Neoadjuvant Chemotherapy with Gemcitabine-Containing Regimens in Patients with Early-Stage Non-small Cell Lung Cancer

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Background: Surgical resection alone remains suboptimal for patients with early-stage (I or II) non-small cell lung cancer. Two similar randomized phase II trials were conducted to define an active preoperative regimen in this disease state.

Methods: In the first study, patients were randomized to receive gemcitabine 1000 mg/m^2 on days 1 and 8 plus cisplatin 80 mg/m^2 on day 1 (GC) or gemcitabine 1000 mg/m^2 on days 1 and 8 plus carboplatin area under the curve 5.5 on day 1 (GCb). In the second trial, patients received the same regimen of GCb or gemcitabine 1000 mg/m^2 on days 1 and 8 plus paclitaxel 200 mg/m^2 on day 1 (GP). Cycles were repeated every 21 days for three cycles. The primary end point was pathologic complete response (pCR) rate.

Results: Eighty-seven eligible patients were randomized (GC n = 12, GP n = 35, and GCb n = 40), and 71 (82%) underwent surgery after chemotherapy. The confirmed pCR rate was 2.3% (2 of 87, 95% confidence interval 0.3–8.1). Clinical response rate was 28.7%, complete resection rate was 91.5% (65 of 71 patients), and perioperative mortality rate was 2.8%. As of October 2006, median survival for all patients was 45 months (65.5% censored), with 87.2% alive at 1 year and 69.8% alive at 2 years.

Discussion: Neoadjuvant chemotherapy with gemcitabine was feasible and well tolerated, and outcomes were similar to other reports of this treatment strategy. However, no regimen achieved the predefined pCR rate that would be sufficient to warrant further evaluation in the phase III setting. This trial design provides an efficient way of providing a rationale for choosing or rejecting regimens of potential value.

Key Words: Multimodality, Early stage, NSCLC, GINEST, Gemcitabine, Resectability.

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Non-small cell lung cancer (NSCLC) remains a leading cause of mortality throughout the world, accounting for approximately 80% of the 1.18 million deaths from lung cancer each year.[1,2] Treatment has been determined largely through diagnostic staging, and curative surgery is indicated in only a small minority who present with localized disease without evidence of mediastinal lymph node involvement.[3–5] Nonetheless, overall survival (OS) among patients receiving surgical resection alone remains less than optimal. Among patients who present with the best clinical prognosis (clinical T1N0), the 5-year survival rate is 61 to 63% (or 67% based on pathologic T1N0).[6–8]

After tumor resection, distant recurrence is the dominant mode of relapse and the most common cause of mortality. Improved molecular techniques and methods of detection have confirmed the presence of occult micrometastatic disease in many patients at the time of resection.[9–12] Eradication of this additional burden forms the rationale for adjuvant and neoadjuvant strategies in early-stage NSCLC. Several large early-stage trials have confirmed a modest survival benefit associated with adjuvant therapy.[13–17] Neoadjuvant (preoperative) therapy theoretically provides the added benefit of tumor downstaging before surgery, improving the chances of a complete resection. Nonetheless, experience with preoperative treatment has concentrated mostly on patients with locally advanced (stage III), rather than early-stage (I or II) disease.[18,19]

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A large, randomized French Thoracic Cooperative Group study (355 patients) showed an 11-month median improvement in survival with preoperative chemotherapy compared with surgery alone in stage I to IIIA patients (37 to 26 months, $p = 0.15$).[20] When including only patients with stage I or II disease, the survival benefit of neoadjuvant therapy was found to be statistically significant (odds ratio = 0.68, $p = 0.027$). A large phase II study in patients with stage I or II disease also demonstrated the feasibility of the preoperative approach in early-stage patients.[21] Additional trials also found that downstaging after chemotherapy predicted improved survival, and patients who had pathologic complete response (pCR) to chemotherapy displayed the best survival.[18,22]

Gemcitabine (Gemzar, Eli Lilly and Company, Indianapolis, IN) is a pyrimidine antimetabolite[23] that has demonstrated independent antitumor activity in diverse tumor types, including advanced or metastatic NSCLC.[24–26] In advanced-stage disease, several novel regimens have been used, with no single treatment strategy demonstrating superior outcomes.[27,28] One of the difficulties in conducting randomized combined modality trials is that phase III studies often are not large enough to demonstrate definitive differences even when provocative results are reported with hundreds of enlisted patients.[20] A series of randomized phase II trials was chosen as our study design with phase II end points applying to each treatment arm. This design allows patients to be assigned to a treatment without investigator bias, and permits a relatively small number of patients to be enlisted to determine whether there is a likelihood of either inferior or superior results with a regimen when seen in the context of currently reported trials. Thus, more effective regimens can be chosen based on trial results for further study in larger phase III trials. Given the need for more effective therapy for stage I and II disease, the promising results of neoadjuvant trials (including one randomized study), and the efficacy and tolerability of gemcitabine-based chemotherapy in advanced NSCLC, we conducted two similar randomized phase II trials to better characterize the activity and safety of chemotherapy regimens.

The pCR rate was chosen as the primary end point because the results are easily demonstrated and clearly show the activity of chemotherapy in this setting. Although prior studies have noted the best survival outcomes in those patients achieving a pCR from chemotherapy, it must be noted that in those with stage III extent, it has been easier to achieve complete clearing of cancer cells in nodal metastases than in the primary tumor.[29]

Clinical stage I and II disease was chosen given the data that neoadjuvant therapy seems to have the greatest benefit in these stages.[20] Stage I was included because of the poor survival of clinical stage I patients, and because previous studies have indicated a high incidence of upstaging between clinical and pathologic stage. We did not exclude stage IA based on a relatively arbitrary distinction of $\leq$3.0 cm or $\geq$3.1 cm, but anticipated that few patients with stage IA would be included, especially with the need for tissue confirmation of NSCLC.

PATIENTS AND METHODS

Patient Selection

The Gemcitabine in Neoadjuvant Early-Stage Trials (GINEST) project consisted of two similar phase II trials, conducted in a total of 23 investigative sites (12 and 11 for each trial, respectively), involving 87 patients with clinical stage I or II NSCLC. Patients were required to have a histologically or cytologically confirmed diagnosis, a negative mediastinal evaluation (defined as all mediastinal lymph nodes $<$1 cm by computed tomography (CT) scan and a negative positron emission tomography scan; or a negative mediastinoscopy if either CT or positron emission tomography was suspicious), an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, age $\geq$18 years, and measurable or evaluable disease documented by chest radiography or contrast-enhanced CT scan (for all measurable lesions). In addition, patients were required to have adequate organ function (defined as an absolute granulocyte count $\geq 1.5 \times 10^9$ cells/liter, platelets $\geq 100 \times 10^9$ cells/liter, serum creatinine = 1.5 times the institutional upper limit of normal, and calculated creatinine clearance = 40 ml/min). All patients were required to have a calculated postresection (ppo) forced expiratory volume in 1 second $>$40% of the predicted value and a ppo diffusing capacity of the lung for carbon monoxide (DLCO)/alveolar volume $>$40% of the predicted value. Prior systemic chemotherapy or use of other investigational therapy was not allowed; however, prior resection of lung disease was allowed, provided 5 years had elapsed before enrollment.

Patients with bronchioloalveolar carcinoma or stage IIB tumor involving the superior sulcus (Pancoast tumors) were excluded. In addition, female patients who were pregnant or nursing, and patients with postobstructive pneumonia or other serious infection at the time of randomization or any other serious underlying medical condition that would impair the ability of the patient to receive treatment were excluded. Patients were required to provide written informed consent, and the Institutional Review Boards of participating centers were required to approve the protocol before study initiation.

Trial Design and Treatment Plan

Schemas for the GINEST project are summarized in Figure 1. Patients were randomized to receive neoadjuvant therapy in one of two similar, multicenter, phase II clinical trials. Patients in the first trial were randomized to receive gemcitabine 1000 mg/m^2 on days 1 and 8 followed by cisplatin 80 mg/m^2 or carboplatin at area under the curve (AUC) 5.5 on day 1. Patients in the second trial were randomized to receive gemcitabine 1000 mg/m^2 on days 1 and 8 followed by paclitaxel 200 mg/m^2 or carboplatin at AUC 5.5 on day 1. Treatment cycles were repeated every 21 days for 3 cycles. Carboplatin dosing was based on the formula described by Calvert et al.[30] All therapies were administered intravenously; gemcitabine over 30 minutes, cisplatin over 30 to 90 minutes, carboplatin over 30 minutes, and paclitaxel over 60 minutes.

Before chemotherapy, if neutrophils were $<1.5 \times 10^9$ cells/liter or platelets $<$100,000, chemotherapy doses of all

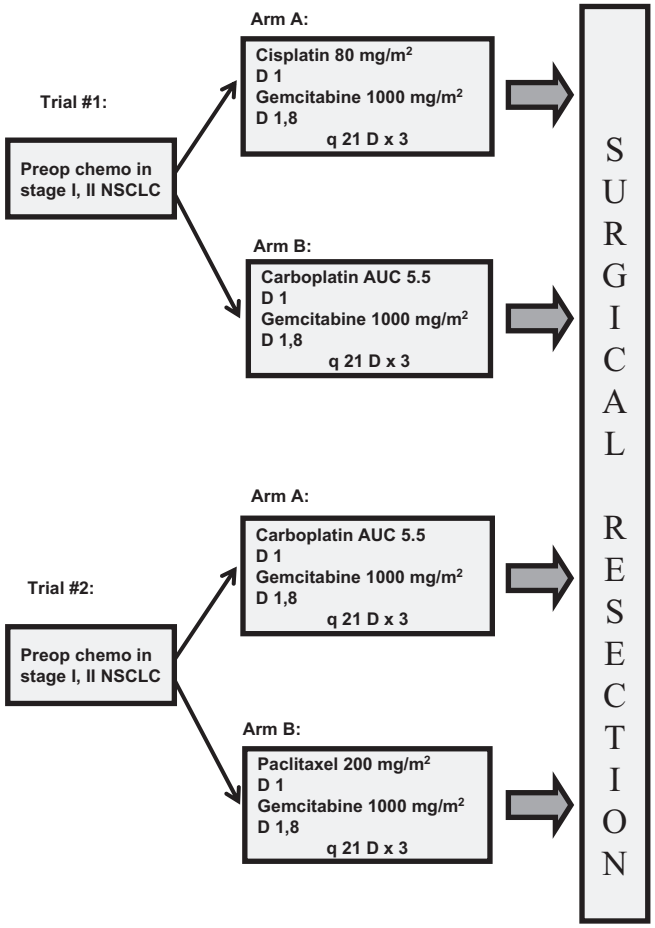

FIGURE 1. The GINEST project schema.

therapies were to be reduced by half. If neutrophils were $<1.0 \times 10^9$ cells/liter or platelets <50,000, chemotherapy was to be delayed until sufficient recovery. Guidelines for dose adjustments were also provided in the event of febrile neutropenia, bleeding, cisplatin-related nephrotoxicity, or cisplatin- or paclitaxel-related neurologic toxicity.

Surgery

Between 2 and 6 weeks after the last dose of chemotherapy, patients underwent resection. In addition, patients with clear evidence of progressive disease (PD) before the third cycle of therapy could proceed to surgery, if resectable. Every effort was made to carry out a complete resection (R0). Extent of resection (lobectomy, bilobectomy, or pneumonectomy) was performed on the basis of the prechemotherapy CT scan. Surgical resection included a systematic sampling of mediastinal lymph nodes in each ipsilateral and subcarinal nodal station (2, 4, 7, 9 on the right and 4, 5, 7, 9 on the left). Level 10 hilar nodes were also included. If no nodes could be found after opening the pleura and exploration of a nodal station, then this station was classified as negative.

Evaluations

The search for residual tumor after induction chemotherapy was carried out as was routinely performed in the particular institution. No extra techniques or sectioning were required. pCR was defined as no viable tumor cells in the specimen, as determined by light microscopy. The operative notes of all pCR and near-pCR cases were centrally reviewed to assure that the quality of surgery was appropriate, and if a pCR was either reported or felt to be likely, then the tissue was examined by a central referee pathologist (M.B.Z.).

During chemotherapy, physical examination, blood chemistry, PS evaluation, and chest radiography were performed before each cycle. At the end of each cycle, toxicity was evaluated according to National Cancer Institute common toxicity criteria. At the end of induction therapy, a CT scan was performed and pulmonary function reassessed. If there was a drop of >20% in forced vital capacity or DLCO, patients underwent additional investigation. To be eligible for surgery, patients needed to have either a ppo forced expiratory volume in 1 second and ppo DLCO/VA >40% or an exercise test with a VO_{2max} >15 ml/kg/min. Surgical morbidity was defined as any common toxicity criteria grade 3 or 4 event occurring within 30 days of surgery that the investigator believed was related to surgery.

Statistical Analysis

The primary end point of the study was the pCR rate; patients evaluable for this calculation included all who underwent resection as well as patients who were removed from the study before resection because of clear evidence of disease progression after treatment with at least one cycle of chemotherapy. Other end points of this study included clinical response (CR) rate, OS, and disease-free survival (DFS). These end points were assessed in the intent-to-treat (ITT) population, defined as all patients who were enrolled and eligible, regardless of what treatment was actually received. Secondary end points also included toxicity and operative mortality. Toxicity was assessed in all patients who received at least one cycle of chemotherapy (designated as the safety population). Pulmonary toxicity was evaluated in detail and will be the subject of a separate publication. Operative mortality was assessed in all patients who underwent surgery with the intent to resect. Finally, secondary end points also included preoperative and postoperative quality of life, which will also be reported in a separate publication.

Complete CR was defined as the radiographic disappearance of all known disease, determined by two observations not less than 3 weeks apart. Partial response (PR) was defined as a ≥50% decrease in bidimensional measurements of the lesions that have been measured to determine the effect of therapy by two observations ≥3 weeks apart. In addition, there had to be no appearance of new lesions or progression of any lesion. PD was at least a 25% increase in the bidimensional measurements of at least one measurable lesion or the appearance of new lesions. Survival and DFS were assessed from the date of randomization to the date of death or progression. Although the randomized phase II design of these studies did not allow direct comparison of the treatment arms, it provided data for the evaluation of the activity and relative toxicities of the regimens.

Both studies used the same two-stage design for each treatment arm, as randomized phase II trials. Initially, 15

patients were enrolled in each treatment arm and pathologic response rate was assessed at the time of surgery. If at least 1 of 15 patients in an arm showed a complete pathologic response, then accrual in that arm was expanded to 35 patients to better characterize the true pCR rate for that treatment regimen. If complete pathologic response was seen in none of the first 15 treated, then that arm was closed. With no response in 15 patients (a 0% observed rate), it was concluded that the regimen is associated with a true pCR rate of <20% at $\alpha = 0.05$, which is below our predetermined minimum pCR rate. Accrual was continued in other treatment arms independent of the closure of that treatment arm. If at least one pCR was found in the initial 15 patients, an additional 20 patients were added to further characterize the pCR rate. This was to further test whether the regimen had a true pCR rate of ≥20% at $\alpha = 0.05$. If the observed pCR rate was higher in the 35 patients, the regimen would be of sufficient interest to pursue further.

The planned sample size for each of the two independently conducted studies was estimated at 30 to 70 patients per arm, depending on the activity or the regimens, as discussed earlier. However, the first trial was discontinued after enrolling 28 patients as a result of slow patient accrual (12 were randomized to receive gemcitabine + cisplatin [GC] and 16 received gemcitabine + carboplatin [GCb]). In the second trial, enrollment reached 54 patients (24 received GCb and 35 received gemcitabine + paclitaxel [GP]). This trial was stopped at this point because the GP arm had reached full accrual and >35 patients had received GCb when both trials were taken together. With the nearly identical study design for each of these phase II studies, for the purpose of statistical analysis, the GCb arms from the two trials were combined because of the identical nature of patient eligibility criteria and treatment plans between the two studies.

RESULTS

Patients

Between June 2001 and December 2004, 87 patients with stage I or II NSCLC were accrued at 16 investigational centers in the United States. Twelve patients were assigned to GC, 35 were assigned to GP, and 40 were assigned to GCb. All 87 patients received at least one dose of study drug. Baseline characteristics and patient disposition for all three treatment groups are summarized in Table 1. Median age of all patients was 63 years, and most (75%) had an ECOG PS of 0. Almost half (49%) of all patients had stage IB (T2N0) disease. Among all patients, 39% were diagnosed with squamous cell carcinoma, 36% with adenocarcinoma, 17% with disease not otherwise specified, and 2% with large cell carcinoma.

TABLE 1. Baseline Characteristics and Disposition (Intent-to-Treat Population, $n = 87$)

	GC ($n = 12$)	GP ($n = 35$)	GCb ($n = 40$)
Median age, yr (range)	61.5 (42–83)	63.0 (33–79)	63.5 (36–82)
Gender			
Male	5 (41.7)	20 (57.1)	21 (52.3)
Female	7 (58.3)	15 (42.9)	19 (47.5)
ECOG PS			
0	8 (66.7)	24 (68.6)	33 (82.5)
1	4 (33.3)	11 (31.4)	7 (17.5)
Histology			
Squamous	5 (41.7)	17 (48.6)	12 (30.0)
Adenocarcinoma	5 (41.7)	6 (17.1)	20 (50.0)
NSCLC, NOS	2 (16.7)	9 (25.7)	4 (10.0)
Large-cell undifferentiated	0 (0)	0 (0)	2 (5.0)
Other	0 (0)	3 (8.6)	2 (5.0)
Clinical stage			
IA (T1N0)	2 (16.7)	6 (17.1)	10 (25.0)
IB (T2N0)	7 (58.3)	18 (51.4)	18 (45.0)
IIA (T1N1)	0 (0)	0 (0)	3 (7.5)
IIB (T2N1, T3N0)	3 (25.0)	11 (31.4)	9 (22.5)
Cycles administered			
One	12 (100)	35 (100)	40 (100)
Two	10 (83.3)	32 (91.4)	40 (100)
Three	9 (75.0)	31 (88.6)	40 (100)
Surgical population	9 (75.0)	29 (82.9)	33 (82.5)
Type of resection			
Upper lobe right	2 (22.2)	8 (27.6)	9 (27.3)
Middle lobe right	2 (22.2)	3 (10.3)	3 (9.1)
Lower lobe right	1 (11.1)	3 (10.3)	2 (6.1)
Upper lobe left	2 (22.2)	9 (31.0)	10 (30.3)
Lower lobe left	1 (11.1)	2 (6.9)	4 (12.1)
Central right	1 (11.1)	3 (10.3)	3 (9.1)
Central left	1 (11.1)	2 (6.9)	3 (9.1)
Multiple lobes	0 (0.0)	1 (3.4)	1 (3.0)
Discontinuations			
Study completed	9 (75.0)	28 (80.0)	33 (82.5)
Adverse event	2 (16.7)	2 (5.7)	0 (0)
Death due to unknown cause	0 (0)	0 (0)	1 (2.5)
Distant recurrence	0 (0)	2 (5.7)	1 (2.5)
Patient decision	1 (8.3)	0 (0)	0 (0)
Other	0 (0)	3 (8.6)	5 (12.5)

Values given are *n* (%) values, unless indicated otherwise.
NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PS, performance status.

Comparison of GCb Groups

Characteristics and outcomes from the GCb groups of the two trials were similar. In comparing patients from trial 1 ($n = 16$) versus trial 2 ($n = 24$), median age was 62.0 versus 63.5 years, 93.7% versus 75% had an ECOG PS of 0, 50% versus 50% had adenocarcinoma, and 81.3% versus 62.5% had stage I disease, respectively. In addition, 18.8% versus 20.8% had a PR, 43.8% versus 45.8% had grade 3 or 4 leukopenia, and 12.5% versus 20.8% had grade 3 or 4 thrombocytopenia, respectively. Given the observed similarities between the two GCb groups (none of the differences in efficacy or toxicity parameters between GCb groups were statistically significant) it seemed reasonable to combine the two for analysis.

Of the 87 patients enrolled in the study, 249 cycles of treatment were administered, a mean of 2.9 cycles per patient. Among all patients, the mean number of doses for gemcitab-

ine was 5.2 (of planned six doses) and the mean number of doses for cisplatin, paclitaxel, or carboplatin was 2.8 (of three planned doses). Primary reasons for premature discontinuation included adverse event ($n = 4$), distant disease recurrence ($n = 3$), death ($n = 1$), and patient decision ($n = 1$). Seventy one patients (82%) underwent surgery, consisting of similar rates of patients from all three treatment groups. In the surgical population, upper lobe left (29.6%) and upper lobe right (26.8%) were the most common types of localization.

Most cycles of chemotherapy were fully administered during three cycles of therapy. Among all patients, median relative dose intensity was 97.5% for gemcitabine, 98.1% for cisplatin, 98.0% for paclitaxel, and 99.2% for carboplatin. Compared with other treatment groups, however, GCb had the highest percentage of patients with dose reductions, delays, and omissions. In the GC group, only one dose reduction occurred (8.3%). In the GP group, 11 of the 35 patients receiving therapy (31.4%) received dose reductions. By comparison, of the 40 patients receiving GCb, 22 had dose reductions (55.0%). Three doses were delayed in the GC group (25.0%), four doses were delayed in the GP group (11.4%), and 22 doses were delayed in the GCb group (22.5%). There were a total of six dose omissions in the GC group (50%), 13 dose omissions in the GP group (37.1%), and 26 dose omissions in the GCb group (65.0%).

Toxicity

All 87 patients were evaluated for safety. Results are summarized in Table 2. Grade 3 or 4 hematologic and nonhematologic events occurred with a low frequency; the most common event in any treatment group was leukopenia (grade 3 = 35.0% and grade 4 = 10.0% of patients in GCb). Alopecia most frequently occurred in the GP group (42.9% versus 8.3% in the GC group and 5.0% in the GCb group). Other grade 2 events, including arthralgia, dyspnea, diarrhea, asthenia, and myalgia were more frequent in the GP group.

Response to Neoadjuvant Chemotherapy

The overall CR rate for all 87 patients was 28.7% (95% confidence interval [CI] 19.5–39.4) including one patient (1.1%) with CR, 24 with PR (27.6%), 39 with stable disease (SD; 44.8%), and 8 with PD (9.2%). The single CR occurred in a patient from the GC treatment group. The overall response rates for each treatment group were 41.7% for GC (95% CI 15.2–72.3), 34.3% for GP (95% CI 19.1–52.2), and 20.0% for GCb (95% CI 9.1–35.7).

Surgical Procedures and Outcomes

Table 3 summarizes surgical procedures and outcomes of surgery. Of the 87 patients assessable for resection, 71 underwent surgery (82%). Surgical procedures performed were lobectomy ($n = 49$), pneumonectomy ($n = 12$), bilobectomy ($n = 8$), and other procedures ($n = 2$).

Complete resections in those going to surgery occurred in 91.5% of patients (65 of 71; 95% CI 82.5–96.8), with five patients undergoing incomplete resection and one undergoing grossly incomplete resection. In all patients entered into the trial, 74.7% had complete resection (65 of 87, 95% CI 64–83.4). Resectability rate was not statistically different across treatment arms. Perioperative mor-

TABLE 2. Preoperative Hematologic and Nonhematologic Toxicity (Safety Population, $n = 87$)[a]

	GC ($n = 12$)		GP ($n = 35$)		GCb ($n = 40$)	
	G3	G4	G3	G4	G3	G4
Hematologic						
Anemia						
Leukopenia			6 (17.1)	1 (2.9)	14 (35.0)	4 (10.0)
Thrombocytopenia					4 (10.0)	3 (7.5)
Nonhematologic						
Alopecia (G2 only)	1 (8.3)		15 (42.9)		2 (5.0)	
Arthralgia			3 (8.6)			
Asthenia			1 (2.9)		1 (2.5)	
Cellulitis				1 (2.9)	1 (2.5)	
Chest pain			1 (2.9)		1 (2.5)	
Constipation						
Diarrhea			1 (2.9)		1 (2.5)	
Dyspnea			1 (2.9)			
Myalgia			1 (2.9)			
Neurotoxicity	2 (16.7)		2 (5.7)			
Rash	1 (8.3)					
Vomiting						

Values given are *n* (%) values, unless indicated otherwise.
[a] Blank cells indicate a frequency of 0 (0.0%).
G = NCI CTC grade.
GC = gemcitabine-cisplatin.
GP = gemcitabine-paclitaxel.
GCb = gemcitabine-carboplatin.

TABLE 3. Surgical Procedures and Outcomes (Patients with Tumor Resection, $n = 71$)

Procedure	
Lobectomy	49 (69.0)
Pneumonectomy	12 (16.9)
Bilobectomy	8 (11.2)
Other	2 (2.8)
Outcome	
Complete resection (R0)	65 (91.5)
Incomplete resection (R1)	5 (7.0)
Grossly incomplete resection (R2)	1 (1.4)
Pathologic stage	
Complete response (T0N0)	2 (2.8)
IA (T1N0)	17 (23.9)
IB (T2N0)	26 (36.6)
IIA (T1N1)	4 (5.6)
IIB (T2N1, T3N0)	14 (19.8)
IIIA (T3N1, T2N2)	3 (4.2)
IIIB (T4N0, T4N2, T4NX)	3 (4.2)
Missing	2 (2.8)
Perioperative mortality	2 (2.8)
Morbidity within 30 d	
Pain	7 (9.9)
Dyspnea	7 (9.9)
Atrial fibrillation	2 (2.8)
Infection	2 (2.8)
Sepsis	1 (1.4)
Ascites	1 (1.4)
Hypotension	1 (1.4)
Constipation	1 (1.4)
Ileus	1 (1.4)
Apnea	1 (1.4)
Hypoxia	1 (1.4)
Pneumonia	1 (1.4)
Pneumothorax	1 (1.4)
Delirium	1 (1.4)

Values given are *n* (%) values.

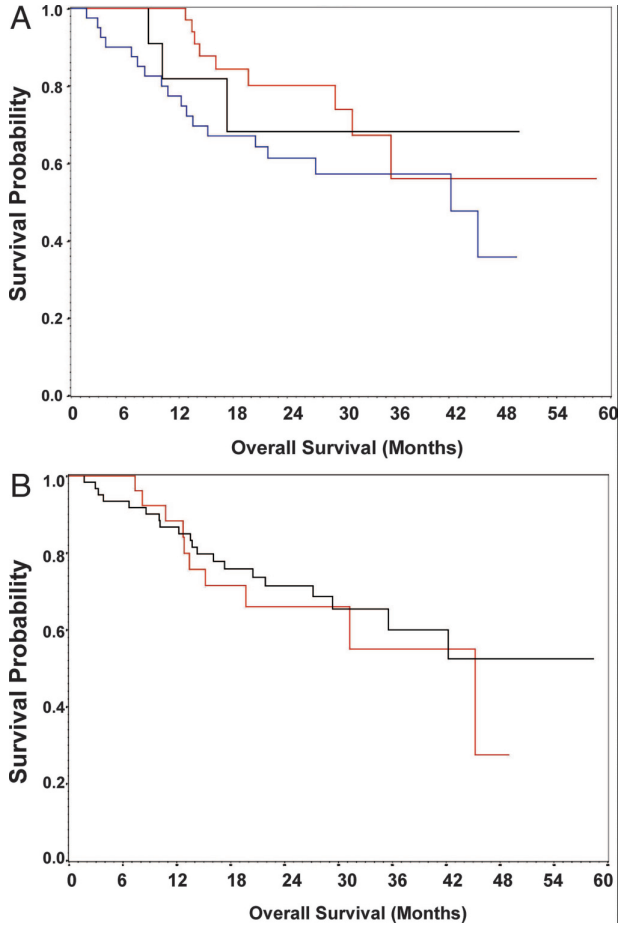

FIGURE 2. *A,* Overall survival stratified by treatment administered. Black: gemcitabine/cisplatin (n = 12), Red: gemcitabine/paclitaxel (n = 35), Blue: gemcitabine/carboplatin (n = 40). *B,* Overall survival stratified by clinical stage I ($n = 61$) or stage II ($n = 26$) disease. Black: stage I, Red: stage II.

tality occurred in two patients (2.8%), subsequent to one lobectomy and one pneumonectomy. The most common grade 3 or 4 postoperative adverse events (within 30 days) were pain and dyspnea (9.9% each), followed by atrial fibrillation and infection (2.8% each), and other events occurring in one patient each.

Pathologic Response

Two confirmed pCRs were observed in this study, both of which were in the GP treatment group. The overall confirmed pCR rate was 2.3% (2 of 87 patients, 95% CI 0.3–8.1). One patient with a pCR had stage I disease, and one had stage II disease. By treatment arm, pCR rate was 0% (95% CI 0.0–33.6) for GC, 6.9% (95% CI 0.8–22.8) for GP, and 0% (95% CI 0.0–10.6) for GCb.

Survival and DFS

OS by treatment administered is summarized in Figure 2*A*. As of October 2006, 35% of patients with at least one follow-up visit (30 of 87) had died. Censoring at the date of last follow-up visit for the patients who were still alive, median OS was 45 months (95% CI 35.5 to not evaluable [NE]). For all patients, 1-year survival was 87.2% (95% CI 80.1–94.3), and 2-year survival was 69.8% (95% CI 59.5–80.1). Median OS was NE (95% CI 17.3 to NE) for patients who had received GC, NE (95% CI 31.2 to NE) for patients who had received GP, and 42 months (95% CI 20.5 to NE) for patients who had received GCb.

Figure 2*B* summarizes OS by clinical disease stage. Of the 61 patients with stage I disease, OS was NE (95% CI 35.5 to NE). Of the 26 patients with stage II disease, OS was 31 months (95% CI 15.2 to NE). The censorship rate was 68.9% for patients with stage I disease and 57.7% for patients with stage II disease. Survival at 1 year was 88.4% (95% CI 80.3–96.5) for patients with stage I disease and 84.4% for patients with stage II disease. Two-year survival was 73.1% (95% CI 61.4–84.9) for patients with stage I disease and 61.9% (95% CI 41.9–82.0) for patients with stage II disease.

DFS is summarized in Figure 3. Overall, median DFS was 27 months (95% CI 19.4–38.6; 48% censored). Median

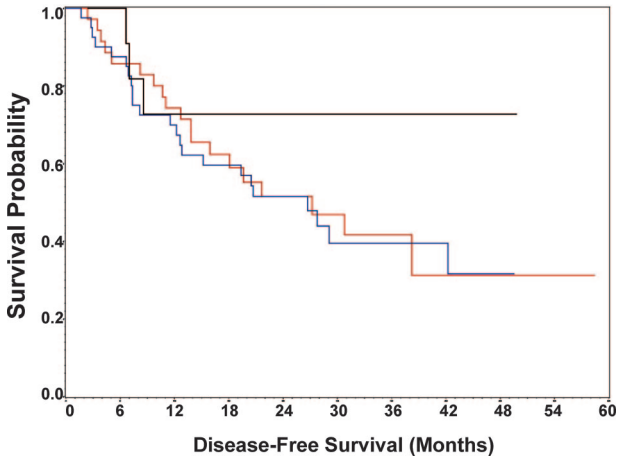

FIGURE 3. Disease-free survival by treatment administered. Black: gemcitabine/cisplatin (n = 12), Red: gemcitabine/paclitaxel (n = 35), Blue: gemcitabine/carboplatin (n = 40).

DFS was NE (95% CI 8.6 to NE) for GC, 27 months (95% CI 13.8 to NE) for GP, and 27 months (95% CI 12.6 to NE) for GCb. For all patients, 1-year DFS rate was 72.1% (95% CI 61.0–82.7). By treatment group, 1-year DFS rate was 72.7% for GC, 74.3% for GP, and 69.9% for GCb. For all patients, 2-year DFS was 57.4% (95% CI 44.4–70.4), with rates of 72.7% for GC, 51.5% for GP, and 51.5% for GCb.

DISCUSSION

Although the overall outcomes available to date in this largely stage IB and stage IIB population are competitive with older trials, the pCR rate when examined as a prospective end point was low, and did not meet the target rate established for these studies. Nonetheless, these studies indicate that even relatively small randomized phase II trials in this setting can characterize the activity of chemotherapy regimens in combined modality settings. The randomized phase II design demonstrated the safety of neoadjuvant chemotherapy as part of either a platinum or nonplatinum doublet, in terms of chemotherapy induction and in the operative safety. Although the design of these independently conducted studies prevented formal statistical comparison of treatment arms, the studies did provide data to assess the activity and the relative toxicities of the three regimens.

For patients undergoing surgery, complete resection rate was 91.5%, which compares with the 89.6% rate reported by Depierre et al.,[20] and the perioperative mortality rate of 2.8% in this study was in the low range of previously reported studies.[20,31,32] As a percentage of the overall ITT population, the complete resection rate was 74.7%, which was lower than the 85.3% rate reported in the Depierre et al. study.[20] The collective results support the premise that preoperative therapy might complement surgical outcomes. Postsurgical morbidity rates were low and comparable across treatment groups. Pain and dyspnea were the most common events within 30 days of surgery.

All three treatment regimens demonstrated clinical activity. CR rates, however, were variable across treatment groups, ranging from 20.0% for GCb to 41.6% with GC. These response rates compare with the 41% rate reported in Southwest Oncology Group (SWOG) 9900.[33] The intent of this trial design was not to evaluate the included regimens against each other; instead the design was to explore the value of each regimen for use in potential future trials. Recent meta-analyses have indicated higher response[34] and survival rates[34–36] with third-generation regimens using cisplatin versus carboplatin in patients with advanced disease. In all patients, survival rates of 87.2% at 1 year and 69.8% at 2 years were promising. Similar studies have reported 1-year survival rates ranging from 69 to 85% and 2-year survival rates ranging from 56 to 65%.[37–41] SWOG 9900, which had a ratio of stage I:II disease of 70%:30%, did seem to be the closest match to the current study. An interim report from that study showed a 2-year survival rate of 69% among patients treated in the neoadjuvant setting.[33] Because of high censorship at the time of data capture, the median survival of 45 months among all patients from the current report was likely underestimated.

Of the three regimens used, GCb was associated with the greatest percentage of patients with dose adjustments and myelosuppression. In contrast, GP was associated with increased alopecia, and GC was associated with increased neurotoxicity. Few grade 4 events occurred in GC or GP, and grade 4 leukopenia and thrombocytopenia occurred with frequencies of 10.0% and 7.5% in GCb, respectively. A recent analysis of 1126 patients receiving front-line GCb in randomized trials found that patients receiving carboplatin at AUC 5 experience approximately half the incidence of grade 4 neutropenia and thrombocytopenia as patients receiving carboplatin at AUC 5.5, without compromising clinical activity.[42] It is possible that the tolerability of GCb in this study could have been improved by dosing carboplatin at an AUC of 5.

Previous studies have correlated pCR rate with survival in neoadjuvant studies.[37] The importance of pCR implies that marked effect on large tumor deposits may translate to an effect on micrometastases. Theoretically, only through control of micrometastatic disease (present in 90% or more of stage III patients, and in more than 20% of stage I patients)[10] can long-term survival for a large number of patients be expected. Thus, improvement of pCR rates through use of systemic therapy is a desired goal in combined modality treatment, and serves as a stringent surrogate marker for the ability to eradicate occult distant metastases.

Unfortunately, the pCR rate observed in the current studies (2.8%) was low. Previous studies of neoadjuvant therapy have produced pCR rates ranging from 6 to 19%.[20,21,29,37] Explanations for low pCR rates in prior studies have focused on the number of cycles administered. However, the Depierre et al. trial[20] used only two cycles of treatment and the Martini et al. trial[29] used either two or three cycles, and the PCR rates in these trials were similar for both groups (11% versus 13%, respectively). Curiously, trials with higher pCR rates included patients with stage III disease, whereas the Pisters et al. trial, which included only patients with stage I or II disease, reported a pCR rate of 6%.[39] It is possible that pCR rates may generally be overestimated. It

may not be surprising that when pCR is prospectively the primary end point and is checked by an independent reference pathologist with prior experience in this area, the verified pCR rate is lower than anticipated.

Ramnath et al. recently reported the results of a phase II study of induction therapy with gemcitabine and vinorelbine in resectable (stage IB to IIIa) NSCLC ($n = 62$).[40] The authors noted that the treatment effect of this combination produced a lower response rate, but an improved toxicity profile, and comparable survival compared with platinum regimens. Ramnath et al. reported a pCR rate similar to that of the current study (2%). Martin et al. also noted promising survival data despite a pCR rate of 4.5% in resectable patients.[38] At the 2007 American Society of Clinical Oncology Annual Meeting, Felip et al. reported preliminary results from the Neoadjuvant Taxol/Carboplatin Hope trial.[43] Among the patients receiving neoadjuvant treatment in the trial, the pCR rate was 9%, and 75% had pathologic N0-1 disease (compared with 73.6% N0-1 in the ITT population of our studies). Given that none of the trials summarized earlier achieved the 20% pCR rate prospectively defined by our statistical methods, it is likely that this goal was overambitious.

The randomized phase II trial design used permitted three regimens to be explored for possible incorporation into future phase III trials. The characterizations of these regimens in patients with stage I and II extent allowed for a rational basis to select or reject particular regimens for larger trials. We feel that this same design will allow other regimens, perhaps adding molecularly targeted agents or based on patient pharmacogenomics, to be explored for suitability for use in neoadjuvant settings. The current trials were troubled by slow patient accrual, especially in the smaller trial. One reason for this was the presentation of positive results from adjuvant studies, which was felt to have had a similar impact of slow accrual on the early-stage neoadjuvant SWOG 9900 trial as well.

The current report focuses on reporting standard clinical end points. Patient end points related to quality of life and pulmonary function were also prospectively collected in patients enrolled in these trials. These analyses will be included in future reports, which may provide additional insight with respect to treatment options. We feel that this trial design is an efficient and practical approach to examining different chemotherapy regimens in a combined modality setting. Clearly, the information derived from several large, randomized studies, such as SWOG 9900,[33] and the Neoadjuvant Taxol/Carboplatin Hope trial,[43] will be of great interest although the LU22 trial recently reported negative results.[44] Mature results from these studies will further delineate the role of neoadjuvant therapy in early-stage NSCLC.

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