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Oral Etoposide Preceding Cisplatin in Advanced Non Small Cell Lung Cancer (NSCLC). A Phase II Study

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Abstract—*Forty male patients with locally advanced (LD; 11 patients) and extensive (ED; 29 patients) NSCLC were treated with oral etoposide (240 mg/m² days 1–3) preceding intravenous cisplatin (100 mg/m² day 4) at 4 weekly intervals. Eleven patients achieved major response (27.5%; 1 CR, 10 PR). Minor response (MR) occurred in seven patients (17.5%); stable disease (SD) in seven patients (17.5%) and progressive disease (PD) in 15 (37.5%). The median duration of response in major responders was 31 weeks.*

The median survival time (MST) in all patients was 42 weeks. Patients achieving response, and stable disease lived significantly longer than progressors ($P < 0.0001$; 56 vs. 9 weeks respectively). The MST of non-progressors in both LD and ED was significantly increased as compared to progressors. Two patients with poor risk prognostic variables died from myelosuppression-related infection early during the first course of chemotherapy. The remainder of the courses were without severe hematological complications. Alopecia was the most common side-effect. Gastro-intestinal, neurological and renal complications were mild to moderate.

Intravenous etoposide can be replaced by the oral formulation with preservation of antitumoral activity in NSCLC patients, offering the advantage of maximal treatment outside the hospital.

INTRODUCTION

COMBINATION CHEMOTHERAPY with intravenous cisplatin and etoposide produces amongst the best and most reproducible results in advanced NSCLC patients [1]. One of the major disadvantages of therapy with intravenous etoposide is that frequent visits to the outpatient clinic for repeated administrations are mandatory to obtain optimal activity of the drug. Animal studies have shown that better therapeutic results can be achieved with repeated doses compared to a single administration [2]. In small cell lung cancer, superior responses have been obtained when equitoxic doses of etoposide were given orally for 3 consecutive days compared to one single intravenous administration [3]. The combination of cisplatin and etoposide given partly by the intravenous and oral route has produced a high level of activity with excellent tolerance in a previously published NSCLC study [4]. Therefore, mainly in order to minimize hospital or outpatient visits, we evaluated in a phase II trial the feasibility and antitumoral activity of a combination regimen with oral etoposide given on 3 consecutive days at home before cisplatin.

PATIENTS AND METHODS

Patients with histologically proven NSCLC with no prior chemotherapy, presenting with measurable and/or evaluable lesions classified as stage II or stage III disease according to the AJC criteria [5] or as limited (LD) or extensive (ED) disease according to the VALSG criteria [6], considered unsuitable for local treatment or having relapsed after local treatment were eligible for the study.

Before entry into the study the following staging procedures were routinely performed: clinical examination; chest X-ray, eventually completed with tomograms or CAT-scan; echotomography of the liver; bone scintigram and/or X-ray survey of the skeleton; computerized brain tomodensitometry; complete biochemical and hematological blood screening.

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Additional procedures were allowed to stage the patients properly.

Exclusion criteria were: performance score (PS) (Karnofsky index) <50; abnormal renal (serum creatinine >1.5 mg %), hepatic (serum bilirubin >1.5 mg %) and bone marrow function (WBC <4000/ml, platelets <100,000/ml).

Patients were expected to survive at least 2 months after entry.

The therapeutic regimen was as follows: patients received 240 mg/m^2 etoposide (Vepesid®) orally days 1–3 as soft gelatin capsules; on day 4 cisplatin (Platinol®) was administered either in the outpatient clinic (majority of patients) at the end of the afternoon (6–8 p.m.) or through hospital admission of at least 24 h.

One hundred mg/m^2 cisplatin dissolved in 1/2 l normal saline were infused during 30 min. In the ambulatory schedule 1 l normal saline was infused during 1 h before and after cisplatin administration. For patients with in-hospital treatment, a prehydration of 1 l normal saline during 1 h was delivered before cisplatin administration and continued afterwards during 4 h for a total of four times.

The antiemetic coverage consisted of either 125 mg methylprednisolone (Solumedrol®) and 50 mg metoclopramide (Primperan®) 1/2 h before and 1/2 h after cisplatin administration for the ambulatory patients, or 1.5 mg/kg metoclopramide, 20 mg dexamethasone and 50 mg promethazine (Phenergan) 1/2 h before cisplatin administration and subsequently 1.5 mg/kg metoclopramide at 2 h intervals five times afterwards for in-hospital patients.

Treatment courses were repeated every 4 weeks. A new treatment course was delayed by 1 week if no full hematological recovery was observed on day 28. Dosage adjustments were made for etoposide and/or cisplatin according to hematological toxicity for etoposide (dosage reduction of 25% for WBC count <1000/mm^3 and platelet count <25,000/mm^3 at nadir) and to nephrotoxicity for cisplatin (discontinuation of treatment if serum creatinine >2 mg %). Toxicity of therapy was graded for each course according to WHO criteria [7]. Tumor response was assessed after two courses using standard SWOG criteria for complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Minor response (MR) was defined as a >25% but <50% decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions maintained for at least 6 weeks. Responding patients (CR, PR, MR) and patients with SD were regularly reevaluated (after their 4th, 6th, 8th and 10th course) and received maximally 10 courses. The median duration of response and survival of the various subgroups was analyzed and compared according to the Wilcoxon and log-rank methodology. Analysis and comparison of prognostic variables within response categories was performed using the *t*-test and/or Fisher's exact test.

RESULTS

Patient characteristics are summarized in Table 1. Patients with prior surgery and/or radiotherapy presented with evaluable and/or measurable indicator lesions outside the area previously tested.

Table 1. *Patient characteristics*

	Number	Median	Range	SC	AC	LC
Total patients entered	40					
Age		66	(41–83)			
Sex	40 male					
Performance status		70	(50–100)			
Stage						
stage 1				—	—	—
stage 2				2	1	—
stage 3						
LD				7	—	1
ED				17	12	—
Histological subtype*				26	13	1
Prior therapy						
surgery	4			4	—	—
radiotherapy	1			1	—	—
surgery + radiotherapy	2			1	1	—
chemotherapy	0			—	—	—
Evaluable and/or measurable indicator lesions						
primary tumor	18			15	2	1
primary + metastases	18			9	9	—
metastases	4			2	2	—

*Abbreviations: SC, squamous cell carcinoma; AC, adenocarcinoma; LC, large cell carcinoma.

The indicator lesion was the primary lung tumor in 18 patients. In an additional 18 patients it was the lung plus one or more metastatic sites. In four patients the only indicator lesion was the metastatic site (three patients with more than one lesion).

In 10 patients one or more osteolytic bone lesions were present; these were not considered evaluable and/or measurable.

Response

All patients were considered evaluable for response. Two patients died shortly after the first cycle of chemotherapy (see section Toxicity) and were considered as treatment failures.

Eleven patients achieved a major response (1 CR, 10 PR) (27.5%), seven MR (17.5%), seven SD (17.5%) and 15 (37.5%) progressed under treatment (Table 2).

Major responses occurred more frequently in the squamous cell carcinoma subtype (9/26) as compared to the non squamous cell carcinoma subtype (2/14) (not significantly different). Prognostic variables such as PS, age and extent of disease were not significantly correlated with response (Table 3). In all patients showing a major response, tumor reduction of all evaluable and/or measurable lesions was observed.

The median duration of response in major responders was 31 weeks (range 9+ to 82+ weeks). Due to the small sample size in the LD subgroup (two major responders only), valid statistical conclusions about the eventual difference in duration of response between LD and ED patients could not be drawn.

If the results of the median duration of response of CR, PR, MR and SD are pooled and compared between LD and ED patients no statistically significant difference appeared (26 weeks for LD patients vs. 31 weeks for ED patients; P value = 0.94).

Survival

The MST of all the patients studied was 42 weeks (range 0–113 weeks).

Survival (S) was not significantly different among subgroups of patients presenting with PS scores of either 50–70, 80, or 90–100. Nor was S influenced by age or histological subtype. The MST of all patients (including early toxic deaths) in the LD

Table 2. Influence of prognostic variables on response

Response	1 CR	10 PR	7 MR	7 SD	15 PD
PS					
median	70	80	70	80	70
range	—	60–100	50–100	50–100	50–90
Age					
median	75	66	66	64	66
range	—	54–76	47–73	37–78	41–83
Disease extent					
LD (11)	—	2	4	2	3
ED (29)	1	8	3	5	12
Histology*					
SC	1	8	4	3	10
AC	–	2	2	4	5
LC	—	—	1	—	—

*Abbreviations: see Table 1.

Table 3. Median survival time (weeks)

	CR + PR	MR + SD	Non progressors (CR, PR, MR, SD)	PD
LD				
range	9+–48	27–113	9+–113	0–48
median	NR	64.5	48	26
ED				
range	27–86	18+–86	27–86	0–21
median	56	58	56	6.5
LD + ED				
range	9+–86	18+–113	9+–113	0–48
median	54	58	56	12

NR: not reached.

and ED subgroups was respectively 48 and 34 weeks ($P = 0.26$; NS). Within the ED subgroup, the MST of patients achieving major response (CR + PR) was not significantly different from those achieving only MR or SD (Table 3). Due to the small number of patients achieving CR + PR in the LD subgroup, a statistical conclusion about eventual differences in the MST between CR + PR and MR + SD could not be drawn (Table 3).

The apparent superior MST between non progressors in the ED subgroup compared to LD patients (56 weeks vs. 48 weeks) was not significant.

Patients progressing while on the initial two courses of chemotherapy lived significantly less long than non progressors (9 weeks vs. 56 weeks; $P < 0.001$) (Fig. 1).

Toxicity

One hundred and eighty-five cycles of chemotherapy were administered (median number 3; range 1–10), 161 on a fully ambulatory basis (31 patients) and 24 (9 patients) during in-hospital treatment.

All patients were evaluable for toxicity and the results are listed in Table 4. Some side-effects were common. Alopecia was universal and occurred mainly from the second cycle of treatment (grade 2–4 in approx. 100% of patients). Myelosuppression, mainly leucopenia, was the second most important toxicity. Life-threatening infections with septicemia and shock occurred during the first cycle of treatment in two patients. These presented with low PS (50 and 60) and major organ involvement (bone and liver metastases). Additionally, nine other episodes of infection occurring after the 2nd cycle in the presence of WHO leucopenia grade 0–3 were observed. All were accurately treated with antibiotics.

Gastrointestinal, neurological and renal toxicity was less severe.

Other less important events due to therapy were: profound and long-lasting asthenia and anorexia in two patients, pulmonary edema in one patient due to fluid overload and diarrhea in one patient due to metoclopramide administration.

The overall reasons for terminating the study protocol were PD in 27 patients and compliance and/or toxicity in five (Table 5). Seven patients completed 10 cycles of chemotherapy. One patient was still on treatment at the time of analysis.

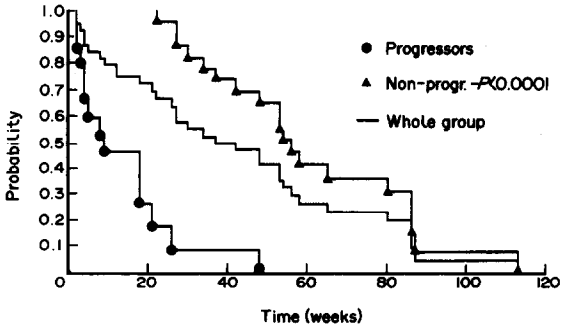

Fig. 1. Log-rank survival estimates of progressors (●) vs. non progressors (▲). The difference of the median survival of progressors (9 weeks) and non progressors (56 weeks) is statistically significant (P < 0.001).

DISCUSSION

The present study was performed to assess the feasibility of combining oral etoposide, given on a fully ambulatory schedule, with cisplatinum and to determine the antitumoral activity of this association in NSCLC. The dosages of both cytotoxic agents were comparable to those previously described [1]. Due to its altered bioavailability, when administered orally, we used a dosage of oral etoposide that was twice that of intravenous etoposide as suggested by several previous studies [8–10].

The intake of oral soft gelatin capsules was scheduled before the administration of cisplatin to prevent eventual intake difficulties which occur frequently after cisplatin administration.

The administration of cisplatin was performed in the late afternoon between 6 and 8 p.m. with low volume pre- and posthydration in the majority of patients (161 courses in 31 patients). In the remainder (24 courses in nine patients), merely due to lack of administration facilities between 6 and 8 p.m., cisplatin was given with high volume forced diuresis at noon (see section Patients and Methods). It has been shown previously that the time of administration between 6 and 8 p.m. might be considered as the best for cisplatin according to its circadian pharmacokinetics [11]. As a result, none of the patients treated in the fully ambulatory schedule had evidence of renal toxicity exceeding grade 1. On the other hand also in patients with in-hospital treatment no major nephrotoxicity appeared. This can be due to effective protective measures (e.g. high volume hydration) but also to the low number of courses (median 2; range 2–6) administered by this route and consequently the low number of patients at risk for developing cumulative toxicity. Neurotoxicity and acute gastrointestinal toxicity were mild in most instances.

The potent coverage with high dose metoclopramide either with methylprednisolone (161 ambulatory courses) or with dexamethasone and promethazine (24 in hospital courses) apparently effectively prevented cisplatin nausea and vomiting. No major gastrointestinal problems occurred after the intake of oral etoposide during the initial 3 days of each course.

Alopecia was most common and unpleasant for most patients but reversible. In contrast, myelosuppression was troublesome in a few patients.

Table 4. Toxicity (WHO grade)

	Grade	Cycle number (number of evaluable courses)									
		1 (40)	2 (32)	3 (24)	4 (19)	5 (15)	6 (15)	7 (13)	8 (11)	9 (9)	10 (7)
Myelosuppression	0	18	20	15	10	7	10	7	6	6	6
	1	9	6	7	6	7	4	5	3	2	1
	2	7	5	1	3	1	1	1	1	1	
	3	4	1	1	—	—	—	—	1	—	—
	4	2	—	—	—	—	—	—	—	—	—
Nausea and vomiting	0	25	10	9	9	8	8	9	6	4	4
	1	9	15	8	6	3	4	2	2	3	2
	2	3	6	7	2	3	1	1	2	1	1
	3	3	1	—	2	1	2	1	1	1	—
	4	—	—	—	—	—	—	—	—	—	—
Renal impairment	0	37	29	23	18	13	12	12	10	8	5
	1	3	3	1	1	2	3	1	1	1	2
	2	—	—	—	—	—	—	—	—	—	—
	3	—	—	—	—	—	—	—	—	—	—
	4	—	—	—	—	—	—	—	—	—	—
Neurotoxicity	0	39	27	22	17	13	13	10	9	6	5
	1	—	2	2	2	2	1	—	1	2	2
	2	—	1	—	—	—	1	2	1	1	—
	3	1	2	—	—	—	—	1	—	—	—
	4	—	—	—	—	—	—	—	—	—	—
Alopecia	0	35	2	—	—	—	—	—	—	—	—
	1	2	5	1	—	—	—	1	—	—	—
	2	2	14	7	3	2	2	1	2	3	2
	3	1	9	11	12	8	8	8	3	5	4
	4	—	2	5	4	5	5	3	6	1	1

Table 5. Reasons for terminating study protocol

	CR	PR	MR	SD	PD
Study completed					
number of patients	—	3	2	2	15
(total number of cycles)*	—	(30)	(20)	(20)	(24)
Progressive tumor					
number of patients	—	4	4	4	—
(total number of cycles)	—	(21)	(18)	(22)	—
Toxicity and compliance					
number of patients	1	2	1	1	—
(total number of cycles)	(6)	(12)	(3)	(7)	—
Ongoing					
number of patients	—	1	—	—	—
(total number of cycles)	—	(2+)	—	—	—

*In parentheses: total number of cycles administered in each category.

As already stated before (see section Results and Toxicity), two patients with poor prognostic variables (low PS, large tumor burden) died from unexpected leucopenia related to septic shock. Increased absorption and bioavailability of etoposide might account for the lethal complications in these patients [12]. In contrast, the remainder of the courses in which grade 2–3 myelosuppression was produced were without severe infectious complications. The dosage of both drugs in NSCLC patients with poor prognostic variables should be reduced to prevent severe hematological toxicity. The extent to which the dosage should be reduced is not clear from the present study.

The overall antitumoral activity of 27.5% compared well with the earlier published cumulative response rate of 32% [1]. It is worth emphasizing that the oral intake of etoposide during 3 consecutive days before cisplatin did not seem to influence either positively or negatively overall activity results. *In*

vitro and *in vivo* studies on cell lines derived from Lewis lung carcinoma have shown that the sequence of administration of etoposide and cisplatin might be critical to reduce toxicity and enhance antitumoral activity. In view of this, the best therapeutic sequence of both drugs producing the least toxicity in mice was etoposide given one day (single dose) before cisplatin (fractionated dose) [13]. Accordingly randomized clinical studies should be performed to assess the value of this approach.

In conclusion, the association of oral etoposide preceding cisplatin is a feasible, not severely toxic approach in locally advanced and/or extensive NSCLC. The present regimen should nevertheless be administered only at full dosage to patients with good prognostic variables to avoid excessive myelosuppression. Patients with less good prognostic variables should be offered dosage reduction. The schedule with oral etoposide reduces the patient visits to the hospital from four to two (the first being the visit on day 1 of each cycle for hematological control and clinical evaluation and the second being day 4 for either admission in the hospital or outpatient visit for the administration of cisplatin). This schedule will allow patients to enjoy a good quality of life through maximal treatment outside the hospital, while retaining antitumoral activity comparable to other chemotherapy protocols.

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