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ORIGINAL ARTICLE

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Docetaxel and mitomycin as second-line treatment in advanced non-small cell lung cancer

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Abstract *Purpose*: To evaluate the feasibility, toxicity and efficacy of the combination of docetaxel and mitomycin C as second-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). *Patients and methods*: Thirty-eight patients with histologically confirmed, locally advanced or metastatic NSCLC were included in this phase II trial. All patients had been previously treated with a platinum-based regimen. Treatment consisted of docetaxel (75 mg/m^2) followed by mitomycin C (8 mg/m^2) on day 1, every 21 days. Patients received a minimum of three courses unless progressive disease was detected. *Results*: A total of 190 courses of docetaxel-mitomycin C were administered (median five courses per patient). This combination was well tolerated with grade 3–4 toxicity experienced with the following frequency: neutropenia in five patients (13%), fatigue in four (11%), anaemia, thrombocytopenia, nausea/vomiting and peripheral neuropathy in one each (3%). Three of 38 patients had a partial response (8%, 95% confidence interval 2.6–21.6%), 14 patients (37%) experienced stabilization of disease and 21 (55%) had disease progression. Median time to progression was 3.6 months. Overall median survival was 10.4 months, with the 1-year actuarial survival rate being 35%. *Conclusions*: The addition of mitomycin C to docetaxel as second-line therapy in NSCLC is well tolerated but does not seem to improve the response rate.

Keywords Non-small cell lung cancer · Docetaxel · Mitomycin C · Second-line chemotherapy

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Introduction

For patients with non-small cell lung cancer (NSCLC) stage IIIB (with pleural effusion) or IV with a good performance status, platinum-based chemotherapy confers a modest survival advantage and represents the standard of care in this group. However, virtually all patients who initially respond will eventually become refractory to these agents and, if their performance status so permits, be eligible for further treatment. For this reason, second-line chemotherapy is considered an option for a growing number of patients.

Randomised studies have demonstrated that second-line treatment with docetaxel results in a benefit both in terms of survival and improved quality of life when compared with best supportive care [3, 4] or with vinorelbine or ifosfamide in monotherapy [5]. More recently, the multitarget antifolate pemetrexed has shown equivalent clinical outcomes to docetaxel but with fewer side effects [6]. However, neither of these agents has proven to prolong survival beyond a median of 8 months, nor to increase 1-year-survival rates above 30% and the overall response rates are approximately 10% [3–6]. For these reasons there is an evident need to develop new chemotherapeutic regimens that may improve these results.

Mitomycin C is a first generation drug which has proven activity in first-line treatment of NSCLC, achieving a response rate in monotherapy of approximately 25% [7]. It is normally combined with other drugs when used as initial treatment, and few studies have been published investigating its possible role in the second-line therapy. The experience so far has been in combination with either vindesine [8–10] or cisplatin and vinblastine [11], with response rates varying between 0 and 17% [8–11]. A review of these studies concludes that its role as salvage treatment, either in monotherapy or in combination with other active drugs, requires further investigation [12].

In this context the 50% response rate achieved with the combination of mitomycin C and paclitaxel as salvage therapy in 17 patients with NSCLC may indicate a promising path [13]. Based on these results, which suggest an elevated anti-tumoral activity for the combination of mitomycin C and a taxane, we conducted a prospective, multicentre, phase II study to assess the activity and toxicity of the combination of docetaxel and mitomycin C in patients with unresectable NSCLC who had previously received platinum-based chemotherapy.

Patients and methods

Thirty-eight patients with histologically or cytologically confirmed NSCLC were enrolled between December 2001 and May 2003. All patients had unidimensionally measurable disease, as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) [14]. Patients with pleural effusion, ascites, osteoblastic or previously irradiated lesions were excluded.

Eligible patients were to meet the following inclusion criteria: [1] first-line treatment with a platinum-based regimen, [2] performance status ≤ 2 as defined by the Eastern Cooperative Oncology Group (ECOG) scale; [3] a life expectancy of at least 3 months; [4] adequate bone marrow reserve (i.e. granulocyte count $\geq 2\times10^9$/l and platelets $> 100\times10^9$/l); [5] adequate liver function (i.e. serum bilirubin < 1.25 upper normal limit and transaminase values < 3 times upper normal limit in the absence of hepatic metastases) and [6] adequate renal function (i.e. serum creatinine less than 150 μmol/l or creatinine clearance of at least 60 ml/min). Patients who had undergone radiotherapy were eligible provided that there was at least one measurable lesion outside the radiation field and radiation treatment was completed at least 4 weeks before enrolment. Oral and written informed consents were obtained from all patients according to the local ethics committee guidelines.

Treatment consisted of docetaxel 75 mg/m^2 followed by mitomycin C 8 mg/m^2 on day one of a 21-day cycle. This regimen was repeated for a minimum of three courses per patient unless disease progression was detected. Patients with objective response or disease stabilization continued treatment until disease progression or unacceptable toxicity occurred, to a maximum of six courses.

Docetaxel was administered intravenously as a 1-h infusion. Patients were instructed to take dexamethasone 8 mg twice daily on days -1, $+1$ and $+2$ of each course. Mitomycin C was administered as a slow intravenous push over 15–30 min.

Complete blood counts were obtained before each course of chemotherapy. Full doses of the drugs were given if neutrophil and platelet counts on the day of treatment were at least 1.5×10^9/l and 100×10^9/l, respectively. If grade ≥ 2 neutropenia or ≥ 1 thrombocytopenia was found, chemotherapy was delayed 1 week. Other toxicities were to be $\leq$ grade 1 before continuing treatment. If neutropenia or thrombocytopenia persisted for more than 1 week, the doses were reduced by 25% in the following courses, while as if other toxicities persisted after a 2-week delay chemotherapy was immediately discontinued. The dose of each drug was reduced by 50% in consecutive courses if grade 4 haematological or grade 3–4 non-haematological toxicity occurred.

Patients were assessed for adverse events before each cycle and graded according to the NCI Common Toxicity Criteria, second edition. For toxicity analysis, the highest-grade data for each patient across all courses were used. Patients were assessed clinically on an intent-to-treat basis at least every 3 weeks and radiographically every 9 weeks. The same assessment modality was used throughout the study. RECIST response guidelines were used [14] defining all responses after at least 9 weeks of treatment as follows: complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). All responses were confirmed ≥ 4 weeks later. Time to tumour progression was estimated by the product limit estimation from the date of the first course to the first evidence of disease progression. Survival was calculated by the same method from the date of the first course until the date of death or last known follow-up.

The primary endpoint was response rate. The sample size was designed to reject a response rate of less than 20%. According to the Fleming method [15], 19 patients were to be included. As the response rate was more than 21% up to 35 patients were included, plus an additional 10% to allow for non-assessable subjects, giving a total of 38 patients. The Wilcoxon rank-sum method was used to compare quantitative variables, Fisher's exact test for percentages and the Kaplan–Meier method to estimate survival and duration of response. Progression-free survival was measured from the initiation of chemotherapy to the date on which disease progression or death without progression took place.

Results

A total of 40 patients diagnosed with advanced NSCLC who had previously received platinum-based chemotherapy were evaluated for eligibility during the study period. Thirty-eight patients fulfilled all eligibility criteria. Patients' baseline characteristics are summarized in Table 1. The median age was 58 years (range 36–74).

Table 1 Patient characteristics ($n = 38$)

	No. of patients (%)
Sex	
Male	33 (87%)
Female	5 (13%)
Median age (range)	58 (36–74)
Stage	
IIIB	4 (11%)
IV	34 (89%)
ECOG performance status	
0	8 (21%)
1	27 (71%)
2	3 (8%)
Histology	
Squamous cell	13 (34%)
Adenocarcinoma	16 (42%)
Large cell	9 (24%)
Prior treatments	
Cis/Gem/Vin	20 (53%)
Cis/Gem	15 (39%)
Cabo/Paclitaxel	3 (8%)
Best response to initial chemotherapy	
PR/CR	7 (18%)
NC	19 (50%)
PD	12 (32%)

Cis cisplatinum, *Gem* gemcitabine, *Vin* vinorelbine, *Carbo* carboplatin, *PR* partial response, *CR* complete response, *NC* no change, *PD* progressive disase

Thirty-three patients were males (87%) and 5 were females (13%). Four were stage IIIB patients (11%) and 34 were stage IV (89%). Eight patients (21%) were asymptomatic (ECOG 0), 27 (71%) had a performance status of ECOG 1 and 3 (8%) ECOG 2. Twenty patients (53%) had received a combination of cisplatin, gemcitabine and vinorelbine as first-line treatment, 15 (39%) had received only cisplatin and gemcitabine and three patients had received carboplatin and paclitaxel. Eighteen patients (47%) experienced an objective response to these platinum-based schemes.

A total of 190 courses of chemotherapy was given with a median of 5 per patient (range 1–6). Two patients received less than three courses: in one case due to patient refusal and in the other due to disease progression. Nevertheless, all patients were considered assessable for both efficacy and safety. Nine patients (24%) experienced treatment delays during the study: six due to causes unrelated to the treatment, two because of neutropenia and three because of non-haematological adverse events. The median dose intensity was 23 mg/m^2/week and 2.4 mg/m^2/week for docetaxel and mitomycin, respectively. Thirty-four patients (89%) received at least 90% of the scheduled doses.

Out of 38 patients, a partial response (PR) was achieved in 3 (8% with 95% confidence interval of 2.6–21.6%). In fourteen patients (37%) the disease remained stable, and 21 (55%) had disease progression. Median time to progression was 3.6 months (95% CI 2.6–4.7). Median survival was 10.4 months (95% CI 7.8–13), whereas actuarial 1-year survival was 35%. No relationship between response rate or median survival and ECOG performance status, disease stage, histology or previous treatment regimen was noted. Only one of the 31 patients (3%) who had been deemed resistant or refractory to a first-line platinum-based chemotherapy responded to the second-line regimen of this trial, while there were two (29%) objective responses among the 7 platinum-sensitive patients ($P = 0.07$).

All 38 patients were assessable for toxicity (Table 2). Twenty-eight patients (74%) experienced treatment-related adverse events, the majority of which were of grade 1/2. The main treatment-related adverse events were haematological. No toxic deaths were seen. Six patients (16%) experienced treatment-related grade 3/4 adverse events: neutropenia 5 (13%), fatigue 4 (11%), anaemia, thrombocytopenia, nausea/vomiting and peripheral neuropathy in 1 (3%) each. Grade 1/2 toxicity was: nausea/vomiting in 37% of the patients, neutropenia in 11%, anaemia in 74%, neurotoxicity in 16%, fatigue in 42% and stomatitis in 26%. Twenty-two patients (58%) required administration of erythropoietin, one patient (3%) received blood transfusions and five patients (13%) G-CSF. No patient required antibiotics or platelet transfusion.

Discussion

During the past decade, new drugs have been incorporated into the treatment of NSCLC, improving the survival of patients with advanced or metastatic disease. In fact, the 1-year survival rate has increased from 10% to as high as 35–40% according to some authors [16]. This increase in survival in combination with the availability of new drugs active in this context has contributed to a renewed interest in the second-line chemotherapeutic regimens.

Second-line treatment in NSCLC should be used to prolong survival and improve the quality of life (QoL) of the patients. These objectives should be met through the use of well-tolerated regimens with a reasonably convenient administration scheme in order to avoid frequent visits to the hospital.

For many years docetaxel has been considered the standard second-line treatment in NSCLC. Even though its use has improved survival and QoL for the patients,

Table 2 Treatment toxicities per patient

WHO toxicity	1–2 *n* (%)	3–4 *n* (%)
Nausea/vomiting	14 (37%)	1 (3%)
Anaemia	28 (74%)	1 (3%)
Leucocytes	4 (11%)	5 (13%)
Platelets	4 (11%)	
Peripheral neurotoxicity	6 (16%)	1 (3%)
Asthenia	16 (42%)	4 (11%)
Elevation transaminases	4 (11%)	
Diarrhoea	4 (11%)	
Stomatitis	10 (26%)	
Alopecia	14 (37%)	

as compared to best supportive care [17], the overall survival is only approximately 7–8 months and the overall response rates lower than 10% [3–6]. Recently, several papers comparing weekly administration of docetaxel for 3 weeks have been reported. Lesser grade 3 and 4 toxicity, mainly in terms of haematological [18–20] and fatigue [20] data, were the paramount differences between both schedules of therapy. Furthermore, in spite of similar response rate and overall survival, one of these studies reported a high grade of pain and cough control in association with scarce alopecia. However, diarrhoea was more frequent with this weekly schedule [19].

Several attempts have been made to improve these results combining docetaxel with other drugs such as irinotecan, gemcitabine or vinorelbine [21–25] or combinations of drugs in the phase II setting [26, 27]. All the results indicate that even if the response rates improve with combination therapy, the median overall survival remains in the range of 6–8 months.

In our study, the response rate reaches 8% and median survival is 10.4 months. Even though this represents a longer median survival than that published by other authors caution is advised in the interpretation given the lack of phase III head-to-head comparative trials. The explanation could be existing differences between the studied patient populations that bias the results. In fact, while in our study no patient had previously received more than one line of chemotherapy previous to enrolment, in other trials 25–30% of patients had received two or more lines of treatment [3, 5]. Other possible factors influencing the response rate such as the proportion of patients with performance status ECOG 2, or the number of patients who progressed on first-line treatment, are not significantly different from those presented in other series.

In this exploratory study, we have not included any reference to the impact of chemotherapy in the QoL. However, if the main objective of the study had been completed, a new randomised study with QoL evaluation as secondary endpoint would have been initiated.

Regarding toxicity, there is a noticeable difference in the number of patients developing grade 3–4 neutropenia in our series (13%), as compared to others who have reported this in 40–67% in schemes with docetaxel in monotherapy (75 mg/m^2). This could be due to the fact that in this trial there were no weekly controls of blood count, to avoid unnecessary hospital visits. Even so, we did not detect any case of febrile neutropenia, in striking contrast to the 10–13% reported by other authors [3, 5, 6]. It could also be due to the fact that, as previously mentioned, our patients had received relatively less chemotherapy prior to enrolment in this trial, which affects the regenerative capacity of the bone marrow. Furthermore, there was a surprisingly large number of patients that developed anaemia and/or thrombocytopenia, usually grade 1/2, which can probably be ascribed to the haematological toxicity of mitomycin C. The frequency of other common toxicities such as fatigue, neurotoxicity or stomatitis were similar to what could be expected from docetaxel in monotherapy [3, 5, 6].

In conclusion, addition of mitomycin C to docetaxel as second-line chemotherapy does not improve the response rate. Despite the acceptable toxicity of this scheme together with a moderate increase in median overall survival, the principal objective of the study has not been achieved and therefore we do not consider it advisable to continue this line of investigation. Presently, there are other drugs such as pemetrexed [6], erlotinib [28] and topotecan [29] which are effective in monotherapy as second-line treatment in NSCLC, and their combination with docetaxel should be investigated further.

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