Interferon in Oncological Practice: Review of Interferon Biology, Clinical Applications, and Toxicities

ERIC JONASCH, FRANK G. HALUSKA
Massachusetts General Hospital, Boston, Massachusetts, USA

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ABSTRACT

For the past 40 years, various forms of interferon (IFN) have been evaluated as therapy in a number of malignant and non-malignant diseases. With the advent of gene cloning, large quantities of pure IFN became available for clinical study. This paper reviews the biology, pharmacology, and clinical applications of IFN formulations most commonly used in oncology. It then reviews the most common side effects seen in patients treated with IFN, and makes recommendations for the management of IFN-induced toxicity.

The major oncological indications for IFN include melanoma, renal cell carcinoma, AIDS-related Kaposi’s sarcoma, follicular lymphoma, hairy cell leukemia, and chronic myelogenous leukemia. Unfortunately, IFN therapy is associated with significant toxicity, which can be divided into constitutional, neuropsychiatric, hematologic, and hepatic effects. These toxicities have a major impact on the patient’s quality of life, and on the physician’s ability to optimally treat the patient. Careful attention to all aspects of patient care can result in improved tolerability of this difficult but promising therapy. Conclusion: a better understanding of IFN biology, indications, side effect profiles, and toxicity management will aid in optimizing its use in the treatment of patients with cancer.

In this report, we review the classification of the IFNs and summarize their major mechanisms of action. We then describe the indications for IFN therapy in oncological practice and review the etiology and management of IFN-related side effects.

INTRODUCTION

In 1957 Isaacs and Lindeman described a factor that conferred the property of viral interference [1]. The term interferon (IFN) was coined to describe this new substance. Over the next 40 years, the IFNs have been evaluated as therapeutic modalities in a large number of malignant and nonmalignant diseases. Research has revealed diverse mechanisms of action, including antiviral, immune-enhancing and cytostatic activities.

In oncology, the IFNs are an important treatment for a number of solid tumors and hematological malignancies. These include melanoma, renal cell carcinoma, AIDS-related Kaposi’s sarcoma (KS), follicular lymphoma, hairy cell leukemia, and chronic myelogenous leukemia (CML). IFN therapy is associated with significant side effects which have an impact on the patient’s quality of life and the physician’s ability to optimally treat the patient. An understanding of IFN biology, interactions, indications for use, side-effect profiles, and the management of IFN toxicities will aid in the optimal application of these agents in the management of patients with cancer.

In this report, we review the classification of the IFNs and summarize their major mechanisms of action. We then describe the indications for IFN therapy in oncological practice and review the etiology and management of IFN-related side effects.

IFN CLASSIFICATION

After the discovery of IFN, initial attempts at purification were met with little success, defying efforts at classification. Early clinical trials used crude preparations that were less than 1% IFN by weight [2]. It was only in 1978 and thereafter that IFN was purified to homogeneity in amounts that allowed chemical and physical characterization. The initial nomenclature of α, β, and γ IFN was used to categorize the major HPLC peaks, but was quickly adopted to designate leukocyte, fibroblast, and immune IFNs, respectively [2]. Table 1 summarizes some of the major properties of the various IFN subtypes.

In 1980, at a meeting jointly sponsored by the National Institute of Allergy and Infectious Diseases and the World Health Organization, nomenclature was formally adopted...
classifying IFNs into three categories based on antigenic specificity. IFNs were categorized as alpha (α), beta (β), and gamma (γ), corresponding to the previous designations of leukocyte, fibroblast and immune IFN [3]. More recently, IFNs were divided into two major subgroups by virtue of their ability to bind to common receptor types [4-6]. Type I IFNs all bind to a type I IFN receptor, and include IFN-α, IFN-β, IFN-ω, and IFN-τ. IFN-γ is the sole type II IFN, and binds to a distinct type II receptor [7].

Almost all cell types produce type I IFNs. The prototypical production sites for IFN-α and IFN-β are leukocytes and fibroblasts, respectively. Their induction usually follows exposure to viruses, double-stranded RNA, polypeptides, and cytokines [8]. The type II IFN-γ is produced in T cells and natural killer (NK) cells following a number of immunological stimuli, including T cell-specific antigens, staphylococcal enterotoxin A, and the combination of phytohemagglutinin and phorbol ester [2, 8]. Unlike IFN-α and -β, it is not directly induced in cells following viral infection.

**BIOLOGICAL PROPERTIES OF IFNS**

The IFNs possess a broad spectrum of activity and are involved in complex interactions. They display antiviral activity, impact cellular metabolism and differentiation, and possess antitumor activity. The antitumor effects appear to be due to a combination of direct antiproliferative, as well as indirect immune-mediated effects. Figure 1 summarizes the intracellular signaling, and Figures 2 and 3 summarize the major effects of IFN-α and -γ on NK cells, antigen-presenting cells, macrophages, T cells, and tumor cells.

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**Table 1. IFN classification and properties**

<table>
<thead>
<tr>
<th>IFN Type</th>
<th>IFN categories</th>
<th>Receptor type</th>
<th>Prototypic cell of origin</th>
<th>Direct Antiproliferative effects</th>
<th>Stimulates MHC class I expression</th>
<th>Stimulates MHC class II expression</th>
<th>Stimulates NK cell activation</th>
</tr>
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<tbody>
<tr>
<td>Type I</td>
<td>Alpha (α)</td>
<td>I</td>
<td>Leukocyte</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Beta (β)</td>
<td>I</td>
<td>Fibroblast</td>
<td>Yes</td>
<td>Yes</td>
<td>Slightly</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Omega (ω)</td>
<td>I</td>
<td>Leukocyte</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Tao (τ)</td>
<td>I</td>
<td>Ovine Trophoblast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>Gamma (γ)</td>
<td>II</td>
<td>T-cells</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Less than type I IFNs, delayed</td>
</tr>
</tbody>
</table>

**Figure 1.** For the type I IFNs, there are two receptor subunits known, IFNAR-1 and IFNAR-2, which bind the Janus-activated kinase (Jak) molecules Tyk2 and Jak1, respectively. For IFN-γ there are two receptor subunits known: IFNGR-1 and IFNGR-2, which associate with Jak1 and Jak2, respectively. Upon binding of IFN to its receptor, the receptor undergoes oligomerization, with transphosphorylation of Jaks followed by phosphorylation of the cytoplasmic tails of the receptor molecules. This provides a docking site for the signal transducers and activators of transcription (Stats) which are then phosphorylated by the Jaks. The phosphorylated Stat dimers are released from the receptor molecules, and translocate to the nucleus, where they activate transcription of IFN-stimulated genes (ISGs). In the case of type I IFNs, ISGs can be identified by the presence of an IFN-stimulated response element (ISRE) in their promoter regions. Enhancers of IFN-γ-inducible genes contain a unique element called the IFN-γ activation site (GAS).
The cloning of the IFN genes resulted in the availability of large quantities of pure IFN-α and -γ, allowing substantive research to be done on the clinical efficacy of the IFNs in malignant and nonmalignant diseases. The clinical indications for the IFN subtypes are summarized in Table 2.

**CURRENTLY AVAILABLE PREPARATIONS**

The cloning of the IFN genes resulted in the availability of large quantities of pure IFN-α and -γ, allowing substantive research to be done on the clinical efficacy of the IFNs in malignant and nonmalignant diseases. The clinical indications for the IFN subtypes are summarized in Table 2.

IFN-α2a (Roferon A; Roche Laboratories; Nutley, NJ) and IFN-α2b (Intron-A; Schering-Plough Corporation; Kenilworth, NJ) are now produced by recombinant (r)DNA technology. The molecular sequences of the two rIFNs differ from one another by a single amino acid at position 23 [9]. IFN alfacon-1 (Infergen, Amgen; Thousand Oaks, CA) is a recombinant non-naturally occurring IFN, whose 166 amino-acid sequence was derived by scanning the sequences of several natural IFN-α subtypes and assigning the most frequently observed amino acid in each corresponding position. Four additional changes were made to facilitate molecular construction. IFN-α3 (Alferon N; Interferon Sciences Inc.; New Brunswick, NJ) is derived from human leukocytes.

**Figure 2. IFN-α possesses pleiotropic and potentially antagonistic activity in immune cells and tumors. Both stimulatory and inhibitory effects are seen in the T-cell population.**

A stimulatory effect is seen in natural killer (NK) cells and macrophages, which may be antagonized by the IFN-α mediated upregulation of major histocompatibility-1 (MHC1) in tumor cells. Direct cytostatic effects are seen in tumor cells, as well as upregulation of tumor-specific antigens and adhesion molecules. IFN-α may also have antiangiogenic effects mediated indirectly by IFN-γ (Fig. 3).

**Table 2. IFN clinical indications**

<table>
<thead>
<tr>
<th>IFN type</th>
<th>Trade name</th>
<th>Manufacturing technique</th>
<th>FDA-approved indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-α2a</td>
<td>Roferon A</td>
<td>rDNA</td>
<td>NHL, Hairy cell leukemia, CML, AIDS-related KS, Chronic hepatitis C</td>
</tr>
<tr>
<td>IFN-α2b</td>
<td>Intron A</td>
<td>rDNA</td>
<td>Follicular lymphoma, Hairy cell leukemia, AIDS-related KS, Malignant melanoma, Condyloma accuminata, Chronic hepatitis B, Chronic hepatitis C</td>
</tr>
<tr>
<td>IFN alfacon-1</td>
<td>Infergen</td>
<td>rDNA</td>
<td>Chronic hepatitis C</td>
</tr>
<tr>
<td>IFN-αn3</td>
<td>Alferon N</td>
<td>Purified from human leukocytes</td>
<td>Condyloma accuminata</td>
</tr>
<tr>
<td>IFN-β1a</td>
<td>Avonex</td>
<td>rDNA (Chinese hamster ovary cells)</td>
<td>Relapsing-remitting MS</td>
</tr>
<tr>
<td>IFN-β1b</td>
<td>Betaseron</td>
<td>rDNA (E. coli)</td>
<td>Relapsing-remitting MS</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Actimmune</td>
<td>rDNA</td>
<td>Chronic granulomatous disease</td>
</tr>
</tbody>
</table>

**Figure 3. IFN-γ is an activator of T-cells and macrophages, working in concert with interleukin-2 (IL-2).**

IFN-γ is capable of upregulating both MHC classes I and II, and has demonstrated direct inhibitory effects on tumor proliferation. IFN-γ is presumed to induce its antiangiogenic effects through the secretion of IFN-γ inducible protein 10 (IP-10) and monokine induced by IFN-γ (MIG).
IFNβ-1b is manufactured by bacterial fermentation of a strain of *Escherichia coli* that bears a genetically engineered plasmid containing the gene for human IFN beta. The native gene was obtained from human fibroblasts and altered in a way that substitutes serine for the cysteine residue found at position 17 [10]. IFN-β1b has 165 amino acids and an approximate molecular weight of 18,500 Da and does not include the carbohydrate side chains found in the natural product. It is given s.c. every other day [11].

IFN-β1a (Avonex; Biogen Inc; Cambridge, MA) and IFN-β1b (Betaseron; Berlex; Richmond, CA) are recombinant proteins. IFN-β1a is a 166-amino acid glycoprotein with a predicted molecular weight of approximately 22,500 Da. It is produced by mammalian cells (Chinese hamster ovary cells) into which the human IFN-β gene has been introduced. The amino acid sequence of IFN-β1a is identical to that of natural human IFN-β. IFN-β1a is also U.S. Food and Drug Administration (FDA)-approved for treatment of relapsing-remitting multiple sclerosis (MS) to reduce frequency of relapses [12]. It may be preferable to IFN-β1b because of the convenience of weekly administration, the relative lack of injection site reactions, and lower incidence of neutralizing antibodies.

IFN-γ (Actimmune; Genentech Inc; San Francisco, CA), is produced using rDNA technology. It is FDA-approved for use in chronic granulomatous disease.

**Pharmacokinetics**

As with most peptides, oral delivery of the IFNs is not practical due to proteolytic degradation. Subcutaneous and i.m. absorption of IFN-α and IFN-γ is >80%, and 30%-70%, respectively [13]. These routes of administration result in a protracted distribution phase, with maximal serum or plasma concentrations occurring after 1 to 8 h, followed by measurable concentrations for 4 to 24 h after injection for both IFN-α and -γ. After i.m. administration, IFN-β levels peak between 3 and 15 h, and then decline at a rate consistent with a 10-h elimination half-life. At therapeutic dosages of 0.25 mg s.c., serum concentrations of IFN-β are low or undetectable [14]. Intravenous administration of IFN-α or -β results in a biexponential decrease in serum concentration, and IFN-γ levels decline monoeXponentially. Terminal elimination half-lives range from 4-16 h for IFN-α, 1-2 h for IFN-β and 25 to 35 min for IFN-γ [15-17]. Serum concentrations are generally measurable for between 8 and 24 h after i.v. injection of IFN-α and up to 4 h after i.v. injection of IFN-β and -γ.

The relationship between dose and biological response varies among disease types. A number of surrogate markers have been investigated to better define the dose-response relationship of IFN. 2′-5′ oligoadenylate synthetase (2-5A), an enzyme induced by both IFN-α and -γ, is involved in IFN-mediated viral RNA degradation [18]. Introduction of 2-5A into cells [19] or expression of 2-5A cDNA inhibited cell growth rates [20]. Increased 2-5A levels were also shown to correlate with decreased cell cycling in melanoma cell cultures treated with IFN [21], suggesting a causal role in its antiproliferative action. Using 2-5A activity as a marker for response, a two- to sixfold increase in 2-5A activity was seen over a 300-fold dose range i.m. using human lymphoblastoid IFN-α [22]. Other biological markers used to evaluate IFN response include neopterin and β2 microglobulin. Neopterin is a pteridine derivative originally found in cultures of stimulated T lymphocytes [23] whose serum and urinary levels correlated with therapeutic IFN dosages in the treatment of hairy cell leukemia [24, 25]. Small studies in melanoma [26-28] provide conflicting data on the utility of neopterin levels in predicting response to immunotherapy. The human MxA protein is a GTPase with antiviral activity against orthomyxoviruses and certain other negative-strand DNA viruses [29]. Unlike 2-5A, β2 microglobulin and neopterin, MxA gene expression is induced solely by type I IFNs [30, 31], and holds promise for future cancer immunology studies. In aggregate, these markers provide laboratory confirmation of immunological stimulation by IFN, but do not provide consistent predictive information on the use of IFN therapy in cancer.

**Application of IFN Therapy in Oncological Practice**

The IFNs have been used to treat a number of malignancies, with varying degrees of success. The following section summarizes the most common applications of IFN in current oncological practice.

**Hairy Cell Leukemia**

The first report of IFN response in patients with hairy cell leukemia was recorded in 1984 [32]. In this study, seven patients were treated with 3 × 10^6 U of partially purified leukocyte IFN-α i.m. daily (qd). Three patients had a complete remission (CR), four had a partial remission (PR), and remissions were maintained for 6 to 10 months. Subsequently, 30 patients with hairy cell leukemia were treated with IFN-α2a, including seven who were previously untreated. Nine (30%) CR and 17 (56%) PR were confirmed by bone marrow core biopsies. All patients’ peripheral blood hematologic indices either improved or normalized [33]. A multicenter phase II study of 64 patients published in 1986 confirmed the drug’s efficacy in hairy cell leukemia [34]. IFN-α2a and 2b were FDA-approved for use in hairy cell leukemia in 1986. IFN-α is usually given over a two-year
period at $3 \times 10^6$ U/day. Unfortunately, upon cessation of therapy, almost all patients will relapse. Although approved for use, IFN-α has been superseded by more effective therapies in hairy cell leukemia, including 2-deoxycoformycin and cladribine.

**CML**

**Early Studies**

Preclinical studies performed in the late 1970s suggested IFN therapy had antiproliferative effects on granulocyte precursors [35]. In 1983, Talpaz et al. reported on seven patients with CML treated with IFN-α $9-15 \times 10^6$ U i.m. qd [36], five of whom developed a hematologic remission. In 1986, the same group reported on 17 patients with early-phase CML who were treated with rIFN-α2a, $5 \times 10^6$ U/m$^2$ i.m. qd [37]. Fourteen patients responded to the treatment, 13 of whom had a complete hematologic remission (CHR) and one had a partial hematologic remission (PHR). Cytogenetic analysis revealed that 20%–25% of patients experienced long-term suppression of the Philadelphia (Ph) chromosome. At least 30 uncontrolled observational studies have been published looking at the effect of IFN-α therapy on patients in chronic-phase CML [38]. These studies vary greatly with respect to their reporting of outcome measures, and overall survival is often not recorded. Most studies record an association between cytogenetic remission and improved survival by landmark analysis*, with a minority failing to show such an association [39]. (*Landmark analysis is an assessment of outcome following the stratification of patients according to a particular endpoint, in this case the achievement of cytogenetic remission.)

**IFN Monotherapy**

In 1994, the Italian Cooperative Group published a study of 322 patients with untreated or minimally treated CML randomized between IFN-α2a and conventional chemotherapy [40]. The rate of karyotypic response was 30% in the IFN group versus 5% in the chemotherapy group. Median time to progression and overall survival were significantly longer in the IFN groups. Table 3 summarizes the five randomized studies comparing chemotherapy (busulfan and/or hydroxyurea) to IFN-α therapy [40-44]. Four of these studies conclude that IFN therapy is better than chemotherapy in patients with early chronic-phase CML [40-43]. In all but one of these studies, IFN was given as monotherapy. The Benelux study [45] randomized patients to IFN plus hydroxyurea as needed to keep the

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n patients</th>
<th>Study design</th>
<th>Hematologic response (%)</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broustet [44]</td>
<td>1991</td>
<td>30</td>
<td>IFN</td>
<td>CHR 53, N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
<td>Hydroxurea</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hehlmann [41]</td>
<td>1994</td>
<td>133</td>
<td>IFN</td>
<td>31, 52</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>186</td>
<td>Busulfan</td>
<td>23, 69</td>
<td>45*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>194</td>
<td>Hydroxurea</td>
<td>39, 51</td>
<td>56</td>
</tr>
<tr>
<td>Italian</td>
<td>1994</td>
<td>218</td>
<td>IFN</td>
<td>CHR + PHR = 45%</td>
<td>72</td>
</tr>
<tr>
<td>Cooperative</td>
<td></td>
<td>104</td>
<td>Hydroxurea/Busulfan</td>
<td>CHR + PHR = 46%</td>
<td>52</td>
</tr>
<tr>
<td>Group [40]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>($p = 0.002$)</td>
</tr>
<tr>
<td>Allan [42]</td>
<td>1995</td>
<td>293</td>
<td>IFN</td>
<td>69, 18</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>294</td>
<td>Hydroxurea/Busulfan</td>
<td>N/A</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>($p = 0.0009$)</td>
</tr>
<tr>
<td>Ohnishi [43]</td>
<td>1995</td>
<td>80</td>
<td>IFN</td>
<td>39, 39</td>
<td>Not reached, but improved survival in IFN arm ($p = 0.029$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>79</td>
<td>Busulfan</td>
<td>54, 43</td>
<td>64</td>
</tr>
<tr>
<td>Benelux [45]</td>
<td>1998</td>
<td>100</td>
<td>IFN</td>
<td>62, N/A</td>
<td>68 NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hydroxurea</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hydroxurea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guilhot [50]</td>
<td>1997</td>
<td>361</td>
<td>IFN</td>
<td>55, N/A</td>
<td>Not reached, but improved survival in IFN-cytarabine arm ($p = 0.02$)</td>
</tr>
<tr>
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<td>Hydroxurea</td>
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<td>Hydroxurea</td>
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</tr>
</tbody>
</table>

NS = not significant; *statistically significant
WBC count below $10 \times 10^9$ versus hydroxyurea alone, with no survival benefit noted in the IFN arm. Differences in trial design, inclusion criteria, treatment and documentation of response make direct comparisons between these trials difficult, but the evidence supports a benefit to IFN-α therapy in patients with early chronic-phase CML.

**Combination Therapy**

In the late 1980s, cytarabine (ara-C) was shown to suppress CML clones selectively in vitro [46] and demonstrated in vivo antitumor efficacy when given as a low-dose continuous infusion [47]. In 1992, Kantarjian et al. published a report on 60 patients with advanced phases of CML who received combination therapy with IFN-α $5 \times 10^6$ U/m² daily, and low-dose ara-C $15$ mg/m² daily for two weeks every four weeks until remission, then for one week every month as maintenance, compared to historical controls receiving IFN-α therapy alone. Patients receiving IFN-α plus ara-C had a better CHR rate compared with those treated with IFN-α, a trend for better Ph suppression and longer survival [48]. More recently, Kantarjian et al. compared 140 patients with chronic-phase CML receiving IFN-α at $5 \times 10^6$ and ara-C $10$ mg daily to historical controls receiving IFN-α alone or IFN-α with intermittent ara-C [49]. The study group demonstrated a CHR in 92% of patients, with cytogenetic response in 74% of patients, 31% of which were complete, results that were significantly better than the control groups. The time to blastic transformation and overall survival was the same as in the control groups. Several other observational studies report a potential benefit to the combination of IFN and ara-C. Subsequently, a randomized study by Guilhot et al. indicated the 360 patients receiving IFN-α2b, hydroxyurea, and ara-C demonstrated a significant improvement in overall survival and cytogenetic response when compared with 361 patients receiving IFN-α2b and hydroxyurea alone [50] (Table 3).

**IFN-γ**

IFN-γ has been used as therapy in chronic-phase CML. In 1987, Kurzrock et al. reported that 6 of 30 patients with chronic-phase CML treated with rIFN-γ demonstrated CHR, and varying degrees of cytogenetic improvement [51]. Subsequent studies using combinations of IFN-α and IFN-γ failed to show an improvement over treatment with IFN-α alone [52, 53], and IFN-γ is not recommended for treatment of CML.

**Bone Marrow Transplantation and IFN**

Concern has been raised about prior IFN-α therapy having a negative influence on allogeneic bone marrow transplant outcomes. Several recent studies have suggested this is not the case in patients who received a matched-related donor [54-56], but one report suggests adverse outcomes for patients who received a greater than six-month course of IFN-α prior to undergoing a matched-unrelated donor transplant [57].

**Summary**

The major decision in otherwise healthy patients with CML is whether to treat with IFN-α initially, or to proceed with early allogeneic bone marrow transplantation. Outcomes after transplantation reveal lower overall survival initially when compared to IFN therapy, with a crossing-over of survival curves at approximately seven years after diagnosis [38]. There appears to be a survival plateau in the transplant patient population, but not in the IFN-α-treated patient population. Unfortunately, most of the transplant data are nonrandomized, and there have been no direct valid comparisons between IFN therapy and transplantation in CML. The recommendations made in an American Society of Hematology-sponsored review [38] do not strongly favor IFN-α therapy or allogeneic bone marrow transplantation therapy, but indicate that both should be considered. The patient’s age, stage of disease, comorbid conditions, and the patient’s and physician’s threshold for risk and treatment-related morbidity need to be taken into consideration when making such a decision.

**Follicular Lymphoma**

IFN-α was first used in the treatment of patients with follicular lymphoma in the early 1980s [58]. Early-phase studies showed a 50% objective response rate. Subsequently, two phase III trials randomized patients between single alkylating agents with or without IFN-α, demonstrating improved remission duration, but no overall survival improvement [58-61]. In addition, two randomized phase III trials evaluated the addition of IFN to combination cytoreductive chemotherapy [62, 63]. In only one of these studies was there an improved median progression-free survival and overall survival in the group of patients receiving IFN [63].

The role of IFN-α as maintenance therapy for patients with low-grade non-Hodgkin’s lymphoma (NHL) who achieved tumor bulk reduction after cytoreductive chemotherapy has also been evaluated [58, 64-69]. Most studies demonstrated an increased failure-free survival in patients on maintenance IFN, but no clear-cut increase in overall survival. One randomized study of IFN-α2b maintenance therapy did reveal an overall survival advantage [69].

Based on the above studies, some authors recommend that IFN-α therapy be used in combination with chemotherapy in clinically aggressive follicular NHL, and as maintenance therapy in patients with high tumor burden after...
cytoreductive therapy [58]. These recommendations have not been universally accepted. We recommend that IFN-α be used in an investigational setting to better define its role in the treatment of follicular lymphoma.

**RENAL CELL CARCINOMA (RCC)**

IFN has been extensively used in the treatment of RCC. Although there is no clear role for its use in the adjuvant setting, extensive work has been done to define its role in the management of metastatic disease. The following sections summarize these findings.

**IFN Monotherapy**

Single-agent IFN has been used in over 50 clinical trials in the treatment of metastatic RCC. Response rates in these trials range between 0% and 50%, with a mean of approximately 15% for IFN-α and 10% for IFN-γ. There does not appear to be a clear dose-response curve in the treatment of metastatic RCC with rIFN-α2a or IFN-α2b [70]. Stratification of trials among those with average daily doses of <5, 5-10 and >10 million units per day does not reveal any statistically significant differences in outcome. A retrospective analysis of prognostic markers of response suggested that pretreatment nephrectomy and lung metastases as sole site of metastatic disease were markers for better outcome. Overall performance status is another important prognostic factor predicting response to therapy [71].

Several randomized studies have been published to quantify the benefit of IFN in metastatic RCC (Table 4A). The Medical Research Council Renal Cancer Collaborators trial randomized 350 patients with metastatic RCC between IFN-α2b and medroxyprogesterone acetate (MPA) [71]. An interim analysis was performed when time-to-progression data were available for 335 patients, showing a statistically significant improvement in median survival in favor of the IFN arm. Pyrhonen *et al.* prospectively randomized 160 patients with locally advanced or metastatic RCC between vinblastine (VBL) alone and IFN-α2a plus VBL for 12 months or until progression of disease [72]. Both the response rates and median survival were superior in the IFN arm.

**Role of Nephrectomy**

The benefit of preimmunotherapy nephrectomy was addressed by the Southwest Oncology Group (SWOG) in a randomized trial designed to determine whether nephrectomy prior to systemic therapy with IFN prolonged survival (Table 4A). Patients with operable metastatic renal cancer were randomized to two arms: immediate IFN therapy or radical nephrectomy followed by IFN therapy. Between June 1991 and October 1998, 246 patients were randomized. Median survival was significantly improved in the nephrectomy arm, but the response rate to IFN was a low 4% in both arms, suggesting the survival advantage was mainly due to surgical debulking, and not because surgery improved the efficacy of IFN therapy.

**Combination with Interleukin 2 (IL-2)**

Subsequent efforts have been made to evaluate IFN together with other biological response modifiers including IL-2, or in combination with chemotherapeutic agents, in particular 5-fluorouracil (5-FU). The combination of IFN-α and IL-2 has been extensively investigated in patients with metastatic RCC. Phase I and II trials have demonstrated response rates of approximately 20%, with 5% CR [73]. Treatment schedules, cytokine doses, patient selection criteria and response criteria differ from study to study. Table 4B

<table>
<thead>
<tr>
<th>Table 4A. RCC: randomized studies</th>
<th>Study design</th>
<th>Response rates (%)</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IFN and Chemo- or Hormonal Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC [71] 1999</td>
<td>174</td>
<td>IFN 10 MU s.c. tiw × 12 wks</td>
<td>14</td>
</tr>
<tr>
<td>176</td>
<td>MPA 300 mg PO qd × 12 wks</td>
<td>7</td>
<td>8.5*</td>
</tr>
<tr>
<td>Pyrhonen [72] 1999</td>
<td>81</td>
<td>VBL 0.1 mg/kg q 3 wks</td>
<td>2.5</td>
</tr>
<tr>
<td>79</td>
<td>VBL 0.1 mg/kg q 3 wks</td>
<td>16.5</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>IFN 3 MU s.c. tiw wk 1 then 18 MU s.c. tiw</td>
<td>(p = 0.0025)</td>
<td>(p = 0.0049)</td>
</tr>
<tr>
<td><strong>IFN ± Nephrectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG [156] 2000</td>
<td>123</td>
<td>Nephrectomy</td>
<td>4</td>
</tr>
<tr>
<td>123</td>
<td>Nephrectomy plus IFN 5 MU/m² s.c. tiw until progression</td>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p = 0.033)</td>
<td></td>
</tr>
</tbody>
</table>

* statistically significant
Jonasch, Haluska

Table 4B. RCC: randomized studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n patients</th>
<th>Study design</th>
<th>Response rates (%)</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins</td>
<td>1993</td>
<td>71</td>
<td>IL-2 0.6 MIU/kg i.v. q 8 h × 14 days 1-5 and 15-19</td>
<td>11</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IL-2 0.36 MIU/kg i.v. q 8 h × 14 days 1-5 and 15-19</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
<td>IFN 3 MU/m² IV q 8 h × 14 days 1-5 and 15-19</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Lissoni</td>
<td>1993</td>
<td>15</td>
<td>IL-2 3 MU s.c. bid 5 days/wk × 6 wks</td>
<td>33 (Survival at one year: NS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>IL-2 3 MU s.c. bid 5 days/wk × 6 wks</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Lumen</td>
<td>1996</td>
<td>30</td>
<td>IFN-γ 200 µg s.c. q wk</td>
<td>0</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>IL-2 4.8 MIU/m² s.c. qid days 1, 22 4.8 MIU/m² s.c. bid days 2, 23 2.4 MIU/m² s.c. bid days 3-5, 8-12, 15-19, 24-26, 29-33, 36-40</td>
<td>23 (p = 0.01) (p = 0.49)</td>
<td></td>
</tr>
<tr>
<td>Negrier</td>
<td>1998</td>
<td>138</td>
<td>IL-2 18 MU s.c. qd CI days 1-5, 15-19 × 2; then days 1-5 q 3 wks</td>
<td>6.5</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN 18 MU s.c. tiw × 10 wks</td>
<td>7.5</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>140</td>
<td>IL-2 18 MU/m² CI qd days 1-5, 15-19 × 2; then days 1-5 q 3 wk</td>
<td>18.6 (p = 0.01) (p = 0.55)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN 6 MU s.c. tiw in the wks IL-2 is given.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jayson</td>
<td>1998</td>
<td>29</td>
<td>IL-2 18 MU s.c. days 1-5 × 3-4 wks</td>
<td>7</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29</td>
<td>IL-2 18 MU s.c. days 1-5 × 3-4 wks</td>
<td>0</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN 9 MU tiw × 3-4 wks</td>
<td>7 (p = 0.98)</td>
<td></td>
</tr>
<tr>
<td>Boccardo</td>
<td>1998</td>
<td>22</td>
<td>IL-2 18 MU/m² CI qd × days 1-4 wks 1.3, 7, 9, 13, 17, 21, 25</td>
<td>22.7</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>IFN 6 MU/m² IM days 1, 3, 5 × 52 wks</td>
<td>9.0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>IL-2 18 MU/m² CI qd × days 1-4 wks 1.5, 9, 13, 17, 21</td>
<td>9.0</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN 6 MU/m² i.m. days 1, 3, 5 wks 2-4, 6, 8, 10-12, 14-16, 18-20, 22-24</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Henriksson</td>
<td>1998</td>
<td>63</td>
<td>Tamoxifen 40 mg PO qd</td>
<td>3.2*</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65</td>
<td>Tamoxifen 40 mg PO qd</td>
<td>7.7*</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IL-2 4.8 MIU/m² q 8 h days 1, 22 4.8 MIU/m² q 12 h days 2, 23 2.4 MIU/m² q 12 h days 3-5, 8-12, 15-19, 24-26, 29-33, 36-40</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN 3 MU/m² days 3, 5, 24, 26, 6 MU/m² days 8, 10, 12, 15, 17, 19, 29, 31, 33, 36, 38, 40</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant; *complete response only

summarizes seven randomized trials assessing the efficacy of combination cytokine therapy in metastatic RCC. In a phase II trial, Atkins et al. randomly assigned patients to receive treatment with either IL-2 alone or IL-2 and IFN-α. After 28 patients were entered onto each arm, the IL-2/IFN arm was closed because of a failure to meet predetermined efficacy criteria. An additional 43 patients (total 71) were assigned to receive IL-2 alone. Responses were seen in 3 of 28 patients (11%) on IL-2/IFN-α and 12 of 71 patients (17%) on IL-2 alone. The Groupe Francais d’Immunotherapie randomized 425 patients with metastatic RCC to a continuous i.v. infusion of IL-2, s.c. injections of IFN-α2a, or both [74]. Response
rates and event-free survival rates were significantly better in the combination therapy group, but overall survival rates were not significantly different. The other randomized studies assessing the role of combination IFN and IL-2 therapy failed to demonstrate a survival advantage to this combination when compared with cytokine monotherapy [75-79] (Table 4B). In summary, as numerous studies have failed to show a survival advantage for patients with metastatic RCC receiving combination cytokine therapy, it cannot be recommended as standard treatment.

Combination with IL-2 and 5-FU

Combinations of IFN-α, IL-2, and 5-FU have been evaluated in metastatic RCC. In vitro data suggest improved efficacy of 5-FU when given in combination with IFN-α [80, 81]. An overall response rate of approximately 30% has been seen in most studies [73, 82-90]. Two recent randomized studies presented in abstract form address the efficacy of chemoimmunotherapy in metastatic RCC [91, 92] (Table 4C). Negrier et al. randomized 131 patients between IL-2, IFN and IL-2, IFN and 5-FU, and reported no significant difference in response between the two treatment arms. Atzpodien et al. randomized patients between Tamoxifen and IFN, IL-2 and i.v. 5-FU, and found a highly significant improvement in response rate and survival in the combination therapy arm. The results from the Atzpodien study are encouraging, but in the absence of a confirmatory study, are insufficient to make IL-2, IFN, and 5-FU standard care in metastatic RCC.

Summary

In conclusion, IFN monotherapy in patients with metastatic RCC provides a modest but significant prolongation of survival with manageable side effects. A subset of patients, in particular those with good performance status, lung-only disease and resected primaries, may benefit from combination chemoimmunotherapy, but more data are needed to determine whether combination therapy is superior to IFN alone. At the current time, the best approach is to enter patients into well-designed phase III trials that will help answer these questions.

MELANOMA

In 1980, Bart et al. reported on the inhibition of B16 melanoma in vitro and in vivo by murine IFN [93]. Subsequent phase I studies using partially purified leukocyte IFN at doses below 10 × 10^6 U/day resulted in few responses [94]. Other reports using rIFN-α2a 12 × 10^6 U/m^2 three times a week (tiw) [95], and 50 × 10^6 tiw i.m., respectively [96], for three months revealed response rates at both dose levels of around 20%. IFN monotherapy in patients with metastatic melanoma induces responses in approximately 15% and CR rates on the order of 5% [97]. Predictors of favorable response were uninterrupted schedules of therapy regardless of route, with no clear advantage of lower or higher dosages in the range between 10 × 10^6 U/m^2 and 50 × 10^6 U/m^2 qd or tiw. Intermittent cyclic therapy was associated with a poorer outcome [97]. Suggestions of response durability set IFN apart from DTIC as a therapy for metastatic melanoma [98].

Combination Therapy

More recently, IFN-α has been used in the context of combination therapy for the treatment of metastatic melanoma. Numerous trials have been performed combining IFN with IL-2, with single-agent chemotherapy, and with Tamoxifen (Table 5A). The addition of IFN to IL-2 did not result in a

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n patients</th>
<th>Study design</th>
<th>Response rates (%)</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negrier [91]</td>
<td>1997</td>
<td>70</td>
<td>IL-2 9 MIU s.c. days 1-6 wks 1, 3, 5, 7 IFN 6 MU s.c. days 1, 3, 5 wks 1,2,5, 7</td>
<td>1.4</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>61</td>
<td>IL-2 9 MU s.c. days 1-6 wks 1, 3, 5, 7 IFN 6 MU s.c. days 1, 3, 5 wks 1,2,5, 7 5-FU 600 mg/m^2 CI days 1-5 wks 1,5</td>
<td>8.2</td>
<td>(p = 0.10)</td>
</tr>
<tr>
<td>Atzpodien [92]</td>
<td>1997</td>
<td>41</td>
<td>IL-2 10 MIU/m^2 s.c. bid days 3-5 wks 1, 4, 5 5 MIU/m^2 s.c. days 1, 3, 5 wks 2,3 IFN 6 MU s.c. day 1 wks 1, 4 and days 1, 3, 5 wks 2,3 IFN 9 MU/m^2 s.c. day 1 wks 1, 4 and days 1, 3, 5 wks 2,3 5-FU 1.000 mg/m^2 q wk wks 5-8</td>
<td>39</td>
<td>&gt;42 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37</td>
<td>Tamoxifen 45 mg/m^2 PO bid wks 1-8</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(p &lt; 0.04)</td>
</tr>
</tbody>
</table>
significantly greater response rate or survival, with significantly more side effects [99]. An early study looking at the combination of IFN and DTIC chemotherapy was promising [100], but subsequent investigations failed to demonstrate an advantage to this combination [101-103].

Chemoimmunotherapy has been assessed in patients with metastatic melanoma [104-109]. Table 5B summarizes some of the major studies looking at this treatment modality. Although increased response rates have been shown in most of these trials, this has not translated into an increase in overall survival. A recent abstract from the M.D. Anderson Cancer Center randomized patients between cisplatin, VBL and DTIC (CVD) and CVD plus sequential infusion IL-2 and IFN therapy. This study demonstrated a survival improvement in the chemoimmunotherapy arm that approached statistical significance [110]. The major question in treating patients with metastatic melanoma who are eligible for these trials is whether the severe toxicities encountered with chemoimmunotherapy are worth the as-yet unproven survival benefits. The Eastern Cooperative Oncology Group (ECOG) 3695/Cancer and Leukemia Group B (CALGB) 509802, a study currently accruing patients and randomizing them to CVD or concomitant CVD plus IL-2 and IFN, will hopefully provide information to help answer this question.

### Adjuvant Therapy

Several trials looked at the role of IFN-α in the adjuvant setting for melanoma patients at high risk for relapse, including patients with deep primary lesions and those with lymph node involvement [111-116]. Studies using relatively low doses of IFN (3 × 10⁸ U tiw) failed to show an overall survival benefit in this patient group. In 1996, Kirkwood et al. published the results of ECOG 1684, which demonstrated both a disease-free and overall survival benefit for patients with stage III (lymph node-positive) melanoma treated with maximally tolerated doses of IFN-α [113]. The regimen used in

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n patients</th>
<th>Study design</th>
<th>Response rates (%)</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sparano [99]</td>
<td>1993</td>
<td>44</td>
<td>IL-2 6 MU/m² i.v. 14 doses days 1-5, 15-19</td>
<td>5</td>
<td>10.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41</td>
<td>IL-2 4.5 MU/m² i.v. 8 doses days 1-5, 15-19 IFN-α 3 MU s.c. tiw</td>
<td>10</td>
<td>9.7</td>
</tr>
<tr>
<td>Falkson [100]</td>
<td>1991</td>
<td>31</td>
<td>DTIC 200 mg/m² i.v. days 1-5 q 28 days</td>
<td>20</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>IFN-α 15 MU/m² i.v. M-F × 3 wk, then 10 MU/m² s.c. tiw DTIC 200 mg/m² i.v. days 1-5 q 28 d starting wk 4</td>
<td>53</td>
<td>17.6</td>
</tr>
<tr>
<td>(p &lt; 0.05)</td>
<td>(p &lt; 0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomson [103]</td>
<td>1993</td>
<td>83</td>
<td>DTIC 800 mg/m² i.v. q 21 days</td>
<td>17</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>DTIC (200-800 mg²) i.v. q 21 days IFN-α 9 MU s.c. qd</td>
<td>21</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>76</td>
<td>DTIC 800 mg/m² i.v. q 21 days IFN-α 3 MU s.c. tiw</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>DTIC 800 mg/m² i.v. q 21 days IFN-α 3 MU IM days 1-3, 6 MU days 4-6 then 9 MU IM qd</td>
<td>23</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>DTIC 800 mg/m² i.v. q 21 days IFN-α 3 MU IM days 1-3, 6 MU days 4-6 then 9 MU IM qd</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Falkson [101]</td>
<td>1998</td>
<td>69</td>
<td>DTIC 200 mg/m² i.v. days 1-5 q 28 days</td>
<td>15</td>
<td>9.99</td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>IFN 15 MU/m² i.v. days 1-5 wks 1-3, then 10 MU/m² s.c. tiw DTIC 200 mg/m² i.v. days 1-5 q 28 days, starting day 22</td>
<td>21</td>
<td>9.35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>DTIC 200 mg/m² i.v. days 1-5 q 28 days Tamoxifen 20 mg PO qd IFN 15 MU/m² i.v. days 1-5 wks 1-3, then 10 MU/m² s.c. tiw</td>
<td>19</td>
<td>9.54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>DTIC 200 mg/m² i.v. days 1-5 q 28 days Tamoxifen 20 mg PO qd</td>
<td>18</td>
<td>7.97</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(p = 0.85)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

NS = not significant
ECOG 1684 involved administration of IFN-α at $20 \times 10^6$ U/m$^2$ i.v. qd for five days/week for four weeks, followed by $10 \times 10^6$ U/m$^2$ s.c. tiw for 11 months. Based on the findings from this study, the FDA approved the uses of IFN-α in stage III and stage IIB melanoma. The follow-up study ECOG 1690 showed a disease-free survival advantage in similar patient groups, but an overall survival advantage was not seen [114]. Of note, overall survival of both the IFN and control groups in ECOG 1690 is higher than the IFN arm in ECOG 1684. This may be due to a number of reasons, including patient crossover, or a favorable patient cohort in the control arm of ECOG 1690. Results from ECOG 1694, which randomized patients between standard high-dose IFN and GM-K, a ganglioside vaccine developed at the Memorial Sloan-Kettering Cancer Center, will be available soon. This study was closed prematurely, because a significantly greater number of relapses occurred in the vaccine arm.

**Summary**

Although concerns have been raised regarding the toxicity of IFN therapy, the authors recommend its use in the adjuvant setting. For stage IV disease, the role of IFN-α is less clear. The promising response rates of chemoimmunotherapy have not translated into a hoped-for prolongation in survival. Nevertheless, in patients with good performance status, low disease burden and favorable disease sites (lung, skin), chemoimmunotherapy should be considered, preferably in the setting of a clinical trial. Results from several studies will be available in the near future to help clarify the role of IFN therapy in both the adjuvant and metastatic settings.

**KS**

IFN has been used in the treatment of HIV-associated KS since 1981 [117]. Initial treatment regimens employed doses in the $20 \times 10^6$ U/d range, which were associated with significant response rates, but also high levels of toxicity [118]. In subsequent studies [119], the probability of responding to therapy was correlated with CD4 count. Patients with CD4 counts greater than 400/mm$^3$ responded, whereas none of those with CD4 counts of less than 150/mm$^3$ had a response.

---

**Table 5B. Melanoma: randomized studies**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n patients</th>
<th>Study design</th>
<th>Response rates (%)</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keilholz [105]</td>
<td>1997</td>
<td>66</td>
<td>Starting d 3: IL-2 18 MIU/m² i.v. CI over 6 h, then 18 MIU/m² i.v. CI over 12 h, then 4.5 MIU/m² i.v. CI qd x 3 days</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN-α 10 MU/m² s.c. days 1-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Starting d 3: IL-2 18 MIU/m² i.v. CI over 6 h, then 18 MIU/m² i.v. CI over 12 h, then 4.5 MIU/m² i.v. CI qd x 3 days</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN-α 10 MU/m² s.c. days 1-5</td>
<td>(p = 0.04)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cisplatin 100 mg/m² day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenberg [109]</td>
<td>1999</td>
<td>52</td>
<td>Cisplatin 25 mg/m² i.v. days 2-4 and 23-25, DTIC 220 mg/m² i.v. days 2-4 and 23-25, Tamoxifen 20 mg PO qd starting day 1</td>
<td>27</td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cisplatin 25 mg/m² i.v. days 2-4 and 23-25, DTIC 220 mg/m² i.v. days 2-4 and 23-25, Tamoxifen 20 mg PO qd starting day 1</td>
<td>44</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN-α 6 MU/m² s.c. days 5-8 and 26-29, IL-2 0.72 MU/kg i.v. q 8 h days 5-8 and 26-29 to patient tolerance</td>
<td>(p = 0.071)</td>
<td>(p = 0.052)</td>
</tr>
<tr>
<td>Eton [110]</td>
<td>2000</td>
<td>92</td>
<td>Cisplatin 20 mg/m² i.v. qd days 1-4, 22-25, DTIC 800 mg/m² i.v. day 1, 22 VBL 2 mg/m² i.v. days 1-4, 22-25</td>
<td>25</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cisplatin 20 mg/m² i.v. qd days 1-4, 22-25, DTIC 800 mg/m² i.v. day 1, 22 VBL 1.5 mg/m² i.v. days 1-4, 22-25</td>
<td>48</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN 5 MU/m² s.c. days 5-9, 17-21, 26-30</td>
<td>(p = 0.001)</td>
<td>(p = 0.055)</td>
</tr>
</tbody>
</table>

NS = not significant; CI = continuous infusion
The combination of lower dosages of IFN-α and zidovudine (AZT) was found to be effective in treating HIV-associated KS, including those with lower CD4 counts [120], but with dose-limiting hematological side effects. In 1991, Scadden et al. reported that the use of GM-CSF as an adjunct to combination IFN-α/AZT therapy resulted in an improved end-of-study absolute neutrophil count [121, 122]. Another report indicated that although GM-CSF decreased the incidence of neutropenia in patients on IFN-α and AZT, other IFN-related side effects precluded any dose escalation [123]. More recently, Shepherd et al. reported on treatment of HIV-related KS with IFN-α and IFN-γ at two dose levels. All patients received AZT 500 mg daily and were randomized to receive IFN-α 1 × 10^6 U or 8 × 10^6 U s.c. qd. Response was reported in 31% of high-dose therapy and 8% of low-dose therapy patients (p = .011). Response at both dose levels was higher for patients with CD4 (+) counts greater than 150/mm³. The median time to progression was longer for patients in the 8-million U arm (18 versus 13 weeks; p = .002). Both hematologic and nonhematologic toxicities were higher in the high-dose arm; 50 of 54 patients who received 8 × 10^6 U required dose alterations in the first four months compared with only 19 of 53 patients who received 1 × 10^6 U (p = .0002) [124].

A phase II/III study assessed effectiveness of IFN-γ therapy in the treatment of HIV-associated KS, and showed clinical response in 3 of 17 patients [125]. There does not appear to be any role for IFN-γ in the treatment of KS.

For widespread, symptomatic KS, combination cytotoxic chemotherapy is usually the treatment of choice [126]. Paclitaxel has recently been evaluated in the treatment of AIDS-related KS demonstrating promising results [127, 128]. The exciting initial findings with paclitaxel will prompt direct comparisons between paclitaxel and IFN-α. Further study will allow us to determine the definitive role for IFN-α therapy in KS.

In summary IFN-α, either as monotherapy or in combination with AZT, shows activity in HIV-positive patients provided they possess relatively elevated CD4 (+) lymphocyte counts (i.e., greater than 150/mm³). For more advanced disease, combination chemotherapy is currently the accepted means of treatment for KS.

**Toxicities**

Treatment with IFN is always considered in the context of its significant side-effect profile. Four major side effect groups occur: constitutional, neuropsychiatric, hematologic, and hepatic. These vary in degree, persistence and our ability to manage them. Side effects can also be divided into those that occur acutely but decrease over time, and those that are chronic. The severity of many side effects appears to be directly related to the dose and duration of IFN therapy [129]. This section summarizes the major types of toxicity and their etiology, and concludes with proposed toxicity management guidelines.

**Acute Toxicity**

Toxicity can be divided into acute and chronic manifestations. In the acute setting, the patients experience fevers, chills and rigors, usually between 3 and 6 h after receiving IFN. Patients may also experience headaches, myalgias, and malaise. With prolonged and uninterrupted administration of IFN, tolerance can develop to these symptoms. However, treatment breaks as short as a few days can result in the redevelopment of rigors and chills. Transaminases and neutropenia may occur within the first few days of treatment, and can be controlled by adjusting the IFN dose. Both resolve rapidly upon cessation of treatment. If the transaminitis is not followed closely, it can result in fatal hepatotoxicity [113].

**Chronic Toxicity**

The chronic symptoms experienced by patients on IFN include fatigue (70%-100% of patients), anorexia (40%-70%), and neuropsychiatric symptoms (up to 30%). These symptoms appear to be dose-related, and cumulative, worsening over time [9].

**Mechanisms of Toxicity**

The mechanisms of IFN-induced toxicity are unclear, but are most likely multifactorial. These will be summarized in the following section.

**Fatigue**

Fatigue is the most common symptom associated with chronic use of IFN-α, occurring in more than 70% of patients. It is frequently the dose-limiting toxicity [130]. The exact etiology of the fatigue is unclear, but there appears to be both a psychological and neuromuscular component [130, 131]. Chronic fatigue generally worsens with continued therapy, does not exhibit tolerance, is dose-related, and does not respond to therapy with steroids or antiinflammatory drugs. Little research has been done to analyze the neuromuscular axis in patients on IFN to determine whether there are clear structural or biochemical changes that can be quantified. Assessment with muscle biopsy and other diagnostic modalities has not been performed. Clearly, further study into the etiology of IFN-induced fatigue is needed to better manage this prevalent and debilitating side effect. The first step will be to build into clinical trials an accurate, objective and reproducible evaluation of patient fatigue.

**Neurological Toxicities**

Central nervous system toxicities include somnolence, confusion, lethargy, dizziness, and impaired mental status.
Peripheral nervous system toxicities include numbness and tingling.

Duration of therapy appears to be the most important factor in determining the degree of cognitive impairment [132, 133]. Absolute dose appears to be less important.

Caraceni et al. evaluated neurotoxicities of 113 patients receiving IFN-α 3 × 10^6 U s.c. tiw for 36 months as part of a randomized trial. Particular emphasis was placed on the development of extrapyramidal signs and symptoms, psychiatric symptoms, attention, memory, reasoning capability, psychological adaptation, and quality of life [134]. Significant differences between study and control groups included a higher incidence of action tremor in the treatment group. Cognitive performance did not differ between the two groups, but a higher level of anxiety was recorded in the IFN group. In the quality-of-life assessment, there was a significantly greater number of patients who experienced fatigue.

Mood Disorders

Patients with cancer in general have a higher risk of developing clinical depression [133]. A significant minority of patients on IFN therapy becomes depressed, in some cases leading to suicide. There are also several reports of mania in patients on IFN [135-138]. Mood disorders can occur in patients without predisposing factors or past history of psychiatric problems.

In non-cancer patients, depression is associated with alterations in a number of bodily systems, including the endocrine system [133]. The mechanism by which IFN causes psychiatric disturbances is poorly understood, and research into the mechanisms underlying endogenous depression has been performed in patients receiving IFN to better understand the etiology of IFN-induced mood disturbances. Neuroendocrine disturbances, including perturbation of the hypothalamic-thyroid-adrenal axis and alteration in dopamine and serotonin production have all been implicated [139], as have alterations in the secretion of secondary cytokines, especially IL-1 [133].

Endocrine Dysfunction

In 1983, Ernstoff et al. reported that human leukocyte IFN administration resulted in an increase in cortisol levels via adrenocorticotropic hormone (ACTH) stimulation [140]. More recent studies revealed that IFN-β and IFN-γ both induced ACTH, prolactin, growth hormone and cortisol levels in patients [141], although other investigators did not find any effect of IFN-β on anterior pituitary function [142]. An assessment of IFN-α-induced endocrine stimulation in patients with myeloproliferative disorders revealed that on day 1 of therapy, a significant stimulation of the hypothalamic-pituitary axis was apparent, an effect that had disappeared by the third week of therapy [143]. The acute stimulatory effect of IFN-α on cortisol release appears to be mediated by the release of hypothalamic corticotropin releasing hormone [143].

There have been reports of alterations in the levels of sex hormones during IFN therapy, and male sexual dysfunction does occur [139]. The hypothalamic-pituitary-gonadal axis can be suppressed during acute and chronic illness, and this effect appears to be cytokine-mediated [139]. Thus it is possible that IFN-induced alteration in sex hormone levels is mediated via direct or indirect pathways.

Autoimmune-Mediated Thyroid Dysfunction

Thyroid dysfunction occurs in 8%-20% of patients receiving IFN-α therapy [139]. Numerous studies report the development of overt or subclinical hyper- or hypothyroidism in patients on IFN-α for various malignancies [144-149]. The pattern demonstrated by most patients is one of an autoimmune thyroiditis, with a period of hyper- followed by hypothyroidism [139]. A few patients with hepatitis C have developed symptoms of Grave’s disease while on IFN-α [139]. Investigation into etiologies of IFN-α-induced thyroiditis suggests an indirect effect via activation of other cytokines, including IFN-γ. Preexisting autoimmune disease or baseline serological abnormalities appear to predispose patients to developing overt autoimmune disease while on IFN-α [147, 148]. Antithyroid antibodies occur in up to 16% of women and 1.5% to 3% of men in the general population, and individuals expressing baseline antithyroid antibodies have a 60% risk of developing clinical thyroid disease during the course of therapy [139]. Treatment of MS patients with IFN-β was shown to induce antithyroid autoantibodies and symptoms of overt hypothyroidism in a small series of patients [150]. Treatment with IFN-γ paradoxically did not appear to induce the same number of autoimmune side effects as IFN-α [151]. A recent study correlated the degree of autoimmune disease with improved prognosis in renal cancer patients treated with IFN-α and IL-2, suggesting that autoimmune disease while on cytokine therapy is a marker for breaking immunologic tolerance in patients with cancer [152].

Although it is unclear how much of the IFN-mediated toxicity is due to endocrine dysfunction, a serum thyroid stimulating hormone (TSH) determination is indicated in a patient on IFN who complains of severe and persistent fatigue, cold sensitivity, or other symptoms suggestive of hypothyroidism.

STUDIES AND SIDE-EFFECT PROFILES

Due to the variation in dosing and schedule, dose adjustment, duration of follow-up, data presentation, and disease
type in which IFN has been administered, it is difficult to make direct comparisons of side-effect profiles seen in various studies.

Some general trends can be observed. In Table 6, side effects resulting from treatment of melanoma, NHL, and KS with high-dose levels of IFN (10 × 10^6 to 50 × 10^6 U/m²) are compared. Fatigue symptoms at this dose level occur at levels approaching 90% in the studies that categorized this symptom. A very high incidence of fevers is also recorded. The one study that categorized depression recorded a rate of 47%. Other side effects are difficult to compare due to the incompleteness of the data, but in general it appears that the incidence of severe toxicities (grade III or greater) is much greater at these higher doses.

Table 7 summarizes the side-effect profiles of patients who received IFN dosages in the range of 3 × 10^6 U to 5 × 10^6 U/m² for a variety of cancers. Although direct comparisons may not be quantitative, and several studies only recorded the incidence of grade 3 and higher toxicities, in general the degree of constitutional toxicities appears to be considerably lower than is seen in the studies with the higher doses seen in Table 6, and the incidence of dose-limiting hepatic, neuropsychiatric and hematologic toxicities appears to be negligible.

**QUALITY OF LIFE**

Due to the substantial toxicities encountered during IFN therapy, a number of groups have looked at the quality of life of patients undergoing IFN therapy. Cole et al. evaluated the quality of life of patients receiving high-dose IFN therapy in the ECOG 1684 trial for stage III melanoma using the Quality-Adjusted Time Without Symptoms and Toxicity (Q-TWiST) methodology [153], which estimates the mean time spent in a series of clinical health states that differ in terms of quality of life. Q-TWiST adjusts each time period depending on how much value the patient places on the quality of life of each health state [153]. Even if patients were to place a very low value on the time spent on IFN, there would still be a net prolongation in overall survival on the ECOG 1684 trial.
combination chemotherapy with or without IFN-α2b for the treatment of advanced follicular lymphoma [63, 154]. An advantage in terms of quality-adjusted survival was seen in the patients receiving IFN regardless of the value placed on the time patients were undergoing IFN therapy [154].

Kilbridge et al. interviewed 107 patients with superficial melanomas who did not require IFN therapy, asking them what value they place on a prolongation of life secondary to IFN therapy, were they to need it. The authors assessed patient preference for a particular health state as a function of toxicity and outcome. A great majority of respondents indicated they preferred experiencing even severe treatment-related side effects for a gain in disease-free survival [155].

**MANAGING IFN TOXICITY**

Communication among all members of the treating team is imperative in managing patients on IFN therapy. Each team member is in a position to obtain complementary information that, when put together, gives a complete picture of the patient’s side-effect profile. The following section will summarize management of the major IFN side effects.

**Constitutional Side Effects**

Constitutional side effects are managed with copious hydration and acetaminophen. Acetaminophen is useful in controlling the shakes, fevers and myalgias experienced by the patient at the onset of therapy. Nonsteroidal anti-inflammatory medications may be used if acetaminophen is not adequate in controlling these symptoms, but should be used only if adequate control is not achieved with acetaminophen alone.

There is no recognized pharmacological antidote for IFN-induced fatigue. It is equally unclear what can be done to alleviate this symptom short of dose decrement, or cessation of treatment. Suggestions include mild exercise, good nutritional intake, copious fluid ingestion, and stress management techniques. The treating team needs to remember that a treatment-induced decrement in functional status can be a serious blow to a patient’s self-esteem and sense of independence [130], and that patients need encouragement and positive feedback from their treating team. On the other hand, patients also need to be told that it is acceptable to draw on social resources, which include family, friends, or hospital-based social services if the patients feel they are unable to cope.

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<td>Melanoma III</td>
<td>CML chronic-phase</td>
<td>CML chronic-phase</td>
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<td>Type/dose IFN</td>
<td>IFN-α2a 3 mu i.m. qd (\times 4) wks, then tiw until disease progression</td>
<td>IFN-α2a Mu s.c. tiw (\times 18) mos</td>
<td>IFN-α2b 5 MU i.m. tiw (\times 12) mos</td>
<td>IFN-α5 10 mg s.c. until progression</td>
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</table>

**Table 7. Summary of toxicities in patients receiving low-dose IFN for malignancies**
Mood Disorders

Forty percent of patients on IFN will experience some degree of mood impairment, and up to 10% may become overtly depressed [113, 130]. It is important that the treatment team be aware of the potential for depression, and to incorporate questions about the patient’s mood and emotional state into the patient’s routine evaluation. Early psychiatric referral is important, and IFN-related mood disorders can often be managed with measures similar to those used to treat endogenous depression. The occurrence of mania in patients on IFN also needs to be kept in mind, especially after patients undergo significant dose-reduction or treatment breaks [138]. The clinician’s natural instinct is to interdict the use of IFN in patients with any past history of depression, or a strong family history of mood disorders. We recommend that patients with any of the above risk factors be evaluated prior to treatment by a psychiatrist versed in the assessment and management of cancer patients, and ideally with prior experience in treating IFN-related mood disorders [138]. These patients should not be denied treatment, but should be followed closely for signs of depression, with mood-related questions as part of the review of systems at each visit.

Hepatotoxicity

In patients receiving high-dose i.v. IFN for stage III melanoma, liver function tests (LFTs) need to be drawn at least weekly, assessing for grade III transaminitis. Withholding treatment until LFTs decrease to a grade I toxicity and restarting with a 30%-50% dose reduction is a standard approach. Recently, a report was published suggesting that less aggressive dose reduction can be performed with no decrease in patient safety or compliance [161]. Once a steady-state level of treatment is achieved, LFTs are fairly stable and assessment of liver function can be decreased to monthly or bimonthly blood draws.

Hematologic Toxicity

Weekly blood draws assessing for grade III neutropenia need to be performed in patients receiving high-dose i.v. IFN. Dose-reduction algorithms are the same as those for hepatotoxicity. In patients on s.c. IFN regimens, once a steady-state of treatment is established, neutrophil counts are fairly stable, although they may drift down further in some patients. In general, blood draws can be decreased to a monthly or even bimonthly schedule once stable dosing occurs.

Endocrine Toxicity

Recognition of the occurrence of hypothyroidism is important in the management of patients on IFN. Initially, monthly TSH measurements should be performed, and if three sequential values are stable and within a normal range, bimonthly or quarterly evaluations may be sufficient.

Summary and Recommendations

IFN is a promising but incompletely understood anticancer agent. Clinical trials have established a number of indications for the IFNs in both the hematological and solid tumor arenas, although the effectiveness of the IFNs is modest in most applications of the agent.

The side-effect profiles of the IFNs are substantial, and at high doses, daunting, making the choice of IFN therapy one that has to be weighed against the near certainty of a decrement in quality of life while on the agent. It is important that the treating physician be aware of the four major categories of IFN toxicity: constitutional, neuropsychiatric, hepatic, and hematologic. An ongoing dialogue must occur between the patient and the treating team to ensure that all aspects of IFN toxicity are addressed. A number of steps can be taken to minimize the morbidity of IFN therapy, resulting in an improvement in both quality of life and patient compliance.

IFN has been FDA-approved for use in a number of clinical applications. Treatment with IFN outside of these recommendations should be performed in the context of a clinical trial designed to assess immunological endpoints and to carefully measure type and degree of toxicities. Companion studies designed to ask specific questions regarding the etiology of IFN-induced toxicities should also be encouraged, as this knowledge will be extremely useful in the evolution of IFN as a useful agent in the oncological armamentarium.

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