Treatment of Kaposi's Sarcoma With Interferon Alfa-2b (Intron® A)

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The activity of the alpha interferons against AIDS-related Kaposi's sarcoma (KS) has been demonstrated in numerous clinical trials. Unfortunately, most reports have involved small patient cohorts and a variety of dosages and schedules of administration. We report here a series of Phase II trials with interferon alfa-2b (Intron® A, Schering Corp., Kenilworth, NJ) involving 114 patients using three dose regimens. Patients received 50×10^6 IU/m^2 intravenously (high dose), 30×10^6 IU/m^2 subcutaneously (intermediate dose), or 1×10^6 IU/m^2 subcutaneously (low dose). Clinical responses were seen in all regimens and, overall, 35% of the patients obtained complete or partial remissions. The response rates in the low-, intermediate-, and high-dose groups were 33%, 28%, and 45%, respectively. In addition, high-dose therapy was associated with more rapid time to response. Patients with low-stage (I or II) disease and those who lack B symptoms were more likely to respond to therapy; *i.e.,* response rates for patients without B symptoms were 38%, 44%, and 60% in the low-, intermediate-, and high-dose groups, respectively. Seventy (61%) patients had died at the time of data collection, with a median survival of 15 months. Disease stage and the presence of B symptoms significantly affected mortality. Responders enjoyed significantly longer survival ($P < 0.10$) than did nonresponders both overall and when adjusted for disease stage. Interferon alfa-2b was generally well tolerated, although almost all patients experienced flu-like symptoms. No life-threatening toxicities occurred and only six (6%) patients discontinued treatment due to adverse reactions. No significant improvement in immunologic parameters was detected during this study. These studies suggest that, in this disease setting, interferon alfa-2b may be acting through direct antiproliferative effects rather than as an immunomodulator, and higher doses appear to be more effective than very low doses.

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THE RECOGNITION of the relatively rare tumor Kaposi's sarcoma (KS) in a large cohort of young homosexual men led to the first report of the acquired immune deficiency syndrome (AIDS).[1,2] By January 1986, 16,458 AIDS cases had been identified in the United States by the Centers for Disease Control (CDC).[3] The incidence of AIDS continues to rise, and current projections predict a doubling of reportable new cases in the United States every 11 months. KS remains the most common malignancy associated with AIDS and occurs in approximately 25% to 33% of these patients.

Although classical KS has been reported to be sensitive to several cytotoxic chemotherapeutic agents, *e.g.,* vinca alkaloids and etoposide, the use of these agents in treating AIDS-related KS is frequently limited by the patient's compromised baseline immunologic status.[4,5] Single-agent and combination chemotherapy trials have tended to produce responses of only brief duration and have also resulted in considerable toxicity.[4,6] As an alternative therapy with potential antiviral, antiproliferative, and immunoregulatory activities, interferon was identified as a potential therapeutic candidate for testing in AIDS-related KS soon after the disease was first described. Many reports have now confirmed interferon's activity against KS in AIDS patients.[7-12] Unfortunately, many of these studies involved small cohorts of patients and used various preparations of interferons administered in a variety of doses and schedules. We now report our large clinical experience with recombinant interferon alfa-2b (Intron® A) involving 114 patients in a series of Phase II studies using three dose levels.

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Methods

Interferon

Recombinant interferon alfa-2b (Intron® A) was provided by Schering Corporation (Kenilworth, NJ). This

highly purified interferon, with a specific activity of 2×10^8 IU/mg protein, was produced and purified by means previously described.[13]

Study Design and Patients

Study protocols were approved by the Investigational Review Boards of the respective institutions, and informed consent was obtained from all patients. Patients who met the CDC criteria for AIDS-related KS were entered into one of three Phase II studies conducted from August 1982 to March 1984. Twenty patients were initially enrolled in a randomized study in which they received either high-dose (50×10^6 IU/m^2) intravenous (IV) or low-dose (1×10^6 IU/m^2) subcutaneous (SC) interferon alfa-2b. Both doses were administered daily for 5 days every other week for 8 weeks. Preliminary results of this study have been reported elsewhere.[9] After the entry of the first 20 patients, the low-dose SC therapy appeared to be inferior to the high-dose IV regimen. Consequently, this arm of the study was closed to further entry. An additional 21 patients were then entered into the high-dose group. Subsequently, a third group of 73 men meeting the same entry criteria entered into a nonrandomized study of an intermediate dose of interferon alfa-2b (30×10^6 IU/m^2) administered SC three times weekly (*i.e.,* Monday, Wednesday, and Friday). In all protocols, response was assessed following 8 weeks of treatment, and patients with objective responses or stable disease were permitted to continue on maintenance therapy at the same dose and regimen.

Inclusion criteria for all studies were that patients must be male, 18 years of age or older, have biopsy-proven KS, life expectancy ≥6 months, Karnofsky performance status of 80% to 100%, hemoglobin ≥10 gm/dl; platelet count ≥50,000/mm^3, and demonstrate normal renal and hepatic function. No exposure to any investigational or antineoplastic agent within 4 weeks prior to entry was permitted. Patients with active infections at the time of entry were not considered evaluable. Detailed medical and sexual histories were obtained from all patients. Complete blood and platelet counts, serum chemistries, urinalyses, chest radiographs, and electrocardiograms (ECGs) were performed at baseline and regularly throughout the study in all patients. Immunologic assessments were also done as previously reported.[9]

The investigators recorded all adverse experiences, both subjective and objective, according to the World Health Organization's criteria for grading toxicity (Grades I–IV). Dose modifications were then made accordingly.[14] Grade III or IV toxicity usually necessitated brief discontinuation of therapy, followed by resumption of treatment at 50% of the prior dose. Survival curves were generated using Cox's regression model.

Evaluating Clinical Response

At entry, all visible lesions were noted and two-dimensional measurements of at least five representative skin lesions or measurable lymph nodes were recorded. Endoscopic examination was encouraged, but not required. Patients were staged according to the system described by Krigel *et al.*[15] Response was assessed monthly and was based on changes in size and appearance of lesions. In the initial protocol design, a standard oncologic criterion (bidimensional measurement of lesions) for response was used. However, this method proved inadequate to follow the course of AIDS-related KS. Specifically, many patients who presented with raised nodular dark purple lesions responded to interferon alfa-2b with a fading and flattening of the lesions to the point of their becoming flush to the skin and taking the appearance of a scar or tattoo. In view of these findings, the criteria for response were modified as follows.

Patients were considered to have a complete response (CR) when all lesions had completely disappeared or flattened and any remaining visible lesions contained no KS as confirmed by biopsy. A partial response (PR) was judged as complete flattening or disappearance of one half of the lesions, without necessarily having a full 50% reduction in the sum of the products of all measured lesions. No new lesions could have appeared. No change, or stable disease, represented a decrease of less than 50% in the size of measurable lesions and no new lesions. Progression was defined as the appearance of any new lesion, even if other lesions decreased in size.

Results

From 1981 to 1984, 114 men entered into these studies. All were homosexual or bisexual. Their mean age was 35.4 years (range, 21–56 years). The life-style and medical histories of the patients in all three studies were similar in terms of number of sexual partners, recreational drug use, and history of sexually transmitted diseases. These histories were similar to other reported populations of patients with AIDS-related KS.[16]

Of the 114 participants, 103 were considered evaluable for an analysis of efficacy. Four patients had active opportunistic infections at entry, which was a predetermined exclusion criterion. They are included in analysis of toxicity. The remaining seven unevaluable participants received less than 4 weeks of treatment and were therefore felt not to have had an adequate course of therapy. Twenty-four patients (21%) had a history of opportunistic infections before entry into the study; 43 (38%) had a history of such B symptoms as unexplained fever or weight loss of greater than 10%, or both. Twenty-three (20%) patients had Stage IA or IIA disease; 40 (35%) had Stage IIIA or IVA disease. Seven (6%) patients had Stage IB or

TABLE 1. Response by Disease Stage and Subtype

	Overall response rate* (%)	Disease status	Evaluable patients	Response			
				CR	PR	NC	PD
Low-dose SC (N = 9)	3/9 (33%)	Stages I and II	5	1	1	1	2
		Stages III and IV	4	1	0	2	1
		Subtype A	8	2	1	3	2
		Subtype B	1	0	0	0	1
Intermediate-dose SC (N = 65)	15/65 (28%)	Stages I and II	5	0	0	2	3
		Stages III and IV	60	5	13	6	36
		Subtype A	36	5	11	6	14
		Subtype B	29	0	2	2	25
High-dose IV (N = 33)†	15/33 (45%)	Stages I and II	20	3	8	0	9
		Stages III and IV	13	1	3	0	9
		Subtype A	20	3	9	0	8
		Subtype B	13	1	2	0	10

CR: complete response; IV: intravenous; NC: no change; PD: progressive disease; PR: partial response; SC: subcutaneous.

* Overall response rate is the number of patients achieving complete or partial response divided by the total number of patients in the treatment group.

† Twenty-nine patients received IV treatment only; four patients who began treatment on the low-dose SC regimen switched to high-dose IV therapy.

IIB disease, and 36 (32%) patients had Stage IIIB or IVB disease.

Nine patients were treated with the low-dose regimen; 65 patients received the intermediate dose, and 33 patients were treated with the high dose. Four patients who switched from low-dose SC to high-dose IV therapy are counted in both categories for analysis. Patients in the low-dose group tended to have lower stage disease. Participants who received the intermediate-dose regimen were more likely to have Stage III or IV disease than patients who were treated with high-dose interferon. Nevertheless, the distribution of patients with B symptoms at entry was similar in the intermediate- and high-dose groups.

Response

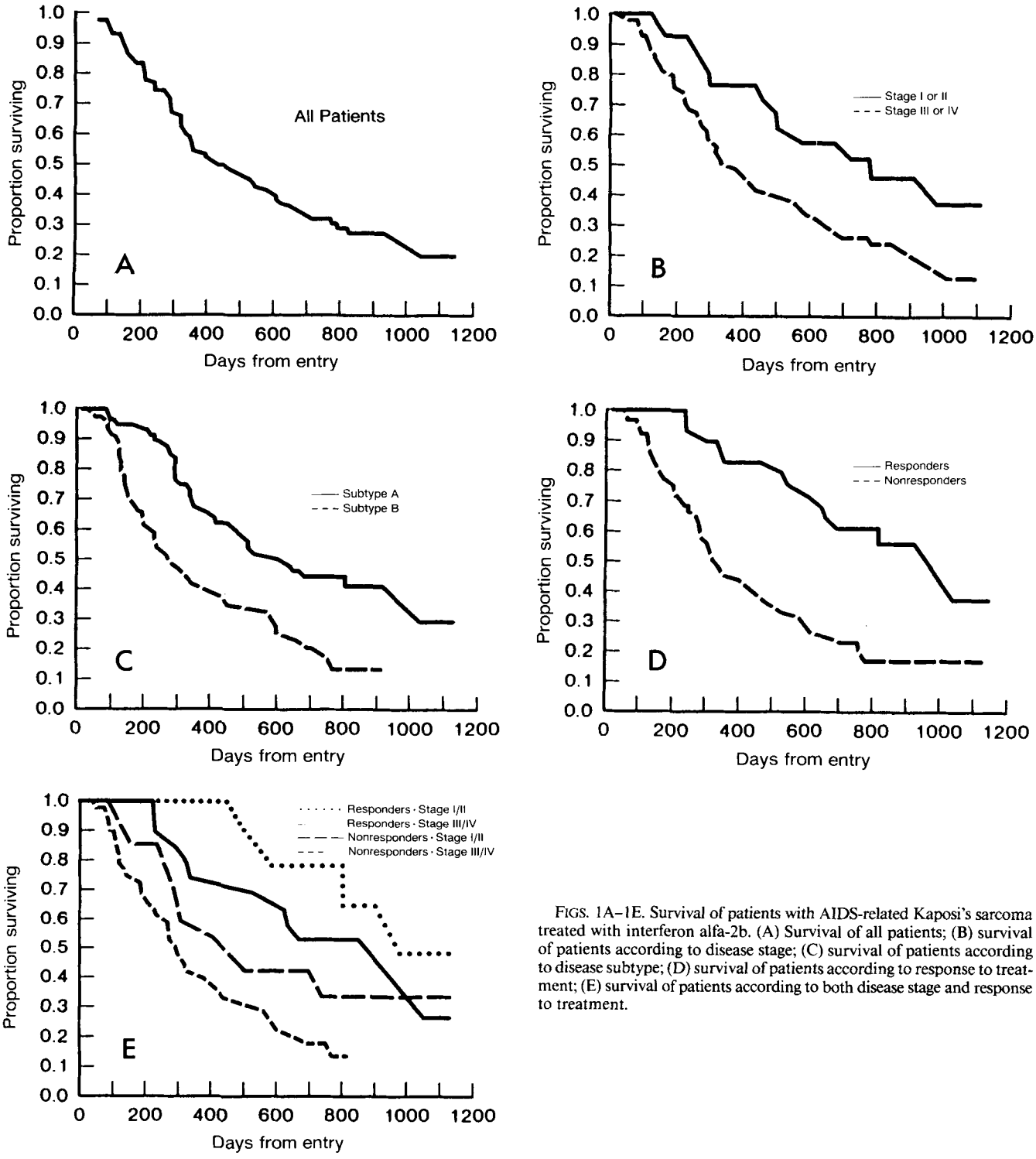
Objective responses (CR and PR) were seen with all three regimens. Overall, 36 (35%) of 103 evaluable patients had either a complete (11 patients) or partial (25 patients) response to interferon alfa-2b. The respective response rates of the low-, intermediate-, and high-dose groups were 33%, 28%, and 45%. However, these groups were not evenly balanced for known prognostic factors. Table 1 shows the responses for each regimen by disease stage and subtype. In all regimens, patients with low-stage (I or II) disease had higher response rates than did patients with Stage III or IV disease. Overall, objective responses were seen in 13 of 30 patients with Stage I or II disease compared with 23 of 77 patients with Stage III or IV disease ($P = 0.25$, Fisher's exact test). Similarly, asymptomatic patients (subtype A) were more likely to respond to treatment than those with B symptoms, 31 of 64 patients *versus* five of 43 patients ($P < 0.01$, Fisher's exact test). Response rates for patients without B symptoms were 38%, 44%, and 60% in the low-, intermediate-, and high-dose groups, respectively. Three of the four patients who failed to respond to the low-dose regimen responded when placed on the high-dose regimen. The median time to response with high-dose interferon was 4 weeks (range, 2–18 weeks) compared with 11 weeks for the low-dose regimen (range, 3–41 weeks) and 8 weeks for the intermediate-dose regimen (range, 8–11 weeks).

Survival

Seventy (61%) patients had died at the time of data collection. In all cases, deaths were due to extensive KS, opportunistic infections, or both. In no case was death judged to be related to treatment. Survival analyses are presented in Figures 1A–1E and Table 2. Median survival for the entire group was 15 months. Both disease stage and the presence of B symptoms significantly affected mortality. The comparison of survival in responders and nonresponders suggested a trend favoring responders when analyzed overall ($P < 0.10$) and when adjusted for disease stage ($P < 0.10$). Survival did not differ whether patients received intermediate-dose SC or high-dose IV therapy.

Opportunistic Infections

Table 3 summarizes the incidence of opportunistic infections before and during treatment. Twenty-four (21%) of 114 patients had a history of opportunistic infections before entering the study. In the high-dose group, two patients (both nonresponders) developed pneumocystis carnii pneumonia (PCP) during treatment. Among pa-



FIGS. 1A–1E. Survival of patients with AIDS-related Kaposi's sarcoma treated with interferon alfa-2b. (A) Survival of all patients; (B) survival of patients according to disease stage; (C) survival of patients according to disease subtype; (D) survival of patients according to response to treatment; (E) survival of patients according to both disease stage and response to treatment.

tients who received the intermediate-dose treatment, seven developed PCP during treatment; four of these seven patients had histories of infections. Of the seven patients in the intermediate-dose group who developed infections, two were partial responders.

Immunologic Data

In 98 patients for whom data were available, baseline ratios of T-helper to T-suppressor cells (Th:Ts) ranged from 0.04 to 1.9. These ratios are substantially lower than

TABLE 2. Survival Analysis

Patient group	Total	Dead	Alive	Median Survival (mo)
All patients	114	70	44	15.0
Stage I or II disease	29	13	16	27.3*
Stage III or IV disease	84	56	28	11.5
Subtype A	65	33	32	20.3*
Subtype B	48	36	12	9.2
Responders to therapy	36	14	22	33.0*
Nonresponders to therapy	67	47	20	10.5

* $P < 0.10$.

the normal range of 1.8 to 2.4 and are consistent with those reported in the literature for patients with AIDS-related KS. Comparison of baseline and end point T-cell ratios did not reveal any consistent improvement or deterioration. Moreover, analysis revealed no difference in the baseline immunologic measurements or post-treatment measurements between responders and nonresponders.

Treatment-Related Toxicity

Interferon alfa-2b treatment was generally well tolerated, both subjectively and objectively, in all patients (Table 4). Almost all patients experienced flu-like symptoms, *e.g.*, fever, chills, myalgias, and particularly fatigue. One patient on high-dose therapy developed Grade IV hypotension, which responded rapidly to fluid replacement therapy. This patient continued treatment at a reduced dose without further incident. Tolerance to interferon appeared to increase as therapy continued. At all dosages, hematologic and hepatic toxicity were mild, and toxicity was manageable in all cases by modifying the drug dose. No patient in the low- or high-dose group discontinued therapy because of abnormal laboratory test values.

TABLE 3. Incidence of Opportunistic Infections

	N	OI during treatment*
Patients with prior OI	24	4
Patients without prior OI	90	5
Total	114	9

OI: opportunistic infections.
* Includes up to 2 weeks after treatment.

In the intermediate-dose group, 6 (8%) of 73 patients discontinued treatment due to adverse reactions. Three patients had intolerable flu-like symptoms. Two patients (one with a history of alcoholism) developed elevated liver enzyme levels and one patient who entered study with an abnormal ECG (prominent R waves, particularly in leads V1–V3) had further ECG changes (T-wave inversion in leads V2–V4). This patient was discontinued from the study, and later he was diagnosed as having cytomegalovirus (CMV) myocarditis.

Discussion

In these studies, each of the three regimens produced clinical responses, confirming the previously reported activity of alpha interferon against KS.[7-12] The importance of certain prognostic factors[17] was also verified as all regimens produced higher response rates in patients who had low-stage disease or lacked B symptoms. The optimal dose and schedule for administration of alpha interferon as

TABLE 4. Incidence of Adverse Experiences Related to Treatment*

	1 million IU/m² SC		30 million IU/m² SC		50 million IU/m² IV	
	No. of patients (n = 10)	%	No. of patients (n = 73)	%	No. of patients (n = 35)	%
Alopecia	0	(0)	9	(12)	0	(0)
Cardiovascular disorders	0	(0)	0	(0)	2†	(6)
Central nervous system disorders‡	1	(10)	15	(21)	12	(34)
Flu-like symptoms	8	(80)	73	(100)	35	(100)
Gastrointestinal disorders	0	(0)	15	(21)	4	(11)
Nausea and vomiting	1	(10)	20	(27)	7	(20)
Skin reactions						
Pruritis	0	(0)	5	(7)	2	(6)
Rash	0	(0)	7	(10)	2	(6)
Weight loss	0	(0)	4	(5)	0	(0)

IV: intravenous, SC: subcutaneous.
* Patients may have had more than one adverse experience.
† One patient developed cytomegalovirus myocarditis, and one patient experienced hypotension.
‡ These consisted primarily of somnolence.

well as many other biologic response modifiers remain unknown. In the studies summarized here, interferon alfa-2b was administered in three different doses and in two different administration schedules in a disease setting in which it has clear activity. In this setting, a highdose IV interferon regimen appeared superior to a very low-dose SC regimen given in the same schedule and an intermediate dose given by a different route and schedule. Moreover, time to response was shorter with the high-dose regimen than with the intermediate- and low-dose regimens. This presumed dose-response effect of alpha interferon and the lack of significant immunologic improvement in measured parameters suggest that interferon may be active against AIDS-related KS through direct antiproliferative effects rather than as an immunomodulator.

The median survival for the entire group was 15.0 months. This is somewhat lower than that reported in other studies[18,19] and probably reflects the high proportion of poor-risk participants in this study, *i.e.*, 84 (74%) patients with Stage III or IV disease, and 48 (42%) patients with B symptoms. The importance of disease stage and symptoms as prognostic factors has been described previously[15] and was confirmed in this larger series where both patients with low-stage (I or II) disease and those without B symptoms had significantly improved survival. Comparisons of survival in responders and nonresponders are fraught with inherent limitations and possibly reflect artifact rather than differences resulting solely from the treatment itself.[20–22] Nonetheless, with these caveats in mind, at present there is a significant improvement in the responders' survival, both overall and when adjusted for stage. Survival did not differ between patients who responded to IV or SC therapy.

Alpha interferons have not been shown to be effective in reversing the immune deficiency in patients with CDC-defined AIDS.[3,5,6] Since alpha interferon has been shown to be capable of inhibiting HTLV-III replication *in vitro*, it remains possible that interferon might have further potential in inhibiting the progression of AIDS when given to patients with early HTLV-III infection.[23,24] However, it would appear that when given to patients with advanced stages of AIDS who have developed KS, interferon alone is not particularly effective in reversing the immune defects and T-cell abnormalities. As further studies delineate the pathogenesis of the HTLV-III infection, we might better understand the potential role for interferon and other antiviral agents. Nevertheless, the ability of interferon to induce remission in KS remains clear. Further long-term studies will be necessary to determine if this effect can meaningfully improve survival or quality of life for AIDS patients.

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