A Phase II Study of Gemcitabine plus Oral Etoposide in the Treatment of Patients with Advanced Nonsmall Cell Lung Carcinoma

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BACKGROUND. The authors have designed a non-cisplatin-based chemotherapy regimen for the treatment of patients with advanced nonsmall cell lung carcinoma (NSCLC). This regimen capitalizes on the mild toxicity of gemcitabine, a novel nucleoside analog.

METHODS. A total of 46 chemotherapy-naive patients with histologically confirmed Stage IIIB or IV NSCLC were enrolled. Eligible patients were treated with gemcitabine 1000 mg/m^2 on Days 1, 8, and 15, plus oral etoposide 50 mg daily for 14 days, which was increased to 21 days if there was no World Health Organization (WHO) Grade 3 or 4 toxicity in the 1st 2 cycles (each cycle was 28 days long). All patients were included for analysis of response and survival according to an intention-to-treat principle.

RESULTS. The overall response rate was 43.5% (95% confidence interval [CI], 30.7–60.2%). There was 1 complete response (2.2%) and 19 partial responses (41.3%). The median survival was 48.0 weeks (95% CI, 38.1–75.9 weeks) and the 1-year survival rate was 45% (95% CI, 29–62%). The median time to progression for all patients was 39.2 weeks (95% CI, 35.7–49.7 weeks). World Health Organization (WHO) Grade 3 and 4 anemia, neutropenia, and thrombocytopenia was reported in 29%, 32%, and 18% of patients, respectively. Two patients had reactivation of hepatitis B viral infection that resulted in WHO Grade 4 hepatic dysfunction. Other nonhematologic toxicities were uncommon.

CONCLUSIONS. This non-cisplatin-based regimen of gemcitabine and oral etoposide achieved a high response and survival rate. Toxicity appeared to be less severe than that associated with existing cisplatin-based regimens. A randomized study of this regimen versus a cisplatin-based regimen is indicated. ***Cancer* 2000;89: 543–50.** *© 2000 American Cancer Society.*

KEYWORDS: gemcitabine, oral etoposide, advanced nonsmall cell lung carcinoma, non-cisplatin-based regimen, toxicity.

Cisplatin-based combination chemotherapy has been established as the standard treatment for patients with advanced nonsmall cell lung carcinoma (NSCLC).[1] The Clinical Practice Guideline of the American Society of Clinical Oncology recommended that no more than eight cycles of cisplatin-based combination chemotherapy be given to patients with good performance status. Small but definite improvement in survival has been documented.[2,3] The combination of cisplatin, and more recently developed cytotoxic drugs such as vinorelbine, paclitaxel, and gemcitabine, has further increased the response rate and promised longer survival.[4] However, such benefits are commonly offset by toxicity. The incidence of World Health Organization (WHO) Grade 3 and 4 neutropenia associated with vinorel-

bine plus cisplatin, paclitaxel plus cisplatin, and gemcitabine plus cisplatin was 79%, 73%, and 58%, respectively.[5–7] Given this significant toxicity and the limited improvement in survival, we have investigated the possibility of developing a non-cisplatin-based regimen to capture the benefit of high response rate and low toxicity of gemcitabine.

Gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN) is a novel nucleoside analog with a biochemical structure similar to that of cytosine arabinoside. The primary mechanism of action is DNA synthesis inhibition.[8] The drug is phosphorylated into the nucleotide by deoxycytidine kinase and incorporated into DNA. Huang et al.[8] described the "masked chain termination," which is the addition of normal nucleotide after incorporation of gemcitabine in DNA. As result, gemcitabine is protected from excision by DNA repair mechanisms. Gemcitabine, as single-agent therapy, is active in treatment of advanced NSCLC.[9–11] The response rate was greater than 20% and toxicity was mild. Less than 10% of patients experienced WHO Grade 3 and 4 hematologic toxicity. Phase II studies on combination chemotherapy of gemcitabine and cisplatin reported response rates of 30–54%.[12–16] Results of at least one randomized Phase III study showed survival benefit with the gemcitabine combination therapy over single-agent cisplatin.[7]

Etoposide is a semisynthetic epipodophyllotoxin with inhibitory effects on topoisomerase II. The drug has been established as an important component in standard cisplatin-based combination chemotherapy.[17] Oral etoposide (Vepesid; Bristrol-Myers Squibb, Princeton, NJ) is a safe and convenient alternative method of administration.[18] The response rate for single-agent oral etoposide was 20%, and this increased to 51% in combination therapy with cisplatin infusion.[19,20] Hematologic toxicity of oral etoposide is dose dependent and correlates with serum etoposide concentration.[21] The toxicity of low dose oral etoposide (50 mg daily) is mild, and the agent is usually well tolerated.[22]

In this study, we aimed to develop a non-cisplatin-based regimen that is equally effective as cisplatin-based combination chemotherapy but without the latter's toxicity. We chose the current regimen because, as noted above, both gemcitabine and oral etoposide are active in advanced NSCLC and both have an acceptable toxicity profile at therapeutic dosage in single-agent therapy. Both drugs can be conveniently administered as an outpatient therapy. A preclinical in vitro study on the Lewis lung carcinoma cell line showed that the cytotoxic actions of gemcitabine and etoposide were synergistic.[23] Clinical synergism also has been reported with either drug in combination chemotherapy.[17,24]

To our knowledge, this is the first Phase II report of non-cisplatin-based combination chemotherapy comprising gemcitabine and oral etoposide for the treatment of advanced NSCLC. The objective of the study was to assess the effectiveness of this new regimen with respect to response rate, toxicity, time-to-progression, and survival.

PATIENTS AND METHODS

This single-center Phase II study was conducted in the Department of Clinical Oncology, at the Chinese University of Hong Kong. The study protocol and consent form (in both Chinese and English) were approved by the ethics committee of the University. The Principles of Good Clinical Practice were closely followed. Before enrollment, the investigator(s) explained to each patient the nature of the study and obtained written informed consent. The study was activated on May 12, 1997, and the database was frozen for analysis on March 20, 1999.

Eligible patients (age 18–75 years old) had advanced (Stage IIIB and IV by TNM classification) histologically proven NSCLC and were chemotherapy naive. At least one disease site had to be measurable bidimensionally. Bone metastases and pleural effusion were not classified as measurable. All patients were required to have a performance status of 0, 1, or 2 on the Eastern Cooperative Oncology Group scale. Prior palliative radiation was permitted so long as the treatment was greater than 3 weeks before entry into the current study and outside the field of measurable disease. Patients had to be mentally competent and to understand the diagnosis, treatment, and nature of trial and to have a life expectancy of at least 12 weeks.

We excluded patients with brain metastasis, hypercalcemia, and other life-threatening medical conditions. Patients with serum creatinine levels greater than 1.5 times the upper normal limit (UNL) or proteinuria levels greater than 1 g in 24 hours also were excluded, as were those with inadequate liver function: aspartate aminotransferase levels greater than 3 times UNL, alanine aminotransferase levels greater than 3 times UNL, serum bilirubin levels greater than 2 times UNL, or prothrombin time greater than 1.5 times control. Pregnant or lactating females and patients not able to comply with daily oral medication also were excluded.

Treatment

Gemcitabine was administered over 30 minutes on Days 1, 8, and 15 at a dosage of 1000 mg/m^2 in 250 mL normal saline (28-day cycle). Oral etoposide (50-mg capsule) was given daily for 14 days in the 1st 2 cycles. Because there was little information on the toxicity of

this combination, we only increased the duration of oral etoposide to a total of 21 days if there was no WHO Grade 3 or 4 toxicity in the 1st 2 cycles. A relative low dose of oral etoposide was chosen to minimize the hematologic toxicity of this noncisplatin containing regimen. We advised the patient not to take the oral etoposide within 1 hour of eating. Dose adjustment for the oral etoposide was made according to hematologic toxicity. Patients who developed WHO Grade 3 or 4 toxicity on 21-day treatment had the duration of oral etoposide reduced to 14 days in the subsequent cycle, and patients on 14-day treatment had it reduced to 10 days. Dose adjustment on gemcitabine was made according to the incidence of nonhematologic toxicity (with the exception of nausea, vomiting, and alopecia). For WHO Grade 3 or 4 toxicity, the dosage of gemcitabine was reduced to 800 mg/m^2 in subsequent cycles

Patients received intravenous metoclopramide and dexamethasone as routine pretreatment antiemetic therapy. Oral metoclopramide was taken as required. A maximum of eight cycles of treatment was planned. Treatment was discontinued in presence of disease progression, intolerable toxicity, or concurrent serious medical conditions. Palliative radiation to measurable disease could be given after discontinuation of protocol treatment.

Assessment

All patients had a chest radiograph and/or computed tomography (CT) scan within 4 weeks before the first treatment. The chest X-ray was repeated after each cycle. If measurable disease could only be defined on CT scan or abdominal ultrasound, the respective imaging was repeated after the second cycle and at the end of treatment. Patients classified as having achieved complete or partial response had the confirmatory imaging performed at least 4 weeks apart. We adopted the WHO response criteria. Complete response (CR) was defined as complete disappearance of all measurable and evaluable disease. Partial response (PR) was defined as a reduction of 50% of the sum of products of the bidimensional measurements of measurable disease on chest X-ray, ultrasound, or CT scan. All other patients were considered nonresponders.

Disease-related symptoms including cough, dyspnea, chest pain, and hemoptysis were evaluated before each treatment cycle and at 1 month after discontinuation of therapy. The symptoms were graded as none, mild, moderate, and severe. Laboratory investigation including complete blood count, renal function tests, liver function tests, serum calcium, prothrombin time, blood glucose, hepatitis B serology, creatinine clearance, and 24-hour urine collection for total protein were performed before enrollment. Complete blood cell count was performed weekly, and serum liver and renal function were measured monthly during treatment. Urine was checked for proteinuria before each cycle. Other toxicities were documented monthly. Toxicity was classified according to WHO recommendation for acute toxicity evaluation.

Overall survival was defined as the time from enrollment to death from any cause. Time to progression was determined from the time of first infusion. Evaluation of survival outcome and response rate was based on intention-to-treat principle for all enrolled patients.

Statistical Considerations

Sample size was calculated according to Simon Two Stage Phase II Design.[25] Assuming a target response of 40% and the lower activity level to be 20%, the stopping rule for Stage I and II was 3 of 13 and 12 of 43, respectively. This was designed with an alpha value of 0.05 and a power of 0.80.

The response rate, overall survival, and progression free survival analysis were calculated using all 46 patients according to an intention-to-treat principle. Assessment of the incidence of toxicity was performed on patients who have received at least one course of chemotherapy. The 95% confidence interval (CI) for response rate was calculated using method of Fleiss.[26] including a continuity correction factor. Time-to-event data were analyzed by the Kaplan–Meier method. A 95% CI for the median survival data was determined using the method by Brookmeyer and Crowley.[27] The median time-to-response and median duration of response were performed on the subset of patients who had responded to treatment. A logistic regression analysis was performed to investigate the association of baseline prognostic factors to patient response status. A Cox regression model was used to assess the association of baseline prognostic factors to overall survival. The incidence of toxicity was summarized descriptively. The proportions of patients who had an improvement after four cycles of chemotherapy, with respect to disease-related symptoms, were compared with those who had deterioration, by using a binomial test. A significant result implies that the specific symptom improvement, as opposed to deterioration, is not due to chance alone.

RESULTS

Between May 1997 and July 1998, we enrolled 46 consecutive patients. Twenty-seven patients had unresectable Stage IIIB disease (local extensive disease: 10 patients; supraclavicular lymph node metastasis: 10;

TABLE 1
Patient Characteristics

Characteristic	No. of patients
Total no. of patients	
Enrolled	46
Did not receive protocol treatment	2
Evaluable for toxicity	44
Evaluable for response and survival	46
Gender	
Male	39
Female	7
Age (yrs)	
Median	56
Range	31–73
Disease stage at entry	
Stage IIIB	29
Stage IV	17
Performance status (ECOG)	
0	29
1	17
Histology	
Adenocarcinoma	24
Squamous cell carcinoma	5
Unspecified NSCLC	17
Hepatitis B surface antigen	
Positive	3
Negative	43

ECOG: Eastern Cooperative Oncology Group; NSCLC: nonsmall cell lung carcinoma.

pleural effusion: 5; and both supraclavicular lymph node metastasis and pleural effusion: 2), and 19 patients had Stage IV disease. Two patients did not receive protocol treatment: one developed pericardial tamponade, and the other suffered from seizures secondary to brain metastasis. Therefore, 44 patients were evaluable for toxicity, and 46 patients were evaluable for survival and response. Patient characteristics are summarized in Table 1.

A total of 211 courses of chemotherapy was administered (oral etoposide for 14 days: 111 courses; oral etoposide for 21 days: 100 courses). The mean and median numbers of cycles completed were 4.8 and 5, respectively. Five patients had WHO Grade 3 toxicity in the 1st 2 cycles and stayed on the shorter regimen, and 3 had reduction of oral etoposide to 10 days. An additional 3 patients experienced WHO Grade 3 hematologic toxicity on the 21-day regimen and had dose reduction to the 14-day regimen. Palliative radiation to lung was offered to seven patients upon disease progression (Stage IIIB: 3 patients; Stage IV: 4 patients). Palliative radiation to other sites including brain (6 patients), bone (9 patients), and lymph nodes (3 patients) was given to 14 patients for symptom control. Only 1 of the 10 patients with local extensive Stage IIIB disease received radical radiotherapy. The other patients were not eligible for combined therapy for the following reasons: poor lung function: 2 patients, bulky disease with extensive chest wall or mediastinal involvement: 2 patients, failed to response to chemotherapy: 4 patients, and new central nervous system metastasis: 1 patient. Six patients received salvage chemotherapy (cisplatin plus etoposide or paclitaxel plus carboplatin) upon disease progression; none had significant response.

Responses and Survival

Of the 46 patients, 1 had a CR (2.2%) and 19 had a PR (41.3%). The overall response rate was 43.5% (95% CI, 30.7–60.2%). There was no significant difference in response rate between Stage IIIB (41%) and Stage IV (47.3%) patients ($P = 0.429$). Twenty-six patients had no response (56.5%); of these, 13 had stable disease. The median duration of follow-up was 62 weeks (95% CI, 43–81 weeks). At the time of evaluation, 14 Stage IIIB and 6 Stage IV patients were alive. The maximum and minimal duration of follow-up for the survivors was 76.4 and 26.7 weeks, respectively. The median survival of the 46 patients was 48.0 weeks (95% CI, 38.1–75.9 weeks) (Fig. 1). The 1-year survival rate was 45% (95% CI, 29–62%). None of the patient characteristics was significantly related to response. The median duration of survival for the responders (72.4 weeks) was significantly longer than the nonresponders (39.9 weeks) ($P = 0.010$). Stage was the only significant prognostic factor in a Cox regression model for overall survival. The median survival for Stage IIIB and Stage IV was 52.9 and 34.7 weeks, respectively, and the 1-year survival rate was 50.2% and 33.8%, respectively ($P = 0.046$). Median time to progression for all patients was 39.2 weeks (95% CI, 35.7–49.7 weeks).

The patient with CR was enrolled after diagnosis of recurrent lung tumor 1 year after primary resection. The time to progression for this case was 12 months, and the patient was alive, with disease at the time of this analysis. Eighteen patients died from disease progression. Four died from other causes including pneumonia and suicide.

Most of the responders (80%) had evidence of response after the second cycle of chemotherapy. Only 1 patient (5%) and 3 patients (15%) responded after 3rd and 4th cycles, respectively. The median time to response was 7 weeks, and the range was from 3.3 to 16 weeks. The median duration of response for the responders was 26 weeks (range, 11.4–53.5 weeks).

Toxicity

Severe neutropenia (WHO Grade 3 and 4) occurred in 14 patients (31.8%), but only 2 patients had neutro-

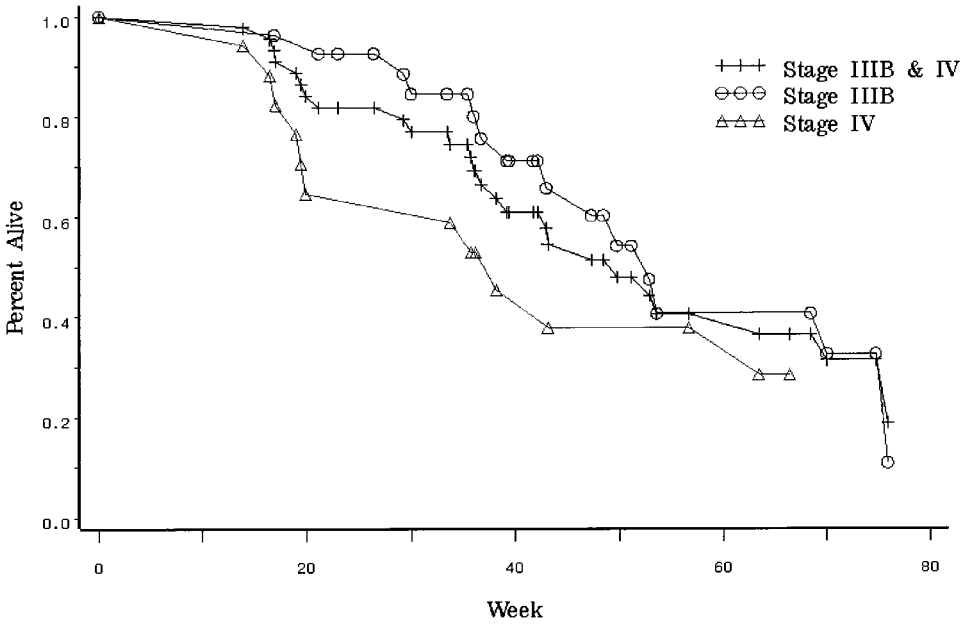

FIGURE 1. Overall survival for the Stage IIIB, Stage IV, and all patients according to the intention-to-treat principle is shown.

TABLE 2
WHO Hematologic/Nonhematologic Toxicity

	WHO grade (n = 44)									
	0		1		2		3		4	
Toxicity	n	%	n	%	n	%	n	%	n	%
Anemia	7	16	12	27	12	27	12	27	1	2
Leukopenia	4	9	15	34	12	27	11	25	2	5
Neutropenia	10	22	13	30	7	16	12	27	2	5
Thrombocytopenia	23	52	6	14	7	16	5	11	3	7
Nausea/vomiting	20	26	17	39	4	9	3	7	0	0
Mucositis	24	55	13	30	7	16	0	0	0	0
Rash	23	53	6	14	13	30	2	5	0	0
Flu-like symptoms	37	84	5	11	1	2	1	2	0	0
Fever	29	66	4	9	8	18	3	7	0	0
Hepatic										
Alkaline phosphatase	26	59	13	30	4	9	1	2	0	0
AST	40	91	2	5	0	0	1	2	1	2
Bilirubin	42	95	1	2	0	0	1	2	0	0
Renal										
Creatinine	44	100	0	0	0	0	0	0	0	0
Proteinuria	12	27	24	55	6	14	2	5	0	0

WHO: World Health Organization; AST: aspartate aminotransferase.

penic fever that required hospitalization and antibiotic therapy (Table 2). There were no septic deaths related to neutropenia. Of the 111 courses of the 14-day regimen, 16.2% were associated with WHO Grade 3 or 4 neutropenia, as compared with 8.1% of the 21-day regimen. Eight patients had WHO Grade 3 or 4 thrombocytopenia (19.2%), but only 1 patient required platelet transfusion. None had a major hemorrhagic event related to thrombocytopenia. Both nadir neutropenia and thrombocytopenia usually occurred at approximately Day 15. Anemia was common after the second or third cycle of chemotherapy, and eight patients required blood transfusion during treatment. Only 7 of the 211 (3.4%) courses of chemotherapy had to be cancelled on Day 8 or 15 of the gemcitabine infusion. However, hematologic toxicity lead to delay of Day 15 infusion in 11 courses (5.2%), and rapid recovery allowed the infusions to be completed by Day 22. Only one patient discontinued treatment because of hematologic toxicity.

Mild nausea, commonly associated with ingestion of oral etoposide, was reported in 47.7% of patients (Table 2). Only 3 patients reported of severe nausea or vomiting related to gemcitabine infusion. Proteinuria was uncommon and renal function was preserved in all patients. Two patients, both known chronic carriers of the hepatitis B virus (HBV) with normal liver function test before chemotherapy, developed abnormal liver function after the fourth and sixth cycles of chemotherapy. Abdominal ultrasound did not show evidence of liver metastases. We tested for HBV DNA by using the branched DNA hybridization assay, and both were very strongly positive. Diagnosis of hepatitis B viral reactivation was confirmed in both cases, and the patients were treated with lamivudine 150 mg daily. One patient developed hepatic encephalopathy requiring hospitalization. He recovered completely after 4 months of lamivudine and received palliative

TABLE 3
Presenting Symptoms at Enrollment (n = 44)

	None		Mild		Moderate		Severe	
Symptom	No.	%	No.	%	No.	%	No.	%
Cough	9	20	24	56	8	18	3	6
Dyspnea	19	43	20	46	4	9	1	2
Hemoptysis	33	75	10	23	1	2	0	0
Pain	22	50	15	34	7	16	0	0

TABLE 4
Change in Disease-Related Symptoms after 4th Cycle (n = 32)

	Improved		Unchanged		Deteriorated		
Symptom	No.	%	No.	%	No.	%	*P* value
Cough	13	40	14	44	5	16	0.03
Dyspnea	8	25	18	56	6	19	0.42
Hemoptysis	7	22	22	69	3	9	0.11
Pain	10	31	14	44	8	25	0.48

radiation as salvage treatment. He remains alive with disease at 19 months from enrollment. The other patient had improvement in liver function but had default follow-up. Other adverse events including mucositis, skin rash, and flu-like syndrome were uncommon and consistently reversible. Only 1 patient had chemotherapy delayed because of WHO Grade 3 mucositis.

Disease-Related Symptoms

The most common presenting symptoms at enrollment were cough and dyspnea (Table 3). We have compared the disease-related symptoms after the fourth cycle with enrollment to capture the improvement of symptom by chemotherapy. Thirty-two patients were assessable for evaluation. Cough showed significant improvement during treatment (Table 4). Although the majority of patients reported either improvement or stabilization in dyspnea, hemoptysis, and pain, the improvement did not achieve statistical significance.

DISCUSSION

This new non-cisplatin-based regimen of gemcitabine and oral etoposide gives a high response rate and low toxicity in the treatment of advanced NSCLC that compares favorably with current cisplatin-based regimens. Most cisplatin-based regimens result in severe toxicity whereas in the current regimen the toxicity was significantly reduced by avoidance of cisplatin. The response rate of our regimen (43.2%) is of the same order as that reported in 5 Phase II trials (52%, 65.3%, 54%, 42%, and 30%)[12–16] and 2 Phase III randomized studies (31% and 40.6%)[7,28] of gemcitabine and cisplatin. Although direct comparison is not possible, the current data suggest that the response rates of new combination chemotherapy of gemcitabine with or without cisplatin are similar.

Patients on this new regimen achieved a median survival of 48.0 weeks (Stage IIIB: 52.9 weeks; Stage IV: 34.7 weeks). The median duration of survival reported in the 5 Phase II studies of the combination of gemcitabine and cisplatin ranged from 24 to 60 weeks.[12–16] Bunn and Kelly summarizing the survival outcomes of 42 Phase II studies involving 1654 patients who received cisplatin-based "new drug" regimens for advanced lung carcinoma[4] reported median survival rates ranging from 32 to 57 weeks. It is not possible to compare our results to those of these Phase II trials because we have a disproportionately large percentage of Stage IIIB patients. However, it is clear that the median survival rates of our Stage IIIB and Stage IV patients are in line with the range reported in these studies.

The current regimen has a more tolerable incidence rate of severe neutropenia (31.8%) and thrombocytopenia (19.2%) (WHO Grade 3 and 4) compared with that associated with gemcitabine plus cisplatin (36–58% and 21–52%, respectively).[29] We monitored the blood count weekly to ensure complete documentation of hematologic toxicity. Severe nonhematologic toxicity was virtually nonexistent whereas nephrotoxicity and gastrointestinal toxicity are common adverse effects of cisplatin-based regimen despite proper hydration and 5-hydroxytryptamine antagonists.

Hepatitis B virus reactivation during chemotherapy in two of the three hepatitis B surface antigen (HBsAg) carriers is a cause of concern. The rate of chronic HBsAg carriage in the general population of Hong Kong is 9.5%,[30] and most reports of HBV reactivation concern patients with hematologic malignancy.[31–34] The development of HBV reactivation in our patients could be either coincidental or related specifically to the current regimen although neither of the drugs used has been linked previously to HBV reactivation. Myelosuppression was only mild in both cases. The application of corticosteroid therapy, as a prechemotherapy antiemetic agent, recently has been implicated as a significant factor contributing to HBV reactivation.[35] In our regimen, the dexamethasone, administered on the day of gemcitabine infusion, may have been involved. We would advise routine screening for hepatitis B status before initiation of chemotherapy, particularly in high incidence areas, and the

avoidance of dexamethasone as antiemetic in those found to be positive.

Other non-cisplatin-based regimens involving new cytotoxic drugs are currently under investigation and those involving gemcitabine have shown early encouraging results. Phase II studies of gemcitabine plus paclitaxel,[36] gemcitabine plus docetaxel,[37] and gemcitabine plus vinorelbine[38] reported response rate of 30.4%, 36.5%, and 41%, respectively. Median survival was 8–9 months. Unfortunately, the hematologic toxicity was similar to cisplatin-based regimens. Severe myelosuppression was reported, and growth factor support was routinely required for patients on the gemcitabine plus docetaxel regimen.

We chose a fixed daily dose of oral etoposide for its simplicity in administration. To our knowledge, there has been only a single previous report of gemcitabine and oral etoposide, and this also used fixed daily dose of oral etoposide. This Phase I/II trial of the combination in advanced solid tumors used an intrapatient dose escalation scheme to establish the maximum tolerated dose.[39] The recommended dose for Phase II study was fixed daily oral etoposide (100 mg daily for 7 days) and weekly gemcitabine (1000 mg/m^2 on Days 1 and 8). In our study, the dosage was adjusted according to hematologic profile that was monitored weekly. We have shown both 14- and 21-day schedules to be safe and tolerable.

The dosage of oral etoposide used in this regimen was low compared with the other studies in which oral etoposide was used at 50 mg/m^2 for 21 days as single-agent therapy.[19] When we designed this non-cisplatin containing regimen, we aimed to minimize toxicity and capture the benefit of synergism between gemcitabine and oral etoposide. Had we used the standard dosage of oral etoposide, we would have expected significant hematologic toxicity. This regimen attained a response rate of 43.2% despite a relative low dose of oral etoposide and is consistent with the synergism reported in preclinical study.[23]

In this prospective Phase II study involving patients with advanced NSCLC, the combination of gemcitabine and oral etoposide appears less toxic and has a similar order of efficacy to that obtained with cisplatin-based regimens. We now are undertaking a randomized comparative study of gemcitabine and oral etoposide versus gemcitabine and cisplatin. In addition to the usual endpoints, we will focus on the comparison of toxicity and quality of life.

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