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Amrubicin and carboplatin with pegfilgrastim in patients with extensive stage small cell lung cancer: A phase II trial of the Sarah Cannon Oncology Research Consortium

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ABSTRACT

Purpose: First-line treatment for patients with extensive-stage small cell lung cancer (SCLC) includes treatment with platinum-based combination chemotherapy. Amrubicin is a synthetic anthracycline with single-agent activity in relapsed/refractory SCLC. In an attempt to improve treatment efficacy, we evaluated amrubicin/carboplatin as first-line therapy for extensive-stage SCLC.

Patients and methods: In this multicenter phase II trial, patients received amrubicin (30 mg/m^2 daily on Days 1, 2, and 3) and carboplatin (AUC = 5 on Day 1); cycles were repeated every 21 days for 4 cycles. Pegfilgrastim (6 mg subcutaneously) was administered on Day 4 of all cycles. Overall survival (OS) proportion at 1 year was the primary endpoint. The target 1-year OS rate was 47%, an improvement of 35% from historical results with carboplatin/etoposide.

Results: Eighty patients received study treatment, and 62% completed the planned 4 courses. The overall response rate was 74% (13% complete responses). The 1-year survival rate was 38% (95% CI: 25, 50). The median survival was 10 months. Myelosuppression was severe but manageable.

Conclusions: The combination of amrubicin/carboplatin was an active first-line treatment for extensive stage SCLC, but showed no indication of increased efficacy compared to standard treatments. Severe myelosuppression was common with this regimen, in spite of prophylactic pegfilgrastim. These results are consistent with those of other trials in showing no role for amrubicin in the first-line treatment of SCLC.

1. Introduction

Small cell lung cancer (SCLC) accounts for approximately 13% of all lung cancer, affects approximately 30,000 people yearly in the United States, and is usually fatal [1]. Unfortunately, little progress has been made in the treatment of patients with extensive-stage SCLC since the development of platinum/etoposide combination chemotherapy over 20 years ago. Median survival remains less than 12 months, and long-term survival is rare.

Amrubicin is a synthetic 9-aminoanthracycline with more activity than other anthracyclines in preclinical models [2]. In non-randomized phase II studies, single-agent amrubicin produced response rates of 50–60% in patients with relapsed or refractory SCLC [3,4]. Subsequently, two randomized phase II studies showed superiority of amrubicin versus topotecan in SCLC patients progressing after platinum-based chemotherapy [5,6]. At the time the trial reported here was designed, randomized trials comparing amrubicin to topotecan were ongoing in previously treated SCLC patients.

Improvement in the efficacy of first-line treatment is more likely to make a major impact on the disease course than is single-agent

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treatment for patients after relapse. The tolerability of amrubicin with carboplatin was demonstrated by Inoue et al. [7]; although 97% of patients had grade 3 or 4 neutropenia, this complication was manageable, and non-hematologic toxicity was moderate. Preliminary efficacy data indicated a high level of activity (overall response rate 89%) [7].

The objective of this phase II trial was to further evaluate the efficacy and toxicity of the amrubicin/carboplatin combination in the first-line treatment of patients with extensive stage SCLC. In an attempt to ameliorate the frequent grade 3/4 neutropenia, eligibility was limited to patients with good performance status (ECOG 0 or 1). In addition, pegfilgrastim was administered to all patients following chemotherapy.

2. Patients and methods

This study was conducted by the Sarah Cannon Research Institute (SCRI) Oncology Research Consortium at 5 centers in the United States (Appendix A). The study was approved by the institutional review boards of all participating sites and patients were enrolled following written informed consent. This trial was registered with ClinicalTrials.gov (NCT01076504).

2.1. Eligibility criteria

Patients with previously untreated, cytologically or histologically confirmed extensive stage SCLC were eligible to enroll. Additional eligibility requirements included: measurable or evaluable disease according to RECIST version 1.1 [8], left ventricular ejection fraction (LVEF) $\geq$50% shown by ECHO or MUGA scans, QTc interval of $\leq$450 milliseconds, and ECOG performance status 0 or 1. Patients were required to have adequate hematologic function (ANC $\geq$1500/μL, platelets $\geq$100,000/μL, hemoglobin $\geq$9.9 gm/dL), as well as adequate renal (serum creatinine $\leq$1.5 X ULN) and liver (total bilirubin $\leq$1.5 X ULN, AST/ALT $\leq$2.5 X ULN or $\leq$5 X ULN if hepatic metastases) function. Patients were excluded if they had active brain metastases; however patients with treated brain metastases were allowed to enroll following certain criteria. Additional exclusion criteria included: mixed small-cell/non-small cell histology or other neuroendocrine lung cancers, suspected diffuse idiopathic interstitial lung, or pulmonary fibrosis, and any concurrent medical or psychiatric illness that would impair study participation.

2.2. Pretreatment evaluation

Before entering the trial, medical histories were evaluated and physical examinations were performed for all patients. In addition, complete blood counts (including differential and platelets), ECOG performance status, PT/PTT/INR (only for patients taking Coumadin or other anti-coagulants), complete metabolic profile, ECG, and ECHO/MUGA scans were assessed. All patients had complete staging of SCLC including computerized tomography (CT) of the chest and abdomen, CT or MRI of the brain, and either PET scan or bone scan.

2.3. Treatment

Patients were treated with carboplatin AUC = 5 IV (day 1) and amrubicin 30 mg/m^2 IV (daily on days 1–3). Pegfilgrastim 6 mg was administered subcutaneously on Day 4. All patients received prophylactic antiemetics for moderately emetogenic chemotherapy according to standard guidelines. Treatment was repeated at 21-day intervals for 4 cycles. A treatment duration of 4 cycles was selected based on results of randomized studies with other first-line SCLC regimens demonstrating comparable results with 4 cycles versus 6–8 cycles [9].

The doses of amrubicin and carboplatin were based on results of a phase I trial [10]. Because of concerns regarding possible myelosuppression with the combination, 10 patients were treated in a lead-in phase, and toxicity was assessed before further accrual was allowed. Complete blood counts were monitored weekly during cycle 1, then on day 1 of subsequent cycles. Neither thoracic radiotherapy nor prophylactic cranial irradiation was mandated as part of this clinical trial; however, use of these treatment modalities was at the discretion of the treating physician after completion of study treatment.

2.4. Dose modifications

Dose modifications for treatment-related toxicity were specified in the protocol. Two dose reductions were allowed for amrubicin (dose level −1, 25 mg/m^2, dose level −2, 20 mg/m^2), and one dose reduction was allowed for carboplatin (to AUC = 4). If hematologic toxicity recurred after two dose reductions, amrubicin and carboplatin were discontinued. If a Grade 3 or Grade 4 non-hematologic toxicity occurred, both drugs were delayed until the toxicity resolved to $\leq$ Grade 1, and study treatment was then resumed with a 1 dose level reduction of the offending agent. Dose re-escalations were not allowed. If Grade 3 or Grade 4 non-hematologic toxicity recurred after maximum dose reductions had been made, study treatment was discontinued. Dose reductions and management of amrubicin-related cardiotoxicity and pulmonary toxicity were detailed in the protocol.

2.5. Assessment of response

After 2 cycles (6 weeks) of treatment, patients were restaged with repeat CT scans. Patients with an objective response or stable disease received another 2 cycles of treatment and were then followed until disease progression. After disease progression, follow-up assessments were performed every 3 months during the first 2 years, then every 6 months during years 3–5, and annually thereafter for survival only.

2.6. Statistical plan

This was a single-arm, multicenter Phase II study with the objectives of determining the efficacy and toxicity of first-line treatment with amrubicin/carboplatin in patients with extensive stage SCLC. The primary efficacy endpoint was the 1-year survival proportion. The estimated 1-year survival for extensive stage SCLC patients treated with the standard regimen of carboplatin/etoposide is approximately 35% [11]. It was hypothesized that the substitution of amrubicin for etoposide would improve the 1-year survival rate by 35% (from 35% to 47%). A sample size of 77 patients was required to achieve 81% power to detect this survival difference using the one-sided binomial test. To account for a 10% non-evaluable rate, the total sample size was determined to be 85 patients [12].

The 1-year survival endpoint was evaluated using Kaplan-Meier survival methods [13]. The objective response rate was defined as the proportion of complete and partial responses among all treated patients. Overall survival (OS) was defined as the time from first treatment until death from any cause. Toxicities were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

3. Results

3.1. Patient characteristics

From March 2010 to July 2011, 81 patients were enrolled. One patient withdrew from the study prior to receiving any treatment. The remaining 80 patients received at least one dose of treatment and are

included in the efficacy and safety analyses. Baseline characteristics are summarized in Table A1 in Appendix A. Median age was 65 years (range, 45–85 years) and the study population was mostly Caucasian (94%) and female (55%).

3.2. Treatment received

The median treatment duration was 4 cycles (range, 1–6) (Table A2 in Appendix A). Fifty-one patients (64%) completed the planned 4 cycles of treatment, while 12 patients (15%) discontinued treatment due to cancer progression prior to completing 4 cycles. The remaining patients stopped treatment for other reasons (toxicity, 11 patients; intercurrent illness, 2 patients; death on study [pneumonia/clinical decline], 2 patients; withdrew consent, 1 patient; physician decision, 1 patient).

During treatment, 23 patients required dose reductions of amrubicin; and 22 patients required dose reductions of carboplatin. For both drugs, the majority of patients required a dose reduction due to hematologic toxicity (amrubicin, 15 patients; carboplatin, 14 patients).

3.3. Treatment efficacy

Treatment efficacy is summarized in Table A3 in Appendix A. Ten patients (13%) had complete responses, and 49 patients (61%) had partial responses, for an overall response rate of 74%. Prior to restaging, 6 patients were withdrawn from study treatment due to death (2 patients), intercurrent illness (2 patients), physician's request (1 patient), and toxicity (1 patient).

The median progression-free survival was 5.5 months (95% CI: 4.8, 7.1), with 4% of patients progression-free at one year (Fig. A1 in Appendix A). After a median follow-up of 12 months, the estimated 1-year OS proportion was 38% (95% CI: 30, 50) (Fig. A2 in Appendix A). The median OS was 10 months (95% CI: 8.5, 13).

3.4. Treatment-related toxicity

Severe (Grade 3 and 4) treatment-related toxicity is summarized in Table A4 in Appendix A. As expected, myelosuppression was the most common toxicity; severe thrombocytopenia and neutropenia were experienced by 45% and 36% of patients, respectively. Ten patients developed febrile neutropenia, 9 patients had bleeding episodes (4 were considered treatment-related), and 15 patients required platelet transfusions. Severe non-hematologic toxicity was less common and included hypokalemia (18%), fatigue (14%), infection (14%), and hyponatremia (13%).

Over the course of the study, 26 patients required a total of 66 hospitalizations for treatment-related toxicity. There were no treatment-related deaths.

4. Discussion

Unlike the treatment of most advanced cancers, therapy for extensive-stage SCLC has not improved for more than 20 years. Most patients respond to first-line combination chemotherapy, but rapidly develop resistance; median survival in most large prospective trials is 9–10 months [11,14,15]. Improvement of chemotherapy efficacy by substituting drugs or adding agents has so far been unsuccessful. To date, no targeted agents have been approved for SCLC, although several are in development.

The activity of anthracyclines in SCLC has long been recognized; doxorubicin was a component of one of the first active regimens (cyclophosphamide, doxorubicin, vincristine; CAV). Amrubicin, a synthetic 9-aminoanthracycline, had more activity than other anthracyclines in preclinical studies [2], and showed substantial single-agent activity in patients with relapsed SCLC [3,4]. In addition, 2 randomized phase II studies suggested that amrubicin was superior to topotecan in this population [5,6]. At the time this study was designed, amrubicin had already been approved in Japan for use in relapsed/refractory SCLC, and similar approval seemed imminent in other countries. Incorporation of amrubicin into first-line combinations seemed the best way to maximize the impact of this active drug.

In the multicenter phase II study reported here, the combination of amrubicin and carboplatin showed a level of activity similar to other platinum-based combinations. The overall response rate in 80 patients treated was 74%, and the median survival was 10 months (95% CI: 8.5, 13). Myelosuppression with this regimen was substantial; even with routine administration of pegfilgrastim, 36% of patients developed at least 1 episode of grade 3/4 neutropenia, and 45% had grade 3/4 thrombocytopenia. Eleven patients were unable to complete 4 cycles of treatment due to severe myelosuppression. Severe non-hematologic toxicity was uncommon.

Unfortunately, subsequent trials with amrubicin did not confirm the early trial results. A randomized phase III trial did not confirm the results of the 2 earlier randomized phase II trials, demonstrating no advantage for amrubicin versus topotecan in patients with relapsed/refractory SCLC and halting the development of amrubicin in the United States [16]. In a randomized phase III study conducted in Japan, first-line treatment with amrubicin/cisplatin was inferior to irinotecan/cisplatin, and was substantially more myelotoxic [17]. Because of these results, amrubicin has not become a standard part of SCLC treatment, and is no longer being developed for this indication.

In summary, the results of this phase II trial are consistent with others in showing the combination of amrubicin and carboplatin to have substantial activity in the first-line treatment of extensive-stage SCLC. However, our study gave no indication that this regimen had superior efficacy to other standard regimens, in spite of a substantial increase in severe myelosuppression. Future improvements in the treatment of SCLC will likely await identification and successful targeting of critical molecular alterations.

Conflict of interest

David Waterhouse received Speaker Honorarium (2015, 2016), which had no bearing on this work. The remaining authors have no conflict of interest to disclose.

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Appendix A. Participating Sites

1. Sarah Cannon Research Institute	Nashville, TN
2. Tennessee Oncology, PLLC	Nashville, TN
3. Florida Hospital Cancer Institute	Orlando, FL
4. Oncology Hematology Care	Cincinnati, OH
5. Chattanooga Oncology Hematology Associates	Chattanooga, TN

Table A1
Patient Characteristics (N = 80).

Characteristic	
Median age, y (range)	65 (45–85)
Gender, n (%)	
Male	36 (45%)
Female	44 (55%)
Race, n (%)	
Caucasian	75 (94%)
African-American/Black	4 (5%)
Unknown	1 (1%)
ECOG Performance Status, n (%)	
0	25 (31%)
1	55 (69%)

Table A2
Treatment Received (N = 80).

Median treatment duration, cycles	4
Treatment duration range, cycles	0–6*
	Number of Patients (%)
Reasons treatment ended	
Completed treatment	51 (64%)
Disease progression	12 (15%)
Toxicity	11 (14%)†
Intercurrent illness	2 (3%)
Death on study	2 (3%)††
Withdrew consent	1 (1%)
Physician's discretion	1 (1%)

* 8 patients received additional study treatment beyond 4 cycles at the discretion of their treating physician.

† Four decreased LVEF events; 2 QTc prolongation events; pneumonia Grade 3; pulmonary embolism Grade 3; weakness Grade 3/fatigue Grade 2; disorientation Grade 3/mental status change Grade 2; nausea, dehydration, vomiting, diarrhea and neutropenia (Grade 3)/anemia Grade 2/thrombocytopenia and leukopenia (Grade 4).

†† CVA; respiratory failure.

Table A3
Summary of Treatment Efficacy (N = 80).

Response, n (%)	
Complete Response (CR)	10 (13%)
Partial Response (PR)	49 (61%)
Stable Disease (SD)	12 (15%)
Progressive Disease (PD)	3 (4%)
Unevaluable (UE)*	6 (8%)
Progression-Free Survival, months (95% CI)	
Median	5.5 (5, 7.1)
12-month Progression-Free Rate	0.04 (0.01, 0.14)
Overall Survival, months (95% CI)	
Median	10 (8.5, 13.0)
12-month Survival Rate	0.4 (0.3, 0.5)
24-month Survival Rate	0.2 (0.1, 0.3)

* Patients stopped study treatment prior to re-staging due to physician discretion (1 pt), toxicity (1 pt), death (2 pts), and intercurrent illness (2 pts).

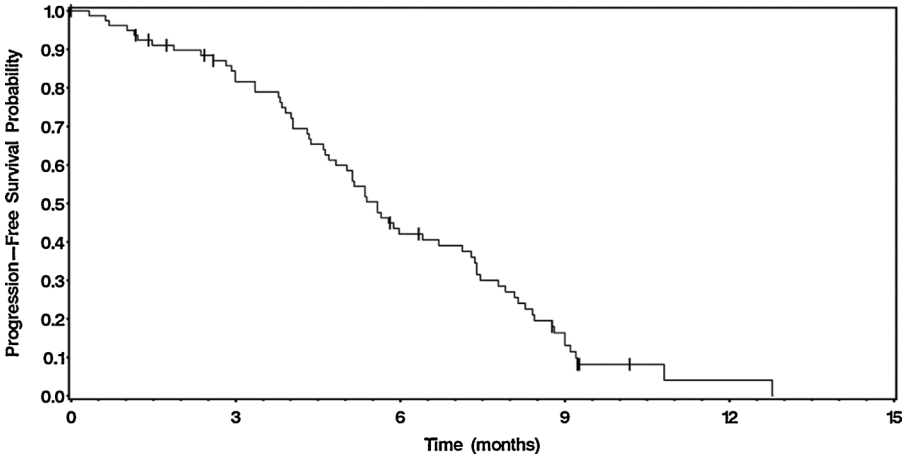

Fig. A1. Progression-free survival (n = 80). The median PFS was 5.5 months (95% CI 4.8, 7.1); 4% of patients were progression-free after 12 months.

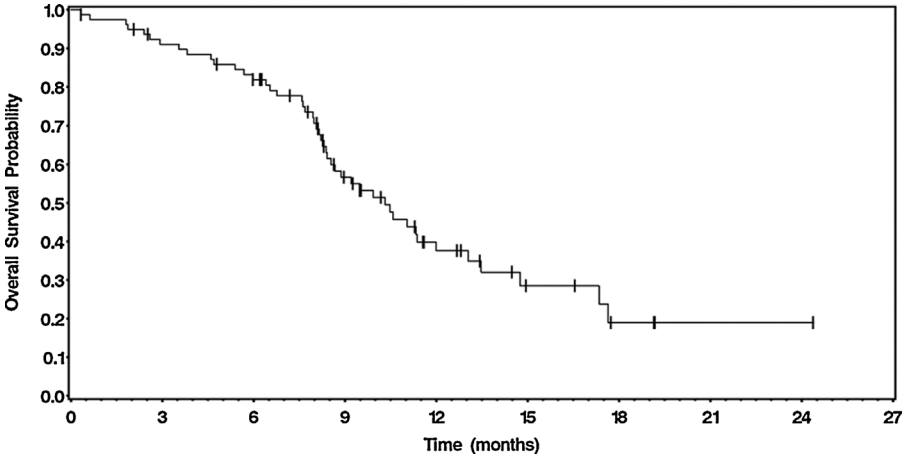

Fig. A2. Overall survival (n = 80). The median survival was 10 months (95% CI 8.5, 13); 38% and 19% of patients were alive at 12 months and 24 months, respectively.

Table A4
Grade 3/4 Treatment-Related Toxicity (N = 80).

	Number of Patients (%)		
	Grade 3	Grade 4	Total
Hematologic			
Thrombocytopenia	12(15%)	24 (30%)	36 (45%)
Neutropenia	6 (8%)	23 (29%)	29 (36%)
Febrile neutropenia	4 (5%)	6 (8%)	10 (13%)
Anemia	20 (25%)	2 (3%)	22 (28%)
Non-Hematologic			
Hypokalemia	11 (14%)	3 (4%)	14 (18%)
Fatigue	10 (13%)	1 (1%)	11 (14%)
Infection*	9 (11%)	2 (3%)	11 (14%)
Hyponatremia	9 (11%)	1 (1%)	10 (13%)
Dehydration	7 (9%)	1 (1%)	8 (10%)
Nausea	8 (10%)	–	8 (10%)
Vomiting	6 (8%)	–	6 (8%)
Muscle weakness	4 (5%)	–	
Hyperglycemia	2 (3%)	1 (1%)	3 (4%)
Thrombosis/embolism	2 (3%)	1 (1%)	3 (4%)
Treatment-Related Hospitalizations	66		
Treatment-Related Deaths	0		

* Pneumonia, 8 pts; sepsis, 2 pts; port-a-cath infection, 1 pt; not otherwise specified (NOS), 1 pt.

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