Phase I Study of Cisplatin Analogue Nedaplatin, Paclitaxel, and Thoracic Radiotherapy for Unresectable Stage III Non-Small Cell Lung Cancer

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Background: The standard treatment of unresectable stage III non-small cell lung cancer is concurrent chemoradiotherapy in patients in good general condition, but where the optimal chemotherapeutic regimen has not been determined.

Methods: Patients with unresectable stage III non-small cell lung cancer received nedaplatin (80 mg/m²) and paclitaxel on day 1 every 4 weeks for 3–4 cycles and concurrent thoracic radiotherapy (60 Gy/30 fractions for 6 weeks) starting on day 1. The dose of paclitaxel was escalated from 120 mg/m² in level 1, 135 mg/m² in level 2 to 150 mg/m² in level 3.

Results: A total of 18 patients (14 males and 4 females, with a median age of 62.5 years) were evaluated in this study. Full cycles of chemotherapy were administered in 83% of patients in level 1, and in 50% of patients in levels 2 and 3. No more than 50% of patients developed grade 4 neutropenia. Transient grade 3 esophagitis and infection were noted in one patient, and unacceptable pneumonitis was noted in three (17%) patients, two of whom died of the toxicity. Dose-limiting toxicity (DLT), evaluated in 15 patients, noted in one of the six patients in level 1, three of the six patients in level 2 and one of the three patients in level 3. One DLT at level 2 developed later as radiation pneumonitis. Thus, the maximum tolerated dose was determined to be level 1. The overall response rate (95% confidence interval) was 67% (41–87%) with 12 partial responses.

Conclusion: The doses of paclitaxel and nedaplatin could not be escalated as a result of severe pulmonary toxicity.

Key words: non-small cell lung cancer – chemoradiotherapy – paclitaxel – nedaplatin – pneumonitis

INTRODUCTION

Locally advanced unresectable non-small cell lung cancer (NSCLC), stage IIIA disease with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions, and/or involvement of the mediastinal or supraclavicular lymph nodes, and occult systemic micrometastases (1). Concurrent chemoradiotherapy, recently shown to be superior to the sequential approach in phase III trials, is the standard medical care for this disease (2–4).

Chemotherapy regimens used concurrently with thoracic radiotherapy in these randomized trials were second-generation platinum-based chemotherapy, such as combinations of cisplatin, vindesine and mitomycin, cisplatin and vinblastine, and cisplatin and etoposide. The third-generation cytotoxic agents including vinorelbine and paclitaxel, which provided a better survival rate in patients with disseminated disease than second-generation agents, must be reduced when administered concurrently with thoracic radiotherapy (5–7). Thus, the optimal chemotherapy for concurrent chemoradiotherapy has not been established.

Nedaplatin (cis-diammine-glycolate-O,O'-platinum II, 254-S) is a second-generation platinum derivative that has an...
antitumor activity comparable to that of cisplatin but is less toxic to the kidney as shown in preclinical experiments (8). Nedaplatin produced a promising response rate for NSCLC, especially for squamous cell lung cancer (9,10). In addition, this drug can be safely administered with full-dose thoracic radiation, as shown in patients with esophageal cancer (11). Paclitaxel is another promising drug for the treatment of stage III NSCLC, as shown by the favorable response rate and survival in phase II trials in combination with platinum and thoracic radiation (6,7).

Our previous study of the nedaplatin and paclitaxel combination in patients with systemic disease showed that the recommended dose of these drugs was 80 mg/m² and 180 mg/m², respectively, repeated every 3–4 weeks. A promising response rate of 55% was achieved in patients with squamous cell lung cancer (12). The objectives of the present study were primarily to evaluate the toxicity of nedaplatin, paclitaxel and concurrent thoracic radiotherapy and determine the recommended dose of these two drugs for a phase II trial, and secondarily to observe the antitumor effect of this regimen in patients with stage III NSCLC.

PATIENTS AND METHODS

PATIENT SELECTION

The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease indicated for curative radiotherapy; no previous treatment; measurable disease; the percentage of the normal lung volume receiving 20 Gy or more (V₂₀) (13) expected to be 30% or less; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; adequate bone marrow function (12.0 × 10⁹/L ≥ white blood cell (WBC) count ≥ 4.0 × 10⁹/L, neutrophil count ≥ 2.0 × 10⁹/L, hemoglobin ≥ 10.0 g/dL and platelet count ≥ 100 × 10⁹/L), liver function (total bilirubin ≤ 1.5 mg/dL and transaminase ≤ twice the upper limit of the normal value), and renal function (serum creatinine ≤ 1.5 mg/dL and creatinine clearance ≥ 60 mL/min); and a PaO₂ of 70 torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

PRETREATMENT EVALUATION

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest X-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan, and radionuclide bone scan.

TREATMENT SCHEDULE

Paclitaxel and nedaplatin were administered as previously described (12). Briefly, paclitaxel diluted in 500 ml of 5% glucose was administered as a 3-h intravenous infusion with premedication consisting of dexamethasone, ranitidine and diphenhydramine. Nedaplatin diluted in 250 ml of normal saline was administered in a 1-h intravenous infusion. This treatment was repeated every 4 weeks for 3–4 cycles. The dose of paclitaxel was escalated as follows: 120 mg/m² (level 1), 135 mg/m² (level 2), and 150 mg/m² (level 2). The dose of nedaplatin was 80 mg/m² through the levels 1–3.

Thoracic radiation therapy was given with photon beams from a linac or microtron accelerator with energy between 6 and 10 MV. The total dose of 60 Gy was delivered at a single dose of 2 Gy once daily Monday through Friday for 6 weeks without interruption beginning on day 1 of the chemotherapy. Three-dimensionnal conformal radiotherapy technique was used in all patients. The gross target volume (GTV) included the primary lesion (GTV1) and involved lymph nodes whose short diameter was 1 cm or larger (GTV2) based on conventional chest X-ray and CT scans. The clinical target volume (CTV) consisted of CTV1 and CTV2, identical to GTV1 and GTV2, respectively, and CTV3, the ipsilateral hilum and bilateral mediastinum area. The contralateral hilum was excluded from the CTV. The supraclavicular fossa was also excluded unless it was involved. The planning target volume (PTV) for the initial dose up to 40 Gy consisted of CTV1-3 with the superior and inferior field margins extended to 1–2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The PTV for the boost 20 Gy included only CTV1-2 based on the second CT scans with the same margins. The spinal cord dose was limited to 44 Gy by using oblique parallel opposed fields.

TOXICITY ASSESSMENT AND TREATMENT MODIFICATION

Complete blood cell counts and differential counts, routine chemistry determinations and a chest X-ray were performed once a week during the course of treatment. Toxicity was graded according to the NCI Common Toxicity Criteria version 2.0. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count <3.0 × 10⁹/L, neutrophil count <1.5 × 10⁹/L, platelet count <100 × 10⁹/L, serum creatinine level ≥ 1.6 mg/dL, infection ≥ grade 2, elevated hepatic transaminase level or total serum bilirubin ≥ grade 2, pneumonitis ≥ grade 2, peripheral neuropathy, musculoskeletal pain ≥ grade 3, fever ≥ 38°C, or performance status ≥ 2. Chemotherapy was terminated if the toxicities did not
recover within 2 weeks. The doses of nedaplatin and paclitaxel were reduced by 25% in all subsequent cycles if any of the dose-limiting toxicities (DLTs) defined below were noted. The dose of nedaplatin was reduced by 25% in all subsequent cycles if the serum creatinine level was elevated to 2.0 mg/dl or higher. Thoracic radiotherapy was suspended if any of the following toxicities was noted: fever ≥38°C, infection ≥grade 2, esophagitis of grade 3, performance status ≥3, or radiation pneumonitis was suspected. Thoracic radiotherapy was terminated if radiation pneumonitis that required corticosteroid administration was noted, or radiotherapy was not completed within 60 days. Both chemotherapy and thoracic radiotherapy were terminated if any of the following was noted: disease progression, any of the grade 4 non-hematological toxicities except abnormal electrolytes, performance status of 4, patient refusal to receive subsequent treatment, protocol violation, or patient death of any cause. Granulocyte colony-stimulating factor and antibiotics were administered if febrile neutropenia was noted.

DLT, MAXIMUM TOLERATED DOSE (MTD), AND RECOMMENDED DOSE FOR PHASE II TRIALS

The DLT was defined as a grade 4 leukopenia, grade 4 neutropenia lasting 7 days or longer, febrile neutropenia, platelet count <20 × 10^9/L, grade 3 or a more severe non-hematological toxicity other than nausea, vomiting and transient electrolyte abnormality, and treatment termination before two cycles of chemotherapy and thoracic radiotherapy were completed. Dose levels were escalated according to the frequency of DLT evaluated during the first and second cycles of chemotherapy and thoracic radiotherapy were completed. Six patients were initially enrolled at each dose level. If none to two of the six patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If three or more of the six patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

RESPONSE EVALUATION

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (15).

STUDY DESIGN, DATA MANAGEMENT AND STATISTICAL ANALYSES

This study was designed as a phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 2 years and a follow-up period of 3 years were planned. Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method (16). Overall survival time was measured from the date of registration to the date of death from any cause or last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression or death from any cause or last follow-up. Patients who were lost to follow-up without event were censored at the date of their most known follow-up. A confidence interval for the response rate was calculated using methods for exact binomial confidence intervals. Response rates among patients with squamous cell carcinoma and those with non-squamous carcinoma were assessed with the χ^2 test. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

REGISTRATION AND CHARACTERISTICS OF THE PATIENTS

From October 2003 to July 2004, six patients were registered at dose level 1, eight patients at dose level 2 and five patients at dose level 3. Two patients at dose level 2 were excluded from the DLT evaluation, because they discontinued receiving the treatment early because of disease progression and anaphylactic shock, respectively. Initially, DLT was noted in only two of the six patients at dose level 2, and therefore, patient registration at dose level 3 was started. However, severe radiation pneumonitis developed 5 weeks after the end of radiotherapy in another patient at dose level 2 and this pneumonitis was counted as DLT. Thus, because DLT was finally noted in three of the six patients at dose level 2, patient registration at dose level 3 was stopped. One patient at dose level 3 was found to be ineligible because the radiation treatment planning showed that the V_{20} exceeded 30%. The patient did not receive the current treatment and was excluded from the analysis. Thus, a total of 18 patients were subjects of this study and their detailed demographic characteristics are listed in Table 1.

TREATMENT DELIVERY

The planned three to four cycles of chemotherapy were administered in 83% of patients in level 1 and in 50% of patients in levels 2 and 3. Radiation delivery was generally well maintained and it did not differ among the three dose levels (Table 2).

TOXICITY, DLT AND MTD

Hematological toxicity was generally mild. No more than 50% of patients developed grade 4 neutropenia, and no one developed grade 2 or higher thrombocytopenia (Table 3). Non-hematological toxicity other than lung toxicity was also well tolerated. One patient developed transient grade 3 esophagitis and grade 3 infection not associated with neutropenia, which were considered DLTs. Another patient developed grade 4 anaphylactic shock 1 min after the second cycle infusion of paclitaxel, but soon recovered with fluid
replacement and oxygen therapy. This patient was excluded from DLT evaluation. One patient in level 1 and another patient in level 2 developed grade 4 pneumonitis after completion of two cycles of chemotherapy and thoracic radiotherapy and they died of the pneumonitis. The \(V_{20}\) and mean lung dose (MLD) of these patients were 23% and 30%, and 1341 cGy and 1675 cGy, respectively.

Both patients were former heavy smokers with a smoking index of 520 and 1680, respectively. The chest CT scan of the former patient disclosed mild emphysematous, but no interstitial changes. A spirometry analysis showed a vital capacity (VC) of 3480 ml (104% of predicted), and a forced expiratory volume one second percent (FEV1.0%) of 82%. The lung diffusing capacity measurement using carbon monoxide (DL CO) was not done in this patient. The \(\text{PaO}_2\) was 93.3 torr. The serum LDH level before treatment was 241 IU/l (the upper limit of the normal value was 229 IU/l).

The chest CT scan of the latter patient disclosed slight changes in the dorsal portion of the both lungs, which were considered the gravitation effect, or fibrotic changes. The VC was 3810 ml (107% of predicted), \% DL CO was 111%, and \(\text{PaO}_2\) was 99.7 torr. The serum LDH level before treatment was 147 IU/l. Another patient in level 2, whose \(V_{20}\) and MLD were 15% and 822 cGy, respectively, developed grade 2 pneumonitis when he received 52 Gy of radiotherapy and the subsequent protocol treatment was stopped. The chest CT scan of this patient before treatment showed no abnormal findings except for lung cancer. Pulmonary function test values were all within normal limits. The serum LDH level before treatment was 178 IU/l. Thus, in total three (17%) of 18 patients developed unacceptable severe pneumonitis induced by the current treatment, which was counted as DLT.
To sum up, DLT was noted in one of six patients in level 1, three of six patients in level 2, and one of three patients in level 3. The DLTs were pneumonitis in three patients, grade 4 leukopenia in one patient, and grade 3 esophagitis and grade 3 infection in one patient. Thus, the MTD was determined to be level 1.

**OBJECTIVE RESPONSE AND SURVIVAL**

All patients were included in the analyses of tumor response and survival. No CR, 12 PRs, and 3 SD were noted among the 18 patients and the overall response rate (95% confidence interval) was 67% (41–87%). The response rate in patients having squamous cell carcinoma was 100%, while that for non-squamous histology was 58%. The median progression-free survival time was 9.7 months. The median overall survival time has not yet been reached and the 1-year survival rate was 78%.

**DISCUSSION**

The feasible doses of anticancer agents in this study were paclitaxel 120 mg/m² and nedaplatin 80 mg/m² every 4 weeks. These figures are lower than those in a randomized phase II trial for stage III NSCLC conducted in the USA, where paclitaxel 135 mg/m² and cisplatin 80 mg/m² were administered every 3 weeks concurrently with thoracic radiotherapy (6). The occurrence of severe pneumonitis hampered the dose escalation of the anticancer agents in this study. A Japanese phase I/II study of weekly paclitaxel, nedaplatin and concurrent thoracic radiotherapy for stage III NSCLC showed that the DLT was also pneumonitis and that the response rate was 75% and progression-free survival was 5.6 months, similar to the outcome of this study (17). The reasons for the frequent pneumonitis in this study remain unknown. Paclitaxel was the most frequently used anticancer agent together with thoracic radiotherapy in patients with NSCLC outside Japan. A randomized phase II study of induction chemotherapy followed by concurrent chemoradiation therapy in patients with stage III NSCLC (CALGB study 9431) showed that grade 3–4 pneumonitis during chemoradiation was noted in 14% of patients treated with gemcitabine and cisplatin, 20% of patients treated with paclitaxel and cisplatin, and 20% of patients treated with vinorelbine and cisplatin. One patient died of pneumonitis in the vinorelbine and cisplatin arm (6). Thus, incidence of pneumonitis in patients receiving paclitaxel was reported to be the same as that for other agents in this setting. Nedaplatin was a new agent but one of the platinum that has been repeatedly shown to be safely administered with radiation (1). A case series of 24 esophageal cancer patients treated with radiation therapy (60–70 Gy) combined with Nedaplatin (80–120 mg) and 5-fluorouracil (500–1000 mg for 5 days) showed that toxicity was mainly hematological and no grade 3 or higher non-hematological toxicity was observed (18). Treatment-related pneumonitis may be more readily developed among Japanese patients, because gefitinib-induced pneumonitis is more common in Japan than in other countries (19–21). Similarly, a relatively high incidence of drug-induced pneumonitis was noted among Japanese patients in association with the use of weekly docetaxel (20) and leflunomide, a newly developed disease-modifying antirheumatic drug that exhibits anti-inflammatory, antiproliferative and immunosuppressive effects (22). Further studies are needed to define ethnic or geographic variation of treatment-related pneumonitis.

Recent dose–volume histogram studies showed that the volume–dose parameters such as the V20 and MLD were significantly associated with development of severe radiation pneumonitis (23). The V20 and MLD in the three patients who developed unacceptable pneumonitis in this study (15–30% and 822–1675 cGy, respectively) were not so large, and therefore, the severe pneumonitis in these patients could not be fully explained by their irradiation volume alone. Patient characteristics such as age, sex, smoking habit, location of the primary tumor and pre-existing lung diseases may be associated with the development of radiation pneumonitis, but their contribution was inconclusive (24).

Radiation pneumonitis is the most common dose-limiting complication of thoracic radiation. Its incidence varies greatly from one report to another: the incidence of grade 2 radiation pneumonitis was between 2% and 33% and that of grade 3 was between 0% and 20% (25). This inconsistency among reports can be explained by the different radiation pneumonitis scoring system and follow-up duration in each study. No scoring system for radiation pneumonitis is perfect. The distinction between grade 2 and grade 3 toxicity is highly subjective. In addition, these scoring systems do not account for intercurrent symptoms from tumor, infection and chronic lung illnesses such as chronic obstructive pulmonary diseases (25).

For future trials, it is an important strategy to reduce the lung volume receiving radiation without an increase in the local recurrence rate. Elective nodal regions with potential subcliminal micrometastases (CTV3 in this study) have been included in the standard irradiation volume. The advent of three-dimensional conformal treatment techniques, however, has allowed for a more precise definition of target volume and may allow the possibility of reduced toxicity and increased radiation dose delivery by the omission of elective nodal irradiation (26). We are conducting a phase I study of high-dose thoracic three-dimensional conformal radiotherapy without elective nodal irradiation concurrently combined with cisplatin and vinorelbine in patients with inoperable stage III non-small cell lung cancer.

In conclusion, the doses of paclitaxel and nedaplatin combined with thoracic radiotherapy could not be escalated owing to severe pulmonary toxicity. We do not recommend a phase II study of this chemoradiotherapy regimen.
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Conflict of interest statement

None declared.

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