Lung Cancer 89 (2015) 61–65

Contents lists available at ScienceDirect

Lung Cancer

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

Randomized phase II trial comparing amrubicin with re-challenge of platinum doublet in patients with sensitive-relapsed small-cell lung cancer: North Japan Lung Cancer Study Group trial 0702

Akira Inoue[a,*], Shunichi Sugawara[b], Makoto Maemondo[c], Yoshiaki Mori[d], Satoshi Oizumi[e], Masao Harada[f], Kageaki Taima[g], Naoto Morikawa[h], Takashi Ishida[i], Ichiro Kinoshita[j], Hiroshi Watanabe[k], Toshiro Suzuki[l], Taku Nakagawa[m], Ryota Saito[a], Toshihiro Nukiwa[a]

[a] Department of Palliative Medicine, Tohoku University School of Medicine, 1-1, Seiryocho, Aobaku, Sendai 980-8574, Japan
[b] Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan
[c] Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan
[d] Department of Respiratory Medicine, Iwate Prefectural Central Hospital, Morioka, Japan
[e] First Department of Medicine, Hokkaido University School of Medicine, Sapporo, Japan
[f] Department of Respiratory Medicine, Hokkaido Cancer Center, Sapporo, Japan
[g] Department of Respiratory Medicine, Hirosaki University, Hirosaki, Japan
[h] Divison of Pulmonary Medicine, Allergy, and Rheumatology, Department of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Japan
[i] Department of Pulmonary Medicine, Fukushima Medical University Hospital, Fukushima, Japan
[j] Department of Medical Oncology, Hokkaido University School of Medicine, Sapporo, Japan
[k] Department of Respiratory Medicine, Saka General Hospital, Shiogama, Japan
[l] Department of Respiratory Medicine, Isawa Hospital, Oshu, Japan
[m] Department of Thoracic Surgery, Omagari Kosei Medical Center, Daisen, Japan

ARTICLE INFO

Article history:
Received 12 February 2015
Received in revised form 24 April 2015
Accepted 25 April 2015

ABSTRACT

Purpose: Amrubicin and re-challenge of platinum doublet are both effective treatments for sensitive-relapsed small-cell lung cancer (SCLC). However, no comparative study of these treatments has been reported. This randomized study was conducted to select the most suitable regimen for future evaluation.
Patients and methods: SCLC patients who had relapsed more than 90 days after their first-line platinum-doublet regimen were randomized to receive amrubicin (40 mg/m^2, days 1–3) or re-challenge with platinum doublet. Primary endpoint was objective response rate (ORR), with secondary endpoints of progression-free survival (PFS), overall survival and toxicity profiles. We assumed that an ORR of 50% indicates potential usefulness, while that of 30% would constitute the lower limit of interest (alpha 0.1; beta 0.1). Initial estimated accrual was 28 patients to each arm.
Results: From February 2008 to June 2013, 60 patients were enrolled and 57 patients (27 amrubicin and 30 re-challenge) were found to be evaluable for efficacy and safety. The ORR and PFS were 67% (90% confidence interval, 52–82) and 5.4 months in the amrubicin group, and 43% (90% confidence interval, 28–58) and 5.1 months in the re-challenge group, respectively. Although grade 3 febrile neutropenia was observed in 19% of patients in the amrubicin group, these episodes were transient and manageable. Non-hematological toxicities were generally moderate and no treatment-related death was observed in either group.
Conclusion: Only amrubicin met the primary endpoint. Moreover, amrubicin demonstrated superior efficacy over re-challenge of platinum with acceptable levels of toxicity. Further evaluation of amrubicin for sensitive-relapsed SCLC is warranted.

* Corresponding author. Tel.: +81 22 717 7366; fax: +81 22 717 7367.
E-mail address: akinoue@idac.tohoku.ac.jp (A. Inoue).

http://dx.doi.org/10.1016/j.lungcan.2015.04.012
0169-5002/

1. Introduction

Lung cancer is the leading cause of cancer death. Approximately 12–15% of patients with lung cancer are classified as having small-cell lung cancer (SCLC) [1]. Despite high response rates to first-line chemotherapy, most SCLC patients experience relapse and die from systemic metastasis. In terms of second-line chemotherapy for relapsed SCLC patients, the duration between the end of first-line chemotherapy and the day of relapse is believed to be important. For refractory-relapsed SCLC where relapse occurred within 60–90 days treatment-free interval (TFI) after completion of first-line chemotherapy, no standard regimen has been established. In these cases, investigational treatment should be considered. By contrast, topotecan is a standard regimen for sensitive-relapsed SCLC where relapse occurred more than 90 days after completing first-line chemotherapy [2]. However, the median survival time (MST) of patients with sensitive-relapsed SCLC is generally less than 10 months [3]. Thus, a more effective treatment for this condition is urgently sought.

Several studies have suggested that combination regimens for relapsed SCLC may be successful. Kubota reported that a dose-intensive weekly chemotherapy regimen with cisplatin, vincristine, doxorubicin, and etoposide achieved a relatively high response rate (88%) in cases of relapsed SCLC [4]. Ardizzoni also reported a phase II study of combination therapy with cisplatin and topotecan, which showed response rates of 29% in cases of sensitive-relapsed SCLC [5]. However, MSTs of these studies (6.1 and 8.1 months) are disappointing in terms of the risk-benefit balance. Re-challenge with the first-line chemotherapy was introduced into the guidelines of the National Comprehensive Cancer Network (NCCN) as a commonly used regimen for SCLC patients who relapsed after more than 6 months [6]. However the evidence was obtained more than 25 years ago when platinum-doublet regimen was not generally used [7,8]. To the best of our knowledge, no prospective study of the re-challenge strategy has been conducted over the past 20 years.

Amrubicin, a fully synthetic 9-aminoanthracycline, was developed in Japan and achieved some promising results [9–12]. Our previous study, which compared amrubicin with topotecan in relapsed SCLC patients, suggested that amrubicin might be effective both in sensitive- and refractory-relapsed SCLC [13]. Before conducting a phase III trial for cases of sensitive-relapsed SCLC using topotecan, we would like to select a suitable regimen involving amrubicin or re-challenge with platinum doublet. Thus we conducted this randomized phase II study.

2. Patients and methods

2.1. Eligibility criteria

Patients older than 20 years of age with histologically or cytologically proven SCLC who had been previously treated with platinum-based chemotherapy and had experienced relapse more than 90 days after the end of their first-line chemotherapy were eligible for this study. Patients were also required to have an ECOG performance status (PS) of at least 2, adequate bone marrow function (absolute neutrophil count (ANC) > 1500/mm^3, platelet count > 100,000/mm^3, and hemoglobin > 9.0 g/dL), hepatic function (AST and ALT < 100 IU/L, total bilirubin level < 2.0 mg/dL), renal function (serum creatinine level < 1.5 mg/dL) and arterial oxygen pressure > 60 mmHg. Written informed consent was obtained from each patient. Patients with symptomatic brain metastasis, massive effusion requiring drainage, or severe comorbidities such as uncontrolled diabetes, heart disease, infectious disease, or pulmonary fibrosis were ineligible. The study protocol was reviewed and approved by the ethics committee or institutional review board of each institution. The trial registration number was UMIN000002617.

2.2. Treatment schedule

Enrolled patients were randomly assigned (1:1) to receive either amrubicin or re-challenge of platinum doublet with a dynamic allocation method. Central randomization was done by a datacenter in Tohoku University Hospital. Patients were stratified according to ECOG PS at baseline (PS 0, 1 vs PS 2), age (<70 years old vs >70 years old), initial clinical stage (limited-disease vs extensive-disease) and use of irinotecan during first-line chemotherapy (yes vs no). All patients and investigators were unmasked to treatment allocation.

Amrubicin was administered intravenously at a dose of 40 mg/m^2 on days 1–3 every 3 weeks. For the re-challenge group, modification of platinum agent (from initial cisplatin to carboplatin) or dose reduction of combined non-platinum agent to 80% of initial dosage was permitted. Each treatment was repeated for at least 3 cycles unless there was obvious disease progression, patient refusal, or intolerable toxicity. Patients were required to have ANC > 1500/mm^3 and platelet count > 100,000/mm^3 without any non-hematological toxicities > grade 2 to start the subsequent cycle of treatment. Granulocyte colony-stimulating factor was permitted as a therapeutic intervention for neutropenia but not for use as a prophylactic.

Subsequent (third- or later-line) chemotherapy after disease progression in this study was not limited. Crossover administration (e.g. third-line amrubicin for patients in the re-challenge group) was permitted. Regimens used for subsequent chemotherapy were also reported by the attending physician.

2.3. Patient assessment

Patient assessment, which included physical examination, complete blood counts and biochemistry, was conducted once a week during the first cycle of treatment and then at least once more for every subsequent cycle of treatment. A computed tomography (CT) scan was performed at baseline and after at least every 2 cycles of treatment to assess the clinical response according to the Response Evaluation Criteria in Solid Tumors version 1.0. A period of 4 weeks was required to determine complete response and partial response to the treatment regimen. Stable disease required at least a 4 week period from the initiation of the protocol treatment. Progression-free survival (PFS) was evaluated for the period from the date of randomization to the date when disease progression was first observed or death occurred. Treatment response and PFS were determined by external review of the CT films by experts who were not aware of the treatment assignments. Overall survival was evaluated for the period from the date of randomization to the date of death. Toxicity was assessed according to National Cancer Institute Common Toxicity Criteria version 3.0.

2.4. Statistical analysis

The primary endpoint of this study was the objective response rate (ORR). The secondary endpoints of the study were PFS, overall survival and toxicity profile. We assumed that an ORR of 50% for eligible patients would indicate potential usefulness, while an ORR of 30% would constitute the lower limit of interest (with alpha = 0.1 and beta = 0.1). The estimated accrual was 28 patients in each arm. Survival estimation was performed using the Kaplan–Meier method and log-rank test.