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Biweekly combination therapy with gemcitabine and carboplatin compared with gemcitabine monotherapy in elderly patients with advanced non-small-cell lung cancer: A randomized, phase-II study☆

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ABSTRACT

Introduction: The strategy of chemotherapy in the elderly is controversial. We wanted to evaluate the efficacy and safety of biweekly gemcitabine and low-dose carboplatin combination therapy in elderly patients with advanced non-small-cell lung cancer (NSCLC).
Methods: In this phase-II trial, chemotherapy-naive elderly patients (aged ≥76 years) with NSCLC were randomly treated with biweekly combination therapy with gemcitabine and carboplatin (1000 mg/m^2 gemcitabine and carboplatin at an area under the curve (AUC) of 3 on days 1 and 15, every 4 weeks) or gemcitabine monotherapy (1000 mg/m^2 on days 1, 8 and 15, every 4 weeks). The primary endpoint was overall response rate and analysis was based on intention-to-treat.
Results: Thirty-one patients were randomly assigned combination therapy and 30 were assigned monotherapy. The median age was 79.0 years. Response rate was 22.6% (95% confidence interval (CI): 11.4–39.8%) for biweekly combination therapy and 10.0% (95% CI: 3.5–25.6%) for monotherapy. Median progression-free survival in combination chemotherapy was 3.9 months (95% CI: 0.5–8.5 months), which was significantly longer that that in monotherapy (2.4 months, 95% CI: 0.5–6.7 months). The prevalence of hematological and non-hematological adverse events reaching grade 3/4 was not significantly different between combination therapy and monotherapy.
Conclusions: Biweekly gemcitabine and low-dose carboplatin combination chemotherapy showed acceptable efficacy, toxicity, and tolerability in those aged ≥76 years with NSCLC. Further investigations with a large population are required to confirm our results.

1. Introduction

Lung cancer is a leading cause of cancer mortality in many countries [1,2]. Because cancer is associated with aging [3] and the number of elderly patients with non-small-cell lung cancer (NSCLC) has been increasing [4,5], the importance of chemotherapy for the elderly is increasingly recognized. In general, as the elderly get older, they have reduced organ function, which can influence metabolism and the elimination of anticancer drugs, and consequently impact upon cancer therapy [3,6,7]. Chemotherapy-induced toxicity has been shown to be increased according to increased age-related changes in patients aged ≥65 years [4,8]. Additionally, the elderly tend to have more co-morbidities [3,4,9]. These features cause the elderly to receive less aggressive chemotherapy than their younger counterparts [8,10,11].

With respect to chemotherapy, therapeutic strategies for the elderly are controversial [12]. There is a view that the elderly should not receive the standard chemotherapy assigned to younger patients [13]. In a retrospective analysis of platinum-based

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chemotherapy in NSCLC patients, a higher prevalence of leukopenia and neuropsychiatric toxicity was observed in those aged ≥70 years [8,14]. Although age is not recommended to be used as a criterion in the treatment of NSCLC [15], age has been taken into consideration when selecting the appropriate chemotherapy regimen [16]. Conversely, some researchers believe that the elderly can benefit from chemotherapy, and that age alone should not preclude any type of treatment [3,4]. Chemotherapy containing platinum in some clinical trials exhibited a similar efficacy and tolerability in elderly patients compared with that seen in younger patients [11,17]. However, participants in clinical trials are usually "healthy" subjects aged <65 years or <70 years with adequate organ function and without severe complications [3,4] and there is a selection bias against the elderly, so extrapolation of these results to clinical practice can be problematic [7]. In particular, studies focusing on chemotherapy for more elderly subjects, such as patients aged ≥75 years, are lacking, although the physiological status of patients aged ≥75 years differs from that of younger patients [18].

Gemcitabine is a third-generation anti-tumor agent. The efficacy and tolerable toxicity profiles enable its use as monotherapy and combination therapy with platinum in the management of NSCLC [15,19]. Hasegawa et al. [20] conducted biweekly chemotherapy with gemcitabine and carboplatin at an AUC of 3. Although it was a small study with 17 patients, the response rate was 29.4% and grade-3 hematological adverse events were anemia in two patients and neutropenia in three patients; grade-4 adverse events were not observed. The good tolerability of this biweekly regimen warranted further study. In the present study, we conducted a phase-II study that compared biweekly combination therapy with gemcitabine and low-dose carboplatin with gemcitabine monotherapy in patients with advanced NSCLC aged ≥76 years. We aimed to determine the efficacy and safety of this biweekly combination therapy for elderly subjects.

2. Patients and methods

2.1. Ethical approval of the study protocol

The study protocol was approved by the Institutional Review Board of each participating institution. Each patient gave written informed consent to be included in the study.

2.2. Patient eligibility

Patients with pathologically confirmed inoperable stage-IIIB NSCLC (without an indication of radiotherapy) or stage-IV NSCLC who were aged ≥76 years who showed Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and who were naïve for previous systemic chemotherapy, were eligible for inclusion. Additional eligibility criteria included adequate function of the bone marrow, liver and kidney (leukocyte count of 4000–12,000/μL and an absolute granulocyte count of >1500/μL; platelet count ≥100,000/μL; hemoglobin ≥9.0 g/dL; serum bilirubin ≤1.5 mg/dL; serum levels of aspartate aminotransferase and alanine aminotransferase less than or equal to twice the upper limit; serum creatinine level ≤1.5 mg/dL). For staging, CT of the thorax and abdomen, MRI of the brain, and radioisotopic bone imaging were carried out. Patients were excluded if they had severe uncontrolled complications or active interstitial lung disease. Co-morbidity was scored using the Charlson co-morbidity index [21].

2.3. Treatment schedule

Patients were randomly assigned to receive gemcitabine monotherapy or biweekly combination therapy with carboplatin and gemcitabine. Randomization was done centrally using a computer program. For the gemcitabine-monotherapy arm, gemcitabine was given at 1000 mg/m^2 on days 1, 8 and 15. For the combination regimen, gemcitabine at 1000 mg/m^2 and carboplatin at an AUC of 3 was given on days 1 and 15. The carboplatin dose was calculated according to the Calvert formula. The glomerular filtration rate was estimated from the Cockcroft–Gault formula. An anti-emetic agent and other supportive treatment could be administered at the discretion of the treating physician. Each treatment regimen was repeated every 4 weeks for a maximum of four courses until disease progression, unacceptable toxicity, or the patient withdrew consent. The scheduled gemcitabine treatment on days 8 and 15 was delayed until recovery (≤2 weeks) if the patient had an absolute granulocyte count ≤1000/μL, a platelet count ≤100,000/μL, hemoglobin ≤9.0 g/dL and/or other ≥ grade-2 non-hematologic toxicities. The eligibility criteria for entry regarding organ functions had to be satisfied to start the next cycle. If an absolute granulocyte count of <500/μL for 4 days, grade-3 chemotherapy-induced febrile neutropenia, grade-4 thrombocytopenia, or non-hematologic toxicity of ≥ grade-3 occurred during the previous course, the dose of gemcitabine was reduced by one level (200 mg/m^2 of gemcitabine) in the monotherapy regimen. As for combination therapy, the dose of carboplatin was reduced to AUC = 2. If recovery from such toxicities at a reduced dose was confirmed, administration at the reduced dose was continued. If dose-limiting toxicities occurred even at the tapered dose, gemcitabine was reduced by one level. If a dose reduction of more than three levels or delay of >2 weeks was required to start the next cycle, the patient was withdrawn from the study.

2.4. Evaluation of response and toxicity

Tumor response was evaluated in reference to the CT findings that had initially been used to define tumor extent every 4 weeks until completion of treatment and every 2 months thereafter. The response was evaluated every cycle according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Adverse events were graded using the Common Toxicity Criteria (version 3.0).

2.5. Statistical analyses

The primary endpoint was overall response rate (ORR). The secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival, and safety. The minimum number of patients to be enrolled in the present study was 27 assuming that the 95% confidence interval (CI) would be 10% below the conditions of an α error of 0.05 (one-sided) and a β error of 0.2, assuming an expected RR of 29% [20] and a threshold RR of 20% [9,22] based on the Simon selection design. According to this design, we aimed for 30 patients after taking patients who dropped out of the study into consideration. The differences between categorized groups were compared by the χ^2 test. Overall survival, which was defined as the time from the date when registration was carried out to the date of death from any cause, or when the subject was last known to have been alive, was estimated by the Kaplan–Meier method. All values were analyzed using JMP version 5.0.1J software (SAS Institute Japan; Tokyo, Japan). All statistical tests were two-sided, and $p < 0.05$ was considered significant.

3. Results

3.1. Patient characteristics

Sixty-one patients were enrolled between July 2008 and August 2011 at six participating institutes in Japan (Fig. 1). Patient characteristics are listed in Table 1. The median age at the time of enrollment was 79.0 years (range, 76–88 years). Thirty patients