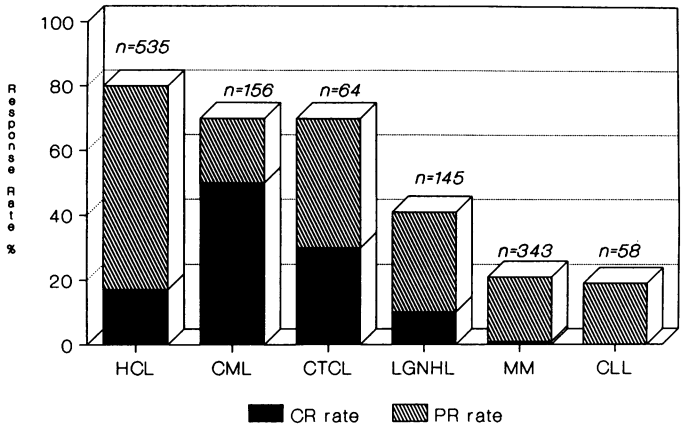

FIG. 1. Antitumor activity of alpha interferon in hematologic malignancies. **HCL,** hairy cell leukemia; **CML,** chronic myelogenous leukemia; **CTCL,** cutaneous T-cell lymphoma; **LGNHL,** low-grade non-Hodgkin's lymphoma; **MM,** multiple myeloma (untreated and refractory); **CLL,** chronic lymphocytic leukemia.

splenomegaly. Decrease in white cell count to at least 50 percent of pretreatment level and below 20,000/μL was called a PR. Of the 51 patients treated, 71 percent achieved a CR and 9 percent a PR. The median time to remission was 14 weeks (range, 2–55 weeks). Cytogenetic responses were also obtained. Twenty of the 36 responding patients showed a reduction in the percentage of (Ph^1)-positive metaphases with five patients having complete disappearance of all Ph^1-positive cells on at least one examination. Optimal response was achieved at a dose of 5×10^6 U/m^2 daily in lower-risk disease, which they defined as newly diagnosed, previously untreated, Ph^1-positive patients with low to moderately high leukocytosis. Similar therapeutic results have been reported in four subsequent series. The cytogenetic changes in these studies, however, were less impressive, apparently because IFN was given in lower doses [104,107–109]. Unfortunately, toxicity is significant when IFN is given in the optimal dose schedule of 5×10^6 U/m^2/day. Nearly one-third of patients experience grade 3 toxicities, consisting of cytopenias, hepatitis, and neurological symptoms. Whether IFN offers long-term therapeutic gain over standard cytotoxic agents to justify this toxicity is not known. Ongoing phase III trials are comparing IFN to hydroxyurea. Alpha IFN is also effective in controlling thrombocytosis in CML and other myeloproliferative disorders [110–113]. IFN activity during the accelerated and blast phases of CML is minimal with only a minority of patients showing brief improvement in the hematologic deterioration [106–109].

The efficacy of gamma IFN in CML is under evaluation and preliminary results suggest that about 25 percent of patients achieve a complete hematologic remission. Particularly interesting is laboratory work showing a potential synergy between alpha and gamma IFN [114]. Clinical trials employing combinations of alpha and gamma IFNs for CML are currently under way. Other investigators are looking at alpha IFN combined with standard cytotoxic agents such as busulfan for the chronic phase of this disease [115].

Lymphomas

Lymphomas are a heterogeneous group of lymphoreticular neoplasms which can be divided into Hodgkin's disease, non-Hodgkin's lymphoma, and a miscellaneous group which includes the cutaneous T-cell lymphomas. As shown in Fig. 1, the best results have been observed in the cutaneous T-cell lymphomas with about 70 percent of

patients responding to alpha IFN. Responses appear to be dose-related and last from three months to more than three years [116–119]. Among the non-Hodgkin's group, IFN is most effective for the low-grade lymphomas with follicular histologies [120–127]. Efficacy might be further improved if IFN were combined with cytotoxic drugs [128,129]. Only limited information is available in Hodgkin's disease and the intermediate and high-grade lymphomas, but they do not appear to be very responsive to alpha IFN [121,122].

Chronic Lymphocytic Leukemia and Acute Leukemias

Alpha IFN exhibits antitumor activity in about 20 percent of patients with chronic lymphocytic leukemia (CLL) but remissions are usually partial and short-lived [121,125,127,130–133]. Early-stage disease is most likely to respond but hematologic improvement is not sustained once IFN is withdrawn [134]. IFN has also very limited activity as induction therapy in the acute leukemias [135–139]. One randomized study, however, suggests that alpha IFN administered after marrow transplantation for acute lymphocytic leukemia may reduce the risk of leukemic relapse [140]. This interesting finding warrants further evaluation.

Multiple Myeloma

Using a 50 percent or greater reduction in the myeloma immunoglobulin as response criteria, about 20 percent of both untreated and refractory myeloma patients achieve remissions with alpha IFN [111,117,141–149]. The median duration of response to IFN ranges from two to more than 14 months, with approximately one-third of the patients having remissions lasting more than one year [141–144]. Although the activity of IFN as a single agent is modest in multiple myeloma (MM), recent studies suggest that IFN may play a more important role when used sequentially or in combination with cytotoxic agents. The Myeloma Group of Central Sweden recently reported a randomized trial showing a higher response rate (82 percent vs. 52 percent, $p < 0.01$) and a lower disease progression (4 percent vs. 21 percent) when alpha IFN was combined with melphalan/prednisone than when this chemotherapy regimen was used alone [150]. IFN may also be useful as maintenance therapy in this disease. In patients who had responded to induction chemotherapy, preliminary results of a multi-center trial have shown significantly longer remission durations in a group of patients randomized to maintenance alpha IFN until relapse compared with control [151]. It is not yet known whether prolongation of remission will translate into a survival advantage.

EXPERIENCE IN SOLID TUMORS

In contrast to the hematologic malignancies, IFN activity in solid tumors is much more modest (Fig. 2). The highest response rate has been observed in epidemic Kaposi's sarcoma (EKS) [152–159]. Alpha IFN has recently received FDA approval for treatment of EKS. Indications for treatment include pulmonary KS, rapidly progressive cutaneous disease, or symptomatic visceral involvement. Higher doses of IFN produce better response rates [157]. At the recommended dose of 3×10^6 U daily, alpha IFN produces tumor regression in 30–40 percent of treated patients. Factors predictive of improved response include: the absence of a previous opportunistic infection, lack of systemic symptoms (fever, sweats, weight loss), and relative immunological competence as measured by the number of circulating CD4 lympho-

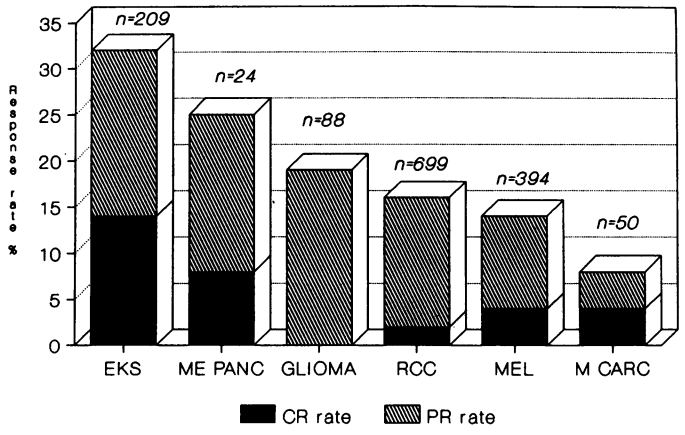

FIG. 2. Antitumor activity of alpha interferon in select solid tumors. **EKS**, epidemic Kaposi's sarcoma; **ME PANC**, malignant endocrine pancreatic tumor; **RCC**, renal cell carcinoma; **MEL**, malignant melanoma; **M CARC**, malignant carcinoid.

cytes and intact skin testing for delayed hypersensitivity. In this subset of patients, the overall response rate exceeds 50 percent [158,159]. Toxicity is significant, however, with up to a third of patients requiring dose reduction because of asthenia or neutropenia [156]. Equivalent response rates can be obtained with several cytotoxic regimens, but some of these agents produce prolonged myelosuppression and the development of opportunistic infections has been observed. Combinations of IFN with cytotoxic drugs are probably no more efficacious at the cost of increased side effects. IFN's activity in this disease may be due in part to a direct anti-retroviral effect [160,161], and current studies are evaluating the combination of IFN with AZT. Phase I trials of gamma IFN have failed to show significant antitumor effect. Based on *in vitro* data, very low-dose gamma IFN alone, or in combination with other cytokines, is currently being investigated [159].

Of the solid tumors, renal cell carcinoma (RCC) and malignant melanoma have been the most amply studied [162–181]. While the overall response rate does not exceed 20 percent in either melanoma (MEL) or renal cancer, alpha IFN is one of the few standard agents with definite and reproducible antitumor activity in these diseases. An occasional patient will experience a sustained remission [164,167,180]. The role of IFN as adjuvant therapy following resection of localized disease is currently being studied in both of these malignancies.

Response rates of 20 percent to systemically administered IFN have also been reported in brain tumors [117,182–186]. This estimate of activity is based, however, on small series which included patients just completing treatment with radiation or surgery, making assessment of objective responses difficult. Alpha IFN is a clinically useful drug in malignant endocrine tumors. Although the objective response is low, 40 percent to 50 percent of patients treated experience subjective improvement in endocrine-related symptoms and have more than a 50 percent reduction in the biologically active peptides [78,187–190].

For ovarian, bladder, head and neck, and cervix cancers, systemic administration of IFNs has largely proven ineffective [117,191–200]. Preliminary evidence, however, suggests that IFN may be synergistic when used with cytotoxic drugs [201]. Locoregional or intralesional administration of IFN also appears promising, and larger-scale studies will be needed to assess the merits of these modalities (Fig. 3). Relapsed ovarian cancer is frequently confined to the peritoneal cavity and intraperito-

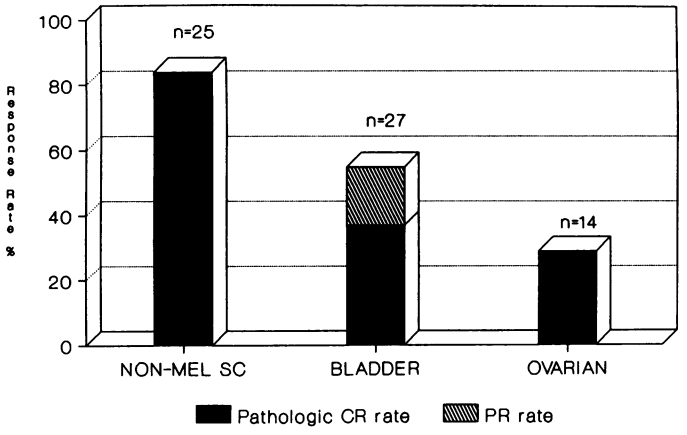

FIG. 3. Antitumor activity of alpha interferon administered locoregionally in select tumors. **NON-MEL SC,** non-melanomatous skin cancer (basal cell and squamous cell carcinoma).

neal (IP) administration of IFN reaches peak concentrations up to 3 logs greater than those obtainable in plasma. Locoregional therapy for ovarian cancer has been reported in one series of 14 patients [202]. All had a positive second-look laparotomy following combination chemotherapy and received IP IFN at the maximally tolerated dose of 50×10^6 U/m^2 per week for 16 consecutive weeks. After completion of therapy, 11 patients were surgically restaged. Five responses were noted, with four patients attaining a complete remission. These four patients all had non-bulky disease at the start of the trial, suggesting that alpha IFN may be most effective in the setting of minimal residual disease. Phase I trials evaluating IP beta and gamma IFN have also been conducted. In one trial, four of seven patients with advanced refractory disease showed a clinical response to beta IFN [203]. Results with IP gamma IFN have been less promising [204].

Carcinoma of the bladder presents as superficial disease in 80 percent of patients. Following transurethral resection, 50 percent of these patients will have a recurrence. Patients with high-grade lesions, multiple recurrences, invasion of the submucosa, and carcinoma in situ (CIS) are candidates for intravesicular therapy. Several agents including cytotoxic drugs and bacillus Calmette-Guerin (BCG) have shown activity in these settings. With these agents, responses in superficial transitional cell carcinoma (TCC) and CIS have ranged from 20–60 percent. Following resection, the recurrence rate of TCC is decreased from 45 percent to 15–20 percent if prophylactic BCG is given [205]. Intravesicular alpha IFN is as effective as standard agents and is less toxic [206]. The optimal dose and duration of therapy of intravesicular IFN is currently under investigation.

In non-melanomatous skin cancers, intralesionally injected alpha IFN exhibits marked antitumor activity. In one series of eight patients with basal cell carcinoma, all achieved a pathologic CR [207]. In 17 patients with squamous and basal cell carcinoma, subsequent resection showed no residual disease in 13 [208]. IFN may be an alternative to surgery in these diseases and in some cases provide a superior cosmetic result.

Intra- or perilesional injections of IFNs have also been employed in some head and neck cancers, in locally advanced carcinoma of the cervix, and in brain tumors. No conclusions in regard to efficacy can be made because of the small numbers treated [208–212]. Some activity, however, has been shown, and multi-center trials are under

way. Unfortunately, IFNs have little or no activity in the more common solid tumors such as breast [213–220], lung [221–225], colon [81,226–231], stomach [117,232], and prostate cancer [233,234]. Osteosarcoma, soft tissue sarcomas, and hepatoma are also usually refractory to IFN therapy [187,232,235].

SUMMARY

Intensive trials have defined the activity of alpha IFN and the maximal tolerated dose. This information is still being accumulated for beta and gamma IFN. Despite early optimism, the IFNs have not proven to be a panacea for cancer treatment. No tumor has been rendered curable with the IFNs, and the most common neoplasms have sadly proved exceedingly resistant. The current clinical significance of the IFNs belies their importance in oncology: IFNs represent the first class of cytokines isolated and placed in clinical trials.

IFN's antitumor effect is reproducible in several hematologic malignancies but only in a handful of solid tumors. IFN is a clear advance in the treatment of HCL, but even this indication is jeopardized by pentostatin. In myeloma, maintenance therapy with IFN enhances the durability of remission and may result in improved survival. For the chronic phase of CML, IFN as a single agent or in combination with cytotoxic drugs may prove to be superior to cytotoxic agents alone.

In responsive solid tumors, IFN seems to be most active in the setting of minimal residual disease. Clinical trials are currently examining IFN as an adjuvant therapy following surgical resection of high-risk melanoma and renal cell carcinoma. IFN is also active as a local therapy in several malignancies, including superficial bladder cancer and locally advanced ovarian carcinoma. It is too early to determine what role IFN will have in the management of these diseases.

Comprehension of the role of the IFNs and other cytokines in the complex function of the immune system remains in its infancy. Early data suggest that IFN used in combination with other biologicals or cytotoxic drugs is more effective than when it is used as monotherapy. As the physiological role of IFN and other cytokines is eventually elucidated, more rational strategies to employ biological proteins in cancer treatment will be designed.

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