Increasing-dose gemcitabine plus low-dose cisplatin in metastatic non-small cell lung cancer

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Gemcitabine, a pyrimidine analog active in non-small cell lung cancer (NSCLC), is widely used with cisplatin. The potential activity of the combination has not been fully assessed: gemcitabine is not used at its maximum tolerated dose (MTD) and cisplatin shows a clearly dose-related toxicity. This trial was designed to assess the MTD and dose-limiting toxicity (DLT) of low-dose cisplatin and increasing gemcitabine dose. Chemotherapy: cisplatin 50 mg/m^2 on day 1, gemcitabine starting at 1400 mg/m^2 on days 1 and 8 every 21 days. Subsequent levels were increased by 200 mg/m^2. Forty-two patients with metastatic NSCLC were enrolled (37 males; median age 61 years; squamous cell carcinoma 19 patients; performance status 2, in 13 patients; 18 patients had significant weight loss). MTD was found to be 2600 mg/m^2 because of DLT in three of six patients: two neutropenic fever and one massive bleeding. Overall toxicity was generally mild consisting mainly of neutropenia. Asthenia was the most common non-hematological effect. Overall response rate was 19 out of 41 patients (46.3%) and median survival was 31 weeks. We conclude that the recommended dose for a phase II dose is gemcitabine 2400 mg/m^2 days 1 and 8 as a 30-min infusion when given with cisplatin 50 mg/m^2.

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Introduction

Non-small cell lung cancer (NSCLC) accounts for 75% of all lung cancers, and remains the leading cause of death in western and developing countries [1]. Despite anti-tobacco efforts, early diagnosis, and improvement in local and loco-regional therapies, most patients, either at diagnosis or later on relapse, develop metastatic disease, and request treatment in order to improve symptom control and increase life expectancy.

The outcome of chemotherapy in patients with advanced NSCLC was controversial until relatively recently, when the results of a comprehensive meta-analysis [2] were reported in 1995. This meta-analysis suggested a benefit for cisplatin-containing regimens (described as a significant 10% survival benefit in comparison to loco-regional treatment or best supportive care alone) in patients with adequate Eastern Cooperative Oncology Group (ECOG) performance status (PS). These findings have been confirmed in randomized trials, translated to commonly used guidelines [3] and eventually to clinical practice.

Newer approaches are now available with recently approved drugs which have different mechanisms of action, moderately higher activity and better toxicity profiles. It is expected that treatment of patients with advanced NSCLC may be improved either by increasing response rate or lessening side effects [4].

Gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN) is one of the new agents approved worldwide for the treatment of NSCLC patients, either alone [5] or in different combinations [6]. It is a deoxycytidine analog whose active metabolite, gemcitabine triphosphate, is incorporated into DNA, inhibiting its synthesis [7] more effectively than ara-C [8] and eventually inducing apoptosis [9]. *In vitro* activity of gemcitabine has been shown to be schedule dependent and a synergism with cisplatin has also been observed. The first phase I trials to determine the maximum tolerated dose (MTD) and toxicity profiles found differences according to the way in which the drug was given. Weekly administration (3 consecutive weeks every 4 weeks or 2 out of 3 weeks) seemed to be the best method and was chosen for further phase II trials. Response rates up to 26% with mild toxicity were reported with 800–1250 mg/m^2 in 476 patients included in six phase II trials [5].

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The gemcitabine/cisplatin combination proved to be superior in terms of response rate, time to progression and quality of life when compared to the combination of cisplatin plus etoposide, which had been considered standard for a time [10]. Even the most recent randomized data confirm the efficacy of gemcitabine/cisplatin [11] in comparison to other modern schemes.

Early phase I trials recommended doses of gemcitabine of 800–1000 mg/m^2, but they were conducted in heavily pretreated patients and probably did not accurately predict what would happen with newly diagnosed patients. Fosella *et al.* [12] reported a phase I trial in chemotherapy-naive patients recommending a gemcitabine dose of 2400 mg/m^2 given as a 30-min infusion for 3 consecutive weeks every 4 weeks.

Cisplatin has been the backbone of many chemotherapy regimens, active both in locally advanced and metastatic disease, but it has failed to show a clear dose–response relationship [13]. Its toxicity, however, is clearly dose dependent and, in the past, some regimens were designed with low-dose cisplatin to ameliorate tolerance. The most remarkable of these regimens was the MIC scheme (mitomycin/ifosfamide/cisplatin 50 mg/m^2) developed by Cullen *et al.* [14]. It was widely used, mostly in Europe, in the early 1990s and recently its value has been confirmed [15].

On this basis, we decided to investigate the possibility of combining low-dose cisplatin with increasing-dose gemcitabine in order to ascertain whether the combination showed activity in metastatic NSCLC. We were looking for a simple, well-tolerated, outpatient combination suitable for those patients requiring treatment with palliative intent.

A phase I trial was conducted in a two-step design in which the primary objective was to determine the MTD of gemcitabine in combination with cisplatin 50 mg/m^2, and to describe the toxicity profile and the dose-limiting toxicity (DLT). Secondary planned objectives were to assess the efficacy of the combination in terms of response rate, time to progression and survival.

Patients and methods

Patient selection

Eligibility criteria included histologically or cytologically confirmed stage IV NSCLC (or stage IIIB with positive pleural effusion); age >18 years; no prior chemotherapy; an ECOG PS of 0–2; adequate baseline organ function: bone marrow (WBC $\geq 3 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l), hepatic (bilirubin <1.5 mg/dl, serum transaminase $<2\times$ the upper limit of normal) and renal (creatinine <1.5 mg/dl); bidimensionally measurable disease; a life expectancy of at least 12 weeks. Prior palliative radiotherapy to symptomatic metastases was allowed provided that these lesions were not considered for tumor response. The study was conducted in accordance with regulations of the local ethics committee and informed consent was obtained from each patient. Patients with severe concurrent medical conditions or a history of prior malignancy were excluded.

Sample size

Cohorts of at least six patients were treated at each level. Dose escalation was performed if no patients showed DLT after the first course. DLT was defined as grade 4 neutropenia or thrombocytopenia or grade 3 or 4 non-hematological toxicity (except for nausea and vomiting and alopecia). Dose escalation was stopped if two of the six patients at a level had DLT and this level was considered the MTD level. Recommended dose was defined as the dose level immediately below the MTD level.

Treatment plan

Treatment consisted of fixed-dose cisplatin 50 mg/m^2 as a 45-min infusion (with hyperhydration and forced diuresis) given in the outpatient clinic on day 1. Gemcitabine was given as a 30-min i.v. infusion on days 1 and 8, starting at 1400 mg/m^2 and increasing by 200 mg/m^2 at each level. Courses were repeated every 21 days. Prophylactic antiemetic therapy included an anti-serotoninergic agent plus dexamethasone on day 1 and dexamethasone alone on day 8. Doses were assigned at registration and no dose escalation was permitted in individual patients. Full doses of chemotherapy were given on days 1 and 8 if neutrophil and platelet counts were at least 1.5×10^9 and 100×10^9/l, respectively. In case of grade 1 or higher neutropenia or thrombocytopenia on day 1, the course was delayed 7 days. Patients without complete hematological recovery by day 28 were excluded from the study. On day 8, 80% dose was given if neutrophil and platelet counts were $\geq 1.0 \times 10^9$ and $\geq 75 \times 10^9$/l, respectively; doses were omitted with lower values.

Patient evaluation

A complete history, physical examination, recording of ECOG PS, complete blood cell count, serum biochemistry and ECG were obtained at baseline for each patient. Staging included computed tomography thoracic scan in every patient and other tests as required. A physical examination, recording any toxic effect, complete blood count and serum biochemistry, was repeated at the beginning of each cycle. Evaluation of response was performed every 3 cycles, repeating the tests that were abnormal at baseline.

Patients with stable or responsive disease after three courses of therapy received additional treatment up to a

maximum of six courses; patients with progressive disease were withdrawn from the study.

Definition of response

Based on the WHO [16], a complete response (CR) was defined as the complete disappearance of all symptoms and signs of disease. A partial response (PR) was defined as reduction of more than 50% in the sum of the products of the perpendicular diameters of all measurable lesions; both CR and PR were required to persist for at least 4 weeks. Stable disease (SD) was defined as less than 50% reduction or less than 25% increase in the sum of the products of two perpendicular diameters of all measured lesions. Progressive disease (PD) was defined as an increase in the product of two perpendicular diameters of any measured lesion by more than 25% or the appearance of new lesions.

Statistical analysis

Every patient receiving at least one cycle of treatment was assessable for toxicity and response. Data from the first course was used to define the MTD. Descriptive statistics were used to summarize the results. Time to progression and survival were calculated from the day of the first course of treatment to the date of progressive disease or death (or last follow-up) and estimated by the Kaplan–Meier method.

Results

Patient characteristics

The study was performed between July 1997 and June 1999 in our institution. A total of 42 patients entered this study through the seven dose levels; baseline characteristics are listed in Table 1. There were 37 male and five female with a median age of 61 years (range 38–76 years). There was only one patient with stage IIIB with positive pleural effusion and the other 41 had stage IV disease. Predominant histologic subtype was squamous cell carcinoma (19 patients). ECOG PS was 0–1 in 29 patients and two in the remaining 13. Weight loss greater than 10% was documented in 18 patients; elevated serum LDH was found in 10 patients. No differences in these major prognostic factors were found between the patients at each level. A total of 177 courses of treatment were given, for a median of 4 courses per patient (range 1–6 courses).

Table 1 **Patient characteristics**

	N	Percentage
Age [median (range) (years)]	61 (38–76)	
Sex		
male	37	88.1
female	5	11.9
PS (ECOG)		
0	4	9.5
1	25	59.5
2	13	31.0
Stage		
IIIb	1	2.4
IV	41	97.6
Histology		
squamous	19	45.2
adenocarcinoma	15	35.8
undifferentiated	8	19.0
Weight loss		
no	24	57.1
yes	18	42.9
High LDH		
no	32	76.2
yes	10	23.8
Metastatic sites		
1	18	42.9
2	18	42.9
3 or more	6	14.2
CNS involvement	11	26.2

Hematologic toxicity

Toxicity was assessed in every patient enrolled. Hematological toxicity was very mild except at the highest dose level. Grade 3 or 4 anemia, neutropenia or thrombocytopenia appeared in nine patients (21.9%) and in 17 courses (9.6%). Distribution by level is described in Table 2. No clear relation with dose level could be observed except for neutropenia, where most cases appeared at the two highest levels. No patient had grade 4 anemia and only three (7.1%) presented grade 3 (one patient received erythropoietin and another one required red cell transfusions during the treatment period). Grade 3 neutropenia occurred in five patients and grade 4 in four patients. This was one of the major causes of DLT, as there were two patients with grade 4 neutropenia and fever at level 7. Grade 3 thrombocytopenia was found in two patients and grade 4 in one patient. Furthermore, there was one patient with massive bleeding that caused death at home during the expected time of myelosuppression. Even though the platelet count could not be assessed, it was considered a toxic death and counted as a case with DLT. (The description given by the patient's relatives did not enable us to determine if the origin was respiratory or from the upper gastrointestinal tract.) Thrombocytosis was also observed: seven patients in nine blood counts performed during the study (4.3%) had transient elevations in platelet counts (median 732×10^9/l, range 610–1300×10^9/l). This effect was not correlated with any episode of clinical relevance and disappeared spontaneously. This effect has already been described for gemcitabine and cytosine arabinoside [17].

Non-hematologic toxicity

Non-hematologic side effects were generally mild. Alopecia was common but reached grade 3 in only three patients. Nausea and vomiting were frequent, but generally very mild: grade 3 in six patients at various levels and no grade 4. Fatigue was an important problem: 10 patients showed severe fatigue with decreased PS that impaired their usual activities, although it was not life threatening. Other side effects did not reach grade 3 and

Table 2 **Hematological toxicity by dose level for all courses given**

Gemcitabine (mg/m^2)	Anemia (grade 3/4)	Neutropenia (grade 3/4)	Thrombopenia (grade 3/4)	Overall
1400	0/0	1/0	0/0	1/0
1600	0/0	0/0	0/0	0/0
1800	1/0	2/0	2/1	5/1
2000	0/0	1/0	0/0	1/0
2200	0/0	0/0	0/0	0/0
2400	1/0	0/2	0/0	1/2
2600	1/0	1/2	0/1[a]	2/3
	3/0	5/4	2/2[a]	10/7 courses 9 patients

[a]A patient with massive bleeding who died during the period of expected thrombopenia has been included.

Table 3 **Non-hematological toxicity by dose level for all courses given**

Gemcitabine (mg/m^2)	Nausea/ vomiting (grade 3/4)	Diarrhea (grade 3/4)	Fatigue (grade 3/4)	Mucositis (grade 3/4)	Overall
1400	2/0	1/0	1/0	0/0	4/0
1600	1/0	0/0	1/0	0/0	2/0
1800	0/0	0/0	0/0	1/0	1/0
2000	2/0	0/0	2/0	0/0	4/0
2200	0/0	0/0	3/0	0/0	3/0
2400	1/0	1/0	1/0	0/0	3/0
2600	0/0	0/0	2/0	0/0	2/0
	6/0	2/0	10/0	1/0	19/0 courses 14 patients

No other grade 3/4 side effects were observed.

only nausea and vomiting, mucositis, diarrhea and transient grade 2 liver enzyme increase were found. Details are shown in Table 3.

Dose intensity and treatment delays

Dose intensity was satisfactory. Of the whole 177 courses given, only 24 (13.6%) were delayed by 1 week. Day 1 chemotherapy (cisplatin and gemcitabine) was administered at almost 100% of the expected dose and day 8 gemcitabine was given at over 80% of the expected dose, almost uniformly at every level. Table 4 gives a more detailed description of dose intensity of both drugs throughout the trial. No differences were found in any parameter of dose intensity (median number of courses per patient, actual dose given or delayed courses) along the levels except for the last, MTD level.

Response evaluation and survival

All 41 patients (97.6%) completing two courses of chemotherapy were evaluable for response. The activity of the combination was significant with an overall response rate (ORR) of 46.3% [95% confidence interval (CI) 31.0–61.6%]. No CRs were seen and all 19 patients who responded had a PR. Seventeen patients (41.5%) had SD as best response. The detailed response rate by dose level is shown in Table 5. There was no tendency towards increased response rate at the higher dose levels.

Table 4 **Dose intensity by dose level**

Gemcitabine (mg/m^2)	Number of courses		Actual dose (%)		Delayed courses (%)
	Total	Median	Day 1	Day 8	
1400	21	3	97.5	83	17.0
1600	30	5	100	90	6.6
1800	26	5	100	77	23.0
2000	30	5	100	92	16.6
2200	31	5.5	100	85.5	9.7
2400	26	4	100	96.1	15.4
2600	13	2	–	–	–
	177	4 (1–6)			

There were no differences in ORR by tumor histology (squamous, eight of 19, 42.1%; non-squamous, 10 of 23, 43.5%). Median duration of response was 30 weeks (95% CI 18–42 weeks), median time to progression was 23 weeks (95% CI 18–28 weeks) and median survival was 31 weeks (95% CI 23–39 weeks) (Fig. 1).

Recommended dose for further phase II trials

Dose escalation was stopped at level 7 (MTD level) because DLT was observed in more than one-third of the patients: after the first course of treatment, two patients experienced neutropenic fever and a third patient died at home after massive bleeding. At this level, dose intensity could not be maintained due to the occurrence of side effects, which was an additional reason to stop the trial at this level. In consequence, the recommended dose of gemcitabine to be combined with cisplatin 50 mg/m^2 was 2400 mg/m^2 on days 1 and 8. Courses should be repeated at 21-day intervals.

Discussion

Gemcitabine has been shown to be one of the most active agents currently available for the treatment of metastatic NSCLC. When given in mono-therapy, chemonaive patients could tolerate 1250 mg/m^2/week 3 out of 4 consecutive weeks. DLT was neutropenia, but it was rarely observed at this dose. Fosella *et al.* [12] reported a trial in which the MTD of gemcitabine was shown to be 2800 mg/m^2 3 times weekly every 4 weeks and recommended further evaluation of the drug at a dose of 2200 mg/m^2 with the same schedule.

In addition, the relevance of cisplatin-based chemotherapy according to the results of a meta-analysis [2] had directed our interest to the combination of cisplatin and gemcitabine, and we had participated with the Spanish Lung Cancer Group in conducting a phase II [18] and a phase III [10] trial confirming its activity. After that, our aim was to try to further improve the efficacy of both drugs given together with a different approach.

The mechanisms of action of cisplatin and gemcitabine are different, and there is evidence of a possible synergism when they are given together. Peters *et al.*

[19] showed that they are synergistic *in vitro* and at least additive in tumour xenografts. This synergism is schedule dependent and was seen when cells were exposed simultaneously to both agents or when cisplatin preceded gemcitabine, depending on the tumor model. Also in clinical trials, a benefit has been shown for this combination even though the best scheme is still to be defined. A pharmacokinetic study has recently been published [20] that will help in designing trials. At least seven phase II trials combined gemcitabine with cisplatin [5]. In all, 314 patients were included and activity data was consistent (ORR 28–54%, median survival 8.4–15.4 months).

In addition, Sandler *et al.* [21] reported a trial comparing single-agent cisplatin 100 mg/m^2 on day 1 versus the combination of cisplatin at the same schedule with gemcitabine 1000 mg/m^2 on days 1, 8 and 15. ORR (30.4 versus 11.1%), time to progression and survival (9.1 versus 7.6 months) favored the combination regimen and toxicity was manageable. The use of the combination gave an increased rate of neutropenia and thrombopenia over single-agent cisplatin, but the percentage of neutropenic fever episodes (less than 5% in both arms) and the absence of hemorrhagic events made these differences relatively unimportant. Sandler *et al.* concluded that the combination of the two drugs was superior to cisplatin alone.

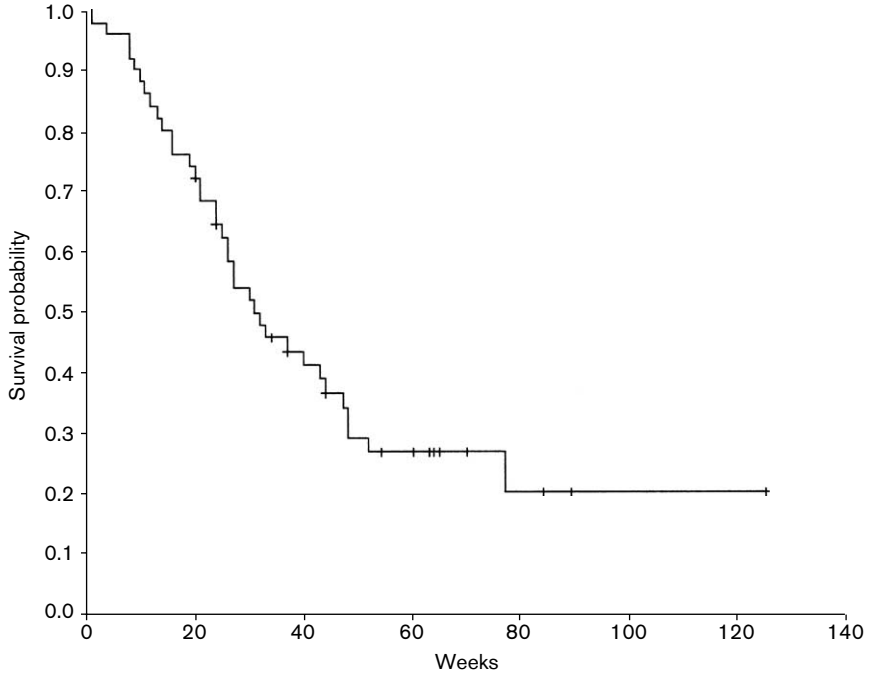
Table 5 **Responses by dose level [*N* (%)]**

Dose level	Evaluable patients	PR	SD	PD
1	6	2 (33.3)	3	1
2	6	3 (50)	3	0
3	6	2 (33.3)	2	2
4	6	4 (66.6)	2	0
5	6	3 (50)	3	0
6	6	2 (33)	3	1
7	5	3 (60)	1	1
	41	19 (46.34%)	17 (41.5%)	5

Fossella *et al.* [12] treated 33 patients (28 stage IV, most adenocarcinoma, PS 0–1) with single-agent, increasing-dose, weekly gemcitabine. They found the MDT was 2800 mg/m^2 and recommended 2200 mg/m^2 every 3 out of 4 consecutive weeks for subsequent trials. In their study, ORR was 24% (27.3% SD), median duration of response was 37 weeks and median survival was 49 weeks.

Several authors have pointed out the absence of a clear dose–response relationship for cisplatin in NSCLC. In a three-arm trial, Gandara *et al.* [22] compared single-agent, low-dose cisplatin (50 mg/m^2 days 1 and 8 every 21 days) versus high-dose cisplatin (100 mg/m^2 days 1 and 8) versus the same high-dose cisplatin plus mitomycin 8 mg/m^2 on day 8. In this trial, ORR was higher only in

Fig. 1



Kaplan–Meier survival curves for the patients included in the trial.

the combination arm (12 versus 14 versus 27%) and there was a greater percentage of PD in the low-dose cisplatin arm. However, survival, which may be considered the most relevant data in a palliative setting, such as metastatic NSCLC, was not significantly different (6.9 versus 5.3 versus 7.2 months; $p = 0.53$). Not surprisingly, toxicity, in the form of ototoxicity, nausea and vomiting, and myelosuppression, was greater in the high-dose cisplatin arms. Klastersky *et al.* [13] included 241 patients in a trial to compare cisplatin 60 versus 120 mg/m^2 per course. No differences in efficacy could be found (ORR, 25 versus 29%; median duration of response, 42 versus 35 weeks; and median survival, 33 versus 28 weeks; $p = 0.138$) and toxicity (mainly myelosuppression) was greater with the higher dose. In conclusion, the authors conclude that no advantages for the use of high-dose cisplatin exist.

The value of low-dose cisplatin combinations was established by Cullen *et al.* [14] in 1988 when they reported a trial with cisplatin 50 mg/m^2, ifosfamide 3000 mg/m^2 and mitomycin 6 mg/m^2, which showed 56% objective responses with a median duration of response of 8.7 months and a median survival time of 9.2 months. The efficacy of this combination has been recently confirmed in a randomized trial comparing it to best supportive care [15] in terms of response and survival.

With this background, our aim in designing this trial was to evaluate a combination of low-dose cisplatin and gemcitabine at the MTD, and to assess whether this combination could be suitable for further upgrading in metastatic NSCLC. In our trial, the MTD was found to be 2600 mg/m^2, so the recommended dose was 2400 mg/m^2 given as a 30-min infusion on days 1 and 8 every 21 days along with cisplatin 50 mg/m^2 on day 1. DLT was mainly hematological (two cases of neutropenic fever and one of massive bleeding), as could be expected from previous experience. Nevertheless, the combination at the lower levels was well tolerated, with only mild side effects.

The theoretical dose intensity of gemcitabine achieved with this regimen is 1600 mg/m^2/week. This dose is much higher than that obtained with usual schemes giving 1000 mg/m^2 days 1, 8 and 15 (calculated dose intensity in these cases is 750 mg/m^2). Furthermore, the actual dose was quite close to the planned dose at every level except the highest one and is also similar to what Fossella *et al.* [12] found with gemcitabine alone (recommended dose 2200 mg/m^2 days 1, 8 and 15 every 28 days; calculated dose intensity 1650 mg/m^2/week), so it may be considered a feasible dosage in clinical practice.

To date, no clear dose–response relationship has been found for gemcitabine, but this issue has not been specifically addressed. When the activity of gemcitabine was assessed by pooling data from all phase II trials, objective responses were not seen in patients receiving less than 900 mg/m^2/week[5]. In the mentioned trial by Fossella *et al.* [12], there seemed to be a tendency towards increased ORR, but the small number of patients precludes any strong conclusions.

The toxic profile of our combination is comparable to that found in other trials of the combination of cisplatin and gemcitabine, and also to the phase I assessment of gemcitabine, with the exception of hepatic toxicity. Fossella *et al.* [12] found three cases of grade 3 toxicity (AST and ALT transient increases without impairment of liver function), two of them at the MTD level, but we did not observe any grade 3 toxicity. There were only minor AST/ALT increases without clinical relevance (grade 1, four patients; grade 2, five patients)

Although neither DLT nor life threatening, fatigue must be considered a relevant problem in a palliative treatment and, in fact, it was the only side effect that disturbed some of our patients, as for several days it impaired their PS. Other side effects (nausea and vomiting, alopecia, flu-like symptoms, and skin rash) were very mild, easily resolved with symptomatic therapies and well tolerated since they did not interfere with daily activities.

The ORR achieved seemed in the range usually reported for the gemcitabine/cisplatin combination. Time to progression and median survival were also acceptable; median survival of 31 weeks, roughly 8 months, is not unexpected in a group of patients like the ones included on this trial. While these points may not be the most important in a trial of this nature, we were concerned with the efficacy of this combination. As no previous experience existed, we tried to avoid reducing our patients' chance to obtain a benefit in terms of efficacy. Responses were monitored throughout the trial; even at the lowest dose level, responses were documented and the activity of this particular combination was confirmed. ORR was less at the first level compared to the others. However, SD was frequent, the percentage of progressive disease acceptable and the survival of the first level patients was not significantly different from that of patients at higher levels. No differences were seen according to histology or other characteristics.

Several patients received second-line chemotherapy (five patients with prior PR and eight patients with SD). Various schemes of treatment were given (carboplatin plus gemcitabine in one patient, single-agent gemcitabine in four patients, paclitaxel in six patients and vinorelbine in two patients). The median number of courses given was 2.5 and no objective responses were achieved with this second-line chemotherapy.

The activity of this combination was significant. Even though patients in our trial were chemotherapy naive, all of them presented with stage IV disease and poor prognosis factors reached significant percentages: 31% of the patients had PS 2, 42.9% had significant weight loss and 26.6% had central nervous system involvement.

Some other recent trials have examined different aspects of gemcitabine dosage. Shepherd *et al.* [23] reported a trial with the combination of cisplatin 25–30 mg/m^2 days 1, 8 and 15 plus gemcitabine 1000–2250 mg/m^2 days 1, 8 and 15. After 50 patients were enrolled, they obtained an ORR of 24% and a median survival of 49 weeks. The recommended dose was cisplatin 30 mg/m^2 and gemcitabine 1500 mg/m^2 both on days 1, 8 and 15. However, this way of dividing cisplatin had been less effective in a prior trial [24]. Rinaldi *et al.* [25] also described a randomized phase II trial with gemcitabine 1000 mg/m^2 days 1 and 8 and cisplatin 70 versus 100 mg/m^2 day 1 every 21 days. ORR (42 versus 47%) and median survival (12 months) were comparable, and high-dose cisplatin was more toxic (leukopenia, nephrotoxicity and vomiting), so the arguments in favor of low-dose cisplatin were strengthened. Kassem *et al.* [26] also reported a phase I trial with high-dose gemcitabine in NSCLC only as an abstract. They could safely give up to 3500 mg/m^2 gemcitabine as a 30-min infusion to 32 patients without reaching the MTD. Toxicity was very mild, and seemed to increase with the dose and have an accumulative effect. The most remarkable finding was the appearance of grade 3 pulmonary toxicity in 10 patients. Some activity was also assessed and OR could be determined in seven of 32 patients.

It may be argued that dose-intensive chemotherapy should not be the aim of treatment for metastatic NSCLC, as to date this approach has shown no benefits [27]. However, this was certainly not the intention of our trial. We did not try to give intensive therapy but to optimize the use of one of the most active drugs in NSCLC, which in most trials is used at a dose that is less than half the MTD. The mild toxicity and the absence of a need for hematological support sustain this view.

After having assessed the value of this approach, it is our intention to continue with this approach and a phase II trial is currently ongoing. In addition, a new phase I trial with protracted perfusion of low-dose gemcitabine and cisplatin is being designed, after a prior phase I trial in solid tumors [28] showed that gemcitabine may be given as a 3-h infusion.

Conclusions

We conclude that the dose of gemcitabine given as a 30-min infusion on days 1 and 8 plus cisplatin 50 mg/m^2 on day 1 every 21 days may be increased up to 2400 mg/m^2, which is the recommended dose based on our results. The MTD appeared at the level of 2600 mg/m^2 and DLT was hematological. At lower levels, the combination was well tolerated and the main side effect was fatigue. This regimen showed efficacy in chemotherapy-naive, metastatic NSCLC patients and the results of our trial prompted us to continue our efforts to improve this combination.

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