A Phase I Study of Topotecan/Paclitaxel Alternating with Etoposide/Cisplatin and Thoracic Irradiation in Patients with Limited Small Cell Lung Cancer


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ABSTRACT

Purpose: Topotecan and paclitaxel are promising cytotoxic drugs with novel mechanisms of action relative to other chemotherapies used in the treatment of small cell lung cancer (SCLC). In an effort to integrate paclitaxel and topotecan into the treatment of limited disease (LD) SCLC, we conducted a Phase I study of these agents administered as initial induction therapy.

Experimental Design: Escalating doses of topotecan (0.8 – 1.4 mg/m² d1–5) and paclitaxel (110 – 175 mg/m² d1) were administered i.v. every 21 days for two cycles to determine the maximum tolerated dose (MTD) in patients with LD SCLC. This was followed by two cycles of etoposide (120 mg/m² d1–3) and cisplatin (60 mg/m² d1) with thoracic radiotherapy. The first 5 subjects received 1.8 Gy once daily x 25 fractions, while subsequent subjects received 1.5 Gy twice daily x 30 fractions. Two additional cycles of chemotherapy (topotecan and paclitaxel, followed by etoposide and cisplatin) were given.

Results: Common toxicities included grade ≥3 neutropenia in 67% of courses of topotecan and paclitaxel and grade ≥2 esophagitis in 71% of patients. The MTD was based on toxicity during the first two cycles of chemotherapy and defined after accrual of 18 patients to four dose levels. Two of three patients developed grade 3 nonhematological toxicity (pneumonia) at the fourth dose level. Thus, the third dose level (topotecan 1.2 mg/m², paclitaxel 160 mg/m²) was defined as the MTD recommended for Phase II studies. One subject died suddenly on day 2 of cycle 1 without autopsy confirmation of the etiology. A second subject died during cycle 3 due to thrombocytopenia, gastrointestinal bleeding, and respiratory failure. Response rates after induction of topotecan and paclitaxel: 16 of 18 (88.8%) partial response, 1 of 18 (5.5%) complete response. Response rates after completion of therapy: 10 of 18 (55.5%) partial response, 7 of 18 (38.8%) complete response.

Conclusions: Induction topotecan and paclitaxel before chemoradiotherapy in patients with LD SCLC is feasible and results in expected toxicities. The outcome of a recently closed Cancer and Leukemia Group B Phase II study of similar design (CLB-39808) should help determine whether or not this approach warrants testing in a randomized setting.

INTRODUCTION

In the United States, ~15–20% of lung cancers are small cell carcinomas (1). One-third of patients with SCLC have LD (2), generally defined as a tumor that is confined to one hemithorax and its surrounding regional lymph nodes (3). Meta-analyses have demonstrated that a combination of chemotherapy and chest radiotherapy confers a survival advantage when compared with chemotherapy alone (4, 5), and concurrent chemoradiation in which radiotherapy is begun early in the induction phase of chemotherapy is the current standard of care for LD SCLC in the United States. The combination of cisplatin and etoposide has become the favored first-line chemotherapy regimen for LD SCLC (6). This combination regimen usually causes manageable myelosuppression and nonhematological toxicity, and when it is administered with full-dose chest irradiation, it results in less toxicity than do other chemotherapy agents (7, 8). Despite receiving aggressive chemoradiotherapy delivered with curative intent, the majority of patients with LD SCLC dies secondary to high rates of both local and distant relapse, including brain metastases (9). To improve current therapies for this disease, new, effective systemic agents and refinements to current radiotherapy techniques are clearly needed.

Received 6/21/02; revised 10/24/02; accepted 1/23/03.

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1 Supported by a grant from GlaxoSmithKline Oncology, and in part by Grant K12 CA088084 from the United States National Cancer Institute, Bethesda, MD.

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3 The abbreviations used are: SCLC, small cell lung cancer; LD, limited disease; ED, extensive disease; CALGB, Cancer and Leukemia Group B; MTD, maximum tolerated dose; CI, confidence interval; CR, complete response; DLT, dose-limiting toxicity; PR, partial response; PCI, prophylactic cranial irradiation.
Topotecan and paclitaxel are promising new cytotoxic drugs with novel mechanisms of action relative to other chemotherapies used in the treatment of SCLC. Topotecan is a water-soluble analogue of camptothecin, a plant alkaloid that has been shown to inhibit the nuclear enzyme topoisomerase I, resulting in single-strand DNA breaks and cell death (10). A Phase II study in chemotherapy-naive patients with ED SCLC demonstrated a 39% response rate (11), and a European Phase II trial in patients who had been treated previously with chemotherapy demonstrated a response rate of 38% in chemotherapy-sensitive disease and 6% in refractory disease (12). Another Phase II study in patients with refractory disease reported an 11% response rate (13). A pivotal Phase III study in patients with recurrent disease compared single-agent topotecan to the combination of cyclophosphamide, doxorubicin, and vincristine, yielding response rates of 24 and 18% (P = 0.285) in the experimental and control arms, respectively (14). In 1998, topotecan received Food and Drug Administration approval for the treatment of SCLC after failure of first-line chemotherapy.

Paclitaxel is another promising cytotoxic agent with a different mechanism of action. Paclitaxel, a plant-derived product, is a diterpene that exerts cytotoxic effects by promoting microtubule assembly, which ultimately leads to disruption of mitosis and cell death (15). Two Phase II studies in chemotherapy-naive ED SCLC reported encouraging single-agent response rates of 34% (16) and 53% (17). A Phase II trial of single-agent paclitaxel in disease that fails to respond to or relapses shortly after treatment with cyclophosphamide, doxorubicin, and etoposide therapy yielded an impressive 29% response rate (18). Recent studies examining the effectiveness of paclitaxel-based chemotherapy combinations in SCLC have demonstrated high response rates (19, 20). The preliminary results of a large randomized trial (CALGB 9732) comparing the use of cisplatin and etoposide with or without paclitaxel in untreated patients with ED SCLC failed to demonstrate a survival advantage, however (21).

During the design phase of this study, other investigators were examining the combination of paclitaxel and topotecan in ED SCLC. A CALGB Phase I study in patients with advanced cancer yielded recommended Phase II doses, given in cycles every 21 days, of 230 mg/m² paclitaxel on day 1 and 1 mg/m² topotecan on days 1–5 with filgrastim support and 80 mg/m² paclitaxel on day 1 and 1 mg/m² topotecan on days 1–5 without filgrastim (22). A subsequent CALGB Phase II study in ED SCLC used this dosing schedule with filgrastim, resulting in an unexpected number of treatment-related deaths (23). Patient accrual was suspended and later restarted with a reduced dose of 175 mg/m² paclitaxel on day 1 (24). Another Phase II study in ED SCLC untreated previously studied the effectiveness of 135 mg/m² paclitaxel on day 5 and 1.25 mg/m² topotecan on days 1–5 every 28 days with filgrastim support. The first 3 patients enrolled in the study developed grade 4 myelosuppression that led to sepsis and death in one case and resulted in a reduction of the topotecan dose to 1 mg/m² on days 1–5 for all subsequent patients (25). In light of these data, we reasoned that in patients untreated previously with LD SCLC, an initial dose level of 0.8 mg/m² topotecan on days 1–5 and 110 mg/m² paclitaxel on day 1 without filgrastim would be appropriate.

In an effort to integrate paclitaxel and topotecan into the treatment of LD SCLC, we conducted a Phase I study of these agents administered as initial induction therapy followed by chest radiotherapy with concurrent cisplatin and etoposide, in addition to two additional cycles of chemotherapy. The main objectives of this trial were to determine the MTD, toxicity profile, and response rate of paclitaxel and topotecan when given as induction therapy in patients with LD SCLC. Other secondary end points included the response rate to the entire treatment regimen, duration of response, rate of progression-free survival, and rate of overall survival.

**PATIENTS AND METHODS**

**Patients.** Eligibility criteria included LD SCLC as documented by chest radiography; computed tomography of the chest, brain, and abdomen; radionuclide bone scan; bone marrow aspiration and biopsy; and physical examination. Patients with N3 disease as manifested by ipsilateral supraclavicular or contralateral mediastinal lymphadenopathy were eligible. Patients with contralateral hilar or contralateral supraclavicular lymphadenopathy were excluded to limit the size of the irradiation field and pulmonary toxicity. Patients with a pleural effusion visible on chest X-ray were excluded. Adequate organ function was required, including an absolute granulocyte count ≥ 1,500/μl, platelets ≥ 150,000/μl, total bilirubin ≤ 1.5 mg/dl, and serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 40 ml/min. A performance status of ≤ 2 on the Zubrod scale, no previous chemotherapy or radiotherapy, no recent history of other malignancies (excluding nonmelanoma skin cancer or carcinoma in situ of the uterine cervix), and written informed consent were also required. The treating radiation oncologist was required to certify that the tumor could be encompassed by irradiation fields that would not “significantly” compromise pulmonary function. The institutional review board at The University of Texas M. D. Anderson Cancer Center approved the protocol. All subjects were accrued and treated at The University of Texas M. D. Anderson Cancer Center.

**Therapy.** This trial was a Phase I study of two cycles (cycles 1 and 2) of topotecan and paclitaxel administered as initial induction therapy in patients with LD SCLC. Patients received two subsequent cycles (cycles 3 and 4) of cisplatin and etoposide with concurrent thoracic radiotherapy, which was then followed by an additional cycle (cycle 5) of topotecan and paclitaxel and a final cycle (cycle 6) of cisplatin and etoposide.

Chemotherapy cycles were administered every 21 days. The dose levels for topotecan and paclitaxel are summarized in Table 1. Paclitaxel was administered i.v. for 3 h on day 1 of cycles 1, 2, and 5. Premedications for paclitaxel consisted of 20 mg of i.v. dexamethasone, 300 mg of i.v. cimetidine, and 50 mg of i.v. diphenhydramine administered 30 min before treatment. Topotecan was administered i.v. for 30 min on days 1–5 of cycles 1, 2, and 5. The dose levels for cisplatin and etoposide are summarized in Table 1. Etoposide was given i.v. for 2 h on days 1–3 of cycles 3, 4, and 6. Cisplatin was given i.v. on day 1 of cycles 3, 4, and 6 after administration of etoposide. Patients received 2.5 liters of i.v. hydration on the days of cisplatin therapy. Carboplatin area under the curve six was substituted for cisplatin in patients with a creatinine clearance ≥ 40 and ≤ 60 ml/min. A complete blood count with differential

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**Table 1. Paclitaxel was administered i.v. for 3 h on day 1 of cycles 1, 2, and 5. Premedications for paclitaxel consisted of 20 mg of i.v. dexamethasone, 300 mg of i.v. cimetidine, and 50 mg of i.v. diphenhydramine administered 30 min before treatment.**

**Topotecan was administered i.v. for 30 min on days 1–5 of cycles 1, 2, and 5. The dose levels for cisplatin and etoposide are summarized in Table 1.**
and platelet counts was obtained weekly and immediately before each cycle began. Serum chemistry assays (electrolytes, blood urea nitrogen, creatinine, total bilirubin, aminotransferases, alkaline phosphatase, and lactate dehydrogenase) were performed before each cycle began. Prophylactic ciprofloxacin, 500 mg

were performed before each cycle began. Prophylactic ciprofloxacin, 500 mg p.o. twice a day on days 6–15, was administered in every chemotherapy cycle.

Acute toxicity was scored with the National Cancer Institute Common Toxicity Criteria. Chemotherapy cycles were held until patients recovered an absolute granulocyte count ≥ 1,200/ml and platelet count ≥ 100,000/ml and the patient’s nonhematological toxicity had been reduced to grade 1 or grade ≥ 2 for patients with esophagitis. Patients with decreased creatinine clearance received carboplatin instead of cisplatin as described previously. Filgrastim was administered for the treatment of neutropenic fever or prolonged grade 4 neutropenia (>7 days) and was given prophylactically with subsequent cycles. Filgrastim was not administered during thoracic radiotherapy. Doses of all chemotherapeutic drugs were reduced one dose level (Table 1) for patients with grade 4 thrombocytopenia, in addition to prolonged grade 4 neutropenia or febrile neutropenia, despite the use of prophylactic filgrastim. An exception was made in cycle 3, in which full doses of cisplatin and etoposide were used with concurrent thoracic radiotherapy even if these toxicities occurred during cycle 2 with topotecan and paclitaxel. During thoracic radiotherapy, cisplatin and etoposide (cycle 4) were not given until esophagitis had been reduced to grade ≥ 2, and one dose level reduction (Table 1) was required if grade 4 esophagitis developed. Grade 3 nonhematological toxicity required a dose reduction of one level, and grade 4 toxicity resulted in treatment discontinuation. Intrapatient dose escalation was permitted for chemotherapy cycles 2 and 5 (topotecan and paclitaxel) in the absence of hematological toxicity greater than grade 2 and nonhematological toxicity greater than grade 1.

Thoracic radiotherapy was begun within 24 h of day 1, cycle 3, of chemotherapy (cisplatin and etoposide). The first 5 patients accrued received 25 daily fractions of 1.8 Gy for 5 weeks (total dose, 45 Gy). Radiotherapy was amended after results from a large Phase III intergroup study demonstrated a survival advantage with twice daily irradiation (26). Subsequent patients received 30 1.5-Gy fractions twice daily for 3 weeks, for a total dose of 45 Gy. The target volume included the primary tumor plus regional hilar, mediastinal, and, in some cases, ipsilateral supraclavicular lymph nodes, with 1–2-cm margins. Ipsilateral supraclavicular irradiation was performed for adenopathy in that region, when necessary for primary tumor coverage (primary tumor in the upper lobe with upper mediastinal node involvement), or for cases of bulky (>5 cm) pre or paratracheal adenopathy. Contralateral hilar or contralateral supraclavicular treatment was not allowed. Dosage to the spinal cord was limited to a total of 35 Gy.

PCI was offered to all patients who achieved a CR after completion of all therapy. Treatment consisted of 10 daily 2.5-Gy fractions for a total dose of 25 Gy.

**Study Design.** This trial was a Phase I dose escalation study of topotecan and paclitaxel given as initial induction therapy to patients with LD SCLC. The primary objective was to determine the MTD in this setting and characterize the toxicity. A secondary objective was to assess response to induction topotecan and paclitaxel and to the entire treatment regimen. Patients were accrued in cohorts of three beginning at dose level 1 as defined in Table 1. Each cohort was followed for a minimum of 3 weeks before any additional patients were accrued. DLT was defined as febrile neutropenia, grade 4 neutropenia of >7 days’ duration, grade 4 thrombocytopenia, or grade ≥ 3 nonhematological toxicity. If none of the 3 patients treated at a dose level experienced DLT in the first cycle, the subsequent cohort was treated at the next higher dose level. If 1 of 3 patients experienced DLT at a dose level, an additional 3 patients were entered at that dose level. If 1 of 6 patients experienced DLT at a dose level, the subsequent cohort was accrued at the next higher dose level. If more than one of three or more than 2 of 6 patients experienced DLT, the subsequent cohort was treated at the next lower dose level. The MTD was defined as the dose level that produced DLT in 2 of 6 patients or that level immediately below the one that produced DLT in >2 of 6 or >1 of 3 patients.

Responses to treatment were assessed with chest radiography after each cycle of chemotherapy and with chest computed tomography after cycle 2 (to document response to topotecan and paclitaxel) and cycle 6 (to document final treatment response). A designation of CR or PR, no change, or progressive disease was made on the basis of standard WHO criteria (27). Survival time was measured from the 1st day of treatment until the date of death and calculated by the Kaplan-Meier method (28). Progression-free survival was measured from the 1st day of treatment to the date on which disease progression was documented. On completion of protocol therapy, patients were seen in the clinic every 3 months for 1 year and subsequently every 6 months. Clinical evaluations included history, physical examination, chest X-ray, and a complete blood count with differential, platelet count, and serum chemistry assays.

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RESULTS

Patients. Between March 1997 and May 1999, 18 patients were entered into this study. Their characteristics are listed in Table 2. Their median age was 67 years, and 12 (67%) were men. All patients had a Zubrod performance status of 1. Patients were accrued at four dose levels. One patient treated at dose level 4 died suddenly on day 2 of the first cycle; the patient had acute dyspnea, chest pain, and, shortly thereafter, cardiac arrest. Although either a pulmonary embolism or a myocardial infarction was the suspected cause of death, a postmortem examination was not performed, precluding any definitive diagnosis. This early death precluded any formal radiological assessment of response to therapy. The patient was categorized as a nonresponder and included in both response and survival analyses. The remaining 17 patients received a total of 92 cycles of chemotherapy, with all 17 patients receiving at least two cycles and 14 patients receiving the full six cycles.

Determination of MTD. A determination of MTD was made on the basis of the occurrence of DLT during the first two cycles of topotecan and paclitaxel. Of the first 6 patients enrolled at dose levels 1 and 2, none developed DLT during the first two cycles. One of the 8 patients treated at dose level 3 developed DLT (febrile neutropenia). A total of 4 patients were entered at dose level 3. As described previously, 1 patient suffered an early sudden death on day 2 of cycle 1, and an additional replacement subject was enrolled at the same dose level. Among the remaining 3 patients treated at dose level 4, 2 required hospitalization for nonneutropenic pneumonia at the end of cycle 2 or the beginning of cycle 3. Both patients received thoracic radiotherapy, but further chemotherapy was not feasible. Because 2 of 3 patients treated at dose level 4 developed DLT (grade 3 infection), dose level 3 (1.2 mg/m² topotecan i.v. on days 1–5, 160 mg/m² paclitaxel i.v. day 1) was defined as the MTD for future Phase II testing.

Toxicity. Dose escalation or reduction and myelosuppressive toxicity for all 48 courses of topotecan and paclitaxel (cycles 1, 2, and 5) are summarized in Table 3. As expected, neutropenia was the most common toxic effect, with grades 3 and 4 neutropenia occurring in 17 and 67% of the total courses, respectively. Febrile neutropenia, however, occurred in only 2% of courses, possibly influenced by the use of prophylactic ciprofloxacin. Grade ≥3 thrombocytopenia and anemia occurred in 8 and 6% of courses, respectively.

Similar hematological toxicity data for all 44 courses of cisplatin and etoposide (cycles 2, 3, and 6) are summarized in Table 3. Grades 3 and 4 neutropenia occurred in 18 and 30% of courses, respectively, with two cases (5%) of neutropenic fever. Grade ≥3 thrombocytopenia and anemia occurred in 11 and 9% of courses, respectively. One patient received chemotherapy cycles 1 and 2 (topotecan and paclitaxel, dose level 2) and subsequently developed grade 4 thrombocytopenia after cycle 3 (cisplatin and etoposide). This patient was hospitalized with gastrointestinal bleeding and subsequently died of respiratory failure.

The frequency of the common grades 2–4 nonhematological toxicities is summarized in Table 4. Grade ≥2 esophagitis, nausea/vomiting, and fatigue occurred in 71, 47, and 47% of patients, respectively. Grade 1 sensory neuropathy was observed in 11 (65%) patients. As expected, grade 2 arthralgia was reported solely during cycles that included paclitaxel, and the majority of grade 2 or higher esophagitis occurred during concurrent chemoradiotherapy. Among the 12 patients who received twice daily radiation, 2 patients developed grade 3 esophagitis, whereas no episodes of grade 3 esophagitis occurred among the 5 patients treated with once daily radiation. The only episode of
grade 4 nausea and vomiting occurred with the receipt of cisplatin and etoposide.

Response. Response was considered a secondary end point of this trial. As described previously, 17 patients received at least two cycles of topotecan and paclitaxel, and all 18 subjects were included in the calculation of response rates. The subject who suffered an early death during cycle 1 was categorized as a nonresponder. Sixteen completed thoracic radiotherapy, and 14 completed both radiotherapy and six cycles of chemotherapy. After two cycles, PR and CR rates were 88.8 and 5.5%, respectively, for an overall response rate of 94.4% (95% CI, 72.7–99.9%). After all six cycles, PR and CR rates were 55.5 and 38.8%, respectively, for an overall response rate of 94.4% (95% CI, 72.7–99.9%). Eleven patients subsequently received PCI. The median period between completion of therapy and PCI was 44 days (range: 26–91 days).

Survival and Patterns of Recurrence. The survival rate was not an end point in this Phase I trial, but the data were calculated and reported. Six patients were alive at the time of analysis, with a median follow-up time of 39 months. Five of these patients have no evidence of recurrent disease. Local and distant recurrences have occurred in 5 and 8 subjects, respectively, with 2 individuals experiencing both local and distant recurrences. Median survival time for all 18 patients was 15.1 (lower 95% CI, 10.7) months with a median progression-free survival time of 11.5 (lower 95% CI, 8.4) months (upper 95% CI not estimable in either case because of censored values at upper ranges). Two- and 4-year survival rates were 39% (95% CI = 22–69%) and 31% (95% CI = 15–64%), respectively.

DISCUSSION

Paclitaxel and topotecan are representative of an increasing number of recently developed cytotoxic agents with different mechanisms of activity against SCLC. In theory, the incorporation of these agents into first-line chemotherapy with cisplatin and etoposide may be effective against resistant subclones and improve patient outcome. To investigate the use of topotecan and paclitaxel in the initial treatment of LD SCLC, we conducted this Phase I study examining the use of these agents together before treatment with standard chemotherapy concurrent with thoracic irradiation. As anticipated, neutropenia was the primary toxic effect. During the first two cycles, grade 4 neutropenia developed in 13 of 17 (76%) patients, although there was only 1 case of febrile neutropenia. We found the treatment regimen to be feasible and highly active, with a 94.4% (95% CI, 72.7–99.9%) response rate after two cycles of topotecan and paclitaxel. Our data support our Phase II dose recommendation of 1.2 mg/m² topotecan i.v. on days 1–5 and 160 mg/m² paclitaxel i.v. on day 1 with ciprofloxacin prophylaxis.

We are unaware of any published manuscripts that report the use of this chemotherapy regimen in patients with SCLC. However, several groups have recently published preliminary results in limited abstract form, including Phase II studies in patients with untreated ED SCLC. A CALGB trial (29) used 175 mg/m² paclitaxel on day 1 and 1 mg/m² topotecan on days 1–5 every 21 days with filgrastim support and yielded a 68% response rate in 34 evaluable patients. Jacobs et al. (25) used 135 mg/m² paclitaxel (24-h infusion) on day 1 and 1 mg/m² topotecan on days 1–5 every 21 days with filgrastim support and reported a 60% response rate among 28 evaluable patients. Tweedy et al. (30) reported a response rate of 100% in 15 patients treated with the same regimen as the patients in the study by Jacobs et al., except paclitaxel was administered as a 3-h infusion. The smallest of these studies included 14 patients who were treated with 135 mg/m² paclitaxel on day 5 and 1 mg/m² topotecan on days 1–5 with filgrastim support with a response rate of 71% (31). Although preliminary, these data are consistent with our findings that indicate that this combination regimen is highly active in the treatment of SCLC.

The MTDs of topotecan and paclitaxel as defined in this study appear reasonable in the context of the standard doses of these agents. The topotecan dose of 1.2 mg/m² i.v. on days 1–5 every 21 days is 80% of the single-agent dose approved for the second-line treatment of relapsed SCLC (1.5 mg/m² i.v. on days 1–5 every 21 days). In fact, a recent analysis of data pooled from several multicenter second-line SCLC trials suggests that dose reductions to 1.25 mg/m²/day after the first cycle of topotecan are not associated with decreased efficacy (32). Although the paclitaxel dose of 160 mg/m² i.v. for 3 h is 64% of the dose used in the original Phase II trials documenting single-agent activity in SCLC (250 mg/m² for 24 h; Refs. 16 and 17), lower doses of paclitaxel (175–225 mg/m²) are commonly used in combination chemotherapy regimens for other solid tumors, such as non-small cell lung and head and neck cancers (33, 34). One might argue that the paclitaxel doses used in this study were not optimal and that higher doses with filgrastim support would have resulted in improved outcomes. There are no randomized studies in patients with SCLC that directly address this question, although sequential Phase II trials suggest a possible dose response effect with paclitaxel at doses of 135 mg/m² versus 200 mg/m² when administered with carboplatin and etoposide (35). Randomized trials in patients with other solid tumors, such as those with recurrent ovarian and head and neck cancers, however, have not shown a dose response relationship or increased survival benefit for higher doses of paclitaxel (36, 37).

In summary, we have demonstrated the feasibility of using topotecan and paclitaxel before chemoradiotherapy in patients with LD SCLC. We defined an MTD for Phase II studies and observed expected hematological and nonhematological toxicities. By the time we had completed accrual to this study, a Phase II CALGB trial (CLB-39808) with a similar treatment plan for patients with LD SCLC had opened and was accruing patients. In this trial, patients received two cycles of topotecan and paclitaxel given with growth factor support before receiving three cycles of carboplatin and etoposide with concurrent thoracic irradiation. We therefore decided not to pursue Phase II continuation of our trial. The CALGB trial has recently closed after accruing of 75 patients, and efficacy results are awaited with interest. Preliminary toxicity analyses did not demonstrate any obvious increase in adverse events associated with chemoradiotherapy (38). Final response and survival data from this trial should help determine whether or not this approach warrants testing in a randomized setting.
REFERENCES


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