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Phase II study of nimustine hydrochloride (ACNU) plus paclitaxel for refractory small cell lung cancer

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ABSTRACT

Purpose: Bi-weekly administrations of nimustine hydrochloride (ACNU) plus paclitaxel were evaluated in this phase II study in patients with refractory small cell lung cancer (SCLC).
Methods: Patients who had disease progression within 3 months after treatment with irinotecan (CPT-11)-containing regimens were entered. They were treated with every other week administrations of ACNU 50 mg/m^2 plus paclitaxel 110 mg/m^2 on day 1 over 2 weeks.
Results: Twenty-four patients (20 males and 4 females, median age of 64 years, 17 patients with Eastern Cooperative Oncology Group [ECOG] performance status [PS] 0–1 and 7 patients with PS 2) participated in the trial. Of the 24 refractory patients after CPT-11 containing regimens, 17 patients had been given etoposide plus platinum. There were six partial responses, and an overall response rate of 25% (95% confidence interval, 10–46%) was obtained. The median time to progression and the median survival time after enrollment into this study were 2.8 and 5.8 months, respectively. The median overall survival from the first-line treatment was 19.5 months. The major toxicity was myelosuppression. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia was observed in 13% of patients. There was one treatment-related death, attributed to pneumonitis.
Conclusion: Bi-weekly administrations of ACNU plus paclitaxel provided a practical and well-tolerated regimen that was active for CPT-11-refractory SCLC.

1. Introduction

Small cell lung cancer (SCLC) represents 13–20% of all lung cancers [1]. SCLC with no previous therapy is characterized as being sensitive to systemic chemotherapy or radiotherapy [2]. In a Japanese randomized phase III study, a combination of irinotecan (CPT-11) plus cisplatin (CDDP) significantly improved survival when compared with the combination of etoposide plus CDDP (12.8 months vs. 9.4 months; $p < 0.01$) [3], but only one of three studies could replicate this superior survival of CPT-11 [4–6]. Presently, CDDP plus CPT-11, or a platinum compound of CDDP or carboplatin (CBDCA) with etoposide, is the standard of care for first-line chemotherapy [3,7,8]. Patients with limited disease (LD) also benefit from concurrent radiotherapy [9]. A response rate above 80% has been reported in patients with LD, and a rate of 40–50% has been reported in patients with extensive disease (ED). The 5-year survival rate is 10–26% for LD, while it is 1–2% for ED [7,8].

However, the treatment of SCLC patients after failure with first-line chemotherapy remains controversial. Despite high response rates to first-line therapy, a majority of patients relapse within 1 year. Reported response rates (12–50%) to second-line chemotherapy are lower than those for first-line therapy [10–18]. A wide range of reported response rates, from 12 to 50%, might have indicated 2 types of relapse in SCLC: relapse within 2–3 months after completing chemotherapy, which is considered a refractory disease; and relapse beyond 2–3 months after completing chemotherapy, which is considered a sensitive disease [11]. The rescue treatment by the previous chemotherapy is often active for a sensitive disease, but inactive for a refractory disease. In addition to a low response rate in refractory patients, it is problematic that they often have impaired

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bone marrow function, especially neutropenia, after CDDP plus CPT-11 or CDDP/CBDCA plus etoposide, which limits the use of a new heavy chemotherapy.

Nimustine hydrochloride (ACNU) was initially developed as a hydrophilic nitrosourea with decreased absorption into the bone marrow. But its major myelosuppresive side effect is known to be thrombocytopenia. ACNU is a non-platinum alkylator, and it has been reported to have activity in SCLC in combination therapies or monotherapy [19,20]. Due to the hydrophilic character of ACNU, a pharmacokinetic study showed ACNU passage through the blood–brain barrier to be up to 30% [21]. In the treatment of small cell carcinoma of the lung, ACNU reduced the rate of brain metastasis and prolonged the survival of patients [20].

Similarly, paclitaxel has shown interesting activity and tolerability either as first-line chemotherapy or as salvage treatment in SCLC. A 34–41% objective response rate and minimal toxicity were reported for single agent paclitaxel in previously untreated patients with ED-SCLC [22,23]. In previously treated patients, a 23.9–29% objective response rate and minimal toxicity were reported [24,25]. The combination of paclitaxel plus CBDCA represented a relatively active response (response rate, 25%; median time to progression, 5.5 months) and mild toxicity with salvage treatment in refractory and sensitive patients with SCLC [13]. Interestingly, thrombocytopenia with paclitaxel plus CBDCA was not severe, and paclitaxel has been considered to have a platelet-sparing effect [26,27].

Therefore, the combination chemotherapy of paclitaxel plus ACNU may be effective in patients with refractory SCLC with poor bone marrow function. Based on this assumption, a multicenter phase II study with the 2-drug combination was conducted in order to evaluate its activity and toxicity in only patients with refractory SCLC.

2. Patients and methods

2.1. Patients entered

This study was performed in accordance with the Helsinki Declaration (1964, amended in 2000) of the World Medical Association. Prior to their participation in the study, patients were examined to ensure that they met the following criteria: (a) histologic or cytologic diagnosis of SCLC, (b) progression within 3 months after treatment with a CPT-11-containing regimen (refractory disease), (c) measurable disease, (d) performance status of 2 or better on the Eastern Cooperative Oncology Group (ECOG) scale, (e) adequate bone marrow function (white blood cell (WBC) count $\geq$ 4000/mm^3, platelets $\geq$ 100,000/mm^3, hemoglobin $\geq$ 9.5 g/dl), (f) adequate hepatic function (total bilirubin $\leq$ 1.5 mg/dl, transaminases less than twice the upper limit of normal), (g) adequate renal function (serum creatinine $\leq$ 1.5 mg/dl), (h) age 15–75 years, (i) no medical problems severe enough to prevent compliance with the study requirements; and (j) informed consent of the patient, which was obtained before enrollment in the study according to institutional guidelines.

2.2. Treatment schedule

In our phase I study of ACNU plus paclitaxel, the doses of ACNU and paclitaxel were set at 50 mg/m^2 and 110 mg/m^2, respectively, on day 1 of every other week [28]. Initially, ACNU was administered in 50 ml normal saline as a 15-min intravenous (i.v.) infusion, and paclitaxel was administered in 250 ml normal saline over a 90-min period. Patients with no evidence of disease progression were given at least two cycles. For prevention of emesis, 5-hydroxytryptamine 3-receptor antagonist and dexamethasone 12 mg were given i.v. prior to the administration of ACNU and paclitaxel. Patients were premedicated with chlorpheniramine maleate 10 mg i.v. and ranitidine hydrochloride 150 mg i.v. 30 min before infusion of paclitaxel. During the treatment, dosing with ACNU and paclitaxel was withheld on the day it was due if leucopenia (<2000/mm^3) and thrombocytopenia (<80,000/mm^3) were present.

Granulocyte colony-stimulating factor (G-CSF) was administered when Grade 3 leukopenia (<2000/mm^3) and/or neutropenia (<1000/mm^3) were observed. Platelet transfusion was permitted when the platelet count was <20,000/mm^3. Erythropoietin was not used.

2.3. Evaluation

Patients underwent restaging evaluation by physical examination, chest X-ray, bone scintiscan, and computed tomography (CT) of the head, chest and abdomen. In cases where a patient needed the full examination, bone marrow aspiration and/or fiberoptic bronchoscopy were added. Staging procedures followed those of the LD was defined as that confined to one hemithorax, including bilateral mediastinal and bilateral supraclavicular nodes; any involvement beyond these confines was defined as ED.

Prior to the first course of treatment, each patient was subjected to chest X-rays and chest CT. Chest X-ray was assessed at least once 2 weeks after the initial evaluation. CT was performed in order to confirm response, and, thereafter, was planned every 2 months. Tumor response was classified in accordance with RECIST-criteria. Prior to the first course of treatment, each patient was subjected to a complete blood count (CBC), serum chemistry for renal and hepatic functions, electrolyte analysis, and urinalysis. CBC, serum chemistry, electrolyte analysis and urinalysis were assessed at least once 2 weeks after the initial evaluation. The NCI Common Toxicity Criteria, version 2.0 grading system, was used to grade organ system damage.

2.4. Statistical analysis

The aim of this study was to show that at least 10% of patients with refractory SCLC responded to ACNU plus paclitaxel. Therefore, the sample size for this phase II study was calculated by the response rate, and it was determined to be 24 patients. We chose a 25% response rate as a desirable target level and a 10% response rate as uninteresting. Our design had a power in excess of 90%, and a less than 10% type I error. As secondary endpoints, Progression free survival (PFS) and survival curves were drawn using the Kaplan–Meier method, and the median PFS and the median survival time (MST) were calculated from the day of the first treatment with ACNU plus paclitaxel to death or last follow up.

3. Results

3.1. Patients entered

Between February 2002 and October 2007, 24 patients participated in the trial. The characteristics of this patient population are given in Table 1. Four patients were women and 20 were men, and the median age was 64 years. At the time they entered the study as refractory patients, all 24 patients exhibited ED. Most of the patients had good ECOG performance status (PS), but 7 were PS 2. All the patients had been previously treated with CPT-11 containing regimens (CDDP + CPT-11, 21 patients; CBDCA + CPT-11, 2 patients; CPT-11 monotherapy, 1 patient), but their SCLC relapsed within 3 months. Furthermore, etoposide plus platinum had been given to 17 patients before the CPT-11 treatments. Five patients had previously received thoracic radiotherapy. Seven patients received ACNU plus