Table 1 Open Cooperative Group Phase III Trials in Early-Stage Non–Small-Cell Lung Cancer

Trial	Subtype and Stage	Treatment	Outcome	Number of Patients
ACOSOG Z4032	Stage I NSCLC, poor PFT	Sublobar resection with or without brachytherapy seeds (^{125}I)	Recurrence	226
CALGB 140503	Stage IA ≤ 2 cm	Lobectomy versus sublobar resection	DFS	1297
CALGB 30506	Stage I 2-6 cm	Observation versus adjuvant chemotherapy; stratification by lung metagene score	OS	1294
ECOG 1505	Resected stage IB-IIIA	4 Cycles of adjuvant chemotherapy with or without bevacizumab	OS	1500
ECOG 5597	Resected stage I	Selenium versus placebo × 4 years	Recurrence	1960
EORTC LungART	Resected N2	With or without postoperative radiation therapy	DFS	700
JCOG0707	Stage I > 2 cm	UFT versus S-1	OS	960
JCOG0802	Stage I < 2 cm	Segmentectomy versus lobectomy	OS	1100
RTOG 0617	Locally advanced	Carboplatin/paclitaxel/XRT with or without cetuximab with or without high-dose XRT (74 Gy)	OS	500

Abbreviations: ^{125}I = iodine-125; ACOSOG = American College of Surgeons Oncology Group; CALGB = Cancer and Leukemia Group B; DFS = disease-free survival; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; JCOG = Japanese Cooperative Oncology Group; NSCLC = non–small-cell lung cancer; OS = overall survival; PFT = pulmonary function test; RTOG = Radiation Therapy Oncology Group; UFT = uracil-tegafur; XRT = radiation therapy

endpoints being clinical to pathologic stage correlation, OS, DFS, and translational research through tissue and serum collection.

Cancer and Leukemia Group B

CALGB 9633 was a crucial trial for our understanding of the adjuvant therapy benefit in stage IB NSCLC. To date, CALGB 9633 is the only large platinum-based adjuvant chemotherapy trial exclusively targeting stage IB disease.[14,15] The study compared surgical resection with or without adjuvant paclitaxel/carboplatin. Though results failed to show a statistically significant OS benefit, patients with tumors ≥ 4 cm in size did appear to have benefit (hazard ratio [HR], 0.66; 90% CI, 0.45-0.97; $P = .04$).[16]

Other early-stage trials by CALGB include the recently completed C39904, looking at dose-escalated, accelerated, 3-dimensional conformal radiation therapy (3D-CRT) in patients with inoperable stage I NSCLC. Ongoing studies include C140203, a phase II trial assessing intraoperative sentinel lymph node mapping using Technetium Tc 99 sulfur colloid in 150 patients with stage I NSCLC, and C140503, looking at lesser resections for small stage I tumors. Lobar resection at this time is the standard approach for stage I NSCLC,[17] but in this era, especially in small peripheral primary tumors, questions have been raised about the necessity of these extensive resections. C140503 is a phase III trial with a target enrollment of nearly 1300 patients, comparing lobectomy with sublobar resection for small stage IA NSCLC (≤ 2 cm in size) with stratifications based on tumor size, histology, and smoking status. Patients are randomized to lobectomy by open thoracotomy or video-assisted thoracoscopic surgery (VATS) versus a wedge resection or anatomic segmentectomy by open thoracotomy or VATS. A preresection mediastinoscopy is required to confirm N0 status by frozen section examination of nodal levels 4, 7, and 10 on the right side and 5, 6, 7, and 10 on the left side.

Another large adjuvant therapy effort led by CALGB is C30506, a randomized phase III trial (N = 1294) for patients with resected stage I NSCLC 2-6 cm in size, who are randomized to observation or adjuvant chemotherapy after complete resection. Patients will be stratified based on a genomics prognostic model known as the lung metagene score (LMS).[18] Patients with a low LMS are felt to be at low risk for recurrence. The study will require fresh tissue collection for RNA extraction.

The CALGB has been a leader in establishing current guidelines for the therapy of stage III NSCLC and the importance of combined chemoradiation. Current efforts include C30106, looking at targeted agents as radiosensitizers, which will lead into 30605, a larger trial of induction chemotherapy with radiation and erlotinib for patients with stage III PS 2; C30407, which assessed novel chemoradiation therapy with or without cetuximab and was presented at ASCO this year[19]; and C30105, assessing high-dose radiation to 74 Gy, leading into C30609, a randomized phase III Intergroup trial discussed further in the RTOG section herein (RTOG 0617).

The eicosanoid pathway has been of particular interest to CALGB. In their first effort to modulate this pathway, the phase II CALGB 30203 trial used carboplatin/gemcitabine as a backbone regimen and added either zileuton, celecoxib, or both.[20] No OS benefit was found in any of the arms in an unselected group, and the study failed to meet its primary endpoint; however, immunohistochemistry (IHC) analysis for COX (cyclooxygenase)-2 indicated that high levels were a positive predictor for benefit with celecoxib (improved survival with an OS HR of 0.294; $P = .004$ for those with elevated COX-2 levels with or without celecoxib) but an overall negative prognostic factor for survival in all patients (OS HR, 2.51; $P = .023$ for elevated COX-2 levels). This result has led to development of CALGB 30801 for patients with previously untreated advanced-stage NSCLC with elevated COX-2 levels who receive a platinum doublet (carboplatin/gemcitabine or carboplatin/pemetrexed at investigators' discretion) and are randomized to celecoxib or placebo until progression. The selection of only those with elevated COX-2 levels is a step toward more individualized patient care.

The TALENT (Tarceva Lung Cancer Investigation outside of the United States) and TRIBUTE (Tarceva Lung Cancer Investigation within the United States) trials of erlotinib plus first-line chemotherapy failed to show a survival advantage with the combination, but the small number of never-smokers in the TRIBUTE study did show an OS advantage with the addition of erlotinib (10.1 months

Table 2 Cooperative Group Phase III Trials in Advanced-Stage Non–Small-Cell Lung Cancer

Trial	Selection	Treatment	Number of Patients
CALGB 30801	Elevated COX-2	Platinum doublet with or without celecoxib	TBD
CALGB 30607	–	Sunitinib vs. placebo maintenance	240
E5508[a]	Nonsquamous	Bevacizumab vs. pemetrexed vs. both as maintenance	TBD
EORTC-EURTAC	EGFR mutation	Erlotinib vs. platinum doublet chemotherapy	146
EORTC-BREC	First-line	Customized chemotherapy by BRCA1	432
WJTOG 3605	First-line	Carboplatin/paclitaxel vs. carboplatin/S-1	600
N0723 MARVEL	Second-line	Erlotinib vs. pemetrexed; stratified by EGFR-FISH	1200
NCIC-CTG BR.29	First-line	Carboplatin/paclitaxel with or without cediranib 20 mg	750
SWOG S0819[a]	EGFR−/IHC+	Chemotherapy (plus bevacizumab if eligible) with or without cetuximab	1545

[a]Planned.
Abbreviations: CALGB = Cancer and Leukemia Group B; COX-2 = cyclooxygenase-2; EGFR = epidermal growth factor receptor; EORTC = European Organization for Research and Treatment of Cancer; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; NCIC-CTG = National Cancer Institute of Canada Clinical Trials Group; SWOG = Southwest Oncology Group; TBD = to be determined; WJTOG = West Japan Thoracic Oncology Group

vs. 22.5 months with erlotinib).[21] CALGB 30406 was designed to further explore this observation and was a randomized phase II study of never-smoker (< 100 cigarettes in their lifetime) and light smoker (< 10 pack-years and quit over 1 year ago) smoker patients with newly diagnosed advanced-stage NSCLC. Patients were randomized to either receive daily oral erlotinib or 6 cycles of carboplatin/paclitaxel plus erlotinib followed by erlotinib. In both arms, the erlotinib was continued until disease progression. The trial is now closed to enrollment and will include extensive correlative evaluation of EGFR mutational status, *EGFR* expression by IHC and fluorescence in situ hybridization (FISH) and *KRAS* mutation status in addition to proteomic analysis.

Cancer and Leukemia Group B is focusing heavily on studies with the VEGFR TKI sunitinib. Sunitinib is approved for the treatment of patients with gastrointestinal stromal tumors and renal cell carcinoma and has demonstrated encouraging single-agent activity in NSCLC.[22] To build on this, 4 randomized trials are either under way or in development using sunitinib. CALGB 30607, a randomized phase III trial of 240 patients, will randomize patients with advanced-stage NSCLC who have stable or responding disease after 4 cycles of a platinum doublet to either sunitinib 37.5 mg/day or placebo. The maintenance therapy (sunitinib or placebo) is continued until disease progression, with a planned follow-up to at least 1 year. Progression-free survival is the primary endpoint. Patients may receive bevacizumab with the 4 cycles of chemotherapy, but the bevacizumab must be discontinued at the time of randomization to sunitinib or placebo. Patients who do not enroll in 30607 are eligible for the randomized phase II study 30704, with a target enrollment of just over 200 patients. This study is also powered to look at PFS but will enroll previously treated patients to receive either pemetrexed alone (500 mg/m^2 every 3 weeks), sunitinib alone (37.5 mg orally daily), or the combination of both agents at full doses. The other sunitinib trials are C30804, which compares sunitinib with pemetrexed in elderly patients (aged < 75 years) with a good PS; C30602, a window-of-opportunity study with the drug in extensive-stage SCLC; and C30504, a randomized phase II study of sunitinib or placebo maintenance after completion of 6 cycles of platinum/etoposide chemotherapy for patients with extensive-stage SCLC.

In SCLC, C30610 is open to patients with limited-stage disease. All patients will receive standard cisplatin/etoposide chemotherapy and prophylactic cranial irradiation (PCI). The randomization is to 1 of 3 radiation strategies, to start with the first cycle of chemotherapy. The 3 radiation regimens are standard 45 Gy twice daily over 3 weeks compared with either 61.2 Gy given on a daily fractionation schedule (no weekends) over 5 weeks or 70 Gy given in daily fractions over 7 weeks. The primary endpoint is OS.

Eastern Cooperative Oncology Group

E1505, which opened in June 2007 with an accrual goal of 1500 patients, has accrued nearly 500 patients to date and is the largest adjuvant trial within the cooperative group system. The study is open to patients with resected stage IB ≥ 4 cm)–IIIA NSCLC of any histology and stratifies by stage, histology, sex, and chemotherapy regimen. A minimum mediastinal lymph node sampling, to include level 7 for all patients, level 4 for right-sided tumors, and level 5 or 6 for left-sided tumors, is required for adequate staging. Patients receive 1 of 4 cisplatin-based doublet regimens for 4 cycles and are randomized to receive either bevacizumab 15 mg/kg every 3 weeks continued for 1 year or no additional therapy beyond the 4 cycles of chemotherapy. The primary endpoint is OS. Extensive correlate studies are planned, with blood and tissue specimens being collected from all patients.

E5597, an ongoing Intergroup chemoprevention trial, randomizes patients with completely resected stage I NSCLC, 6-36 months postresection, to 4 years of selenium supplementation (200 µg as selenized yeast) versus placebo (N = 1960). The study now allows for adjuvant chemotherapy before enrollment. Multiple correlative studies including methylation of p16 and O6-methylguanine-DNA methyltransferase are built into the trial, which is nearing its enrollment goal.

Eastern Cooperative Oncology Group's recent major effort for locally advanced NSCLC was E3598, which looked at the addition of thalidomide to concurrent chemotherapy/radiation, using a carboplatin/paclitaxel backbone. Thalidomide, an antiangiogenic agent, failed to improve either PFS or OS but led to increased thrombosis and will not be further developed in this setting.[23]

Table 3 Small-Cell Lung Cancer Phase III Trials[a]

Trial	Selection	Treatment	Number of Patients
EORTC 08072/BR.26 (CONVERT)	LS	66 Gy daily fractions vs. 45 Gy twice-daily fractions	532
JCOG0202	LS	Cisplatin/etoposide/XRT with consolidation PE vs. cisplatin/irinotecan	250
JCOG0509	ES, first-line	Cisplatin/amrubicin vs. cisplatin/irinotecan	282
JCOG0605	ES, second-line	Nogitecan vs. PE/irinotecan	180
SWOG S0938	ES	PE with or without cediranib	600

[a]Other novel agents in earlier phases of development for SCLC include GDC-0449, Hedgehog pathway inhibitor; cixutumumab (IMC-A12), insulin-like growth factor receptor inhibitor; sunitinib, vascular endothelial growth factor receptor inhibitor; and others.
Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; ES = extensive-stage; JCOG = Japanese Cooperative Oncology Group; LS = limited-stage; PE = platinum/etoposide; SCLC = small-cell lung cancer; SWOG = Southwest Oncology Group; XRT = radiation therapy

The issue of maintenance chemotherapy has become an important topic in the treatment of patients with advanced-stage NSCLC, with several trials now showing an improvement in PFS with this approach[24,25] and 1 showing a definite OS benefit.[25] The question of how long to continue bevacizumab has also been raised repeatedly, and ECOG's attempt to look further at these issues is the E5508 randomized phase III trial for patients with chemotherapy-naive, nonsquamous, bevacizumab-eligible advanced-stage NSCLC. The study will randomize patients who have at least stable disease (SD) after completing 4 cycles of carboplatin/paclitaxel/bevacizumab to bevacizumab alone, or pemetrexed alone, or a combination of the two.

Also building on the E4599 platform but focused in a select group of patients, E2507 is currently in development for patients without a smoking history with previously untreated advanced-stage NSCLC. Eligible patients will receive carboplatin/paclitaxel (with or without bevacizumab, depending on bevacizumab eligibility) with a randomization to receive concurrent erlotinib or not. In the ECOG 2507 trial, all patients receive chemotherapy with randomization to erlotinib or not, in contrast to the otherwise similar CALGB 30406, in which all patients receive erlotinib with randomization to chemotherapy or not. E3503 will also use erlotinib as first-line therapy for NSCLC, building on work with a proteomic analysis that predicts for response to erlotinib.[26]

Other novel agents under investigation include cetuximab and cixutumumab (IMC-A12), an antibody against the insulin-like growth factor receptor-1 (IGF-1R). E4508 randomizes 180 newly diagnosed patients with advanced-stage NSCLC to receive either carboplatin/paclitaxel with cetuximab, cixutumumab, or both in a "pick-the-winner" design looking for a 2-month improvement in PFS. E3508 will also look at the addition of cixutumumab in patients with newly diagnosed advanced-stage NSCLC but with the addition of bevacizumab as well. This randomized phase II study of 180 patients, looking for PFS improvement, randomized patients to receive carboplatin/paclitaxel/bevacizumab (E4599 regimen) with or without intravenous cixutumumab 6 mg/kg weekly.

Eastern Cooperative Oncology Group has recently opened E1508, looking at 2 exciting novel pathways in the therapy of SCLC. This randomized phase II study uses a backbone regimen of cisplatin/etoposide for patients with newly diagnosed extensive-stage SCLC. The 3-arm study includes a reference arm and 2 experimental arms adding either GDC-0449, an inhibitor of the Hedgehog pathway or cixutumumab, the inhibitor of IGF-1R discussed above, to the cisplatin/etoposide backbone.

European Organization for Research and Treatment of Cancer

Nearly every country in Europe has at least 1 country-based cooperative group, and most have 10-20 phase III trials open in NSCLC at the current time. The EORTC spans multiple European countries and has been a leader in several critical lung cancer trials.

There remains significant controversy about the use of PORT for resected stage IIIA NSCLC. Despite guidelines supporting the use of PORT, and encouraging data from a recent subset analysis of the ANITA (Adjuvant Navelbine International Trialist Association) trial[27] and the Surveillance, Epidemiology and End Results database,[28] prospective, randomized data supporting this modality are lacking. The LungART trial (EORTC 2205-08053), initiated by the French cooperative group, will include broad participation by the EORTC, NCIC-CTG, and others. Enrollees are randomized to receive a dose of 54 Gy in 30 fractions to the thorax or no adjuvant radiation therapy after complete resection of stage IIIA (N2 involved) NSCLC. The study is aimed for patients with unexpected N2 disease discovered at the time of surgical resection. Patients are stratified for postoperative (or preoperative) chemotherapy (to be completed before randomization to radiation). Target enrollment is > 700 to show a 10% improvement in 3-year DFS (30%-40%), with extensive correlates included.

Most of the efforts of EORTC in lung cancer are in metastatic disease. A study focused in elderly patients (aged > 70 years), EORTC 08086, is a randomized phase II trial evaluating the standard agent vinorelbine versus albumin-bound paclitaxel.

In the move toward more personalized care, many European groups, including EORTC, will be supporting the EURTAC (European Randomized Trial of Tarceva vs. Chemotherapy) study, led by the Spanish Lung Cancer Group, for newly diagnosed patients with NSCLC with known EGFR-activating mutations comparing first-line erlotinib 150 mg/day versus a standard platinum doublet (4 standard options), followed by a crossover. Additionally, EORTC is participating in the BREC (BRCA1 Expression Customization) trial, also led by the Spanish Lung Cancer Group, which is open to patients with newly diagnosed NSCLC. The study is looking at customizing chemotherapy by assigning therapy to patients on the experimental arm based on RAP80 levels and BRCA1 levels, which

predict response or lack of response to cisplatin and docetaxel, compared with a standard arm of docetaxel/cisplatin for all patients.

In SCLC, there are the EORTC08061 and EORTC08062 trials. EORTC08061 looks at the VEGFR TKI sunitinib 37.5 mg orally daily continuously as either first- or second-line therapy in patients with extensive-stage SCLC. This is a window-of-opportunity type trial in 48 patients (24 first-line and 24 second-line) with stopping after 4 weeks based on PET/CT results at that time. EORTC08062 is a nearly completed randomized phase II study looking at the new anthracycline amrubicin with or without cisplatin versus cisplatin/etoposide. The results of this study will be used to design a randomized phase III trial comparing the winning arm with standard cisplatin/etoposide. EORTC will also participate in the CONVERT (Concurrent ONce-daily VErsus twice-daily RadioTherapy; EORTC 08072) exploring 66 Gy in daily fractions versus the standard 45 Gy in twice-daily fractions with cisplatin/etoposide chemotherapy (radiation start with cycle 2) for limited-stage SCLC. It is hoped that this randomized phase III trial will enroll 532 patients.

The EORTC has also been active in mesothelioma. The results of EORTC08031 were presented at the ASCO 2009 annual meeting. This study looked at using extrapleural pneumonectomy with consolidation radiation after 3 courses of chemotherapy. The study found a 42% success rate as defined by patients being alive and without grade 3 or 4 toxicity at 90 days, which fell short of the predefined 50% success rate needed to call the trial positive.[29] E08052 is an ongoing mesothelioma single-arm phase II study of bortezomib plus cisplatin as first-line therapy and is accruing well, having passed the initial hurdle in a Simon 2-stage design with PFS at 18 weeks as the endpoint.

Japanese Cooperative Groups, Including the Japanese Clinical Oncology Group

For early-stage NSCLC, Japanese cancer cooperative groups have focused on the oral fluorinated pyrimidine uracil-tegafur (UFT) as the adjuvant therapy of choice, especially in patients with stage I adenocarcinoma. Traditionally, the drug has been given for 2 years as daily oral therapy. The HR for survival for UFT given as adjuvant therapy for patients with stage I NSCLC in a meta-analysis of 6 trials (95% stage I, N > 2000) was 0.73 (95% CI, 0.58-0.92; $P = .0066$).[30] The current major adjuvant effort is JCOG0707, open to patients with resected stage I tumors (> 2 cm), who are randomized to either 2 years of UFT or 1 year of S-1 (another 5-fluorouracil derivative) as adjuvant therapy after complete resection (N = 960). The West Japan Thoracic Oncology Group (WJTOG) 0101 study is a recently completed randomized phase III trial (N = 600) of UFT versus gemcitabine as adjuvant therapy, with results pending.

Japanese Clinical Oncology Group has several surgical-based studies for early-stage NSCLC. Patients with ground-glass opacities (GGOs) < 2 cm in size undergo a wide wedge resection, provided there is < 25% of the lesion that is solid. These lesions are considered noninvasive cancer, and the endpoint will be recurrence-free survival. For patients with invasive NSCLC (< 2 cm and ≥ 25% consolidation if the lesion is a GGO), JCOG0802 randomizes patients to limited surgery (segmentectomy) versus lobectomy, each with lymph node dissection (N = approximately 1100). The primary endpoint is OS.

For patients with locally advanced NSCLC, the phase I/II study JCOG0402 will evaluate cisplatin/vinorelbine with radiation followed by gefitinib in 37 patients. JCOG0301 is open for elderly patients with stage III NSCLC to receive radiation alone or in combination with carboplatin, with an OS endpoint (N = 200). The WJTOG recently presented a randomized phase III (WJTOG 0105) trial looking at 3 different platinum-based regimens in combination with radiation therapy in locally advanced disease and found no significant differences between the doublet and triplet regimens, but increased toxicity was observed.[31]

An ongoing randomized phase III trial, WJTOG 3605, randomizes newly diagnosed patients with advanced-stage NSCLC (N = 600) to carboplatin/paclitaxel versus carboplatin/S-1. Another ongoing study, WJOG 5108L, randomized patients, regardless of EGFR mutational status, to gefitinib versus erlotinib (N = 560). WJOG 5208L randomized patients with previously untreated squamous cell lung carcinoma to either receive cisplatin/docetaxel or nedaplatin (N = 250). JCOG has another study of elderly patients in development that will compare docetaxel alone or with cisplatin for patients with newly diagnosed advanced-stage NSCLC.

The North East Japan Gefitinib Study Group, established in 2004, completed an ongoing phase III trial (N = 320) of first-line gefitinib versus carboplatin/paclitaxel for patients with advanced-stage NSCLC with known EGFR-activating mutations. In the end, 98 patients received gefitinib, and 100 patients received chemotherapy. The overall response rate was 75% with gefitinib and 29% with the chemotherapy with a significant improvement in PFS.[13] The WJOG has a similar study, WJTOG3405, limited to patients with exon 19 deletion and L858R mutations within the EGFR, randomized to first-line gefitinib 250 mg/day or cisplatin/docetaxel every 3 weeks × 3-6 cycles. A phase II trial limited to elderly patients aged > 75 years with advanced-stage NSCLC and known EGFR-activating mutations is also ongoing.

The JCOG has 4 ongoing/planned trials in SCLC. JCOG0202 is the primary effort in limited-stage disease. This phase III study of 250 patients will look for an OS benefit for cisplatin/etoposide with concurrent radiation therapy (1 cycle given with twice-daily fractioned radiation) followed by consolidation with 3 cycles of cisplatin/irinotecan compared with the standard cisplatin/etoposide with concurrent radiation therapy followed by consolidation with the same cisplatin/etoposide regimen for 3 cycles. For patients with extensive-stage SCLC, the first-line option is the phase III JCOG0509, which looks for an OS benefit with cisplatin 60 mg/m^2 on day 1 plus amrubicin 40 mg/m^2 days 1-3 compared with cisplatin 60 mg/m^2 on day 1 plus irinotecan 60 mg/m^2 on days 1, 8, and 15 in 282 randomized patients. The chemotherapy is given in 4-week cycles for 4 cycles. For those with sensitive relapsed SCLC, JCOG0605 is a phase III trial for 180 patients comparing nogitecan with the triplet of cisplatin/etoposide/irinotecan. Finally, in patients with refractory/relapsed SCLC, a study in development will look at the response rate in 80 patients receiving single-agent amrubicin.

National Cancer Institute of Canada Clinical Trials Group

The NCIC-CTG BR.10 trial remains one of the most positive adjuvant chemotherapy trials, even now, with 9 years of follow-up.[32]

The follow-up trial, BR.19, explored the use of adjuvant gefitinib and enrolled > 500 patients before closing prematurely in 2005 based on other negative gefitinib trials (ISEL [Iressa Survival Evaluation in Lung Cancer][33] and SWOG 0023[34]). The primary endpoint of OS is expected to be available in the next year or so after a data-lock in April 2009. Extensive correlates with tumor tissue and blood are ongoing. The NCIC-CTG is involved in E1505 as well as E5597. The NCIC-CTG is also leading a separate economic analysis of E1505, with health utilization data collected prospectively for all Canadian patients. The NCIC-CTG will also participate in LungART (BR.27) and CALGB 140503, among other Intergroup efforts.

For patients with medically inoperable localized NSCLC, NCIC-CTG BR.25 is a just-completed study of accelerated hypofractionated 3D-CRT at doses ≤ 60 Gy administered over 2.5-3 weeks. The 80 accrued patients will be followed by 5 years.

First-line advanced-stage NSCLC efforts of the NCIC-CTG thoracic group have been focused on VEGFR TKI cediranib. BR.24, a randomized phase II/III trial of first-line carboplatin/paclitaxel with or without cediranib, met its primary efficacy endpoint in phase II but with excessive toxicity observed in the cediranib arm, despite dose reductions to 30 mg daily (down from 45 mg daily). Based on those results, BR.24 was closed, but BR.29 is now open, using the same randomized phase II/III design but with a 20-mg dose of cediranib.

The predominant second-line effort of the NCIC-CTG thoracic committee will be participation in N0723 (MARVEL). For SCLC, the recently completed BR.20 looked at vandetanib, a dual EGFR and VEGFR TKI. The drug did not show superiority to placebo in this trial and will not be further developed in this manner. For limited-stage SCLC, the NCIC-CTG will participate in the CONVERT trial, discussed in the EORTC section, known within the NCIC-CTG as BR.26.

For mesothelioma, a phase II study of sunitinib is in development. The NCIC-CTG has an extensive team for correlate studies, which are an important part of all trials run within the group.

North Central Cancer Treatment Group

The NCCTG, centered at the Mayo Clinic in Minnesota, has participating centers in 30 states, Puerto Rico, and 2 provinces in Canada. The group is actively participating in the E1505 study for early-stage disease and other Intergroup efforts. For locally advanced NSCLC, N0321 is a phase I/II study examining the use of bortezomib in combination with paclitaxel/carboplatin and radiation therapy. Another trial in development in locally advanced disease, N0921, is for patients aged ≥ 70 years with stage III NSCLC who will receive pemetrexed and cetuximab with concurrent radiation therapy.

The VEGFR TKI sorafenib is being studied as an addition to pemetrexed for second-line therapy of nonsquamous NSCLC in the N0626 trial. This randomized phase II study of pemetrexed with or without sorafenib has reached 50% of the accrual goal. N0528 is a randomized phase II first-line trial of gemcitabine and carboplatin with or without cediranib (AZD2171), another VEGFR TKI. Accrual goal is just under 100 patients, using a dose of cediranib of 30 mg.

N0723, also known as the MARVEL (MARker Validation of Erlotinib in Lung cancer) study, is the largest NCCTG effort. This study, which opened in October 2008, randomizes patients to either erlotinib or pemetrexed as second-line therapy for advanced NSCLC and is focused on whether PFS is improved in subsets of patients based on various biomarkers, in particular EGFR overexpression by FISH. Target accrual is 1200 patients, with the hope of finding 956 with FISH results (required for randomization). It is expected that 30% of the patients will be EGFR FISH positive and 70% will not. The study is now being modified to register patients before initiation of first-line chemotherapy, with the FISH analysis and randomization performed on all patients with ≥ SD after completion of 4 cycles of a platinum doublet. This modification is in accordance with treatment pattern changes with maintenance therapy.

The only cooperative group trial focused on oligometastatic advanced-stage disease is N0724, a phase II study that randomizes patients to either observation or radiation therapy to known sites of disease after completion of 4 cycles of platinum-based chemotherapy. Another focused advanced-stage NSCLC study is N0821, a phase II study of pemetrexed, carboplatin, and bevacizumab in patients with good PS who are aged ≥ 70 years.

Other concepts in development are exploring MK-0426 in advanced-stage squamous cell lung cancer, up-front thoracic radiation therapy in bulky advanced-stage NSCLC, and a phase II study of γ-secretase inhibitor R04929097 in patients with advanced-stage NSCLC.

The NCCTG has a small-cell study examining the IGF-1R antibody cixutumumab in combination with carboplatin and etoposide for extensive-stage NSCLC, N0922. All patients receive 4 cycles of carboplatin/etoposide, and all patients receive maintenance cixutumumab, with a randomization to receive the antibody either concurrently with the chemotherapy or after completion of the chemotherapy. Another small-cell study in development is N0923, using NTX-010, a replication-competent picornavirus, given after completion of chemotherapy.

Radiation Therapy Oncology Group

The stated mission of the RTOG is to improve the survival and quality of life of patients with cancer through the conduct of high-quality clinical trials that focus primarily on optimizing radiation therapy. The RTOG has a broad portfolio of trials in lung cancer from early to locally advanced stages that address the role of treatment intensification through radiation dose escalation or hypofractionation and/or combination with systemic therapies.

In early-stage lung cancer, RTOG 0236 was the first North American cooperative group trial of stereotactic body radiation therapy (SBRT), a treatment modality involving high-precision delivery of highly conformal and dose-intensive radiation therapy to small-volume tumors, as an alternative to resection in strictly medically inoperable patients with peripherally located T1-3 tumors (< 5 cm in size without lymph node or distant metastasis). The dose was 54 Gy (corrected) in 3 fractions over 8-14 days. Between May 2004 and October 2006, the trial completed its target accrual of 55 evaluable patients. As reported at the 2009 World Congress on Lung Cancer, at a median follow-up of 25 months, the 2-year local control was 98% (with a single local failure), regional control was 100% (with 2 regional relapses that occurred after 2 years), and the OS rate was 72%. There were no treatment-related deaths and only 2 protocol-defined grade 4 toxicities.

This has led to the initiation of RTOG 0618, a phase II study of the same SBRT regimen in patients with the same tumor characteristics but who are physiologically able to tolerate complete resection. Since December 2007, the trial has accrued approximately half of its target of 33 patients and is likely to be completed by 2010. If results are encouraging, the plan is to move forward with a randomized phase III trial of surgery versus SBRT.

Because of concerns of increased toxicity of SBRT in more centrally located tumors, the RTOG is also exploring a slightly less dose-intensive approach for tumors close to the proximal bronchial tree. RTOG 0813 is a phase I/II dose-escalation trial designed for medically inoperable patients with centrally located stage I NSCLC, with a starting dose of 50 Gy in 5 fractions. The study was activated in February 2009, with an accrual goal of 94 patients. Future plans include a randomized trial of different dose/fractionation SBRT regimens for medically inoperable early-stage lung cancer.

In locally advanced lung cancer, the RTOG completed a phase I/II study of an escalated radiation dose (74 Gy) with concurrent chemotherapy, RTOG 0117, as well as a phase II trial of escalated systemic therapy (carboplatin/paclitaxel plus cetuximab) with concurrent radiation therapy (63 Gy), RTOG 0324. In both of these studies, patients with predominantly inoperable stage IIIA/IIIB NSCLC had median survival times of 21.6 months and 22.7 months, respectively—highly promising compared with the 17-month median survival observed in RTOG 9410, the study that established concurrent chemoradiation therapy as the standard of care for locally advanced NSCLC in the RTOG. Thus, the RTOG has initiated and is the coordinating group for the Intergroup study RTOG 0617, a 4-arm phase III randomized trial of standard-dose (60 Gy) versus high-dose (74 Gy) radiation with concurrent carboplatin/paclitaxel with or without cetuximab for patients with unresectable stage IIIA/IIIB NSCLC. The study opened in November 2007 and has accrued 123 of 500 planned patients to date.

The RTOG has also coordinated a randomized phase III Intergroup study of PCI versus observation for patients without evidence of brain metastases and without progression after initial treatment for locally advanced NSCLC. RTOG 0214 closed early after failing to meet its original accrual goal of 1058 patients, but analysis of 340 randomized patients revealed a statistically significant reduction of the rate of brain metastasis from 18% to 7.7% at 1 year with PCI.[35] This was at the cost of decreased performance on a verbal learning test in the PCI group, but there was no significant difference in mini–mental status examination and quality of life. With the limited accrual, there was insufficient power to detect a difference in PFS or OS.

Protocols currently under development will focus on multimodality therapy. RTOG 0839 is a proposed study that will study carboplatin/paclitaxel/cetuximab with full-dose concurrent radiation therapy (61 Gy) as preoperative therapy for resectable stage IIIA disease with minimal N2 nodal metastasis. RTOG 0937 is a proposed randomized phase II study of consolidative radiation therapy to thoracic and limited extrathoracic sites after chemotherapy and PCI for extensive-stage SCLC. In addition, all of the currently active and proposed protocols include a translational research component to investigate the predictive and/or prognostic value of blood and/or urine biomarkers.

Southwest Oncology Group

Building on earlier work in superior sulcus (Pancoast) tumors, S0920 will explore the addition of cetuximab to the regimen studied in the recently completed S0220 but will include patients with more advanced disease (IIB, IIIA, and IIIB, including ipsilateral supraclavicular nodal disease, all T3 or T4). Enrolled patients will receive cisplatin 50 mg/m^2 on days 1, 8, 29, and 36 and etoposide 50 mg/m^2 on days 1-5 and 29-33 with concurrent thoracic radiation therapy of 54 Gy (the SWOG standard NSCLC regimen) in combination with cetuximab 250 mg/m^2 weekly after a loading dose. Patients will then proceed to surgical resection, with additional consolidation chemotherapy. The primary endpoint is the pathologic complete response rate.

Also for early-stage NSCLC, SWOG is participating in E1505 and E5597 and has other SWOG-led studies, in particular S0720, focused on personalizing adjuvant chemotherapy. S0720 is founded on work by Zheng et al,[36] as well as others[37] demonstrating that ERCC1 and RRM1 levels provide both prognostic value and predictive value for platinum-based chemotherapy in NSCLC. S0720 will test the feasibility of pharmacogenomically directed adjuvant therapy by accruing patients with completely resected stage I NSCLC (≥ 2 cm in size) and assigning therapy based on assessment of ERCC1 and RRM1 levels from the surgical specimen. The primary endpoint of S0720 is feasibility, defined by the percentage of patients who can be assigned treatment appropriately, reflecting the adequacy of tumor specimen collection and analysis.

Another early-stage NSCLC study is S0424, which is investigating the molecular epidemiology of early-stage NSCLC in smoking and nonsmoking men and women. By performing extensive tissue- and blood-based analyses on multiple pathways, this study assesses the influence of smoking, hormonal factors, and other exposures on sex differences in lung cancer. The study is nearly completed but requires more never-smoking men to finish accrual.

The major first-line NSCLC trial for SWOG is S0819, a phase III trial that will randomize patients to carboplatin/paclitaxel (plus bevacizumab in eligible patients) with or without cetuximab. The 4-drug regimen was studied in S0536 with encouraging results and promising correlate trial work.[38] SWOG's initial work with cetuximab, S0342, combined the agent with carboplatin/paclitaxel in different schedules with favorable results in the concurrent arm, especially in patients with EGFR overexpression by FISH analysis.[39] EGFR FISH analysis will be an important component of S0819, which aims to screen 1545 patients to identify adequate number of patients with EGFR expression by IHC (required for study entry) and 618 FISH-positive patients.

For patients with poor PS with advanced-stage NSCLC, S0709 will evaluate erlotinib versus erlotinib plus chemotherapy using a serum proteomics pattern suggestive of erlotinib benefit.[26] Patients on the chemotherapy arm will received carboplatin/paclitaxel on day 1 then erlotinib on days 2-16 of each 21-day cycle to allow for "pharmacodynamic separation," as previously piloted at University of California, Davis.[40]

Another agent that SWOG is studying is conatumumab (AMG 655), a proapoptotic agent that directly activates TRAIL-TR-2. S0810 will enroll 60 patients per arm who will be randomized to conatumumab 15 mg/kg every 3 weeks or the same dose plus pemetrexed

500 mg/m^2. Conatumumab is also being added to standard first-line cisplatin/pemetrexed chemotherapy either with (S0814) or without (S0813) bevacizumab with maintenance conatumumab in both studies after completion of 6 cycles of chemotherapy. S0814 will also include maintenance bevacizumab. The accrual goal is 70 patients per trial.

In SCLC, SWOG is looking at a trial of large-volume chemoradiation for limited-stage disease (S0908), and in extensive-stage disease, cediranib will be combined with cisplatin/etoposide in a randomized phase III study, S0938. S0938 will enroll 600 patients who will be randomized to standard cisplatin/etoposide chemotherapy with or without cediranib (which will be continued as a single agent after completion of 4 cycles of chemotherapy), with an OS endpoint. The study has embedded marker validation with a biomarker-embedded design. Aflibercept (VEGF Trap) and topotecan combination therapy will be studied for recurrent SCLC in S0802.

Patients with newly diagnosed mesothelioma will be eligible for S0905, which will randomize patients to cisplatin/pemetrexed with cediranib or placebo after completion of the phase I dose-escalation period. This study is building on encouraging single-agent activity of second-line cediranib for mesothelioma in the S0509 study presented at the ASCO 2009 annual meeting.[41] Also in mesothelioma, S0722 is exploring the use of everolimus (RAD001).

Conclusion

The cooperative group system plays a vital role in the advancement of therapy for NSCLC, SCLC, and mesothelioma. The cooperative groups of North America have been pivotal in showing benefit with the anti-VEGF agent bevacizumab and the anti-EGFR drug erlotinib, as well as the importance of adjuvant chemotherapy among other advances. As outlined in this article, the portfolios of the groups and international cooperative groups are full of varied and important studies. The use of an antiangiogenesis approach, as seen in E1505 with adjuvant bevacizumab, in BR.29 with first-line cediranib, and in multiple other trials incorporating anti-VEGFR TKIs, is a primary focus. The groups are also very involved in investigating therapies in the EGFR pathway, including cetuximab, and better understanding of how to use erlotinib and gefitinib in patients with activating mutations and other indicators of benefit such as proteomic profiles.

The cooperative groups provide a mechanism for asking critical questions such as the value of postoperative radiation therapy and the role of lesser resections for smaller stage I tumors that would be very difficult in any other setting. One of the incredible strengths of the cooperative groups is the breadth and depth of translational science possible within trials. This translational strength is seen in the multitude of trials currently active or in development looking at real-time sample analysis of EGFR mutations, RRM1 expression, and others in the move toward personalized therapy. Multiple other targeted agents, including those targeting IGF-1R, Hedgehog, and direct inducers of apoptosis are also in trials within the cooperative group system. Within the context of the cooperative group system, the future of thoracic malignancy therapy looks promising.

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A Phase II Study of Cisplatin and Irinotecan as Induction Chemotherapy Followed by Accelerated Hyperfractionated Thoracic Radiotherapy with Daily Low-dose Carboplatin in Unresectable Stage III Non-small Cell Lung Cancer: JCOG 9510

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Objective: It is important to find optimal regimens of cisplatin (CDDP)-based third-generation chemotherapy and radiotherapy for patients with unresectable Stage III non-small cell lung cancer (NSCLC).
Methods: This Phase II study was designed to determine the toxicity and efficacy of two courses of chemotherapy (CDDP 80 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on days 1 and 8) followed by accelerated hyperfractionated thoracic radiotherapy (60 Gy/40 fractions in 4 weeks) combined with daily carboplatin (CBDCA) administration. CBDCA was administered at a target area under the plasma level–time curve of 0.4 × (24 h creatinine clearance + 25), according to Calvert's formula.
Results: Twenty-six patients were enrolled in the study. The patients' median age was 63 years (range 40–74 years) and included 22 males and 4 females. Seven patients were Stage IIIA and 19 were Stage IIIB. Twenty had a performance status (PS) of 1 versus six with a PS of 0. There was one treatment-related death due to sepsis and pneumonia associated with Grade 4 neutropenia and diarrhea during chemotherapy. Grade 3 or 4 neutropenia and diarrhea were observed in 14 and 5 patients, respectively. Toxicity of the radiotherapy was mild. There were 0 complete response and 13 partial responses, giving a response rate of 50.0%. Median survival time and 2-year survival were 16.4 months and 21.5%, respectively. This study was designed with Simon's two-stage design, and the response rate did not meet the criteria to proceed to the second stage and the study was terminated early.
Conclusions: This regimen might be inactive for patients with unresectable Stage III NSCLC.

Key words: cisplatin – irinotecan – carboplatin – chemoradiotherapy – non-small cell lung cancer

INTRODUCTION

Over the past 2 decades, a great number of clinical trials have gradually proven the benefits of a chemotherapeutic approach for treatment of unresectable non-small cell lung cancer (NSCLC) (1,2). In unresectable Stage III NSCLC, in which the tumor is apparently confined to the chest but is surgically unresectable, several randomized trials have shown that combinations of chemotherapy and thoracic radiotherapy have improved survival compared with radiotherapy alone (3–6). It is important to find optimal regimens of combined chemotherapy and radiotherapy and to evaluate the feasibility and efficacy of those combinations.

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Irinotecan (CPT-11) is an antitumor agent which inhibits the nuclear enzyme topoisomerase I (7,8). CPT-11 has played a significant role in the development of chemotherapy for NSCLC since the initial reports of its efficacy as a single agent (9,10). Combination chemotherapy of CPT-11 and cisplatin (CDDP), which is also a commonly used agent for NSCLC, is a promising regimen for NSCLC, as its high antitumor activity and manageable toxicity have been reproducibly reported (11,12). One critical but uncommon toxicity of CPT-11 is reported to be pulmonary toxicity (10), and it is necessary to clarify how the chemotherapy regimen should be combined with thoracic radiotherapy in patients with Stage III NSCLC.

In addition to combined radio-chemotherapy, concomitant treatment with low doses of radiosensitizers has also been investigated in patients with Stage III NSCLC. Schaake-Koning et al. (13) reported that daily low-dose CDDP combined with thoracic radiation improved the local control of tumors in a randomized study. Furthermore, its favorable results were also confirmed in another Phase II study (14). Carboplatin (CBDCA) has also been investigated as a radiosensitizer (15). It has been suggested that CBDCA may be superior to CDDP in this role because it would provide a greater platinum concentration within cells at the time of irradiation (16). We have reported the concurrent daily CBDCA (25 mg/m^2) and accelerated hyperfractionated thoracic radiotherapy (AHRT) in locally advanced NSCLC (17). Of the 31 patients, the response rate was 84% (26/31) and the median survival time (MST) was 9.8 months. Major acute toxicity (Grade $\geq$3) included 55% with leukopenia, 16% with thrombocytopenia and 23% with esophagitis. Area under the plasma level–time curve (AUC) of CBDCA was significantly correlated with efficacy and leukopenia. In this setting, we concluded that daily CBDCA AUC of 0.4 plus concurrent AHRT was the most effective and safe treatment in locally advanced NSCLC.

On the other hand, the CDDP plus CPT-11 regimen is one of the standard platinum-based combination chemotherapies including a new agent in Stage IIIB/IV NSCLC in Japan (11). Therefore, in order to improve therapeutic outcome in patients with unresectable Stage III NSCLC, we have conducted a Phase II study of a regimen of two courses of CDDP plus CPT-11 as an induction chemotherapy, followed by AHRT with daily low-dose CBDCA administration.

PATIENTS AND METHODS

Patient Selection

Patients with histologically or cytologically confirmed unresectable Stage III NSCLC who had not received cancer therapy were enrolled in this study. Staging for entry criteria was performed according to the lung cancer staging system of the International Union against Cancer. Staging procedures included chest X-ray, computed tomography (CT) scan of the chest, CT scan or magnetic resonance imaging of the brain, CT scan or ultrasound of the abdomen and isotope bone scanning. N-status was mainly based on size criteria in chest CT scan. Patients with pleural or pericardial effusion were excluded from the study. Each patient was required to meet the following criteria: Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; <75 years of age; predicted area of radiation field is less than half of one lung; adequate hematological, pulmonary, renal and hepatic function, i.e. white blood cell (WBC) count $\geq$4000/μL, hemoglobin level $\geq$10 g/dl, platelet count $\geq$130 000/μL, PaO_2 $\geq$70 torr, blood urea nitrogen and serum creatinine level no higher than the upper limit of normal, creatinine clearance (Ccr) $\geq$60 ml/min, serum total bilirubin level $\leq$1.5 mg/dl and serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) levels less than twice the upper limit of normal.

Patients with uncontrolled heart failure or infection, chronic pulmonary disease which restricts thoracic radiation, prolonged diarrhea, ileus, gastrointestinal bleeding or history of myocardial infarction in the last 3 months were excluded from the study. Female patients in pregnancy or lactation during chemotherapy were also excluded. All patients were required to give their own written informed consent.

Treatment Schedule

After enrollment in the study, the patients received chemotherapy consisting of intravenous infusion of 80 mg/m^2 of CDDP on day 1 and 60 mg/m^2 of CPT-11 on days 1 and 8. The chemotherapy was repeated 3–4 weeks after the start of the first course, as long as the patients had sufficiently recovered from toxicity. The chemotherapy was to be performed for two courses, unless unacceptable toxicity or disease progression occurred.

Four weeks after the start of the second course of chemotherapy, thoracic radiotherapy was started. The initial opposing anterior–posterior treatment fields encompassed the primary tumor, the bilateral mediastinal lymph nodes and the ipsilateral hilar nodes. The supraclavicular nodes were included within the field when there was clinical evidence of their involvement. A 1.5 cm tumor-free margin was required. The fraction size delivered was 1.5 Gy, given twice per day, 5 days per week. Thus, the total radiation dose was 60 Gy in 40 fractions over 4 weeks. The methods for spinal block and boost after the first 30 Gy delivery was left to the discretion of the treating radiation oncologist. On each day of thoracic radiotherapy, the patients also received intravenous CBDCA. CBDCA was dosed to a target AUC of 0.4 × (24 h Ccr + 25), according to Calvert's formula (18), and was administered intravenously over 15 min immediately before the first radiation of the day. The CBDCA AUC of 0.4 was determined based on our previous study (17).

CPT-11 on day 8 was skipped if the WBC count was <3000/μL, platelet count <75 000/μL or Grade 2 or higher diarrhea or abdominal pain was seen. During chemotherapy, if the WBC count fell <2000/μL or the neutrophil count

dropped $<1000/\mu L$, daily granulocyte colony-stimulating factor (G-CSF) was administered subcutaneously until the WBC count increased to $\geq 10\,000/\mu L$ or was no longer clinically indicated. Radiotherapy and concomitant use of G-CSF was contraindicated. When the second course of CDDP plus CPT-11 was started, each patient was required to meet the following criteria: WBC count $\geq 4000/\mu L$, neutrophil count $\geq 2000/\mu L$, platelet count $\geq 130\,000/\mu L$, serum creatinine level ≤ 1.5 mg/dl, serum GOT and GPT levels Grade 0 or 1, Ccr ≥ 30 ml/min, body temperature $<38.0°C$ and PS 0, 1 or 2. For patients receiving G-CSF, 3 days after discontinuation, patients were required to meet the aforementioned hematological toxicity criteria prior to starting the second course of CDDP plus CPT-11. If the second course was delayed 2 weeks or more due to toxicity, chemotherapy with CDDP plus CPT-11 and low-dose CBDCA was terminated and only radiotherapy was used. According to toxicities in the first course of chemotherapy, the dose of CDDP was reduced by 25% for Grade 4 leukopenia, Grade 4 neutropenia ≥ 7 days, Grade 3 thrombocytopenia, Grade 3 or 4 mucositis or Grade 2 or higher renal toxicity, and by 50% for Grade 4 thrombocytopenia. The dose of CPT-11 was reduced by 25% for Grade 3 or 4 diarrhea and administration of CPT-11 was terminated if Grade 2 or higher pulmonary toxicity was seen.

Criteria for starting AHRT with daily low dosage CBDCA administration were the same as mentioned above for the second course of CDDP plus CPT-11. Six weeks after initiation of the second course of chemotherapy, if the same criteria were not fulfilled, CBDCA administration was terminated. In that case, only radiotherapy was used.

During chemoradiation, if the WBC count fell $<2000/\mu L$, neutrophil count $<1000/\mu L$ or platelet count $<50\,000/\mu L$, daily use of CBDCA was suspended and only radiotherapy was continued. After recovery from neutropenia, administration of CBDCA was restarted. In case of Grade 4 hematological toxicities, chemoradiation was to be terminated. However, if any toxicity improved Grade 2 or lower, only radiotherapy could be used. If the PaO_2 level decreased by 10 torr or more compared with baseline value, chemoradiation was suspended and if it returned to baseline, treatment could be started again carefully. If Grade 3 or 4 radiation-related esophagitis was seen, chemoradiation was suspended but could be started again when this toxicity improved to Grade 2 or lower. If patients had a fever of 38°C or higher, chemoradiation was suspended until they were afebrile. Chemoradiation was also suspended when deterioration of PS to 3 or 4 occurred, and PS 0, 1 or 2 was necessary to restart the protocol treatment.

Treatment Evaluation

Tumor response and toxicity were evaluated according to World Health Organization response criteria (19) and Japan Clinical Oncology Group (JCOG) toxicity criteria (20), respectively. Complete response (CR), partial response (PR) and no change (NC) were reviewed and confirmed by central review with chest radiographs or CTs at the regular disease-group meeting. Complete blood cell count and routine blood chemistry were checked twice a week, and arterial blood gas and chest radiographs were checked at least once a week, until the patient had apparently recovered from all acute toxic effects after the completion of the treatment. In this trial, the methods to follow-up the patient after the protocol treatment were not clearly defined. In addition, not only late toxicities but also recurrence patterns after finishing protocol treatment were not routinely recorded in the case report form (CRF). Therefore, the interval of evaluation for late toxicities was left to the discretion of the treating physician. Consequently, the frequency of visiting the doctors and radiologic examinations was heterogeneous among the patients.

Study Design and Statistical Methods

This trial was designed as a multicenter prospective single-arm Phase II study, and the study protocol was approved by the Clinical Trial Review Committee (protocol review committee) of JCOG (21) and the institutional review board of each participating institution before study activation. After pre-treatment staging and eligibility evaluation, patients were registered at the JCOG Data Center by telephone or fax. The study was performed by the JCOG Lung Cancer Study Group and all study data were managed by the JCOG Data Center.

The primary endpoints of this study were the overall response rate (ORR) and overall survival (OS). The ORR was defined as the proportion of the patients with CR or PR out of all eligible patients. The confidence intervals for the ORR were calculated based on the exact method. The OS was measured from the date of patient registration to the date of death due to any cause. If a patient was alive at the final follow-up survey, OS was censored at the last contact date. The estimates of survival distribution were calculated by the Kaplan–Meier method and confidence intervals were based on Greenwood's formula (22). And 2-year OS was expected to be ~40%. The progression-free survival was not measured in this study.

We set an expected level (P1) of response rate as 80%, threshold level (P0) as 60%, α-error level was 0.05 and β-error level was 0.10. We set the planned total sample size as 45 according to Simon's minimax two-stage design (23). If 15 or fewer patients out of 26 patients showed objective responses at the first stage, the study was to be terminated early. The OS was followed up to 20 months after the last enrollment.

RESULTS

Patient Characteristics

Between February 1996 and January 1999, 26 patients from 5 institutions were enrolled in this study and all received induction chemotherapy. The pace of enrollment was approximately one-fourth of the planned one in the protocol.

For the pre-specified first stage decision, the accrual was temporarily closed and the response rate was assessed. Characteristics of the 26 patients are listed in Table 1. The patients included 22 men and 4 women, with a median age of 63 (range, 40–74) years. The histologic classifications included adenocarcinoma in 14 patients and squamous cell carcinoma in 12. Seven patients were in Stage IIIA and 19 were in Stage IIIB. Six patients had ECOG PS of 0 and 20 had that of 1. All of the 26 patients were eligible and evaluable for both tumor response and toxicity.

Treatment Delivery and Protocol Compliance

Of the 26 patients enrolled in the study, 15 completed both of the scheduled chemotherapy and radiotherapy. Protocol compliance in the 26 patients is summarized in Tables 2 and 3. In six patients, treatment was terminated after the first course of chemotherapy. The reasons for the withdrawal were disease progression in three patients and toxicity in three. In three patients with disease progression after the first course of CDDP plus CPT-11, one patient could receive sequential chemoradiation. In one patient Cre >1.5 mg/dl persisted, whereas in another patient, Grade 4 diarrhea, Grade 2 neutropenia and Grade 2 fever caused deterioration of PS and resulted in termination of induction chemotherapy. That patient died of sepsis and pneumonia from Grade 4 neutropenia and diarrhea which we categorized as treatment-related death. One patient had disease progression after two courses of chemotherapy and could not receive radiotherapy. One patient experienced Grade 4 leukopenia and the dose of CDDP in the second course should have been reduced to 75% of the original dosage. However, this patient received only CPT-11 and CDDP was improperly omitted in the second course, which was judged as a protocol violation. Delay in the start of the second course occurred in three patients. CPT-11 administration on day 8 was skipped in four patients and three patients had dose reduction of CPT-11 in the second course. The reason for dose omission or dose reduction was diarrhea in five patients.

Twenty patients received thoracic radiotherapy according to the protocol but 3 of the 20 patients could not receive the whole 60 Gy of radiation with daily CBDCA because of hypoxemia, emesis or onset of herpes zoster in the radiation field in each patient, respectively. Radiotherapy could not be delivered for six patients. The reason for not receiving radiotherapy was disease progression in four patients and toxicity in two patients including treatment-related death in one patient. Of the 20 patients receiving radiotherapy, actual mean radiation dose and actual mean number of CBDCA infusion was 56.8 Gy and 17.5 times, respectively (Table 3).

Table 1. Patient characteristics

Characteristics		No.	%
Age (years)			
Median	63		
Range	40–74		
Sex			
Male		22	84.6
Female		4	15.4
Histology			
Adenocarcinoma		14	53.8
Squamous cell carcinoma		12	46.2
Others		0	0
Clinical Stage			
Stage IIIA		7	26.9
Stage IIIB		19	73.1
T-stage			
T1		4	15.4
T2		6	23.1
T3		5	19.2
T4		11	42.3
N-stage			
N0		2	7.7
N1		2	7.7
N2		11	42.3
N3		11	42.3
Performance status (ECOG)			
0		6	23.1
1		20	76.9

ECOG, Eastern Cooperative Oncology Group.

Table 2. Dose intensity of chemotherapy phase ($n = 26$)

	Planned DI	Actual DI	%[a]
CDDP	26.7	23	86
CPT-11	40	33.3	83

DI, dose intensity (mg/m^2/week); CDDP, cisplatin; CPT-11, irinotecan. [a]Percentage of the drug dose actually delivered, vs. the planned dose, is presented.

Table 3. Chemoradiation delivery ($n = 20$)

	Planned delivery	Actual delivery, mean
AHRT	60 Gy	56.8 Gy
CBDCA infusion	20 times	17.5 times

AHRT, accelerated hyperfractionated thoracic radiotherapy; CBDCA, carboplatin.

Toxicity

There was one treatment-related death due to septic shock and pneumonia associated with Grade 4 neutropenia, Grade 4 thrombocytopenia and Grade 4 diarrhea. That patient had CDDP and CPT-11 administration on day 1 and CPT-11 on day 8 in the first course and suffered from serious toxicity. *Pseudomonous aeruginosa* was detected in the microbiological culture test from the stool of the patient. This patient died on day 35 from toxicities mentioned above. Toxicities in the 26 patients are listed in Table 4. Grade 3 or 4 neutropenia occurred in 54% of the patients. Grade 3 or 4 thrombocytopenia occurred in four patients and one patient required platelet transfusion.

The most frequent non-hematological toxicity was diarrhea, and Grade 2 or more occurred in 46% of the patients. Five patients had Grade 2 esophagitis during radiotherapy but it did not cause termination of the therapy. Pulmonary toxicity was not evident during the radiotherapy, as well as CPT-11 including chemotherapy. In one patient, radiotherapy was terminated due to a decrease in arterial oxygen pressure by 17 torr when compared with baseline but that patient also had disease progression during the therapy and it was difficult to evaluate the causal relationship to the protocol treatment. In this trial, late toxicities after finishing protocol treatment were not routinely recorded in CRF.

Table 4. Toxicity in 26 patients (JCOG grade)

	0	1	2	3	4
Leukopenia	4	5	10	7	0
Neutropenia	4	2	6	8	6
Anemia	2	4	13	7	—
Thrombocytopenia	16	5	1	3	1
Bilirubin	22	—	3	1	0
GOT	18	7	1	0	0
GPT	10	11	3	2	0
ALP	19	7	0	0	0
Creatinine	21	4	1	0	0
Arterial oxygen pressure	5	18	3	0	0
Hypo/hypernatremia	9	12	4	1	0
Hypo/hyperkalemia	23	1	1	1	0
Emesis	1	13	11	1	—
Cardiac dysfunction	24	1	0	0	1
Proteinuria	22	4	0	0	0
Hematuria	21	5	0	0	0
Diarrhea	3	11	7	3	2
Esophagitis	8	13	5	0	0
Fever	20	3	3	0	0
Weight loss	8	9	8	1	—

JCOG, Japan Clinical Oncology Group; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; ALP, alkaliphosphatase.

Response and Survival

Objective tumor response is summarized in Table 5. Among the 26 patients, there were 13 PRs and 0 CR, giving a response rate of 50% (95% confidence interval, 30–70%). In 10 patients, a PR was achieved before the start of radiotherapy. Disease progression occurred during chemotherapy in four patients, who had to terminate the protocol treatment. Tumor response could not be evaluated in the patient with treatment-related death. The response rate at the first stage did not meet the criteria to proceed to the second stage and the study was terminated early. Figure 1 shows the OS curve of all patients enrolled in the study. After follow-up for 20 months after the last enrollment, the MST was 16.4 months. The 1- and 2-year survival rates in the 26 patients were 65.4% and 21.5%, respectively.

DISCUSSION

The findings of the present study suggest several important points that should be applied in future studies of Stage III NSCLC, although the response rate of this combination therapy was not as high as expected. First, the protocol regimen may not be sufficiently optimized in order to keep high compliance. The inferior tumor response and the high frequency of disease progression during the induction chemotherapy with CPT-11 and CDDP appeared to be the major reason for the disappointing results, which led to the early termination of the present study. Only 10 out of the 26 patients showed >50% tumor reduction during chemotherapy. It appeared unsatisfactory when one considers

Table 5. Clinical response to the therapy in 26 patients

CR	PR	NC	PD	NE	% of CR + PR (95% confidence interval)
0	13	5	7	1	50.0 (29.9–70.1)

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable.

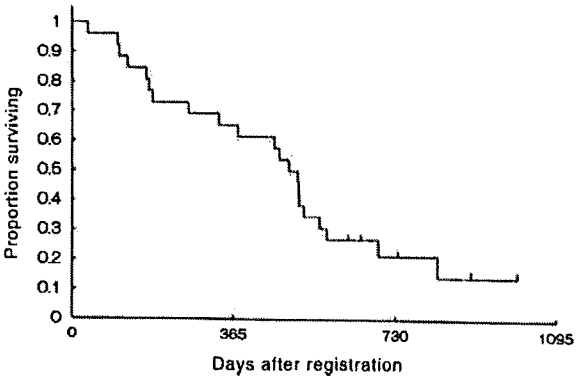

Figure 1. The overall survival curve of all patients enrolled in the study.

that only patients in Stage III were enrolled in the study. Another reason may be the fact that there were comparatively more Stage IIIB patients than Stage IIIA. Although the proportion of Stage IIIA cases was only 26.9% in this trial, in two recent studies, it was 43% and 49% (24,25). This case distribution might have contributed to the poor outcome of this study.

In the view of toxicity management, diarrhea is considered to be key toxicity to be managed carefully in combination chemotherapy using CPT-11. Relative dose intensity of CDDP, CPT-11 and radiotherapy was acceptable in this protocol; however, severe diarrhea caused lowering protocol compliance probably because high-dose loperamide therapy (26) even in the case of severe diarrhea was not used during initial period in this study. It might be possible that the antidiarrhea agent was inadequate and protocol treatment could not be completed in some cases as a result. Had high-dose loperamide therapy been applied appropriately in all eligible cases, better response rate and survival might have been achieved in this study.

It is noteworthy that the strong association between CPT-11 delivery and antitumor response was seen in the present study. In fact, among the 12 patients who had two courses of induction chemotherapy without any delay, omission or dose reduction in CPT-11 administration, 7 showed >50% tumor reduction during the induction chemotherapy and 9 eventually achieved PR after the whole course of therapy (data not shown). This result suggests the possibility that the schedule of CPT-11 administration in this study (days 1 and 8) which was different from the more common regimen (days 1, 8 and 15) may explain the relatively low response rate and the large number of patients with disease progression. Six patients could not receive the protocol radiotherapy because of disease progression or toxicity of the induction chemotherapy. Planned omission of CPT-11 administration on day 15 was intended to reduce risk of pulmonary toxicity during radiotherapy but it might cause unsatisfactory tumor response in the chemotherapy.

Second, the timing of combination of thoracic radiation with chemotherapy may also not be optimized. The present study adopted sequential radiation following induction chemotherapy with CPT-11 and CDDP but suggests that inferior antitumor activity in the chemotherapy could cause failing to receive radiotherapy in some patients. It is difficult to find the best regimen using CPT-11 in the combined modality treatment for Stage III NSCLC.

Because late toxicities were not fully evaluated, the occurrence of both pneumonitis and delayed esophagitis might be possibly underestimated in this study. However, despite the high radiation dose, acute esophagitis were very mild contrary to our expectation, although we cannot clearly explain the reason. Most patients who could proceed to chemoradiotherapy could complete the scheduled radiation with acceptable toxicity. The MST of 16.4 months in the present study was almost as good as in other studies that showed high response rates and survival benefit in Stage III NSCLC. Although our study was prematurely closed after interim analysis because of low response rate, OS which was one of the primary endpoints was comparable with other literatures (24,25,27). In our opinion, AHRT with CBDCA still remains a chemoradiotherapeutic option and should be investigated further with combinations of other chemotherapy regimens.

In recent years, however, some articles have shown that addition of induction chemotherapy before concurrent chemoradiotherapy adds toxicity and provides no survival benefit (24,25). In addition, National Comprehensive Cancer Network (NCCN) practice guideline recommends CDDP plus etoposide or vinblastin with concurrent radiotherapy as preferred standard of cares (category 2A) for patients with unresectable NSCLC (28). Further studies to investigate the role of induction chemotherapy followed by chemoradiotherapy may be not necessary until appearance of more active anticancer agents.

In conclusion, we failed to demonstrate promising efficacy of this regimen, and the development of a brand-new treatment strategy for combining chemotherapy with radiotherapy is necessary for the improvement of the prognosis of the patients with unresectable Stage III NSCLC.

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Conflict of interest statement

None declared.

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A phase-II trial of dose-dense chemotherapy in patients with disseminated thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9605)

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BACKGROUND: To evaluate the safety and efficacy of dose-dense weekly chemotherapy in the treatment of advanced thymoma.

METHODS: Subjects comprised patients with histologically documented chemotherapy-naïve thymoma with stage-IVa or IVb disease. Thymic carcinoma, carcinoid or lymphoma cases were excluded. Patients received 9 weeks of chemotherapy: cisplatin (25 mg m^{-2}) on weeks 1–9; vincristine (1 mg m^{-2}) on weeks 1, 2, 4, 6 and 8; and doxorubicin (40 mg m^{-2}) and etoposide (80 mg m^{-2}) on days 1–3 of weeks 1, 3, 5, 7 and 9. Chemotherapy courses were supported by granulocyte colony-stimulating factor. Post-protocol local therapy was allowed.

RESULTS: From July 1997 to March 2004, 30 patients were entered. Three were ineligible due to different histology. Chemotherapy-associated toxicity was mainly haematological and was well tolerated, with no deaths due to toxicity, and 87% of patients completed the planned 9-week regimen. Overall response rate was 59%, with 16 of the 27 eligible patients achieving partial response. Median progression-fee survival (PFS) was 0.79 years (95% confidence interval: 0.52–1.40 years), and PFS at 1 and 2 years was 37 and 15%, respectively. Overall survival rates at 2 and 5 years were 89 and 65%, respectively.

CONCLUSION: In stage-IV thymoma patients, weekly dose-dense chemotherapy offers similar activity to conventional regimens.

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Thymoma is a rare thoracic tumour, but remains one of the most common tumours originating in the mediastinum (Thomas *et al*, 1999; Giaccone, 2005; Girard *et al*, 2009). Clinical behaviour tends to be indolent, but dissemination into the pleural space eventually occurs and sometimes distant metastasis arise (Thomas *et al*, 1999). Thymoma is frequently associated with paraneoplastic syndromes such as myasthenia gravis or pure red cell aplasia (Thomas *et al*, 1999; Giaccone, 2005). No International Union Against Cancer (UICC) TNM classification is available, and the Masaoka classification has been widely used for clinical staging (Masaoka *et al*, 1981; Girard *et al*, 2009).

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The majority of thymomas are discovered at a limited stage, representing Masaoka stage-I or II, and surgical resection is the treatment of choice for such cases (Thomas *et al*, 1999; Giaccone, 2005; Girard *et al*, 2009). Even when the tumour invades neighbouring organs, as stage-III disease, surgical resection with postoperative radiotherapy is the preferred treatment when complete resection can be achieved (Curran *et al*, 1988; Urgesi *et al*, 1990; Ogawa *et al*, 2002; Strobel *et al*, 2004).

Systemic chemotherapy is usually used for stage-IVa (with pleural or pericardial dissemination) or stage-IVb disease (with lymphogenous or haematogenous metastases), but optimal management is less well established (Thomas *et al*, 1999; Girard *et al*, 2009). Several reports have described favourable outcomes in limited numbers of patients with stage-IVa disease treated using multimodal treatment including surgery (Kim *et al*, 2004; Yokoi *et al*, 2007).

Conversely, thymomas are generally reported to be chemotherapy-sensitive tumours, with response rates of 50–70% to

combination chemotherapy (Fornasiero *et al*, 1990; Loehrer *et al*, 1994, 1997, 2001; Giaccone *et al*, 1996; Berruti *et al*, 1999; Kim *et al*, 2004; Lucchi *et al*, 2006; Yokoi *et al*, 2007). Active agents include cisplatin (CDDP), vincristine (VCR), doxorubicin (ADM), etoposide (ETP), cyclophosphamide (CPM) and ifosfamide (IFX). Recent reports have shown marginal activity of pemetrexed (Loehrer *et al*, 2006) and combined carboplatin and paclitaxel (Lemma *et al*, 2008).

Dose-dense chemotherapy with the CODE combination (CDDP-VCR-ADM-ETP) and addition of granulocyte colony-stimulating factor (G-CSF) can be safely administered to patients with advanced lung cancer (Murray *et al*, 1991; Fukuoka *et al*, 1997). Theoretically, this approach might be suitable for chemosensitive tumours such as small-cell lung cancer and thymoma (Goldie and Coldman, 1983, 1984; Levin and Hryniuk, 1987; Murray, 1987). Because some pilot data in Japan suggested that administration of 12 weeks of the CODE chemotherapy was barely feasible, subsequent Japanese trials used a modified schedule, which was shortened to 9 weeks (Fukuoka *et al*, 1997; Furuse *et al*, 1998).

In 1996, the Japan Clinical Oncology Group (JCOG) initiated two clinical trials for advanced thymoma: one aimed at evaluating the safety and efficacy of the CODE regimen in stage IV, disseminated thymoma (JCOG 9605), and the other aimed at evaluating the safety and efficacy of CODE combination chemotherapy followed by surgical resection and postoperative radiotherapy in initially unresectable stage-III thymoma (JCOG 9606). The primary endpoint in each study was progression-free survival (PFS). The results of JCOG 9605 are reported herein.

PATIENTS AND METHODS

Eligibility criteria

Patients with chemotherapy-naive, histologically documented thymoma at Masaoka stage IVa or IVb were eligible for entry into the study. Thymoma must have been confirmed histologically and thymic tumours with other histology, such as thymic carcinoma, carcinoid or lymphoma, were excluded. Each patient was required to fulfil the following criteria: age, 15–70 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS), 0–2; adequate organ function, that is, leukocyte count $\geqslant 4000\,\mu l^{-1}$, platelet count $\geqslant 10^5\,\mu l^{-1}$, hemoglobin $\geqslant 10.0\,g\,dl^{-1}$, serum creatinine <1.5 mg dl^{-1}, creatinine clearance $\geqslant 60\,ml\,min^{-1}$, serum bilirubin <1.5 mg dl^{-1}, serum alanine transaminase and aspartate transaminase levels less than double the upper limit of the institutional normal range; and $PaO_2 \geqslant 70$ mm Hg. Exclusion criteria included uncontrolled heart disease, uncontrolled diabetes or hypertension, pulmonary fibrosis or active pneumonitis as evidenced on chest radiography, infections necessitating systemic use of antibiotics, disease necessitating emergency radiotherapy such as superior vena cava obstruction syndrome, active concomitant malignancy and women who were pregnant or lactating. Also excluded were those patients with grave complications of thymoma, such as pure red cell aplasia or hypogammaglobulinemia. Myasthenia gravis was allowed and these patients were not excluded *per se*.

Patient eligibility was confirmed by the JCOG Data Center before patient registration. This study protocol was approved by the institutional review board at each participating centre and written informed consent was obtained from all patients prior to enrolment.

Treatment Plan

Chemotherapy Patients received the 9-week CODE combination chemotherapy as described below. Each chemotherapeutic agent was administered intravenously.

Week 1: CDDP $25\,mg\,m^{-2}$ on day 1 with antiemetics and ample hydration; VCR ($1\,mg\,m^{-2}$) on day 1; ADM ($40\,mg\,m^{-2}$) on day 1 and ETP ($80\,mg\,m^{-2}$) on days 1–3.

Weeks 2, 4, 6 and 8: CDDP ($25\,mg\,m^{-2}$) on day 1 with antiemetics and ample hydration and VCR ($1\,mg\,m^{-2}$) on day 1.

Weeks 3, 5, 7 and 9: CDDP ($25\,mg\,m^{-2}$) on day 1 with antiemetics and ample hydration, ADM ($40\,mg\,m^{-2}$) on day 1 and ETP ($80\,mg\,m^{-2}$) on days 1–3.

Each week, G-CSF (filgrastim ($50\,\mu g\,m^{-2}\,day^{-1}$) or lenograstim ($2\,\mu g\,kg^{-1}\,day^{-1}$)) was administered by subcutaneous injection, except on days when chemotherapy was administered or when leukocyte count was $\geqslant 10\,000\,\mu l^{-1}$. Corticosteroid was used only as part of the antiemetic regimen, and the specific drug and dosage were not regulated by the protocol.

Dose and schedule modifications were performed as follows: when leukocyte count decreased to $<2{,}000\,\mu l^{-1}$ or platelet count decreased to $<50\,000\,\mu l^{-1}$, chemotherapy was delayed by 1 week. If PS decreased to 3–4 or temperature reached $\geqslant 38.0°C$, therapy was likewise delayed for 1 week. No dose modification of chemotherapy drugs was adopted for toxicity.

Post-protocol therapy

Surgery or radiotherapy was allowed after the completion of chemotherapy, at the discretion of the attending physician, even in the absence of apparent tumour regrowth. Conversely, additional chemotherapy without evidence of disease progression was not allowed.

Post-treatment after disease progression was not limited by the study protocol.

Patient evaluation and follow-up

Before enrolment into the study, each patient underwent complete medical history taking and physical examination (including neurological check-up for signs of myasthenia gravis), determination of blood cell counts, serum biochemistry testing, arterial blood gas analysis, pulmonary function testing, electrocardiography, chest radiography, computed tomography (CT) of the chest, CT or ultrasonography of the upper abdomen, whole-brain CT or magnetic resonance imaging (MRI) and an isotope bone scan. Blood-cell counts, serum biochemistry testing and chest radiography were performed weekly during each course of chemotherapy.

The toxicity of chemotherapy was evaluated according to the JCOG Toxicity Criteria (Tobinai *et al*, 1993), modified from version 1 of the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Tumour responses were assessed radiographically according to the standard, two-dimensional WHO criteria (Miller *et al*, 1981), and were classified as complete response (CR), partial response (PR), no change (NC), progressive disease (PD) or non-evaluable (NE). After completion of the protocol therapy, patients were followed up with periodic re-evaluation, including chest CT every 6 months for the first 2 years and annually thereafter.

Central review

Radiographic reviews for the eligibility of enrolled patients and clinical responses were performed at the time of the study group meeting, held every 3–4 months. The study coordinator (H Kunitoh) and a few selected investigators from the group reviewed the radiographic films. The clinical response data presented below were all confirmed by this central review. Reviews of pathological specimens were not performed, because of insufficient logistics of the study group at the time of the study activation in 1997.

Endpoints and statistical considerations

The primary endpoint in each study was PFS. Due the rarity of the tumour and the accrual reported in US trials, which required 10 years to register 26 patients with locally advanced (stage-III) disease (Loehrer *et al*, 1997) and 9 years for 31 patients with disseminated (stage-IV) disease (Loehrer *et al*, 1994), we presumed we would be capable of accruing 30 patients in the target accrual period of 4 years. The sample size was, therefore, not determined based on statistical calculations. The expected PFS for the JCOG 9605 study was 2 years, which would give a 95% confidence interval of 1.3–3.0 years with 30 cases.

The initial study design thus envisioned enrolment of 30 fully eligible cases over 3 years for the study, with a follow-up period of 2 years.

Secondary endpoints included toxicity and safety, objective tumour response to chemotherapy, pattern of relapse, and overall survival (OS).

Progression-free survival and OS were calculated from the date of enrolment and estimated using the Kaplan–Meier method. Progression-free survival was censored at the last date verifiable as progression-free, and OS was censored as of the date of last follow-up. During the accrual period, an interim analysis for futility was planned after half of the patients had been registered and followed for $\geqslant 3$ months. All analyses were performed using SAS software version 8.2/9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

A total of 30 patients from seven institutions were enrolled from July 1997 to March 2004. Three patients were later found ineligible due to wrong histology, with two cases of thymic carcinoma and one case of carcinoid. These mistakes occurred due to technical problems in the patient registry. Since the ineligible cases did receive the protocol therapy, all 30 patients were analysed for characteristics and toxicity. Twenty-seven eligible patients were analysed for clinical response and survival (PFS and OS). Patient characteristics are shown in Table 1.

Table 1 Patient characteristics

Item	
Sex	
Male/female	16/14
Age (years)	
Median/range	47.5/29–69
ECOG performance status	
PS0/PS1/PS2	11/18/1
Masaoka stage	
IVa/IVb	22/8
Smoking history	
No	9
Yes (median pack–years)	21 (22)
Myasthenia gravis	
No/yes	28/2
Histology: thymoma and eligible	27
Lymphocyte predominance	12
Mixed cell	9
Epithelioid cell	4
Clear cell	1
Spindle cell	0
Unclassified	1
Histology: not thymoma (ineligible)	3
Carcinoma	2
Carcinoid	1
Lymphoma	0
Prior therapy	
None	26
Surgery	2
Surgery and radiation	2

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status.

Chemotherapy delivery and toxicity

Nine weeks of chemotherapy were performed for 26 of the original 30 patients (87%). The other four patients included one patient receiving 7 weeks, two receiving 6 weeks and one receiving 3 weeks of therapy. Median duration of chemotherapy for the 26 patients who underwent the planned nine cycles was 10 weeks (range, 9–12 weeks).

Table 2 summarises the major toxicities of chemotherapy, which were mainly haematological. Although 70% of patients experienced grade-IV neutropenia, this was generally transient and rarely complicated by infection/fever. Overall, toxicities were well tolerated and no deaths due to toxicity occurred.

Table 2 Toxicity of chemotherapy ($n = 30$)

Toxicity	Grades 1/2	Grade 3	Grade 4	%Grade 3/4
Leukopenia	3/6	12	8	67
Neutropenia	3/1	5	21	87
Anemia	0/5	25	ND	83
Thrombocytopenia	4/6	5	3	27
ALT	9/0	0	0	0
Creatinine	2/1	0	0	0
PaO_2	9/2	0	0	0
Emesis	13/11	2	ND	7
Diarrhoea	4/2	0	0	0
Stomatitis	4/3	0	0	0
Constipation	3/4	2	0	7
Neuropathy	11/2	0	ND	0
Infection	3/4	3	0	10

Abbreviations: ALT = alanine transaminase; ND = not defined (the JCOG toxicity criteria did not define grade IV in these toxicities).

Other and late complications

Four patients showed thymoma-related complications. One patient suffered from myasthenia gravis crisis occurring during chemotherapy, but subsequently recovered. Another patient showed newly diagnosed myasthenia gravis 2.5 years after completion of the protocol therapy, and thymectomy and resection of the residual tumour were performed. Two other cases had pure red cell aplasia occurring later in the clinical course with disease progression of the thymomas.

Clinical response to chemotherapy

Clinical responses of the 27 eligible patients to chemotherapy were judged radiologically and confirmed by central review. Responses were as follows: CR, 0 patients; PR, 16 patients; NC, 10 patients and PD, 1 patient. Overall response rate was 59% (95% confidence interval, 39–78%).

Post-protocol therapy

Post-protocol local therapy was administered to 18 of the 27 eligible patients (67%). Eight patients (all with stage-IVa disease) underwent surgical resection and 13 patients (nine with stage-IVa disease and four with stage-IVb disease) received thoracic radiotherapy, with three patients receiving both. Whether patients received local therapy after disease progression was not recorded on case report forms.

After disease progression, 16 of the 27 patients (59%) received additional chemotherapy. Post-protocol chemotherapy included platinum re-challenge, irinotecan, taxanes and investigational agents. Clinical response data to those therapies are not available.

PFS and OS

Survival data were finally updated in March 2006, 2 years after accrual of the last patient. Figure 1 shows PFS and OS curves of the 27 eligible patients. Median PFS was 0.79 years (95% confidence interval, 0.52–1.40 years) and PFS at 1 and 2 years was 37 and 15%, respectively. Median OS was 6.1 years and OS at 2 and 5 years was 89 and 65%, respectively.

Overall survival was longer for stage-IVa patients than for stage-IVb patients (Figure 2, median, 6.8 years and 3.5 years, respectively), but PFS was similar (Figure 3, median, 0.79 years for IVa patients and 0.78 years for IVb patients).

Pattern of relapse

As of the data cut-off, 26 of the 27 eligible patients had experienced tumour relapse. Sites of initial relapse comprised the primary site only in seven cases (27%), pleural or pericardial dissemination in seven cases (27%) and primary site and pleural/pericardial dissemination in nine cases (35%). Thus, 23 of the 26 patients with relapse initially showed regrowth of the primary and/or pleural or pericardial dissemination, with only three patients (12%) showing initial relapse at distant organs.

DISCUSSION

Few prospective trials of chemotherapy have been described for patients with advanced thymoma. Most prior studies have combined stage-III, localised disease and stage-IV, disseminated disease (Table 3). In addition, most have also included both thymoma and thymic carcinoma histology.

We have reported results for patients with stage-IV disease, for which systemic therapy should be the first choice. Among previous studies, only those from the ECOG separately reported results for stage-III and stage-IV patients (Loehrer *et al*, 1994, 1997). The ECOG took 9 years to accrue 31 patients with stage-IV disease, including patients with thymic carcinoma (Loehrer *et al*, 1994). We prospectively accrued patients with thymoma only and excluded thymic carcinoma, as thymoma and thymic carcinoma clearly differ in clinical presentation and prognosis, and trials involving these pathologies should, thus, be reported separately (Eng *et al*, 2004; Giaccone, 2005; Lemma *et al*, 2008).

Trials of systemic chemotherapy for thymoma have reported response rates of 50–90%, so this tumour is generally considered sensitive to chemotherapy (Thomas *et al*, 1999). Dose-dense chemotherapy such as the CODE four-drug combination has been argued to be theoretically suitable for the treatment of such chemosensitive tumours (Murray, 1987).

Although our results showed that dose-dense CODE chemotherapy could be safely administered to thymoma patients, efficacy was not remarkable. The overall response rate was about 60%, no different from prior reports employing conventional-dose chemotherapy (Table 3). Progression-free survival was 9 months, falling far short of the expected 2 years. Although OS studies compared favourably with the corresponding ECOG trial (Loehrer *et al*, 1994), attempting to reach a valid conclusion would be difficult due to the small sample sizes. In addition, OS could be

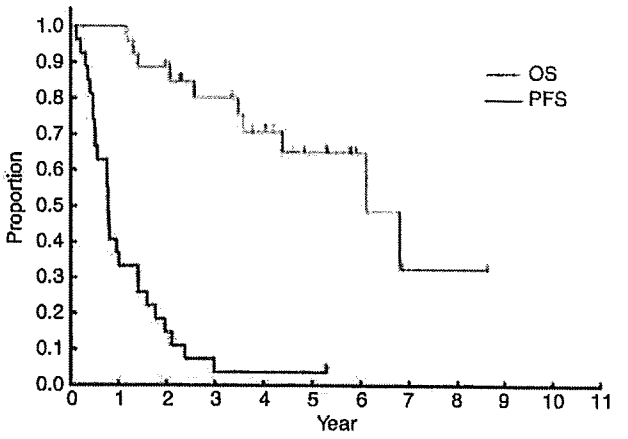

Figure 1 Progression-free survival and OS of the 27 eligible patients.

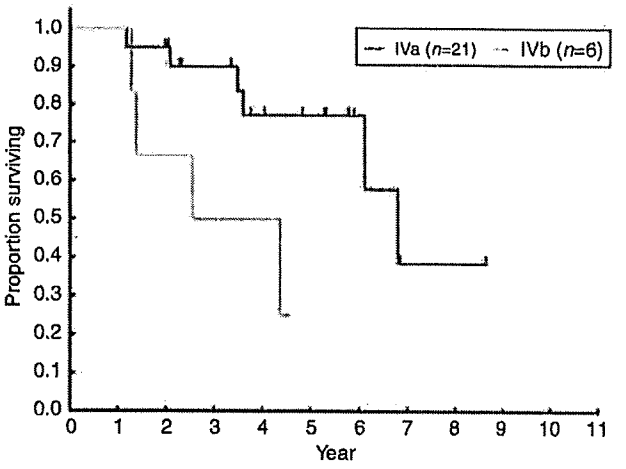

Figure 2 Overall survival according to Masaoka stage (stage IVa *vs* IVb).

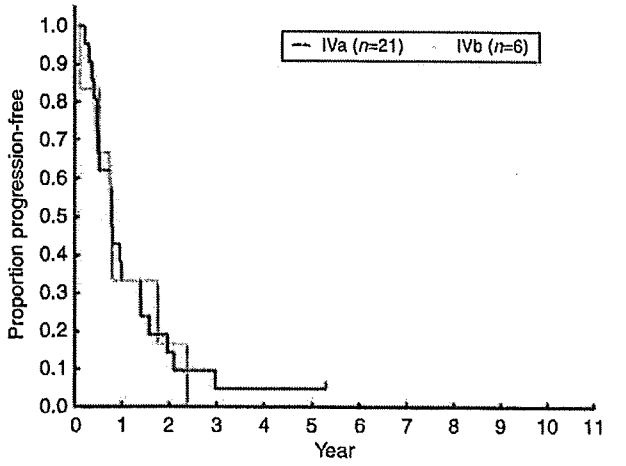

Figure 3 Progression-free survival according to Masaoka stage (stage IVa *vs* IVb).

Table 3 Reports of combination chemotherapy for thymoma

Regimen	Stage	Patients[a]	ORR	Reference
Anthracycline-containing regimens				
ADOC (S)	III/IV	32	91%	Fornasiero et al (1990)
PAC (G)	IV	30	50%	Loehrer et al (1994)
PAC (G)	III	23	70%	Loehrer et al (1997)
ADOC (S)	III/IV	16	81%	Berruti et al (1999)
PAC (G)	III/IV	22	77%	Kim et al (2004)
PAE (S)	III/IV	30	73%	Lucchi et al (2006)
CAMP (S)	III/IV	14	93%	Yokoi et al (2007)
CODE (G)	IV	27	59%	Current study
Non-anthracycline-containing regimens				
PE (G)	III/IV	16	56%	Giaccone et al (1996)
VIP (G)	III/IV	20	35%	Loehrer et al (1997)
CP (G)	III/IV	23	35%	Lemma et al (2008)

Abbreviations: ADOC = doxorubicin, cisplatin, vincristine, cyclophosphamide; CAMP = cisplatin, doxorubicin, methylpredonisolone; CODE = cisplatin, vincristine, doxorubicin, etoposide; CP = carboplatin, paclitaxel; G = prospective multicenter group trial; ORR = overall response rate; PAC = cisplatin, doxorubicin, cyclophosphamide; PAE = cisplatin, epidoxorubicin, etoposide; PE = cisplatin, etoposide; S = single-center experience; VIP = etoposide, ifosfamide, cisplatin. [a]Number of assessable patients.

greatly affected by post-study local therapy especially in patients with stage-IVa disease, as combined therapy trial including stage-IVa patients suggested (Kim *et al*, 2004). In fact, this might be one reason why OS of stage-IVa patients was much longer than that of stage-IVb patients, whereas PFS was similar.

It could be argued that shortened CODE chemotherapy, used in Japan due to feasibility problem, led to inadequate results due to insufficient total dosages of chemotherapy drugs. However, another intensive chemotherapy, ETP-IFX-CDDP (VIP) supported by G-CSF, has also reported disappointingly low response rates and no better survival (Loehrer *et al*, 2001). Hanna *et al* (2001) reported five patients with prior chemotherapy treated with high-dose chemotherapy and stem cell support, but concluded that no superiority to conventional therapy was evident. Taken together with our results, intensification of chemotherapy does not appear sufficiently promising for treating advanced thymoma.

Many prior chemotherapy studies have included platinum and anthracyclines in their regimens. Non-anthracycline approaches contained regimens such as VIP (Loehrer *et al*, 2001), ETP-CDDP (Giaccone *et al*, 1996) and paclitaxel-carboplatin (Lemma *et al*, 2008) tended to yield lower response rates of 32-56% as compared with regimens including anthracycline (Table 3). It might, thus, be suggested that both anthracycline and platinum should, thus, be included in thymoma chemotherapy, at least in current clinical practice.

Favourable results have recently been reported with multimodality therapy, including surgical resection of stage-IVa disease (Kim *et al*, 2004; Yokoi *et al*, 2007). In fact, about two-thirds of eligible patients in our trial received local therapy after chemotherapy, including surgery in eight patients. This could have affected the outcome of the patients, as discussed above. However, small sample size and patient selection preclude reaching any definitive conclusion. When and what local therapy, if any, would benefit patients with disseminated thymoma, remains yet to be established. Further studies are warranted.

The present study shows several additional limitations. One is that we did not perform a central review of histology, and, thus, could not provide WHO classifications of histology (Okumura *et al*, 2002; Travis *et al*, 2004). This makes comparisons with results from other reports difficult. Central pathology review and preferably tissue collection would be very important in future trials.

In addition, due to the shorter-than-expected PFS, the planned CT scan interval of every 6 months might not have accurately evaluated PFS (Freidlin *et al*, 2007). Future trials might require more frequent scans.

In conclusion, we have reported that weekly dose-dense chemotherapy can be safely administered to patients with thymoma. However, efficacy seems similar to that in patients treated with conventional doses. More research on optimal systemic therapy and the role of local modalities would appear to be necessary.

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