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Feasibility study of chemoradiotherapy followed by amrubicin and cisplatin for limited-disease small cell lung cancer

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Key words

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To evaluate the feasibility of amrubicin plus cisplatin (AP) following chemoradiotherapy for limited-disease small-cell lung cancer, chemo-naïve patients aged 20–70 years with a performance status of 0 or 1 and normal organ functions were treated with etoposide 100 mg/m^2 on days 1–3, cisplatin 80 mg/m^2 on day 1 and concurrent thoracic radiotherapy at 45 Gy/30 fractions (EP-TRT), followed by three cycles of amrubicin 40 mg/m^2 on days 1–3 and cisplatin 60 mg/m^2 on day 1 every 3 weeks. The EP-TRT could be completed in 21 patients (15 male and 6 female patients with a median age of 62 years). Of these, 2, 1 and 18 (86%) patients received one, two and three cycles of AP, respectively. Sixteen (76%) patients required granulocyte-colony stimulating factor (G-CSF) support. Grade 3/4 neutropenia occurred in all patients. Grade 3 febrile neutropenia was observed in 9 patients, lasting for 1 day in 5 patients. The incidences of grade 3/4 thrombocytopenia and anemia were 43 and 24%, respectively. Grade 3 infection and anorexia occurred in 2 and 3 patients, respectively. The response rate was 95%. The median (95% confidence interval [CI]) progression-free survival (PFS) was 41.9 (0–102) months, and the 5-year PFS rate (CI) was 41.9% (20.4–63.4%). The median overall survival (OS) has not been reached yet, and the 5-year OS rate (CI) was 57.8% (35.2–80.4%). In conclusion, EP-TRT followed by AP therapy was well-tolerated, although a large number of patients required G-CSF support.

Small-cell lung cancer (SCLC), which accounts for approximately 13% of all malignant pulmonary tumours, is an aggressive malignancy with a propensity for rapid growth and early widespread metastases. Limited disease (LD), defined as disease confined to one hemithorax, can be encompassed by a single radiation therapy port, and accounts for roughly 30 to 40% of all cases of SCLC at presentation.[(1)] LD-SCLC has been treated with chemotherapy and thoracic radiotherapy (TRT). A phase III trial of concurrent versus sequential twice-daily TRT (45 Gy/30 fractions over 3 weeks) in combination with four cycles of etoposide plus cisplatin (EP) therapy in patients with LD-SCLC (JCOG 9104) showed that the concurrent treatment yielded better outcomes than the sequential treatment, with a median survival time of 27 months and 5-year survival rate of 24%.[(2)] Another phase III trial comparing single-daily TRT (45 Gy/25 fractions over 5 weeks) versus twice-daily TRT (45 Gy/30 fractions over 3 weeks) concurrently with four cycles of EP therapy in patients with LD-SCLC resulted in survival benefit in the twice-daily TRT group; the median survival time was 23 months and the 5-year survival rate was 23%.[(3)] In addition, prophylactic cranial radiation (PCI) in patients showing complete response (CR) during the induction treatment has been shown to decrease the cumulative incidence of brain metastasis by half and to improve the

3-year survival rate by 5.4%.[4] Thus, four cycles of EP therapy and twice-daily TRT beginning with cycle 1 of chemotherapy followed by PCI is regarded as the standard treatment for patients with LD-SCLC.

Although LD-SCLC is initially highly responsive to both chemotherapy and radiotherapy, the majority of patients ultimately relapse and die of the disease. The effects of the addition of a third agent to EP therapy and an increase in the total dose of TRT have been investigated to enhance the therapeutic effect. These attempts, however, have produced substantial toxicity and have failed to improve survival.[1] In contrast, we have made modifications to the chemotherapy regimen following the induction standard chemoradiotherapy. Two phase II trials of three cycles of cisplatin plus irinotecan after EP therapy and twice-daily TRT in patients with LD-SCLC showed promising 3-year survival rates of 30–38%,[5,6] although this regimen failed to show superiority to the standard regimen in a phase III trial.[7]

Amrubicin, a totally synthetic 9-amino-anthracycline and potent topoisomerase II inhibitor, has been developed for the treatment of SCLC. A phase II trial of amrubicin monotherapy in chemo-naïve patients with extensive SCLC showed an objective response rate (ORR) of 76% and median overall survival (OS) of 11.8 months, comparable to the results obtained with EP therapy.[8] When combined with cisplatin, amrubicin showed promising antitumor effects against extensive disease (ED)-SCLC in a phase II trial with an ORR of 88% and a median OS of 13.6 months.[9] In addition, providing a chemotherapy regimen in the consolidation phase different from that in the induction phase may be important to suppress the emergence of chemo-resistant clones in tumors. Thus, the introduction of cisplatin plus amrubicin chemotherapy (AP therapy) for treatment of LD-SCLC may be worthwhile, although a recent phase III trial in patients with ED-SCLC failed to show superiority of AP therapy to a combination of irinotecan and cisplatin.[10]

The objectives of the present study were to evaluate the toxicity and feasibility of AP therapy following EP therapy plus twice-daily TRT, and to observe the antitumor effects of this regimen in patients with LD-SCLC.

Patients and Methods

Study design. This study was designed as a multi-institutional feasibility study. The protocol and consent form were approved by the Institutional Review Board of each institution. The primary endpoint was the treatment completion rate (TCR), and the secondary endpoints were toxicity, ORR, progression-free survival (PFS) and OS.

Patient selection. The eligibility criteria were: (1) histologically or cytologically proven SCLC; (2) LD (confined to one hemithorax, but excluding contralateral hilar lymph node involvement); (3) age between 20 and 70 years; (4) Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; (5) measurable disease; (6) percent volume of the normal lung receiving 20 Gy or more (V_{20}) ≤ 35%, and indication for curative thoracic radiotherapy determined by a radiation oncologist; (7) no previous treatment for SCLC; (8) no previous chemotherapy for other tumors, except for oral chemotherapy as adjuvant chemotherapy after surgery; (9) adequate bone marrow function (white blood cell [WBC] count $\geq 4.0 \times 10^9$/L, hemoglobin ≥9.0 g/dL, and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin ≤1.5 mg/dL and transaminase ≤2.5 times the upper limit of the normal range), renal function (serum creatinine ≤1.25 times the upper limit of the normal range) and pulmonary function (PaO_2 ≥70 Torr under room air); and (10) availability of written informed consent. Patients were excluded if they had: (1) malignant pleural or pericardial effusion, with the exception of small effusions (1 cm or less) seen only on chest computed tomography (CT) scan; (2) active prior malignancies with a disease-free interval of <5 years, except for carcinoma in situ cured by local therapy; or (3) concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 6 months, uncontrolled arrhythmia, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified on chest x-ray, infection, mental disorder or other diseases representing contraindications for chemotherapy or radiotherapy, and any diseases requiring systemic steroid administration. Pregnant or lactating women were ineligible.

Pretreatment evaluation. The pretreatment assessment included a complete blood count, routine chemistry determinations, measurement of the creatinine clearance, blood gas analysis, electrocardiography, lung function testing, chest x-ray examination, chest CT, brain CT or magnetic resonance imaging, abdominal CT, and radionuclide bone scintigraphy or positron emission tomography.

Treatment schedule. Induction EP therapy consisted of one cycle of cisplatin 80 mg/m^2 on day 1 and etoposide 100 mg/m^2 on days 1 to 3. Cisplatin was administered by i.v. infusion over 60 to 120 min with 2500 to 3000 mL of i.v. hydration fluids and standard prophylactic antiemetic therapy consisting of a 5-hydroxytryptamine-3 receptor antagonist and a steroid.

On day 2 of the EP therapy, TRT was begun and delivered from a megavoltage equipment (6–10 MV) at a fraction dose of 1.5 Gy twice daily, with at least a 6-h interval between the fractions, to a total dose of 45 Gy administered in 30 fractions over 3 weeks. All patients underwent a 3-D treatment-planning CT 3 to 7 days before the start of the treatment. The gross tumor volume (GTV) was defined as the primary tumor delineated on pulmonary windows of the chest CT. Atelectasis or secondary changes in the peripheral lung region of the primary tumor were not included. Metastatic lymph nodes were defined as nodes 1 cm or larger in the short axis diameter visualized on mediastinal windows of the CT images. The clinical target volume (CTV) included the GTV (CTVprimary and CTVnode) and uninvolved regional lymph nodes, including ipsilateral hilar and bilateral mediastinal (#2, 3, 4, 7) lymph nodes (CTVsubclinical). The other regions were not routinely included unless metastatic nodes were noted. The contralateral hilar lymph node was excluded from the CTV. The planning target volume (PTV) was determined as the CTV plus 1.0 cm for the anterior, posterior, medial and lateral margins, and 1.0 to 2.0 cm for the superior and inferior margins, taking into account setup variations and internal organ motions. A total of 30 Gy was delivered to the PTVprimary, PTVnode and PTVsubclinical, and a boost radiation dose of 15 Gy was delivered to the PTVprimary and PTVnode only. Lung heterogeneity corrections were not applied. The spinal cord dose was limited to 36 Gy.

Following chemoradiotherapy, the patients were assessed to determine their fulfillment of the following criteria for the start of AP therapy: PS of 0–1, WBC count $\geq 3.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, serum hepatic transaminase levels ≤2.5 times the upper limit of the normal range, total serum bilirubin level ≤ 1.5 mg/dL, serum creatinine ≤1.5 mg/dL, fever <37.5°C, and no active infection. Stable radiation pneumonitis was allowed if all of the following criteria were met: (1) no aggravation of symptoms, including cough, fever or dyspnea; (2) PaO_2 ≥ 70 Torr or SpO_2 ≥ 93%; (3) no infiltrates

or consolidation over the irradiated area on a chest X-ray; and (4) no requirement of oxygen or steroid therapy.

Amrubicin 40 mg/m^2 on days 1 to 3 and cisplatin 60 mg/m^2 on day 1 were started on day 29 of the induction chemotherapy, and repeated every 3 to 4 weeks for three cycles. After the AP therapy, PCI at a total dose of 25 Gy in 10 fractions was added for patients showing CR or near CR, defined as a reduction by >70% of the sum of the greatest dimensions of the lesions.

Toxicity assessment and treatment modification. Complete blood counts, routine chemistry determinations, and a chest x-ray were performed at least once a week during the course of treatment. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The lung toxicity grade was defined as the highest grade among those for cough, dyspnea, airway obsturction, pneumonitis/pulmonary infiltrates and pulmonary fibrosis in the pulmonary/upper respiratory section of the CTCAE version 3.0.[11]

Subsequent cycles of AP therapy were delayed if any of the following toxicities were noted on day 1: WBC count $<3.0 \times 10^9$/L, platelet count $<100 \times 10^9$/L, serum hepatic transaminase levels >2.5 times the upper limit of the normal range, total serum bilirubin level >1.5 mg/dL, fever ≥37.5°C, active infection, unstable pneumonitis or PS of 2 3. If these toxicities did not recover within 6 weeks from day 1 of the previous cycle of AP therapy, subsequent cycles were not administered. If the serum creatinine level was 1.6 2.0 mg/dL on day 1, the dose of cisplatin was reduced to 45 mg/m^2, and if it was above 2.0 mg/dL, cisplatin administration was omitted. If grade 3 febrile neutropenia was noted, prophylactic granulocyte-colony stimulating factor (G-CSF) support was started on day 5 of the subsequent cycles. If grade 3 febrile neutropenia was noted again despite the prophylactic G-CSF support, then the dose of amrubicin was reduced by 10 mg/m^2 in subsequent cycles. If grade 4 thrombocytopenia or grade 3 non-hematological toxicity other than nausea, vomiting and transient electrolyte disturbances was noted, the dose of amrubicin was reduced by 10 mg/m^2 in subsequent cycles. Any protocol-defined treatments were terminated if grade 4 non-hematological toxicities other than transient electrolyte disturbances or a PS of 4 was noted.

Response evaluation. Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.[12]

Statistical analyses. The primary objective of this study was to evaluate the feasibility of a new combination chemotherapy following induction chemoradiotherapy. However, the criteria of feasibility in this setting have not yet been established. Thus, we arbitrarily defined treatment completion (TC) as completion of two to three cycles of AP therapy without grade 4 non-hematological toxicity or treatment-related death, and the TCR, the primary endpoint of this study, as the percentage of patients achieving TC relative to the total number of patients. In conformity with phase I trials of investigational new agents, if four to six of the initial six patients met the criteria of TC, then 6–15 patients were added to confirm that the TC rate would be two-thirds or higher. We did not calculate the sample size to ensure the alpha-error or beta-error of the TC rate.

The PFS and OS were estimated using the Kaplan–Meier method. They were measured from the date of registration to the occurrence of an event, defined as the date of detection of disease progression, date of death from any cause, or date of the last follow-up for evaluation of the PFS, and the date of death from any cause or that of the last follow-up for evaluation of the OS. Patients who were lost to follow-up without events were censored at the last known date of follow-up. A confidence interval (CI) for the response rate was calculated by the method used for exact binomial CI. The STATA statistical software, version 11 (StataCorp LP, TX USA), was used for the statistical analyses.

Results

From August 2007 to June 2009, 21 patients were enrolled in this study, and their characteristics are summarized in Table 1. There were 15 male patients and 6 female patients, with a median age of 62 years (range, 46 70 years). All the patients had LD-SCLC and were in good general condition.

Of the 21 patients, EP therapy was completed without dose modification in 20 patients, and 1 patient received cisplatin on day 1 and etoposide on days 2 3, but etoposide on day 3 had to be omitted because of the development of grade 3 diarrhea. TRT was completed at the full dose in all patients. The toxicity of EP therapy administered concurrently with TRT was mainly hematological. Grade 3 4 neutropenia and grade 3 febrile neutropenia were noted in 91 and 29% of the patients, respectively, but they were manageable in all cases (Table 2).

With a median (range) interval between the EP and AP therapies of 28 (28–43) days, AP therapy was started in all patients. Three cycles of AP therapy were administered in 18 patients, two cycles in 1 patient, and one cycle in 2 patients. Thus, the TC rate was 90.5% (19/21). The reasons for administration of no more than one to two cycles of AP therapy only in 3 patients were severe toxicity, delay in recovery from toxicity, and patient refusal in 1 patient each. The median (range) interval between the first and second cycles of AP therapy in 19 patients was 28 (21–36) days, and that between the second and third cycles of AP therapy in 18 patients was 27.5 (21–35) days. A reduction in the amrubicin dose in subsequent cycles was necessitated in 7 (33%) patients. G-CSF support was used in 16 (76%) patients, whereas transfusion of red blood cells and platelets was required in 3 (14%) patients each.

Grade 3–4 leukopenia and neutropenia were noted in all patients. Grade 3 febrile neutropenia was noted in 9 (43%) patients, but the duration of fever ≥38°C was only 1 day in 5 patients, 3 days in 1 patient, and 5 to 7 days in three

Table 1. Patient characteristics

Characteristics	*N*	%
Sex		
Male	15	71
Female	6	29
Age		
Median (range)	62	46–70
Performance status		
0	17	81
1	4	19
Body weight loss (%)		
0	17	81
0.1–4.9	2	10
5.0	2	10
V_{20}* (%)		
Median (range)	19	10–34

*V_{20}: The percent volume of the normal lung receiving 20 Gy or more.

Table 2. Toxicity of induction chemoradiotherapy

Grade	1	2	3	4	3 + 4	%
Leukopenia	0	1	12	8	20	95
Neutropenia	0	2	6	13	19	91
Anemia	16				0	0
Thrombocytopenia	12	4			0	0
Febrile neutropenia	0	0	6		6	29
AST elevation	2				0	0
ALT elevation	4	1			0	0
Hyperbilirubinemia	3	2			0	0
Creatinine elevation	3				0	0
Hyponatremia	7	0	2		2	10
Hyperkalemia	4				0	0
Allergic reaction	1	1			0	0
Anorexia	9	5	2		2	10
Nausea	7	10			0	0
Vomiting	5	2			0	0
Mucositis	2				0	0
Diarrhea	1	0	1		1	5
Constipation	4	1			0	0
Esophagitis	8	12			0	0
Dermatitis associated with radiation	8				0	0

Table 3. Toxicity of cisplatin plus amrubicin chemotherapy

Grade	1	2	3	4	3 + 4	%
Leukopenia	0	0	7	14	21	100
Neutropenia	0	0	4	17	21	100
Anemia	3	13	4	1	5	24
Thrombocytopenia	4	6	6	3	9	43
Febrile neutropenia	0	0	9		9	43
AST elevation	4				0	0
ALT elevation	3				0	0
Hyperbilirubinemia	3	1			0	0
Creatinine elevation	6				0	0
Hyponatremia	9	0	1		1	5
Hyperkalemia	5	0	1		1	5
Infection	0	0	2		2	10
Allergic reaction	1				0	0
Anorexia	7	7	3		3	14
Nausea	8	6			0	0
Vomiting	1	3			0	0
Mucositis	1	3			0	0
Diarrhea	3	0	1		1	5
Constipation	6	2	1		1	5
Esophagitis	6	7	1		1	5
Pneumonitis	4	3			0	0
Dermatitis associated with radiation	4	1			0	0

patients. All of these patients recovered, and no treatment-related deaths were noted (Table 3).

Seventeen (81%) patients received PCI. The reasons for not administering PCI were persistent toxicity of previous AP therapy in 1 patient, not achieving CR or near CR in 2 patients, and patient refusal in 1 patient.

The tumor response was not assessable in 1 patient because she refused to receive subsequent therapy after one cycle of AP therapy. Among the remaining 20 patients, 2 CR and 18 partial responses were observed, and, therefore, the ORR in the 21 patients was 95% (95% CI, 76.2–99.9%). The median

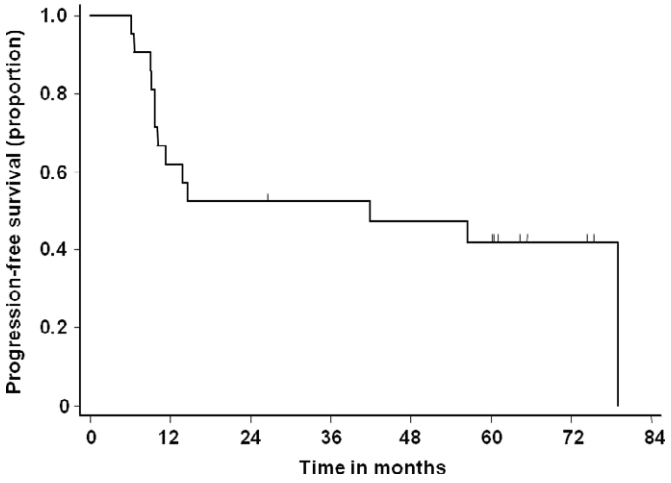

Fig. 1. Progression-free survival (n = 21).

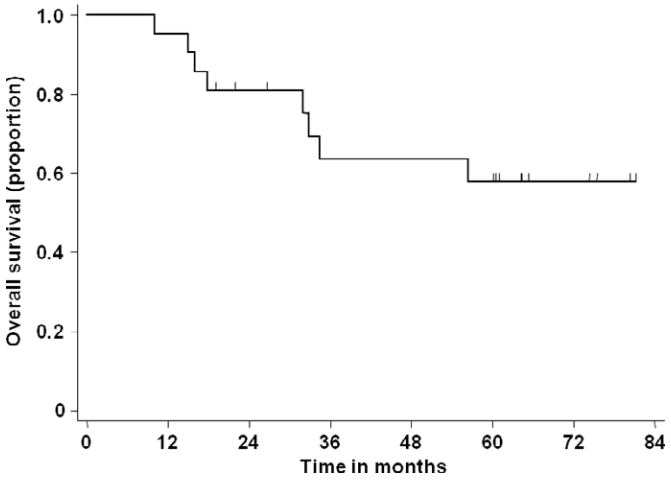

Fig. 2. Overall survival (n = 21).

progression-free survival (PFS) was 41.9 months (95% CI, 0–102 months), and the 3-year and 5-year PFS rates were 52.4% (95% CI, 31.0–73.8%) and 41.9% (95% CI, 20.4–63.4%), respectively (Fig. 1). The median overall survival (OS) has not been reached yet, and the 3-year and 5-year OS rates were 63.6% (95% CI, 41.8–85.4%) and 57.8% (95% CI, 35.2–80.4%), respectively (Fig. 2).

Discussion

The TC rate, the primary endpoint of this study, was 90.5%, which exceeded the protocol-defined criteria of feasibility of 67%. In addition, full cycles of AP therapy were delivered in 18 (86%) patients. These results suggest that administration of three cycles of AP therapy following EP therapy and TRT is feasible in patients with LD-SCLC.

The dose of amrubicin needed to be reduced in 33% (7 of 21) of the patients. This figure is comparable to that in a previous phase I/II study of AP therapy for previously untreated extensive SCLC, where dose escalation was determined based on the data from the first course of chemotherapy. In this study, the dose of amrubicin was reduced in 17% of patients

in the second cycle, 21% of patients in the third cycle, and 31% of patients in the fourth cycle.[9] Unlike in the previous study, however, this study targeted patients with LD-SCLC, which is potentially curative as long as sufficient chemotherapy has been administered. Thus, the initial dose of chemotherapy should not be reduced too quickly in patients with LD-SCLC.

The interval between cycles of AP therapy was set at 3 to 4 weeks in the protocol, and the current results showed that the actual median interval was 28 days. It is well known that recovery of myelosuppression is delayed when TRT is added to systemic chemotherapy. In the JCOG phase III study comparing concurrent and sequential TRT combined with four cycles of EP therapy, the interval between cycles of the EP therapy was 4 weeks in the concurrent treatment group and 3 weeks in the sequential treatment group, and the actual hematological toxicity was more severe in the former treatment group.[2] Thus, the interval between cycles of AP therapy of 28 days in this study is considered to be acceptable in concurrent chemoradiotherapy.,

Myelotoxicity, the primary toxicity in this study, was severe, as suggested by grade 3–4 neutropenia developing in all patients and grade 3 febrile neutropenia developing in 9 (43%) patients. More than half of these patients, however, recovered within 1 day, and there were no treatment-related deaths. G-CSF support was used in 16 (76%) patients, suggesting that prophylactic G-CSF support will be helpful for subsequent studies.

Limitations of this study included the number of patients, which was insufficient for obtaining statistical power, and the fact that it was conducted in five high-volume cancer centers in Japan. Thus, the feasibility of this regimen as well as its antitumor activity against LD-SCLC should be confirmed in a phase II study conducted with the participation of many city hospitals, followed by a large phase III study.

Although evaluation of the antitumor activity in this study was limited by the small number of patients, the results were impressive. The 5-year PFS rate was 41.9% (95% CI, 20.4–63.4%), and the 5-year OS rate was 57.8% (95% CI, 35.2–80.4%). With the encouraging results, we are conducting a randomized phase II trial of the AP therapy or weekly combination chemotherapy (CODE regimen) following the EP/TRT therapy in patients with chemo-naïve LD-SCLC (JCOG1011).

In conclusion, EP-TRT followed by three cycles of AP was well-tolerated, although most patients required G-CSF support.

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Disclosure Statement

This study was conducted in the National Cancer Center Hospital, Hyogo Cancer Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, National Cancer Center Hospital East and Shizuoka Cancer Center. All the authors of this manuscript were staff doctors of these hospitals when this study was conducted, and were involved in the plan, conduct and analysis of this study. Patient management in this study was done by all the authors as well as other staff doctors and residents in each hospital. The manuscript was mainly prepared by the first author (I. S.) and discussed by all the authors. The other authors have no conflict of interest to declare.

References

1 Socinski MA, Bogart JA. Limited-stage small-cell lung cancer: The current status of combined-modality therapy. *J Clin Oncol* 2007; **25**: 4137–45.
2 Takada M, Fukuoka M, Kawahara M *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002; **20**: 3054–60.
3 Turrisi AT 3rd, Kim K, Blum R *et al.* Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999; **340**: 265–71.
4 Auperin A, Arriagada R, Pignon JP *et al.* Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999; **341**: 476–84.
5 Kubota K, Nishiwaki Y, Sugiura T *et al.* Pilot study of concurrent etoposide and cisplatin plus accelerated hyperfractionated thoracic radiotherapy followed by irinotecan and cisplatin for limited-stage small cell lung cancer: Japan Clinical Oncology Group 9903. *Clin Cancer Res* 2005; **11**: 5534–8.
6 Saito H, Takada Y, Ichinose Y *et al.* Phase II study of etoposide and cisplatin with concurrent twice-daily thoracic radiotherapy followed by irinotecan and cisplatin in patients with limited-disease small-cell lung cancer: West Japan Thoracic Oncology Group 9902. *J Clin Oncol* 2006; **24**: 5247–52.
7 Kubota K, Hida T, Ishikura S *et al.* Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy (JCOG0202): A randomised phase 3 study. *Lancet Oncol* 2014; **15**: 106–13.
8 Yana T, Negoro S, Takada M *et al.* Phase II study of amrubicin in previously untreated patients with extensive-disease small cell lung cancer: West Japan Thoracic Oncology Group (WJTOG) study. *Invest New Drugs* 2007; **25**: 253–8.
9 Ohe Y, Negoro S, Matsui K *et al.* Phase I-II study of amrubicin and cisplatin in previously untreated patients with extensive-stage small-cell lung cancer. *Ann Oncol* 2005; **16**: 430–6.
10 Satouchi M, Kotani Y, Shibata T *et al.* Phase III study comparing amrubicin plus cisplatin with irinotecan plus cisplatin in the treatment of extensive-disease small-cell lung cancer: JCOG 0509. *J Clin Oncol* 2014; **32**: 1262–8.
11 Miller KL, Shafman TD, Marks LB. A practical approach to pulmonary risk assessment in the radiotherapy of lung cancer. *Semin Radiat Oncol* 2004; **14**: 298–307.
12 Therasse P, Arbuck SG, Eisenhauer EA *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205–16.