A Randomized Study Comparing Two Different Schedules of Administration of Cisplatin in Combination with Gemcitabine in Advanced Nonsmall Cell Lung Carcinoma

Sergio Ricci, M.D.[1]
Andrea Antonuzzo, M.D.[1]
Luca Galli, M.D.[1]
Carmelo Tibaldi, M.D.[2]
Maurizio Bertuccelli, M.D.[2]
Andrea Lopes Pegna, M.D.[3]
Stefano Petruzzelli, M.D.[4]
Vittorio Bonifazi, M.D.[5]
Cinzia Orlandini, Ph.D.[1]
Pier Franco Conte, M.D.[1]

[1] U.O. Oncologia Medica, Ospedale S. Chiara, Pisa, Italy.

[2] Sezione di Oncologia Medica, Ospedale Civile, Livorno, Italy.

[3] U.O. Pneumologia I, Ospedale Careggi, Florence, Italy.

[4] Fisiopatologia Respiratoria, Ospedale Cisanello, Pisa, Italy.

[5] U.O. Oncologia Medica, Ospedale della Misericordia, Grosseto, Italy.

Presented in part at the 35th annual meeting of American Society of Clinical Oncology, Atlanta, Georgia, May 15–18, 1999. Published as an abstract in *Proc Am Soc Clin Oncol* 1999;18:abstract 1853.

Address for reprints: Pier Franco Conte, M.D., Division of Medical Oncology, Department of Oncology, S.Chiara Hospital and University, Via Roma 67, 56100 Pisa, Italy; Fax: 39-050-992069; E-mail: p.conte@do.med.unipi.it

Received January 3, 2000; revision received May 18, 2000; accepted July 3, 2000.

BACKGROUND. This randomized trial was designed to investigate the feasibility, toxicity, and activity of two different schedules of gemcitabine plus cisplatin in previously untreated patients with advanced (International Union Against Cancer (UICC) Stage IIIB–IV) nonsmall cell lung carcinoma (NSCLC).

METHODS. From February 1997 to September 1998, 82 patients with advanced NSCLC were entered onto the study and were randomized to gemcitabine 1000 mg/m^2 on Days 1, 8, and 15 plus cisplatin 80 mg/m^2 on Day 2 (arm A) or Day 15 (arm B) every 28 days.

RESULTS. All the patients were assessable for toxicity (arm A/arm B: 151/177 cycles; median, 4 of 5 cycles per patient), and the following Grade 3–4 toxicities were reported (percentage of cycles in arm A vs. arm B): anemia, 7.9% and 2.3% ($P < 0.05$); leukopenia, 6.0% and 6.7%; thrombocytopenia, 15.0% and 1.6% ($P < 0.01$); no World Health Organization (WHO) Grade 3–4 nonhematologic toxicities were observed. These side effects led to gemcitabine dose reductions in 35.1% of courses in arm A and 22.0% of courses in arm B ($P < 0.05$) and to gemcitabine omissions in 28.5% of courses in arm A versus 7.3% of courses in arm B ($P < 0.01$). Dose intensities (DIs) of gemcitabine were 607.5 mg/m^2/week in arm A and 711.6 mg/m^2/week in arm B ($P < 0.01$); DIs of cisplatin were 18.1 mg/m^2/week in arm A and 18.8 mg/m^2/week in arm B. The total delivered doses of gemcitabine were 9315.5 mg/m^2 in arm A and 12,631.0 mg/m^2 in arm B ($P < 0.01$); the total delivered doses of cisplatin were 277.1 mg/m^2 in arm A and 333.0 mg/m^2 in arm B ($P < 0.01$). Response rates according to intention to treat were 40.4% (95% confidence interval [CI], 25.5–55.3) in arm A and 45% (95% CI, 29.5–60.5) in arm B. The overall median duration of response was 7.4 months; the median time to disease progression was 6 months (95% CI, 3–9) in arm A and 9 months (95% CI, 4–14) in arm B ($P < 0.02$); the median overall survival was 10 months (95% CI, 7.0–12.5) in arm A and 17 months (95% CI, 13.0–21.6) in arm B ($P < 0.01$); the 1-year survival rates were 34% and 63%, respectively.

CONCLUSIONS. Our data show that arm B (cisplatin on Day 15) is less toxic than arm A (cisplatin on Day 2) and allows the administration of significantly higher total doses and dose intensities of chemotherapy. No significant differences in response rates were observed between the two schedules; patients on arm B experienced a significantly more prolonged progression free and overall survival; however, the study was not powered to detect differences in these outcomes. ***Cancer* 2000;89: 1714–9.** © *2000 American Cancer Society.*

KEYWORDS: gemcitabine, cisplatin, nonsmall cell lung carcinoma, randomized trial.

Lung carcinoma is a major public health problem in North America and Europe.[1,2] Nonsmall cell lung carcinoma (NSCLC) accounts for approximately 75–80% of all primary malignant lung tumors; most

patients present with locally advanced or metastatic disease, and most of them are candidates for chemotherapy.[3] A metaanalysis of cisplatin-based chemotherapy versus best supportive care in advanced NSCLC has documented a small but significant survival gain.[4] The modest survival benefit reported with standard cisplatin-based chemotherapy led to test new cytotoxic drugs with good activity and favorable toxicity profile.[5] Among the new agents, gemcitabine (2′,-2′ difluorodeoxycytidine), a nucleoside antimetabolite of deoxycitidine with novel metabolic properties and mechanism of action seems promising.[6,7]

Gemcitabine as a single agent administered at doses of 800–1250 mg/m^2 once a week for 3 of 4 weeks has produced 20–26% objective response rates with median survivals longer than 8 months and minimal toxicity in previously untreated patients with UICC Stage IIIB and IV NSCLC.[8–13] In view of its mechanism of action, the lack of overlapping toxicities with other active agents, and the favorable toxicity profile, gemcitabine has been considered for combination regimens. Synergism between gemcitabine and cisplatin has been shown in preclinical and clinical models, probably due to the inhibition of the excision-repair DNA mechanism involved in cisplatin-induced DNA adducts formation, but there is no clear evidence of the best sequential schedule of administration of the two drugs.[14]

Five Phase II studies have evaluated the activity and safety profile of gemcitabine in combination with cisplatin; in all these studies gemcitabine was given weekly for 3 weeks followed by a 1-week rest in a 28-day cycle whereas cisplatin was administered on Days 1, 2, or 15.[15–19] Response rates varied from 42% to 54%, median survivals ranged between 8.4 and 15.1 months in Stage III and between 7.6 and 15.4 months in Stage IV disease, and 1-year survivals of 35–61% were observed; different toxicity profiles also were reported. World Health Organization (WHO) Grade 3 and 4 thrombocytopenia was the most frequent toxicity, which induced the omission of gemcitabine administration on Day 15 in 50% of the chemotherapy cycles when cisplatin was given on Days 1 or 2; conversely, relatively fewer patients required omissions of the gemcitabine dose in the studies when cisplatin was administered on Day 15. Three randomized Phase III studies comparing gemcitabine plus cisplatin (100 mg/m^2 on Day 1 or 2) to other chemotherapy regimens have documented a significantly higher activity with more frequent WHO Grade 3–4 thrombocytopenia in the gemcitabine-cisplatin combinations.[20–22]

However, to our knowledge, no direct comparison of the different schedules of administration of gemcitabine and cisplatin has been performed.

We therefore have designed a randomized trial aimed to compare the feasibility, toxicity, and activity of two different gemcitabine-cisplatin combinations in previously untreated patients with advanced NSCLC. The study was conducted in 12 hospitals in Tuscany.

MATERIALS AND METHODS

Patient Eligibility

Chemotherapy-naive patients 18–70 years of age with hystologically or cytologically confirmed locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC were eligible for study entry.

Additional eligibility requirements were measurable disease; Eastern Cooperataive Oncology Group performance status (PS) ≤ 2; life expectancy of at least 12 weeks; adequate bone marrow reserve, i.e., leukocyte count $> 4000/\mu$L, platelet count $> 100{,}000/\mu$L, hemoglobin level > 9 g/dL; adequate renal and liver function, i.e., total bilirubin level < 1.5 mg/dL, serum aspartate aminotransferase/alanine aminotransferase levels less than twice the upper limit of normal, serum creatinine level < 1.5 mg/μL. Patients were required to have no active infection, severe heart disease, or concomitant malignancy. The presence of symptomatic brain metastases or hypercalcemia were considered exclusion criteria. The study was approved by the ethic committees of participating centres, and informed consent was obtained from each patient.

TREATMENT

Randomization was performed centrally at the Division of Medical Oncology, Department of Oncology, S. Chiara Hospital of Pisa, Italy. Patients were randomized to 1 of the 2 study arms: gemcitabine 1000 mg/m^2 once a week for 3 weeks, followed by a 1-week rest and cisplatin 80 mg/m^2 on Day 2 (arm A) or on Day 15 (arm B); cycles were repeated every 4 weeks. Gemcitabine was administered intravenously over 30 minutes; before cisplatin administration patients received intravenous hydration of 2 L over a 4-hour period, furosemide and an antiemetic prophylaxis consisting of 5-hydroxytryptamine-3 receptor antagonist plus 20 mg of dexamethasone. Six cycles were planned per patient. The doses of each drug were modified according to hematologic and nonhematologic toxicities. Dose reductions based on Days 8 and 15 blood counts were as follows: leukocyte count $> 3500/\mu$L and platelet count $> 100{,}000/\mu$L, gemcitabine and cisplatin continued at the same dose; leukocyte count 3000–3500/μL or platelet count 75,000–100,000/μL, gemcitabine reduced at 75% dose and cisplatin at 50% dose; leukocyte count 2000–3000 or platelet count 50,000–75,000, gemcitabine reduced at 50% and cisplatin omitted; leukocyte count < 2000 or platelet count $< 50{,}000$, gemcitabine and cisplatin omitted. If

WHO Grade 3 or greater nonhematologic toxicity (except for nausea/vomiting or alopecia) was observed, the dose was omitted. The next course was delivered if leukocyte count was $> 3500/\mu L$ and platelet count $> 100{,}000/\mu L$. Delay for longer than 3 weeks resulted in withdrawal from study.

Response and Toxicity Evaluation

Responses and toxicities were evaluated according to the WHO response criteria.[23] Patients were considered assessable for antitumor efficacy according to the intention to treat analysis. Responses had to be mantained for at least 4 weeks. Dose reductions and omissions were recorded for Days 1, 8, and 15 of all cycles. Delivered dose intensity was calculated by dividing the total dose received for the number of weeks under treatment. Relative dose intensity was expressed as the ratio between delivered dose intensity and the planned dose intensity (planned dose intensity, gemcitabine 750 mg/m^2/week and cisplatin 20 mg/m^2/week).

Statistical Analysis

To detect a 30% difference in WHO Grade 3–4 hematologic toxicity (percentage of cycles) with an 80% power at the 5% significance level (2 sided), assuming a median number of 4 cycles per patient, 82 patients had to be enrolled in the study. Differences in toxicity were evaluated by χ^2 test of significance; differences in mean dose intensities (DIs) and total delivered dose between the two arms were compared with Student t test. Patient characteristics, toxicities, activity, time to progression (TTP), and survival analysis were provided for all treated patients (intention-to-treat population). An independent radiology review assessed all responses submitted by each center. The duration of response was calculated 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 first cycle to the date of disease progression. Survival was calculated from the start of treatment to death or to the last follow-up. Kaplan–Meier methodology was used for plots of progression free survival and overall survival, and the log rank test was used for calculate differences in progression free survival and overall survival in the two arms.[24]

RESULTS

From February 1997 to September 1998, 82 patients with inoperable advanced (Stage IIIB) or metastatic (Stage IV) NSCLC were enrolled onto the study. Forty-two patients were randomized to arm A and 40 patients to arm B. The characteristics of the patients are listed in Table 1; median age was 62 years in both arms; most patients were male (80.5%) and had adenocarcinomas (52.4%). Most of the patients had Stage IV disease (73%), and there were more patients with Stage IIIB disease in arm B (35% vs. 19%).

TABLE 1
Patient Characteristics

Characteristic	Arm A	Arm B
No. of patients	42	40
Age (yrs), median (range)	62 (36–70)	62 (43–70)
Gender (male/female)	35/7	31/9
ECOG performance status		
0	24	23
1	12	16
2	6	1
Histology		
Adenocarcinoma	20	23
Squamous cell carcinoma	15	11
Others	7	6
Clinical stage[a]		
IIIB	8	14
IV	34	26

ECOG: Eastern Cooperative Oncology Group.
[a] Classification and stage grouping based on International Union Against Cancer TNM.

The 82 patients received 328 cycles of chemotherapy, 151 in arm A (median, 4; range, 1–6) and 177 in arm B (median, 5; range, 1–6). Patients who achieved a partial response (PR) received a median of 5 courses (range, 4–6), and those with stable disease (SD) received a median of 6 courses (range, 4–6). Six of 42 (14%) patients enrolled in arm A and 14 of 40 (35%) patients enrolled in arm B received the planned 6 courses of therapy.

WHO Grade 3–4 (percentage of cycles) leukopenia, thrombocytopenia, and anemia were 6.0%, 15.0%, and 7.9% in arm A and 6.7%, 1.6%, and 2.3% in arm B, respectively. There was a statistically significant difference between the two arms with respect to thrombocytopenia ($P < 0.01$) and anemia ($P < 0.05$); however, no patient required platelet transfusions because of bleeding. The occurrence of severe anemia, requiring red blood cell transfusions, was observed in 3% of patients. WHO Grade 1–2 renal toxicity was observed in 6.6% of cycles in arm A compared with 2.3% of cycles in arm B. No WHO Grade 3–4 nonhematologic toxicities were observed. No toxic death occurred (Table 2).

The numbers of dose reductions or omissions per treatment arm are reported in Table 3. Most of gemcitabine reductions/omissions occurred on Day 15 in arm A and on Day 8 in arm B.

The delivered dose intensity of gemcitabine was 607.5 mg/m^2/week in arm A and 711.6 mg/m^2/week in arm B (planned, 750 mg/m^2/week; $P < 0.01$); the delivered dose intensity of cisplatin was 18.1 mg/m^2/week in arm A and 18.8 mg/m^2/week in arm B

TABLE 2
Toxicities per Treatment Arm

Toxicity	Arm A (%)	Arm B (%)	*P* value
Leukopenia (Grade 3–4)	9 (6.0)	12 (6.7)	0.975
Thrombocytopenia (Grade 3–4)	23 (15.0)	3 (1.6)	0.001
Anemia (Grade 3–4)	12 (7.9)	4 (2.3)	0.037
Renal (Grade 1–2)	10 (6.6)	4 (2.3)	0.1

TABLE 3
Dose Reductions and Omissions per Treatment Arm

Dose adjustment	Arm A (%)	Arm B (%)	*P* value
No. of cycles	151	177	
Gemcitabine			
Reductions	53 (35.1)	39 (22.0)	0.012
Omissions	43 (28.5)	13 (7.3)	0.0001
Cisplatin			
Reductions	9 (5.9)	21 (11.9)	0.092
Omissions	2 (1.3)	4 (2.3)	0.795

(planned, 20 mg/m^2/week); the relative dose intensities of gemcitabine and cisplatin were 0.81 and 0.91 in arm A and 0.95 and 0.94 in arm B, respectively. The total delivered dose of gemcitabine was 9315.5 mg/m^2 in arm A and 12,631.0 mg/m^2 in arm B ($P < 0.01$); the total delivered dose of cisplatin was 277.1 mg/m^2 in arm A and 333.0 mg/m^2 in arm B ($P < 0.01$).

All the patients were evaluated according to the intention-to-treat analysis; 7 patients (1 arm A, 6 arm B) received only 1 course of chemotherapy due to early progression (1 patient), skin reactions (2 patients), cardiovascular event not drug related (2 patients), and early death (2 patients). These patients were classified as having progressive disease. Objective response rates in arm A and B were PR, 40.4% (95% confidence interval [CI], 25.5–55.3) and 45% (95% CI, 29.5–60.5); SD, 28.6% and 27.5%; progressive disease, 31% and 27.5%, respectively. There were no statistically significant differences in response rates according to stage (Stage IIIB, 55%; Stage IV, 38%) or histology. The median overall duration of response was 7.4 months; the median duration of response was 5.3 months in arm A and 9.9 months in arm B. The median progression free survival was 6 months (95% CI, 3–9 months) in arm A and 9 months (95% CI, 4–14 months) in arm B ($P < 0.02$). The median survival was 10 months (95% CI, 7.0–12.5 months) in arm A and 17 months (95% CI, 13.0–21.6 months) in arm B ($P < 0.01$). The 1-year survival rates were 34% in arm A and 63% in arm B; corresponding figures for Stages IIIB and IV were 73% and 27% in arm A and 69% and 57% in arm B, respectively (Figs. 1 and 2). Thirty-five patients had a PS of 1 or 2 at study entry; 11 of 35 (31.5%) experienced an improvement in PS at the end of therapy.

DISCUSSION

In the last years, several clinical trials have tested the combination of gemcitabine and cisplatin in advanced NSCLC; in these trials, gemcitabine, at doses of 1000–1200 mg/m^2, was administered weekly for 3 weeks followed by 1-week rest, and cisplatin, at the dose of 100 mg/m^2, was given on Days 1, 2, or 15.[15–19] Response rates and median survivals were similar across studies, whereas important differences in toxicities were reported. When cisplatin was given on Day 1 or 2, thrombocytopenia was the most frequent toxicity which caused the omission of gemcitabine on Day 15 in 50% of the courses; moreover, anemia led to blood transfusions in 33% of patients.[15] Conversely, when cisplatin was administered on Day 15 fewer patients required omissions or modifications of gemcitabine doses because of toxicity; 34% of patients received blood transfusions during treatment.[18,19]

Our randomized trial was designed to compare the toxicities and activity of gemcitabine 1000 mg/m^2 given on Days 1, 8, and 15 and cisplatin 80 mg/m^2 administered on Day 2 (arm A) or Day 15 (arm B). The dose of cisplatin was reduced to 80 mg/m^2 taking into account the toxicities observed in the Phase II studies and on the basis of the lack of correlation between cisplatin dose and response rates.[25]

The results of this randomized trial demonstrate that the administration of cisplatin on Day 15 (arm B) induces a significantly low incidence of Grade 3–4 thrombocytopenia (1.6% vs. 15%, $P < 0.001$) and anemia (2.3% vs. 7.9%, $P < 0.02$). These toxicities were usually short lasting: no patient required platelet transfusions, and only 3% of the patients required blood transfusions. This percentage is significantly lower than that reported in Phase II studies; the reduced dose of cisplatin in our regimen might have contributed to the decreased requirement of blood transfusions. However, as a consequence of these differences in toxicity, the doses of gemcitabine were more frequently reduced/omitted, and the median number of courses were lower in arm A; therefore, these patients received significantly lower dose intensities of gemcitabine (607.5 mg/m^2/week vs. 711.6 mg/m^2/week, $P < 0.01$) and significantly lower total doses of gemcitabine (9315.5 mg/m^2 vs. 12,631 mg/m^2, $P < 0.01$) and cisplatin (227 mg/m^2 vs. 333 mg/m^2, $P < 0.01$).

Irrespectively of schedule, the cisplatin/gemcitabine combination has confirmed a high level of activity (response rate, 42.7% according to intention-to-treat) in a multicentric study conducted in 2 teaching hos-

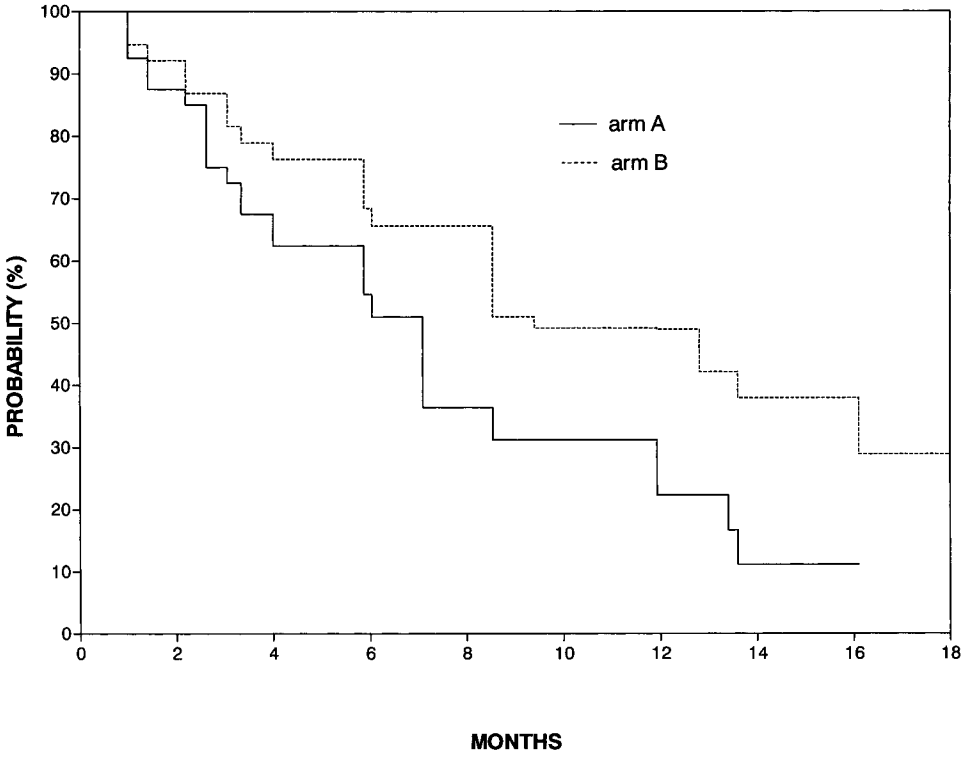

FIGURE 1. Progression free survival of patients in arm A and arm B is shown.

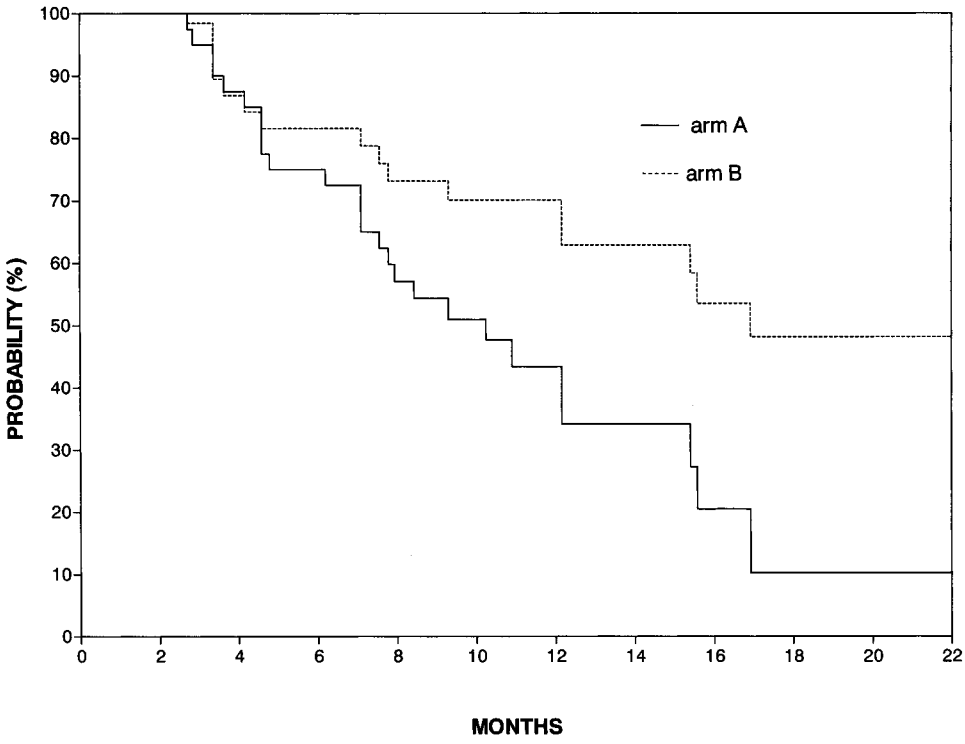

FIGURE 2. Overall survival of patients in arm A and arm B is shown.

pitals and 10 community hospitals; of interest is also the percentage of patients who experienced an improvement in their PS during treatment (31.5%). Despite the significant differences in dose intensities and total doses, there was no significant difference in response rates between the two arms. Surprisingly, both median progression free and overall survivals were significantly more prolonged in arm B (median progression free surival: arm A, 6 months; arm B, 9 months; $P < 0.02$; median survival: arm A, 10 months;

arm B, 17 months; $P < 0.01$); however, this study was not powered to detect possible differences in these parameters, it therefore is quite likely that these differences occurred by chance or as a consequence of imbalanced prognostic parameters (there were 8 Stage IIIB patients in arm A and 14 in arm B).

In conclusion, we have shown that the schedule of administration of cisplatin when combined with weekly gemcitabine has significant effects on the incidence of Grade 3–4 thrombocytopenia and anemia; the best schedule is cisplatin administered on Day 15, which allows for higher dose intensity and total dose of chemotherapy. However, despite the better tolerance in the Day 15 schedule, gemcitabine and cisplatin reductions/omissions are necessary in 29% and 14% of the courses, respectively.

For this reason, we currently are comparing this schedule to the 21-day schedule with cisplatin given on Day 1 and gemcitabine at the dose of 1200 mg/m^2 on Days 1 and 8; this regimen has produced high activity with an acceptable toxicity profile.[19,25,26]

REFERENCES

1. Gadzar AF, Minna JD. Cigarettes, sex, and lung adenocarcinoma. *J Natl Cancer Inst* 1997;89:1563–5.
2. Esteve J, Kricker A, Ferlay J, Parkin DM. Facts and figure of cancers in the European community. Lyon: IARC, 1993.
3. Inde DC. Chemotherapy for lung cancer. *N Engl J Med* 1992;327:1434–41.
4. Non-small cell lung cancer collaborative group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ* 1995;311:899–909.
5. Lilenbaum RC, Green MR. Novel chemotherapeutic agents in the treatment of non-small-cell lung cancer. *J Clin Oncol* 1993;11:1391–1402.
6. Hertel LW, Broder GB, Kroin JS, Rinzed SM, Poore GA, Todd GC, et al. Evaluation of the antitumor activity of gemcitabine (2′,-2′ difluorodeoxycytidine). *Cancer Res* 1990;50:4417–22.
7. Lund B, Kristjansen PEG, Hansen HH. Clinical and preclinical activity of 2′,-2′ difluorodeoxycytidine (gemcitabine). *Cancer Treat Rev* 1993;19:45–55.
8. Anderson H, Lund B, Bach F, Thatcher N, Walling J, Hansen HH. Single-agent activity of weekly gemcitabine in advanced non-small cell lung cancer. A phase II study. *J Clin Oncol* 1994;12:1821–6.
9. Gatzemeier U, Shepherd FA, Le Chevalier, Waynants P, Cottier B, Groen HJ, et al. Activity of gemcitabine in patients with non-small cell lung cancer. A multicentre extended phase II study. *Eur J Cancer* 1996;32A:243–8.
10. Abratt RP, Bezwoda WR, Falkson G, Goedhals L, Hacking D, Rugg TA. Efficacy and safety profile of gemcitabine in non-small cell lung cancer: a phase II study. *J Clin Oncol* 1994; 12:1535–40.
11. Perng RP, Chen YM, Ming-Liu J, Tsai CM, Lin WC, Yang KY, et al. Gemcitabine versus the combination of cisplatin and etoposide in patients with inoperable non-small cell lung cancer in a phase II randomized study. *J Clin Oncol* 1997; 15:2097–102.
12. Manegold C, Bergman B, Chemaissani A, Dornoff W, Drings P, Kellokumpu Lehtinen P, et al. Single-agent gemcitabine versus cisplatin-etoposide: early results of a randomized phase II study in locally advanced or metastatic non-small cell lung cancer. *Ann Oncol* 1997;8:525–9.
13. Ricci S, Antonuzzo A, Galli L, Tibaldi C, Bertuccelli M, Lopes Pegna A, et al. Gemcitabine monotherapy in elderly patients with advanced non-small cell lung cancer. A multicenter phase II study. *Lung Cancer* 1999;27:75–80.
14. Peters GJ, Bergman AM, Ruiz van Haperen VWT, Veerman G, Kuiper CM, Braakhuis BJ. Interaction between cisplatin and gemcitabine in vitro and in vivo. *Semin Oncol* 1995;22: 72–9.
15. Steward WP, Dunlop DJ, Dabouis G, Lacroix H, Talbot D. Phase I/II study of gemcitabine and cisplatin in non-small cell lung cancer: preliminary results. *Semin Oncol* 1996; 5(Suppl 10):43–7.
16. Crinò L, Scagliotti G, Marangolo M, Figoli F, Clerici M, De Marinis F, et al. Cisplatin-gemcitabine combination in advanced non-small cell lung cancer: a phase II study. *J Clin Oncol* 1997;15:297–303.
17. Sandler A, Crinò L, Steward WP, Abratt RP. Extended survival in stage III and IV non-small cell lung cancer (NSCLC) patients treated with gemcitabine plus monthly cisplatin. Proceedings of the 21st ESMO. *Ann Oncol* 1996;7(Suppl 5): 91a.
18. Abratt RP, Hacking DJ, Bezwoda WR, Goedhals L. Weekly gemcitabine with monthly cisplatin: effective chemotherapy for advanced non-small cell lung cancer. *J Clin Oncol* 1997; 15:744–9.
19. Anton A, Artal A, Carrato A, Diaz-Fernandez N, Gonzalez Larriba JL, Vadell C, et al. Gemcitabine plus cisplatin in advanced NSCLC [abstract 1656]. *Proc Am Soc Clin Oncol* 1997;16:461.
20. Cardenal F, Paz Lopez-Cabrerizo M, Anton A, Alberola V, Massuti B, Carrato A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. *J Clin Oncol* 1999;17:12–8.
21. Sandler A, Nemunaitis J, Dehnam C, Cornier Y, von Pawel J, Niyikiza C, et al. Phase III study of cisplatin with or without gemcitabine in patient with advanced NSCLC [abstract 1747]. *Proc Am Soc Clin Oncol* 1998;17:454.
22. Crinò L, Scagliotti GV, Ricci S, De Marinis F, Rinaldi M, Gridelli C, et al.. Gemcitabine and cisplatin versus mitomycin, ifosfamide and cisplatin in advanced non-small-cell lung cancer: a randomized phase III study of the Italian Lung Cancer Project. *J Clin Oncol* 1999;17:3522–30.
23. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–14.
24. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observations of each patient. *Br J Cancer* 1977;35:1–39.
25. Gandara DR, Crowley J, Livingston RB, Perez EA, Taylor CW, Weiss G, et al. Evaluation of cisplatin intensity in metastatic non-small-cell lung cancer: a phase III study of the Southwest Oncology Group. *J Clin Oncol* 1993;11:873.
26. Castellano D, Lianes P, Paz-Ares L, Hidalgo M, Guerra JA, Gomez Martin C, et al. A phase II study of a novel gemcitabine plus cisplatin regimen administered every three weeks for advanced non-small lung cancer. *Ann Oncol* 1998;9: 457–9.