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Phase II trial of paclitaxel and cisplatin in patients with extensive stage small cell lung cancer: Cancer and Leukemia Group B trial 9430

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Abstract

Background—Cancer and Leukemia Group B (CALGB) trial 9430 was a randomized phase II trial which investigated the safety and activity of four novel doublets in untreated extensive stage small cell lung cancer (ES-SCLC). The results of the paclitaxel and cisplatin arm have not been reported.

Patients and Methods—Patients received paclitaxel 230 mg/m^2 followed by cisplatin 75 mg/m^2 on day 1 every 21 days. All patients received granulocyte colony stimulating factor (G-CSF) 5 μg/kg/day beginning on day 3 of each cycle.

Results—The patient characteristics of the 34 patients assigned to this treatment arm were: median age 61.5 years (range 41 to 82), male (76%), performance status 0 (41%), 1 (32%), and 2 (26%). An objective response was observed in 23 patients (68%; 95% confidence interval (CI): 49% to 83%); 2 complete responses (6%) and 21 partial responses (62%). Median progression-free survival time was 5.6 months (95% CI: 4.8 to 7.1 months), and median overall survival time was 7.7 months (95% CI: 7.2 to 12.6 months). The one year survival rate observed was 29% (95% CI: 15 to 45%). Grade 3/4 neutropenia and thrombocytopenia was observed in 5 (15%) and 4 (12%) patients, respectively. Two patients developed febrile neutropenia including one patient who died from neutropenic sepsis. Grade 3/4 non-hematologic observed were: sensory neuropathy in 8 patients (24%); and hyperglycemia, malaise and nausea were all observed in 4 patients (12%).

Conclusions—CALGB will not pursue further investigation of paclitaxel and cisplatin due to the modest activity and the toxicity observed on this trial.

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Keywords

CALGB; paclitaxel; chemotherapy; lung cancer; small cell lung cancer

Introduction

Lung cancer is the leading cause of cancer mortality in the United States, and it is estimated that in 2008 more patients will die of lung cancer than prostate, breast, and colorectal cancer combined.[1] Of the estimated 215,000 new cases of lung cancer, it estimated that 13% of the cases will be small cell histology (approximately 28,000 cases).[1, 2] The majority of the patients will have extensive stage disease at the time of diagnosis.[2] In the United States the standard chemotherapy for extensive stage small cell lung cancer (ES-SCLC) has been cisplatin and etoposide which was developed in the 1980's.[3] A variety of different treatment strategies have been investigated to improve the survival observed with cisplatin and etoposide. These include the use of additional cycles of topotecan,[4] maintenance chemotherapy,[5, 6] increasing the dose density of therapy[7], and alternating multi-agent chemotherapy.[8, 9] Unfortunately none of these strategies has revealed in an improvement in overall survival. More recent clinical trials have investigated the combination of a newer cytotoxic agent with cisplatin or carboplatin.[10-13] Recently a phase III trial by the Japanese Clinical Oncology Group demonstrated superior overall survival with treatment with cisplatin and irinotecan in comparison to cisplatin and etoposide.[10] However, these results were not confirmed in a North American phase III trial.[12]

At the time this trial was developed single agent paclitaxel had demonstrated significant activity in two cooperative phase II trials in untreated ES-SCLC,[14, 15] and activity in patients with relapsed SCLC.[16] A phase II trial performed by the North Central Cancer Treatment Group (NCCTG) investigated the activity of paclitaxel 250 mg/m^2 infused over 24 hours with granulocyte stimulating factor (G-CSF) every three weeks in 43 patients with untreated ES-SCLC. This trial revealed a response rate of 53%, and a median survival of 9.1 months.[15] A phase II trial performed by Eastern Cooperative Oncology Group (ECOG) investigated paclitaxel 250 mg/m^2 over 24 hours in 36 patients with untreated ES-SCLC. The response rate observed on this trial was 34% and a median survival of 9.9 months.[14] Smit et al investigated paclitaxel 175 mg/m^2 in patients with refractory disease, defined as progression within 3 months of cytotoxic chemotherapy, and reported a response rate of 29%.[16] Based upon the single agent activity of paclitaxel in ES-SCLC in phase II trials Cancer and Leukemia Group B (CALGB) initiated several trials investigating paclitaxel n ES-SCLC.[17, 18]

CALGB trial 9430 was a randomized phase II trial to investigate the activity of three novel chemotherapy combinations: cisplatin 75 mg/m^2 on day 1 and topotecan 1 mg/m^2 on days 1-5 (arm 1), cisplatin 75 mg/m^2 and paclitaxel 230 mg/m^2 (arm 2) and paclitaxel 230 mg/m^2 on days 1 and topotecan 1 mg/m^2 on days 1-5 (arm 3). The randomized phase II trial design was chosen in order to assess multiple investigational combinations, and the goal of the trial was to identify a combination for a potential phase III trial in comparison to cisplatin and etoposide. Each treatment arm was evaluated independently for efficacy and toxicity. Treatment arm 1 (cisplatin and topotecan) was closed after 12 patients were enrolled due to excessive toxicity including three deaths.[19] Thirteen patients were assigned to treatment arm 3 and no complete responses were observed and excessive toxicity including three deaths were observed, and accrual was stopped to this treatment arm. The trial was amended and a fourth treatment arm (paclitaxel 135 mg/m^2 and topotecan 1 mg/m^2 days 1-5) was incorporated and 32 patients were assigned to that treatment arm.[19] The doses of cisplatin and paclitaxel were selected based on the data available from previous phase I trials.[20, 21] The decision was made to publish the three topotecan containing arms as a separate manuscript due to the fact there was significant

interest in further investigation of topotecan-based therapies and the toxicity observed, and to publish the cisplatin and paclitaxel arm separately. While it may have been preferable to publish all four arms in a single publication the results of the paclitaxel and cisplatin arm have not been previously published and are relevant to the treatment of ES-SCLC.

Patients and Methods

Patients were eligible for participation if they met all of the following criteria: histologically or cytologically confirmed diagnosis of SCLC, CALGB performance status of 0-2, life expectancy of > 2 months, measurable or evaluable disease, extensive stage disease, and ability to provide informed consent. Extensive stage disease was defined as those patients with extra thoracic metastases, malignant pleural effusions, or contralateral supraclavicular or hilar lymphadenopathy (precluding definitive radiation therapy). Measurable disease was defined as a mass reproducibly measurable in two perpendicular diameters. Evaluable disease was defined as assessable lesions on physical exam or radiographic studies that did not fit the category of measurable. Patients were required to be ≥ 2 weeks since any major surgery and patients with brain metastases were eligible if they were ≥ 3 weeks from completion of cranial irradiation. Laboratory requirements were: absolute neutrophil count (ANC) ≥ 1,800/μl; hemoglobin ≥ 10 gm/dl, platelet count ≥ 100,000/μl; creatinine ≤ 1.5 times upper limit of institutional normal or calculated creatinine clearance of ≥ 60 ml/min; bilirubin ≤ 1.5 mg/dl; and aspirate aminotransferase < 2 times the upper limit of institutional normal. Patients who were age < 16, pregnant, who receive prior mediastinal or pelvic radiation, systemic chemotherapy, or required ongoing corticosteroid administration, were excluded. Patients with a prior or concomitant malignancy (except curatively treated carcinoma in situ of the cervix or basal cell skin cancer) or primary cancer that had been completely resected < 5 years ago were excluded. There was no upper limit of age for enrollment on the trial. The following tests were required at study entry: a complete history and physical examination, electrocardiogram, chest x-ray, computed tomography (CT) of the chest and upper abdomen, and CT scan or magnetic resonance imaging (MRI) of the brain, and bone scan. This protocol was reviewed by the Institutional Review Board (IRB) at the participating institutions, and all patients were required to provide informed consent prior to initiating study treatment.

As part of the quality assurance program of the CALGB, members of the Data Audit Committee visit all participating institutions at least once every three years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 10 patients (10.4%) of the 96 patients under this study. The study chair reviewed the eligibility for all the patients enrolled on the trial, and all the case report forms related to patient's treatment, toxicity, and efficacy on the trial.

Treatment

Patients received paclitaxel 230 mg/m^2 administered intravenously as 3-hour infusion and after completion of the paclitaxel infusion patients received cisplatin 75 mg/m^2 administered intravenously every 21 days. All patients received dexamethasone 10 mg, diphenhydramine 50 mg and ranitidine 50 mg (or equivalent) intravenously prior to the paclitaxel infusion. G-CSF support was initiated at 5 μg/kg/day starting on day 3 and continued until white blood cell count was > 10,000 μl after day 11. Prophylactic anti-emetics, hydration, and mannitol were used at the discretion of the treating physician. Patients who experienced stable disease or a response after two cycles continued treatment for a maximum of six cycles, until disease progression, unacceptable toxicity, or patient decision to discontinue therapy. For patients who

obtained a complete response, prophylactic cranial irradiation was allowed at the discretion of the investigator.

Dose modifications of the paclitaxel and cisplatin were specified in the protocol for myelosuppression, nephrotoxicity, neurotoxicity, and hepatic dysfunction. If grade 2 or 3 neurotoxicity developed, therapy was held until resolution to ≤ grade 1, and then if medically appropriate resumed with a reduction of the paclitaxel dose of 25%. Cisplatin was discontinued in patients who developed grade 3 neurotoxicity. Patients were required to have adequate hematological recovery (defined as an ANC ≥ 1,800/μl or platelet count ≥ 100,000/μl) by day 22. If patients did not have adequate hematological recovery treatment was delayed one week, and if adequate recovery occurred by day 42 no dose reduction was required for subsequent cycles. If recovery was delayed beyond day 42 protocol therapy was discontinued. Dose reduction was required for all patients experiencing neutropenic fever requiring hospitalization, a nadir platelet count of ≤ 25,000/μl or neutropenia with an ANC < 500/μl lasting > 4 days.

Assessment of Response and Toxicity

Response was assessed after every two cycles of therapy. A complete response was defined as the complete disappearance of tumor on clinical and radiologic examinations without the appearance of new lesions. A partial response was characterized as a reduction by at least of 50% of the products of longest perpendicular diameters of all measurable lesions and no growth of new lesions lasting at least four weeks. Stable disease was defined as a decrease in the sum of the products of two perpendicular diameters of all measured lesions by < 50% or an increase by < 25% after a minimum of two cycles. Progressive disease was defined as an increase in the product of the longest diameters of measured lesion by ≥ 25% or the appearance of new lesions. Regression of disease was defined as the definite decrease in the size of evaluable lesions that was agreed upon by two independent investigators and no development of new lesions for > 8 weeks.

Toxicities were assessed immediately prior to each treatment cycle and graded according to the CALGB toxicity criteria. Serum chemistry and liver tests were obtained before each cycle of chemotherapy, and neurotoxicity was assessed by history and physical examination. Patients had a complete blood count (CBC) checked at least weekly, and bi-weekly while receiving G-CSF and prior to each treatment cycle.

Statistical Design

The primary objective was to evaluate the activity of four novel combinations in patients with ES-SCLC using a randomized phase II trial design. This study was not a comparative trial and each treatment arm was evaluated independently. Patients were randomized using permuted block randomization, and no stratification factors were used. The purpose was to determine if each combination had sufficient activity to merit further investigation.[22]. A single stage phase II design was used for each treatment regimen to differentiate between a complete response rate of 10% and 30%. Assuming tests would be conducted with 90% power at a 0.05 level of significance, an accrual goal of 33 patients was set for each arm. If fewer than six patients experienced a complete response it would be concluded that the combination had insufficient activity to merit further investigation. Secondary objectives were to determine the overall and progression-free survival, overall response rate (defined as complete and partial responses combined), and toxicity. Kaplan-Meier curves were used to describe overall and progression-free survival. Survival was defined as time from treatment initiation to death or last know follow-up. Progression-free survival was defined as time between initiation of treatment until disease progression, death, or last known follow-up (whichever occurred first). The frequency of toxicity was tabulated by the most severe occurrence. Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review

of the data by CALGB Statistical Center staff, and statistical analyses were performed by CALGB statisticians.

Results

Between May 1995 and March 1996 34 patients were assigned to receive paclitaxel and cisplatin. The majority of the patients were men (76%), had an initial performance status of 0-1 (73%), and had < 5% weight loss (76%) (Table 1). The median age was 61.5 years (range, 41-82 years). The patient characteristics of arm 1 (n=12), arm 3 (n=13) and arm 4 (n=32) are provided in Table 2. The majority of the patients on the other treatment arms were male (58%), had an initial performance status of 0-1 (91%), and had < 5% weight loss (60%).[19]

The total number of cycles administered was 156, and the median number of cycles per patient was 5.5 (range 1 to 6). The reasons for discontinuation of treatment are reported in table 3. The most common reasons were completion of protocol therapy (n=16, 47%), and progressive disease (n=9, 26%). The rates of grade ≥ 3 toxicities are listed in table 4. The primary grade 3/4 hematologic toxicities were neutropenia (n=5, 15%) and thrombocytopenia (n=4, 12%). One patient experienced grade 3 febrile neutropenia without documented infection and one patient died from neutropenic sepsis due to gram negative bactremia. The primary non-hematologic toxicities were grade 3 sensory neuropathy (n=8, 24%), malaise (n=4, 12%), nausea (n=4, 12%), and hyperglycemia (n=4, 12%). Of note six patients (18%) developed grade 2 sensory neuropathy as well. One patient died of unknown causes on day 11 of treatment.

All 34 patients were included in the response evaluation, and the patient's best response is characterized in table 5. Of the 34 patients who received paclitaxel and cisplatin, twenty four responses were observed yielding a response rate of 68% (95% confidence interval (CI) 49 to 83 %). The responses observed included 2 complete responses (6%), and 21 partial responses (62%). Of the 34 patients assigned to the treatment arm 33 have died and one patient was registered on December 15, 1995 and the last known of date of contact was January 26, 2001. The median progression-free and one-year progression-free survival were 5.6 months (95% CI, 4.8 to 7.1 months) and 9% (95% CI, 2 to 24%), respectively (Table 4 and Figure 1). The median overall survival and one-year survival rate were 7.7 months (95% CI, 7.2 to 12.6 months) and 29% (95% CI, 15 to 45%), respectively (Table 4 and Figure 2). The overall response rates observed on arms 1, 3 and 4 were 42% (95% CI, 13 to 76%), 54% (95% CI, 22 to 83%), and 69% (95% CI, 48 to 85%), respectively.[19] The other treatment were assessed for failure-free survival, defined as time between randomization and disease progression, death, or last known follow-up, and overall survival (Table 6). The median failure-free survival time observed on arms 1, 3 and 4 were 4.7 (95% CI, 1.4 to ∞), 7.4 (95% CI, 1.5, ∞) and 5.2 (95% CI, 4.5, 6.9) months, respectively. The median overall survival times for arms 1, 3 and 4 were 5.7 (95% CI, 4.7 to ∞), 13.8 (95% CI, 1.8 to ∞) and 9.9 (95% CI, 7.6 to 15) months, respectively.

Discussion

The results of this trial reveal that the combination of paclitaxel and cisplatin with G-CSF support is active in ES-SCLC, and the overall response rate (68%) observed was comparable to other chemotherapy combinations. The complete response rate (6%); however, is below the predefined threshold for further investigation. The median survival observed was 7.7 months which is lower than the median survival observed on previous CALGB trials in a similar patient population.[19, 23] The median survival observed on the cisplatin and paclitaxel arm is also numerically lower than the median survival observed on recent phase III trials with cisplatin in combination with etoposide, topotecan, or irinotecan.[11, 12]

The overall response rate observed on arms 1, 3, and 4 (42%, 54%, and 69%, respectively) were similar to other chemotherapy combinations as well.[19] The median survival time observed on arms 1, 3, and 4 were 5.7, 13.8 and 9.9 months, respectively. The excessive toxicity observed on arm 1 precluded any further investigation of that combination, and no complete responses and excessive toxicity were observed on arm 3, and that combination was not investigated further. The complete response rate, failure-free survival time, median survival time, and one-year survival rate observed on arm 4 were similar to the results of a previous CALGB trial with cisplatin and etoposide, and that combination was not investigated further..[23]

The most frequent non-hematologic toxicity was sensory neuropathy; 18% of patients experienced grade 2 and 24% experienced grade 3 sensory neuropathy. The rate of grade 3 sensory neuropathy observed on this trial is similar to other trials in advanced non-small cell lung cancer (NSCLC) and breast cancer with this combination.[24, 25] The hematologic toxicity was moderate with the use of prophylactic G-CSF supportive therapy, but one patient did experience febrile neutropenia and one patient did experience fatal neutropenic sepsis. The rate of toxicity observed with this combination is not substantially different from currently available combination therapies.

Other CALGB trials have investigated the activity of paclitaxel in untreated ESSCLC. CALGB trial 39901 investigated single agent paclitaxel in patients with untreated ES-SCLC (n=36).[17] Patients received paclitaxel 150 mg/m^2 over 3 hours weekly for six consecutive weeks every 8 weeks. The overall response rate observed on this trial was 33% (3% complete response and 30% partial response), and the median progression-free and overall survival observed were 3.7 (95% CI, 3.3 to 5.8) and 9.2 months (95% CI, 6.7 to 14.8), respectively. CALGB trial 9732 was a phase III trial which investigated cisplatin/etoposide with and without paclitaxel (n=587).[18] There was no statistically significant difference between the standard treatment arm and the paclitaxel containing arm, but the toxicity was greater on the paclitaxel containing arm. The median survival time observed on the cisplatin and etoposide and cisplatin, etoposide, and paclitaxel treatment arms were 9.9 months (95% CI, 9.2 to 10.8) and 10.6 months (95% CI, 9.9 to 11.2) respectively; and both were superior to the median survival time observed on the current trial.

The combination of paclitaxel and carboplatin has previously been investigated in patients with untreated ES-SCLC in two phase II trials.[26, 27] A phase II trial performed by Thomas et al investigated treatment with paclitaxel and carboplatin every three weeks (n=50).[26] The response rate observed was 65% (95% CI, 51 to 80%) with three complete responses and 27 partial responses. The median overall survival observed was 38 weeks. A second phase II trial performed by Gridelli et al investigated paclitaxel and carboplatin every four weeks (n=48).[27] The response rate observed was 54.2% (95% CI, 39.2 to 68.6%) with three complete responses and 23 partial responses. The median overall survival observed was 9.6 months (95% CI, 7.2 to 14.6 months). The overall response rates and the number of complete responses observed on these two trials are similar to the results observed on our trial.

In addition to these phase II trials two phase III trials have compared paclitaxel and carboplatin to anthracycline containing treatments regimens.[28, 29] A phase III trial performed by de Jong et al compared treatment with cyclophosphamide, doxorubicin, and etoposide (CDE) every three weeks versus paclitaxel and carboplatin every three weeks.[28] The median progression-free survival times observed on the paclitaxel and carboplatin and CDE treatment arms were similar (5.2 vs. 4.9 months, respectively; p=0.60), and the median overall survival times were similar as well (6.7 vs. 6.8 months, respectively). The preliminary results of a second phase III trial which compared paclitaxel and carboplatin every three weeks to cyclophosphamide, doxorubicin, and vincristine (CAV) every three weeks are available as well.[29] Patients who

had limited and extensive stage disease with a prognostic score in the intermediate and poor range were enrolled, and the objectives were to determine the one-year survival rate, the objective response rate, and toxicity. There was a statistically significant difference in survival time favor of the paclitaxel and carboplatin (p=0.014). The one year survival rates and the median survival time for CAV and paclitaxel and carboplatin were 6% and 13%, respectively, and 94 days and 154 days, respectively. The poor median survival times observed on this trial may be related to the selection of patients with intermediate and poor prognostic scores. The results of these trials indicate that it is unlikely that the combination of paclitaxel and carboplatin will provide a clinically significant improvement in survival in comparison to currently available therapies for patients with ES-SCLC.

In conclusion, the results of CALGB 9430 do not support the continued investigation of paclitaxel and cisplatin in ES-SCLC given the low complete response rate, modest median survival, and toxicities observed.

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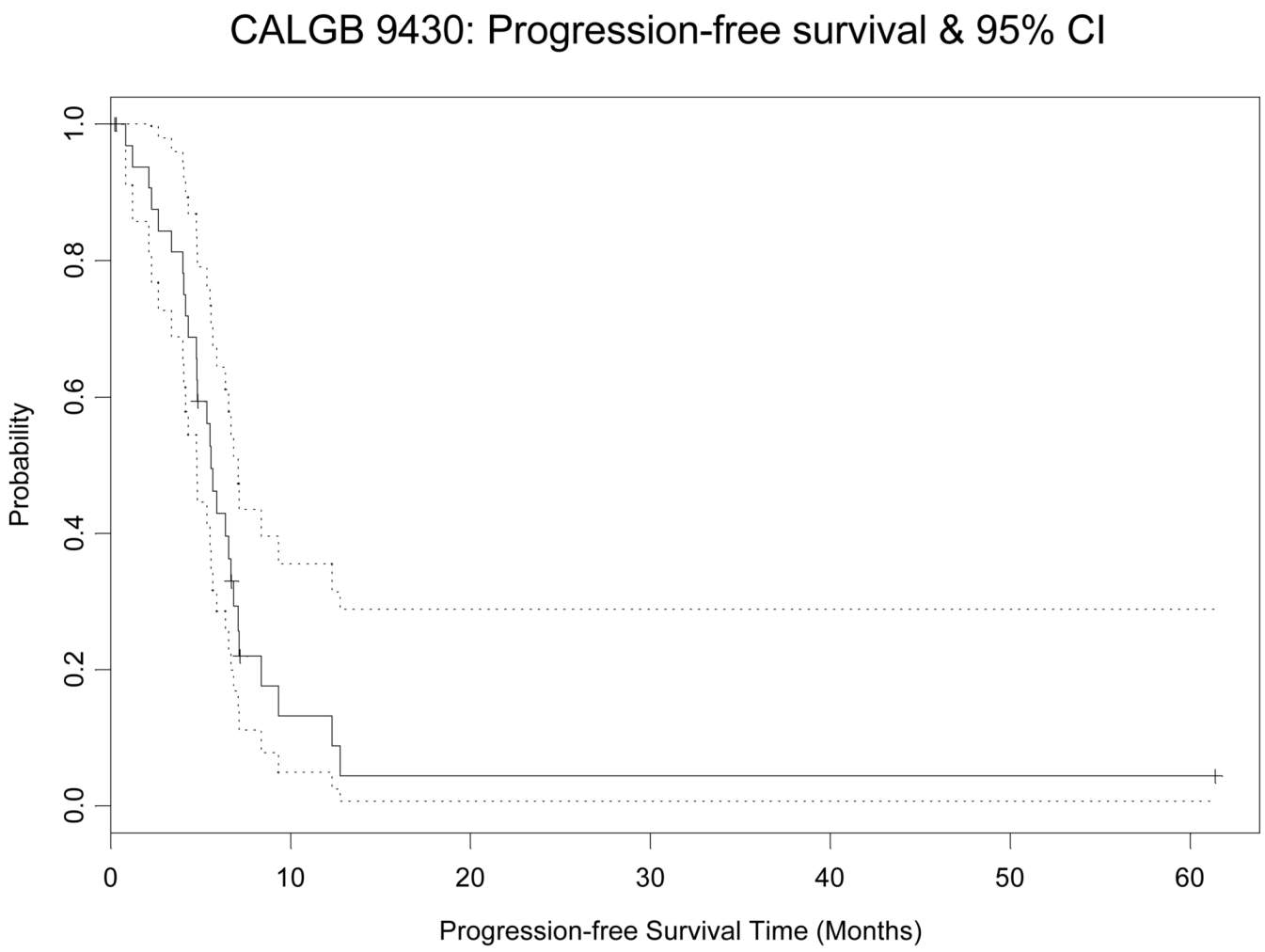

Figure 1.
Progression-free survival with 95% CI. Median progression free survival time 5.6 months, and one-year progression-free survival rate 9%.

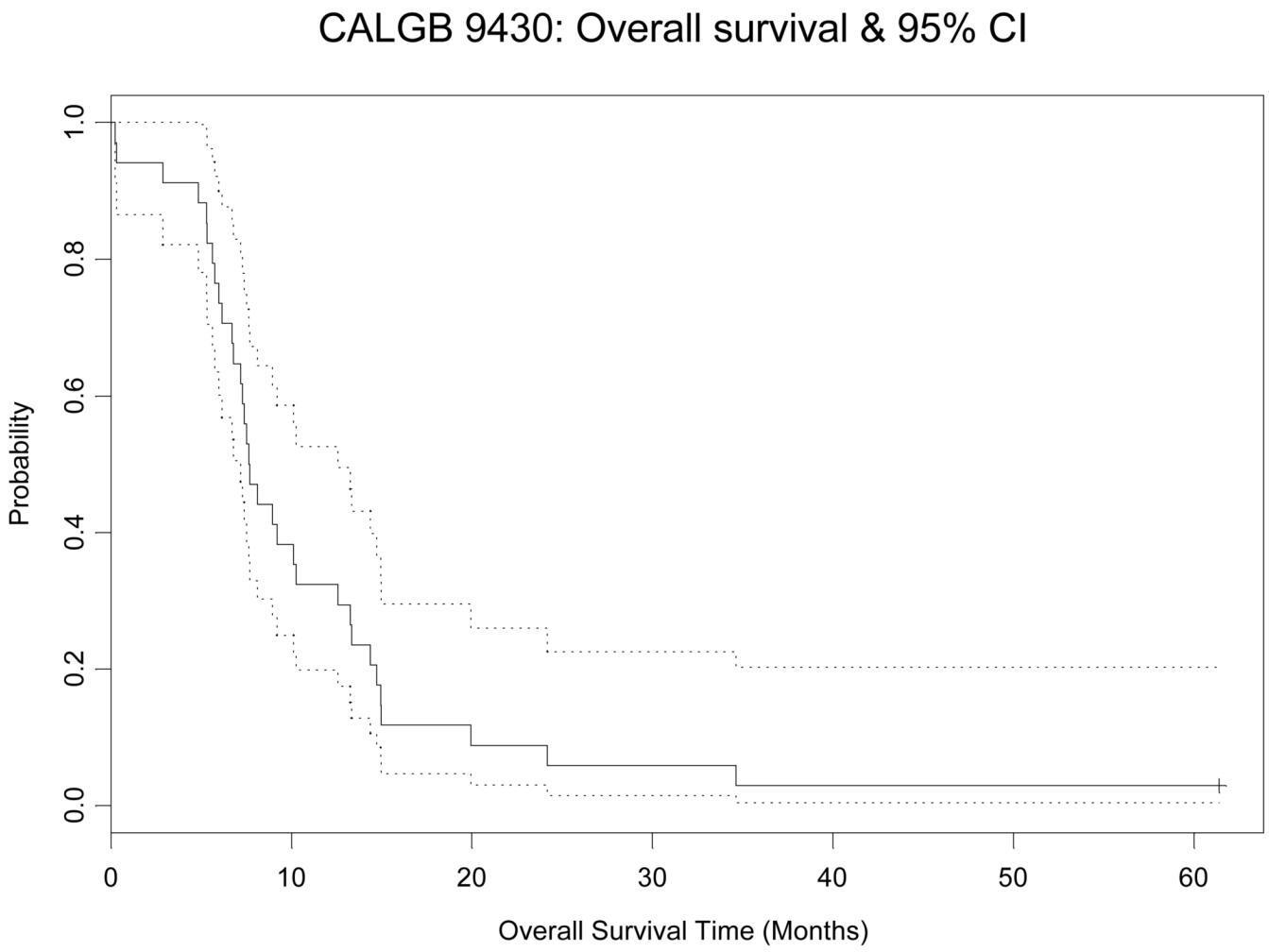

Figure 2.
Overall survival with 95% CI. Median overall survival time 7.7 months, and one year overall survival rate 29%.

Table 1

Patient Characteristics of cisplatin and paclitaxel arm

Characteristic	No. of Patients (%)
Patients Enrolled	34
Median Age (Range)	61.5 years (41-82 years)
Gender Male	26 (76%)
Female	8 (24%)
Performance Status	
0	14 (41%)
1	11 (32%)
2	9 (26%)
Weight Loss	
<5%	26 (76%)
5-10%	4 (12%)
>10%	4 (12%)

Table 2

Patient Characteristics of Other Treatment Arms[19]

Characteristic	No. of Patients (%)		
	Arm 1	Arm 3	Arm 4
Patients	12	13	32
Median Age (Range)	59.5 (50,76)	67.5 (45,74)	60 (33,83)
Gender Male	10 (83%)	6 (46%)	17 (53%)
Female	2 (17%)	7 (54%)	15 (47%)
Performance Status			
0	2 (17%)	3 (23%)	9 (28%)
1	8 (67%)	7 (54%)	23 (72%)
2	2 (17%)	3 (23%)	0
Weight Loss			
<5%	6 (50%)	10 (77%)	18 (56%)
5-10%	5 (42%)	2 (15%)	8 (25%)
>10%	1 (8%)	1 (8%)	4 (13%)
Unknown	0	0	2 (6%)

Arm 1: cisplatin/topotecan; Arm 3: paclitaxel (230 mg/m^2)/topotecan; Arm 4: paclitaxel (175 mg/m^2)/topotecan

Table 3

Reasons for discontinuation of study treatment for the cisplatin and paclitaxel arm (N=34)

Reason	No. of Patients (%)	
Completed Protocol Therapy	16	(47%)
Progressive Disease	9	(26%)
Patient Withdrawal of Consent	3	(9%)
Adverse Events	2	(6%)
Death	2	(6%)
Doctor Decision	2	(6%)

Table 4

Toxicity of Cisplatin and Paclitaxel in ES-SCLC (N=34)*

	Number of Patients (%)		
	Grade 3	**Grade 4**	**Grade 5**
Hematologic			
Leukopenia	3 (9%)	1 (3%)	-
Neutropenia	2 (6%)	3 (9%)	-
Anemia	1 (3%)	-	-
Thrombocytopenia	3 (9%)	1 (3%)	-
Febrile Neutropenia	1 (3%)	-	1 (3%)
Non-Hematologic			
Nephrotoxicity	1 (3%)	2 (6%)	-
Hyperglycemia	4 (12%)	-	-
Sensory Neuropathy	8 (24%)	-	-
Nausea	4 (12%)	-	-
Hypersensitivity	-	1 (3%)	-
Malaise	4 (12%)	-	-
Infections without neutropenia	2 (6%)	-	-

* Maximum toxicity grade experienced per patient

Table 5

Response and Survival Rates of Cisplatin and Paclitaxel

	No. of Patitients (%)	
Response Parameter		
Complete Response	2	(6%)
Partial Response	21	(62%)
Regression of Disease	1	(3%)
Stable Disease	4	(12%)
Progression Disease	3	(9%)
Non-Evaluable for Response	3	(9%)*
Progression-free Survival		
Median Overall (95% CI)	5.6 months (4.8, 7.1)	
1-Year Progression-free Survival Rate (95% CI)	9% (2%, 24%)	
Overall Survival		
Median Overall (95% CI)	7.7 months (7.2, 12.6)	
1-Year Overall Survival Rate (95% CI)	29% (15%, 45%)	

* 3 patients were non-evaluable: 2 patients due to early death, and 1 patient did not undergo disease reassessment

Table 6

Response and Survival Rates for Other Treatment Arms[19]

	Arm 1	Arm 3	Arm 4
No. of Pts	12	13	32
Complete Response	1 (8%)	0	2 (6%)
Partial Response	4 (33%)	7 (54%)	20 (63%)
Stable Disease	2 (17%)	0	3 (9%)
Progressive Disease	2 (17%)	2 (15%)	3 (9%)
Early Death	3 (25%)	2 (15%)	2 (6%)
Non-Evaluable for Response	0	2 (15%)	2 (6%)
Failure-free Survival			
Median (95% CI) in months	4.7 (1.4,∞)	7.4 (1.5,∞)	5.2 (4.5, 6.9)
1-yr Failure-free Survival Rate	8% (1%, 54%)	8% (1%, 50%)	3% (0.5%, 21%)
Overall Survival			
Median (95% CI) in months	5.7 (4.7, ∞)	13.8 (1.8,∞)	9.9 (7.6, 15)
1-yr Overall Survival Rate	17% (5, 59%)	62% (40%, 95%)	40% (26%, 61%)

Arm 1: cisplatin/topotecan; Arm 3: paclitaxel (230 mg/m^2)/topotecan; Arm 4: paclitaxel (175 mg/m^2)/topotecan