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Original Paper

Carboplatin–Oral Etoposide Personalised Dosing in Elderly Non-small Cell Lung Cancer Patients

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The toxicity and therapeutic activity, including the effect on quality of life, of the carboplatin–oral etoposide combination, given with an intrapatient dose escalation, was tested in 38 non-small cell lung cancer (NSCLC) patients aged over 70 years, and in 8 younger patients with a performance status of 2. In the absence of grade 3–4 toxicity, doses were escalated as follows: first course (carboplatin AUC 4; etoposide 50 mg twice daily orally days 1–14); second course (carboplatin AUC 5; etoposide 50 mg twice daily orally days 1–14); third course (carboplatin AUC 5; etoposide 50 mg twice daily orally days 1–21). A total of 141 chemotherapy cycles were delivered. The treatment was, in general, well tolerated and no toxic deaths occurred. More than 60% of patients received 100% of the planned dose intensity. Transient grade 4 neutropenia or thrombocytopenia occurred in 6 and 2 patients, respectively, but only 2 patients had to be hospitalised because of fever. All patients were evaluated for activity on an 'intention to treat basis'. Ten partial responses and 20 stable disease were recorded, for an overall response rate of 22% (95% confidence interval (CI) = 11–36). 9/38 (24%; 95% CI = 12–41) elderly patients obtained a partial response. The median response duration was 4 months. A quality of life improvement was observed in 19 of the 46 enrolled patients (41%; 95% CI = 27–57), and 15/46 (33%; 95% CI = 19–48) showed a performance status improvement. The quality of life score improved in 17/38 (45%) elderly patients. 8/10 responders and 11/20 patients with stable disease showed a concomitant improvement in quality of life. At a median potential follow-up of 16 months (range 2–21), 31 patients had had progression of disease and 23 had died, for a median time to progression (TTP) and overall survival (OS) of 5 and 10 months, respectively. The median survival time was 11 months in elderly patients. The median time to subjective impairment (TSI) was 6 months (7 months in the elderly group). One-year estimated TTP, TSI and OS rates were 22, 29 and 41%, respectively. At multivariate Cox analysis, a > 25% improvement in the quality of life score was more predictive of a better survival outcome than the response achievement. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

LUNG CARCINOMA is the major cause of death in Western countries, and non-small cell lung cancer (NSCLC) accounts for at least 80% of cases. Currently, a platinum-based treatment seems generally advisable in patients with advanced disease in view of its clear, although moderate, survival advantage over best supportive care [1]. However, the benefit of aggressive chemotherapy seems more uncertain in certain subsets of patients, such as those showing poor performance status at diagnosis or in elderly patients, since they may have an impairment of hepatic, renal and particularly bone marrow function, all of which usually have a negative impact on

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tolerability of antineoplastic chemotherapy. In a randomised ECOG study, single agent carboplatin offered a statistically significant survival advantage over other commonly used cisplatin-based regimens, despite a response rate of only 9% [2]. Also etoposide, in spite of its marginal activity against NSCLC as a single agent, is an interesting drug in view of its synergism with platinum compounds, and its peculiar schedule-dependent toxicological and therapeutic profile. In fact, recent studies suggest that prolonged oral administration may be more effective than the standard intravenous schedule [3].

The combination of carboplatin and oral etoposide has shown considerable activity in small cell lung cancer (SCLC) patients and even in elderly patients it produced a 71% objective response rate with a median survival of 46 weeks [4]. Also, in NSCLC, this combination produced an overall response rate exceeding 20% [5]. Recently, its use in elderly NSCLC patients has been reported with a disappointing response rate [6]. However, both carboplatin and oral etoposide show a wide pharmacokinetic and pharmacodynamic interpatient variability. Therefore, it could be more appropriate to adjust the dose of these drugs to be delivered on the basis of some individual parameters, for example, creatinine clearance.

Carboplatin is rapidly eliminated by the kidney, with approximately 75% of the drug excreted within the first 24 h. In view of this, many investigators recommend the estimation of the area under the curve (AUC) for carboplatin dosing. Escalating doses of carboplatin combined with a fixed dose of oral etoposide and granulocyte-colony stimulating factor (G-CSF) have been recently reported by us from a phase I/II study [7]. The determination of carboplatin AUC permitted a better prediction of myelotoxicity and response rate, than the dose of carboplatin delivered [7].

On the basis of all these considerations, at the end of 1995 the Gruppo Oncologico Cooperativo sud-Italia started a multicentre phase II study testing the intrapatient dose escalation of carboplatin (dosed according to the Calvert formula) and oral etoposide in elderly or poor performance status NSCLC patients.

PATIENTS AND METHODS

Design of the study

The aim of this phase II study was to define the capability of this regimen of improving the quality of life in both elderly (> 70 years) or poor performance status patients. In this poor prognosis subset of NSCLC patients, we aimed to obtain an improvement in quality of life in 40% of patients and set 20% as the lowest percentage of interest; the type I and type II errors chosen were 5% and 20%, respectively. According to the optimal design of Simon and colleagues [8], if less than 4 patients within the first 13 enrolled showed an improvement in quality of life, the trial would be stopped because of the low activity of the treatment; otherwise, the enrolment would continue for up to 43 patients.

Eligibility criteria

Patients with histologically/cytologically documented locally advanced (IIIB) or metastatic NSCLC were eligible for this treatment. They had to be aged between 71 and 80 years (with an ECOG performance status between 0 and 2), or be any age with a poor performance (ECOG 2). Other eligibility criteria included normal bone marrow, renal and hepatic functions. The presence of central nervous system metastases, severe infections, severe cardiac arrythmia or heart failure, acute myocardial infarction within 4 months prior to study entry, previous or concurrent malignancy (except inactive non-melanoma skin cancer, *in situ* carcinoma of the cervix, or other cancer if the patient had been disease-free for more than 5 years), life expectancy less than 12 weeks, were all considered as exclusion criteria.

All patients gave written informed consent and the trial was approved by the ethical committees of participating institutions.

Treatment

The eligible patients received three courses of chemotherapy at escalating doses: first course, carboplatin AUC 4 day 1 + etoposide 50 mg twice a day orally days 1–14 every 4 weeks; second course, carboplatin AUC 5 day 1 + etoposide 50 mg twice a day orally days 1–14 every 4 weeks; third course, carboplatin AUC 5 day 1 + etoposide 50 mg twice a day orally days 1–21 every 4 weeks. The escalation was performed provided that grade 3–4 toxicity did not occur.

Patients showing a major response (complete or partial response) after three courses, received an additional three courses at the same doses given in the third course.

The total dose of carboplatin in mg was determined as follows: (creatinine clearance + 25) × chosen AUC. The creatinine clearance was calculated using the Cockroft–Gault formula.

Adjustments according to toxicity

Toxicities were graded according to WHO criteria [9]. Haematological toxicity was assessed by performing a weekly blood cell count, and reported as the worst grade of toxicity encountered in each course. In the presence of grade 3 myelosuppression at nadir occurring in one of the first two courses, the planned dose escalations were not performed. If grade 4 haematological or grade 3–4 non-haematological (except for vomiting and alopecia) toxicity occurred, the dosages were taken back to those given at the preceding course. If these toxicities were seen at the first course, the duration of etoposide administration was reduced to only 1 week. If a carboplatin AUC of 4 mg/ml/min combined with a 1-week oral etoposide administration again caused unacceptable toxicity, the patient was withdrawn from the study. If grade 1 neutropenia or thrombocytopenia persisted at subsequent cycles, in spite of the absence of dose-limiting myelosuppression at nadir, chemotherapy was given at 75% of the doses planned for that course. The treatment was delayed by 1 week if > grade 1 haematological toxicity, or non-haematological toxicity of any grade persisted at subsequent cycles. After more than a 3-week delay, the patient was withdrawn from the study. In the presence of grade 3–4 neutropenia or thrombocytopenia during the administration of oral etoposide, the intake of this drug was discontinued. The use of G-CSF or granulocyte-macrophage colony stimulating factor (GM-CSF) was allowed for grade 4 neutropenia, together with prophylactic antibiotics.

Response and quality of life evaluation criteria

The objective response was evaluated according to WHO criteria [9]. The assessment of quality of life was performed by analysing a 10-item questionnaire completed by the patients at diagnosis and every 3 months until death. This questionnaire (Table 1) was derived from the Lung Cancer Symptom Scale (LCSS) [10]. We included in the first section

Table 1. *Quality of life questionnaire*

	Score				
	0	1	2	3	4
Disease-related symptoms					
Cough	Absent	Sometimes during the day. No medication needed	Bothersome. Medication needed	Disturbs sleep and other normal functioning	Nearly constant, disrupts all normal activities
Shortness of breath	Absent	Noted only with major activity	Present when walking at normal pace	Present with minimal activity. Supplemented O_2 used only occasionally	Supplemented O_2 required most or all of the time
Pain	Absent	Present but not requiring medication, or well controlled with non-narcotic medication	Well controlled with codein-containing drugs	Strong narcotic agents are required; pain control satisfactory	Not well controlled with any drugs
Fatigue	Absent	Occasionally troubled by modest fatigue	Usually troubled by modest fatigue	Occasionally troubled by major fatigue	Usually troubled by major fatigue
Loss of appetite	Absent	Loss of appetite only for some food	Occasionally interferes with food intake	Usually interferes with food intake	Appetite so poor that medical intervention is needed
Psycho-social and emotional items					
How do you feel?	Very well	Quite well	Not very well	Bad	Very bad
Do you wish to socialise?	Always	Most of the time	Sometimes	Rarely	Never
Do you carry out normal activity?	Always	Most of the time	Sometimes	Rarely	Never
Do you feel sad?	Never	Rarely	Sometimes	Most of the time	Always
What do you think about the treatment?	It is very effective	It is quite effective	I do not know	It is not very effective	It is not effective
Total score					

the five most frequent disease-related symptoms (cough, loss of appetite, dyspnoea, fatigue, pain), while the other five-item section concerned psychological, social and emotional aspects, and general well being. This questionnaire did not include haemoptysis since, in a retrospective analysis conducted in our lung cancer patients, this symptom occurred in less than 15% of cases. We expanded the number of items concerning the social and emotional aspects, compared with the LCSS, in order to obtain a better evaluation of the subjective aspects of quality of life. Each item was scored according to a five-step scale ranging from 0 (absence of any symptom, or impairment of quality of life) to 4 (the worst symptom grade possible). A decrease of any grade of the summation score (ranging from 0 to 40) was required to define an improvement in quality of life. The proportion of patients achieving an improvement in quality of life and the time to subjective impairment (TSI) (the time between the date of diagnosis and the date of worsening of the quality of life score) were analysed to evaluate the impact of the treatment on quality of life.

RESULTS

46 patients entered the study between October 1995 and March 1997, for a total of 141 chemotherapy cycles delivered. 38 were older than 70 years (15 over 75 years) and 8 were younger with a poor performance status. ECOG performance status was 0–1 in 18 and 2 in 28 patients. 25/46 (54%) had stage IV disease. The majority of patients (36; 61%) had at least one concomitant illness, most frequently chronic obstructive lung disease (15; 33%), diabetes (10; 22%), hypertension (7; 15%) (Table 2).

The treatment was, in general, well tolerated and no toxic deaths occurred. More than 60% of patients received 100%

Table 2. *Patient characteristics*

Total	46
Age (years)	
≤ 70	8
> 70	38
Gender	
Male	39
Female	7
ECOG performance status	
0–1	18
2	28
Stage	
IIIB	21
IV	25
Concomitant illness	36
Chronic obstructive lung disease	15
Diabetes	10
Hypertension	7
Coronaric ischaemia	4

of the planned dose intensity. In particular, chemotherapy was given at the first dose level (carboplatin AUC 4 and etoposide days 1–14) in 56 cycles, at the second dose level (carboplatin AUC 5 and etoposide days 1–14) in 45 cycles and at the third dose level (carboplatin AUC 5 and etoposide days 1–21) in 33 cycles. In an additional seven cycles, the duration of etoposide administration was reduced to only 1 week, due to occurrence of grade 3–4 neutro-thrombocytopenia in the course of etoposide administration. Transient grade 4 neutropenia occurred in 6 patients (all received G-CSF and prophylactic antibiotics), but only 2 patients had to be hospitalised because of fever. Grade 4 thrombocytopenia occurred in only 2 patients, and was never symptomatic. Severe anaemia was observed in 5 patients, and 2 required blood transfusion. Mild gastrointestinal toxicity associated with oral etoposide administration occurred in 7 patients, but never led to suspension of treatment. No episode of severe nephro- or neurotoxicity occurred. All patients were evaluated for activity on an 'intention to treat basis'.

No complete and 10 partial responses, 20 stable disease and 16 progressive disease were recorded for an overall response rate of 22% (95% confidence interval (CI) = 11–36). 9/38 (24%; 95% CI = 12–41) elderly patients obtained a partial response and only 1/8 (15%; 95% CI = 3–53) poor performance status patients ages less than 70 years responded to treatment, 6 partial responses were observed in 18 patients with performance status 0 or 1 (33%) as compared with 3/20 (15%) in patients with a poor performance status. The median response duration was 4 months in the whole group.

Table 3 summarises the quality of life changes observed during this study. A quality of life improvement was observed in 19 of the 46 enrolled patients (41%; 95% CI = 27–57), and in 18 of them it happened within 3 months of the start of treatment. 15/46 patients (33%; 95% CI = 19–48) also showed a performance status improvement. The quality of life score improved in 17/38 (45%) elderly as compared with only 2/8 (25%) younger patients with poor performance status.

Table 3. Quality of life changes over time

	Baseline	3 months	6 months	9 months	12 months
Total					
Alive	46	38	29	25	16
Mean score	11.2	9.9	7.0	9.3	10.8
Responders					
Alive	10	10	10	9	8
Mean score	9.4	7.2	6.1	8.5	9.4
Improved		7	8	5	4
Stable		3	1	1	2
Impaired		0	1	3	2
Stable disease					
Alive	20	20	18	16	8
Mean score	10.8	8.5	7.0	9.7	12.2
Improved		11	9	3	2
Stable		4	4	5	4
Impaired		5	5	8	2
Progressive disease					
Alive	16	8	1	0	0
Mean score	13.8	17.2	16		
Improved		0	0		
Stable		1	0		
Impaired		7	1		

8/10 responders and 11/20 patients with stable disease showed a concomitant improvement in quality of life, while none of the 16 patients with progressive disease showed an improvement. The mean summation score of responders and patients with stable disease did not significantly differ at baseline, and at 3 and 6 months. 10 patients (7 responders and 3 with stable disease) showed a maximum decrease in the quality of life summation score of > 25% of the baseline value. The changes in the symptoms and in the emotional/social aspects were not substantially different, although sometimes the chemotherapy side-effects adversely affected the score of the latter section. Among the disease-related symptoms, cough improved in 51%, dyspnoea in 37% and pain in 47% of patients.

At a median potential follow-up of 16 months (range 2–21), 31 patients progressed, with 23 dying, for a median time to progression (TTP) and overall survival (OS) (Figure 1) of 5 and 10 months, respectively. The 1 year estimated TTP and OS rates were 22 and 41%, respectively. The median survival time was 11 months in elderly patients, 12.5 months in those with good or intermediate performance status, and 8 months in those with poor performance status. A median survival time of 7 months was observed in the 8 younger patients with poor performance status. The median TSI was 6 months (7 months in the elderly group and 4 months in the others), with 29 patients having a subjective impairment with a median follow-up of 16 months.

Median survival in the 19 patients with improved quality of life (11.5 months) was not significantly different from that of the 10 patients showing an objective response (13 months). However, it rose to 15 months in the 10 patients who had achieved a more than 25% decrease in the quality of life score. Among the main pretreatment features, a weight loss of more than 10%, an ECOG performance status 2 and a quality of life summation score of more than 10 were the only parameters significantly associated with a worse survival in a multivariate Cox analysis. When both the achievement of an objective response and the best quality of life improvement obtained in the first 6 months (> 25% improvement versus $\leq$ 25% improvement or no improvement) were included in the model as time-dependent covariates, the ECOG performance status at diagnosis (0–1 versus 2; $P = 0.04$) and the quality of life change (> 25% decrease versus others; $P = 0.02$) were the only parameters significantly affecting survival.

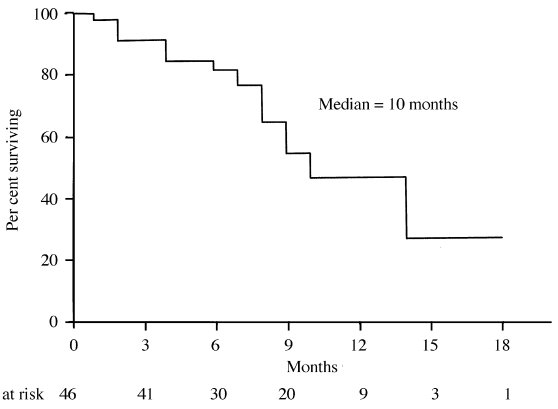

Figure 1. Overall survival of all patients. 23 patients died at a median follow-up of 16 months.

DISCUSSION

There is increasing interest in the treatment of elderly lung cancer patients, since half of all cases are diagnosed in patients aged ≥ 65 years. Until recently, there had been few studies devoted to therapy and in particular to systemic antineoplastic treatment, for lung cancer in the geriatric population. Although it could be hazardous to administer very aggressive chemotherapy in this subset of patients, in view of their unpredictable tolerance (mainly due to the wide variations in the metabolism of cytotoxic agents), it is not reasonable to deny them any effective chemotherapy whatsoever.

The aim of our study was to evaluate whether a carboplatin–oral etoposide personalised dosing in this population could result in both good activity and manageable toxicity.

Since we also hypothesised an impaired tolerability of antineoplastic chemotherapy in patients with poor performance status, we included 8 such patients in the study.

The treatment policy chosen translated into a good overall tolerance of the treatment. In fact, the number of hospitalisations due to fever or other severe toxic episodes was very low. It is interesting to note that we delivered the planned chemotherapy dose in more than 60% of patients.

The overall objective response rate achieved in our study does not appear particularly impressive. However, it must be pointed out that the response rate was slightly higher in the 38 elderly patients (24% versus 12.5% in younger patients with poor performance status), and that many patients in this group also had a poor performance status. Moreover, a relevant proportion of patients achieved a long-lasting stabilisation of the disease and this resulted in a very interesting median time to progression, which was 5 months in the whole population.

Also, the median survival and the proportion of patients alive at 1 year seem of considerable interest, since they look similar to those reported with more aggressive regimens in much more prognostically favourable populations.

The evaluation of quality of life changes represented, however, the main endpoint of this study. Forty-five per cent (17/38) of elderly patients showed an improvement in their quality of life throughout the treatment, whilst this was so in only 2/8 patients with poor performance status. In the majority of patients the treatment was able to delay the impairment of quality of life due to disease progression by at least 3–4 months. In fact, the median time to subjective impairment was 6 months, with 29% of patients still free from subjective impairment at 1 year.

It is of interest to point out that although almost all the responders had an improvement in the quality of life score, such an improvement was also evident in more than 50% of patients showing stable disease. The importance of the quality of life evaluation during the course of disease is confirmed by the fact that median survival of patients with a subjective improvement of any grade was not significantly different from that of responding patients. Moreover, the results of our Cox analysis suggested that a more than 25% decrease in the quality of life score is the more predictive of longer survival than the response itself. It is common practice in many parts of the world to stop treatment after two or three chemotherapy cycles in patients who do not achieve an objective response. Our results would suggest that it could be useful to prolong treatment in those patients with stable disease showing a substantial improvement of their quality of life.

In conclusion, our carboplatin–oral etoposide personalised treatment seems an advisable approach in elderly NSCLC patients, in view of its good impact on both quality of life and overall survival. The clinical benefit and the quality of life improvement seem less relevant in patients with poor performance status, independent of their age. Large randomised trials are needed to better define the role of this treatment in these two subsets of NSCLC patients. Recently, it has been reported that new agents, like gemcitabine, taxanes and vinorelbine may have both a good tolerability and a high antitumour activity in advanced NSCLC.

Some preliminary data concerning the use of these molecules in monochemotherapy in elderly patients seem to suggest that they have good tolerance and adequate antitumour activity [11, 12]. In view of this, randomised trials comparing our combination with these new molecules (used alone or in combination) would be useful in defining the best treatment in this particular NSCLC population.

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