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## Abstract

Twenty-seven previously untreated patients with unresectable non-small cell lung cancer were treated with a 3-drug combination of ifosfamide, cisplatin, and vindesine as a phase II study. Patients received ifosfamide, 1.3g/m<sup>2</sup>, on days 1 to 5; cisplatin, 20mg/m<sup>2</sup>, on days 1 to 5; and vindesine, 3mg/m<sup>2</sup>, on days 1 and 8; with a sufficient parenteral hydration. Courses were repeated every 4 weeks. Twenty males and seven females with a median age of 61 years were treated and fully evaluated. Five patients had stage IIIA, seven had stage IIIB, and 15 had stage IV disease. One patient with adenocarcinoma achieved a complete response and 16 achieved a partial response, for an overall response rate of 63% (95% confidence limit: 45% to 81%). The median duration of response was 34 weeks (range: 9 to 52 weeks). The median survival time was 58 weeks for patients with IIIA/B disease, and 33 weeks for those with IV disease. The major toxicity was myelosuppression, however, it was generally well-tolerated. These results indicate that the 3-drug combination is active against non-small cell lung cancer and warrants further clinical trials.

**KEYWORDS:** non-small cell lung cancer, ifosfamide, cisplatin, vindesine

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## Phase II Study of Ifosfamide, Cisplatin, and Vindesine Combination in Advanced Non-Small Cell Lung Cancer

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Twenty-seven previously untreated patients with unresectable non-small cell lung cancer were treated with a 3-drug combination of ifosfamide, cisplatin, and vindesine as a phase II study. Patients received ifosfamide, 1.3g/m<sup>2</sup>, on days 1 to 5; cisplatin, 20mg/m<sup>2</sup>, on days 1 to 5; and vindesine, 3mg/m<sup>2</sup>, on days 1 and 8; with a sufficient parenteral hydration. Courses were repeated every 4 weeks. Twenty males and seven females with a median age of 61 years were treated and fully evaluated. Five patients had stage IIIA, seven had stage IIIB, and 15 had stage IV disease. One patient with adenocarcinoma achieved a complete response and 16 achieved a partial response, for an overall response rate of 63% (95% confidence limit: 45% to 81%). The median duration of response was 34 weeks (range: 9 to 52 weeks). The median survival time was 58 weeks for patients with IIIA/B disease, and 33 weeks for those with IV disease. The major toxicity was myelosuppression, however, it was generally well-tolerated. These results indicate that the 3-drug combination is active against non-small cell lung cancer and warrants further clinical trials.

*Key words* : non-small cell lung cancer, ifosfamide, cisplatin, vindesine

The vast majority of patients with non-small cell lung cancer (NSCLC) have locally advanced or disseminated disease at the time of diagnosis. The prognosis of such patients receiving chemotherapy is still very poor; even the most active combinations seldom produce complete response, and the median survival time in almost all studies

ranges between 6 to 10 months (1,2). In such a situation, it is important to continue to evaluate new drugs and combinations to improve the response and survival in patients with unresectable NSCLC. Cisplatin, vindesine, and mitomycin C have been estimated to be most active among drugs used in the treatment of NSCLC; their administration as single drugs resulted in response rates of approximately 15%

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to 20% (3,4). Ifosfamide, an analog of cyclophosphamide, possesses a spectrum of toxicity and an activity different from the mother compound (5). Summarizing nine phase II studies of ifosfamide in which a total of 326 previously untreated patients were enrolled, Ettinger reported a mean response rate of 21%, with a range of 5% to 35% (6). These encouraging results prompted us to assess a 3-drug combination of ifosfamide, cisplatin, and vindesine in previously untreated patients with either unresectable locally advanced or disseminated NSCLC.

This paper supplements a preliminary report of the 3-drug combination (7) with an extension of patient number and follow-up time.

## Subjects and Methods

Previously untreated patients 75 years of age or less with unresectable locally advanced or disseminated disease were eligible for entry into the study if they had histologically or cytologically confirmed NSCLC. Patients were required to have measurable disease and performance status of 0, 1, 2, or 3. Patients were required to have a white blood cell (WBC) count of  $\geq 4,000/\mu\text{l}$  and a platelet (PL) count of  $\geq 100,000/\mu\text{l}$ . Patients were also required to have a normal hepatic function (total bilirubin of  $\leq 1.5\text{ mg}/100\text{ ml}$  and sGOT/sGPT of  $\leq 2$  times normal), and a normal renal function (creatinine clearance of  $\geq 60\text{ ml}/\text{min}$ ). Patients with symptomatic brain metastases, a history of congestive heart failure, or any other cardiac disorder that might compromise an adequate hydration were considered to be ineligible.

Pretreatment staging procedures included a history and physical examination, fiberoptic bronchoscopy, chest X-ray including computerized tomographic scans (CT), radionuclide bone scan, CT of the brain and the upper abdomen, complete blood cell counts, and blood chemistry profile.

The treatment program was as follows: ifosfamide,  $1,300\text{ mg}/\text{m}^2$ , intravenously (i.v.) infused over 30 min, on days 1 to 5; cisplatin,  $20\text{ mg}/\text{m}^2$ , i.v., infused over 20 min, on days 1 to 5; vindesine  $3\text{ mg}/\text{m}^2$ , i.v., on days 1 and 8. Courses were repeated every 4 weeks. All patients were hospitalized and hydrated with 2.5l of normal saline/day throughout the period of therapy. Antiemetics

such as metoclopramide were not routinely used; only patients who encountered moderate to severe upper gastrointestinal symptoms received antiemetics and/or dexamethasone. For responsive patients, courses were repeated while the tumor lesions continued to respond or until toxicity became intolerable. Doses of ifosfamide and cisplatin were attenuated by 20% for a WBC count of  $3,500\text{--}4,000/\mu\text{l}$  or a PL count of  $75,000\text{--}100,000/\mu\text{l}$  on the day of therapy and when a patient encountered an infection-related fever in the previous course. For a WBC count of  $< 3,000/\mu\text{l}$  and/or a PL count of  $< 75,000/\mu\text{l}$ , all drugs were withheld for 1 week. Cisplatin was withheld if creatinine clearance fell to  $< 40\text{ ml}/\text{min}$ .

Patients were evaluated for tumor response after completion of each course by physical examination, follow-up chest X-ray, and other studies which had displayed a positive tumor image. A complete response (CR) was defined as the disappearance of all clinical evidence of tumor for at least 4 weeks. A partial response (PR) was defined as a  $> 50\%$  reduction in the product of two perpendicular diameters of all measurable lesions for at least 4 weeks.

## Results

Of 29 patients who entered into the study, two patients were eliminated from the analysis because their histologies were disclosed to be relapsing breast carcinomas by autopsy. Characteristics of the 27 patients who were fully evaluated for tumor response and toxicity are shown in Table 1. There were 20 males and seven females, and median age was 61 years (range: 40 to 74 years). Nineteen patients had adenocarcinoma, one had squamous cell carcinoma, and seven had large cell carcinoma. Eighteen patients had PS of 0 or 1, and nine had PS of 2 or 3. There were five patients with stage IIIA, seven with stage IIIB, and 15 with stage IV disease.

Patients received a median of 3 courses of the treatment (range: 1 to 6 courses). Tumor response by histopathology is shown in Table 2. Of 27 evaluable patients, one patient with adenocarcinoma achieved a CR, and 11 with adenocarcinoma, one with squamous cell carcinoma and four with large cell carcinoma

achieved a PR, for an overall response rate of 63 % (95 % confidence limit: 45 % to 81 %). The overall response rate was 67 % for patients with

stage IIIA/B disease and 60 % for those with stage IV disease. The median duration of response was 34 weeks, ranging 9 to 52 weeks. As shown in Fig. 1, the median survival time was 58 weeks for patients with stage IIIA/B disease and 33 weeks for those with stage IV disease. The two-year survival rate was 25 % for the former and 13 % for the latter.

Toxicities were evaluated among 27 eligible patients. Myelosuppression was the major dose-limiting toxicity; the nadir WBC count was less than  $1,000/\mu\text{l}$  in 69 %, and the nadir PL count

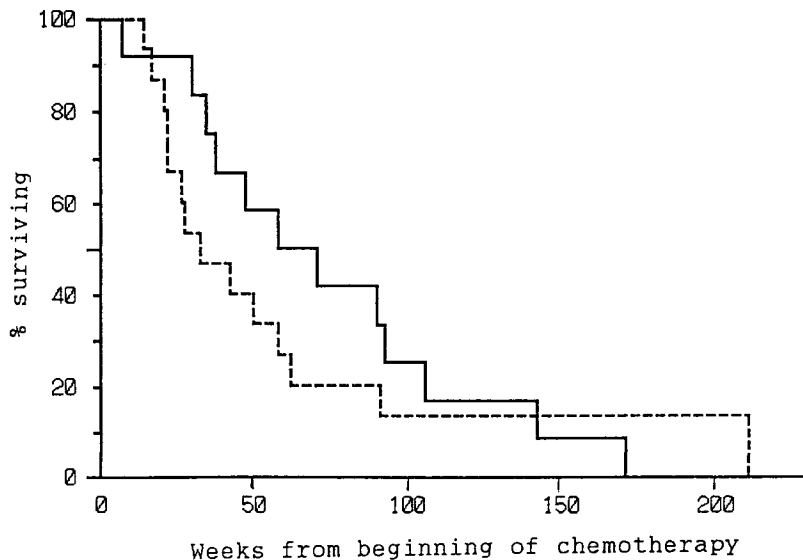
**Table 1** Characteristics of patients studied

Total no. of patients	29
No. excluded	2
No. evaluated	27
Median age (range)	61 (40-74)
Sex:	
Male	20
Female	7
Histology:	
Adenocarcinoma	19
Squamous cell carcinoma	1
Large cell carcinoma	7
Stage:	
III A	5
III B	7
IV	15
Performance status:	
0-1	18
2-3	9

**Table 2** Response rate by histology

Histologic type	No. of patients	No. (%) of	
		CR	CR + PR
Adenocarcinoma	19	1 (5)	12 (63)
Squamous cell carcinoma	1		1
Large cell carcinoma	7		4 (57)
Total	27	1 (4)	17 (63)

CR: complete response, PR: partial response



**Fig. 1** Patient survival by stage. A solid line represents 12 patients with stage IIIA/B disease. A broken line represents 15 patients with stage IV disease. The median survival time was 58 weeks for the former and 33 weeks for the latter. A tick indicates a patient surviving.

was less than 50,000/ $\mu$ l in 35 %, among 74 treatment courses evaluated. Hemoglobin content fell to less than 8g/100ml in 42 % of patients within three treatment courses. Of those, six patients required red blood cell transfusions. One patient experienced a bleeding tendency and required PL transfusions. There were 23 episodes of neutropenia-associated fever among 98 treatment courses evaluated. One patient died of sepsis while neutropenic after the second course. Upper gastrointestinal symptoms were common among patients receiving the chemotherapy, but generally well-tolerated. One patient developed paralytic ileus on the day 10 of the first course of treatment, however, it was reversible with a conservative treatment. Peripheral neuropathy of grade 2 was seen in four patients and hearing disability in one. Creatinine clearance fell to less than 40ml/min in four patients, but no patient developed renal failure. No patient experienced macrohematuria or central nervous system toxicity such as lethargy and mental confusion while receiving ifosfamide.

## Discussion

NSCLC is among tumors most resistant to drug therapy. To date, combination of cisplatin and vindesine has been used most widely, and the combination has been considered to have a substantial activity against NSCLC (8). However, no drug therapy including such a combination has shown unquestioned benefit, *i.e.*, a significant prolongation of life, for those with unresectable NSCLC (9). Ifosfamide is regarded as one of the most active drugs against NSCLC, with a spectrum of toxicity and clinical activity different from the mother compound, cyclophosphamide (5). It has been evaluated in varying doses and schedules, and produces response in approximately 20 % of patients (6,10). In lung cancer trials, fractionated administration of ifosfamide in a total of 6.0 to 9.0g/m<sup>2</sup> over 5 consecutive days appears to have resulted in response rates compa-

rable with those produced by bolus dose of 5.0g/m<sup>2</sup> on day 1, but the fractionation schedule appears to be associated with less severe toxicity (6,10).

The noteworthy outcome of ifosfamide as a single agent led to several studies of this drug in combination with other drugs known to be active against NSCLC. Drings *et al.* (11) evaluated 71 patients receiving the combination of ifosfamide 2.0g/m<sup>2</sup> on days 1 to 5 and cisplatin 75mg/m<sup>2</sup> on day 1, repeating every 4 weeks. The overall response rate was 35 % including a CR rate of 6 %. The median duration of response and median survival time were reported to be 8 months and 8.3 months, respectively. Similar results were reported in two smaller trials by Papermaster-Bender *et al.* (12) and Araujo *et al.* (13). In these studies, in which cisplatin and ifosfamide were both fractionated over 5 days, the overall response rates were 28 % and 33 %, respectively.

The current study was conducted in an attempt to assess the effect and toxicity when adding ifosfamide to a cisplatin and vindesine combination, which was considered to be one of the most active regimens in NSCLC. Rosell *et al.* (14) and Schroeder *et al.* (15) also assessed the 3-drug combination of ifosfamide, cisplatin, and vindesine. Rosell *et al.* evaluated 50 patients receiving ifosfamide 3.0g/m<sup>2</sup> on day 1, cisplatin 100mg/m<sup>2</sup> on day 1, and vindesine 3mg/m<sup>2</sup>, on days 1, 8, and 15, repeating every 4 weeks. Schroeder *et al.* evaluated 40 patients receiving ifosfamide 1.5/m<sup>2</sup> on days 1-5, cisplatin 80mg/m<sup>2</sup>, on day 1, and vindesine 3mg/m<sup>2</sup>, on day 1, repeating every 4 weeks. The overall response rates were somewhat disappointing (14,15); 20 % for the former study and 18 % for the latter study, although there were three CRs lasting 30+, 25+, and 19+ months in the latter one. Nevertheless, our study results were encouraging; of 27 patients evaluated, one achieved a CR and 16 achieved a PR, for an overall response rate of 63 % (67 % for IIIA/B disease, 60 % for IV disease). The median duration of response

was 34 weeks, and the median survival time was 58 weeks for patients with stage III A/B disease and 33 weeks for those with stage IV disease. In our preliminary report (7), the overall response rate was 60 % and the projected median duration of response was 30 weeks, in which 20 patients had been enrolled, but a patient with erroneous histologic interpretation was eliminated. These figures were stable when extending a patient number and follow-up period. The response rate of 63 % in our series was substantially superior to those of 2-drug combination of cisplatin and vindesine, which showed an overall response rate of 32 % with a range of 12 % to 43 % when analysing 13 trials of the combination in which a total of 632 patients was enrolled (8).

The 3-drug combination chemotherapy was moderately to severely myelosuppressive. A majority of the patients encountered leukocytopenia less than  $1,000/\mu\text{l}$ , at least once, while receiving repeated treatments. There were 23 episodes of neutropenia-associated fever among 98 treatment courses evaluated. One patient died of sepsis while neutropenic. However, thrombocytopenia was less frequent, suggesting that this type of myelosuppression might be attenuated by the use of growth factors such as recombinant human granulocyte colony stimulating factor.

To confirm an advantage of ifosfamide in the treatment of NSCLC, further clinical trials with a randomized fashion would be required in the future. Our study results provide evidence that warrants further clinical trials.

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