Current Trial Report

A Randomized Phase III Study Comparing Carboplatin With Nab-Paclitaxel Versus Docetaxel for Elderly Patients With Squamous-Cell Lung Cancer: Study Protocol

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Abstract

Background: Treatment with carboplatin (CBDCA) with weekly paclitaxel (PTX) has shown survival benefits compared with vinorelbine or gemcitabine in elderly patients with non-small-cell carcinoma (NSCLC). Docetaxel (DOC), however, remains a standard treatment in NSCLC. The 130-nm albumin-bound formulation of PTX (nab-PTX) has shown activity in NSCLC. Treatment with CBDCA with weekly nab-PTX showed significantly higher efficacy than CBDCA with PTX in patients with squamous histology and significantly increased overall survival (OS) in patients aged 70 years and older. **Patients and Methods:** This randomized, multicenter, phase III trial (UMIN000019843) was designed to compare the efficacy and safety of CBDCA with nab-PTX with DOC in patients aged 70 years and older with advanced squamous NSCLC. Elderly patients who have received no previous chemotherapy for advanced/metastatic squamous NSCLC with Eastern Cooperative Oncology Group performance status of 0 or 1 will be randomized 1:1 to DOC (60 mg/m^2 intravenous [I.V.] on day 1) or CBDCA (area under the blood concentration time curve 6 on day 1) with nab-PTX (100 mg/m^2 I.V. on days 1, 8, and 15) of each 21-day cycle. The primary end point is OS. Recruitment began in December 2015 and planned enrollment is 250 patients. **Conclusion:** If OS is greater in patients treated with CBDCA with nab-PTX than with DOC, this study will provide a new standard of care for elderly patients with squamous NSCLC.

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Introduction

Several clinical trials have evaluated chemotherapy regimens in elderly patients with advanced non-small-cell lung cancer (NSCLC). The ELVIS (Elderly Lung Cancer Vinorelbine Italian Study),[1] MILES (Multicenter Italian Lung Cancer in the Elderly Study),[2] and WJTOG (West Japan Thoracic Oncology Group) 9904[3] trials showed that anticancer drugs can prolong overall survival (OS), even in elderly patients. On the basis of these results, the current

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standard therapies for advanced NSCLC in elderly patients in Japan include monotherapy with agents such as docetaxel (DOC), vinorelbine (VNR), and gemcitabine (GEM).

Recent clinical trials have evaluated platinum-based combination therapies in elderly patients with NSCLC. For example, a randomized phase III trial compared VNR or GEM alone with carboplatin (CBDCA) and weekly paclitaxel (wPTX) in patients aged 70 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 to 2.[4] That study reported that OS was longer in the CBDCA with wPTX group, resulting in CBDCA with wPTX becoming a new standard first-line chemotherapy regimen for elderly patients.[4]

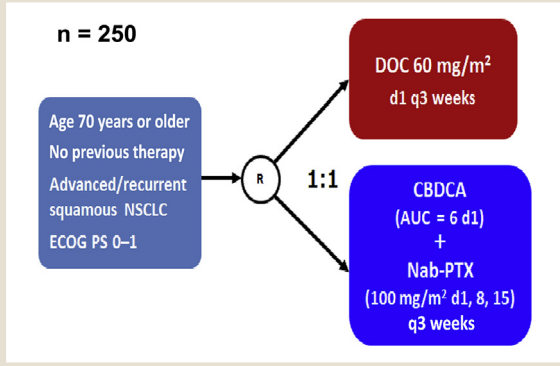
In Japan, a phase III trial compared DOC with weekly cisplatin (CDDP) together with DOC in patients aged 70 years or older with an ECOG PS of 0 to 1 who were unsuitable for bolus CDDP administration.[5] That trial, however, was terminated early because of futility on the basis of the results of an interim analysis, making it unclear whether the additional use of weekly CDDP had any advantages over DOC alone as first-line chemotherapy for elderly patients with advanced NSCLC.

A randomized phase II trial compared CBDCA with wPTX and CBDCA with paclitaxel (PTX) administered every 3 weeks in NSCLC patients aged 70 years or older. No significant difference was observed in the response rate (RR), which was the primary end point. However, the results suggested superior safety in the CBDCA with wPTX group. Furthermore, a randomized phase II trial that compared CBDCA and wPTX with DOC alone, the current standard therapy for elderly patients in Japan, reported that CBDCA with wPTX had higher RR and longer progression-free survival (PFS) with lower toxicity than DOC alone.[6]

The 130-nm albumin-bound formulation of PTX (nab-PTX) is a form of PTX bound to human serum albumin and formulated into nanoparticles. It is superior to conventional PTX because it can be administered to patients who are hypersensitive to solvents or alcohol, and it allows for shorter infusion times without necessitating steroid prophylaxis. A phase III international joint trial that compared PTX and CBDCA (PTX group) with nab-PTX and CBDCA (nab-PC group) reported that RR, the primary end point, was 25% in the PTX group and 33% in the nab-PC group (ratio 1.313; 95% confidence interval [CI], 1.082-1.593; $P = .005$).[7] In a subgroup analysis of patients with squamous-cell carcinoma (Sq), the RR was 41% in the nab-PC group and 24% in the PTX group (ratio 1.680; 95% CI, 1.271-2.221; $P < .001$).[8] Another subgroup analysis of patients aged 70 years or older showed PFS of 6.8 and 8.0 months (hazard ratio [HR], 0.187; 95% CI, 0.420-1.123; $P = .134$), OS of 10.4 and 19.9 months (HR, 0.583; 95% CI, 0.388-0.875; $P = .009$), and RRs of 24% and 34% (RR ratio, 1.385; $P = .196$) for the PTX and nab-PC groups, respectively, suggesting that nab-PTX with CBDCA might be an effective treatment option for elderly patients with Sq.[8]

The KEYNOTE-024 trial showed that patients with advanced NSCLC and a programmed death ligand 1 (PD-L1) tumor proportion score of ≥50% who were treated with pembrolizumab had longer PFS and OS than those given platinum-based combination therapy.[9] The efficacy was observed regardless of histologic type. Therefore, pembrolizumab is standard of care for the patients with advanced Sq and with tumor PD-L1 expression levels ≥50% in the first-line setting. In subset analysis of KEYNOTE-024, the HR of patients older than 65 years was 0.45 (better than the HR for patients younger than 65 years old).

Figure 1 Design of the Trial



Abbreviations: AUC = area under the blood concentration time curve; CBDCA = carboplatin; d1 = day 1; DOC = docetaxel; ECOG PS = Eastern Cooperative Oncology Group performance status; Nab-PTX = nab-paclitaxel; NSCLC = non–small-cell lung cancer; q3 = every 3; R = randomization.

Patients and Methods

Study Design and Treatment

This multicenter, randomized, unblinded phase III trial has been designed to compare the efficacy and safety of DOC alone with nab-PTX together with CBDCA in elderly patients with stage IIIB/IV or recurrent Sq, and to assess whether nab-PTX with CBDCA is a promising treatment for these patients. The study has been approved by the clinical research ethics committee of each participating institution and written informed consent has been or will be obtained from each patient before participation in the study. The patients will be randomly assigned to the nab-PTX and CBDCA or DOC group (Figure 1). Patients will be randomized using minimization, with adjustment for PS, clinical stage, sex, age, and institution. Patients in the DOC group will receive DOC (60 mg/m^2), administered over 60 minutes on day 1 every 3 weeks; patients in the nab-PTX with CBDCA group will be administered CBDCA (area under the blood concentration time curve 6) on day 1 and nab-PTX (100 mg/m^2) on days 1, 8, and 15 every 3 weeks. Treatments in both groups will be repeated until disease progression or the appearance of unacceptable toxicity; however, because administering >6 cycles of CBDCA raises the risk of allergic reactions, the upper limit will be set at 6 cycles. During cycle 7 and thereafter, patients in the nab-PTX with CBDCA group will be administered nab-PTX alone.

Eligibility Criteria

Patients will be considered eligible if they are aged 70 years or older and have histologically or cytologically confirmed advanced squamous-cell NSCLC, an ECOG PS of 0 or 1, and adequate bone marrow, liver, and kidney function (Table 1). All patients will have stage III or IV or postoperative recurrent disease without pretreatment, although treatment with immune checkpoint inhibitors (eg, anti-programmed death-1, anti-PD-L1, and/or anti-cytotoxic