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Cisplatin and Teniposide Chemotherapy for Advanced Non-small Cell Lung Cancer

Valter Iberti, Michela Donadio and Giuseppe Giaccone

30 patients with advanced non-small cell lung cancer were treated with cisplatin 80 mg/m², day 1, and teniposide 100 or 120 mg/m², days 1, 3 and 5, every 3 weeks. Myelotoxicity, nausea and vomiting and alopecia were the main side-effects. 8 patients of 26 evaluable had partial responses (31%): 6 had received 120 mg/m² teniposide and 2 had received 100 mg/m² teniposide. Overall median survival time was 251 days. Myelotoxicity was significantly lower in patients who received 100 mg/m² teniposide. Although the number of patients is small and they were not randomly assigned to the two different teniposide doses, it appears that higher dose of teniposide determined a greater degree of myelotoxicity, and also a higher response rate.
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INTRODUCTION

ADVANCED non-small cell lung cancer (NSCLC) is relatively resistant to chemotherapy [1]. Cisplatin is believed to be an important ingredient of combination regimens, and syngergistic effects between cisplatin and other drugs, such as etoposide, have been suggested [2]. Teniposide (VM26), an epipodophyllotoxin like etoposide, has shown some activity in NSCLC [3]. In this study we investigated the combination of teniposide with cisplatin in a group of NSCLC patients not previously treated with chemotherapy.

PATIENTS AND METHODS

30 consecutive patients were entered in the study. Locally advanced (confined within one hemithorax and regional lym-

Table 1. Treatment outcome

	W.H.O. grade				
	0	1	2	3	4
Teniposide 120 mg/m² (n = 15)*					
Leukopenia	1	0	3	6	5
Thrombocytopenia	3	2	3	4	3
Anaemia	3	2	7	2	1
Nausea and vomiting	0	0	5	10	0
Hair loss	0	2	3	10	0
Diarrhoea	12	0	2	1	0
Stomatitis	11	1	3	0	0
Infection	7	1	6	0	1
Peripheral neurotoxicity	12	2	0	1	0
Ototoxicity	13	2	0	0	0
Others†	12	1	1	1	0
Partial response	6				
No change	6				
Teniposide 100 mg/m² (n = 14)‡					
Leukopenia	4	6	4	0	0
Thrombocytopenia	3	5	6	0	0
Anaemia	3	5	5	1	0
Nausea and vomiting	0	1	4	9	0
Hair loss	0	1	2	11	0
Diarrhoea	13	0	0	1	0
Stomatitis	10	3	1	0	0
Infection	11	1	1	1	0
Peripheral neurotoxicity	10	2	2	0	0
Ototoxicity	13	1	0	0	0
Others§	12	1	1	0	0
Partial response	2				
No change	10				
Progression	2				

No. of patients.
* Including a treated patient discovered at necropsy to have wrong histology.
† 1 case of phlebitis (grade 1), and 2 cases of severe symptomatic hypokalaemia with dehydration.
‡ 1 patient of 15 treated at this dose did not complete the first cycle of treatment and therefore is not included.
§ 1 case of cystitis (grade 2) and 1 of phebitis.

phatics, including ipsilateral supraclavicular nodes and pleural effusion) or metastatic disease and measurable or evaluable sites of disease were required. Additional requirements included: performance status (ECOG) < 3, age less than 71 years, adequate renal, cardiac and liver functions and bone marrow reserve. Informed consent was obtained from all patients. Extensive staging investigations were not performed routinely, and only symptomatic patients were further evaluated with appropriate imaging techniques. Marker lesions were evaluated as frequently as required to estimate response and its duration. Chest X-ray, full blood counts and 12 channel profile were assessed before every cycle. Cell counts were repeated weekly during the first two cycles in order to determine the nadir counts. Toxicity and response assessment were according to WHO criteria [4]. Cisplatin was given at 80 mg/m² on day 1 and teniposide at 120 mg/m² on days 1, 3 and 5, every 3 weeks for a maximum of six cycles in stable disease or responding patients. Dose of both drugs was reduced by 50% if WBC and platelet nadir counts dropped below 1000 or 20 000/mm³, respectively. Treatment was delayed for a maximum of 2 weeks if WBC and platelets were lower than 4000 and 100 000/mm³, respectively. Cisplatin was administered along a forced diuresis program and teniposide was diluted in 500 ml saline and infused over 1 h. After an initial analysis of treatment tolerance in the first 15 patients, myelosuppresion appeared to be excessive, therefore dose of teniposide was reduced to 100 mg/m² in the next 15 patients entered in the study. Duration of response and survival were estimated from therapy commencement. Survival curves were plotted using the Kaplan–Meier method [5] and logrank statistics were used to compare survival curves [6].

RESULTS

Of 30 patients enrolled in the study, 1 was not eligible, because necropsy demonstrated a thyroid carcinoma to be the primary tumour. Of the 29 eligible patients 25 were male; median age was 56.5 years (range 36–67); 20 patients had an ECOG performance status of 0 or 1; 10 had squamous histology, 9 adenocarcinoma, 9 large cell, and 1 undifferentiated carcinoma; weight loss was ≥ 5% in 14 patients. Disease was metastatic in 16; 1 was operated, 4 irradiated and 1 resected and irradiated before entering the study. 14 patients received the high (120 mg/m²) teniposide dose and 15 received the low (100 mg/m²) dose. Response could not be evaluated in 3 patients because of treatment refusal, acute pneumothorax and early death during severe myelosuppression. The main toxicities were myelosuppression, nausea and vomiting, and alopecia (Table 1). Of 26 evaluable patients, 8 had partial response (31%), 16 no change and 2 progression. 6 of 12 evaluable patients (6/14 eligible) responded in the high teniposide dose group, while only 2/14 evaluable patients (2/15 eligible) responded in the low dose group. Dose intensity analysis has been performed: in the high dose teniposide regimen 11 patients (85%) received less than 90% of the projected total dose of cisplatin and teniposide, and 7 patients (54%) received less than 90% of the dose of both drugs in the low teniposide regimen. Histology of responders was large cell carcinomas in 5, squamous cell carcinoma in 2 and adenocarcinoma in 1. Median duration of partial responses and no change were 293 and 158 days, respectively ($P < 0.01$). Median survival of the 29 eligible patients was 251 days. Survival of partial response and no change patients was 578 and 212 days, respectively ($P < 0.025$).

DISCUSSION

Our study demonstrates a moderate activity of the combination of cisplatin and teniposide. The dose of teniposide was reduced halfway through the study, due to excessive leukothrombocytopenia. In fact, before the dose of teniposide was reduced, less than 20% of patients received at least 90% of the planned dose of both drugs, while approximately 50% received at least 90% of the planned dose, after teniposide dosage reduction. Strikingly, the reduction of teniposide dose of only 16% (60 mg/m²) induced a remarkable reduction of myelotoxic-

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ity. Although there was a decrease in response rate, the number of patients was too small and they were not randomly assigned to the two different doses, to allow any conclusion on the presence of a dose-response curve of teniposide in this combination in NSCLC.

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Phase II Study with Mitomycin, Ifosfamide and Carboplatin in Inoperable Non-small Cell Lung Cancer

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In a phase II study of non-small cell lung cancer a new chemotherapy combination of mitomycin 6 mg/m² intravenously on day 1, carboplatin 400 mg/m² intravenously on day 1 and ifosfamide with mesna 5 g/m² intravenously over 24 hours on day 1 was evaluated. A maximum of four chemotherapy cycles was given at intervals of 4 weeks to 34 patients with progressive, inoperable disease. 1 complete and 10 partial remissions were documented, the overall response rate being 32.4%. In a further 13 patients (38.2%) the previously progressing tumours remained stable for at least 6 weeks. The median time to progression for responding patients was 184 days. The median survival time for the whole group has not yet been reached at 293 days. A considerable but easily manageable myelosuppression was the principal toxicity despite a "no dose reduction" policy. Indeed, the dose intensity of the chemotherapy actually given was extremely close (97%) to that intended on protocol. In conclusion, the regimen is active in patients with advanced non-small cell lung cancer but requires regular haematological monitoring to prevent morbidity resulting from myelotoxicity.
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INTRODUCTION

CISPLATIN-BASED combination regimens have the highest and most reproducible response rates (30–35%) in the treatment of advanced non-small cell lung cancer (NSCLC) [1, 2]. The dosage of cisplatin is limited by nephrotoxicity, neurotoxicity and ototoxicity and lung cancer patients are often elderly and have other systemic medical problems. Carboplatin, a cisplatin analogue, lacks many of the toxicities of the parent compound and has activity in NSCLC [3].

Among the other more active drugs in the treatment of NSCLC are mitomycin and ifosfamide. Combinations of these two agents with cisplatin have produced response rates of 40% or greater [4–6]. The main toxicity of carboplatin is myelosuppression whereas this is generally mild for mitomycin and ifosfamide. We therefore combined these three agents in a phase II study for patients with inoperable NSCLC.

PATIENTS AND METHODS

Patients

Between May and November 1989, 34 patients (21 males, 13 females) with progressive, histologically proven non-small cell lung cancer were entered into the study. 27 patients had squamous cell carcinomas, 6 adenocarcinomas and 1 undifferentiated NSCLC. 5 patients had received previous radiotherapy. There were 12 stage IIIB and 22 stage IV patients. Distant metastatic sites included lung/pleura (12 patients), liver (5 patients), bone

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