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Clinical Trial Results

Phase I/II Study of Cisplatin plus Nab-Paclitaxel with Concurrent Thoracic Radiotherapy for Patients with Locally Advanced Non-Small Cell Lung Cancer

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Key Words. Cisplatin • Dose-limiting toxicity • nab-Paclitaxel • Radiotherapy • Non-small cell lung cancer

Trial Information

- **UMIN Trial ID:** UMIN000012531
- **Sponsor:** Kindai University
- **Principal Investigator:** Hidetoshi Hayashi
- **IRB Approved:** Yes

Lessons Learned

- The combination of cisplatin plus nab-paclitaxel with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer is a promising therapeutic strategy.
- Further investigation is warranted.

Abstract

Background. We conducted a phase I/II trial of cisplatin plus nab-paclitaxel with concurrent thoracic radiotherapy for locally advanced non-small cell lung cancer (NSCLC) to determine the recommended dose (RD) of nab-paclitaxel and to evaluate the safety and efficacy of this regimen.

Methods. In the phase I study, escalating doses of weekly nab-paclitaxel were administered together with cisplatin at 75 mg/m^2 every 3 weeks and concurrent radiotherapy. In the phase II study, nab-paclitaxel was administered at the RD.

Results. In the phase I study, whereas no dose-limiting toxicity (DLT) was observed with nab-paclitaxel at 50 or 60 mg/m^2, one of six patients experienced DLT (esophagitis of grade 3) at 70 mg/m^2, determined as the RD. Twenty-four patients at RD were evaluable for safety and efficacy in phase II. Common toxicities included esophagitis (87.5%) and leukopenia (79.2%). Pneumonitis and treatment-related deaths were not observed, but 20 patients (83.3%) experienced radiation pneumonitis, with one case of grade 3 and four of grade 2, after completion of concurrent chemoradiotherapy. The 2-year overall survival and progression-free survival rates were 73.9% and 56.5% (95% confidence interval [CI], 34.3%–74.7%), respectively.

Conclusion. Concurrent chemoradiation with nab-paclitaxel at 70 mg/m^2 and cisplatin at 75 mg/m^2 every 3 weeks showed encouraging feasibility and activity for locally advanced NSCLC.

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Discussion

Twelve patients were enrolled and evaluated for safety in the phase I part of the study. DLT was not observed in the first and second three patients treated at dose levels 1 and 2, respectively (nab-paclitaxel [nab-PTX] at 50 and 60 mg/m^2). At dose level 3 (nab-paclitaxel, 70 mg/m^2), one of the first three patients

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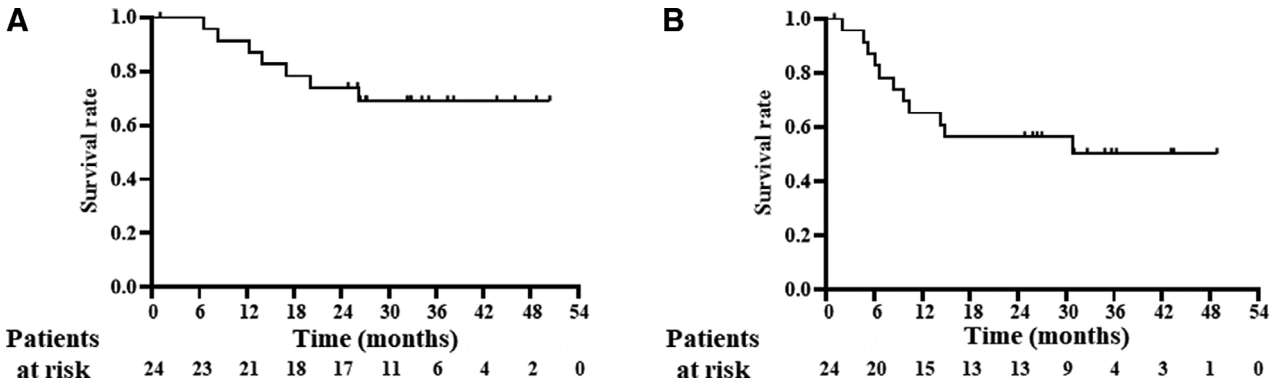

Figure 1. Kaplan-Meier plots: survival rate. **(A):** Overall survival. **(B):** Progression-free survival.

experienced a DLT (esophagitis of grade 3). An additional three patients were therefore enrolled at dose level 3, none of whom experienced a DLT. Both the maximum tolerated dose and RD of nab-PTX were thus determined to be 70 mg/m^2.

For the phase II part of the study, 19 patients were treated at the RD (dose level 3, nab-PTX at 70 mg/m^2). One patient was excluded from analysis as a result of not receiving the study therapy. Therefore, a total of 24 patients, including the 6 patients treated at dose level 3 in the phase I part of the study, were evaluated for safety and efficacy.

Twenty-two patients had an investigator-assessed response, including one patient with a complete response (CR), for an objective response rate (ORR) (proportion of patients with a CR or partial response) of 91.7% with a 95% CI of 78.7% to 100.0%. At the median follow-up time of 27.1 months, the 2-year overall survival (OS) rate was 73.9% (95% CI, 50.9%–87.3%), indicating that the primary endpoint was met. The median OS was not reached (95% CI, 26.1 months to not reached) (Fig. 1A). The 2-year progression-free survival (PFS) rate was 56.5% (95% CI, 34.3%–74.7%), and the median PFS was not reached (95% CI, 9.6 months to not reached) (Fig. 1B). In addition, for the 30 patients who received treatment at any dose, the 2-year OS rate was 69.0% (95% CI, 48.8%–82.4%), with the median OS of 55.6 months (95% CI, 20.3 months to not reached), the 2-year PFS rate of 55.2% (95% CI, 35.6%–71.0%), and the median PFS of 32.0 months (95% CI, 9.6–55.8 months).

All 24 patients who received treatment at the RD were evaluable for toxicity. Major toxicities during the concurrent phase are listed in the table of adverse events. Common nonhematologic toxicities of all grades included esophagitis (87.5%), nausea (70.8%), anorexia (70.8%), and dermatitis (58.3%). There were no cases of febrile neutropenia. After completion of concurrent chemoradiotherapy, 20 patients (83.3%) experienced radiation pneumonitis, including one with grade 3 and four with grade 2, whereas pneumonitis was not observed during the chemoradiation period. There were no treatment-related deaths.

Trial Information	
Disease	Lung cancer – NSCLC
Stage of Disease/Treatment	Primary
Prior Therapy	None
Type of Study	Phase I/II, 3+3
Primary Endpoint	Determine the RD of nab-paclitaxel in the phase I part and the 2-year OS rate in the phase II part.
Secondary Endpoint	PFS, OS, 2-year PFS rate, 1-year PFS and OS rates, ORR, and safety
Additional Details of Endpoints or Study Design	
DLT was defined as toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 during the concurrent chemoradiotherapy period, including pneumonitis of grade 3 or 4, febrile neutropenia of grade 3 or 4, other nonhematologic toxicities of grade 3 or 4, thrombocytopenia of grade 4, any unresolved toxicity requiring a second consecutive skip in the administration of weekly nab-PTX or a delay of >2 weeks in the second cisplatin administration, and any toxicity necessitating a delay of >2 weeks in the completion of radiotherapy. The dose-escalation phase used a standard 3+3 study design.	
The primary endpoint of the phase II part of the study was 2-year OS rate. On the basis of the results of a previous study, the expected 2-year OS rate for the present study was assumed to be 65%, and a 2-year survival of 40% or lower was of no interest. Given this assumption, the study was designed to have a power of 80% and a one-sided alpha level of 0.05, resulting in a requirement of 23 patients. To allow for approximately 10% ineligibility rate, 25 patients in the phase II part of the study, including 3 or 6 patients who received chemoradiation at the RD in the phase I part, were planned to enroll. Secondary endpoints included PFS, OS, 2-year PFS rate, 1-year PFS and OS rates, ORR, and safety. Median PFS and OS were estimated by the Kaplan-Meier method.	
Investigator's Analysis	Active and should be pursued further

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Drug Information: Phase I	
Drug 1	
Generic/Working Name	Nab-paclitaxel
Dose	40 (level 0), 50 (initial dose, level 1), 60 (level 2), or 70 (level 3) milligrams (mg) per squared meter (m^2)
Route	IV
Schedule of Administration	Administered on days 1, 8, and 15 of 3-week cycle.
Drug 2	
Generic/Working Name	Cisplatin
Dose	75 milligrams (mg) per squared meter (m^2)
Schedule of Administration	Administered on day 1 of 3-week cycle.

Dose-Escalation Table: Phase I Control

Dose level	Dose of drug: nab-paclitaxel, mg/m^2	Dose of drug: cisplatin, mg/m^2	Number enrolled	Number evaluable for toxicity
0	40	75	0	0
1	50	75	3	3
2	60	75	3	3
3	70	75	6	6

Drug Information: Phase II	
Drug 1	
Generic/Working Name	Nab-paclitaxel
Dose	70 milligrams (mg) per squared meter (m^2)
Route	IV
Schedule of Administration	Administered on days 1, 8, and 15 of 3-week cycle
Drug 2	
Generic/Working Name	Cisplatin
Dose	75 milligrams (mg) per squared meter (m^2)
Route	IV
Schedule of Administration	Administered on day 1 of 3-week cycle

Patient Characteristics: Phase I	
Number of Patients, Male	8
Number of Patients, Female	1
Stage	Stage IIIA: 8, Stage IIIB: 4
Age	Median: 70
Number of Prior Systemic Therapies	Median: 0
Performance Status: ECOG	0 — 4 1 — 8 2 — 3 — Unknown —
Other	Smoking history: Never: 2; Former-current: 10
Cancer Types or Histologic Subtypes	Adenocarcinoma, 6 Squamous cell carcinoma, 4 NOS, 2

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Patient Characteristics: Phase II	
Number of Patients, Male	18
Number of Patients, Female	6
Stage	Stage IIIA: 16, Stage IIIB: 8
Age	Median: 64
Performance Status: ECOG	0 — 9 1 — 15 2 — 3 — Unknown —
Cancer Types or Histologic Subtypes	Adenocarcinoma, 12 Squamous cell carcinoma, 6 Adeno-squamous cell carcinoma, 4 NOS, 2

Primary Assessment Method: Phase I	
Title	New Assessment
Evaluation Method	RECIST 1.1

Outcome Notes

In the phase I part of the study, 12 patients were enrolled and evaluated for safety. DLT was not observed in the first and second three patients treated at dose levels 1 and 2, respectively (nab-PTX at 50 and 60 mg/m^2). At dose level 3 (nab-paclitaxel, 70 mg/m^2), one out of the first three patients experienced DLT (esophagitis of grade 3). An additional three patients were therefore enrolled at dose level 3, none of whom experienced DLT. Both the maximum tolerated dose and RD of nab-PTX were thus determined to be 70 mg/m^2.

In the phase II part, 24 patients, including 6 patients enrolled in the phase I part, received treatment at the RD and were eligible for efficacy analysis.

At the median follow-up time of 27.1 months, the 2-year OS rate was 73.9% (95% CI, 50.9%–87.3%), indicating that the primary endpoint was met. The median OS was not reached (95% CI, 26.1 months to not reached). The 2-year PFS rate was 56.5% (95% CI, 34.3%–74.7%), and the median PFS was not reached (95% CI, 9.6 months to not reached).

Primary Assessment Method: Phase II	
Title	Efficacy Analysis for the 24 Patients Treated with the RD of the Study Treatment
Number of Patients Screened	25
Number of Patients Enrolled	24
Number of Patients Evaluable for Toxicity	24
Number of Patients Evaluated for Efficacy	24
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 1 (4.2%)
Response Assessment PR	*n* = 22 (91.7%)
Response Assessment SD	*n* = 0 (0%)
Response Assessment PD	*n* = 1 (4.2%)

Outcome Notes

Twenty-four patients, including six patients enrolled in the phase I part, received treatment at the RD and were eligible for efficacy analysis.

At the median follow-up time of 27.1 months, the 2-year OS rate was 73.9% (95% CI, 50.9%–87.3%), indicating that the primary endpoint was met. The median OS was not reached (95% CI, 26.1 months to not reached). The 2-year PFS rate was 56.5% (95% CI, 34.3%–74.7%), and the median PFS was not reached (95% CI, 9.6 months to not reached).

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Adverse Events: Phase I

Treatment-related adverse events during concurrent chemoradiotherapy at dose level 1 in phase I part

Name	NC/ NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
White blood cell decreased	0	0	67	33	0	0	100
Neutrophil count decreased	0	0	67	33	0	0	100
Anemia	34	33	33	0	0	0	66
Platelet count decreased	100	0	0	0	0	0	0
Aspartate aminotransferase increased	100	0	0	0	0	0	0
Dermatitis radiation	33	67	0	0	0	0	67
Anorexia	67	33	0	0	0	0	33
Alanine aminotransferase increased	100	0	0	0	0	0	0
Constipation	67	33	0	0	0	0	33
Esophagitis	34	33	33	0	0	0	66
Fatigue	33	67	0	0	0	0	67
Mucositis oral	100	0	0	0	0	0	0
Peripheral sensory neuropathy	100	0	0	0	0	0	0

Adverse Events Legend
Treatment-related adverse events during concurrent chemoradiotherapy
Dose level 1 corresponds to nab-paclitaxel at 50 mg/m^2 (n = 3).
Abbreviation: NC/NA, no change from baseline/no adverse event.

Treatment-Related Adverse Events During Concurrent Chemoradiotherapy at Dose Level 2: Phase I

Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
White blood cell decreased	1	33	33	33	0	0	99
Neutrophil count decreased	0	0	67	33	0	0	100
Anemia	34	33	33	0	0	0	66
Anorexia	67	33	0	0	0	0	33
Constipation	0	100	0	0	0	0	100
Dermatitis radiation	0	100	0	0	0	0	100
Esophagitis	67	0	33	0	0	0	33
Fatigue	67	0	33	0	0	0	33
Nausea	67	33	0	0	0	0	33
Peripheral sensory neuropathy	100	0	0	0	0	0	0

Adverse Events Legend
Treatment-related adverse events during concurrent chemoradiotherapy
Dose level 2 correspond to nab-paclitaxel at 60 mg/m^2 (n = 3).
Abbreviation: NC/NA, no change from baseline/no adverse event.

Dose-Limiting Toxicities: Phase I Control

Dose level	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity	Dose-limiting toxicity information
1	3	3	0	
2	3	3	0	
3	6	6	1	G3 esophagitis

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Adverse Events: Phase II

All Cycles

Name	NC/NA	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
White blood cell decreased	20	17	42	21	0	0	80
Neutrophil count decreased	24	17	38	17	4	0	76
Anemia	50	25	25	0	0	0	50
Platelet count decreased	71	8	21	0	0	0	29
Esophagitis	12	38	46	4	0	0	88
Nausea	29	46	25	0	0	0	71
Anorexia	29	46	25	0	0	0	71
Dermatitis radiation	42	46	8	4	0	0	58
Constipation	54	38	8	0	0	0	46
Alanine aminotransferase increased	84	8	4	4	0	0	16
Fatigue	84	8	8	0	0	0	16
Aspartate aminotransferase increased	87	13	0	0	0	0	13
Mucositis oral	92	8	0	0	0	0	8
Peripheral sensory neuropathy	92	8	0	0	0	0	8

Adverse Events Legend
Dose levels 3 (RD) correspond to nab-paclitaxel at 70 mg/m^2.
After completion of concurrent chemoradiotherapy, 20 patients (83.3%) experienced radiation pneumonitis among 24 patients, including one with grade 3 and four with grade 2, whereas pneumonitis was not observed during the chemoradiation period. There were no treatment-related deaths.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Chemoradiotherapy, in which platinum and taxane agents are concurrently administered with radiotherapy, is considered a standard care for unresectable stage 3 non-small cell lung cancer (NSCLC) [1, 2]. Although other studies have evaluated the combination of carboplatin (CBDCA) and nab-paclitaxel (nab-PTX) with thoracic radiotherapy (TRT), present clinical trial is the first to evaluate the feasibility of the combination of cisplatin (CDDP) and nab-PTX with TRT in patients with such tumors. Our study determined the recommended dose (RD) of nab-PTX in this regimen as 70 mg/m^2. In addition, our results suggest that this regimen is safe and effective and that it warrants further evaluation as a treatment option for locally advanced NSCLC.

Several dose-finding trials have been performed for the combination of Carboplatin (CBDCA) plus nab-PTX with TRT for locally advanced NSCLC [3–7]. In a phase I trial conducted in the U.S., the RD was determined to be 50 mg/m^2 for nab-PTX and CBDCA at an area under the concentration-time curve of 2 mg mL^{-1} min in the concurrent phase, given that two of four treated patients experienced dose-limiting toxicity (DLT) (esophagitis or radiation dermatitis) at this dose level [5]. A recent Japanese phase I/II trial also determined the RD for nab-PTX to be 50 mg/m^2, with DLT (leukopenia of grade 3 requiring a second consecutive skip in the administration of weekly nab-PTX) being observed at this dose [3]. In addition, severe (defined as grade 3 to 5) leukopenia and neutropenia were observed in 60.7% and 28.6%, respectively, of the 56 evaluated patients in the phase II part of this previous study. Together, these findings thus suggested that myelosuppression and worsening of radiation-related toxicity are the major concerns related to the combination of CBDCA and nab-PTX with TRT. In contrast, CDDP-based chemotherapy is less hematotoxic, especially with regard to thrombocytopenia. An individual-based meta-analysis for small cell lung cancer thus found that thrombocytopenia and severe (grade 3) neutropenia were significantly more frequent in patients treated with CBDCA than in those treated with CDDP [8]. Our present findings also revealed mild hematotoxicity for the CDDP-based regimen, with 20.8% of patients developing severe leukopenia and 16.7% severe neutropenia, with no cases of febrile neutropenia. Conversely, gastrointestinal toxicity—including nausea, vomiting, and appetite loss—as well as nephrotoxicity are more common in patients treated with CDDP than in those treated with CBDCA. However, supportive care, including the administration of neurokinin-1 antagonists for gastrointestinal toxicity and specific hydration therapy for nephrotoxicity, now allows patients with cancer to be treated more easily and safely with CDDP [9]. These considerations support the feasibility of the combination of

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CDDP and nab-PTX with TRT for the treatment of locally advanced NSCLC as suggested by our present results.

Pneumonitis related to either treatment component is also a key adverse event for concurrent chemotherapy and TRT. In the current study, radiation pneumonitis was observed in 83% of patients treated at the RD, although cases were mild, consistent with the results of previous Japanese clinical trials of CBDCA and nab-PTX with TRT. A recent large phase III trial of durvalumab after chemoradiotherapy for patients with locally advanced NSCLC reported an incidence of pneumonitis of only 15% to 20% [10]. Given that all cases of pneumonitis occurred after completion of chemoradiation in the present trial, these events were likely induced by radiotherapy. Although the reason for this high incidence of pneumonitis is not clear, the potential lung toxicity of nab-PTX–based regimens warrant further study.

Despite the limited number of patients enrolled in the current phase I/II trial, encouraging efficacy data were obtained, with an objective response rate and 2-year progression-free survival (PFS) rate of 91.7% and 56.5%, respectively. The 2-year overall survival (OS) rate of 73.9% obtained with CDDP and nab-PTX in our study is similar to that (60.3%) reported for the combination of CDDP and docetaxel for Japanese patients [11]. In addition, the recent phase III study of durvalumab as a consolidative immunotherapy after concurrent chemoradiation found a significant increase in PFS and OS compared with a placebo control in patients with locally advanced NSCLC [10]. It is thus possible that the high efficacy of the combination of CDDP and nab-PTX will allow patients to benefit from consolidation therapy with durvalumab, resulting in a more durable survival outcome.

In conclusion, as far as we are aware, the present study is the first to evaluate the safety and efficacy of concurrent chemoradiotherapy with nab-PTX and CDDP for locally advanced NSCLC. Given that the goal of treatment of locally advanced NSCLC should be a cure, our results suggest that the combination of cisplatin and nab-paclitaxel with TRT is a promising treatment option for patients younger than 75 years with good renal function.

Disclosures

Hidetoshi Hayashi: AstraZeneca K.K, Boehringer Ingelheim Japan Inc., Eli Lilly Japan K.K, Chugai Pharmaceutical Co. Ltd. (C/A), AstraZeneca K.K., Boehringer Ingelheim Japan Inc., Bristol-Myers Squibb Co. Ltd., Eli Lilly Japan K.K., Ono Pharmaceutical Co. Ltd., Taiho Pharmaceutical Co. Ltd. (H), Ono Pharmaceutical Co. Ltd, AstraZeneca K.K, Boehringer Ingelheim Japan Inc (RF); **Hiroshige Yoshioka:** Taiho Pharmaceutical (Other: lecture fees); **Takayasu Kurata:** Taiho (H); **Kaoru Tanaka:** AstraZeneca, Merck Serono, Eisai, Bristol-Myers Squibb, Ono Pharmaceutical, MSD. The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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