Phase III trial of concurrent thoracic radiotherapy with either first- or third-cycle chemotherapy for limited-disease small-cell lung cancer†


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Background: We compared late thoracic radiotherapy (TRT) with early TRT in the treatment of limited-disease small-cell lung cancer (LD-SCLC).

Patients and methods: Patients with LD-SCLC received four cycles of etoposide plus cisplatin every 21 days. Patients were randomly assigned to receive either TRT administered concurrently with the first cycle (early TRT) or the third cycle (late TRT) of chemotherapy. The primary end point was complete response rate.

Results: Two hundred twenty-two patients were randomly assigned. Late TRT was not inferior to early TRT in terms of the complete response rate (early versus late; 36.0% versus 38.0%). Other efficacy measures including overall survival [median, 24.1 versus 26.8 months; hazard ratio (HR) 0.90; 95% CI 0.18–1.62] and progression-free survival (median, 12.4 versus 11.2 months; HR 1.10; 95% CI 0.37–1.84) were not different between two arms. No statistical difference was noted in the pattern of treatment failures. However, neutropenic fever occurred more commonly in the early TRT arm than the late TRT arm (21.6% versus 10.2%; P = 0.02).

Conclusion: In LD-SCLC treatment, TRT starting in the third cycle of chemotherapy seemed to be noninferior to early TRT, and had a more favorable profile with regard to neutropenic fever.

Key words: thoracic radiotherapy, small cell lung cancer, overall survival, complete response

introduction

The concurrent thoracic radiotherapy (TRT) with chemotherapy has been demonstrated to improve overall survival (OS), and is considered to be the standard of care for limited-disease small-cell lung cancer (LD-SCLC) [1]. However, the optimal timing of TRT related to chemotherapy remains unresolved.

Several randomized trials and meta-analyses were conducted to establish whether early TRT is better than late TRT [2–12]. However, the inconsistent results of these studies failed to provide strong guidance for clinical practice. In addition, the conclusions drawn from one meta-analysis were subsequently reversed after an update with new methodology, even though the two sets of analyses were carried out by the same investigators using the same database [9, 12].

For early TRT initiation, some practical limitations should be considered. First, a substantial proportion of patients with LD-SCLC present with bulky tumors that would require large radiation target volumes with concomitant increases in acute or chronic toxic effects. Secondly, the complexity of administering TRT concurrently with the first cycle of chemotherapy could result in some delay in treatment initiation. These considerations in particular led us to prospectively investigate whether TRT administered with the third cycle of chemotherapy is noninferior to TRT initiated during the first cycle of chemotherapy in the management of LD-SCLC. The primary end point was the complete response rate.
patients and methods

patients

Patients were considered eligible for the study when they had histologically or cytologically confirmed LD-SCLC. LD was defined as disease confined to one hemithorax, the mediastinum, and the bilateral supraclavicular fossae. Additional eligibility criteria were that subjects have at least one measurable tumorous lesion, Eastern Cooperative Oncology Group performance status ≤2, and adequate hematological, hepatic, and renal function. For TRT, patients must have adequate pretreatment FEV1 over 1 L/s. Patients who had been previously treated with chemotherapy or radiation therapy were excluded from the study.

study design and treatment plan

This study was a multicenter, randomized phase III trial. Eligible patients were randomly assigned in a 1:1 ratio into the early and late TRT arms. Treatment was assigned using block randomization with variable block sizes. At randomization, patients were stratified by center.

Chemotherapy was administered every 3 weeks for four cycles. Etoposide (100 mg/m² per day on days 1–3) and cisplatin (70 mg/m² on day 1; EP) of each cycle were given by intravenous infusion. After the first cycle of chemotherapy, dose adjustments were allowed according to renal, hematologic, or other toxic effects.

All TRTs were commenced using photons generated from linear accelerators following contrast-enhanced CT simulation and computerized treatment planning. The planning target volume encompassed the clinical target volume (CTV) with adequate margins in all directions (usually 1–1.5 cm). Three-dimensional conformal radiation therapy (3D-CRT) was planned in all patients, and dose constraints for lung were <20 Gy for MLD (mean lung dose) and 35% for V20. Pencil beam convolution algorithm was used for dose calculation and lung tissue correction was applied. Total dose TRT was 52.5 Gy with 2.1 Gy per fraction in once a day and five times a week for consecutive 5 weeks. All gross tumors were fully covered by prescribed dose and spinal cord dose was limited to 50 Gy. TRT was to begin on day 1 of either the first (the early TRT arm) or third cycle of EP chemotherapy (the late TRT arm). In the late TRT arm, the CTV modification reflecting tumor shrinkage following chemotherapy was done with reference to the postchemotherapy chest CT images. The initially involved mediastinal nodal stations, however, were to be included within the CTV even though a significant clinical response had occurred. TRT was to be continued, unless there was an uncontrollable severe toxic effect. Prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks) was administered to the patients who achieved complete response or very good partial response following the planned treatment course.

statistical analysis

The primary end point was the complete response rate as defined by the World Health Organization (WHO) criteria. The secondary end points included OS, progression-free survival (PFS), and objective response rate according to WHO criteria and toxic effect according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

We assumed that the complete response rate in both arms would be 55% based on previous studies [2, 4, 6, 8]. The target sample size was 196 patients to evaluate the noninferiority of late TRT compared with early TRT with a noninferiority margin of 20% for the complete response rate. This sample size would give the study an 80% power at the alpha of 0.05 with a two-sided test. Considering a 10% dropout rate, the total planned sample size was 218 patients.

All eligible patients who received study medication at least once were included in the efficacy and toxic effect analysis. The distribution of a time-to-event end point was estimated using the Kaplan–Meier method and was compared between the two arms by using the log-rank test. All reported P-values are two sided.

results

patient characteristics

From July 2003 to June 2010, 222 patients were randomly assigned to either the early (n = 113) or late TRT arm (n = 109). Two patients in the early TRT arm were excluded from analysis: one had progression with malignant pleural effusion and the other withdrew consent before treatment commenced. One patient in the late TRT arm was also excluded, because the histologic diagnosis was changed to lymphoma after randomization. The remaining 219 patients were analyzed. The median age was 60 years (39–75 years), and most were male (n = 194) and in performance status 0–1 (n = 218). The clinical characteristics were well balanced between the two arms, excepting that more patients with performance status 0 were included in the early TRT arm (n = 12 versus 5). The Consort diagram and clinical characteristics are summarized in supplementary Figure S1 and Table S1, available at Annals of Oncology online.

treatment

The planned treatment of four cycles of EP chemotherapy and 52.5 Gy of TRT was completed in 81.1% (90/111) and 82.4% (89/108) of the patients in the early and late TRT arms, respectively. The compliance with chemotherapy was good in both groups in terms of the number of chemotherapy cycles and the relative dose intensity. Likewise, ~90% of patients in both arms completed the planned 52.5 Gy of TRT without significant interruptions. Prophylactic cranial irradiation was delivered to 49.5% and 55.6% of the patients in the early and late arms, respectively (P = 0.37). The treatment delivery data are summarized in supplementary Table S2, available at Annals of Oncology online.

efficacy

The complete response rate was 36.0% in the early TRT arm and 38.0% in the late TRT arm [95% confidence interval (CI) of the difference (−14.7%, 10.9%)], which met the noninferiority margin. The overall response rates were 91.9% and 89.8% in the early and late TRT arms, respectively (supplementary Table S3, available at Annals of Oncology online). Among 108 patients in the late TRT arm, 82 (75.9%) achieved either a partial (76/82) or complete response (6/82) after the first two cycles of EP chemotherapy.

The median follow-up of the entire group was 59.4 months (range: 14.9–97.5 months). The median OS was 26.8 months (95% CI 22–32) in patients assigned to the late TRT arm compared with 24.1 months (95% CI 20–28) in those assigned to the early TRT arm (HR: 0.90; 95% CI 0.18–1.62; Figure 1A). The OS rates at 2 and 5 years after randomization in the early versus late TRT arms were 50.7% versus 56.0% and 24.3% versus 24.0%, respectively. The median PFS was 11.2 months (95% CI 8–13) in the late TRT arm, compared with 12.4 months (95% CI 9–16) in the early TRT arm (HR: 1.10; 95%
CI 0.37–1.84; Figure 1B). The PFS rates at 1 and 2 years in the early versus the late TRT arms were 51.8% versus 48.1% and 28.0% versus 23.5%, respectively. An exploratory analysis for all patients revealed that the patients who achieved complete responses had a longer OS (31.2 versus 20.3 months; \( P = 0.001 \)) and PFS (15.8 versus 9.5 months; \( P < 0.001 \)) than those who did not achieve complete responses. Complete responses were significantly associated with a longer OS (HR: 0.58; 95% CI 0.41–0.84; \( P = 0.004 \)) when adjusted for other factors such as age, institute, timing of TRT, and performance status by multivariate analysis.

**pattern of failure**

A total of 41 and 52 cases of intrathoracic progression were documented in the early and the late TRT arms, respectively. Although cumulative plots for intrathoracic failure with or without distant progression appeared to project a favorable trend for the early TRT arm, there was no statistical significance (\( P = 0.14 \); supplementary Fig. S2A, available at Annals of Oncology online). The cumulative incidence plots in distant metastases were far more similar between the two arms (\( P = 0.94 \); supplementary Fig. S2B, available at Annals of Oncology online). The proportions of brain-only metastases as the first site of failure were 14 (12.6%) and 12 (11.1%) in the early and late TRT arms, respectively (\( P = 0.73 \)). A cumulative plot of the probability for brain metastases revealed no difference between the two arms (\( P = 0.70 \); supplementary Fig. S3, available at Annals of Oncology online). Prophylactic cranial irradiation did slightly decrease the cumulative incidence of brain metastasis, although the effect was not statistically significant (19.1% versus 28.8%, \( P = 0.09 \)).

**safety**

The adverse event profiles are shown in Table 1. Esophagitis of any grade occurred in 45.0% and 37.0% of patients in the early and late TRT arms, respectively (\( P = 0.23 \)), but grade 3 or 4 esophagitis was uncommon in either arm (3.6% and 0.9%, respectively). Likewise, although radiation pneumonitis of any grade was common in both arms (80.2% and 75.9%, respectively), grade 3 or 4 pneumonitis was rare (4.5% and 2.8%, respectively). It is of note that febrile neutropenia did occur more frequently in the early TRT arm than in the late TRT arm (21.6% versus 10.2%, \( P = 0.02 \)). Similarly, there was a slight increase in the incidence of grade 3 or 4 neutropenia in the early TRT arm compared with that in the late TRT arm (70.3% versus 59.3%; \( P = 0.09 \)). A total of three and two patients in the early and late TRT arms, respectively, died of neutropenic fever. There were no other fatal adverse events.

**salvage chemotherapy**

The proportions of patients who received salvage chemotherapy were well balanced. Among patients with disease progression, 79% in the early TRT arm and 68% in the late TRT arm received at least one line of salvage chemotherapy.

**discussion**

The present study has particular strengths compared with previous randomized trials. First, we used the EP chemotherapy regimen, which is currently a standard regimen when combined with TRT [13]. Second, ∼90% of the patients recruited into our study completed the planned four cycles of chemotherapy, and the relative dose intensity was >93% in both arms. This could disprove the previous assumption that early TRT would be superior to late TRT if it is delivered with uncompromised doses of chemotherapy [8, 13]. Third, we defined late TRT as starting with the third cycle of chemotherapy, unlike most previous randomized trials, which defined late TRT as starting with the fourth to sixth cycles of chemotherapy [2, 5–8]. Based on the high response rate (76%) after the first two cycles of EP chemotherapy in the late TRT arm in our study, we could speculate that chemotherapy delivered over 6 weeks before TRT is sufficient to slow or reserve the progression of SCLC. In addition, two cycles of chemotherapy without concurrent radiotherapy may allow evaluations of the response to the chemotherapy regimen and avoid probable delays in the preparation of TRT concurrent with the first chemotherapy cycle. Although the commencement of radiotherapy with the second cycle of chemotherapy could prevent the delay of the treatment, it
control was slightly hindered within insignifi-
cant range, and subsequent OS was identical to that of the early TRT arm.

It is noteworthy that neutropenic fever developed more frequently in the early TRT arm than the late TRT arm. The incidence of grade 3 or 4 neutropenia also displayed a similar pattern, with a higher frequency observed in the early TRT arm. Although these results should be interpreted with caution because we did not analyze or compare the radiation therapy volume between the two arms, this may be partly explained by increased bone marrow damage in association with the larger radiation therapy volume in the early TRT arm at a time when tumors were larger than those after two cycles of EP chemotherapy. As such, we considered that TRT starting with the third cycle of chemotherapy seemed to be not inferior to the current observations, late TRT administered with the third cycle of EP chemotherapy seemed to be not inferior to early TRT in the treatment of LD-SCLC.

In summary, the treatment compliance and the clinical outcomes of response, OS, and PFS were comparable in the early and late TRT arms. In the late arm, there were significantly fewer neutropenic fevers. However, even though it was statistically insignificant, an increasing tendency of intrathoracic failure in the late arm is worthy of notice. Based on the current observations, late TRT administered with the third cycle of EP chemotherapy seemed to be not inferior to early TRT in the treatment of LD-SCLC.

**Table 1. Adverse events profile**

<table>
<thead>
<tr>
<th></th>
<th>Early TRT arm (n = 111)</th>
<th>Late TRT arm (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic toxic effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>86 (77.5%)</td>
<td>79 (76.6%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>34 (30.6%)</td>
<td>36 (33.3%)</td>
</tr>
<tr>
<td><strong>Nonhematologic toxic effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>63 (56.8%)</td>
<td>63 (58.3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (13.5%)</td>
<td>16 (14.8%)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>50 (45.0%)</td>
<td>40 (37.0%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>22 (19.8%)</td>
<td>28 (25.9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (2.7%)</td>
<td>5 (4.6%)</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>12 (10.8%)</td>
<td>20 (18.5%)</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td>89 (80.2%)</td>
<td>82 (75.9%)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Infection without neutropenia</td>
<td>5 (4.5%)</td>
<td>8 (6.5%)</td>
</tr>
</tbody>
</table>

would be hard to predict tumor sensitivity for specific chemotherapeutic regimens after only one cycle of chemotherapy. As such, we considered that TRT starting with the third cycle of chemotherapy was acceptably delayed and was practically convenient for both patients and physicians. With such a definition of late TRT in our study, local disease control was slightly hindered within insignificant range, and subsequent OS was identical to that of the early TRT arm. It is noteworthy that neutropenic fever developed more frequently in the early TRT arm than the late TRT arm. The incidence of grade 3 or 4 neutropenia also displayed a similar pattern, with a higher frequency observed in the early TRT arm. Although these results should be interpreted with caution because we did not analyze or compare the radiation therapy volume between the two arms, this may be partly explained by increased bone marrow damage in association with the larger radiation therapy volume in the early TRT arm at a time when tumors were larger than those after two cycles of chemotherapy. Significant tumor shrinkage was revealed in 76% of patients in the late TRT arm after the first two cycles of EP chemotherapy, and subsequently, patients were more likely to receive a substantially reduced radiation therapy volume. Similarly, although the incidence of local toxic effects such as esophagitis and radiation pneumonitis appeared comparable between the two arms irrespective of grades, grade 3 and 4 toxic effects were more frequently observed in the early TRT arm. Meanwhile, compared with the previous studies carried out in Western countries [2, 3, 6, 8, 14], grade 3 and 4 esophagitis or pneumonitis were infrequent in both arms of our study. However, the low incidences were consistent with the data from a Japanese phase III trial [7]. Although, we cannot conclude that it was attributed to the ethnic difference or other causes, TRT modality such as 3D and once-daily TRT might in part decrease the toxic effects [14].

We adopted once-daily TRT rather than a twice-daily regimen. Although twice-daily TRT was revealed to improve OS in patients with LD-SCLC [14], it has failed to be adopted as a standard regimen because of the inconvenience for both patients and physicians and the increased rate of severe esophagitis compared with the findings for once-daily TRT [13]. One retrospective study demonstrated that twice-daily TRT had been actually used for only 6% of patients with LD-SCLC [15]. Although the clinical relevance of the higher radiation dose has not yet been established, we intended to increase radiation dose from the previous usual dose of 45–50 Gy (by 1.8 or 2.0 Gy per fraction) at the authors’ institutes to 52.5 Gy (by 2.1 Gy per fraction), considering the practical expectations on the acute side-effects as well as the local tumor control rate.

We used the complete response rate as our primary end point, considering the feasible target number of patients and the known relationship between complete response rate and OS in patients with LD-SCLC [16, 17]. However, we should admit that complete response rate was an inaccurate end point to conclude which arm is inferior or not, because complete response rate has not been validated as a surrogate measure for OS and it could be under- or overestimated. Actually, the complete response rate in our study was lower than expected, because the investigators applied strict criteria and fibrotic lesions after TRT were more likely considered as residual tumors.

In summary, the treatment compliance and the clinical outcomes of response, OS, and PFS were comparable in the early and late TRT arms. In the late arm, there were significantly fewer neutropenic fevers. However, even though it was statistically insignificant, an increasing tendency of intrathoracic failure in the late arm is worthy of notice. Based on the current observations, late TRT administered with the third cycle of EP chemotherapy seemed to be not inferior to early TRT in the treatment of LD-SCLC.

**disclosure**

The authors have declared no conflicts of interest.

**references**

Incidence and risk of treatment-related mortality in cancer patients treated with the mammalian target of rapamycin inhibitors


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Background: Inhibition of the mammalian target of rapamycin (mTOR) is an established treatment for multiple malignancies. We carried out an up-to-date meta-analysis to determine the risk of fatal adverse events (FAEs) in cancer patients treated with mTOR inhibitors.

Patients and methods: PubMed, conferences and clinicaltrials.gov databases were searched for articles reported from January 1966 to June 2012. Eligible studies were limited to approved mTOR inhibitors (everolimus and...