



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/m² 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 ≤ 450 milliseconds, and ECOG performance status 0 or 1. Patients were required to have adequate hematologic function (ANC $\geq 1500/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$, hemoglobin $\geq 9.9 \text{ gm/dL}$), as well as adequate renal (serum creatinine $\leq 1.5 \times \text{ULN}$) and liver (total bilirubin $\leq 1.5 \times \text{ULN}$, AST/ALT $\leq 2.5 \times \text{ULN}$ or $\leq 5 \times \text{ULN}$ 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/m² 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/m², dose level –2, 20 mg/m²), 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

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