Gemcitabine and Docetaxel as Second-Line Chemotherapy for Patients with Nonsmall Cell Lung Carcinoma who Fail Prior Paclitaxel plus Platinum-Based Regimens

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BACKGROUND. Treatment options for patients with recurrent nonsmall cell lung carcinoma (NSCLC) remain limited as a result of poor activity of older agents after platinum-based therapy. In the current Phase II study, the authors evaluated the combination of gemcitabine and docetaxel in patients with recurrent NSCLC.

METHODS. Patients with advanced NSCLC (Stage IIIB–IV), a World Health Organization performance status (PS) ≤ 2, prior paclitaxel plus platinum-based chemotherapy, and unimpaired hematopoietic and organ function were eligible. Chemotherapy was administered as follows: gemcitabine 1000 mg/m^2 was administered on Days 1 and 8 followed by docetaxel 100 mg/m^2 on Day 8, and this regimen was recycled every 21 days. Prophylactic granulocyte-colony stimulating factor was administered on Days 10–14 or until the patient achieved a white blood cell count $\geq 5000/\mu$L.

RESULTS. Of 43 patients who were entered on the study, 41 patients were evaluable for response, and all were evaluable for toxicity. The median patient age was 63 years (range, 47–70 years), the median PS was 1 (range, 0–2), there were 38 male patients, and there were 5 female patients. Four patients had Stage IIIA disease, 17 patients had Stage IIIB disease, and 22 patients had Stage IV disease. Histologies included 19 patients with adenocarcinoma, 18 patients with squamous cell carcinoma, and 3 patients with large cell carcinoma. Metastatic sites included lymph nodes in 28 patients, bone in 6 patients, liver in 5 patients, brain in 5 patients, lung nodules in 8 patients, adrenals in 7 patients, and other sites in 3 patients. All patients had received prior paclitaxel plus platinum-based treatment; 28 patients had received prior paclitaxel, ifosfamide, and cisplatin. Objective responses were partial response (PR) in 14 of 43 patients [33%; 95% confidence interval [95%CI], 18.5–46.6%], stable disease (SD) in 16 of 43 patients (37%; 95% CI, 22.8–51.6%), and progressive disease (PD) in 13 of 43 patients (30%; 95% CI, 16.3–43.7%). The median time to disease progression was 6 months (range, 1.0–20.0+ months), and the median survival was 8.5 months (range, 1.5–20.0+ months). The 1-year survival rate was 28%. Grade 3–4 neutropenia was experienced by 53% of patients (30% Grade 4), with 14% of patients experiencing febrile neutropenia. Grade 3 thrombocytopenia was experienced by 7% of patients (no Grade 4), whereas other Grade 3 nonhematologic toxicities were never encountered.

CONCLUSIONS. The combination of gemcitabine and docetaxel is active and is well tolerated in patients with advanced NSCLC who have failed prior taxane plus platinum chemotherapy. This regimen represents a tolerable and effective combination to apply in the palliative treatment of patients with recurrent NSCLC. ***Cancer*** **2001;92:2902–10.** *© 2001 American Cancer Society.*

KEYWORDS: nonsmall cell lung carcinoma, gemcitabine, docetaxel, paclitaxel.

Despite significant improvements in the management of patients with advanced (Stage IIIB–IV) nonsmall cell lung carcinoma (NSCLC), the vast majority of patients with Stage IIIB NSCLC and all patients with Stage IV NSCLC will develop progressive disease. Treatment options regarding second-line chemotherapy have been limited to date, and, until the year 2000, it was hard to retrieve any data that provided convincing evidence demonstrating the benefit of chemotherapeutic agents in treating patients with recurrent and/or refractory disease over best supportive care (BSC) alone. In the year 2000, a study by Shepherd et al.[1] reported demonstrating a significant advantage of single-agent docetaxel over BSC in both survival and quality of life. Recently, the introduction of several newer cytotoxic agents, such as gemcitabine, vinorelbine, and paclitaxel, that have demonstrated activity in patients with NSCLC has resulted in improved outcomes with first-line treatments that incorporate these agents in combination with platinum drugs. More specifically, gemcitabine has demonstrated improved survival when combined with cisplatin versus cisplatin alone,[2] whereas similar benefits have been reported with vinorelbine plus cisplatin versus either vinblastine with cisplatin or vinorelbine alone.[3] However, neither paclitaxel (recently)[4] nor etoposide (in the last decade)[5] has demonstrated any advantage when combined with cisplatin compared with high-dose cisplatin monotherapy.

For a long time, second-line chemotherapy for patients with NSCLC has not been taken into consideration given the notoriously poor outcome when patients receive traditional cytotoxic agents. However, to date, taxanes (and, in particular, docetaxel) have demonstrated reproducible activity and therapeutic value in patients with recurrent NSCLC who received platinum pretreatment.[1,6–8] Gemcitabine, which is a deoxycytidine analogue, recently demonstrated satisfactory activity as second-line treatment in patients with NSCLC.[9–11]

Docetaxel, which is a semisynthetic taxane analogue with definite activity in patients with NSCLC, represents an agent that, due to its favorable toxicity profile, can be combined with other active agents in this setting, and its value as a single agent has been determined in patients with NSCLC with exposure to prior treatment.[1,7] Currently, as many more patients with advanced NSCLC derive clinical benefit with newer first-line regimens, more patients with a good performance status (PS) will be candidates for second-line treatment. Because most patients with advanced NSCLC are given first-line treatment with standard or experimental paclitaxel and platinum-based regimens, it appears particularly attractive to combine gemcitabine and docetaxel in those with recurrent or refractory disease. This also should provide a good test for in vivo noncross resistance between the two taxanes.

In the current Phase II study, we evaluated the activity and safety of a gemcitabine plus docetaxel regimen in patients with advanced NSCLC that progressed during or after standard paclitaxel plus carboplatin or experimental triplet (paclitaxel, ifosfamide, and cisplatin [PIC])[12] first-line regimens. The drug doses of the current docetaxel and gemcitabine regimen were based on a previous Phase I study in which gemcitabine doses of 800 mg/m^2 on Days 1, 8, and 15 and docetaxel doses of 100 mg/m^2 on Day 1 without granulocyte-colony stimulating factor (G-CSF) support were recommended for further Phase II testing.[13] We thought that omitting gemcitabine on Day 15 (because this frequently is not feasible due to hematologic toxicity) and giving docetaxel on Day 8 rather than on Day 1 (because the nadir neutrophil count for Day 1 docetaxel occurs on Day 8), as recommended in a recent Phase II study of first-line treatment for patients with advanced NSCLC,[14] would allow a more practical schedule of administering the regimen every 21 days.

MATERIALS AND METHODS

Patient Selection

Patients with histologically confirmed, advanced NSCLC (Stage IIIA/IIIB and IV) that had recurred after receiving or progressed during a paclitaxel and platinum analogue combination regimen and had never received docetaxel were candidates for the current study. Eligibility included 1) histologically confirmed, recurrent NSCLC not potentially curable by surgery and/or radiotherapy; 2) a World Health Organization PS $\leq$ 2; 3) life expectancy $\geq$ 3 months; 4) adequate hematopoietic (absolute neutrophil count [ANC] $>$ 1500/μL and platelet count [PLT] $>$ 100,000/μL), liver (bilirubin $<$ 1.5 mg/dL; aspartate and alanine transferase levels $<$ 2 $\times$ upper normal limit [nl], unless caused by tumor; and serum albumin $>$ 3.0 g/dL), and renal function (blood urea nitrogen and creatinine $<$ 1.5 nl [nl = 1.5 mg/dL in our laboratory] or creatinine clearance $>$ 50 mL per minute); 5) disease progression after or during prior chemotherapy with a paclitaxel and platinum analogue-based regimen (PIC;[12,15] paclitaxel, gemcitabine, and cisplatin; or paclitaxel and carboplatin); 6) the absence of active coronary artery disease (in the form of unstable angina or myocardial infarction over the last 12 months), unstable diabetes mellitus, or peripheral neuropathy

≥ Grade 2 according to the National Cancer Institute Common Toxicity Criteria; 7) no prior irradiation to areas encompassing > 30% of marrow-bearing bone apart from emergency radiotherapy for superior vena cava obstruction, imminent vertebral or weight-bearing long bone fracture as a result of metastatic involvement, or symptomatic rapidly progressive brain metastases; and 8) the presence of bidimensionally measurable disease with or without evaluable disease sites (however, all patients had to have at least one bidimensionally measurable lesion) located outside a previously irradiated field, unless definite evidence of disease progression at this site was documented. The study was approved according to institutional policies, and informed consent was obtained from each patient before study entry.

Treatment Schedule

Eligible patients were treated as follows: Docetaxel was administered at a dose of 100 mg/m^2 diluted in 500 mL 0.9% normal saline (N/S) over 1 hour by intravenous (IV) infusion on Day 8, and gemcitabine was administered at a dose of 1000 mg/m^2 diluted in 250 mL 0.9% N/S over 30 minutes by IV infusion on Days 1 and 8. Antiemetic medications included 8 mg of ondasetron or 3 mg of granisetron IV over 15 minutes just before the administration of chemotherapy drugs. No subsequent antiemetic drug doses were planned unless the patient experienced nausea or emesis, in which case, he was instructed to take additional oral doses of ondasetron 8 mg three times daily or granisetron 1 mg every day until nausea and/or emesis was resolved, usually for 1–2 days postchemotherapy. In patients with nausea and/or emesis ≥ Grade 2, dexamethasone 8 mg was added with the standard HT3 antagonist before chemotherapy drug administration. Both docetaxel and gemcitabine were administered as described above on Days 1 and 8 of each cycle and recycled every 21 days.

Supportive Care

Hematopoietic growth factors included prophylactic G-CSF 5 μg/kg subcutaneously on Days 10–14 or until the white blood cell count reached ≥ 5000/μL, with the last dose of G-CSF administered at least 48 hours before the next chemotherapy cycle, and recombinant human erythropoietin (rh-Epo) 10,000 IU subcutaneously three times per week (not on chemotherapy days) whenever a drop of hemoglobin (Hb) ≤ 10.5 g/dL was seen, and this was continued until the Hb level reached ≥ 12 g/dL. Dexamethasone 20 mg IV on the day of treatment and 4 mg twice a day for the next 3 days was administered to prevent docetaxel-related hypersensitivity reactions and fluid retention.

Dose Modifications

The prerequisites for dose modifications were set as follows: 1) any episode of Grade 4 neutropenia lasting > 7 days; 2) any episode of febrile neutropenia ≥ Grade 3; 3) any episode of Grade 4 thrombocytopenia requiring platelet transfusions; and 4) any nonhematologic Grade 3 or 4 toxicity, excluding nausea and emesis, flu-like illness, and alopecia.

The following guidelines were applied with respect to dose reductions for toxicity: 1) For patients with neutropenia that met the aforementioned criteria, both gemcitabine and docetaxel doses were reduced by 20% in subsequent cycles, and, if toxicity reappeared after a total of 40% reduction from the starting dose in consecutive cycles, then treatment was stopped; however, the patient was evaluable for toxicity and response. 2) For patients with Grade 4 thrombocytopenia requiring platelet transfusions, reduction of gemcitabine and docetaxel doses by 20% was applied as specified for patients with neutropenia. 3) For patients with mucositis ≥ Grade 3, the doses of gemcitabine and docetaxel were reduced by 20% in subsequent cycles. 4) For patients with neuropathy ≥ Grade 3, treatment was interrupted.

For patients with blood counts that had not recovered to ANC ≥ 1500/μL and PLT ≥ 100,000/μL on Day 1 of therapy, treatment was withheld until recovery, and, after a maximum delay of 2 weeks, no further therapy was administered for patients with counts that did not return to normal. In patients with ANC levels of 1000–1500/μL and/or PLT levels of 75,000–100,000/μL on Day 8, both drugs were given after a 20% dose reduction. For patients with levels that reached ANC ≤ 1000/μL and/or PLT ≤ 75,000 on Day 8, no treatment was given on that day, and subsequent doses were reduced by 20% for both drugs throughout treatment.

Pretreatment, Follow-up Studies, and Response Evaluation

Tumor measurements were performed by physical examination and the specific radiologic test that documented measurable disease before treatment. Clinical examination, full blood counts, biochemical tests, appropriate serum tumor marker measurements, and a chest X-ray were carried out before each cycle of therapy. Blood counts were checked on the days of treatment (Days 1 and 8) and weekly thereafter or every 3 days in patients with neutropenia until full recovery. Evaluation of response was performed every two cy-

cles of therapy with computed tomography scans of the chest and abdomen or radiologic examinations that detected disease in other sites. Patients who experienced toxic death despite objective responses at measurable disease sites were categorized as treatment failures. Complete remission (CR) was defined as the disappearance of all signs and symptoms of disease for at least 1 month, with the documented disappearance of all known lesions by physical examination, X-rays, computed tomography scans, and bone scans and the development of no new lesions. Partial remission (PR) indicated a decrease $\geq$ 50% (compared with pretreatment measurements) in the sum of the products of the two largest perpendicular dimensions of all measurable lesions and no concomitant growth of new lesions for at least 1 month (confirmation after 1 month was required for all responders). There could be no deterioration of symptoms or performance status unless such deterioration was secondary to drug toxicity. Stable disease (SD) indicated a decrease $<$ 50% or an increase $<$ 25% in tumor size over the original measurements. There could be no deterioration of symptoms or performance status unless such deterioration was secondary to drug toxicity. Progressive disease (PD) was defined as an increase $\geq$ 25% over the original measurements in the sum of the products of the two largest perpendicular dimensions of any measurable lesions, and disease was categorized as recurrent after a period of response when a former lesion reappeared or enlarged as described above or when a new lesion appeared. Full staging evaluation had to be performed, as described above, before treatment initiation. Follow-up disease evaluation was performed at approximately 3-month intervals after the end of treatment.

Statistical Methods

Patients who received at least two cycles of treatment were evaluable for response, and patients who received at least one cycle of treatment were evaluable for toxicity. Response duration was measured from the day of its initial documentation until confirmed disease progression, time to disease progression was calculated from study entry until evidence of PD, and overall survival was measured from the day of entry until last follow-up or death. Actuarial survival was estimated by the product-limit method of Kaplan and Meier.[16]

According to the two-stage, minimax design by Simon,[17] a sample of 40 patients has approximately 80% power to accept the hypothesis that the true response rate (RR) is $>$ 30% and 5% significance to reject the hypothesis that the true RR is $<$ 20% if fewer than 8 responses occur. At the first stage, if fewer than 5 responses occur out of the first 21 patients, then the study will conclude that the anticipated RR is $<$ 20% and will be terminated. Thereby, the probability of accepting a therapy with a real response rate $<$ 20% and the risk of rejecting a treatment with a response rate $>$ 30% in both cases would be $<$ 10%.

TABLE 1
Patient Characteristics

Characteristic	No. of patients	%
Total patients	43	100
Gender		
Male	38	88
Female	5	12
Age (yrs)		
Median	63	—
Range	47–70	—
Performance status (WHO)		
0	14	33
1	24	56
2	5	11
Stage at initial diagnosis		
IIIA	4	9
IIIB	17	40
IV	22	51
Histology		
Squamous	18	42
Adenocarcinoma	19	44
Large cell/unspecified	3/3	7/7
Prior nonmedical therapy		
Surgery	8	19
Radiotherapy	17	40
Previous first-line chemotherapy		
Paclitaxel/ifosfamide/cisplatin	28	65
Paclitaxel/gemcitabine/cisplatin	5	12
Paclitaxel/carboplatin	10	23
Metastatic sites of recurrence		
Liver	5	12
Bone	6	14
Brain	5	12
Lung nodules	8	19
Adrenals	7	16
Pleural effusion	7	16
Lymph nodes	28	65
No. of metastatic sites		
1	12	28
$\geq$ 2	31	72

WHO: World Health Organization.

RESULTS

Patient characteristics

Forty-three patients were entered on the current study, and their characteristics are shown in Table 1. Forty-one patients received at least two cycles of therapy and were evaluable for response, and all patients

were evaluable for toxicity. Two patients developed PD soon after the first cycle and were considered nonresponders. The median patient age was 63 years (range, 47–70 years), and the median PS was 1 (range, 0–2). With regard to gender, 38 patients were male, and 5 patients were female. There were 4 patients with Stage IIIA disease, 17 patients with Stage IIIB disease, and 22 patients with Stage IV disease at the time of initial diagnosis. Tumor histology included 19 patients with adenocarcinoma, 18 patients with squamous cell carcinoma, 3 patients with large cell carcinoma, and three patients with tumors of unspecified histology. Metastatic sites included lymph nodes in 28 patients, bone in 6 patients, liver in 5 patients, brain in 5 patients, lung nodules in 8 patients, adrenals in 7 patients, and other sites in 3 patients. All patients had received prior paclitaxel and platinum treatment; 28 patients had received PIC;[12,15] 5 patients had received paclitaxel, gemcitabine, and cisplatin; and 10 patients had received paclitaxel and carboplatin. Nineteen patients (44%) were resistant to first-line treatment (experienced PD or had SD or recurrent disease within 3 months from completion of first-line treatment), whereas the remaining 24 patients (66%) were sensitive to taxane and platinum and experienced disease recurrence after a prior response that lasted $>$ 3 months from the end of first-line chemotherapy (Table 1).

Response to Treatment and Survival

The objective responses included PR in 14 of 43 patients (33%; 95% confidence interval [95%CI], 18.5–46.6%), SD in 16 of 43 patients (37%; 95%CI, 22.8–51.6%), and PD in 13 of 43 patients (30%; 95%CI, 16.3–43.7%). The RR to gemcitabine plus docetaxel in patients who were refractory to first-line treatment was 5 of 19 patients (27%), whereas the RR in patients with sensitive disease was 9 of 24 patients (37.5%), which did not differ significantly. The median time to disease progression was 6 months (range, 1.0–20.0+ months), the median survival was 8.5 months (range, 1.5–20.0+ months), and the 1-year survival rate was 30% (Fig. 1).

Toxicities

Toxicities are shown in Table 2. Grade 3–4 neutropenia was seen in 53% of patients, with 13 of 43 patients (30%) developing Grade 4 neutropenia, whereas 6 patients (14%) developed 8 episodes of febrile neutropenia were managed successfully with broad-spectrum antibiotics. Five patients (12%) who were included in the current study required red blood cell transfusions, because rh-Epo was initiated whenever a drop of Hb $<$ 10.5 g/dL was seen and was continued until the Hb level reached $\geq$ 12 g/dL. Seventeen patients (39.5%) required rh-Epo and oral iron supplements at some time during treatment, usually after the third or fourth chemotherapy cycle. Grade 3 thrombocytopenia was seen in 3 of 43 patients (7%; there was no Grade 4 thrombocytopenia), and other Grade 3 nonhematologic toxicities were not encountered. Mild asthenia and/or fatigue (Grade 2) were seen in 18% of patients, usually after four or five cycles of chemotherapy. One

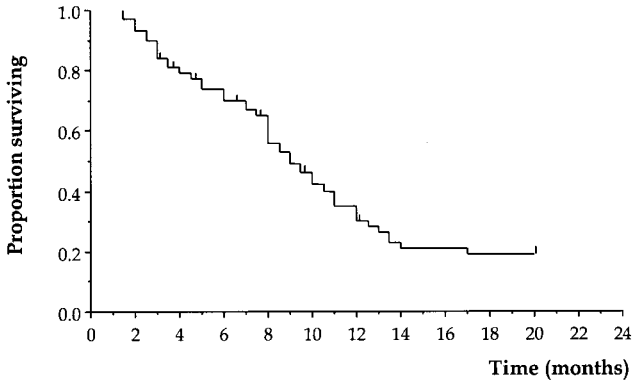

FIGURE 1. Actuarial survival analysis of patients with nonsmall cell lung carcinoma who were treated with the gemcitabine plus docetaxel second-line combination chemotherapy regimen after experiencing disease recurrence or no response to paclitaxel plus platinum-based regimens (Kaplan–Meier plot).

TABLE 2
Toxicities (National Cancer Institute Common Toxicity Criteria Grade) of Gemcitabine/Docetaxel Regimen

	NCI-CTC grade (% of patients, all cycles)				
Toxicity	**0**	**1**	**2**	**3**	**4**
Hematologic					
Leukopenia	2	16	26	30	26
Neutropenia	2	12	33	23	30
Thrombocytopenia	65	12	16	7	0
Anemia	20	47	21	12	0
Febrile neutropenia	—	—	—	14%	—
Nonhematologic					
Nausea and emesis	69	26	5	0	0
Mucositis	89	9	2	0	0
Peripheral neuropathy	46	40	14	0	0
Diarrhea	75	16	9	0	—
Alopecia	0	19	44	37	0
Cutaneous (rash)	91	9	0	0	0
Skin/nail	67	26	7	0	0
Hepatic	95	5	0	0	—
Asthenia/fatigue	49	33	18	0	—
Flulike syndrome	98	2	0	—	—
Pulmonary	98	0	2	0	0

NCI-CTC: National Cancer Institute Common Toxicity Criteria.

patient developed a syndrome of dyspnea, cough, fever, and diffuse pulmonary infiltrates on chest X-rays that responded promptly to oral corticosteroids and did not necessitate treatment discontinuation. Moreover, he had never received chest radiotherapy. This was considered gemcitabine and/or docetaxel-related pneumonitis (Grade 2), because both drugs have been implicated in the development of this complication. No treatment-related deaths were seen in the current study.

Compliance with Treatment

A total of 185 treatment courses were administered, with a median of 4 courses per patient (range, 1–6 courses per patient) and a mean of 4.3 cycles administered per patient. Dose reductions or omissions for myelosuppression were required for 13 of 43 patients (35%). The median delivered dose intensity was 74% of the planned dose intensity. Twenty patients (46.5%) received $\geq$ 80% of the planned dose intensity for both drugs.

DISCUSSION

Because increasing proportions of patients with advanced NSCLC are deriving clinical benefits and prolonged survival with novel drug-platinum combinations, such as paclitaxel and carboplatin, docetaxel and cisplatin, vinorelbine and cisplatin, or gemcitabine and cisplatin, it is anticipated that many of these patients will require some type of salvage chemotherapy after they experience disease recurrence. Based on past experience, such an option has been rather limited given low response rates for platinum-based first-line regimens and poor PS for these patients.[18] Therefore, the RR of 33% that we observed in the current study with gemcitabine plus docetaxel as second-line treatment for patients with advanced NSCLC appears adequately encouraging for further evaluation.

One recent report that evaluated the regimen of weekly gemcitabine 800 mg/m^2 on Days 1, 8, and 15 and docetaxel 100 mg/m^2 on Day 1 every 4 weeks in 40 patients with recurrent or resistant NSCLC demonstrated an objective RR of 32%, a median time to disease progression of 9 months, a median survival of 8.1 months, and a 32% 1-year survival rate.[19] It is important to note that 65% and 25% of patients had received prior first-line treatment with platinum plus vinorelbine or platinum plus etoposide, respectively, whereas 10% of patients had received prior single agents without platinum. Moreover, the mean delivered dose intensity for gemcitabine and for docetaxel in their regimen was 73% and 95%, respectively, which is comparable to our regimen despite the omission of almost 40% of the planned gemcitabine doses on Day 15 due to myelosuppression.[19] In addition, no prophylactic G-CSF was applied in the above study. In contrast to the study of Spiridonidis et al.,[19] all of our patients were pretreated with paclitaxel and platinum-based regimens, and almost 60% had clinical responses to first-line therapy;[12,15] however, no patients in the current study had prior exposure to docetaxel, and only five patients had received prior treatment with a regimen of gemcitabine, paclitaxel, and cisplatin. The RR of 33% in our study essentially replicates the 32% RR observed in the study by Spiridonidis et al.[19] Docetaxel in combination with gemcitabine suggests but does not establish overcoming cross resistance to paclitaxel in patients with NSCLC based on the above two studies. A similar phenomenon when docetaxel is given after paclitaxel failure has been described in patients with metastatic breast carcinoma.[20]

The individual contribution of each of these two cytotoxic agents, gemcitabine and docetaxel, to the activity of the regimen after failure of first-line taxane and platinum-based treatment cannot be discerned reliably. Several studies have evaluated gemcitabine in patients who failed prior platinum-based regimens and yielded RRs ranging from 3% to 25%.[9–11,21,22] The most impressive results with single-agent gemcitabine were reported by Crino et al.;[11] a 19% RR and a 1-year actuarial survival rate of 45% in a group of patients who had failed prior platinum-based therapy, whereas only 15% of those patients had received taxane and platinum-based combinations. Therefore, it can be said that the majority of their patients received suboptimal therapy by today's standards, which may explain the 45% 1-year survival rate. Moreover, RRs of 3%[9] and 21%[10] with no 1-year survival data available to date have been reported in other Phase II studies of single-agent gemcitabine salvage therapy in paclitaxel and carboplatin-resistant and/or refractory patients, thus indicating that the differences observed may have been the result of varying definitions of resistance to prior therapy and the inclusion of some patients in those studies who had more indolent or less disseminated disease at the time of recurrence.

Docetaxel appears to represent the only newer drug with a single-agent activity rate of 17% in cisplatin-pretreated patients with NSCLC, an RR approaching that of the most active drugs used in first-line treatment.[6] This was confirmed recently in an extended, multicenter, Phase II trial involving 80 patients with platinum-refractory or platinum-resistant NSCLC in which an RR of 16% was obtained with no impact of the platinum sensitivity status on the RR.[8] Both docetaxel and paclitaxel are promising for their

inherent antineoplastic activity against NSCLC. Docetaxel has the advantage of a longer intracellular half-life, leading to higher intracellular concentrations than paclitaxel,[23] and it is 100 times more potent than paclitaxel with respect to bcl-2 phosphorylation.[24] For these reasons, and because docetaxel has promising single-agent activity in patients with untreated[25–27] and platinum-resistant NSCLC,[6,8] we decided to develop a combination regimen of gemcitabine and docetaxel in paclitaxel plus platinum-pretreated patients with NSCLC. Although docetaxel has established activity as a single-agent and in combination with cisplatin in the first-line treatment of patients with advanced NSCLC,[28–30] in general, the results obtained in second-line treatment with docetaxel monotherapy have been modest. One recent, randomized, three-arm study comparing single-agent docetaxel 100 mg/m^2 or 75 mg/m^2 every 3 weeks with vinorelbine 30 mg/m^2 per week and with ifosfamide 6 g/m^2 (divided over 3 days) every 3 weeks in platinum-pretreated patients with recurrent NSCLC demonstrated a 1% RR among 245 patients who were allocated to a single-agent ifosfamide or vinorelbine arm.[7] However, there was no limit in that study on the number of prior chemotherapy regimens, and most patients may have been pretreated heavily.

Single-agent gemcitabine has demonstrated an improvement in quality of life but no survival prolongation over BSC alone in a recent randomized Phase III trial concerning chemonaïve patients with advanced NSCLC[31] and a 22.5% RR when combined with vinorelbine in a previous Phase II study of our group.[32] However, to date, between all newer agents, only docetaxel has demonstrated reproducible activity in extended Phase II studies[8] and proven value over BSC in a randomized Phase III trial in the salvage setting.[1] Moreover, the 7.4 month median survival in the single-agent docetaxel arm in that study is similar to the median survival achieved in our present Phase II study as well as the study of Spiridonidis et al.[19] Therefore, randomized Phase III trials between the gemcitabine plus docetaxel regimen versus single-agent docetaxel will be warranted before recommending the combination as a standard second-line treatment for patients with NSCLC who have received pretreatment with taxane and platinum-based regimens. Apart from salvage therapy with gemcitabine and docetaxel, a recent, large, multi-institutional, randomized Phase III study from Greece compared the above combination (at closely similar doses and same schedule) with docetaxel plus cisplatin first-line treatment in patients with advanced NSCLC and showed equivalent results and better tolerability of the docetaxel plus gemcitabine combination.[33]

Recent Phase I/II studies have demonstrated substantial activity of the weekly gemcitabine/docetaxel combination administered in chemotherapy-naïve patients with Stage IIIB–IV NSCLC.[34–36] In those studies, the objective RRs ranged from 30% to 40%, median OS ranged from 8.0 months to 12.5 months, and the 1-year survival rate was 35–48%. In two studies, gemcitabine on Days 1 and 8 with docetaxel on Day 8 (every 3 weeks) were given, and this has been most convenient and least toxic schedule used to date,[34,35] whereas schedules with docetaxel given on Day 1, many gemcitabine doses on Day 8 had to be omitted as a result of nadir neutropenia.[19,35]

The combination of gemcitabine and docetaxel was well tolerated in the current study of patients with NSCLC who were pretreated with paclitaxel plus platinum, which also was the case in the study by Spiridonidis et al.[19] However, febrile neutropenia was encountered in 14% of patients in our study and in 10% of patients in the study by Spiridonidis et al. We believe that the 100mg/m^2 docetaxel dose may be quite high in pretreated patients after dose-intensive first-line regimens, and the 75 mg/m^2 dose may be more tolerable in the palliative setting of second-line therapy (in combination with gemcitabine), like what was found in the large randomized study of two docetaxel doses compared with BSC.[1] This dose level also may obviate the need of prophylactic G-CSF administration that appeared necessary in the current study.

Although delivery of the treatment regimen studied was feasible in patients with refractory or recurrent NSCLC, the hematologic toxicity encountered may limit its further application in this palliative setting. Based on the activity of the regimen, it would appear reasonable to study a modified regimen with a lower docetaxel dose. Otherwise, the regimen may be suited best for chemotherapy-naïve patients, who may have a lower incidence of neutropenic fever and severe hematologic toxicity.

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