Oshita et al. [5] prospectively evaluated the feasibility of cisplatin-based chemotherapy in patients aged 75 years or older. Only 10 (29%) out of the 34 patients fulfilled the eligibility criteria for the cisplatin-based regimen. Furthermore, the majority of these eligible patients had grade 4 neutropenia and infectious episodes requiring antibiotics. In another analysis of cisplatin pharmacokinetics, the area under the plasma concentration versus time curve (AUC) of the ultrafilterable and total plasma platinum increased with age, and this was an independent predictor of cisplatin pharmacokinetics [6]. Therefore, the administration of cisplatin is restricted to highly select elderly patients.

(Glycolate-*O,O'*)-diammine platinum (II) (nedaplatin) is a second-generation platinum analog synthesized by Shionogi & Co., Ltd. (Osaka, Japan). In the preclinical studies, nedaplatin is highly active against solid tumors and has higher aqueous solubility than cisplatin [7–9]. The emesis and nephrotoxicity of nedaplatin are substantially reduced, compared with those of cisplatin, and multiple days of hydration for renal protection are not required [10]. Dose-limiting toxicity (DLT) is thrombocytopenia, and recommended dose in Japanese patient ≤70 years is 100 mg/m^2 every 4 weeks. This agent is active against NSCLC, with a response rate of 20.5% for previously untreated patients [10]. In a pharmacokinetic analysis, thrombocytopenia was significantly correlated with renal function (i.e., creatinine clearance [Ccr]), and nadir platelet count could be predicted from the following formula [11]:

$$[\text{Nadir platelet count}](/\text{mm}^3) = -64,264.7 + 2,783.4 \times [\text{Ccr}](\text{mL/min})$$

We conducted a dose-finding and pharmacokinetic study of nedaplatin in elderly patients with NSCLC, stratified into two groups based on renal function. This study was conducted to determine the recommended dose, and evaluate the toxicity profiles, pharmacokinetics and antitumor activity.

Patients and methods

Eligibility

Patients with histologically and cytologically confirmed chemotherapy-naïve advanced or metastatic non-small cell lung cancer were eligible for this study. Other eligibility criteria included the following: (1) age ≥70 years; (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (3) adequate bone marrow (white blood cell [WBC] count ≥4,000/mm^3, absolute neutrophil count [ANC] ≥2,000/mm^3, hemoglobin level ≥9.0 g/dL and platelet [PLT] count ≥100,000/mm^3), hepatic (serum total bilirubin level ≤1.5 mg/dL, serum asparatate aminotransferase [AST] level ≤100 IU/L and serum alanine aminotransferase [ALT] level ≤100 IU/L), renal (serum creatinine [Cr] level ≤1.5 mg/dL, creatinine clearance [Ccr] ≥40 mL/min) and pulmonary (PaO_2 ≥60 torr) functions.

The exclusion criteria were as follows: (1) symptomatic brain metastasis; (2) pleural or pericardial effusions and ascites requiring drainage; (3) serious pre-existing medical conditions such as uncontrolled infections, severe heart disease, uncontrolled diabetes and psychogenic disorders; and (4) hepatic B or C virus or human immunodeficiency virus infection.

Written informed consent was obtained from all the patients. This study was approved by the Institutional Review Board of the National Cancer Center.

Study design, dosage and dose escalation

This study was designed to determine the recommended dose of nedaplatin for elderly patients with advanced NSCLC, stratified into two groups based on renal function. The primary objective was to determine the recommended dose, and the secondary objectives were to evaluate toxicity profiles, pharmacokinetics and antitumor activity.

Patients were stratified into two groups based on their renal function at the time of study entry: Group A, Ccr ≥60 mL/min; and Group B, 40 ≤ Ccr < 60 mL/min. Ccr was measured on three consecutive days, and the mean value was used for stratification. Each Ccr was calculated using the following formula:

$$\text{Ccr}(\text{mL/min}) = [\text{urine volume}(\text{mL/min}) \times \text{urine creatinine}(\text{mg/dL})]/\text{serum creatinine}(\text{mg/dL})$$

In Group A, the initial dose of nedaplatin was 80 mg/m^2, and this was escalated to 100 mg/m^2. In Group B, the initial dose was 60 mg/m^2, and this was escalated to 80 and 100 mg/m^2. At least three to six patients were enrolled at each dose level, and the unacceptable dose was defined as the dose level at which >50% of the patients experienced DLT. The definition of DLT was as follows: (1) ≥grade 3 leukopenia, neutropenia or thrombocytopenia; (2) ≥grade 3 non-hematological toxicities except for alopecia, nausea and vomiting; (3) ≥grade 3 nausea and vomiting for ≥5 days. The recommended dose was defined as one dose level below the unacceptable dose level in each treatment arm.

Nedaplatin administration

Nedaplatin (Aqupla, (glycolate-*O,O'*)-diammine platinum (II); Shionogi Pharmaceutical Company, Osaka, Japan) was obtained commercially. Premedication, consisting of

3 mg of granisetron and 16 mg of dexamethasone diluted in 100 mL of 0.9% saline, was administered via a 30-minute intravenous (IV) infusion. The calculated doses of nedaplatin in both treatment groups were diluted in 300 mL of 0.9% saline and were administered using a 1-h IV infusion every 4 weeks. Following the nedaplatin administration, 500 mL of 0.9% saline was administered intravenously to provide minimal hydration.

Pretreatment and follow-up evaluation

On enrollment into the study, history and physical examination was performed. Complete differential blood cell count (including WBC count, ANC, hemoglobin and PLT), and clinical chemistry analysis (including serum total protein, albumin, bilirubin, Cr, AST, ALT, gamma-glutamyltransferase, and alkaline phosphatase) were performed. These above were performed at least twice a week throughout the study. Tumor measurement was planned every cycle, and antitumor response was assessed using the WHO standard response criteria. Toxicity was evaluated according to the National Cancer Institute common toxicity criteria (version 2.0).

PK study

Pharmacokinetic (PK) evaluations were performed in all patients during the initial cycle of treatment. Heparinized venous blood samples (7 mL) were taken before infusion, at 30 min and just before the end of infusion, as well as at 15 and 30 min and 1, 2, 3, 5, 7, 11, 23 and 47 h after the end of infusion.

Blood samples were centrifuged immediately at 4,000 rpm for 10 min. One milliliter of plasma was stored at −20°C or below in a polyethylene tube until the measurement of total plasma platinum (total-Pt) concentration. Residual plasma was transferred to an Amicon Centrifree tube (Amicon, Inc., Beverly, MA, USA) and centrifuged at 4,000 rpm for 20 min. Ultrafiltrate of the plasma was taken and stored at −20°C or below in a polyethylene tube until the measurement of the plasma-free platinum (free-Pt) concentration. The total-Pt and free-Pt concentrations were measured using flameless atomic absorption spectrometry, as previously reported [12].

The PK parameters were estimated using a nonlinear least-squares regression analysis (WinNonlin, Version 5.2; Bellkey Science, Inc., Chiba, Japan) with a weighting factor of $1/year^2$. The individual plasma concentration–time data were fitted to one-, two- and three-exponential equations using a zero-order infusion input and first-order elimination (corresponding to a one-, two- and three-compartment PK model). The model was chosen on the basis of Akaike's information criteria [13]. Fitted parameters (coefficients and exponent of exponential equations) were permitted in the computation of the following PK parameters: half life ($t_{1/2}$), area under the plasma concentration versus time curve (AUC), systemic clearance (CL), and volume of distribution at steady state (V_{dss}).

To assess the pharmacodynamic effect, percentage decrease was calculated in WBC, ANC or PLT according to the following formula:

$$\text{Percentage decrease} = [(\text{pretreatment count} - \text{nadir count})/(\text{pretreatment count})] \times 100.$$

These percentages were related to the AUC according to the sigmoid E_{max} model, as follows:

$$\text{Effect}(\%) = [E_{max}(\text{AUC})^k]/[\text{AUC}_{50}^k + \text{AUC}^k] \times 100.$$

A nonlinear least-squares regression using WinNonlin was used to estimate the AUC that produces 50% of the maximum effect (AUC_{50}) and the sigmoidicity coefficient (k).

Results

Patient characteristics

Between June 1996 and July 2001, 39 patients were stratified into two groups (22 in Group A and 17 in Group B) based on their renal functions at entry into the study (Table 1). They received a total of 83 cycles of therapy. The patients comprised 35 males and 4 females with good performance status, and the median age was 76 years in both treatment groups. All the patients were included in the toxicity evaluation. A total of 28 (72%) patients were included in the PK analysis and the remaining 11 (28%) were excluded because of insufficient PK samplings. Eight patients (two from Group A and six from Group B) had stage IIIA disease, but were not candidates for thoracic radiotherapy because of their poor pulmonary function. Six patients (five from Group A and one from Group B) received surgical resections for primary tumors. As much as 21 patients (54%, 12 from Group A and 9 from Group B) had squamous cell carcinoma. Nine patients (4 from Group A and 5 from Group B) received only one cycle of therapy because of progressive disease (PD) and 22 patients (12 from Group A and 10 from Group B) received two cycles of treatment. Among these 22 patients, partial response (PR), stable disease (SD) and PD were observed in 8, 10 and 4 patients, respectively. Five of eight patients with PR, two of ten with SD and one of four with PD received sequential thoracic radiotherapy for primary lesion following two cycles of treatment. Two of ten patients with SD and one of four with PD received palliative

radiotherapy for metastatic lesion. Two of four patients with PD received second-line chemotherapy. The remaining nine patients received supportive care according to the patients' request.

Toxicity

All the 39 patients were included in the toxicity evaluation. Major toxicities were hematological, such as leukopenia, neutropenia and thrombocytopenia, in both groups, and these hematological toxicities increased in severity with increased dose level of nedaplatin. In Group A, 1 (6.7%) out of the 15 patients treated at a dose level of 100 mg/m^2 had grade 3 neutropenia; this dose level was considered to be acceptable (Table 2). In Group B, three (50%) out of six patients treated at a dose level of 80 mg/m^2 had ≥grade 3 hematological toxicities (one with grade 3 neutropenia, another with grade 4 neutropenia and febrile neutropenia, and the other with grade 3 leukopenia, anemia and grade 4 thrombocytopenia). The patient with grade 4 thrombocytopenia required a platelet transfusion. At a dose level of 100 mg/m^2, three (60%) out of five patients had ≥grade 3 hematological toxicities (one with grade 3 leukopenia and neutropenia, another with grade 3 thrombocytopenia and grade 4 neutropenia, and the other with grade 3 leukopenia, thrombocytopenia and grade 4 neutropenia). These three patients had also febrile neutropenia. In Group B, a dose level of 100 mg/m^2 was considered to be unacceptable (Table 2).

Non-hematological toxicities, mainly nausea and anorexia, were generally mild in severity and were not dose limiting in either group (Table 3). Renal toxicity,

Table 1 Patient characteristics

	Group A (Ccr ≥60 mL/min)		Group B (40 ≤ Ccr < 60 mL/min)	
	No. of patients	Percentage	No. of patients	Percentage
Total patients enrolled	22	100	17	100
Assessable for toxicity	22	100	17	100
Assessable for PK analysis	15	68	13	76
Age, median (range), years	76 (70–82)		76 (70–78)	
Sex				
Male	19	86	16	94
Female	3	14	1	6
ECOG PS				
0	6	27	1	6
1	16	73	15	88
2	0	0	1	6
Stage				
IIIA	2	9	6	35
IIIB	4	18	6	35
IV	11	50	4	24
Postoperative recurrence	5	23	1	6
Pathological subtype				
Squamous cell carcinoma	12	54	9	53
Adenocarcinoma	9	41	8	47
P/D carcinoma	1	5	0	0
Dose of nedaplatin (mg/m^2)				
60	–	–	6	35
80	7	32	6	35
100	15	68	5	30
Treatment cycle				
Median (range)	2 (1–5)		2 (1–4)	
1 cycle	4	18	5	29
2 cycles	12	55	10	59
≥3 cycles	6	27	2	12

PK pharmacokinetics, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *P/D carcinoma* poorly differentiated carcinoma

Table 2 Hematological toxicity

Group A (Ccr ≥60 mL/min)	Dose level (mg/m^2), (number of patients)									
	80 (n = 7) Grade					100 (n = 15) Grade				
Event	0	1	2	3	4	0	1	2	3	4
Leukopenia	6	1	0	0	0	12	1	2	0	0
Neutropenia	6	1	0	0	0	8	4	2	1[a]	0
Anemia	4	2	1	0	0	5	7	3	0	0
Thrombocytopenia	7	0	0	0	0	12	2	1	0	0
No. of patients with febrile neutropenia	0					0				
No. of patients with DLT	0					1				

Group B (40 ≤ Ccr < 60 mL/min)	Dose level (mg/m^2), (number of patients)														
	60 (n = 6) Grade					80 (n = 6) Grade					100 (n = 5) Grade				
Event	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Leukopenia	5	1	0	0	0	2	1	2	1[a]	0	2	0	1	2[a]	0
Neutropenia	5	1	0	0	0	2	2	0	1[a]	1[a]	1	1	0	1[a]	2[a]
Anemia	4	1	1	0	0	3	1	1	1[a]	0	1	2	2	0	0
Thrombocytopenia	6	0	0	0	0	3	1	1	0	1[a]	2	1	0	2[a]	0
No. of patients with febrile neutropenia	0					1					3				
No. of patients with DLT	0					3					3				

[a] DLT

characterized as an increase in Cr, was also mild, and only one out of five patients treated at a dose level of 100 mg/m^2 in Group B had a grade 2 Cr increase. Considering the toxicity profiles, the recommended doses in Groups A and B were determined to be 100 and 80 mg/m^2, respectively.

Response and survival

The antitumor response was assessed in all the 39 patients (Table 4). Of the 39 patients who achieved PR, 13 had an overall response rate of 33%. Similar antitumor responses were observed in both treatment groups; that is, 6 (27%) of 22 and 7 (41%) of 17 patients had PRs in Groups A and B, respectively. Furthermore, 12 of the 13 patients with PRs in both groups had squamous cell carcinoma, and the response rate among patients with squamous cell carcinoma was 57%. Survival follow-up was completed in all the enrolled patients. The median survival time was 11.2 months (95% confidence interval: 7.7–14.6 months), and the 1-, 2- and 5-year survival rates were 46, 23 and 5%, respectively.

Pharmacokinetics

Pharmacokinetic analysis was performed using data from 28 (72%) of the 39 patients. The first patient enrollment in both treatment groups was started in 1996, and techniques of the sample centrifuging and measurement were not fully developed at the beginning of this pharmacokinetic study. Therefore, the remaining 11 patients (28%) were excluded for pharmacokinetic analysis. The mean plasma concentration–time profiles of total-Pt and free-Pt of nedaplatin are illustrated in Fig. 1. The plasma disappearances of total-Pt and free-Pt were biphasic, and the mean terminal half lives in all the assessable patients averaged 6.28 and 3.57 h, respectively. The C_{max} and AUC of the total-Pt and free-Pt tended to increase with the dose of nedaplatin. The AUCs of the total- and free-Pt at a dose of 100 mg/m^2 in Group A seemed similar to those at a dose of 80 mg/m^2 in Group B (Table 5), and there were no significant differences between these two treatment subgroups (P = 0.293 for total-Pt AUC and P = 0.336 for free-Pt AUC). Furthermore, the AUCs of free-Pt at the recommended doses in both groups (i.e., 100 mg/m^2 in Group A and 80 mg/m^2 in Group B) seemed also similar to that in patients aged 70 years or under who had been treated with 100 mg/m^2 of nedaplatin [14]. In the sigmoid Emax model assessing the pharmacodynamic effect of nedaplatin, the percentage decrease in the neutrophil counts were well correlated with the total-Pt (r = 0.652) and free-Pt (r = 0.723; Fig. 2).

Table 3 Non-hematological toxicity

Group A (Ccr ≥60 mL/min)	Dose level (mg/m^2), (number of patients)									
	80 (n = 7) Grade					100 (n = 15) Grade				
Event	0	1	2	3	4	0	1	2	3	4
Nausea	5	1	1	0	0	3	9	3	0	0
Vomiting	6	1	0	0	0	15	0	0	0	0
Anorexia	5	1	1	0	0	7	4	4	0	0
Diarrhea	6	1	0	0	0	14	1	0	0	0
Stomatitis	7	0	0	0	0	15	0	0	0	0
Hyperbilirubinemia	6	0	1	0	0	15	0	0	0	0
AST increase	6	1	0	0	0	13	2	0	0	0
ALT increase	6	1	0	0	0	13	2	0	0	0
ALP increase	7	0	0	0	0	15	0	0	0	0
Cr increase	7	0	0	0	0	15	0	0	0	0

Group B (40 ≤ Ccr < 60 mL/min)	Dose level (mg/m^2), (number of patients)														
	60 (n = 6) Grade					80 (n = 6) Grade					100 (n = 5) Grade				
Event	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Nausea	1	4	1	0	0	1	3	2	0	0	1	1	3	0	0
Vomiting	6	0	0	0	0	5	1	0	0	0	5	0	0	0	0
Anorexia	4	2	0	0	0	1	3	2	0	0	1	1	3	0	0
Diarrhea	6	0	0	0	0	5	1	0	0	0	5	0	0	0	0
Stomatitis	6	0	0	0	0	6	0	0	0	0	5	0	0	0	0
Hyperbilirubinemia	6	0	0	0	0	6	0	0	0	0	4	0	1	0	0
AST increase	4	2	0	0	0	5	0	1	0	0	4	0	1	0	0
ALT increase	5	1	0	0	0	5	0	1	0	0	4	0	1	0	0
ALP increase	6	0	0	0	0	5	1	0	0	0	5	0	0	0	0
Cr increase	6	0	0	0	0	4	2	0	0	0	4	0	1	0	0

AST asparatate aminotransferase, *ALT* serum alanine aminotransferase, *ALP* alkaline phosphatase, *Cr* creatinine

Discussion

In this dose-finding study, we evaluated the toxicities, pharmacokinetics as well as antitumor activity, and determined the recommended doses of nedaplatin for elderly patients with advanced NSCLC based on renal function. The predominant toxicities were hematological, such as leukopenia, neutropenia and thrombocytopenia, in both groups. These hematological toxicities tended to increase in severity with the increased dose level of nedaplatin. Non-hematological toxicities were acceptable and those were not dose limiting in either group. The recommended dose was determined as 100 mg/m^2 every 4 weeks in elderly patients with a renal function of Ccr ≥ 60 mL/min, which is the same dose recommended for patients aged ≤70 years. On the other hand, for elderly patients with a renal function of 40 ≤ Ccr < 60 mL/min, the recommended dose was 80 mg/m^2 every 4 weeks. In this study,

Table 4 Response

Group	Dose level (mg/m^2)	No. of patients	Response				PR	
			CR	PR	SD	PD	Sq.	Non-sq.
Group A (Ccr ≥60 mL/min)	80	7	0	2	3	2	2	0
	100	15	0	4	6	5	4	0
Group B (40 ≤ Ccr < 60 mL/min)	60	6	0	3	2	1	2	1
	80	6	0	3	1	2	3	0
	100	5	0	1	1	3	1	0
Total		39	0	13	13	13	12	1

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *Sq.* squamous cell carcinoma, *Non-sq.* non-squamous cell carcinoma

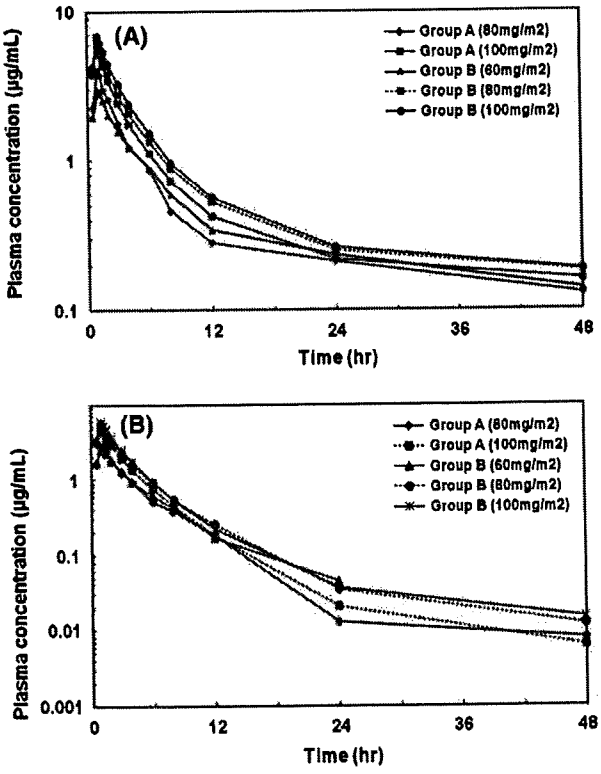

Fig. 1 Mean plasma concentration–time profiles for: **a** total-Pt and **b** free-Pt of nedaplatin

an additional nine patients were enrolled at the dose level of 100 mg/m^2 in Group A. First, the favorable antitumor response was observed in squamous cell carcinoma and we intended to evaluate the antitumor response mainly for squamous cell carcinoma. Then, five of nine additional patients enrolled had squamous cell carcinoma. Second, the recommended dose was determined as 100 mg/m^2 in Group A, which was the same dose in younger patients. We intended to confirm the toxicity and pharmacokinetic profiles in this elderly subgroup.

In the development of chemotherapy for elderly patients, the selection of appropriate agents is extremely important. Candidate agents must have confirmed antitumor activities and acceptable toxicity profiles in younger patients (e.g., aged ≤70 years). In this study, we investigated nedaplatin as it had a lower incidence of associated emesis and nephrotoxicity, compared with cisplatin, and favorable antitumor activity in NSCLC patients aged ≤70 years. Furthermore, the current standard treatment for elderly patients with advanced NSCLC, that is, third-generation single-agent chemotherapy such as vinorelbine, gemcitabine or docetaxel, had not been established at the time of planning of the study [15–17]. The DLT of nedaplatin in patients aged ≤70 years was reported to be thrombocytopenia, which is correlated with renal function; therefore, we expected that nedaplatin could be safely administered to elderly patients by stratifying the patients according to renal function. Patients with a Ccr ≥40 mL/min were eligible for inclusion in this study based on the results of a previous PK analysis examining the correlation between the nadir platelet count and renal function (described in "Introduction") [11]. When younger patients with a Ccr ≥40 mL/min were treated with 100 mg/m^2 of nedaplatin, the predicted nadir platelet count was ≥50,000/mm^3. Therefore, the initial doses of nedaplatin in Group A (Ccr ≥60 mL/min) and Group B (40 ≤ Ccr < 60 mL/min) were determined to be 80 and 60 mg/m^2, respectively. The dose escalation over 100 mg/m^2 was not planned, because the recommended dose in younger patients (aged ≤70 years) had already been determined at 100 mg/m^2.

In this study, milder criteria of DLT was applied, compared with that used in conventional phase I studies. In this developmental strategy, we pursued "the recommended dose with moderate and acceptable toxicities for the majority of elderly patients", instead of "the recommended dose with the severe toxicities in a small and limited number of patients, as per most conventional phase I studies", because the physiological and pharmacological function of elderly patients is highly variable.

Table 5 Pharmacokinetic parameters of total-Pt and free-Pt

Group	Dose level (mg/m^2)	No. of patients	No. of assessables for PK analysis	C_{max} (μg/mL)	AUC (μg/mL h)	V_{dss} (L)	$T_{1/2}$ (h)	CL (L/h)
PK parameters of total-Pt								
Group A (Ccr ≥60 mL/min)	80	7	2[a]	4.02 (3.49, 4.57)	22.58 (13.46, 31.69)	64.24 (35.27, 93.21)	14.15 (3.25, 25.04)	6.00 (3.60, 8.40)
	100	15	13	5.94 ± 1.38	21.65 ± 4.54	31.50 ± 13.40	3.28 ± 1.35	7.63 ± 1.74
Group B (40 ≤ Ccr < 60 mL/min)	60	6	2[a]	3.02 (2.91, 3.12)	19.78 (14.87, 24.68)	57.05 (33.21, 80.89)	10.77 (4.08, 17.46)	5.21 (4.16, 6.25)
	80	6	6	6.35 ± 1.11	25.99 ± 9.68	29.29 ± 13.18	7.88 ± 8.97	6.10 ± 1.13
	100	5	5	6.83 ± 1.20	32.11 ± 7.86	32.84 ± 22.00	6.62 ± 4.55	5.01 ± 1.57
PK parameters of free-Pt								
Group A (Ccr ≥60 mL/min)	80	7	2[a]	2.72 (2.13, 3.31)	10.56 (7.05, 14.06)	42.30 (37.98, 46.62)	3.49 (2.70, 4.28)	12.08 (8.11, 16.04)
	100	15	13	5.11 ± 1.51	16.20 ± 3.34	32.26 ± 11.17	3.51 ± 4.02	10.26 ± 2.46
Group B (40 ≤ Ccr < 60 mL/min)	60	6	2[a]	2.55 (2.46, 2.64)	11.59 (11.38, 11.79)	49.33 (33.22, 65.43)	6.16 (2.98, 9.34)	8.45 (7.89, 9.01)
	80	6	6	5.52 ± 1.25	18.53 ± 7.12	29.51 ± 9.11	3.40 ± 0.65	7.25 ± 2.21
	100	5	5	5.91 ± 1.21	20.69 ± 5.52	29.63 ± 12.32	2.92 ± 0.66	7.87 ± 2.71
Patients ≤70 years [14]	100	5	5		15.9			

Data are shown as mean ± SD excepting the dose level of 80 mg/m^2 in Group A and 60 mg/m^2 in Group B

PK pharmacokinetics, *total-Pt* total platinum, *free-Pt*, free platinum, C_{max} maximum plasma concentration, *AUC* area under the plasma concentration versus time curve, V_{dss} volume of distribution at steady-state, $T_{1/2}$ terminal half life, *CL* systemic clearance

[a] Data are shown as mean (actual data)

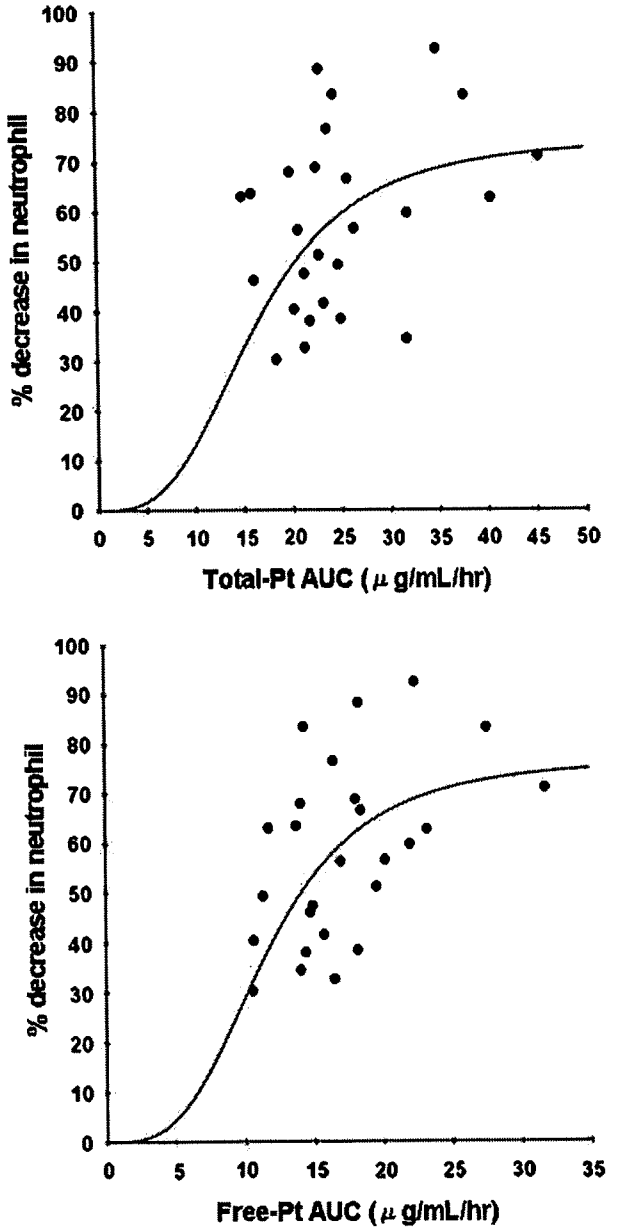

Fig. 2 Relationship between AUCs of total/free-Pt and the percentage decrease in the neutrophil count

In the pharmacokinetic analysis, the free-Pt AUC at a dose of 100 mg/m^2 in Group A seemed similar to that of 80 mg/m^2 in Group B, and there was no significant difference between these two treatment subgroups ($P = 0.336$). These results endorsed an almost equivalent drug exposure in both patient groups, stratified according to renal function. Furthermore, the AUC values in both groups seemed similar to historical data (obtained in a study with a small sample size) for patients aged ≤70 years [14]. However, a significant correlation was not observed between the renal function (i.e., the Ccr value) and the nadir platelet count, as in a previous report examining younger patients. These were possibly attributed to the wide inter-patient physiological and pharmacological variability among elderly patients or just the consequence of the adaptation of dose [11]. For elderly patients, a strict dose calculation of nedaplatin based on renal function, such as the dose calculation for carboplatin using the Calvert formula [18], is not required, and a simple dose selection of nedaplatin stratified according to renal function is considered to be reasonable.

A total of 13 (33%) of the 39 patients achieved partial responses. In this study, 21 patients with squamous cell carcinoma were enrolled, 12 patients achieved PR and the response rate was 57%. The biological mechanism responsible for the antitumor activity of nedaplatin against squamous cell carcinoma of the lung remains unknown. In the pharmacokinetic analysis, no significant differences were observed in responding patients with squamous cell carcinoma compared with non-responding others. However, nedaplatin also has a favorable antitumor activity against head and neck cancer and esophageal cancer, which also have a high frequency of squamous cell histology [19–22]. Although antitumor activity was evaluated only in elderly patients in this study, the development of this activity is worthwhile in the treatment of NSCLC with squamous cell histology. Furthermore, a translational study to identify the biological and/or genetic mechanism responsible for the antitumor activity of nedaplatin against squamous cell carcinoma is also warranted.

In conclusion, the recommended doses of nedaplatin for elderly patients with NSCLC were determined based on renal function, a dose of 100 mg/m^2 every 4 weeks was recommended for patients with a Ccr ≥60 mL/min, and a dose of 80 mg/m^2 every 4 weeks was recommended for patients with 40 ≤ Ccr < 60 mL/min. Nedaplatin can be safely administered to elderly patients with an acceptable level of toxicity and favorable antitumor activities against NSCLC, especially squamous cell carcinoma.

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Cooperative Group Research Endeavors in Small-Cell Lung Cancer: Current and Future Directions

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Abstract

The International Lung Cancer Congress (ILCC), now in its ninth year, is a key forum for representatives of cooperative groups in North America, Europe, and Japan to discuss ongoing and planned clinical trials in lung cancer. Many of the significant strides in lung cancer treatment often originate from investigations designed within the cooperative group system and were a feature of the 2008 ILCC. Small-cell lung cancer (SCLC) represents 15% of all lung cancers diagnosed annually and is characterized by rapid growth kinetics, disseminated metastases, and development of chemotherapy resistance. Many questions remain regarding the optimal use of radiation therapy and approaches for enhancing the effects of chemotherapy to improve clinical outcomes. Herein, we explore and outline the scientific vision of each cooperative group's SCLC research portfolio, as presented at the 2008 ILCC. Highlights include an ongoing Intergroup phase III study exploring differing radiation therapy schemes for limited-stage SCLC and a Southwest Oncology Group 0124 trial establishing platinum/etoposide as the standard of care for untreated extensive-stage SCLC in North America. Continued research efforts sponsored by these groups will represent the future of SCLC diagnosis and management.

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Introduction

Lung cancer is a strikingly prevalent malignancy and is the leading cause of cancer-related death in worldwide. Small-cell lung cancer (SCLC) represents 15% of all lung cancers, and in 2009, an estimated 32,000 new cases will be diagnosed in the United States.[1] Small-cell lung cancer is characterized by aggressive growth kinetics and disseminated metastases, with 60%-70% of patients presenting with advanced- (or "extensive-") stage disease. Despite high initial tumor response rates following platinum-based chemotherapy, SCLC rapidly develops drug resistance, subsequently leading to tumor progression and patient death. Unfortunately, progress in SCLC management has been agonizingly slow, with a glaring lack of therapeutic advances, despite a wealth of new chemotherapeutic drug classes and targeted agents. With median survivals of 7-11 months and a 2-year survival rate of < 5% for patients with extensive-stage disease, the need to improve outcomes is apparent.[2]

The US cooperative groups, sponsored by the taxpayer-supported National Cancer Institute, as well as cooperative groups from Canada, Europe, and Asia, all play a critical role in overcoming the slow progress in SCLC drug development by incorporating SCLC-specific clinical trials into their respective research portfolios. Within the United States, there are 4 general oncology cooperative groups active in lung cancer research: the Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), North Central Cancer Treatment Group (NCCTG), and the Southwest Oncology Group (SWOG).[3] The CALGB, ECOG, and SWOG include member institutions from throughout the country, whereas NCCTG is a regional cooperative group centered at the Mayo Clinic. Within Canada, the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) oversees cooperative oncology efforts. In addition, a focused cooperative oncology

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group that plays a pivotal role and crosses the US/Canadian border is the Radiation Therapy Oncology Group (RTOG). The 2008 International Lung Cancer Congress (ILCC), now in its ninth year, provides a unique forum to gather representatives from the North American cooperative groups as well as international groups such as the European Organization for Research and Treatment of Cancer (EORTC) and the Japan Clinical Oncology Group (JCOG). This article, the fourth in a series that outlines the scientific vision of each group, will focus on clinical research in SCLC.

To provide a foundation for discussion, one must first consider current treatment perspectives in SCLC. The standard therapeutic approach for patients with limited-stage SCLC (LS-SCLC) who are not candidates for a clinical protocol is 4 cycles of chemotherapy with concurrent thoracic irradiation. Based on its preclinical synergy and superiority in efficacy and tolerability with concomitant irradiation, cisplatin and etoposide chemotherapy has supplanted alkylator/anthracycline–based regimens as the chemotherapy backbone.[4] Thoracic irradiation results in local control and a survival benefit; however, the timing of radiation appears critical.[5,6] For example, early concurrent chemoradiation yields a small, but significant, survival advantage when compared with late concurrent or sequential thoracic irradiation; yet, the optimal radiation dose and fractionation regimen remains controversial.[7,8] For patients with excellent performance status and an adequate baseline pulmonary reserve, administration of twice-daily thoracic irradiation to 45 Gy with cisplatin/etoposide has shown encouraging long-term survival results.[9] However, in practice, this schedule is logistically difficult to administer and yet unknown to be superior to a biologically equivalent dose of a once-daily thoracic irradiation regimen. Patients with LS-SCLC who attain a complete response (CR) after concurrent chemoradiation are offered prophylactic cranial irradiation (PCI) based on a meta-analysis reporting a 5.4% improvement in 3-year overall survival (OS; 20.7% PCI-treated vs. 15.3% control) and a 25% reduction in the incidence of brain metastases (33.1% PCI-treated vs. 58.6% control).[10]

In North America and Europe, the cornerstone of treatment for extensive-stage SCLC (ES-SCLC) consists of platinum (cisplatin or carboplatin) and etoposide chemotherapy. The primary role of radiation therapy is for palliating symptomatic sites of disease. Recently, PCI has been incorporated into the treatment algorithm on the basis of results from a phase III clinical trial randomizing 286 patients with ES-SCLC with any response to initial chemotherapy to either PCI or observation.[11] At 1 year, PCI significantly reduced the incidence of symptomatic brain metastases (14.4% PCI-treated vs. 40.4% control; hazard ratio [HR], 0.27; $P < .001$) and increased OS (27.1% PCI-treated vs. 13.3% control; [HR], 0.68; $P = .003$). Indeed, this has led to the recommendation that PCI be offered for patients with ES-SCLC who respond to first-line chemotherapy, after a thorough discussion of the potential risks and benefits.

Unfortunately, the disease recurs in the majority of patients shortly after initial treatment. Although second-line chemotherapy can result in tumor regression, responses are short-lived, and median survival is often < 6 months.[2] A key factor guiding the selection of future therapy, and its possible efficacy, is the type of response gained after exposure to a first-line platinum-based regimen. Historically, patients are classified into 1 of 3 groups of relapsed disease: platinum sensitive, platinum resistant, or refractory. Platinum sensitivity is arbitrarily defined as a chemotherapy-free interval > 90 days, whereas patients with platinum-resistant disease have recurrent disease within 90 days of completing chemotherapy.[2] Refractory SCLC refers to those who do not respond to, or progress during, first-line chemotherapy. Patients with platinum-resistant and refractory disease are often grouped together and generally have poor responses to subsequent chemotherapy (≤ 10%) and shorter median survivals than patients with platinum-sensitive disease. Although there is no standard second-line treatment option, a number of agents have shown single-agent activity, such as the camptothecin analogues (topotecan, irinotecan), paclitaxel, vinorelbine, and gemcitabine.[2] Multiple-agent regimens, such as retreatment with platinum/etoposide, are also a common treatment choice for platinum-sensitive tumors. In the late 1990s, a randomized phase III trial for patients with recurrent SCLC compared single-agent topotecan with cyclophosphamide, doxorubicin, and vincristine (CAV) and found topotecan to be equally efficacious but with greater palliative effects on common lung cancer symptoms.[12] Topotecan, as a result of its US Food and Drug Administration (FDA) approval for second-line SCLC therapy in platinum-sensitive relapsed disease, has emerged as the standard of comparison in most phase III clinical trials.[13]

These perspectives highlight the current state of SCLC management, which has not changed significantly in the past decade. We will now explore the scientific progress and research endeavors pursued by the large multi-institutional cooperative groups.

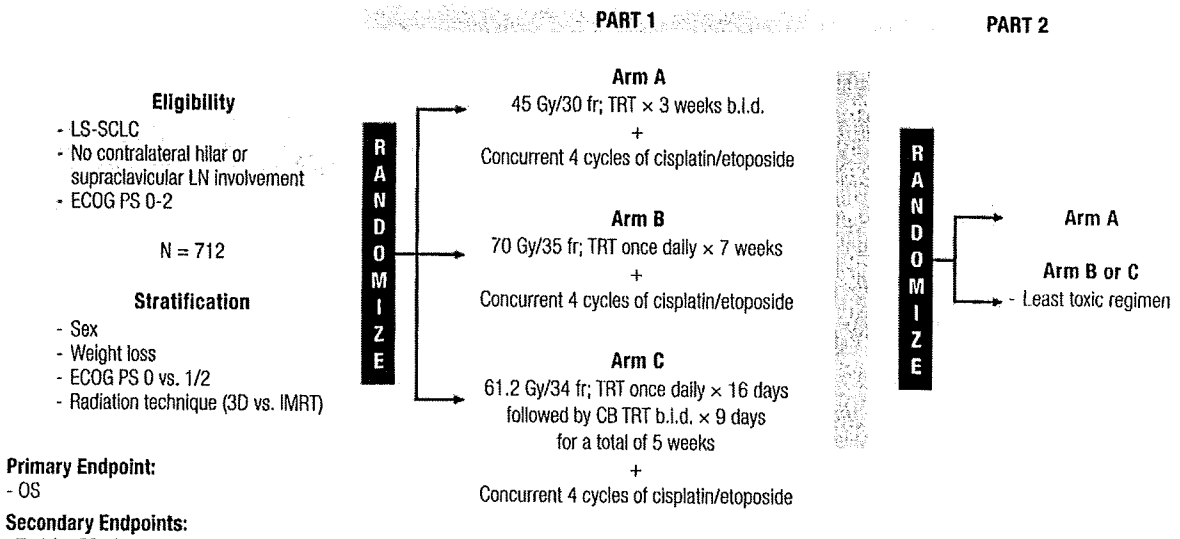
Cancer and Leukemia Group B

In 1987, the CALGB published a seminal report (CALGB 8083) describing the benefits of thoracic irradiation when given concurrently with chemotherapy for patients with LS-SCLC.[14] Improvements in local control, failure-free survival, and OS strengthened the case for shifting the standard of care to a chemoradiation therapy approach. Unfortunately, in 2009, many questions still remain unanswered regarding the optimal dose and delivery of thoracic irradiation.

Cancer and Leukemia Group B has been instrumental in exploring the 70-Gy maximum-tolerated dose (MTD) of once-daily radiation therapy in a phase II setting.[13,15] For example, CALGB conducted CALGB 39808, in which 57 patients with LS-SCLC were treated with 70 Gy in 35 once-daily fractions concurrently with carboplatin/etoposide following 2 cycles of induction paclitaxel and topotecan.[16] The reported 2-year survival was 48%, and the incidence of grade 3 dysphagia was 16%. However, the experience with 70 Gy of concurrent thoracic chemoradiation remains limited and, as a consequence, the de facto practice still calls for once-daily radiation therapy to be delivered at a total dose of 50-60 Gy in 1.8-2.0–Gy fractions.

Hyperfractionating radiation therapy is believed to offer additional clinical benefits. An Intergroup 0096 phase II trial randomized 417 patients to receive 4 cycles of cisplatin/etoposide with either 45 Gy of concurrent thoracic irradiation given twice daily over 3 weeks or once-daily for 5 weeks. Thoracic irradiation was scheduled to coincide with the start of chemotherapy. This pivotal trial found a significant 5-year OS benefit favoring twice-daily

Figure 1 **CALGB 30610/RTOG 0538 Treatment Schema: Phase III Trial Comparing Thoracic Radiation Therapy Regimens in Limited-Stage Small-Cell Lung Cancer**



Abbreviations: 3D = 3-dimensional conformal radiation therapy; b.i.d. = twice daily; CALGB = Cancer and Leukemia Group B; CB = concomitant boost; ECOG = Eastern Cooperative Oncology Group; FFS = failure-free survival; fr = fractions; IMRT = intensity-modulated radiation therapy; LN = lymph node; LS-SCLC = limited-stage small-cell lung cancer; OS = overall survival; PS = performance status; RR = response rate; RTOG = Radiation Therapy Oncology Group; TRT = thoracic radiation therapy

thoracic irradiation compared with once-daily fractionation (26% vs. 16%; $P = .04$) and a lower incidence of local failure (36% vs. 52%; $P = .06$).[9] Grade 3 esophagitis was the most significant toxicity with twice-daily radiation therapy (26% twice-daily vs. 11% once-daily), but the incidence of grade 4 esophagitis did not differ between regimens.

Radiation Therapy Oncology Group has examined an alternative fractionation scheme using a concomitant boost technique to escalate dose while keeping the total treatment duration at 5 weeks. Initially, thoracic irradiation is administered once-daily for 3 weeks, followed by 2 weeks of twice-daily thoracic irradiation. This dose/fractionation regimen is hypothesized to counteract accelerated repopulation, the increased tumor cell growth rate that is known to often occur several weeks into treatment. The MTD for the concomitant-boost technique, when combined with cisplatin/etoposide chemotherapy, has been determined at 61.2 Gy.[17] Thus, there are 3 plausible treatment regimens for delivering concurrent thoracic radiation therapy in LS-SCLC at relatively similar biologically effective doses: (1) CALGB's 70-Gy once-daily fractionation for 7 weeks, (2) the Intergroup 0096 regimen of 45-Gy twice-daily fractionation for 3 weeks, and (3) RTOG's 61.2-Gy concomitant-boost technique for 5 weeks duration.

To address the important radiation therapy questions of optimal dose and fractionation schemes, CALGB 30610, an Intergroup study, has now been developed (Figure 1). This pivotal phase III trial for patients with treatment-naive LS-SCLC is the first of its kind in well over a decade. It consists of 2 parts; part 1 has 3 treatment arms with patients randomized in a 1:2:2 fashion: arm A, 45 Gy (1.5 Gy twice daily × 3 weeks); arm B, 70 Gy (2.0 Gy once daily × 7 weeks); arm C, 61.2 Gy (1.8 Gy once daily × 16 days followed by 1.8 Gy twice daily × 9 days for a total duration of 5 weeks). Four cycles of cisplatin and etoposide are given concurrently, starting on day 1 of radiation therapy for all arms of this study. After interim analysis for toxicity assessment, only 1 experimental arm (arm B or arm C) will be selected for further accrual in part 2 of the study. The primary endpoint will be OS, and the projected total accrual is approximately 712 patients.

Several randomized trials have attempted to build on the platform of platinum/etoposide chemotherapy for ES-SCLC; however, these attempts have been met with disappointing results. For example, the addition of topotecan consolidation, paclitaxel, BEC2 vaccination, or thalidomide to the platinum/etoposide backbone have not shown any significant survival advantage.[18-22] Furthermore, CALGB 30103, a randomized phase II trial, evaluated the Bcl-2 antisense oligonucleotide, oblimersen (G3139), in combination with carboplatin/etoposide in 56 chemotherapy-naive patients with ES-SCLC. Although Bcl-2 is an overexpressed apoptotic inhibitor implicated in SCLC oncogenesis and chemotherapy resistance, CALGB 30103 suggested poorer clinical outcomes for patients who received oblimersen than for those who did not (1-year OS rates, 24% and 47%).[23]

Sunitinib, an oral small-molecule, multitargeted receptor tyrosine kinase inhibitor, has been FDA approved for the treatment of patients with renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumors. It has potent inhibitory effects of the platelet-derived growth factor receptors (PDGFRs)-α and

-β, vascular endothelial growth factor receptors (VEGFRs)-1, -2, and -3, stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT-3), colony stimulating factor receptor (CSF)-1R, and the glial cell line–derived neurotrophic factor receptor (RET). Given its promiscuity in inhibition, sunitinib is hypothesized to affect multiple hallmarks of cancer, including angiogenesis and tumor cell proliferation. CALGB 30504 is an ongoing phase I/II clinical trial investigating the combination of sunitinib plus cisplatin/etoposide for patients with ES-SCLC. The phase I portion of the trial will determine the MTD to be used for the phase II portion. Sunitinib will be given daily concurrent with 6 cycles of cisplatin/etoposide, followed by maintenance sunitinib until the development of progressive disease (PD) or excessive toxicity. The phase II portion of the trial will randomize patients, after initial treatment with sunitinib plus cisplatin/etoposide, to maintenance therapy with either sunitinib or placebo. The primary endpoint will be progression-free survival (PFS), with an accrual goal of 107 patients.

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Bevacizumab, a monoclonal antibody (MoAb) targeting VEGF, has shown to improve survival when combined with chemotherapy in patients with advanced NSCLC, as described in the ECOG 4599 trial.[24] Given these positive results, further evaluation of bevacizumab was felt to be warranted in SCLC because of its high degree of vascularization and VEGF expression.[25] ECOG 3501, a phase II trial of bevacizumab with cisplatin/etoposide in ES-SCLC, has completed accrual. A 21-day cycle of intravenous (I.V.) cisplatin 60 mg/m^2 day 1, etoposide 120 mg/m^2 days 1-3 I.V., and bevacizumab 15 mg/m^2 day 1 was administered for 4 cycles with maintenance bevacizumab given thereafter until PD or unacceptable toxicity. The primary endpoint was to detect an improvement in 6-month PFS from 16% to 33% in 66 patients. Updated survival analysis reported at the 2008 ILCC showed a 6-month PFS of 35% and a 1-year OS rate of 37%.[26] Median PFS and OS were 4.7 months and 11.1 months, respectively. Of the evaluable patients, there were no grade 3/4 hemorrhagic events, despite the known predisposition for SCLC to be centrally located. In another nonrandomized phase II study, CALGB 3036, 72 patients with previously untreated ES-SCLC received a maximum of 6 cycles of cisplatin 30 mg/m^2 days 1 and 8 I.V., irinotecan 65 mg/m^2 days 1 and 8 I.V., and bevacizumab 15 mg/m^2 day 1 without maintenance therapy. The regimen was feasible, and the 1-year PFS and OS rates were 18.3% and 48.9% (median PFS, 7.1 months; median OS, 11.7 months), respectively.[27] VEGF and PDGF levels showed no correlation with response, PFS, or OS. Overall, these studies are forming the rationale for the industry to evaluate bevacizumab in the phase III setting.

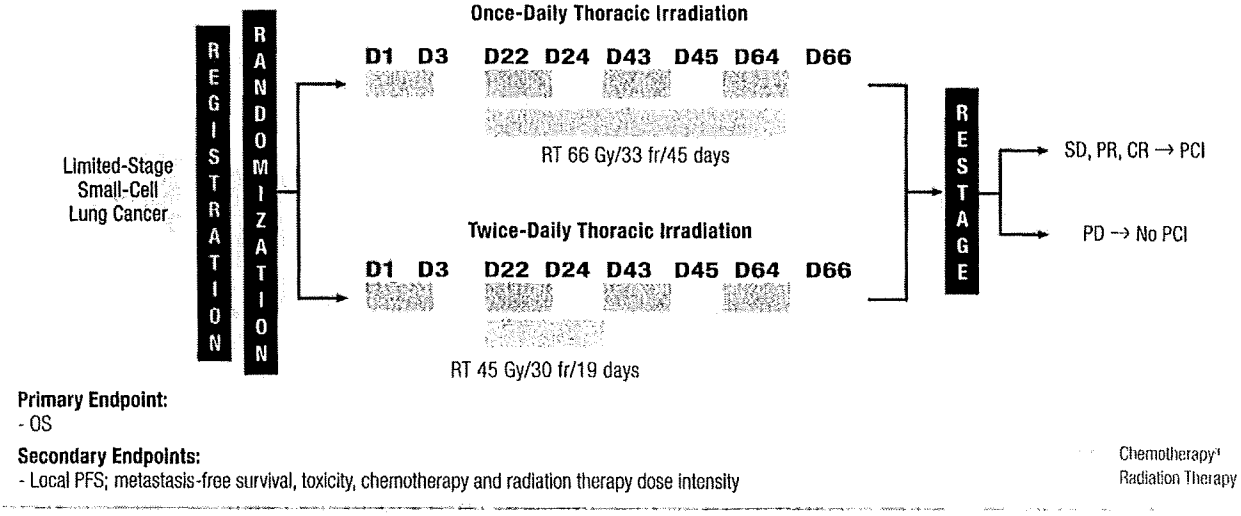
The Hedgehog (Hh) pathway is an essential embryonic signaling cascade implicated as an oncogenic catalyst in a variety of malignancies. There is evidence supporting persistent activation of the Hh pathway in SCLC, and in cell lines treated with a potent Hh inhibitor, cyclopamine, significant growth inhibition has been observed.[28,29] GDC-0449 is an orally bioavailable synthetic inhibitor of Hh signal transduction and has shown safety and clinical benefit in a phase I clinical trial for patients with advanced solid tumors.[30] Similarly, inhibition of the insulin-like growth factor (IGF) pathway is a promising new target with therapeutic efficacy in a variety of tumor models. This pathway is thought to mediate chemotherapy resistance as well as resistance to certain novel agents in SCLC.[31,32] Cixutumumab (IMC-A12), a MoAb targeting the IGF type I receptor (IGF-1R), is in clinical development. ECOG is proposing an ECOG 1508 three-armed, randomized phase II trial to determine "proof of activity." Patients with ES-SCLC will be randomized to receive (1) cisplatin/etoposide alone, (2) cisplatin/etoposide plus GDC-0449, or (3) cisplatin/etoposide plus cixutumumab for a total of four 21-day cycles. PFS is the planned primary endpoint, and the statistical design will include 74 patients per arm to have 85% power to detect a 33% reduction in the HR for PFS, corresponding to a 50% improvement in median PFS from 5.0 months to 7.5 months. Extensive correlative analysis will be integrated within this trial, with particular emphasis on Hh ligand and IGF-1R expression.

European Organization for the Research and Treatment of Cancer

The EORTC extends over multiple European countries and is a key contributor to clinical lung cancer research. Building upon the Intergroup 0096 study in LS-SCLC, the CONVERT (Concurrent ONce-daily VErsus Radiotherapy Twice-daily) trial hypothesizes that increasing the total dose of once-daily thoracic irradiation will improve efficacy and negate the benefit of twice-daily fractionation, thus making the once-daily regimen more practical and logistically easier to deliver. The CONVERT trial is a 2-arm, multicenter, randomized phase III Intergroup trial comparing a once-daily with a twice-daily schedule, given concurrently with cisplatin and etoposide (Figure 2). The radiation therapy regimen put forth by the Intergroup 0096 trial (45 Gy, twice-daily fractionation over 3 weeks) will be compared with 66 Gy, once-daily fractionation over 6.5 weeks. Unlike in the CALGB 30610 trial, thoracic irradiation will commence with the second cycle of chemotherapy. The primary endpoint will be OS, and the goal for accrual is 532 patients within a 4-year time span. The study is currently open in a number of EORTC member institutions.

Amrubicin is a novel cytotoxic agent being evaluated for the treatment of patients with ES-SCLC. It is a completely synthetic 9-amino-anthracycline that is converted to its 13C alcohol metabolite amrubicinol, which has greater antitumor activity than its parent molecule, in stark contrast to the traditional anthracycline derivatives, doxorubicinol and daunorubicinol.[31] Moreover, amrubicin has been found to be less cardiotoxic than doxorubicin in animal models.[33] In a study of patients with refractory and sensitive relapsed SCLC, amrubicin has shown activity as a single agent. The overall response rate (ORR) was approximately 50% in each group, and the median PFS, median OS, and 1-year survival times in the refractory and sensitive groups were 2.6 months and 4.4 months, 10.3 months and 11.6 months, and 40% and 46%, respectively.[34] EORTC 08062 is a phase II trial equally randomizing chemotherapy-naive patients with ES-SCLC to 1 of 3 treatment arms: arm 1, amrubicin 45 mg/m^2 on days 1-3; arm 2, amrubicin 40 mg/m^2 on days 1-3 plus cisplatin 60 mg/m^2 on day 1; and arm 3, cisplatin 75

Figure 2 **Treatment Schema: Phase III CONVERT Trial**



[a]Maximum of 6 cycles of cisplatin/etoposide.
Abbreviations: CONVERT = Concurrent ONce-daily VErsus Radiotherapy Twice-daily; CR = complete response; D = day; fr = fractions; OS = overall survival; PCI = prophylactic cranial irradiation; PD = progressive disease; PFS = progression-free survival; PR = partial response; RT = radiation therapy; SD = stable disease

Table 1 **Japan Clinical Oncology Group Research Portfolio of Ongoing and Proposed Clinical Trials in Small-Cell Lung Cancer**

Protocol Number	Phase	Population	Reference Arm	Experimental Arm	Accrual Target, N	Primary Endpoint
JCOG 0202	III	Treatment-naive LS-SCLC	Cisplatin/etoposide + RT → Cisplatin/etoposide	Cisplatin/etoposide + RT → Cisplatin/irinotecan	250	Overall survival
JCOG 0509	III	Treatment-naive ES-SCLC	Cisplatin/irinotecan	Cisplatin/amrubicin	282	Overall survival
JCOG 0605	III	Relapsed SCLC: sensitive	Nogitecan	Cisplatin/etoposide/irinotecan	180	Overall survival
[a]PC 705	II	Relapsed SCLC: refractory	–	Amrubicin	80	Response rate

[a]Proposed clinical trial in development.
Abbreviations: ES-SCLC = extensive-stage small-cell lung cancer; JCOG = Japan Clinical Oncology Group; LS-SCLC = limited-stage small-cell lung cancer; PC = protocol concept; RT = radiation therapy; SCLC = small-cell lung cancer

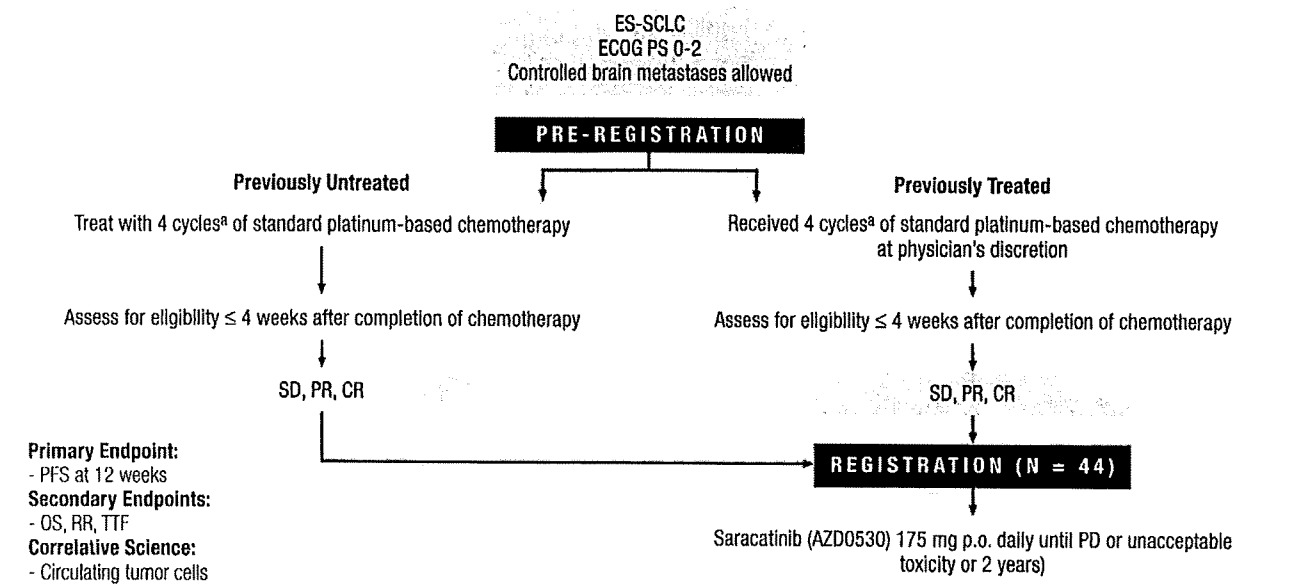
mg/m^2 on day 1 plus etoposide 100 mg/m^2 I.V. on day 1 followed by oral etoposide 200 mg/m^2 on days 2 and 3. In all arms, treatment is repeated every 21 days in the absence of progressive disease or unacceptable toxicity. Patients are stratified based on institution, sex, and performance status. The primary endpoint is RR, with secondary endpoints examining PFS, OS, and toxicity. Amrubicin is already approved in Japan and is currently being investigated in the United States in a multinational, randomized phase III trial for patients with SCLC who do not respond to first-line therapy. Considerable hope exists for this agent, but its role will need to be more clearly defined.

Finally, a proposal is in place for a phase II EORTC 08061 trial treating patients with chemotherapy-naive or sensitive relapsed ES-SCLC. Sunitinib will be given as a single oral agent (150-mg loading dose followed by 37.5 mg daily) until progressive disease. Disease control rate at 4 weeks after the start of treatment will be the primary endpoint.

Japan Clinical Oncology Group

Although there are a number of cooperative oncology groups in Japan, JCOG and the North Japan Lung Cancer Study Group (NJLCSG) are particularly active in SCLC research efforts. JCOG draws from its 190 participating institutions to enroll patients into its trials. In SCLC, there are 3 ongoing phase III trials, in addition to 1 phase II protocol in development that is evaluating amrubicin in the relapsed/refractory setting (Table 1). However, the featured trial at the 2008 ILCC was NJLCSG 0402, a randomized phase II trial comparing amrubicin with topotecan in previously treated SCLC. Sixty patients, stratified according to performance status and type of relapse (chemotherapy sensitive or refractory), were randomly assigned to receive amrubicin 40 mg/m^2 days 1-3 or topotecan 1 mg/m^2 days 1-5 for a minimum of three 21-day cycles. The primary endpoint of ORR was 38% for the amrubicin arm and 21% in the topotecan arm.[35] In sensitive relapse, the ORRs for amrubicin and topotecan were 53% and 21%, and in refractory relapse, 17% and 0%, respectively. There were no significant advantages of either therapy in median PFS and OS. Neutropenia was severe for those treated with amrubicin, with 79% of the patients experiencing grade 4 neutropenia and 14% of the patients experiencing febrile neutropenia. Moreover, 1 treatment-related death was observed resulting from sepsis. Encouragingly, amrubicin has activity, particularly in chemotherapy-refractory relapse, which is

Figure 3 NCCTG 0621 Treatment Schema: Phase II Trial of Saracatinib (AZD0530) in Extensive-Stage Small-Cell Lung Cancer



[a]1 cycle = 21 days.
Abbreviations: CR = complete response; ECOG = Eastern Cooperative Oncology Group; ES-SCLC = extensive-stage small-cell lung cancer; NCCTG = North Central Cancer Treatment Group; OS = overall survival; PD = progressive disease; PFS = progression-free survival; p.o. = orally; PS = performance status; RR = response rate; SD = stable disease; TTF = time to treatment failure

notoriously difficult to treat. Results are limited by the small sample size but still warrant further evaluation in larger-scale trials.

North Central Cancer Treatment Group

The NCCTG is a regional cooperative network based in the Mayo Clinic in Minnesota with a number of centers scattered across the United States, Canada, and Puerto Rico. The NCCTG customarily focuses on phase II clinical trial designs with novel therapeutic agents and also participates in Intergroup protocols such as the ongoing CALGB 30610 trial described earlier. The NCCTG research portfolio recently featured a phase II NCCTG 0621 trial evaluating a novel oral c-SRC inhibitor, saracatinib (AZD0530), administered daily in nonprogressing patients with ES-SCLC who received a maximum of 4 cycles of standard platinum-based chemotherapy (Figure 3). The trial was designed for a primary endpoint of 12-week PFS, and secondary endpoints included RR, OS, and time to treatment failure. Incorporated within the study is an intriguing analysis of the effects of saracatinib treatment on the levels of circulating tumor cells (CTCs) as well as correlative science attempting to determine potential predictive markers of response in CTCs. Complete analysis of the results are eagerly anticipated.

National Cancer Institute of Canada Clinical Trials Group

The NCIC-CTG is the only adult cooperative oncology group based in Canada with a national membership supporting a spectrum of clinical trials ranging from phase I testing of novel therapeutic agents to the conduct of large, randomized, controlled phase III trials. The importance of its contributions to the treatment of lung cancer is well recognized. Historically, the NCIC-CTG has been an active participant of SCLC trials initiated by other cooperative groups. NCIC-CTG BR.28, also known as the previously described CONVERT trial, is one such effort that has recently opened to accrual in NCIC-CTG member institutions.

Radiation Therapy Oncology Group

In lung cancer, RTOG research endeavors are intended to decipher the optimal methods of using radiation therapy in a consistently effective and safe manner. Besides being a key collaborator in the CALGB 30610 trial, designated as RTOG 0538 within the group, RTOG has been instrumental in discerning the best method of delivering PCI in LS-SCLC. RTOG 0212, closed to accrual in February 2008, was designed to determine the optimal dose of PCI after a meta-analysis suggested a reduced incidence of brain metastases with higher PCI doses. Patients with LS-SCLC who were complete responders to primary treatment were randomized to receive standard (25-Gy/10-fraction/12 days) or higher PCI doses (36-Gy) administered using either conventional (18 fractions/24 days) or accelerated hyperfractionated radiation therapy (24 twice-daily fractions/16 days). This phase II/III trial had significant contributions from CALBG, ECOG, EORTC, and SWOG, with results presented at the 2008 American Society of Clinical Oncology meeting. A total of 720 patients were enrolled, and although there was a nonsignificant trend for reduced 2-year brain metastases incidence with high-dose PCI compared with standard-dose PCI (24% vs. 30%; $P = .13$), there was a significantly marked increase in chest relapse (48% vs. 40%; $P = .02$) and mortality (2-year OS 37% with high-dose PCI vs. 42% with standard-dose PCI; $P = .03$).[36] Thus, the prevailing PCI dose of 25 Gy remains the standard of care for LS-SCLC.

Intergroup 0096 showed a survival benefit using an accelerated fractionation schedule compared with daily radiation therapy. RTOG 0239, a phase II trial, evaluated an innovative radiation therapy design where once-daily radiation therapy along with concurrent chemotherapy was given followed by a hyperfractionated schedule, a concomitant boost, in LS-SCLC (61.2 Gy/34 fractions). This schedule was found to be tolerable but was associated with a high incidence of myelosuppression.[37] RTOG 0623 is a phase II trial designed to overcome this adverse event by incorporating filgrastim with concurrent chemoradiation therapy and pegfilgrastim, with adjuvant cisplatin/etoposide chemotherapy in patients with LS-SCLC. Historically, hematopoietic growth factors have not been recommended during combined modality chemoradiation therapy based on early theoretical concerns that growth factors might release progenitor cells and expose them to the damaging effects of radiation therapy, but significant improvements in supportive care and delivery of radiation therapy could make these concerns less applicable. The primary endpoint of RTOG 0623 is to evaluate the safety and efficacy of filgrastim in reducing grade ≥ 3 neutropenia when given with concurrent chemoradiation. Unfortunately, this trial is accruing poorly and is expected to close soon.

Southwest Oncology Group

The premier effort of the SWOG research portfolio in SCLC is the recently reported S0124 phase III trial, a study in which CALGB, ECOG, and NCCTG also participated as part of the Intergroup.[38] This protocol duplicated the treatment regimen of a small phase III study conducted by JCOG (JCOG 9511) demonstrating the superiority of the cisplatin/irinotecan combination over cisplatin/etoposide in patients with chemotherapy-naive ES-SCLC with respect to RR, PFS, and OS.[39] After an interim analysis, the trial was closed to further accrual, with only 154 patients entered. Because of its small sample size and possible effects from pharmacogenomic differences between Japanese and North American populations, further confirmatory studies were prompted.

In a comparative North American and Australian phase III trial directed by the Hoosier Oncology Group, 331 patients were randomized to receive a modified dose schedule of cisplatin/irinotecan or cisplatin/etoposide.[40] The modified treatment regimens were intended to improve delivery, reduce toxicity, and be more consistent with the dosages and schedules administered in the United States.[31] In this trial, there were no differences in outcome between cisplatin/irinotecan and cisplatin/etoposide. Because of the differing dose schedules, questions remained regarding the validity of cisplatin/irinotecan as an optimal regimen for ES-SCLC.

The Southwest Oncology Group sought to conduct a confirmatory, appropriately powered trial (S0124) by designing a similar study to JCOG 9511 by using identical cisplatin/irinotecan and cisplatin/etoposide treatment doses and schedules, thereby determining whether the results were reproducible and relevant to a Western population.[38] Correlative studies were incorporated to seek out the possible role of population-related pharmacogenomic variability in irinotecan metabolism due to genetic polymorphisms. Over a 4-year time span, 671 patients were randomized to receive a maximum of 4 cycles of either cisplatin 60 mg/m^2 on day 1 plus irinotecan 60 mg/m^2 on days 1, 8, and 15 every 28-days or cisplatin 30 mg/m^2 on day 1 plus etoposide 100 mg/m^2 on days 1-3 every 21-days. Patients were stratified based on performance status, number of metastatic sites, weight loss, and lactate dehydrogenase levels. The primary endpoint was OS. Cisplatin/irinotecan efficacy outcomes were similar to cisplatin/etoposide, with an ORR of 60% versus 57%, median PFS of 5.8 months versus 5.2 months (P = .07), and a median OS of 9.9 months versus 9.1 months (P = .71), respectively.[38]

Evaluation of the adverse events between the S0124 and JCOG9511 trials demonstrated a significantly higher hematologic toxicity in Japanese patients compared with North American patients with either treatment regimen ($P \leq .02$), but the incidence of nonhematologic toxicities did not differ significantly. Of those enrolled in the S0124 trial, 142 patient samples were analyzed for pharmacogenetic variability of select genes in irinotecan metabolism performed on genomic DNA from peripheral blood mononuclear cells. Intriguingly, significant correlations for genetic polymorphisms and hematologic and gastrointestinal toxicities were found.[38]

Thus, S0124 did not confirm the results of JCOG9511 in a Western population. The putative mechanisms underlying the differences in efficacy and toxicity are hypothesized to be related to allelic variants of genes involved in irinotecan metabolism. SWOG has confirmed that in North America, platinum/etoposide remains the standard of care for previously untreated ES-SCLC.

The Southwest Oncology Group also recently reported S0435, a phase II study investigating the role of sorafenib in ES-SCLC.[41] Sorafenib, an oral multikinase inhibitor with effects on tumor proliferation and angiogenesis, is FDA-approved for the treatment of advanced renal cell and hepatocellular carcinoma. Patients with ES-SCLC treated with only 1 previous platinum-based chemotherapy regimen were stratified according to platinum sensitivity and treated with sorafenib 400 mg orally twice daily on a continuous basis for a 28-day cycle. Of 80 evaluable patients, 3 patients with platinum-sensitive disease had a partial response (PR; 8%), whereas only 1 patient with platinum-resistant disease had a PR (2%). The stable-disease rates were similar between both groups (32% and 31%, respectively). Median PFS was 2 months for both strata, and OS was 7 months for platinum-sensitive patients and 5 months for platinum-resistant patients. Given these results and the general tolerability of sorafenib, further study of this agent in SCLC is warranted.

Conclusion

Through their capacity to offer a wide range of scientific and patient resources, multi-institutional cooperative groups have a vital responsibility to ensure that significant strides in SCLC research continue to be made. As many SCLC trials have traditionally been underpowered, the importance of large collaborative research efforts to maximize accrual cannot be overemphasized. In addition, the trend to incorporate translational science studies into each trial offers an avenue to discern the underlying mechanisms of SCLC chemotherapy resistance and to perhaps develop future prognostic and predictive biomarker profiles. However, considerable work remains in order to overcome 2 decades of stagnant gains in SCLC management. The focus has shifted to first optimizing the delivery

of known effective treatments, such as thoracic irradiation in LS-SCLC, before expanding upon the paradigm so that therapeutic advances are built on a solid foundation. Moreover, novel targeted agents will certainly be added to the SCLC treatment armamentarium, ideally based on strong preclinical rationale and an appropriate "druggable" target, but to date, no targeted therapy has been approved for patients with SCLC. Indeed, the ongoing and planned research endeavors of the cooperative group system are essential to ensure that the future progress for SCLC management remains encouraging.

Disclosures

Dr. Gandara has served on the Board of Directors or held other leadership positions with Response Genetics, Inc.; has received research funding from Abbott Laboratories, Bristol-Myers Squibb Company, and Eli Lilly and Company; has served as a paid consultant or been on an Advisory Board for AstraZeneca, Bayer Pharmaceuticals Corporation, Genentech, Inc., Pfizer Inc., Response Genetics, Inc., and sanofi-aventis U.S.; and is a member of the Speaker's Bureau for Eli Lilly and Company.

Dr. Saijo has held stock or equity ownership in Takeda Pharmaceuticals.

Dr. Baas has served as a paid consultant or been on an Advisory Board for Hospira; Merck & Co., Inc.; Pfizer Inc.

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Cooperative Group Research Efforts in Thoracic Malignancies 2009: A Review From the 10th Annual International Lung Cancer Congress

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Abstract

Critical advances in the treatment of patients with lung cancer have occurred in the past few years. The cooperative groups in North America and internationally have played crucial roles in these advances. The leaders of the groups meet on a regular basis to review the progress of their trials. However, they rarely have a chance to discuss all ongoing and planned trials, except at the annual Lung Cancer Congress held each June. This article captures this exchange from the 10th Annual Lung Cancer Congress held in June 2009. Exciting efforts are ongoing for all stages of non–small-cell lung cancer, small-cell lung cancer, and mesothelioma. A major focus of the groups at this time is a push toward more personalized medicine, as reflected in the selection criteria for many of the trials, along with planned correlates to better define populations most likely to benefit. Agents targeting the vascular endothelial growth factor (VEGF) pathway, including many tyrosine kinase inhibitors against the VEGF receptor, and those targeting the epidermal growth factor receptor pathway, are under extensive development with many combination trials ongoing.

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Introduction

Progress in therapy for thoracic malignancies has been increasing dramatically in recent years. We have known for some time that chemotherapy improves survival and quality of life compared with best supportive care for advanced-stage disease.[1] Guidelines published by the American Society of Clinical Oncology (ASCO) and the American College of Chest Physicians endorse either a platinum or nonplatinum doublet as initial therapy for patients with good performance status (PS) with newly diagnosed advanced-stage non–small-cell lung cancer (NSCLC).[2,3] For early-stage NSCLC that has been resected, both ASCO and the National Comprehensive Cancer Network endorse cisplatin-based adjuvant chemotherapy for resected stage II and IIIA NSCLC, with controversy surrounding therapy of stage I disease and the use of postoperative radiation therapy.[4-6]

For advanced-stage disease, efforts to add a third drug to the standard 2-drug doublet regimens had not met with success until recent trials that have included bevacizumab and cetuximab, both antibodies targeted to pathways now known to be important in NSCLC.[7-9] These pathways include the vascular endothelial growth factor (VEGF) pathway critical for angiogenesis targeted by bevacizumab and the epidermal growth factor receptor (EGFR) pathway targeted by cetuximab. The benefit of the addition of bevacizumab to chemotherapy was first demonstrated by E4599, a phase III trial led by one of the large cooperative oncology research

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groups of North America, the Eastern Cooperative Oncology Group (ECOG)[8]; the National Cancer Institute of Canada Clinical Trial Group (NCIC-CTG) directed the BR.21, which led to approval of the anti-EGFR targeted agent erlotinib[10]; and one of the key trials showing a benefit from adjuvant chemotherapy in early-stage disease was led by NCIC-CTG,[11] highlighting the critical role the North American cooperative oncology groups, as well as cooperative groups abroad, have played in establishing the current standards of care for patients with NSCLC.

Within the United States, there are 4 general oncology cooperative groups active in lung cancer research sponsored by the National Cancer Institute, with member institutions scattered throughout the country: Cancer and Leukemia Group B (CALGB), ECOG, the North Central Cancer Treatment Group (NCCTG), and the Southwest Oncology Group (SWOG). Within Canada, the NCIC-CTG oversees cooperative oncology clinical trials. More modality-focused cooperative groups in North America (both in the United States and Canada) include the American College of Surgeons Oncology Group (ACOSOG) and the Radiation Therapy Oncology Group (RTOG). Europe has multiple cooperative groups within each country, but the European Organization for Research and Treatment of Cancer (EORTC) works across borders for important trials. Most Asian countries also have cooperative group efforts, with the work in Japan highlighted in this article, particularly that of the Japanese Clinical Oncology Group (JCOG).

The newest advances in lung cancer treatment have been toward more personalized therapy of the disease. Patients with activating mutations in EGFR have a known increased sensitivity to the tyrosine kinase inhibitors (TKIs) that target the pathway, gefitinib and erlotinib. The recently published IPASS (Iressa Pan Asia Study) looked at first-line gefitinib versus chemotherapy for clinically selected patients more likely to have these mutations and found that for those with the mutations, gefitinib improved progression-free survival (PFS) more than chemotherapy.[12] A recent effort from one of the Japanese cooperative groups added further to this observation in a trial that only included patients with EGFR mutations and found a very robust benefit to the first-line gefitinib.[13] Ongoing efforts within other cooperative groups are looking for other markers of benefit from the EGFR inhibitors.

Better selection of specific chemotherapy drugs for individual patients is another area of active investigation within the cooperative group system. The cooperative groups are also focused on novel therapeutic agents, particularly the TKIs targeting VEGF receptor (VEGFR) and others. Most trials looking at novel agents are also designed to determine biomarkers that will predict which patients are most likely to benefit from individual drugs.

This report explores cooperative group research strategies in NSCLC (Tables 1 and 2), small-cell lung cancer (SCLC; Table 3), and mesothelioma as presented at the 10th Annual Lung Cancer Congress. The group's efforts are presented in alphabetical order by group name. Further details about the open studies can be found online at clinicaltrials.gov.

American College of Surgeons Oncology Group

The stated purpose of the ACOSOG is to evaluate the surgical management of patients with malignant solid tumors. ACOSOG includes surgeons and other oncology specialists throughout the United States and internationally. The aims of the thoracic committee of this group are to improve local control in early-stage NSCLC and to enhance therapeutic efficacy through biologic and molecular markers.

Ongoing ACOSOG trials in early-stage NSCLC explore alternatives to lobectomy in patients who are high-risk surgical candidates. Z4032 is a randomized phase III trial of sublobar resection with or without brachytherapy in high-risk patients (based on pulmonary function and medical comorbidity) with stage IA/IB NSCLC ≤ 3 cm in size. Brachytherapy is administered by placement of a mesh with iodine-125(^{125}I) seeds at the resection margin. The study opened in July 2005 and to date has accrued over 200 of the target 226 patients, with completion expected in 2009. The primary and secondary endpoints will be time to local recurrence, treatment-related toxicity, overall survival (OS), disease-free survival (DFS), impact of complete resection, pulmonary function, and quality of life.

Z4033 is a pilot study assessing the efficacy of a nonsurgical local thermal ablation treatment modality, radiofrequency ablation, in patients with stage IA NSCLC who are not operative candidates based on poor pulmonary function or other significant comorbidities. The primary and secondary objectives are local recurrences at 2 years and regional and distant recurrence. The trial opened in September 2006 and, by June 2009, had accrued 43 patients of its target enrollment of 55, with completion expected in 2009.

There are currently 2 proposed studies in ACOSOG for patients with limited mediastinal nodal metastasis. The first is a prospective phase II trial of surgical resection and postoperative chemotherapy in patients with single-station N2 disease by clinical staging studies, ie, computed tomography (CT), positron emission tomography (PET), and mediastinoscopy and/or endobronchial ultrasound transbronchial needle biopsy. This is intended as a feasibility study with the primary objective of evaluating the effectiveness of the above clinical staging modalities. It also includes a correlative science endpoint of predicting chemotherapy sensitivity by genetic markers of chemotherapy resistance in tumor tissue.

The second addresses the role of postoperative radiation therapy (PORT) after resection of clinically early-stage NSCLC with initially unsuspected mediastinal nodal metastasis. Although uncontrolled retrospective studies suggest a survival benefit to PORT in addition to that of postoperative chemotherapy in this setting, prospective, randomized data are lacking. This question is currently being addressed in a large, international, randomized phase III study of PORT versus observation in patients with surgically detected N2 disease, the LungART (Lung Adjuvant Radiotherapy Trial), primarily involving European cooperative groups and participating institutions (discussed further in the EORTC section). The ACOSOG has proposed coordinating a North American Intergroup study of PORT, which will also be a randomized phase III trial comparing PORT (conformal radiation therapy to 50.4 Gy over 6 weeks, with a boost of 10.8 Gy if there is nodal extracapsular extension) with observation. The primary endpoint will be OS, with secondary endpoints of treatment-related toxicity, local control, DFS, and patterns of recurrence.

Although surgery typically is not a primary treatment modality for SCLC, there are data to support its role in very limited stage. A prospective study of surgery for clinical stage IA SCLC is proposed, with