Lung Cancer 73 (2011) 345–350

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Phase II trial of amrubicin and carboplatin in patients with sensitive or refractory relapsed small-cell lung cancer

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ARTICLE INFO

Article history:
Received 9 August 2010
Received in revised form
25 September 2010
Accepted 25 December 2010

Keywords:
Amrubicin
Carboplatin
Phase II trial
Refractory relapsed
Sensitive relapsed
Small-cell lung cancer

ABSTRACT

Amrubicin is a novel, totally synthesized anthracycline derivative, and has antitumor activity against several human tumor xenografts. The combination of amrubicin with platinum derivative showed additive effect against a human small-cell lung cancer (SCLC) cell line. Until now, the combination of amrubicin plus carboplatin has not been studied in patients with previously treated SCLC. Therefore, we examined the safety and efficacy of the combination of amrubicin plus carboplatin in patients with sensitive or refractory relapsed SCLC. Patients with previously treated SCLC were eligible if they had a performance status of 2 or less, were 75 years or younger, and had adequate organ function. Twenty-five patients were enrolled (21 men and 4 women; median age, 65 years; age range 55–73 years). Patients received the combination of amrubicin (30 mg/m^2 on days 1–3) plus carboplatin (with a target area under the concentration-versus-time curve of 4 mg min/ml using the Calvert formula on day 1) every 3 weeks. The overall response rate was 36.0% (95% confidence interval [CI], 18.0–57.5%). Response rates differed significantly between patients with sensitive relapse (58.3%; 95% CI, 27.7–84.8%) and those with refractory relapse (15.4%; 95% CI, 1.9–15.4%; $p = 0.03$). The median survival time (MST) from the start of this treatment was 7 months (range: 1–42 months); the MST of patients with sensitive relapse (10 months) was significantly longer than that of patients with refractory relapse (5 months: $p = 0.004$). The median progression-free survival (PFS) time was 3 months (range: 1–14 months): the median PFS time of patients with sensitive relapse (5 months) was significantly longer than that of patients with refractory relapse (2 months; $p = 0.01$). The most frequent grade 3–4 toxicity was myelosuppression, especially neutropenia, which developed in 88% of patients. Grade 3–4 thrombocytopenia developed in 44% of patients, and anemia developed in 56%. Nonhematologic toxicities were generally mild to moderately severe and temporary. None of the patients had cardiotoxicity. In conclusion, this therapy is effective and well tolerated for previously treated SCLC.

1. Introduction

Most patients with small-cell lung cancer (SCLC) show favorable responses to first-line chemotherapy. However, SCLC often recurs during the subsequent 2 years: the 2-year cumulative relapse rate is 75% in patients with limited disease (LD) and nearly 100% in patients with extensive disease (ED) [1]. The prognosis of patients who have relapsed SCLC and do not receive additional therapy is extremely poor: expected survival is 2–4 months [2]. On the other hand, some patients are still good candidates for second-line chemotherapy, because they maintain a good performance status (PS) and have adequate organ function despite relapse.

In a phase III trial for patients with SCLC that relapsed more than 60 days after completion of first-line chemotherapy, i.e. sensitive relapse, topotecan achieved an equivalent response rate (24% versus 18%) and median survival time (MST) after relapse (25.0 weeks versus 24.7 weeks) to those of the 3-drug combination of cyclophosphamide, doxorubicin, and vincristine and also achieved higher quality of life scores and better symptom control [3]. As a result of this phase III trial, topotecan has been approved by the United States Food and Drug Administration for patients with relapsed SCLC. However, the efficacy of topotecan has not been satisfactory. Therefore, a more effective chemotherapy regimen is urgently needed for relapsed SCLC.

Amrubicin is a novel, totally synthesized anthracycline derivative that is structurally distinguishable from doxorubicin due to an amino group at position 9 and its unique sugar moiety [4]. The potent therapeutic activity of amrubicin is attributed to the selective distribution of its highly active 13-hydroxy metabolite,

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doi:10.1016/j.lungcan.2010.12.015

amrubicinol, in tumors [5]. The catatonic activity of amrubicinol *in vitro* is 18–220 times as great as that of its parent compound amrubicin [5]. The inhibitory effects of amrubicin and amrubicinol on cell growth appear to be primarily related to the inhibition of DNA topoisomerase II, although anthracyclines have been reported to have diverse molecular effects, such as DNA intercalation, inhibition of topoisomerase II, and stabilization of topoisomerase II alpha cleavable complexes [6]. Amrubicin has greater antitumor activity than does doxorubicin against several human tumor xenografts implanted in nude mice [7]. In addition, amrubicin does not induce cardiotoxicity or exacerbate doxorubicin-induced cardiotoxicity in dogs or rabbits [8,9]. In two phase II trials of 40 mg/m^2 of amrubicin alone on days 1–3 in patients with sensitive or refractory relapsed SCLC, overall response rates were 38% and 52% and MSTs were 8.1 months and 11.2 months [10,11].

The combination of amrubicin with cisplatin showed additive effect against a human SCLC cell line [12]. In a phase II study of amrubicin plus cisplatin for untreated ED-SCLC, the response rate was 87.8%, the MST was 13.6 months, and the 1-year survival rate was 56.1% at the recommended dose (RD) of 40 mg/m^2 of amrubicin on days 1–3 and 60 mg/m^2 of cisplatin on day 1 [13]. On the other hand, in a phase I study of amrubicin plus carboplatin for patients 70 year or older with previously untreated SCLC, the RD of amrubicin and carboplatin were determined to be 35 mg/m^2 and the target area under the concentration versus time curve (AUC) of 4 mg min/ml [14].

To the best of our knowledge, the combination of amrubicin plus carboplatin has not been studied in patients with sensitive or refractory relapsed SCLC. Therefore, we performed a phase II study to assess the antitumor activity and toxicity of the combination of amrubicin plus carboplatin in patients with sensitive or refractory relapsed SCLC.

2. Patients and methods

2.1. Eligibility criteria

Patients with previously treated SCLC were enrolled. The criteria for study entry were as follows: (1) histologically or cytologically confirmed SCLC; (2) age 75 years or less; (3) Eastern Cooperative Oncology Group PS of 2 or less; (4) measurable or assessable lesions; (5) life expectancy of at least 8 weeks; (6) adequate bone marrow function (white blood cell [WBC] count from 4000/ul or more, neutrophil count of 2000/ul or more, platelet count of 100,000/ul or more, and hemoglobin level of 9 g/dl or more), hepatic function (total serum bilirubin level less than the upper limit of the normal range, levels of aspartate aminotransferase and alanine aminotransferase less than or equal to twice the upper limits of the normal ranges), and renal function (serum creatinine level less than 1.5 mg/dl, creatinine clearance rate of 50 ml/min or more), and arterial oxygen pressure of 60 mmHg or more. Patients were excluded if they had prior amrubicin treatment, pulmonary fibrosis, uncontrolled diabetes mellitus, severe heart disease, active infection, symptomatic brain metastasis, or active second malignancy. The study protocol was approved by the institutional review board of the Showa University School of Medicine, and all patients provided written informed consent.

2.2. Treatment schedule

Carboplatin (target AUC, 4 mg min/ml) was diluted in 500 ml of normal saline and given over 30 min as an intravenous drip infusion after the amrubicin infusion on day 1. The carboplatin dose was calculated with Calvert's formula and the 24-hour creatinine clearance rate. Amrubicin was diluted in 20 ml normal saline and given intravenously as a 5-min infusion on days 1–3. This chemotherapy regimen was repeated every 3 weeks for maximum of 4 courses. Prophylactic antiemetic treatment with ondansetron and dexamethasone were routinely given to all patients before carboplatin. Palliative radiotherapy was permitted to control persistent pain associated with bone metastasis. The first 4 patients were treated every 3 weeks with carboplatin (target AUC, 4 mg min/ml on day 1) plus amrubicin (35 mg/m^2 on days 1–3) according to the above phase I study [14]. However, the amrubicin dosage had to be reduced in all 4 patients who were treated with this dosage because of grade 4 neutropenia lasting 3 days or longer in 4 patients and grade 4 thrombocytopenia in 3 patients. Thus, we decreased the amrubicin dosage from 35 to 30 mg/m^2.

Chemotherapy was discontinued for grade 3 or higher nonhematologoic toxicity, except for nausea/vomiting, anorexia, constipation, alopecia, and fatigue at any time, or if the treatment outcome was progressive disease at any time. If 2 or more weeks had passed after the scheduled start of the next course until these criteria were satisfied, the patient left the study at that time but was still included in the analysis.

The next course of treatment was started when the neutrophil count returned to 1500/μl, the platelet count returned to 75,000/μl, and nonhematologoic toxicity decreased to grade 2 or less. The amrubicin dosage was reduced by 5 mg/m^2 if the patient had grade 4 leukopenia or neutropenia lasting 3 days or longer, grade 4 thrombocytopenia or had received a platelet transfusion for grade 3 thrombocytopenia, or if day 2 or 3 of the previous course had been omitted because of severe toxicity. The carboplatin dosage was reduced by 1 mg min/ml if the patient had grade 4 thrombocytopenia or had received a platelet transfusion for grade 3 thrombocytopenia. If the leukopenia or neutropenia had developed grade 3 or 4 after chemotherapy, granulocyte colony-stimulating factor (G-CSF) was administered until the WBC and the neutrophil count recovered, according to the guideline of the Japanese Ministry of Health, Labour and Welfare.

2.3. Evaluation

Evaluation before treatment included a baseline history and physical examination, complete blood count with differential, routine chemistry profiles, chest radiography, computed tomography (CT) of the chest and abdomen, magnetic resonance (MR) or CT of the brain, and radionucleotide bone scan. Complete blood counts with differential and routine chemistry profiles were determined at least once a week during chemotherapy. Chest radiography was performed once per week during chemotherapy. Electrocardiograms were obtained before and after chemotherapy.

The disease was categorized according to the response to first-line therapy as sensitive relapse or refractory relapse. A refractory relapse was defined as radiographically documented progression as best response to first-line chemotherapy, radiographically documented response or stable disease with subsequent progression during continued chemotherapy, or relapse within 3 months after the completion of first-line chemotherapy. A sensitive relapse was diagnosed when the SCLC relapsed more than 3 months after the completion of first-line chemotherapy.

Tumor response was classified according to Response Evaluation Criteria in Solid Tumors (RECIST) Guideline version 1.0 [15]. Toxicities were assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. All patients who had received at least 1 cycle of chemotherapy were assessable for response, toxicity, and survival.