[CANCER RESEARCH 48, 2574–2578, May 1, 1988]

Phase I Trial of Escalating Dose Doxorubicin Administered Concurrently with α_2-Interferon[1]

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ABSTRACT

The clinical use of α_2-interferon and doxorubicin is based on *in vitro* and preclinical *in vivo* observations of synergistic antitumor efficacy. To test this combination a Phase I clinical and pharmacokinetic study of the concurrent use of α_2-interferon and doxorubicin was initiated in patients with malignant solid tumors. Each 5-wk treatment cycle consisted of 3 wk of drug administration and 2 wk of rest. The α_2-interferon was administered s.c. at a constant dose of 10 million IU/m^2 on Mondays, Wednesdays, and Fridays in all patients while the doxorubicin was administered weekly beginning with a dose of 5 mg/m^2 and escalated to the maximum tolerated dose of 25 mg/m^2. At least three evaluable patients were entered at each dose level, and no dose escalations were allowed within patients. The dose-limiting toxicities were granulocytopenia and thrombocytopenia. Hepatic enzyme elevations and systemic symptoms due to interferon occurred at all dose levels. None was severe or dose limiting, and all were reversible. These toxicity data suggest that the hepatotoxic effects of interferon do not enhance doxorubicin toxicity when given by this dose and schedule. Doxorubicin plasma levels were measured at each dose level. The recommended dose of doxorubicin is 25 mg/m^2 per wk when administered with 10 million IU/m^2 of interferon in this schedule. This schedule allows for the administration of a greater total dose of doxorubicin than has been achieved when given every 3 wk with the same dose and schedule of α_2-interferon in a parallel study.

INTRODUCTION

Although interferons have demonstrated cytostatic activity *in vitro* as well as in preclinical *in vivo* systems, their spectrum of activity as single agents against common carcinomas has been disappointing. Almost all Phase II single agent trials have tested either natural interferon or recombinant α-interferons. Phase II data on recombinant γ- and recombinant β-interferon are just beginning to appear; therefore conclusions as to the activity of these compounds are premature. However, the potential to widen this spectrum may occur with the addition of chemotherapeutic agents. Synergistic activity *in vitro* has been demonstrated between a number of interferons and cytotoxic drugs (1–3). Specifically, *in vitro* synergistic activity has been demonstrated for recombinant α_2-interferon with doxorubicin (4–7) and cisplatin (6, 8). Clinical trials combining recombinant α_2-interferon with single agent chemotherapy and in some cases with multiple agent chemotherapy have also begun (9, 10). In some of these trials the early data appear promising; however, conclusions about activity are premature. In our previous study combining etoposide (VP-16) and α_2-interferon in patients with untreated epidemic Kaposi's sarcoma, we encountered an unexpectedly high incidence of severe myelotoxicity which had not been seen in our previous experience with either drug alone (9). Therefore, prior to exploring future Phase II interferon and cytotoxic combinations we elected to determine the maximum tolerated dose and the limiting toxicities in Phase I clinical trials. The objective of the current Phase I trial was to determine the type and diversity of the toxicities in patients receiving a constant dose of recombinant α_2-interferon with weekly escalating doses of doxorubicin.

MATERIALS AND METHODS

Patients. Patients were prospectively allocated in groups of at least three to receive doxorubicin given weekly on a Wednesday and α_2-interferon (Intron A; Schering Corp., Kenilworth, NJ) given 3 times a wk on Mondays, Wednesdays, and Fridays. The dose of interferon was constant at 10 million IU/m^2 given s.c., while doxorubicin was given over 15 min i.v. once per wk starting at 5 mg/m^2 and escalating to 25 mg/m^2. Dose escalations of doxorubicin were not allowed until 3 patients had safely completed each dosage group. A cycle was defined as 3 wk of treatment followed by 2 wk without any treatment. Dose-limiting toxicity was defined as being equal to or greater than ECOG[2] Grade II toxicity in any organ site (11). Prior to entry a complete medical history and physical exam were conducted, and the histopathology was reviewed. Eligibility criteria included an ECOG PS of less than or equal to 2, a signed institutional review board approved informed consent, platelet count greater than 100,000/mm^3, hemoglobin greater than 10 g/dl, serum creatinine less than 2.0 mg/dl, total bilirubin less than 2.5 mg/dl, and serum hepatic enzymes no more than 3 times normal. Patients with prior cardiac arrhythmias or history of ischemic heart disease were not eligible. Prior doxorubicin therapy was acceptable if the cumulative dose was less than 250 mg/m^2. Patients were seen each week during the study and were followed with a weekly history and physical examination, an estimate of ECOG PS, complete blood count, platelet, and differential count. Prior to the start of each cycle, patients also had blood drawn for serum liver enzymes, serum electrolytes, blood urea nitrogen, and creatinine; an electrocardiogram; a urinalysis; and a measurement of the tumor size if measurable disease was present. Patients were withdrawn from the study for disease progression, for severe life-threatening toxicity, or if the patient withdrew consent to participate in the study.

Two h prior to the administration of α_2-interferon, 650 to 1000 mg of acetominophen were given p.o. and repeated 3 h later. Patients were precluded from receiving steroids, nonsteroidal antiinflammatory drugs, prostaglandin inhibitors and hormones, or other chemotherapeutic drugs. Tumor responses were defined according to standard ECOG criteria (11). All responses had to last for at least 4 wk without deterioration of performance status, appearance of new lesions, progression of existing lesions, or weight decrease of 5% or more. A complete response indicated complete absence of any prevailing detectable disease. A partial response indicated a reduction of at least 50% in the sum of the products of the largest diameter and its perpendicular. If hepatomegaly was to be the indicator, then a 30% reduction of the sum of the liver measurements below the right costal margin at the midclavicular line and xiphoid was required, without worsening of liver function. Progression was defined as a 25% increase in the area of the lesion as defined above and/or development of new areas of disease and/or a fall in performance status and loss of weight of 5% or more.

Pharmacological Studies. The pharmacokinetics of doxorubicin was studied in at least one patient per dose level during the first doxorubicin administration. Anticoagulated blood specimens were obtained at 0, 5, 15, and 30 min and at 1, 2, 6, 8, 24, and 48 h after the end of doxorubicin injection. Plasma was obtained immediately by centrifu-

Received 11/17/86; revised 4/27/87, 10/27/87; accepted 12/17/87.

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[1] Supported by a grant from the Schering Corporation.

[2] The abbreviations used are: ECOG, Eastern Cooperative Oncology Group; PS, performance status; HPLC, high-pressure liquid chromatography; PR, partial response.

gation and frozen at −20°C. Samples were thawed at the time of analysis by HPLC, and 200 μg of daunorubicin were added as an internal standard. The samples were then extracted in chloroform:propranol (3:1). The organic phase was aspirated off and evaporated to dryness under nitrogen gas. The residue was resuspended in 350 μl of 9 mM ammonium phosphate-formate buffer at pH 2.5 (mobile Phase A). Ten to 100 μl of sample were then injected by means of a WISP automated sampler (Waters Associates, Milford, MA). Chromatography was performed on a 5-μm x 25-cm phenyl column (SOTA Chromatography, New York, NY). Gradient elution was carried out with mobile Phase A and 100% acentonitrile as mobile Phase B using a 10-min linear gradient (40% B increasing to 60%), at a flow rate of 1.5 ml/min. Regeneration time between injections was 4 min. The anthracyclines were detected using a Kratos Model 970 fluorometer with excitation at 482 nm, emission at 515 nm, and sensitivity set at 0.01 μV. Data were recorded on a Hewlett-Packard Model 3388A integrator. Areas of the anthracycline peaks were obtained by automated integration, and the concentration of doxorubicin was calculated by the internal standard method using a calibration table derived from standard curves of both doxorubicin and daunorubicin (10 to 450 ng/ml). Lower limits of detection for the method were 5 ng/ml of doxorubicin, and reproducibility was better than 90%. Urine was collected over 6-h and aliquots for 48 h. Internal standard was added to 1 ml of urine, and 100 μl were directly injected with the same HPLC parameters as above. Total doxorubicin excretion was determined for the 48-h period as the percentage of initial drug injected.

RESULTS

Twenty patients were entered into the study: 13 were male and 7 were female. The median age was 60 yr with a range of 34 to 72 yr. Seven had an ECOG performance status of 0, 11 a PS of 1, and 2 a PS of 2. Ten patients had received prior chemotherapy, including 3 who had received doxorubicin and 4 patients who had received both prior radiation and prior chemotherapy (one of these having had doxorubicin treatment). Six patients were previously untreated. Thirteen of the patients had metastatic malignant melanoma; 3 had renal cancer; and 1 each had small cell lung cancer, bladder cancer, breast cancer, and adenocarcinoma of unknown primary site.

The number of patients who received drug at each dose level is shown in Table 1 together with the median number of cycles. Dose-limiting toxicity was hematological. Both the platelets and WBC count were affected as demonstrated by nadirs of the first cycle. Nonhematological toxicities occurred at all dosage levels and consisted primarily of elevation of serum liver enzymes (Table 2) and systemic symptoms (Table 3). There did not appear to be any dose-response effect attributed to doxorubicin, and these changes reflect the known hepatocellular toxicity of interferon. Table 3 demonstrates the variety of systemic symptoms which occurred throughout all doxorubicin dose levels, again suggesting that these effects were due to interferon and were not exacerbated by the addition of doxorubicin. Most of these symptoms were the classic flu-like symptoms of lethargy, chills, fever, and muscle aches. Seven patients had severe muscular pain (ECOG Grade 3) not attributable to malignancy, and one patient developed impotence during treatment. The dose-limiting toxicities observed in this trial were neutropenia and thrombocytopenia. The maximum tolerated dose of doxorubicin was 25 mg/m² in this schedule. Since the hepatic toxicity was reversible and the systemic symptoms tolerable, neither of these was considered dose limiting.

Pharmacological studies were performed in six patients. Plasma doxorubicin levels were detectable in all patients. Peak levels for all six patients were observed within 5 to 15 min (Table 4) and appear to be dose related. The percentage of unchanged urinary excretion of doxorubicin for the entire group was 5.6 ± 0.84% (mean ± SEM). Patient 2, treated at 10 mg/m², showed only 1.9% unchanged urinary doxorubicin excretion in 48 h (Table 4), which was considerably lower than the others (range, 5.0 to 7.9%). This patient was taking multiple medications including digoxin, quinidine, propranolol, allopurinol, and Dyazide and had disproportionately high peak drug concentrations. These data most likely represent a drug-drug interaction.

There were two responses, both in patients with malignant melanoma. Both patients were previously untreated. One was a 64-yr-old female who developed a complete response in extensive visceral and skin disease at the 5-mg/m² level of doxorubicin. The time to complete response was 5 mo. The duration of the complete response from first treatment was 10 mo, and the duration of the complete response from the time of response was 6 mo. The other patient was a 34-yr-old male who developed a partial response at the 7.5-mg/m² level of doxorubicin. The time to PR was 5 mo, and the duration of response from first treatment was 9 mo and from the onset of PR was 4 mo.

DISCUSSION

Since the first recombinant interferon tested clinically was α_2-interferon, a considerable body of clinical information pertains to this subtype. Activity has been clearly demonstrated in hairy cell leukemia and is being further tested in favorable histology lymphoma, renal cell carcinoma, and Kaposi's sarcoma.

In an effort to improve both the response rates in the above

Table 1 *Hematological toxicity*

Dose level (mg/m²)	No. of patients in each level	Median no. of cycles	WBC		Platelets	
			Cycle 1	Cycle 2	Cycle 1	Cycle 2
			Median No.	Median No.	Median	Median
5.0	4[a]	2	3.9 3 (3.5–6.5)[b]	6.7 2 (3.0–10.3)	212 (160–344)	327 (194–460)
7.5	3	2	2.6 3 (2.2–4.7)	2.6 3 (2.2–3.0)	162 (159–566)	175 (172–177)
10.0	3	3	5.4 3 (2.5–6.8)	7.3 2 (4.2–10.3)	387 (190–444)	340 (251–429)
15.0	4	4	3.0 (4) (1.9–3.3)	2.7 3 (2.5–4.4)	323 (270–394)	367 (260–534)
20.0	3	4	2.2 3 (1.1–2.7)	2.5 2 (1.8–3.2)	104 (101–108)	123 (103–142)
25.0	3	3	2.0 3 (1.8–2.8)	2.1 2 (1.8–2.4)	111 (80–152)	130 (128–132)
	20					

[a] One patient died prior to acquisition of nadirs.
[b] Numbers in parentheses, range.

Table 2 *Hepatotoxicity*

Dose level (mg/m²)	No. of patients	SGOT[a]		LDH		ALK PHOS	
		On study median	Worse median	On study median	Worst median	On study median	Worse median
5	3	45 (27–108)[b]	105 (71–669)	241 (180–1101)	338 (222–3906)	143 (79–197)	198 (70–1626)
7.5	3	14 (10–95)	43 (17–181)	196 (165–498)	354 (216–538)	113 (109–183)	103 (101–186)
10	3	19 (14–21)	32 (19–35)	140 (125–154)	160 (152–202)	143 (52–581)	137 (60–560)
15	4	18 (15–33)	103 (65–132)	269 (232–325)	465 (368–525)	83 (65–435)	159 (90–549)
20	3	32 (20–60)	77 (39–107)	241 (148–320)	295 (222–410)	143 (64–327)	143 (136–376)
25	3	25 (17–28)	90 (51–183)	180 (160–292)	242 (240–750)	84 (49–106)	94 (93–173)

[a] SGOT, serum glutamic oxaloacetic transaminase; LDH, lactic dehydrogenase; ALK PHOS, alkaline phosphatase.
[b] Numbers in parentheses, range.

Table 3 *Systemic symptoms*

Dose (mg/m²)	No.	Flu-like symptoms		Other symptoms[a]	
		1–2[b]	3	1–2	3
	4	2	5.0 (mg/m²)	2	0[c]
7.5	3	1	2	0	1
10.0	3	3	0	0	0
15.0	4	1	3	2	1
20.0	3	3	0	0	2
25.0	3	1	2	1	0

[a] Other toxicities that were Grade 3 included pain, palpatations, weakness, upper respiratory infection, cough, shortness of breath, alopecia, blurred vision, impotence, and cardiac arrhythmia.
[b] ECOG grade.
[c] Patient expired right after treatment; therefore, information is unobtainable.

Table 4 *Doxorubicin plasma and urine values in patients treated concurrently with α-interferon*

Patient	Dose (mg/m²)	Total dose (mg)	Peak plasma concentration (ng/ml)	Total urine excretion (% of dose injected)
1	5	8	40.1	6.1
2	10	19	238	1.9
3	15	26	163	6.6
4	20	40	146	7.9
5	25	46	132	6.6
6	25	50	383	5.0

diseases as well as to hopefully broaden the spectrum of antitumor activity of the interferons, combinations with chemotherapy regimens and other immunomodulators are being tested. The rationale for the combination of interferon with chemotherapy is similar to that for combining different classes of chemotherapeutic drugs. Interferon is an immune modulator causing activation of natural killer cells (12) as well as causing direct cytotoxicity (13, 14). It also appears to modulate the expression of tumor antigens of the HLA system (15, 16), reduce oncogene expression (17, 18), and cause differentiation of transformed cells *in vitro* (19, 20). It has a different spectrum of toxicity compared to cytotoxic drugs; importantly its dose-limiting toxicity is not myelotoxicity. Since the mechanism of tumor cell killing is different from that of cytotoxic drugs, cross-resistance does not appear to develop. We can therefore combine these non-cross-resistant agents at close to the maximum or even maximally tolerable doses.

An added advantage may be the diminution of chemotherapy-induced toxicity as has been demonstrated by the protection against 5-fluorouracil toxicity in normal tissues when administered with α_2-interferon (21). This protective effect does not appear to abrogate the cytoxic effect *in vitro* (22). This Phase I study was designed to test the hypothesis that α_2-interferon could be administered with doxorubicin at close to maximally tolerated doses for both drugs.

We initiated Phase I testing with doxorubicin because it has a wide spectrum of single-agent activity in lymphomas, carcinomas, and sarcomas and because we wished to integrate α_2-interferon into doxorubicin-containing regimens for lymphomas and epidemic Kaposi's sarcoma. Our own experience with the combination of etoposide (VP-16) and α_2-interferon in previously untreated patients with epidemic Kaposi's sarcoma demonstrated an unexpectedly high incidence of Grade IV myelosuppression (9). This toxicity rate may have been due to increased susceptibility of the patient population tested.

Early studies of the combination of doxorubicin and α_2-interferon were performed by Welander and associates in both the laboratory and the clinic. They initially demonstrated synergistic activity of these two compounds against human ovarian cell lines in culture (6). They subsequently conducted a broad Phase II study of the concurrent administration of α_2-interferon, simultaneously administering 10 million IU/m² i.m. and 10 million IU/m² i.v., and doxorubicin, 20 mg/m² (23). Treatments were given weekly for 3 wk. Although many tumor types were treated there was a predominance of gynecological cancers. Clinical responses were seen in ovarian, endometrial, and cervical cancers as well as sarcomas. Of considerable interest is the demonstration of antitumor activity in 6 of 20 patients with ovarian cancer, all of whom had been pretreated including 2 with prior doxorubicin treatment. Responses were also seen in 5 of 15 patients with uterine cervical carcinoma. Using the same schedule, Muss *et al.* could not demonstrate antitumor activity in 15 patients with renal cancer (24). The only toxicities described were the flu-like symptoms attributable to the interferon.

Synergistic activity with these compounds has also been demonstrated *in vitro* in a Burkitt's lymphoma cell line, confirming both the single agent activity of both doxorubicin and α_2-interferon as well as the enhanced effect in combination (5). Human lymphocyte and immune interferons have also been tested with alkylating agents (1, 3, 7, 25, 26), *Vinca* alkaloids (3, 4, 27), nitrosoureas (28), and antimetabolites (2, 3) and have shown a range of enhancement of activity ranges from simply additive to synergistic. However, the translation of this *in vitro* experience into clinical efficiency requires careful progression through Phase I trials.

Using the human tumor cloning system, Von Hoff has demonstrated activity of single agent recombinant α_2-interferon against a wide variety of solid tumors. He demonstrated both a dose-response effect and a time-exposure effect.[3] Continuous

[3] D. D. Von Hoff, personal communication.

exposure of the tumors to α_2-interferon resulted in a greater number of the patient's tumors being sensitive than when they were exposed for 1 h. When both agents were administered together as a continuous exposure, synergy was noted in more than $^2/_3$ of the specimens across a number of tumor types. These preclinical data were followed by a Phase I clinical trial similar in design to the one described in this paper, using a doxorubicin schedule of once every 3 wk, starting at a dose of 20 mg/m^2 and escalating to 40 mg/m^2 (29). The interferon was administered s.c. 3 times a wk at a dose of 10 million units/m^2. Dose-limiting toxicity occurred at 40 mg/m^2 of doxorubicin and consisted of granulocytopenia (less than 1000 granulocytes) in four of six patients. The recommended dose of doxorubicin administered with 10 million IU/m^2 of interferon for patients with no prior therapy and good performance status was 40 mg/m^2 given every 3 wk and 30 mg/m^2 in patients with poor performance status.

In the study described in this paper 18 of the 20 patients entered had a performance status of 0 or 1. The dose-limiting toxicities were neutropenia and thrombocytopenia. Hepatic toxicity and systemic symptoms due to interferon were reversible and were not considered to be dose limiting. The recommendation based on our results in this favorable group is a starting dose of doxorubicin of 25 mg/m^2 per wk for 3 wk. This is equivalent to 75 mg/m^2 over 3 wk, about twice the dose of that obtained in the study described above (29).

Although the toxicities in the trial presented here were tolerable, the consistent abnormalities in liver function could potentially interfere with the metabolism of doxorubicin. The studies of Balkwill *et al.* suggest that interferon could alter the metabolism of doxorubicin through effects on microsomal and cytoplasmic enzymes (30). Increased toxicity of doxorubicin in the setting of abnormal liver functions has been demonstrated in a number of studies (31, 32–35). It is feasible that the dose-limiting toxicity of doxorubicin when given as large single boluses may be influenced by the inability to metabolize and excrete these large doses. Similarly, when given in smaller doses, the impairment in liver function may not be great enough to affect the metabolism of doxorubicin to the extent that hematological toxicity occurs (36).

Since the weekly administration of doxorubicin appears to be the better tolerated of the two schedules and since higher total doses can be administered, we recommend this schedule for future Phase II studies using the combination of doxorubicin and interferon. Furthermore, since the preclinical data suggest that the continuous exposure of tumor cells to doxorubicin and interferon is superior to 1-h exposure, further development of these combinations should utilize at least a weekly administration schedule of doxorubicin until continuous infusion of doxorubicin with interferon demonstrates equal or lesser toxicity.

ACKNOWLEDGMENTS

The authors wish to thank Peggy Nixdorf and Sharon Dynes for secretarial assistance.

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