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Phase I/II study of gemcitabine and epirubicine in stage IIIB-IV non small cell lung cancer

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1. ABSTRACT

Platinum-based chemotherapy currently represents standard treatment for advanced non-small cell lung cancer (NSCLC). Gemcitabine is one of the most promising agents currently in use in advanced NSCLC. As a single-agent, epirubicin, showed tumour response rates ranging from 17% to 36% in NSCLC. The aim of the present study was to evaluate the combination of gemcitabine and epirubicin in a phase I-II study. Thirty chemotherapy-naive patients with stage III B - IV NSCLC received gemcitabine at a fixed dose of 1000 mg/m^2 on days 1 and 8 every 3 weeks; epirubicin was administered every 21 days on day 1 at the initial dose of 80 mg/m^2 which was subsequently escalated. Neutropenia was dose-limiting toxicity since it occurred in 3 out of five patients receiving epirubicin at the dose of 110 mg/m2. An objective response was observed in 14/30 patients, including 2 (7%) complete responses and 12 (40%) partial responses. Median duration of response was 12 months (range: 3 to 53 + months). Median overall survival was 16 months (range: 4 to 55 + months). The combination of gemcitabine and epirubicin is well tolerated. While the observed activity of this combinated treatment matches that of platinum-based regimens, the duration of response and survival have been sufficiently promising to initiate a phase II trial which is currently under way.

2. INTRODUCTION

Lung carcinoma currently represents the leading cause of death from malignant disease in Western countries (1). Non small cell lung cancer (NSCLC) constitutes approximatively three quarters of primary malignant lung tumours and is unresectable in 70% of cases. The issue of the benefit of chemotherapy over the best supportive care in advanced NSCLC has been addressed by several randomized trials. Some important meta-analyses of these trials have been published and have demonstrated a small but significant survival benefit for chemotherapy with concurrent improvement in quality of life (2,3,4). In spite of the fact that cisplatin-containing regimens are currently considered the treatment of choice for advanced NSCLC, cisplatin has several disadvantages such as nephro-, neuro-, and ototoxicity. Therefore, nonplatinum-containing regimens have been studied to find less toxic therapies with similar efficacy. Phase III studies have reported similar response rates and overall survival in cisplatin and noncisplatin-based regimens. However, in the majority of these trials the nonplatinum regimens had a more favourable toxicity profile (5,6,7,8,9).

Gemcitabine (Gem) is among the most extensively used drugs in NSCLC. Although structurally similar to cytarabine, Gem (2',2'-difluorodeoxycytidine) has a

different spectrum of antitumor activity, probably as a result of the different kinetic of accumulation and elimination.

Gem is a prodrug with a greater membrane permeability and a higher affinity for deoxycytidine kinase than the parent compound. This leads to the intracellular synthesis of the active metabolite, Gem triphosphate, which achieves higher concentrations and is retained significantly longer than other pyrimidine analogs (10). A number of phase II studies of Gem in advanced NSCLC have been performed, and a consistent reproducible response rate of 20% to 26% has been demonstrated, with mean response durations and median overall survival times of approximately 9 months. In all of these studies, in which Gem was used at weekly doses ranging from 800 to 1,250 mg/m2 for 3 weeks every 28 days, toxicity was considered mild (11,12,13). Epirubicin (Epi) is another commonly used drug in NSCLC. When used as single-agent, Epi has shown tumour response rates ranging between 17% and 36% in NSCLC (14,15,16). The main toxicities of Epi are myelosuppression, mucositis, and cardiomyopathy (14,15,16). The feasibility and activity of Epi combined with Gem was studied in phases I and II study (17). In this trial, a dose of 1125 mg/m^2 Gem on days 1 and 8 of each 21-day cycle was chosen since this dose leads to a dose intensity of 750 mg/m^2 week 1, which is similar as the schedule in which single-agent Gem 1000 mg/m^2 is given weekly for 3 consecutive weeks in a 28-day schedule. The nadir of Epi is expected 12–15 days after administration; therefore, Gem was omitted on day 15. The phase II trial continued with a dose of 100 mg/m^2 Epi because in the preceeding phase I dose-escalation trial, a maximum tolerated dose of 120 mg/m^2 was reached. The haematologic toxicity of this regimen was acceptable with granulocytopenia grade 4 in 33% and thrombocytopenia grade 4 in 12% of the cycles. Febrile neutropenia occurred in 14% of patients. Nonhaematologic toxicity was mainly mucositis grade 2 and 3 in 35% of patients. Cardiotoxicity measured as a significant decrease of left-ventricular ejection fraction (LVEF) was observed in 7% of patients. The tumour response rate was 49% and the median survival time was 42 weeks (17). The aim of the present study was to evaluate the efficacy and tolerance of combination Gem and Epi in untreated NSCLC patients stage IIIB and IV. We tested the combination of a fixed dose of Gem 1000 mg/m^2 on days 1 and 8 of a 21-day cycle with escalating doses of Epi on day 1, from 80 mg/m2 to 120 mg/m^2.

3. PATIENTS AND METHODS

3.1. Patient Selection

Eligibility criteria for study entry included histologically or cytologically confirmed stage III B or IV NSCLC; age 18 to 70 years; no prior chemotherapy; an Eastern Cooperative Oncology Group performance status of 0 to 2; adequate baseline organ function, defined as a WBC count of at least 3,000 /µL, a platelet count of at least l00,000/µL, a bilirubin level of less than 1 .5 mg/dL, serum transaminase levels of less than 2 times the upper limit of normal, and a creatinine value of less than 1.4 mg/dL; and a life expectancy of at least 12 weeks. Prior chemotherapy was not allowed. Prior palliative radiotherapy to symptomatic metastases was allowed, provided that these lesions were not monitored for tumour response. Radiotherapy was allowed if completed at least 4 weeks before recruitment. Written informed consent was required from each patient.

3.2. Treatment Plan

Treatment consisted of Gem administered at fixed dose of 1000 mg/m^2 on days 1 and 8 every 3 weeks and Epi administered on day 1 at the initial dose of 80 mg/m^2 which was subsequently escalated by 10 mg/m2 at any step. 5-Hydroxytryptamine-3 receptor antagonists were routinely used as antiemetics. Full doses of chemotherapy were given if neutrophil and platelet counts were at least 2 x 10^9/L and 100 x 10^9/L respectively. In cases of World Health Organization grade 1 or higher neutropenia or thrombocytopenia on day 1 or day 8, treatment was delayed 1 week. In patients with persistent grade 1 neutropenia or thrombocytopenia after 1 week, treatment was given at doses reduced by 25% on both day 1 and day 8. Patients with persisting higher-grade toxicity after 1week were taken off study. Cohorts of at least three patients were treated at each dose level. Dose escalation proceeded if no patients had dose-limiting toxicity (DLT) after the first cycle. If one of the three patients had DLT, three more patients were enrolled at that level. Dose escalation was stopped if at least one third of patients of a given cohort had DLT, which was defined as grade 4 neutropenia or thrombocytopenia or grade 3 or 4 nonhematologic toxicity (except for nausea and alopecia). Maximum-tolerated dose (MTD) was defined as the dose level immediately below that causing DLT in one third of patients or more.

3.3. Patient Evaluation

A complete history, physical examination, recording of performance status, complete blood cell count with differential, serum biochemistry, urinanalysis, and ECG and LVEF measured by MUGA scan were obtained at baseline for each patient. Patients were monitored weekly throughout treatment by physical examination, recording of toxic effects, and complete blood cell count with differential; the serum chemistry determination and ECG were repeated at the beginning of each cycle. LVEF was measured every 9 weeks and at the end of treatment and 9 weeks after treatments. Evaluation of tumour response was performed every three cycles, with repetition of all tests that were abnormal at baseline and was performed according to RECIST criteria. Patients with stable or responsive disease after three courses of chemotherapy received additional treatment up to a maximum of six courses; patients with progressive disease were withdrawn from the study. No radiation consolidation was planned for stage IIIB patients. Duration of response was measured from the date of documentation of first response to the date of first evidence of progressive disease, Time to progression was measured from the date of initial treatment to the date of disease progression. The first cycle of treatment assessed the MTD that was reached if any of the following DLTS occurred in at least 2 of 3 or 3 out 6 pts: granulocytes = 500/mmc for more than 7 days, febrile neutropenia, thrombocytopenia = 25.000/mmc or bleeding associated, extra haematological toxicity (excluding alopecia, nausea and vomiting) grade 3 or 4 or persistent

Table 1. Patient Characteristics

No. of patients	n=30
Age, years	
Median	59.5
Range	43-67
Sex	
Male	28
Female	2
Performance status	
0	10
1	16
2	4
Stage	
IIIB	6
IV	24
Histology	
Adenocarcinoma	8
Large-cell	4
Epidermoid	18

grade 2 toxicity at the start of the next cycle or cardiac toxicity as defined by clinical signs of cardiac failure or an absolute decrease of LVEF to level below the normal limit (50% for our institution).

4.RESULTS

4.1. Patient Characteristics

From October 1998 to October 2002, 30 patients (28 males, 2 females) with NSCLC stage IIIB-IV were enrolled into the study. The enrolled patients displayed the following characteristics: median age was 59 years (range 43-67); the Eastern Cooperative Oncology Group performance status was: 0 in 10, 1 in 16 and 2 in 4 patients. Six patients had stage IIIB disease, and twenty-four patients had stage IV disease. Eighteen patients had squamous cell carcinoma, 8 patients had adenocarcinoma and 4 patients had large cell carcinoma. Patient characteristics are listed in Table 1. A total of 125 courses of treatment were given, for a median of 4 courses for patient (range, three to six courses). No patients had been treated with prior radiotherapy on the primary tumour.

4.2. Hematologic Toxicity

Neutropenia was observed in 0 patients treated at the first two dose levels; 2 patients treated at the third dose level had grade 2 neutropenia; and 3 patients treated at the fourth dose level had neutropenia, which reached grade 3 in 1 patients and grade 4 in 2 patient. All two patients with grade 4 neutropenia had fever, which lasted 8 and 10 days, and resolved without overwhelming infections. Therefore, neutropenia was considered DLT, dose escalation was stopped at this step, and the dose level immediately below was considered the maximum tolerated dose. Neutropenia was not cumulative, and its severity was not related to patient pre-treatment characteristics. Thrombocytopenia was not observed at the first dose level and reached grade 1 in one patient each at the third and fourth dose levels. One patient had grade 4 uncomplicated thrombocytopenia at fourth dose level. 4 patients at second and third level showed thrombocytosis, which required medical treatment, but was not complicated by thrombotic events. Dose escalation data are summarized in Table 2.

4.3. Nonhematologic toxicity

Nonhematologic side effects were generally mild. Alopecia was common; nausea and vomiting occurred frequently, but reached grade 3 in only four patients. Liver enzyme derangement was observed in two patients, and no renal abnormalities occurred. Supraventricular ectopic beats were recorded in two completely asymptomatic patient during a routine ECG. LVEF dropped below 50% in only one patient. All nonhematologic toxic effects were reversible and vanished rapidly after treatment interruption. Details on nonhematologic toxic effects are listed in Table 3.

4.4. Treatment Delays

Treatment was delayed 1 week in 30 courses because of neutropenia and/or thrombocytopenia. No drug dose reductions were performed. Epirubicin mean delivered dose intensity at the fourth step was 93.5 mg/m^2 . No patient was withdrawn from the study because of failure to achieve haematologic recovery.

4.5. Response Evaluation

All patients completed at least three cycles and were evaluated for response. The drug combination exhibited a significant degree of antitumor activity. The overall response rate was 47% (95% confidence interval, 32% to 62%). In particular, two complete responses (7%) and twelve partial responses (40%) were observed among the 30 patients. At the first dose level, no patient achieved an objective response; at the second dose level, 3 patients achieved a PR; at the third dose level 2 CR and 7 PR were observed. Among the patients treated at the fourth dose level, 2 PRs were observed. Response by dose level are listed in Table 4. Median duration of response was 12 months (range, 3 to 53+ months). Median time to progression was 7 months. Median overall survival was 16 months (range, 4 to 55+ months); the 1-year and 2-year survival was 36 %, and 17% respectively. Median duration of SD was 5 months (range, 3 to 11 months).

4.6. Recommended Dose for Phase II Studies

Dose escalation was stopped at the fourth step because of DLT in more than one third of patients. The recommended epirubicin dose for phase II studies in this combination regimen with gemcitabine is 100 mg/m^2. Treatment should be recycled at 21-day intervals, depending on the observed toxicity.

5. DISCUSSION

Several strategies have been pursued to improve the results of standard platinum-based chemotherapy, among which cisplatin dose intensification. However, both the European Organization for Research on Treatment of Cancer (EORTC) (18) and the Southwest Oncology Group (SWOG) (19) studies failed to show a survival advantage for platinum-intensified combinations, which showed a greater toxicity. Another strategy aimed at improving the results of standard chemotherapy consisted in the increase in the number of drugs (20). However, taken as a whole, these studies turned out to be negative and three-drug regimens are now to be permanently abandoned.

Table 2. Haematologic toxicity (n=30)

		Neutropenia			Thrombocytopenia		
Dose level	No. of Patients	1-2	3	4	1-2	3	4
1	3	-	-	-	-	-	-
2	3	-	-	-	-	-	-
3	19	2	-	-	1	-	-
4	5	-	1	2	1	-	1

Table 3. Non hematologic Toxicity (n=30)

Side Effect	Number of patients	
	WHO grade 1-2	**WHO grade 3**
Alopecia	20	10
Nausea and vomiting	20	4
Renal	-	-
Liver enzyme derangement	2	-
Mucositis	5	-
Cardiac arrhythmias	2	-
LVEF decrease < 50%	-	1

Table 4. Response by dose level

Dose Level	**No. of Patients**	**CR**	**PR**	**SD**	**PD**
1	3	-	-	1	2
2	3	-	3	-	-
3	19	2	7	7	3
4	5	-	2	2	1

CR: complete response, PR: partial response, SD: stable disease, PD: progression disease

Encouraging response data of SWOG 9806 study (21), that evaluated platinum-based doublets followed by a taxane, did not translate into a survival advantage.

On the other hand, efforts to reduce treatment toxicity are being pursued and non-platinum-containing regimens look a suitable palliative options. Epi and, especially, Gem have been frequently employed in this setting.

The combination of Epi and Gem has already undergone a phase III evaluation (22). In this study, which compared Cisplatin/Gem and Epi/Gem, response rates and progression-free survival were similar in the 2 treatment arms, while the study was underpowered to detect survival differences. However, quite unexpectedly, toxicity was judged worse in the arm Epi/Gem, due to the greater incidence of neutropenia, febrile neutropenia, elevation of serum transaminases, mucositis and fever.

The combination of Epi and Gem has proven feasible and effective in our hands. Furthermore, it can be easily administered on an outpatient basis, and this increases its appeal. As expected, neutropenia was DLT, but its complications were never life-threatening. Nonhematologic toxicity, including cardiac toxicity, was mild. The observed activity was encouraging, since a 47% response rate matches that observable with the most active regimens. However, the ongoing phase II study will provide us with a better understanding of the activity.

In our view, the future of this treatment strategy could be its combination with new biologic agents, which have mechanisms of action and toxicity profiles which are largely non-overlapping with those of Epi and Gem, and we are planning further studies in this direction.

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