Phase II study of nedaplatin and irinotecan with concurrent thoracic radiotherapy in patients with locally advanced non-small-cell lung cancer

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**BACKGROUND:** Current international guidelines recommend the use of platinum-based chemotherapy with thoracic radiotherapy (TRT) for patients with locally advanced non-small-cell lung cancer (NSCLC). Patients with unresectable stage IIIA or IIIB NSCLC were treated with nedaplatin (NP) at 50 mg m⁻² on days 1 and 8 every 4 weeks for two to four cycles with concurrent TRT (2 Gy per day, total 60 Gy).

**RESULTS:** All 35 patients were able to receive a total of 60 Gy. Adverse effects and events in chemotherapy with TRT were grade 3 or 4 anaemia, neutropenia and thrombocytopenia, which occurred in 3.0%, 32.8% and 6.0% of patients, respectively. There was no grade 3 pneumonitis or oesophagitis. Adverse effects and events in chemotherapy alone were mild. There was no treatment-related death. An overall response rate was 94.3%. The median progression-free and overall survivals were 13.0 and 36.0 months, respectively. The 5-year disease-free and overall survival rates were 25.7% and 40.0%, respectively.

**CONCLUSION:** NP and CPT treatment with concurrent TRT is effective and safe for patients with unresectable, locally advanced NSCLC.

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Locally advanced stage III non-small-cell lung cancer (NSCLC) can be thought of as a two-compartment model: a local-regional compartment in the chest and a distant compartment harbouring potential micrometastases. At the most basic level, thoracic radiation therapy (TRT) is directed towards the intrathoracic tumour burden, whereas chemotherapy works to eradicate systemic microscopic metastatic deposits below current levels of detection by computerised tomography scanning or positron emission imaging with fluorodeoxyglucose. Chemotherapy may contribute a radiosensitising effect locally, as well as providing cytoreduction of bulky locoregional disease. Four different treatment paradigms have emerged in recent years for application of chemoradiotherapy (CRT): sequential, concurrent, induction chemotherapy followed by concurrent CRT and concurrent CRT followed by consolidation chemotherapy (Gandara et al, 2005). Current international guidelines recommend the use of platinum-based chemotherapy with TRT for patients with locally advanced NSCLC (Pfister et al, 2004). A randomised phase III study comparing induction chemotherapy with concurrent CRT using an identical chemotherapy regimen demonstrated that chemotherapy using cisplatin, vindesine and mitomycin C with concurrent TRT significantly improved survival in comparison with a sequential approach such as chemotherapy followed by TRT (Furuse et al, 1999). The study demonstrated that median survival time (MST) and 5-year survival rate were 16.5 months and 16% in the concurrent arm compared with 13.3 months and 9%, respectively. However, increased toxicity was noted with concurrent therapy, primarily consisting of intensified toxicities within the TRT field, notably oesophagitis with associated nutritional problems and potential dehydration. There may also be an increased risk of pneumonitis and severe myelotoxicities. Thus, concurrent TRT may be too toxic for selected patient groups with NSCLC, especially for elderly patients and those with poor performance status (PS).

Nedaplatin (NP) is an analogue of cisplatin, showing relatively low neurotoxicity and nephrotoxicity, and high in vivo bioavailability, ensuring the position of NP as a primary chemotherapeutic agent for the treatment of patients with advanced lung cancer (Kameyama et al, 1990). Our previous phase I/II study of NP and irinotecan (CPT) showed high activity against NSCLC, including a 31.0% response rate (RR), an MST of 341 days and a 1-year survival rate of 45.2% (Oshita et al, 2003). Mild toxicities were also demonstrated, and a subsequent phase II study of this combination demonstrated its efficacy and feasibility for elderly patients with NSCLC (Oshita et al, 2004). Three-dimensional analysis models have demonstrated a remarkable synergistic interaction of concurrent NP with CPT (Kanzawa et al, 2001), and we expected that infusion of the two drugs on the same day combined with concurrent TRT would yield a stronger effect. Some patients with locally advanced unresectable NSCLC have received sequential
TRT after completion of NP and CPT chemotherapy at the Kanagawa Cancer Center. These patients experienced only mild localised lung damage in the radiation field after completion of full-dose TRT. These data suggested that chemotherapy using NP and CPT would be feasible when combined with concurrent TRT. Therefore, we conducted a phase II study to examine the feasibility and effect of NP and CPT concurrent with TRT, planning to combine TRT with the first course of NP and CPT chemotherapy.

PATIENTS AND METHODS

The institutional review board of the Kanagawa Cancer Center reviewed and approved this study before commencement.

Patients

Patients with histologically or cytologically confirmed NSCLC were registered. Eligibility criteria were clinical stage IIIA or IIIB, cytologically proven N2, unresectable cancer, an expected survival of at least 12 weeks, a TRT field less than half of the unilateral lung, patient age <70 years, Eastern Cooperative Oncology Group PS score ≤1, leukocyte count ≥4000 per µl, haemoglobin ≥10 g per 100 ml, platelet count ≥100 000 per µl, total serum bilirubin <1.5 mg per 100 ml, aspartate aminotransferase and alkaline aminotransferase ≤90 IU l⁻¹, serum creatinine ≤1.5 mg per 100 ml and PaO₂ ≥70 torr. None of the patients had received chemotherapy, radiotherapy or surgical resection previously. Patients with pleural or pericardial effusion were excluded. Written informed consent was obtained from every patient.

Chemotherapy and TRT

Nedaplatin was administered at a dose of 50 mg m⁻² on days 1 and 8. Irinotecan was also administered at a dose of 60 mg m⁻² on days 1 and 8. Patients were given a 5-HT₃ antagonist and dexamethasone reduced by 10 mg m⁻² to reduce toxicities, except alopecia. If the dose-limiting toxicity (DLT) was reached, the dose of NP and CPT in the subsequent cycle was reduced by 10 mg m⁻². Dose reduction was allowed once, and any patient who experienced DLT twice was withdrawn from the protocol. Dose-limiting toxicity was defined as toxicity in every cycle consisting of grade 4 neutropenia lasting 4 days or more; grade 4 neutropenia with fever of 38°C or higher; grade 4 thrombocytopenia; grade 2 depression of PaO₂; grade 2 dyspnoea; or grade 3 or 4 other non-haematological toxicity, except alopecia, nausea and vomiting. Physical examination, a complete blood cell count, biochemical tests and chest radiography were performed weekly. Chemotherapy was repeated for a maximum of four cycles, unless the disease progressed, but was stopped if the tumour response was judged to be stable disease (SD) after two cycles.

Thoracic radiotherapy using photon beams from a linac or microtron accelerator, with energy between 6 and 10 MV at a single fraction of 2 Gy once daily, 5 days per week, total 60 Gy, was begun on day 1 or 2 of the first cycle of NP and CPT chemotherapy. The clinical target volume was based on conventional chest X-ray and CT scans, and included the primary lesion (CTV1), involved lymph nodes with a short diameter of 1 cm or larger (CTV2) and the ipsilateral pulmonary hilum and bilateral mediastinum area (CTV3). Anterior and posterior parallel opposed fields encompassed the initial planned target volume (PTV), consisting of CTV1–3, with the superior and inferior field margins extended to 1.5 cm and lateral field margins extended to 1.5 cm to allow for respiratory variation and fixation error. The spinal cord dose was limited to 50 Gy using oblique parallel opposed fields. When grade 4 leucopenia, neutropenia or thrombocytopenia, fever ≥38°C, grade 2 pneumonitis or other grade 3 or 4 non-haematological toxicities appeared, radiation therapy was stopped until the toxicities ameliorated.

Evaluation of response and toxicities

Tumour response was evaluated according to the RECIST criteria (Therasse et al, 2000). Complete response (CR) was defined as the complete disappearance of all evidence of tumour for at least 4 weeks. Partial response (PR) was defined as at least a 50% reduction in the sum of the product of the two greatest perpendicular diameters of all indicator lesions or a reduction of more than 50% in evaluable disease for at least 4 weeks, with no appearance of new lesions or progression of any existing lesions. Progressive disease (PD) was defined as at least a 25% increase in the tumour area or the appearance of new lesions. All other outcomes were classified as SD. Toxicities were evaluated according to the National Cancer Institute-Common Toxicity Criteria ver. 2 criteria (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf).

Study design

We chose an 80% RR as a desirable target level and a 60% RR as uninteresting. The study design had power in excess of 95% and <20% error, and therefore 13 assessable patients in the first step and 22 in the second step were required according to the minimax design of Simon (1989). We decided to stop the study if there were fewer than nine responders in the first step. The regimen was defined as active if there were 26 or more responders out of the total of 35 patients. Overall, survival was estimated by the method of Kaplan and Meier.

RESULTS

Patient characteristics

Between August 2002 and June 2005, 35 patients were registered in the phase II study (Table 1). A total of 22 patients were registered...
for assessment of response in the first stage. Of the 22 patients in the first stage, 20 responded and 13 patients were registered in the second stage. A total of 25 patients were male and 10 were female, with a median age of 62 years (range 43–69 years). Nine patients had a PS of 0 and 26 had a PS of 1. In all, 22 patients had adenocarcinoma, 10 had squamous cell carcinoma and the remaining patients had other cancers. A total of 30 patients had clinical stage IIIA and five had stage IIIB. Every patient was proven cytologically to have N2 disease by broncoscopic examination.

### Treatment delivery

A total of 67 cycles were administered with concurrent TRT. After completion of TRT, a total of 48 cycles were administered. A total of 28 patients received three or four cycles of chemotherapy, and the median number of chemotherapy cycles was four. Chemotherapy dose reduction was required in two patients in the second cycle and in one patient in the fourth cycle because of grade 4 neutropenia lasting 4 days or more. Three patients were unable to continue the second cycle of chemotherapy because of grade 2 pneumonitis in two and delayed neutropenia in one. The reasons for discontinuing chemotherapy after two cycles were PD (bone metastasis) in two cases and patient refusal in two cases. All 35 patients were able to receive a total of 60 Gy of TRT. A total of 67 cycles were administered with concurrent TRT. After completion of TRT, a total of 48 cycles were administered. A total of 25 patients were male and 10 were female, with a median age of 62 years (range 43–69 years). Nine patients had a PS of 0 and 26 had a PS of 1. In all, 22 patients had adenocarcinoma, 10 had squamous cell carcinoma and the remaining patients had other cancers. A total of 30 patients had clinical stage IIIA and five had stage IIIB. Every patient was proven cytologically to have N2 disease by broncoscopic examination.

### Toxicities

Adverse effects and events in cycles 1 and 2 of chemotherapy with concurrent TRT are summarised in Table 2. Grade 3 or 4 anaemia, leukopenia, neutropenia and thrombocytopenia occurred in 3.0, 38.8%, 32.8% and 6.0%, respectively. There were no grade 4 toxicities, except for leukopenia and neutropenia. There was no treatment-related death.

### Table 2  Adverse effects and events in chemotherapy and concurrent thoracic radiation

| Toxicity         | Grade | Percentage of G3 and 4 |
|------------------|-------|------------------------|
| Haemoglobin      | 0     | 9 46 10 2 0 0 3.0      |
| Leukocytes       | 1     | 7 29 25 1 38.8         |
| Neutrophils      | 2     | 8 14 23 18 4 32.8      |
| Platelets        | 3     | 32 27 4 4 0 6.0        |
| Bilirubin        | 4     | 57 8 2 0 0            |
| Creatinine       |       | 67 0 0 0 0 —          |
| SGOT             | 0     | 40 8 0 0 0 —          |
| SGPT             | 1     | 49 16 2 0 0 —         |
| Fatigue          | 2     | 0 60 6 1 0 1.5        |
| Nausea/vomiting  | 3     | 46 17 3 1 0 1.5       |
| Diarrhoea        | 4     | 44 23 0 0 0            |
| Pneumonitis      |       | 58 5 4 0 0 —         |
| Fever            | 0     | 59 7 1 0 0            |
| Febrile neutropenia | 1   | 61 — — 6 0 9.0    |
| Neuropathy–sensory | 2   | 64 3 0 0 0 —         |
| Alopecia         | 3     | 44 23 0 0 0            |
| Oesophagitis     | 4     | 36 28 3 0 0 —      |
| Gastritis        | 0     | 62 5 0 0 0            |
| Cystitis         | 1     | 66 1 0 0 0 —         |
| Sense of smell/dysgeusia | 2   | 59 8 0 0 0 —       |
| Constipation     | 3     | 61 6 0 0 0 —         |
| Stomatitis       | 4     | 64 3 0 0 0 —         |
| Epistaxis        |       | 66 1 0 0 0 —         |

Abbreviations: NCI-CTC ver.2 = National Cancer Institute-Common Toxicity Criteria; SGOT = serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase.

### Table 3  Adverse effects and events in 3 and 4 courses of chemotherapy

| Toxicity         | Grade | Percentage of G3 and 4 |
|------------------|-------|------------------------|
| Haemoglobin      | 0     | 4 27 12 5 0 10.4      |
| Leukocytes       | 1     | 10 7 14 15 2 35.4     |
| Neutrophils      | 2     | 13 7 11 12 8 41.7     |
| Platelets        | 3     | 24 10 6 7 1 16.7      |
| Bilirubin        | 4     | 45 2 1 0 0 —         |
| Creatinine       |       | 47 1 0 0 0 —         |
| SGOT             | 0     | 42 6 0 0 0 —         |
| SGPT             | 1     | 40 8 0 0 0 —         |
| Fatigue          | 2     | 0 45 3 0 0 —         |
| Nausea/vomiting  | 3     | 38 10 0 0 0 —        |
| Diarrhoea        | 4     | 35 13 0 0 0 —       |
| Pneumonitis      | 0     | 35 9 4 0 0 —        |
| Fever            | 1     | 47 1 0 0 0 —         |
| Febrile neutropenia | 2   | 46 — — 2 0 4.0    |
| Neuropathy–sensory | 3   | 48 0 0 0 0 —       |
| Alopecia         | 4     | 17 31 0 0 0 —       |
| Oesophagitis     | 0     | 44 4 0 0 0 —        |
| Gastritis        | 1     | 45 3 0 0 0 —         |
| Cystitis         | 2     | 48 0 0 0 0 —         |
| Sense of smell/dysgeusia | 3   | 43 5 0 0 0 —       |
| Constipation     | 4     | 46 2 0 0 0 —         |
| Stomatitis       | 0     | 47 1 0 0 0 —         |

Abbreviations: NCI-CTC ver.2 = National Cancer Institute-Common Toxicity Criteria; SGOT = serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase.

### Figure 1  Progression-free (a dotted line) and overall (a bold line) survival curves constructed using the Kaplan–Meier method. The median progression-free survival was 13.0 months (range 4.6 to 91.0+ months) and 5-year disease-free survival rate was 25.7% (Figure 1). The MST was 36.0 months (range 8.0 to 91.0+ months) and the 1-, 3- and 5-year survival rates were 88.6%, 51.4% and 40.0%, respectively (Figure 1).

**Table 3**  Adverse effects and events in 3 and 4 courses of chemotherapy

| Toxicity         | 0 | 1 | 2 | 3 | 4 | Percentage of G3 and 4 |
|------------------|---|---|---|---|---|------------------------|
| Haemoglobin      | 4 | 27| 12| 5 | 0 | 10.4                   |
| Leukocytes       | 10| 7 | 14| 15| 2 | 35.4                   |
| Neutrophils      | 13| 4 | 11| 12| 8 | 41.7                   |
| Platelets        | 24| 10| 6 | 7 | 1 | 16.7                   |
| Bilirubin        | 45| 2 | 1 | 0 | 0 | —                      |
| Creatinine       | 47| 1 | 0 | 0 | 0 | —                      |
| SGOT             | 42| 6 | 0 | 0 | 0 | —                      |
| SGPT             | 40| 8 | 0 | 0 | 0 | —                      |
| Fatigue          | 0 | 45| 3 | 0 | 0 | —                      |
| Nausea/vomiting  | 38| 10| 0 | 0 | 0 | —                      |
| Diarrhoea        | 35| 13| 0 | 0 | 0 | —                      |
| Pneumonitis      | 35| 9 | 4 | 0 | 0 | —                      |
| Fever            | 47| 1 | 0 | 0 | 0 | —                      |
| Febrile neutropenia | 46| — | — | 2 | 0 | 4.0                    |
| Neuropathy–sensory | 48 | 0 | 0 | 0 | 0 | —                      |
| Alopecia         | 17| 31| 0 | 0 | 0 | —                      |
| Oesophagitis     | 44| 4 | 0 | 0 | 0 | —                      |
| Gastritis        | 45| 3 | 0 | 0 | 0 | —                      |
| Cystitis         | 48| 0 | 0 | 0 | 0 | —                      |
| Sense of smell/dysgeusia | 43| 5 | 0 | 0 | 0 | —                      |
| Constipation     | 46| 2 | 0 | 0 | 0 | —                      |
| Stomatitis       | 47| 1 | 0 | 0 | 0 | —                      |

Abbreviations: NCI-CTC ver.2 = National Cancer Institute-Common Toxicity Criteria; SGOT = serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase.

**Nedaplatin, irinotecan and radiation for lung cancer**

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The use of an additional chemotherapy component remains investigational. The consolidation chemotherapy approach and the administration of concurrent chemotherapy and radiation therapy were considered more effective in achieving a complete remission. However, the optimal timing, dosage, and combination of chemotherapy agents with radiation therapy remain to be determined. Further clinical trials are needed to establish the most effective approach for patients with NSCLC.
addition of targeted therapies to concurrent TRT are currently under investigation. Careful consideration must be given to the exact role a novel therapeutic agent is expected to have in a combined modality therapy setting; that is, in addition to CRT, should the agent be a single drug active against NSCLC, a radiosensitising agent or an agent to control distant micrometastasis? Additional data regarding docetaxel consolidation have been obtained from the SWOG and also from trials in Japan. A non-randomised study by the SWOG evaluated docetaxel consolidation after cisplatin and etoposide CRT, and suggested that 75 mg m\(^{-2}\) docetaxel was better tolerated without loss of efficacy (Gandara et al, 2003). In a phase II trial in Japan, 97 patients with unresectable stage III NSCLC received docetaxel consolidation after concurrent CRT using cisplatin and vinorelbine for three cycles (Sekine et al, 2006). Only 37% of patients completed all three cycles of docetaxel. Pneumonitis was the most common reason for early discontinuation, and four patients died of this complication.

Tyrosine kinase inhibitors directed against epidermal growth factor receptor (EGFR) have been shown to be effective for the treatment of advanced NSCLC (Fukuoka et al, 2003). A retrospective study has demonstrated that NSCLC patients with EGFR mutation have a better outcome with Gef treatment than do patients with wild-type EGFR (Mitsudomi et al, 2005). A randomised phase III study comparing Gef with standard carboplatin plus paclitaxel has demonstrated that Gef conferred significantly superior progression-free survival as first-line chemoradiotherapy in stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. J Clin Oncol 20: 3454 – 3460

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