Randomized Phase III Study of Thoracic Radiation in Combination With Paclitaxel and Carboplatin With or Without Thalidomide in Patients With Stage III Non–Small-Cell Lung Cancer: The ECOG 3598 Study

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ABSTRACT

Purpose

The primary objective of this study was to compare the survival of patients with unresectable stage III non–small-cell lung cancer (NSCLC) treated with combined chemoradiotherapy with or without thalidomide.

Patients and Methods

Patients were randomly assigned to the control arm (PC) involving two cycles of induction paclitaxel 225 mg/m² and carboplatin area under the curve (AUC) 6 followed by 60 Gy thoracic radiation administered concurrently with weekly paclitaxel 45 mg/m² and carboplatin AUC 2, or to the experimental arm (TPC), receiving the same treatment in combination with thalidomide at a starting dose of 200 mg daily. The protocol allowed an increase in thalidomide dose up to 1,000 mg daily based on patient tolerability.

Results

A total of 546 patients were eligible, including 275 in the PC arm and 271 in the TPC arm. Median overall survival, progression-free survival, and overall response rate were 15.3 months, 7.4 months, and 35.0%, respectively, for patients in the PC arm, in comparison with 16.0 months ($P = .99$), 7.8 months ($P = .96$), and 38.2% ($P = .47$), respectively, for patients in the TPC arm. Overall, there was higher incidence of grade 3 toxicities in patients treated with thalidomide. Several grade 3 or higher events were observed more often in the TPC arm, including thromboembolism, fatigue, depressed consciousness, dizziness, sensory neuropathy, tremor, constipation, dyspnea, hypoxia, hypokalemia, rash, and edema. Low-dose aspirin did not reduce the thromboembolic rate.

Conclusion

The addition of thalidomide to chemoradiotherapy increased toxicities but did not improve survival in patients with locally advanced NSCLC.

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INTRODUCTION

Treatment of locally advanced non–small-cell lung cancer (NSCLC) has evolved in the last few decades. In the late 1980s, two randomized phase III studies—CALGB (Cancer and Leukemia Group B) 8433 and RTOG (Radiation Therapy Oncology Group) 8808—demonstrated survival benefit with the addition of induction cisplatin and vinblastine to thoracic radiation. Median overall survival (OS) and 5-year survival in patients receiving sequential chemoradiotherapy were 13.2 to 13.7 months and 8% to 17%, respectively, in comparison with 9.6 to 11.4 months and 5% to 6% in

those treated with radiation alone.^{1,2} Subsequent studies in the 1990s showed that survival could be improved further by administering the two modalities concurrently instead of sequentially. In a randomized phase III trial in which cisplatin, vindesine, and mitomycin were administered with radiation, concurrent treatment significantly prolonged survival in comparison with the sequential approach, with a median survival of 16.5 versus 13.3 months and 5-year survival of 15.8% versus 8.9%, respectively.³ The survival advantage of concurrent over sequential chemotherapy and radiation was also confirmed in other studies using different platinum-based regimens such as cisplatin plus vinblastine,⁴

cisplatin plus vinorelbine,⁵ and cisplatin plus etoposide.⁶ Thus, combined chemoradiotherapy became the standard of care for patients with locally advanced NSCLC with high performance status and minimal weight loss (frequently < 10%), a group more likely tolerate the higher toxicities induced by these regimens. Nevertheless, the chance of curing the disease remains low because of the high risk of local and distant failure. Therefore, novel treatment approaches are clearly needed.

Angiogenesis is an essential event in many physiologic as well as pathologic processes. Therefore, angiogenic inhibition has become an attractive cancer treatment strategy. Thalidomide is an oral agent originally introduced as a sedative and antiemetic, but it was quickly taken off the market when it was found to induce catastrophic fetal abnormalities. It has since been postulated that the limb defects seen in fetuses and newborns resulted from an inhibition of blood vessel growth in the developing fetal limb bud. Further research using a rabbit cornea micropocket assay demonstrated the antiangiogenic activity of thalidomide.⁷ Therefore, thalidomide has been investigated as an antiangiogenic agent for the treatment of macular degeneration as well as a variety of cancers, which has led to the approval of this drug in multiple myeloma.

This randomized open-label phase III study—ECOG (Eastern Cooperative Oncology Group) 3598—was conducted in the early 2000s to determine if adding thalidomide to the third-generation chemotherapy doublet of paclitaxel and carboplatin and radiation would improve survival outcome in unresectable stage III NSCLC. We hypothesized that the addition of thalidomide to chemoradiotherapy

and its maintenance use would not only improve local control but also reduce the risk of distant failures from micrometastases.

PATIENTS AND METHODS

Patients

Eligible patients were required to have histologically confirmed, unresectable stage IIIA or IIIB NSCLC without significant pleural effusion; measurable disease; ECOG performance status of 0 to 1; adequate bone marrow, liver, and kidney function; and no grade 2 or greater neuropathy and to be 18 years of age or older. Patients with stage IIIA disease with mediastinal lymph node enlargement of 1 cm or larger but not exceeding 2 cm on computed tomography scans had to undergo mediastinoscopy or thoracoscopy to rule out resectability. Because of the known teratogenic effects of thalidomide, patients could not be pregnant or breastfeeding. Women of childbearing potential and sexually active men were required to use two accepted and effective methods of contraception.

Study Design and Treatment

Stratified by histology (squamous *v* nonsquamous), performance status (0 *v* 1), and disease stage (IIIA *v* IIIB), patients were randomly assigned to one of two treatment arms (Fig 1). In the control (PC) arm, patients received induction chemotherapy with paclitaxel 225 mg/m² and carboplatin area under the curve 6 intravenously on day 1 every 3 weeks for two cycles. In the investigational (TPC) arm, patients received thalidomide daily in addition to paclitaxel and carboplatin. The starting dose of thalidomide was 200 mg, which was subsequently increased by 100 mg every week as tolerated up to a total daily dose of 1,000 mg.

Fig 1. ECOG (Eastern Cooperative Oncology Group) 3598 treatment schema. (*) Patients did not have stage III disease (n = 24), had significant pleural effusion (n = 8), did not have required surgical mediastinal staging (n = 5), did not have baseline scans within 28 days of registration (n = 3), inadequate histologic confirmation (n = 1), and severe hypertension (n = 1). Chemo, chemotherapy; CR, complete remission; NSCLC, non-small-cell lung cancer; PC, paclitaxel plus carboplatin; PR, partial response; RT, radiation; SD, stable disease; T, thalidomide; TPC, paclitaxel plus carboplatin with thalidomide.

After two cycles of induction chemotherapy, patients with progressive disease went off study, whereas those with a response or stable disease underwent thoracic radiation therapy with (TPC arm) or without (PC arm) daily thalidomide, initiated between days 43 through 50 from the start of induction therapy. A total radiation dose of 60 Gy using linear accelerator photon beams of at least 6 MeV energy was delivered to the lung tumor and nodal disease at 2-Gy per fraction per day for 30 fractions, five fractions per week, over 6 weeks. Both two- and three-dimensional planning, but not intensity-modulated radiation therapy, was permitted. Two target volumes were used in this protocol. Initially, no concurrent chemotherapy was delivered with thoracic radiation. However, as the data supporting concurrent chemoradiotherapy became more robust during the trial, after enrollment of 303 patients, the protocol was amended to add weekly paclitaxel 45 mg/m² and carboplatin area under the curve 2 concurrently with radiotherapy in both arms (Addendum 4 on June 4, 2003). After chemoradiotherapy, patients with at least stable disease in the PC arm were monitored without additional therapy, whereas their counterparts in the TPC arm continued to receive thalidomide for a total of 24 months or until disease progression or intolerance. After enrolling 438 patients, because of an increased incidence of thromboembolism (8%) observed in the TPC arm, Addendum 6 required patients in this arm to take prophylactic aspirin 81 mg daily while receiving thalidomide.

To evaluate tumor response, patients in both arms underwent chest computed tomography scans at baseline, end of induction chemotherapy (before radiation), 1 month post chemoradiotherapy, and then every 2 months for the first 24 months from study entry, every 3 months in year 3, every 4 months in year 4, and every 6 months in year 5.

Statistical Analysis

The primary end point of this randomized phase III study was OS. Secondary clinical end points were progression-free survival (PFS), best response rate, and toxicity. The study had 83% power to detect an OS hazard ratio (HR) of 0.77 comparing TPC with PC with a one-sided significance level of .025. The study design relied on the O'Brien-Fleming function for the group sequential boundary of the log-rank test at a one-sided significance level of .025, allowing for three interim and one final analyses at each 25% increment of information time, with full information at 506 deaths.⁸ Early stopping for lack of a thalidomide effect was also considered using the methodology of Jennison et al⁹ for repeated CIs. Assuming fewer than 5% of randomly assigned patients would violate the protocol eligibility, a maximum of 588 patients was required to adequately satisfy the design objectives.

This analysis reports on data acquired as of December 23, 2009. Kaplan-Meier curves were used to estimate event-time distributions. Cox proportional hazards models, stratified by histology, performance status, and stage (per randomization), were used to estimate HRs and test for significance for OS. PFS was compared using log-rank tests. Adverse events, patient demographics and disease characteristics, and response rates were compared using Fisher's exact tests or the Wilcoxon rank sum test for continuous variables. All *P* values are two sided, and CIs are at the 95% level. Laboratory end points that include analysis for aberrant methylation of *p16*, *MGMT*, *DAPK*, and other genes in sputum and serum, as well as evaluation of a methylation prognostic biomarker in serum, will be presented in another report.

RESULTS

Between January 2000 and October 2006, a total of 589 patients were enrolled. In April 2007, at the third interim analysis of OS among eligible patients (73.9% information), the data monitoring committee recommended stopping the trial for futility because the 95% repeated CI for the OS HR was 0.81 to 1.34, and the conditional power was approximated to be 3.8%. Of all accrued patients, 43 were deemed ineligible (Fig 1). Eleven enrolled patients did not receive the assigned therapy. Data from 546 eligible patients, including 275 in the PC arm and 271 in the TPC arm, were included in the primary efficacy analysis.

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	PC Arm (n = 275)	TPC Arm (n = 271)	All Patients (N = 546)	<i>P</i>
Age, years				.77
Median	63	63	63	
Range	38-84	33-83	33-84	
Sex, %				.66
Male	62	60	61	
Female	38	40	39	
Performance status, %				.51
0	47	45	46	
1	53	55	54	
2	< 1	0	< 1	
Histology, %				.25
Adenocarcinoma	34	41	37	
Squamous cell	34	35	35	
Large cell	6	5	5	
Adenosquamous	2	2	2	
BAC	< 1	< 1	< 1	
NOS	24	15	19	
Other	< 1	1	1	
6-month weight loss, %				.98
< 5	68	70	69	
5 to < 10	19	18	18	
10 to < 20	11	9	10	
> 20	2	2	2	
Other	< 1	< 1	< 1	
Disease stage, %				.38
IIIA	36	40	38	
IIIB	64	60	62	
Recurrent	< 1	0	< 1	
Pleural effusion, %				.57
No	91	89	90	
Yes (clinical assessment only)	7	9	8	
Yes (cytologically negative)	2	2	2	

Abbreviations: BAC, bronchioloalveolar carcinoma; PC, paclitaxel plus carboplatin; NOS, not otherwise specified; TPC, paclitaxel plus carboplatin with thalidomide.

Patient Characteristics

The clinical characteristics of the patients in the two treatment arms were similar with regard to age, sex, race, performance status, histology, weight loss, and disease stage (Table 1). Median age was 63 years. More than one third of patients were women. Almost half had ECOG performance status of 0. The most common histologic subtypes were adenocarcinoma (37%) and squamous cell carcinoma (35%). Thirty percent of patients reported weight loss of 5% or more within the prior 6 months, including 12% losing 10% or more of their weight. Two thirds of patients had stage IIIB disease. Ten percent of patients had pleural effusion that was cytologically negative (2%) or deemed clinically insignificant (8%). Patients in each arm received a similar dose of thoracic radiation, with a median dose of 60 Gy (*P* = .26).

Efficacy Analysis

At the time of the analysis, 493 of 546 eligible patients had died. The median follow-up for living patients was 61.8 months. Overall, there was no significant difference in OS or PFS between the two treatment arms (Table 2). Median OS was 16.0 months in patients receiving TPC, as compared with 15.3 months in those receiving PC,

Table 2. Treatment Outcome

Result	PC Arm (n = 275)		TPC Arm (n = 271)		P
	No.	%	No.	%	
Survival, months					
Median	15.3		16		.99
PFS	7.4		7.8		.96
Response					.47
CR	11	4.2	7	2.7	
PR	80	30.8	92	35.5	
SD	106	40.8	94	36.3	
PD	32	12.3	37	14.3	
Unevaluable	31	11.9	29	11.2	
Missing	15		12		

Abbreviations: CR, complete response; PC, paclitaxel plus carboplatin; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TPC, paclitaxel plus carboplatin with thalidomide.

with an HR of 1.00 ($P = .99$; Fig 2A). PFS was 7.8 months in the TPC arm, as compared with 7.4 months in the PC arm ($P = .96$; Fig 2B). Response to treatment was also similar between the two arms, with overall response rate of 38.2% in the TPC arm versus 35.0% in the PC arm ($P = .47$).

The effects of thalidomide on survival were not statistically significant for any patient subgroup based on sex (male, female), age (≥ 65 , < 65 years), performance status (0, 1), disease stage (IIIA, IIIB), or histology (squamous, nonsquamous). In the subset of 66 patients with pleural effusion, those receiving thalidomide seemed to derive some benefit, with an estimated HR of 0.47 (95% CI, 0.22 to 1.01; $P = .05$). However, the number of patients was too small to draw any conclusion. A forest plot of HRs for OS in patient subgroups is displayed in Figure 3. Similarly, there was no PFS advantage with thalidomide in any subgroup (data not shown).

In the investigational arm, thalidomide daily dose was escalated to 400 mg or higher in 54% of patients, including 14% receiving 600 to 799 mg and 15% receiving 800 to 1,000 mg. We found no indication that survival was associated with maximum prescribed thalidomide dose in exploratory analyses (not shown).

In addition, we retrospectively analyzed the impact of Amendment 4 with the addition of concurrent chemotherapy to radiation on the study outcome. In a stratified Cox model adjusted for randomized treatment and whether a patient was receiving concurrent chemotherapy, no survival benefit with thalidomide was observed (OS HR, 1.0; $P = .97$). It seems that patients registered after Amendment 4 (thus receiving concurrent chemoradiotherapy) fared better than those registered before the amendment (radiation without concurrent chemotherapy), with an OS HR of 0.79 ($P = .02$). However, there was no thalidomide by concurrent chemoradiotherapy interaction.

Toxicity Analysis

Data for 577 patients who received treatment, including 289 in the PC arm and 288 in the TPC arm, were analyzed for toxicity. Overall, grade 3 adverse events were seen more often in the TPC than the PC arm (53% v 44%; $P = .004$). There was no difference in grade

Fig 2. (A) Overall and (B) progression-free survival according to assigned treatment. PC, paclitaxel plus carboplatin; TPC, paclitaxel plus carboplatin with thalidomide.

4 and 5 incidence between the two regimens, with 32% of grade 4 and 1% of grade 5 events observed in each arm (Table 3).

The addition of thalidomide to chemotherapy and chemoradiotherapy did not increase bone marrow toxicity such as neutropenia or neutropenic infection, anemia, and thrombocytopenia. However, there was a significantly higher rate of grade 3 or greater thromboembolic events in the TPC arm (11%) compared with the control arm (3%; $P < .001$), even with the addition of prophylactic aspirin. Before Addendum 6, grade 3 to 5 thromboembolism was reported in 11.2% of patients in the TPC arm (three deaths) in comparison with 2.8% of patients in the PC arm (one death). After

Fig 3. Hazard ratios for survival in patient subgroups. Area of each box is proportional to inverse of variance of log hazard ratio (small boxes correspond to large variances). Horizontal line through box gives 95% CI on ratio. PC, paclitaxel plus carboplatin; PS, performance status; TPC, paclitaxel plus carboplatin with thalidomide.

the institution of Addendum 6, which required the use of prophylactic low-dose aspirin with thalidomide, 13.5% (no deaths) in the TPC arm experienced thromboembolism in comparison with 5.5% (no deaths) in the PC arm. Of note, the thromboembolic events seemed to occur at any time point during the course of treatment with thalidomide: induction chemotherapy, concurrent chemoradiotherapy, or thalidomide maintenance.

In addition, compared with the PC arm, patients in the TPC arm also reported more grade 3 or higher instances of fatigue (15% *v* 6%; $P < .001$), depressed level of consciousness (5% *v* < 1%; $P < .001$), dizziness (6% *v* < 1%; $P < .001$), sensory neuropathy (11% *v* 6%; $P = .01$), tremor (2% *v* 0%, $P = .03$), constipation (9% *v* 1%; $P < .001$), dyspnea (13% *v* 7%; $P = .006$), hypoxia (4% *v* 1%; $P = .04$), hypokalemia (4% *v* 2%; $P = .03$), rash (7% *v* 1%; $P = .001$), and edema (3% *v* < 1%; $P = .02$). On the other hand, there was no increase in hemoptysis, GI bleeding, or bowel perforation in patients receiving thalidomide. Thalidomide also did not increase radiation-induced toxicities such as dermatitis, esophagitis, and pneumonitis or pulmonary fibrosis.

DISCUSSION

This randomized phase III study investigated the activity of the antiangiogenic agent thalidomide administered with third-generation chemotherapy and radiation in patients with unresectable stage III NSCLC. The study failed to show clinical benefits of thalidomide in combination with the conventional treatment in this setting. Overall, there was no difference in OS, PFS, or response

Table 3. Adverse Events

Adverse Event	PC Arm (n = 289)			TPC Arm (n = 288)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Hematologic, %						
Anemia	2	1	—	1	< 1	—
Leukopenia	20	3	—	26	2	—
Neutropenia	25	26	—	35	20	—
Febrile neutropenia	3	—	—	2	< 1	—
Infection with grade 3 or 4 neutropenia	2	1	< 1	4	1	—
Thrombocytopenia	3	—	—	2	—	—
Nonhematologic, %						
Thrombosis/embolism*	1	< 1	< 1	4	6	1
Fatigue*	5	< 1	—	14	1	—
Depressed consciousness*	< 1	—	—	5	—	—
Dizziness*	< 1	—	—	5	< 1	—
Sensory neuropathy*	5	< 1	—	11	—	—
Tremor	—	—	—	2	—	—
Constipation*	1	—	—	9	—	—
Dyspnea*	6	1	—	11	2	—
Hypoxia*	1	—	—	3	< 1	—
Hypokalemia*	1	< 1	—	4	—	—
Rash/desquamation*	1	—	—	7	—	—
Edema*	< 1	—	—	3	—	—
Allergic reaction	3	2	—	3	1	—
Hypotension	1	—	—	2	< 1	—
Hypertension	< 1	—	—	< 1	—	—
Cardiac ischemia	< 1	—	—	< 1	—	< 1
Weight loss	1	—	—	2	—	—
Anorexia	3	< 1	—	4	—	—
Nausea	5	1	—	5	—	—
Vomiting	4	1	—	2	—	—
Ileus	—	—	—	1	—	—
Bowel fistula	—	< 1	—	—	—	—
GI bleeding	—	—	—	< 1	—	—
Motor neuropathy	2	—	—	3	—	—
Pneumonitis/lung infiltrates	2	1	—	4	—	< 1
Pulmonary fibrosis	1	—	—	—	—	—
Radiation dermatitis	1	—	—	1	—	—
Radiation-related esophageal dysphagia	1	—	—	1	—	—
Any adverse event, %†	44	32	1	53	32	1

Abbreviations: PC, paclitaxel plus carboplatin; TPC, paclitaxel plus carboplatin with thalidomide.

*Statistically significant *P* value for sum of grades 3 to 5.

†Statistically significant *P* value for grade 3.

in patients receiving thalidomide with chemoradiotherapy compared with those treated with chemoradiotherapy alone. Retrospective, unplanned analysis also failed to identify subgroups of patients who may derive benefits from this investigational regimen. Furthermore, the use of thalidomide was associated with higher incidence of grade 3 or greater toxicities, such as sedation, fatigue, hypotension, constipation, edema, tremor, sensory neuropathy, and thromboembolism.

A particular finding in this study is an increase in thromboembolic events associated with thalidomide (11% *v* 3%; $P < .001$). It seemed that taking low-dose aspirin daily did not prevent or reduce the incidence of thromboembolic events in our study. On the other

hand, there was no thromboembolism-associated mortality in patients taking prophylactic aspirin with thalidomide. Because the numbers were quite small, we are not able to draw any conclusions as to the efficacy of aspirin in reducing mortality related to thromboembolic events. Several trials have been conducted in patients with multiple myeloma to investigate the prophylactic use of aspirin, low-molecular weight heparin, or warfarin in preventing this adverse event. The current guideline recommends the use of low-molecular weight heparin or adjusted-dose warfarin in patients with myeloma receiving thalidomide with chemotherapy or dexamethasone.¹⁰ Another observation in this study with regard to safety and tolerability is that thalidomide did not increase radiation-related toxicities. Of note, thalidomide did not increase the risk of bleeding, organ perforation, or hypertension, which are class effects seen with other antiangiogenic drugs targeting vascular endothelial growth factor (VEGF) or VEGF receptors.

The design of this study reflects the evolution of treatment strategies for locally advanced NSCLC. In the original protocol, the treatment plan was to administer chemotherapy and radiation in sequential fashion based on best available data at that time.^{1,2} Paclitaxel and carboplatin were chosen instead of older drugs based on the emerging role of third-generation cytotoxic agents in advanced disease.^{11,12} With subsequent evidence from other studies showing the superiority of the concurrent treatment approach,^{3,4} the protocol was amended to administer chemotherapy concurrently with radiation after two cycles of induction chemotherapy at full doses. The rationale for using low-dose paclitaxel and carboplatin with radiotherapy was based on clinical studies demonstrating activity of the two drugs in this approach.^{13,14} Although concurrent low-dose paclitaxel and carboplatin was added to radiation later during the study, the median OS observed in our study (15.3 months with PC alone and 16.0 months with TPC) is comparable with results reported in several other randomized trials of full-dose chemotherapy administered concurrently with radiation.³⁻⁶

Thalidomide was also investigated in combination with chemotherapy in three randomized studies in advanced lung cancer in Europe—one in NSCLC and the other two in small-cell lung cancer (SCLC). In the NSCLC trial, 722 patients with stage IIIB or IV disease were randomly assigned to receive gemcitabine and carboplatin with or without thalidomide 100 to 200 mg daily.¹⁵ In the first SCLC trial, 119 patients with extensive disease were treated with etoposide, cisplatin, cyclophosphamide, and epidoxorubicin (PCDE) with or without thalidomide 400 mg daily.¹⁶ In the second SCLC trial, 724 patients with limited or extensive disease received etoposide and carboplatin with or without thalidomide 100 to 200 mg daily.¹⁷ All three studies failed to show a survival advantage with the addition of thalidomide to chemotherapy in advanced NSCLC or SCLC. Similar to our study, peripheral neuropathy and thrombotic events were observed more often in patients receiving thalidomide.

The strategy of combining angiogenic inhibition with chemoradiotherapy in localized advanced lung cancer has been investigated with other antiangiogenic drugs. In a randomized phase III study in stage III NSCLC, AE-941 (Neovastat, Aeterna Laboratories, Quebec, Quebec, Canada)—a shark cartilage extract with antiangiogenic properties was tested with induction chemotherapy consisting of paclitaxel plus carboplatin or vinorelbine plus cisplatin followed by concurrent

chemoradiotherapy.¹⁸ After an enrollment of 379 patients, the study was closed early because of slow accrual. In comparison with placebo, AE-941 did not demonstrate improved median survival (14.4 v 15.6 months; $P = .73$), time to progression (11.3 v 10.7 months; $P = .65$), or response rate (39% v 48%; $P = .12$).

On the basis of the results of ECOG 4599, the VEGF-targeting monoclonal antibody bevacizumab has been approved for use with paclitaxel and carboplatin in metastatic nonsquamous NSCLC.¹⁹ This agent was also investigated in two phase II trials in locally advanced lung cancer, one in patients with stage III nonsquamous NSCLC and the other with limited-stage SCLC.²⁰ In both studies, bevacizumab was administered concurrently with chemotherapy and radiation and alone as maintenance therapy. Unfortunately, the studies were closed early because of high incidence of tracheoesophageal (TE) fistula and related morbidity and mortality. Of five enrolled patients with NSCLC, two developed TE fistulae. Of 29 patients with SCLC, two developed TE fistulae (one death), and another died of aerodigestive hemorrhage. It was postulated that the formation of the fistula was a result of esophagitis or esophageal injury from the interaction of chemoradiotherapy and bevacizumab. In our study, we did not observe any TE fistulae.

In summary, our study showed that adding thalidomide to chemoradiotherapy increased toxicities related to this agent but did not improve survival in patients with locally advanced NSCLC. Therefore, we do not recommend the use of thalidomide in this setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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