

Phase II Study of Consolidation Amrubicin After Concurrent Chemoradiotherapy in Patients With Limited-stage Small-cell Lung Cancer

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Abstract. *Background:* Concurrent chemoradiotherapy (CCRT) is the gold standard for limited-stage small-cell lung cancer (LS-SCLC); however, most patients inevitably experience relapse. We hypothesized consolidation amrubicin following CCRT to be a potential treatment for LS-SCLC. *Patients and Methods:* All enrolled patients were treated using induction CCRT consisting of four cycles of etoposide and cisplatin plus concurrent thoracic radiotherapy. Eligible patients then received three cycles of amrubicin as consolidation therapy (consolidation population). The primary endpoint was the 2-year progression-free survival rate in the consolidation population. *Results:* Of the 36 intention-to-treat patients, 28 (78%) received amrubicin and 24 (67%) completed all planned treatments. The 2-year progression-free survival rate and overall response rate were 35.7% and 86%, respectively. The median progression-free and overall survival were 14.3 and 60.9 months, respectively. There were no treatment-related deaths in the intention-to-treat population. *Conclusion:* This study was terminated due

to slow patient accrual; however, this treatment strategy was feasible and demonstrated promising efficacy.

Approximately 15% of all lung cancers are diagnosed as small-cell lung cancer (SCLC), and approximately one-third are classified as limited-stage (LS)-SCLC in the US (1). For decades, the standard treatment for LS-SCLC has been concurrent chemoradiotherapy (CCRT), consisting of four cycles of etoposide and cisplatin plus concurrent thoracic radiotherapy (TRT) (2-4). Although SCLC is highly sensitive to both chemotherapy and radiotherapy, most patients eventually experience relapse, resulting in only one out of four patients surviving for more than 5 years (3, 4).

Amrubicin, a fully synthetic 9-aminoanthracycline, is converted to an active metabolite, amrubicinol, by reduction of the 13-position ketone. Amrubicin has a structure similar to that of doxorubicin, which mainly acts as a DNA intercalator, whereas amrubicin and amrubicinol have cytotoxic effects as DNA topoisomerase II inhibitors instead of DNA intercalators (5). Although a phase III study failed to demonstrate the superiority of amrubicin in terms of overall survival (OS) compared with standard topotecan in patients with relapsed SCLC, the overall response rate (ORR) and progression-free survival (PFS) were significantly better in the amrubicin arm. Of note, the OS was significantly better in the amrubicin arm in the refractory relapsed subset (6). Since its approval in 2002, amrubicin has been widely used as a standard second-line treatment for SCLC in Japan.

LS-SCLC is potentially curable by chemoradiotherapy; however, once relapsed, it is markedly difficult to cure.

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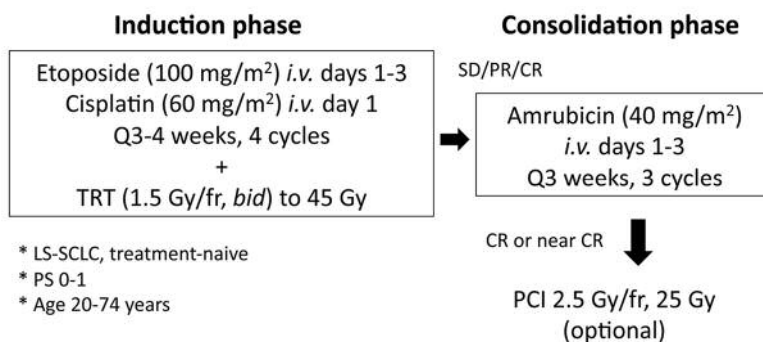


Figure 1. Study schema. bid: Twice daily; CR: complete response; i.v.: Intravenously; LS-SCLC: limited-stage small-cell lung cancer; PCI: prophylactic cranial irradiation; PR: partial response; PS: performance status; SD: stable disease; TRT: thoracic radiotherapy.

Therefore, potentiating initial treatment is essential for improving the cure rate in patients with LS-SCLC. Considering its efficacy, especially for refractory relapsed SCLC, we considered the integration of amrubicin into the initial treatment for LS-SCLC to be a promising strategy. Thus, we conducted a phase II study to evaluate the safety and efficacy of consolidation amrubicin following standard CCRT in patients with LS-SCLC.

Patients and Methods

Patient selection. Patients with histologically or cytologically confirmed LS-SCLC were eligible for the study. LS-SCLC was defined as disease confined to one hemithorax, including the ipsilateral hilar, bilateral mediastinal, and bilateral supraclavicular lymph node metastases. Pleural effusion of less than 1 cm by chest computed tomography (CT) was allowed, but patients with malignant pleural effusion were excluded. Each patient was required to meet the following criteria: No prior chemotherapy or radiotherapy, age 20-74 years, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, measurable lesions, adequate hematological function [white blood cell count (WBC) $\geq 3,000/\text{mm}^3$; platelets $\geq 100,000/\text{mm}^3$; hemoglobin ≥ 9.0 g/dl], and sufficient hepatic function [aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 100 IU/l; total bilirubin ≤ 1.5 mg/dl] and renal function (creatinine ≤ 1.5 mg/dl). Patients with pericardial effusion, active concomitant malignancy, prior second primary cancer, active infection, severe heart disease, history of myocardial infarction in the previous 3 months, unstable angina, uncontrollable diabetes mellitus or hypertension, interstitial pneumonia or active lung fibrosis on chest radiograph, or psychiatric disease were excluded. This study was approved by the Institutional Review Board of each participating institution. Written informed consent was received from all patients (Clinical trial registration: UMIN000002352).

Treatment schedule. The study schema is shown in Figure 1. Induction treatment, consisting of etoposide at 100 mg/m² on days 1-3 and cisplatin at 60 mg/m² on day 1, was started within 7 days from registration. Etoposide was administered as a 1- to 2-h intravenous infusion, and cisplatin as a 1- to 2-h intravenous

infusion with sufficient hydration. TRT was started on day 1 of the first cycle of etoposide-cisplatin and administered at a fraction dose of 1.5 Gy twice daily to a total dose of 45 Gy in 3 weeks. The second cycle of etoposide-cisplatin was given 4 weeks after the first cycle of etoposide-cisplatin, and an additional three cycles of etoposide-cisplatin was continued every 3 weeks unless the disease progressed or intolerable toxicities were observed. All the patients who were enrolled in the study were defined as the intention-to-treat (ITT) population.

After the induction treatment, patients were reassessed for the following criteria for the administration of consolidation amrubicin: completion of the defined induction treatment, no progressive disease [complete response (CR), partial response (PR), or stable disease (SD)] within 42 days from the start of the fourth cycle of etoposide-cisplatin, ECOG PS of 0-2, WBC $\geq 3,000/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, bilirubin ≤ 1.5 mg/dl, AST and ALT ≤ 100 IU/l, creatinine ≤ 2.0 mg/dl, fever $< 37.5^\circ\text{C}$, no active infection, radiation dermatitis or esophagitis of grade 2 or less, and no pulmonary infiltration beyond the irradiated field. All eligible patients received three cycles of amrubicin at 40 mg/m² on days 1-3 every three weeks (consolidation population). Amrubicin was administered as a 5-min intravenous injection. Prophylactic cranial irradiation (PCI) was optional for patients who achieved CR or near CR by the above treatment.

Thoracic radiotherapy. TRT was delivered from 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 in 30 fractions in 3 weeks. All patients underwent three-dimensional treatment-planning computed tomography within 7 days before the start of the treatment. The gross tumor volume (GTV) included the pretreatment primary GTV and metastatic lymph nodes of 1 cm or larger in the short axis diameter on computed tomographic images. The clinical target volume (CTV) was equal to the GTV and uninvolved mediastinal and ipsilateral hilar nodes. 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) included the CTV plus sufficient margins (typically 0.5-1.0 cm laterally and 1.0-2.0 cm craniocaudally). The volume of the lung unaffected by cancer which would receive 20 Gy or more was kept to 35% or less. Heterogeneity corrections were applied to monitor unit calculations.

Table I. Patient characteristics.

		ITT population (N=36)	Consolidation population (N=28)
Age	Median (range)	65 (54-75)	64 (54-74)
Gender	Male	25 (69%)	18 (64%)
	Female	11 (31%)	10 (36%)
ECOG PS	0	30 (83%)	22 (79%)
	1	6 (17%)	6 (21%)

ITT: Intention-to-treat; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

Table II. Treatment delivery.

Treatment cycle	Cycle	n (%)
Etoposide/cisplatin	1	36 (100)
	2	34 (94)
	3	33 (92)
	4	31 (86)
Amrubicin	1	28 (78)
	2	26 (72)
	3	24 (67)

ITT: Intention-to-treat; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

Evaluation of toxicity and dose modification. Toxicity was evaluated based on the National Cancer Institute-Common Terminology Criteria, version 4.0 (7). Blood tests and chest x-ray were required at least once a week during TRT, and at least once 2 weeks after the completion of TRT. If patients had WBC $<1,000/\text{mm}^3$, neutrophils $<500/\text{mm}^3$, platelets $<25,000/\text{mm}^3$, or grade 3 non-hematological toxicities other than nausea, vomiting, fatigue, alopecia, and transient electrolyte disturbances, the doses of etoposide, cisplatin, and amrubicin were reduced by 20, 10, and 5 mg/m², respectively, in subsequent cycles. If the creatinine level was greater than 1.5 mg/dl during the etoposide-cisplatin treatment, the dose of cisplatin was reduced to 50 mg/m². The next cycle of etoposide-cisplatin was started when a patient had a WBC $\geq 3,000/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, bilirubin ≤ 2.0 mg/dl, AST and ALT ≤ 100 IU/l, creatinine ≤ 1.5 mg/dl, PS of 0-2, and fever $<37.5^\circ\text{C}$. Amrubicin was started when a patient had a WBC $\geq 3,000/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, bilirubin ≤ 2.0 mg/dl, AST and ALT ≤ 100 IU/l, creatinine ≤ 2.0 mg/dl, PS of 0-2, and fever $<37.5^\circ\text{C}$. If PS of 3 or 4, grade 2 pneumonitis or pulmonary infiltrates, or a fever of 38.0°C or higher developed, radiotherapy was withheld until recovery. If toxicities persisted and patients did not meet the above criteria for up to 14 days from the completion of the previous cycle of chemotherapy or from the termination of TRT, the study treatment was terminated. Use of granulocyte colony stimulating factor (G-CSF) agents was allowed at the discretion of the treating physician, but prophylactic use was permitted only during the consolidation phase.

Evaluation of tumor response. Tumor response was assessed after the completion of TRT, during 8 to 28 days from the start of the fourth cycle of etoposide-cisplatin, and after the last cycle of amrubicin. Post-treatment evaluation was performed every 2 months until death or progressive disease. The ORR was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (8).

Statistical analyses. The primary endpoint of the study was the 2-year PFS rate in the consolidation population. The secondary endpoints were the ORR, PFS, OS, and toxicities in the ITT and consolidation populations. The targeted sample size was 33 for the consolidation population, with a one-sided alpha of 0.1, a beta of 0.2, and expected and threshold 2-year PFS rates of 40% and 25%, respectively. Assuming the CCRT consisting of TRT and four cycles of etoposide-cisplatin to be completed by 85% of the patients, and

a disease control rate of 95%, a total of 41 patients were required for the ITT population. If fewer than eight patients completed the three cycles of consolidation amrubicin among the first 17 patients, the study was to be terminated due to unfeasibility. The PFS and OS were estimated using the Kaplan-Meier method. The PFS was measured from the date of the first registration to disease progression, death from any cause, or the last follow-up. OS was measured from the date of the first registration to the date of death from any cause or the last follow-up. Patients who were lost to follow-up without events were censored at the last known date of follow-up. All patients who received at least one cycle of chemotherapy were considered assessable for response evaluation, and toxicity. All analyses were performed using JMP 14 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. Between January 2010 and September 2016, 36 patients were enrolled in this study. Patient characteristics in the ITT population are listed in Table I. The median age was 65 years (range=54 to 75 years), 25 (69%) patients were male, and 30 (83%) patients had an ECOG PS of 0.

Treatment delivery. All 36 patients completed the TRT of 45 Gy and 31 (86%) completed the four cycles of etoposide-cisplatin (Table II). The reasons for discontinuation of etoposide-cisplatin treatment were persisting toxicity in four (two of neutropenia, and one each of esophagitis, and creatinine increase) and cancer-unrelated death in one. Among the 31 patients who completed the induction phase, three did not enter the consolidation phase (one with progressive disease, one due to toxicity, and one patient refusal). Patient characteristics for the consolidation population are also listed in Table I. Of the ITT population, 28 (78%) entered the consolidation phase and 24 (67%) completed the planned three cycles of amrubicin (Table II). The reasons for discontinuation of amrubicin were patient refusal for one and worsening of radiation pneumonitis for three. Dose adjustment for etoposide-cisplatin and amrubicin

Table III. Antitumor response.

		Phase	
		Induction (n=36)	Consolidation (n=28)
Overall response	No. of patients with response	30	2
	Percentage of patients (95% CI)	83 (68-92)	7 (2-23)
Objective response	Complete response	7 (19)	0 (0)
	Partial response	23 (64)	2 (7)
	Stable disease	2 (6)	23 (82)
	Progressive disease	1 (3)	3 (11)
	Not evaluable	3 (8)	0 (0)

CI: Confidence interval.

was required in 11 (31%) and one patient (4%), respectively. After the completion of all planned treatments, 18 out of 24 patients (75%) received PCI.

Response and survival. Antitumor responses are shown in Table III. In the induction phase, seven (19%) patients achieved CR and 23 (64%) had PR with an ORR of 83% [95% confidence interval (CI)=68-92%]. In the consolidation phase, 2 (7%) had PR with an ORR of 7% (95% CI=2-23%). Consequently, the ORR was 86% (95% CI=69-94%) in the consolidation population. The median PFS was 13.4 (95% CI=7.5-19.0) months and 14.3 (95% CI=10.8-46.6) months in the ITT and consolidation populations, respectively. The 2-year PFS rate was 30.6% (95% CI=18.0-46.9%) and 35.7% (95% CI=20.7-54.2%) in the ITT and consolidation populations, respectively (Figure 2A). After a median follow-up of 29.8 months (range=6.6-102.4 months), the median OS was 60.9 months (95% CI=29.8 months-not reached) and 60.9 months (95% CI=29.8 months-not reached) in the ITT and consolidation populations, respectively (Figure 2B).

Toxicity. Both hematological and non-hematologic toxicities are summarized in Table IV. During the induction phase, grade 3 or 4 neutropenia developed in 36 (100%) patients, thrombocytopenia in five (14%), and febrile neutropenia in seven (19%). G-CSF was required for 32 (89%) patients, but none required red blood cell or platelet transfusion. Grade 3 creatinine increase, anorexia, stomatitis, and esophagitis were observed in one (3%) patient each.

During the consolidation phase, grade 3 or 4 neutropenia developed in 11 (39%) patients, anemia in seven (25%), thrombocytopenia in four (14%), and febrile neutropenia in two (7%). G-CSF was administered to 18 (64%) patients, of whom six (33%) received it as primary prophylaxis. Two (7%) patients required red blood cell transfusion, but none required platelet transfusion. Five (18%) patients developed

grade 3 pneumonitis; all cases were considered radiation-associated pneumonitis and steroid-sensitive. There were no treatment-related deaths in the ITT population.

Discussion

In this study, we evaluated the safety and efficacy of consolidation amrubicin following standard CCRT. This study was terminated due to slow patient accrual. Therefore, no statistical conclusions can be made. However, this treatment strategy was feasible and demonstrated promising efficacy.

For decades, the standard treatment for LS-SCLC has been CCRT consisting of four cycles of etoposide-cisplatin plus concurrent TRT, associated with a 5-year survival rate of approximately 25%. New treatment strategies are eagerly anticipated to improve outcomes in this setting. One such attempt is to modify the TRT dose and schedule. The CONVERT study team conducted a randomized phase III study comparing two different radiation schedules: 45 Gy in 30 twice-daily fractions of 1.5 Gy versus 66 Gy in 33 once-daily fractions of 2 Gy in combination with 4-6 cycles of etoposide-cisplatin; however, there was no significant survival difference between the two arms (9).

Another such approach is to modify the chemotherapy regimen. The Japan Clinical Oncology Group (JCOG) demonstrated significant OS benefits of irinotecan plus cisplatin over etoposide-cisplatin for extensive-stage SCLC (10). Based on the results, JCOG conducted a randomized phase III study comparing irinotecan plus cisplatin with etoposide-cisplatin following concurrent TRT concomitant with one cycle of etoposide-cisplatin in patients with LS-SCLC; however, irinotecan plus cisplatin failed to exhibit any survival advantages (11). Recently, a Japanese group conducted a feasibility study of amrubicin plus cisplatin following concurrent TRT concomitant with one cycle of etoposide-cisplatin in patients with LS-SCLC, and reported 5-year PFS and OS rates of 41.9% and 57.8%, respectively. Although hematological toxicities were severe, and all patients developed grade 3 or 4 neutropenia and required G-CSF support, these data are encouraging (12). Combined with our results, the data show the strategy of consolidation amrubicin after CCRT in LS-SCLC is promising and warrants further investigation.

In recent years, immune checkpoint inhibitors have been extensively investigated for many malignancies, including SCLC, and atezolizumab, an antibody against programmed death-ligand 1, significantly improved the survival from extensive-stage SCLC in combination with chemotherapy (13). Future studies for LS-SCLC should focus on immune checkpoint inhibitors, and there are several on-going studies using them to target LS-SCLC. However, as chemotherapy is the mainstay in the treatment of SCLC, continuous effort to improve its effectiveness is essential.

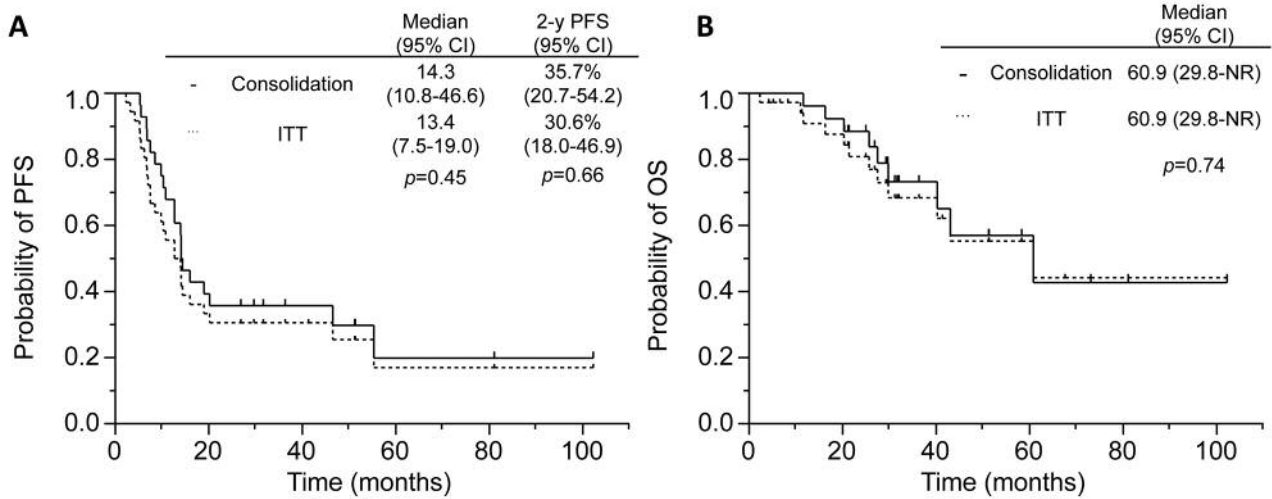


Figure 2. Kaplan-Meier curves for progression-free survival (PFS) (A) and overall survival (OS) (B). CI: Confidence interval; ITT: intention-to-treat; NR: not reached.

Table IV. Hematological and non-hematological toxicities.

Grade	Induction phase (n=36)						Consolidation phase (n=28)					
	0	1	2	3	4	≥3, n (%)	0	1	2	3	4	≥3, n (%)
Neutropenia	0	0	0	7	29	36 (100)	10	4	3	6	5	11 (39)
Anemia	5	5	26	0	0	0 (0)	5	5	11	7	0	7 (25)
Thrombocytopenia	14	12	5	4	1	5 (14)	17	4	3	4	0	4 (14)
Febrile neutropenia	29	0	0	6	1	7 (19)	26	0	0	2	0	2 (7)
Bilirubin	34	0	2	0	0	0 (0)	27	1	0	0	0	0 (0)
AST increase	27	9	0	0	0	0 (0)	20	8	0	0	0	0 (0)
ALT increase	25	11	0	0	0	0 (0)	24	3	1	0	0	0 (0)
Creatinine increase	23	7	5	1	0	1 (3)	24	4	0	0	0	0 (0)
Nausea	15	19	2	0	0	0 (0)	19	8	1	0	0	0 (0)
Vomiting	33	3	0	0	0	0 (0)	28	0	0	0	0	0 (0)
Fatigue	8	24	4	0	0	0 (0)	10	15	3	0	0	0 (0)
Anorexia	11	17	7	1	0	1 (3)	15	12	1	0	0	0 (0)
Diarrhea	33	2	1	0	0	0 (0)	27	1	0	0	0	0 (0)
Constipation	14	22	0	0	0	0 (0)	22	6	0	0	0	0 (0)
Stomatitis	28	7	0	1	0	1 (3)	22	6	0	0	0	0 (0)
Alopecia	13	18	5	0	0	0 (0)	14	12	2	0	0	0 (0)
Pneumonitis	32	3	1	0	0	0 (0)	6	8	9	5	0	5 (18)
Rash	32	4	0	0	0	0 (0)	25	3	0	0	0	0 (0)
Esophagitis	13	19	3	1	0	1 (3)	28	0	0	0	0	0 (0)

AST: Aspartate aminotransferase; ALT: alanine aminotransferase.

Conclusion

This study was terminated due to slow patient accrual; however, consolidation amrubicin following standard CCRT consisting of four cycles of etoposide-cisplatin plus concurrent TRT was feasible and demonstrated promising efficacy in patients with LS-SCLC.

Conflicts of Interest

The Authors declare no conflicts of interest in regard to this study.

Authors' Contributions

Y.H.K. designed the study. H.Y. and Y.H.K. contributed to the analysis and interpretation of data, and the writing of the article.

H.N., Y.S., H.O., T.N., K.T., T.H., Y.M., Y.I., T.M., and K.Y. contributed to data collection and interpretation. All Authors reviewed the article.

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References

- Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, Spitznagel EL and Piccirillo J: Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol* 24: 4539-4544, 2006. PMID: 17008692. DOI: 10.1200/JCO.2005.04.4859
- Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, Brodin O, Joss RA, Kies MS, Lebeau B, Onoshi T, Østerlind K, Tattersall M and Wagner H: A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 327: 1618-1624, 1992. PMID: 1331787. DOI: 10.1056/NEJM199212033272302
- Turrisi AT 3rd, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, Wagner H, Aisner S and Johnson DH: Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 340: 265-271, 1999. PMID: 9920950. DOI: 10.1056/NEJM199901283400403
- Takada M, Fukuoka M, Kawahara M, Sugiura T, Yokoyama A, Yokota S, Nishiwaki Y, Watanabe K, Noda K, Tamura T, Fukuda H and Saijo N: 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* 20: 3054-3060, 2002. PMID: 12118018. DOI: 10.1200/JCO.2002.12.071
- Hanada M, Mizuno S, Fukushima A, Saito Y, Noguchi T and Yamaoka T: A new antitumor agent amrubicin induces cell growth inhibition by stabilizing topoisomerase II-DNA complex. *Jpn J Cancer Res* 89: 1229-1238, 1998. PMID: 9914793. DOI: 10.1111/j.1349-7006.1998.tb00519.x
- von Pawel J, Jotte R, Spigel DR, O'Brien ME, Socinski MA, Mezger J, Steins M, Bosquée L, Bubis J, Nackaerts K, Trigo JM, Clingan P, Schütte W, Lorigan P, Reck M, Domine M, Shepherd FA, Li S and Renschler MF: Randomized phase III trial of amrubicin *versus* topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol* 32: 4012-4019, 2014. PMID: 25385727. DOI: 10.1200/JCO.2013.54.5392
- National Cancer Institute, Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse Events (CTCAE), v4.0, published May 28, 2009. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026
- Faivre-Finn C, Snee M, Ashcroft L, Appel W, Barlesi F, Bhatnagar A, Bezjak A, Cardenal F, Fournel P, Harden S, Le Pechoux C, McMenemin R, Mohammed N, O'Brien M, Pantarotto J, Surmont V, Van Meerbeeck JP, Woll PJ, Lorigan P and Blackhall F: Concurrent once-daily *versus* twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): An open-label, phase 3, randomised, superiority trial. *Lancet Oncol* 18: 1116-1125, 2017. PMID: 28642008. DOI: 10.1016/S1470-2045(17)30318-2
- Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, Fukuoka M, Mori K, Watanabe K, Tamura T, Yamamoto S and Saijo N: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 346: 85-91, 2002. PMID: 11784874. DOI: 10.1056/NEJMoa003034
- Kubota K, Hida T, Ishikura S, Mizusawa J, Nishio M, Kawahara M, Yokoyama A, Imamura F, Takeda K, Negoro S, Harada M, Okamoto H, Yamamoto N, Shinkai T, Sakai H, Matsui K, Nakagawa K, Shibata T, Saijo N and Tamura T: 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* 15: 106-113, 2014. PMID: 24309370. DOI: 10.1016/S1470-2045(13)70511-4
- Sekine I, Sumi M, Satouchi M, Tsujino K, Nishio M, Kozuka T, Niho S, Nihei K, Yamamoto N, Harada H, Ishikura S and Tamura T: Feasibility study of chemoradiotherapy followed by amrubicin and cisplatin for limited-disease small cell lung cancer. *Cancer Sci* 107: 315-319, 2016. PMID: 26748638. DOI: 10.1111/cas.12875
- Horn L, Mansfield AS, Szczęśna A, Havel L, Krzakowski M, Hochmair MJ, Huemer F, Losonczy G, Johnson ML, Nishio M, Reck M, Mok T, Lam S, Shames DS, Liu J, Ding B, Lopez-Chavez A, Kabbavar F, Lin W, Sandler A and Liu SV: First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 379: 2220-2229, 2018. PMID: 30280641. DOI: 10.1056/NEJMoa1809064

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