Anti-angiogenic Therapy Using Thalidomide Combined With Chemotherapy in Small Cell Lung Cancer: A Randomized, Double-Blind, Placebo-Controlled Trial

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Background Cancer cells rely on angiogenesis for growth and dissemination, and small cell lung cancer (SCLC) is a highly angiogenic tumor. We evaluated thalidomide, an anti-angiogenic agent, when combined with chemotherapy and as maintenance treatment.

Methods A total of 724 patients (51% with limited and 49% with extensive disease) were randomly assigned to receive placebo or thalidomide capsules, 100–200 mg daily for up to 2 years. All patients received etoposide and carboplatin every 3 weeks for up to six cycles. Endpoints were overall survival, progression-free survival, tumor response rate, toxicity, and quality of life (QoL). Hazard ratios (HRs) for comparing thalidomide against placebo were estimated using Cox regression modeling. Statistical tests were two-sided.

Results The median overall survival was 10.5 months (placebo) and 10.1 months (thalidomide) (HR for death = 1.09, 95% confidence interval [CI] = 0.93 to 1.27; $P = .28$). Among patients with limited-stage disease, there was no evidence of a survival difference (HR for death = 0.91, 95% CI = 0.73 to 1.15), but among patients with extensive disease, survival was worse in the thalidomide group (HR for death = 1.36, 95% CI = 1.10 to 1.68). Progression-free survival rates were also similar in the two groups (HR = 1.07, 95% CI = 0.92 to 1.24). Thalidomide was associated with an increased risk of having a thrombotic event, mainly pulmonary embolus and deep vein thrombosis (19% thalidomide vs 10% placebo; HR = 2.13, 95% CI = 1.41 to 3.20; $P < .001$). There were no statistically significant differences between treatments in hematological and non-hematological toxic effects, except more patients in the thalidomide group had rash, constipation, or neuropathy. Overall, QoL scores were similar in the two treatment groups, but thalidomide was associated with less insomnia and diarrhea and more constipation and peripheral neuropathy.

Conclusions In this large randomized trial, thalidomide in combination with chemotherapy did not improve survival of patients with SCLC but was associated with an increased risk of thrombotic events.

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The survival of patients with small cell lung cancer (SCLC), which accounts for 15%–20% of lung cancers, has improved only marginally in the past 25 years (1). Although patients initially respond to chemotherapy, the majority relapse and die from metastatic disease progression.

Several lines of evidence suggest that angiogenesis plays an important role in this cancer in particular (2). Patients with SCLC express functional vascular endothelial growth factor receptor (VEGFR)-2 and VEGFR-3 on their tumor cells (3) and have increased levels of serum vascular endothelial growth factor (VEGF) (4). Increased pretreatment levels of VEGF and basic fibroblast growth factor are associated with poor response to chemotherapy and shorter survival (5–7). SCLC is more vascularized than non–small cell lung cancer (NSCLC), as shown by a higher microvessel density (8).

It has been hypothesized that the addition of thalidomide—one of the first anti-angiogenic agents discovered (9)—to chemotherapy could improve survival in lung cancer patients because a benefit is seen in a variety of other cancers, particularly multiple myeloma (10–14). Results from previously published small studies (15–17) in

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CONTEXT AND CAVEATS

Prior knowledge

Small cell lung cancer is very angiogenic, and thalidomide is an anti-angiogenic agent that has been used in combination with chemotherapy.

Study design

Randomized controlled trial of thalidomide vs placebo in 724 patients with small cell lung cancer who were undergoing chemotherapy. Overall survival and toxic effects were compared overall and among patients with extensive vs limited disease.

Contribution

Median overall survival was similar in the two groups; in analysis by disease extent, patients with extensive disease who were treated with thalidomide had worse overall survival than those treated with placebo. Patients treated with thalidomide had higher risk of thrombotic events than patients treated with placebo.

Implications

Overall, among patients with small cell lung cancer in this study, treatment with thalidomide did not improve overall survival but increased the risk of having a thrombotic event.

Limitations

The dose of thalidomide given in this study was lower than that given in some previous studies. Because bone or brain scans are not routinely performed in the United Kingdom, results of analysis by disease extent may not be generalizable to other populations with more stringent criteria.

From the Editors

which thalidomide was given concurrently with etoposide and carboplatin and was continued as maintenance therapy (including our phase II study in which the response rate was 68%) (17) suggest that thalidomide might be effective in the treatment of patients with SCLC. In the phase III trial reported here, we used continuous low-dose thalidomide (200 mg) because two earlier studies (15,18) demonstrated that this dose was well tolerated and associated with a survival that was greater than expected. Thalidomide was given concurrently with chemotherapy to decrease tumor vascular permeability and interstitial fluid pressure and thus improve chemotherapy delivery (19–22).

In addition to its anticachexic and immunomodulatory effects (23–25), thalidomide is postulated to have a synergistic effect with platinum-based chemotherapy (26). We used carboplatin instead of cisplatin in combination with etoposide because carboplatin is considerably less toxic (with regard to emesis, neurotoxicity, renal damage, and electrolyte imbalance) and can be given without special hydration as an outpatient treatment and because studies show that carboplatin and etoposide have an activity that is similar to that of standard cisplatin and etoposide (27,28).

Patients and Methods

Study Design

We performed a randomized, phase III, double-blind, placebo-controlled trial to determine whether thalidomide improves survival or quality of life (QoL) among SCLC patients receiving chemotherapy. Approvals from multicenter and local research ethics were obtained for the trial. Written informed consent was obtained from all patients before study entry.

Patients

A total of 724 patients were recruited from 79 centers in the UK National Cancer Research Network (May 2003 to February 2006). Eligibility criteria included histologically or cytologically confirmed SCLC, no previous chemotherapy or radiotherapy, age greater than 18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–3, life expectancy greater than 8 weeks, adequate renal function (EDTA clearance >60 mL/min or creatinine clearance >50 mL/min), and a negative pregnancy test. Patients with symptomatic brain metastases requiring immediate radiotherapy or with a previous malignancy during the 3 years previous to the diagnosis of SCLC (unless nonmelanoma skin cancer or early cervical cancer) were excluded. Follow-up continued until September 2008, when the database was closed for analysis.

Patients were randomly assigned to receive thalidomide or placebo after hospital staff telephoned the Cancer Research UK & University College London Cancer Trials Center. Trial center staff, clinicians, and patients were unaware of the allocation. Stratified randomization was used with a block size of 4, incorporating disease stage (limited or extensive disease), ECOG performance status (0 or 1 vs 2 or 3), center, and alkaline phosphatase (≤1.5 vs >1.5 × upper limit of normal) (29); ClinicalTrials.gov number: NCT00061919.

Trial Treatments

All patients were scheduled to receive etoposide (120 mg/m^2 intravenously on days 1 and 2 and 100 mg orally twice a day, or 120 mg/m^2 intravenously on day 1 and 100 mg orally twice a day on days 2 and 3) and carboplatin (area under the curve [AUC] = 5.0 intravenously on day 1 for patients with extensive-stage disease and AUC = 6.0 intravenously on day 1 for patients with limited-stage disease) every 3 weeks for up to six cycles. Carboplatin dosage was determined using the Calvert formula. The chemotherapy agents were given at full dose every 3 weeks or delayed until hematological recovery following the previous cycle. Dose modifications (delays or reductions) were allowed if results of pretreatment blood tests (whole blood count <3 × 10^9/L, absolute neutrophil count <1.5 × 10^9/L, or platelets <100 × 10^9/L) and/or renal function tests indicated that they were necessary. Thoracic radiotherapy (TRT) and prophylactic cranial irradiation (PCI) were given to patients with a complete or a partial response, according to local practice. The recommended doses were 40 Gy in 15 fractions for a period of 3 weeks (for TRT) and 25 Gy in 10 fractions for a period of 2 weeks (for PCI) to begin approximately 3 weeks after the last cycle of chemotherapy. At the time the study was designed, it was not routine practice to treat limited-disease patients with early and concomitant radiotherapy because a UK trial (30) suggested no survival benefit in patients receiving early chemotherapy. All other comedications were given according to local practice.

Thalidomide or matching placebo capsules were taken orally once daily from the start of chemotherapy for 2 years. The starting dose was 100 mg/d; if this dose was well tolerated, it was increased

to 150 mg/d at the end of chemotherapy for 1 month and then to 200 mg/d for the rest of the trial. The protocol specified that the dose could be either reduced or stopped (in practice, often temporarily) if the patient suffered symptoms including drowsiness, rash, sensory neuropathy, constipation, and dizziness. Strict verbal and written guidelines were given to patients regarding requirements for contraception and pregnancy testing. Women of childbearing potential were asked to abstain from heterosexual intercourse or to use two methods of contraception, and male patients engaging in intercourse with women of childbearing potential were asked to use barrier contraception.

Assessments

Initial assessment included physical examination, full blood count, serum chemistry (including tests for levels of creatinine, bilirubin, aspartate transaminase or alanine transaminase, alkaline phosphatase, lactate dehydrogenase, calcium, and albumin), chest X-ray, and computed tomography (CT) to the chest and upper abdomen to include the adrenal glands. Bone and brain scans were done only if clinically indicated (including elevated alkaline phosphatase, bony pain, or symptoms and signs of raised intracranial pressure). During chemotherapy, before each cycle, we repeated the physical and neurological examinations, hematology and chemistry tests, QoL questionnaires, and chest X-ray. Assessment CT scans were performed at cycle 3 and after the end of chemotherapy, and we recorded study drug compliance and toxicity. Neither the diagnostic pathology nor the radiological response was centrally reviewed. QoL assessments using the EORTC-QLQ C30 and lung cancer module (LC 14) (31) were made at the time of random assignment, during each chemotherapy cycle, at the end of chemotherapy, and then every 6 months until 24 months from the time of random assignment. During follow-up, assessments in the clinic were scheduled every 2 months after chemotherapy for the first 2 years and then for every 3 months. These assessments included a clinical and neurological examination; a chest X-ray; a CT scan of the chest, abdomen, and/or brain (when clinically indicated with symptoms or signs suggesting disease progression); and an assessment of toxicity. Women of childbearing potential had a pregnancy test before starting the study drug, at the beginning of each chemotherapy cycle, and at every monthly visit after chemotherapy if still taking study drug. The database was closed for analysis in September 2008.

Statistical Analysis

The primary endpoint was overall survival measured from the date of random assignment until date of death or date last seen. Secondary endpoints were progression-free survival, tumor response rates (using the RECIST criteria), toxicity (using National Cancer Institute of Canada Common Toxicity Criteria, version 2.0), and QoL. Analyses were by intention to treat (ie, according to the trial arm allocated to, and patients were included whether they took the study drug or not), unless otherwise specified. By this, we performed analyses according to the random allocation of treatment, regardless of what treatment patients actually received. Overall survival and progression-free interval were assessed by calculating the hazard ratio (HR) using Kaplan–Meier analysis and Cox regression modeling and by comparing thalidomide against placebo. For each specified adverse event, the maximum grade that the patient experienced during chemotherapy and follow-up was used, and the proportions were compared between the treatment groups. QoL measurements were examined using a repeated measures analysis allowing for baseline values (Proc Mixed in SAS). All statistical tests were two-sided, and P less than .05 was considered statistically significant.

The target sample size was 720 patients. This was the number of patients required to detect a difference in the 2-year overall survival rate of 7 percentage points (from 12% placebo to 19% thalidomide) (32), with 85% power and 5% two-sided test of statistical significance (log-rank test).

Compliance to trial treatment was examined by calculating, for each patient, the time from random assignment until death or when the treatment was stopped early. This length of time was used to estimate the median time on the study drug in each trial arm. We also expressed the number of days when the patient was taking the study drug as a percentage of the total number of days spent in the study (ie, from time of random assignment until death or date last seen), to allow for those who temporarily stopped their study drug. For example, if a patient who was allocated to receive thalidomide was in the trial for 12 months (from time of random assignment until death) and during this time had stopped the drug for 3 months in total, the proportion of time spent on study drug was taken to be 75%.

Results

A total of 724 patients were randomly assigned to treatment: 359 to placebo and 365 to thalidomide. Limited-stage disease was found in 51% of patients and extensive-stage disease was found in 49%. The two groups were well balanced according to baseline characteristics (Table 1). A similar proportion of patients with limited-stage disease in the thalidomide and placebo groups received chest radiotherapy (57% vs 53%) or PCI (44% vs 38%).

Treatment Administration

A total of 692 patients (96%) started placebo or thalidomide, 28 did not start at all, and data were missing for four (Figure 1). The median time (25th–75th percentile) on the study drug was 7.9 months (4.4–11.6 months) and 6.8 months (2.6–10.4 months) for placebo and thalidomide, respectively (P = .03; Figure 2). A total of 76% of patients on placebo and 67% on thalidomide took their allocated treatment for at least half of the time they were in the study (Supplementary Figure 1, available online). Among the 177 patients with limited-stage disease in the thalidomide group, 101 (57%) had thoracic radiotherapy and 77 (44%) had PCI; among the 191 patients in the placebo group, 102 (53%) had thoracic radiotherapy and 72 (38%) had PCI.

The study drug did not affect compliance to chemotherapy. The proportion of patients who completed all planned six chemotherapy cycles was similar between the placebo and the thalidomide groups—61% (thalidomide) and 65% (placebo) (*see* Supplementary Tables 1 and 2, available online). The proportion of patients whose chemotherapy dose was delayed or reduced also did not differ between the groups. Chemotherapy dose delays occurred in 59% and 60% of patients and reductions occurred in

Table 1. Baseline characteristics*

Characteristic	Thalidomide, n = 365	Placebo, n = 359
Age at random assignment		
≥50 y, No. (%)	344 (94)	332 (92)
Median (range), y	65 (38–85)	65 (40–86)
Sex, No. (%)		
Male	211 (58)	201 (56)
Female	154 (42)	158 (44)
Women of childbearing potential, No. (%)	8/154 (5)	20/158 (13)
Men with a partner of childbearing potential, No. (%)	25/211 (12)	25/201 (12)
ECOG performance status, No. (%)		
0	54 (15)	69 (19)
1	203 (56)	203 (57)
2	95 (26)	58 (16)
3	13 (4)	29 (8)
Stage, No. (%)		
Limited	177 (48)	191 (53)
Extensive	188 (52)	168 (47)
Alkaline phosphatase,† No. (%)		
≤1.5	322 (88)	315 (88)
>1.5	43 (12)	44 (12)
Blood measurements, median (25th–75th percentile)		
Sodium, mmol/L	136 (133–138)	137 (133–140)
Albumin, g/L	38 (34–41)	39 (34–42)
White blood cell count, $\times 10^9$/L	9.6 (8.0–12.2)	9.7 (7.9–12.4)
Lactate dehydrogenase, U/L	502 (386–724)	493 (359–698)

* ECOG = *Eastern Cooperative Oncology Group.*

† Times upper limit of normal range.

30% and 26% of patients during any cycle, in the thalidomide and placebo groups, respectively. Patients in the thalidomide group were more likely than patients in the placebo group to stop treatment before cycle 6 because of toxicity (12% vs 7%).

Efficacy

The median follow-up was 37 months, and 649 patients had died (329 in the thalidomide group and 320 in the placebo group), 87% from progressive SCLC (Supplementary Table 3, available online) at the end of follow-up. There was no evidence of an effect of thalidomide on either overall survival (unadjusted HR for death = 1.09, 95% confidence interval [CI] = 0.93 to 1.27) or progression-free survival (Figure 3). The median overall survival was 10.5 months (placebo) and 10.1 months (thalidomide). After adjustment for age, sex, and the stratification factors used in the random assignment, there was still no difference in overall survival (adjusted HR for death = 1.11, 95% CI = 0.94 to 1.32). After excluding those patients with ECOG performance status 3, overall survival was similar in the two groups (HR for death = 1.10, 95% CI = 0.94 to 1.30). Progression-free survival was also similar in the two groups (HR for progression or death = 1.07, 95% CI = 0.92 to 1.24). No differences were observed in the rates of local relapse according to treatment allocation (thalidomide vs placebo: 40% vs 43%) or distant relapse (thalidomide vs placebo: 51% vs 55%). Objective tumor response rates were similar in the two groups (Supplementary Table 4, available online).

Because there was a difference in the median length of time on the study drug in the two groups, we examined overall survival according to the percentage of time on treatment. Among the 300 patients who took the trial treatment for at least 80% of the time they were in the study, overall survival appeared to be worse in the thalidomide group than in the placebo group (HR for death = 1.35, 95% CI = 1.06 to 1.71; P = .014). Among the 219 patients who took their trial treatment for at least 90% of the time, overall survival was similar in the two groups (HR for death = 1.21, 95% CI = 0.92 to 1.60; P = .18). These results suggest that thalidomide may have unexpectedly increased the risk of dying.

Clinical outcome differs between patients with limited and extensive disease, so we examined the effect of treatment in these two groups. The median survival for patients with limited disease was 12.1 and 13.1 months in the placebo and thalidomide groups, respectively; among patients with extensive disease, the corresponding median survival times were 9.1 and 8.0 months. In an exploratory subgroup analysis, there was an interaction between disease and treatment (P = .011). Among patients with limited disease, survival was similar (HR for death = 0.91, 95% CI = 0.73 to 1.15), but in patients with extensive disease, thalidomide was associated with a higher rate of death (HR for death = 1.36, 95% CI = 1.10 to 1.68) (Supplementary Figure 2, available online). Subgroup analyses were not prespecified, so no other factor was examined in this way.

Toxic Effects

There were no substantial differences between the trial groups in the incidence of grades 3 and 4 hematological and nonhematological adverse effects, although slightly more patients in the thalidomide group had rash, constipation, or neuropathy (Table 2). Toxic effects reported separately during chemotherapy and maintenance are shown in Supplementary Table 5 (available online). Although there was no difference in adverse effects between treatments during chemotherapy, there were more nonhematological toxic effects in the thalidomide group during follow-up (risk difference = 6.3%, 95% CI = 1.4% to 11.2%). Compared with the placebo group, there was a twofold increased risk of developing a thrombotic event in the thalidomide group (19% [68 of 365] vs 10% [35 of 359]; HR = 2.13, 95% CI = 1.41 to 3.20; P < .001). The excess was largely attributable to pulmonary emboli and deep vein thromboses (38 vs 12; Table 3). At 6 months, the estimated risk difference was 9%, and it remained largely constant thereafter (Figure 4). These events tended to occur while patients were on the study drug because the average time on thalidomide was about 7 months. The thromboembolic risk was raised regardless of the ECOG performance score. More details are provided in Supplementary Table 6 (available online). Serious thrombotic events are specified in Supplementary Tables 6 and 7 and Supplementary Figure 3 (available online). Four deaths were recorded from myocardial infarction or pulmonary embolism, all in the thalidomide group, but with so few events, it was not possible to reliably determine whether they were caused by thalidomide.

Quality of Life

Baseline QoL forms were completed by 95% of patients, with 66% completing forms for at least five time points. There were no

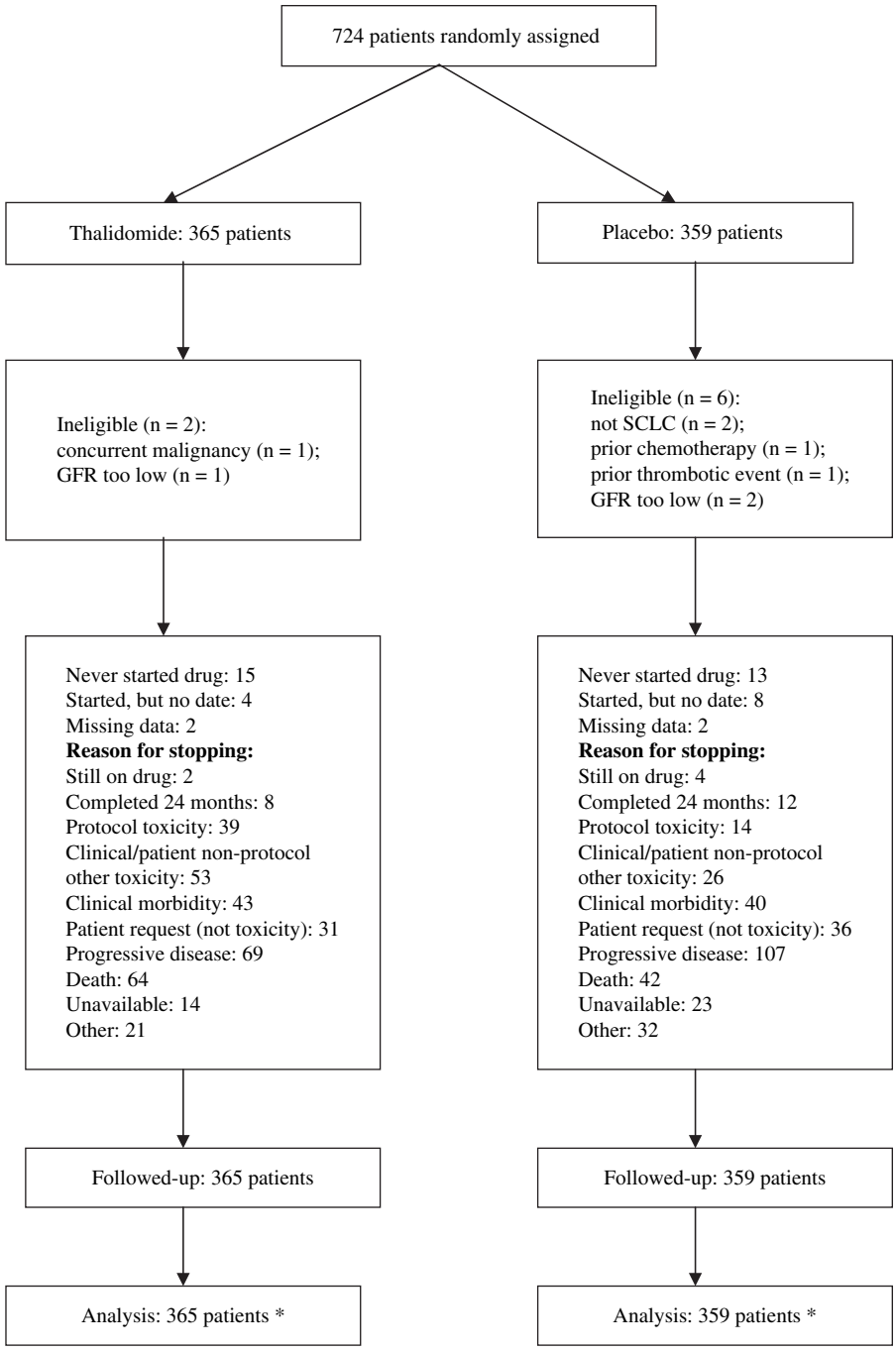
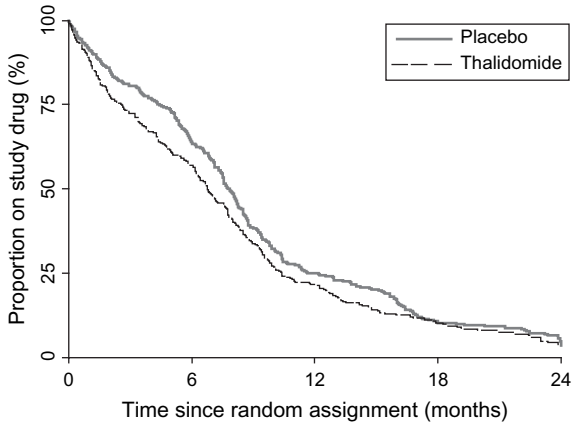


Figure 1. CONSORT diagram of the trial. *The ineligible patients were included because they were already randomly assigned and are few in number. SCLC = small cell lung cancer; GFR = glomerular filtration rate.

substantial differences in QoL scores at baseline (each factor was based on a scale of 0–100). During the study, the mean differences in scores between treatment groups remained similar over time (except for peripheral neuropathy). Thalidomide was associated with less insomnia, pain, and diarrhea, and more dyspnea, constipation, and peripheral neuropathy (most of which were expected). The differences in mean scores were not large: −10.0 (insomnia), −3.2 (diarrhea), −4.3 (pain), 5.3 (dyspnea), 10.6 (constipation), and 6.1 (neuropathy at 24 weeks after random assignment). The effects were similar when the data were restricted to the maintenance treatment period, that is, after chemotherapy ended. Details are shown in Supplementary Tables 8–10 (available online). We also examined whether thalidomide had a beneficial effect on weight during chemotherapy, but there was no evidence of this: the mean increase in weight from baseline to the end of chemotherapy was 1.8 kg in both treatment groups.

Discussion

To our knowledge, this is the first full randomized phase III trial to evaluate an anti-angiogenic agent for the treatment of SCLC and the largest treatment trial conducted in this disease to date. Despite preliminary promising evidence and biological plausibility, thalidomide was not associated with a survival



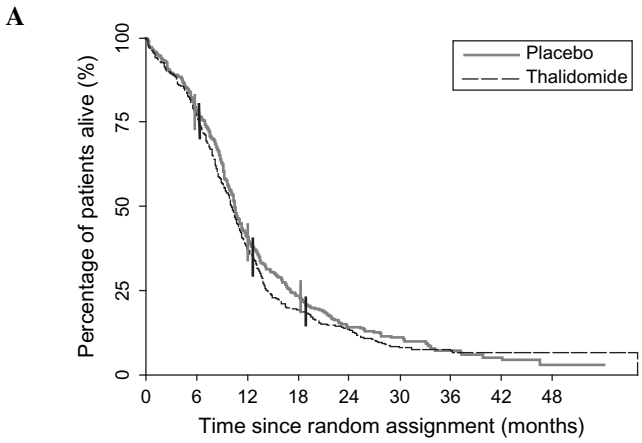
Number of patients on treatment:					
Placebo:	336	209	74	29	11
Thalidomide:	344	189	61	23	5

Figure 2. Time spent on study drug (from random assignment until death, stopped drug early, or end of trial treatment).

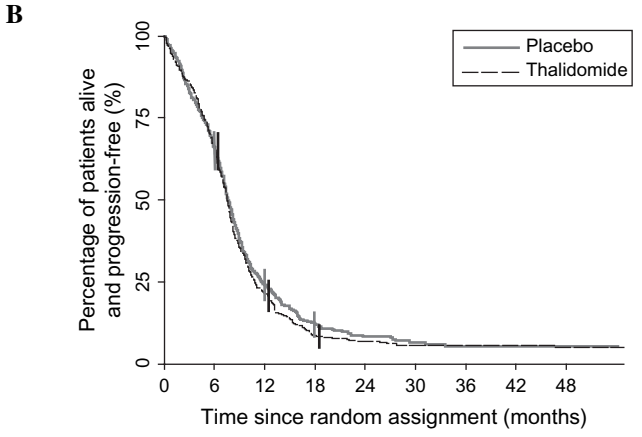
benefit, but it did increase the risk of developing a thrombotic event.

Three previous small studies of thalidomide in SCLC showed promising results (15–17). Two were single-arm phase II studies: Dowlati et al. (15) (thalidomide administered as maintenance therapy at a dose of 200 mg, n = 30) and Lee et al. (17) (thalidomide given concurrent with chemotherapy at a dose of 100 mg, n = 25) with 1-year survival rates of 52% and 46%, respectively, which were greater than the expected rate of 20%–30%. The third was a small, placebo-controlled, randomized study by Pujol et al. (16) (thalidomide given as maintenance therapy at a dose of 400 mg [n = 49 thalidomide and n = 43 placebo]) in which the 1-year survival rates were 49% in patients receiving thalidomide vs 30% in patients receiving placebo, and the median survival times were 11.7 and 8.7 months, respectively. The chance of dying was reduced by a quarter (HR for death = 0.74, 95% CI = 0.49 to 1.12), which was not statistically significant ($P = .16$). Taken together, the results from these studies suggested that thalidomide could have a substantial survival benefit in patients.

In contrast to previous small studies, the results of this large randomized trial with a control group showed that thalidomide was not associated with any benefit on overall survival or progression-free interval. The study was large enough to exclude any clinically important benefit of thalidomide. The objective response rates to chemotherapy, progression-free interval, and overall survival were consistent with previous studies in this patient group. It is unlikely that the lack of effect for thalidomide was due to poor compliance because approximately 70% of patients took their trial treatment for at least half the time they were in the study. In fact, the median duration of the study treatment (about 7 months) was longer than that observed in the study by Pujol et al. (16) (4.5 months). We also examined the treatment effect in compliers (as defined in the "Results") and found no evidence of a survival advantage. The lack of an effect on survival associated with thalidomide treatment was also observed in a large, double-blind, placebo-controlled trial of 722 patients with NSCLC (33), which was conducted by our group at



Number of patients at risk:								
Placebo:	359	280	144	78	39	23	12	6
Thalidomide:	365	276	132	67	42	21	14	10



Number of patients at risk:								
Placebo:	359	236	84	41	22	13	7	4
Thalidomide:	365	237	76	31	20	14	12	9

Figure 3. Kaplan–Meier analysis of outcomes according to treatment group. **A**) Overall survival. Thalidomide: 329 deaths, median = 10.1 months, and 1- and 2-year survival rates were 37% and 13%, respectively. Placebo: 320 deaths, median = 10.5 months, and 1- and 2-year survival rates were 41% and 14%, respectively. Hazard ratio = 1.09 (95% confidence interval [CI] = 0.93 to 1.27), $P = .28$ (two-sided log-rank test). **B**) Progression-free interval. Thalidomide: 337 events, median = 7.6 months, and 1- and 2-year rates were 22% and 7%, respectively. Placebo: 330 events, median = 7.6 months, and 1- and 2-year rates were 24% and 8%, respectively. Hazard ratio = 1.07 (95% CI = 0.92 to 1.24), $P = .39$ (two-sided log-rank test).

about the same time (overall survival: HR = 1.13, 95% CI = 0.97 to 1.32).

It is possible that the 200-mg maintenance thalidomide dose we used in our study was too low [Pujol et al. (16) used 400 mg]. However, the total dose administered to patients in the current study was broadly similar to that administered in the study by Pujol et al. because compliance was better and because many patients in the previous study required dose reduction. Moreover, there is no evidence to support a dose–response relationship for thalidomide in the treatment of multiple myeloma or solid tumors (34,35). In multiple myeloma, thalidomide at 400 mg/d with chemotherapy is associated with an improved survival rate at 5 years

Table 2. Reported grade 3 or 4 toxic effects (except thrombotic events)*

Type of toxic effect	Thalidomide, n = 365	Placebo, n = 359
Hematological, No. (%)		
Anemia	44 (12)	34 (9)
Leucopenia	69 (19)	59 (16)
Neutropenia	171 (47)	179 (50)
Thrombocytopenia	35 (10)	39 (11)
Any (each patient counted once), No. (%)	190 (52)	192 (53)
Absolute risk difference (95% CI)†	−1.4% (−8.7 to 5.8), $P = .70$	
Nonhematological, No. (%)		
Constipation	37 (10)	10 (3)
Diarrhea	8 (2)	11 (3)
Nausea	9 (2)	9 (3)
Vomiting	4 (1)	14 (4)
Mucositis/stomatitis (oral)	3 (1)	4 (1)
Anorexia	6 (2)	7 (2)
Infection (not neutropenic)	15 (4)	13 (4)
Infection (neutropenic)	27 (7)	21 (6)
Dizziness	15 (4)	16 (4)
Somnolence/drowsiness	14 (4)	15 (4)
Neuropathy/sensory	22 (6)	8 (2)
Dry skin	5 (1)	2 (1)
Rash	16 (4)	1 (<1)
Renal	3 (1)	2 (1)
Other	48 (13)	50 (14)
Any (each patient counted once), No. (%)	148 (41)	123 (34)
Absolute risk difference (95% CI)†	6.3% (−0.7 to 13.3), $P = .08$	
Any toxic effect, No. (%)	251 (69)	239 (67)
Absolute risk difference (95% CI)†	2.2% (–4.6 to 9.0), $P = .53$	

* The table is based on the maximum grade observed during chemotherapy or follow-up. *P* values (two-sided) were calculated using χ^2 test. CI = confidence interval.

† Thalidomide minus placebo.

Table 3. Type of first thrombotic event that was observed during chemotherapy or follow-up*

Event type	Thalidomide	Placebo
Pulmonary embolism	25	7
Deep vein thrombosis	13	5
Embolus	7	4
Transient ischemic attack	6	1
Cerebrovascular accident	9	8
Myocardial infarction	5	4
Other	3	6
Total	68	35

* The table shows the number of patients and is based on any severity (eight suspected cases are included).

(12). A multicenter, prospective, randomized trial testing thalidomide 100 or 400 mg/d in patients with refractory or relapsed multiple myeloma demonstrated similar 1-year survival rates, but low-dose thalidomide was better tolerated with less somnolence, constipation, and peripheral neuropathy (34). Although the three previous studies in SCLC used different thalidomide doses, the 1-year survival rates were similar (15–17). Studies in which a higher thalidomide dose was used to treat SCLC or breast cancer reported substantial toxicity and poorer compliance (15,35,36). The dose used in this study was one with proven biological effects in other settings but with a tolerable toxicity profile. If a much higher dose were used in our trial, it is likely that more patients would have had difficulty in continuing to the maintenance phase of therapy.

It is important to consider whether any possible benefit of thalidomide was outweighed by a negative effect on chemotherapy dose intensity. We observed no difference in the number of cycles and dose reductions or delays in the thalidomide and placebo groups. Furthermore, there was no increase in chemotherapy-associated adverse effects, including myelosuppression and febrile neutropenia, in the thalidomide arm. Although thalidomide did not adversely affect overall QoL or tumor response, the reduced compliance with thalidomide compared with placebo suggested poorer tolerability, which was not fully captured using our toxicity and QoL measurements.

The main adverse effect associated with thalidomide was a doubling of the risk of developing a thrombotic event, which is consistent with other studies (37,38). The Independent Data Monitoring Committee observed this doubling during the course of the trial, and the patient information sheet was changed accordingly. Patients already on study were informed of the risks and reconsented to continuing the study drug. Thrombotic events were treated using standard anticoagulants. There was no evidence of a higher risk of recurrent or refractory thromboses.

There was evidence that thalidomide was associated with a poorer overall survival among patients with extensive-stage disease. Overall, there was no difference between the trial groups in the number of deaths reported due to causes other than lung cancer (Supplementary Table 3, available online). Three possible reasons for poorer survival in patients with extensive disease who were treated with thalidomide were the following: 1) thalidomide accel-

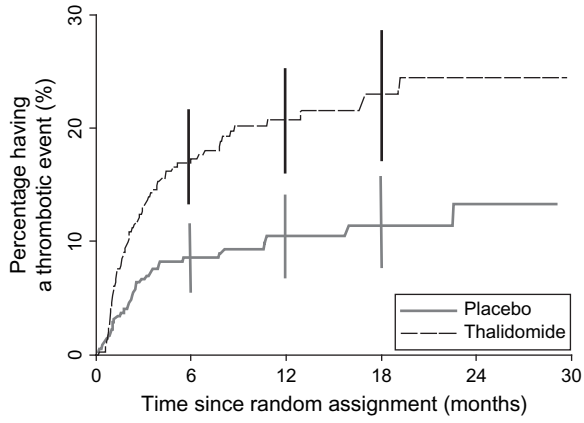


Figure 4. Kaplan–Meier analysis of developing any thrombotic event according to treatment group. Hazard ratio = 2.13, 95% confidence interval = 1.41 to 3.20; $P < .001$ (two-sided log-rank test).

erated lung cancer progression in patients with extensive disease, 2) some of the deaths were incorrectly recorded as being due to lung cancer but were due to a thrombotic event or another adverse effect, or 3) chance alone. Bone or brain CT scans are not routinely performed in the United Kingdom, so it is possible that our less stringent staging criteria may have led to some patients with asymptomatic metastatic disease to be classified as having limited disease. However, the proportion of patients with brain scans should have been similarly distributed between the trial arms due to randomization.

The lack of a benefit using thalidomide is consistent with other studies of anti-angiogenic treatments in SCLC. A randomized phase II study using vandetanib (ZD6474), a VEGF receptor tyrosine kinase inhibitor, as maintenance after chemotherapy in SCLC (39) showed no benefit in terms of overall survival or progression-free interval when compared with placebo. Two randomized phase II studies (40,41) using bevacizumab did not achieve the outcomes required to progress to phase III trials. Nevertheless, caution needs to be exercised when interpreting our findings. Unlike the results reported with bevacizumab, sorafenib, and cediranib in NSCLC, we did not observe an increase in response rates. It is possible that the 200-mg dose used in the current study was too low compared with the trial reported by Pujol et al. (16), which used 400 mg.

Together, these results suggest that targeting anti-angiogenesis in SCLC may not work as well as in multiple myeloma or colorectal cancer, perhaps because of differences in the angiogenic pathways involved in SCLC. There is also emerging evidence suggesting that anti-angiogenic agents may work better with some chemotherapy agents than others (42,43).

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