Cancer Chemother Pharmacol (1991) 28: 142–144
034457049100073S

Cancer Chemotherapy and Pharmacology

A phase II study of ifosfamide and a_{2b}-interferon in advanced non-small-cell lung cancer

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Received 23 August 1990/Accepted 14 January 1991

Summary. A total of 45 patients with advanced non-small-cell lung cancer were treated with a combination of 1.5 g/m^2 ifosfamide given on days 1–5 every 3 weeks for four courses with 3 million IU a_{2b}-interferon (Intron A) given s.c. three times a week for 12 weeks. Nine objective responses were seen, including two complete responses (CRs) and seven partial responses (PRs). Haematological and non-haematological toxicities were generally mild and did not necessitate discontinuation of therapy.

Introduction

Despite the advances in modern cancer chemotherapy, response rates to existing anti-cancer drugs in advanced non-small-cell lung cancer remain poor and this is reflected by low overall survival. It has been shown in a variety of experimental models, mainly cell-culture and xenograft systems, that there is synergy between the interferons and a wide variety of anti-cancer drugs. Balkwill and Moodie [2] have examined the interaction between cyclophosphamide and Adriamycin and human lymphoblastoid interferon in a breast tumour xenograft model growing in nude mice. The combination of interferon with either of these two agents caused regression or disappearance of tumours at doses of drug and interferon that, when these substances were used as single agents, were at best capable only of inhibiting tumour growth. Synergy between ifosfamide and cisplatin and interferon has also been demonstrated in a human xenograft model of non-small-cell lung cancer [7]. The mechanism by which interferon potentiates the action of these drugs is ill understood and may involve an alteration in the cell-cycle duration [3] or a modulation of the whole-body pharmacokinetics of the drug by interferon [9].

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Ifosfamide, an alkylating oxazaphosphorine that is an isomer of cyclophosphamide, has been shown to have good single-agent activity in non-small-cell lung cancer [1]. It has previously been shown that interferon does not alter the pharmacokinetics of ifosfamide [8]. To determine whether a_{2b}-interferon (Intron A) was synergistic with ifosfamide in the clinic, we decided to carry out a phase II study of these two substances in advanced non-small-cell lung cancer.

Patients and methods

Patients. Subjects with advanced, histologically proven non-small-cell lung cancer who had given their informed consent to participate were eligible for entry into this phase II study. All patients were aged <79 years and showed a pretreatment Karnofsky performance status of >50. To be included in the study, patients were required to exhibit pretreatment white blood cell and platelet counts of >3,500 and >150,000/mm^3, respectively. All subjects had measurable and symptomatic disease. Previous treatment with chemotherapy and/or radiotherapy did not render patients ineligible for entry into this study. However, individuals with severe haemoptysis or superior vena cava obstruction were not eligible to participate.

Treatment. a_{2b}-Interferon (Intron A, kindly supplied by Schering-Plough Ltd., Mildenhall, Bury St Edmunds, Suffolk) was given s.c. at a dose of 3 million IU on Mondays, Wednesdays and Fridays of each week for 12 weeks. Interferon was given either via self-administration by the patient or by a relative or the district nurse while the subject was at home. Ifosfamide was given as a 30-min i.v. infusion in 250 ml normal saline at a dose of 1.5 g/m^2 on days 1–5 during weeks 2, 5, 8 and 11 after the commencement of a_{2b}-interferon injections. Ifosfamide infusions were immediately followed by a 12-h i.v. infusion of 1.5 g/m^2 mesna given in 1 l normal saline. Treatment was terminated early if there was progression of disease or if toxicity worse than WHO grade III developed [12]. If the white blood cell count taken prior to a course of ifosfamide was <3,000/mm^3, treatment was postponed for 1 week, after which time the patient went off study if the white blood cell count had not recovered.

Assessment. Each time a patient was admitted for a course of ifosfamide, a full blood count, biochemical profile and clinical assessment were made. The clinical assessment included measurements of all measurable disease. Following the end of therapy, patients were seen monthly for the first 6 months and then every 3 months thereafter. Standard WHO cri-

Table 1. Details of 45 patients with non-small-cell lung cancer receiving ifosfamide and a_{2b}-interferon

	Non-responders	Responders	P^a
Number	36	9	-
Age (years)	59 (37–69)	54 (47–71)	0.8569
Sex (M/F)	25 M, 11 F	5 M, 4 F	0.7768
Karnofsky score	70 (50–90)	70 (60–80)	0.1373
Prior treatment			
No prior XRT	31	9	0.5532
Prior XRT	5	0	
Histology:			
Squamous	17	5	0.8226
Adenocarcinoma	11	3	
Large cell	3	0	
Undifferentiated	5	1	

[a] According to the χ^2 test
Data represent median values; ranges are shown in parentheses. Non-responders include patients with both static and progressive disease.
XRT, Radiotherapy

Table 2. Haematological toxicity in 45 patients receiving ifosfamide and a_{2b}-interferon

	Numbers of patients showing toxicity worse than WHO grade III after ifosfamide course			
	1	2	3	4
Haemoglobin	2/45	3/37	4/27	3/19
White blood count	11/45	12/37	5/27	5/19
Platelets	1/45	1/37	0/27	0/19

teria were used to assess response and progression [12]. Survival was defined as the period from diagnosis until death and response duration, as the interval from response until disease progression.

Results

A total of 45 patients with advanced non-small-cell lung cancer were entered into this trial. Their median age was 58.5 years (range, 37–71 years). The distribution of histological subtypes is shown in Table 1. Five patients had previously received thoracic irradiation, four exhibited liver involvement and four, bony involvement.

A total of 128 courses of ifosfamide were given (8 patients received 1 course, 10 were given 2 courses, 8 received 3, and 19 underwent 4 courses). The reason for early termination of treatment was disease progression in each case; in no instance was treatment discontinued because of toxicity. Haematological toxicity was acceptable (Table 2). The median nadir white cell counts (ranges in parentheses) were as follows: 2.95 $(0.6–11.3)\times10^9$/l for course 1, 2.4 $(0.6–7.5)\times10^9$/l for course 2, 2.85 $(0.9–6.9)\times10^9$/l for course 3 and 2.1 $(0.9–5.3)\times10^9$/l for course 4. Treatment was delayed due to myelosuppression on 23 occasions. During 5 of the 128 courses, antibiotics had to be given i.v. for infection; there was 1 instance of life-threatening infection from which the patient recovered. Patients were transfused with blood on nine occasions. There was no significant episode of thrombocytopenia (<WHO grade III).

Non-haematological toxicity was generally mild. Two patients experienced WHO grade III CNS toxicity due to ifosfamide, which was reversible and did not lead to neurological sequelae. Five patients developed transient and mild elevations in serum creatinine and urea. Alopecia and emesis were universal. Toxicity due to interferon administration was mild, and at no time was interferon therapy stopped because of toxicity. In all, 12 episodes of mild myalgia and 15 cases of pyrexia were attributed to interferon toxicity.

There were two complete responders and seven partial responders (squamous carcinoma), for an objective response rate of 20%. In all, 23 patients exhibited static disease and 13 developed progressive disease. The median survival following diagnosis was 12 months and that following the start of chemotherapy was 6 months. Two patients remain alive at 18 months after diagnosis. There was no statistical difference in median survival between responders and non-responders.

Discussion

The overall response rate following single-agent ifosfamide treatment of advanced non-small-cell lung cancer using a variety of schedules and doses is approximately 21% (range, 0–39%) [5]. Therefore, the objective response rate we observed was well within this range. This indicates that although co-administration of a_{2b}-interferon with ifosfamide does not inhibit the anti-tumour activity of ifosfamide, it does not appear to enhance its activity, which contrasts with the preclinical data showing marked synergy. In a similar study, 33 patients with advanced non-small-cell lung cancer were treated with the same regimen of alpha-interferon used in the present investigation plus 100 mg/m^2 cisplatin given every 4 weeks [10]; the objective response rate obtained was 21%, which is only slightly higher than the 14% overall response rate described for single-agent cisplatin in non-small-cell lung cancer by Bakowsky and Crouch [1]. It is interesting to note that Smyth et al. [10] have now embarked on a second phase II study using a higher dose of alpha-interferon (5 million IU given three times a week). In this second study it would appear that the objective response rate is somewhat higher, being about 50%, although the patient numbers thus far accrued remain small.

Therefore, it may be that the dose of a_{2b}-interferon used in the present study was too low to cause any synergy. Indeed, the dose of interferon used by Balkwill and Moodie [2] in their xenograft model was equivalent to a human dose of 20 million IU/m^2. Furthermore, most of the preclinical evidence suggests that both interferon and the cytotoxic agent should be given together in a continuous manner [11]. It may therefore be more advisable to give interferon continuously as either an s.c. or an i.v. infusion.

No untoward toxicity was seen with the combination of ifosfamide with a_{2b}-interferon. Drurie et al. [6] have described cumulative myelotoxicity in a phase I study of

cyclophosphamide and a_{2b}-interferon; however, the dose of a_{2b}-interferon used by these authors was higher than that used in the present study, and ifosfamide is less myelosuppressive than cyclophosphamide [4]. Drurie et al. [6] also demonstrated that a_{2b}-interferon doses in excess of 5 million IU given three times weekly were poorly tolerated because of subjective toxicity. Subjective toxicity due to a_{2b}-interferon in the present study was mild and the drug was well tolerated. However, the phase I data of Drurie et al. [6] suggest that we would not be able to escalate the dose of interferon much higher than that used in the current investigation. To obtain higher response rates, it might be more sensible to use cisplatin and ifosfamide in combination with a modest dose of a_{2b}-interferon, i.e. 5 million IU given s.c. three times a week. In conclusion, this phase II study failed to demonstrate the synergy observed preclinically between ifosfamide and a_{2b}-interferon in patients with non-small-cell lung cancer.

Acknowledgements. We gratefully acknowledge the support of Schering-Plough Ltd.

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