Survival outcomes of adjuvant chemotherapy with modified weekly nab-paclitaxel and carboplatin for completely resected nonsmall cell lung cancer: FAST-nab

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The relatively low toxicity profile of nab-paclitaxel plus carboplatin and its feasibility as an adjuvant administration was reported previously. This study aimed to evaluate the survival efficacy for completely resected patients with stage IB, II, and IIIA nonsmall cell lung cancer (NSCLC). Twenty-nine eligible patients with NSCLC who received surgical resection for pathological stage IB, II, or IIIA, followed by postoperative adjuvant chemotherapy with modified 3-week cycles of either nab-paclitaxel (nab-P) (100 mg/m\textsuperscript{2}) on days 1 and 8 followed by carboplatin area (area under the curve = 6) on day 1 were prospectively enrolled and assessed for survival outcomes against patients with the same stages who received other postoperative adjuvant chemotherapy regimens during the same period. There were no significant differences in clinicopathological features, including age, gender, smoking status, performance status, surgical procedures, tumor histology, and pathological stage between the two groups. The cumulative overall survival (OS) rates at 5 years of the experimental and control groups in pathological stage IB–IIIA were 85.4% and 63.9%, respectively (P = 0.598), while recurrence-free survival (RFS) rates in these groups at 5 years were 65.2% and 34.8%, respectively (P = 0.344). Moreover, the cumulative OS rates of the experimental and control groups in pathological stage II–IIIA were 83.6% and 63.6%, respectively (P = 0.970), while RFS rates in these groups at 5 years were 61.1% and 37.3%, respectively (P = 0.460). This new regimen was considered an attractive alternative postoperative adjuvant chemotherapy option with relatively low toxicity and moderate survival outcomes for completely resected NSCLC.

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Introduction

Lung cancer is the most common cancer (11.6%) according to the GLOBOCAN 2018 database covering 185 countries and 36 cancer types, and is the leading cause of cancer-related mortality worldwide, accounting for 18.4% of the total cancer cases analyzed in 2018 worldwide [1]. Nonsmall cell lung cancer (NSCLC) comprises about 85% of these cases. With advances in screening techniques and the increase in reliance on computed tomography scans, the incidence of early-stage NSCLC is expected to increase in the coming years. According to the most recent updates, in 2016, the total number of surgical resections for primary lung cancer in Japan had reached 42,482, showing a steady increase over the years [2]. Among these, 18,028 (42.4%) patients with pathological stage IB–III were possible candidates for postoperative adjuvant chemotherapy.

For certain patients with early-stage NSCLC, adjuvant chemotherapy is the accepted standard of care and is largely based on several randomized trials and meta-analyses [3–7]. For patients with stage II and III NSCLC and patients with stage IB disease who have tumors ≥4 cm, adjuvant platinum-based chemotherapy is the standard of care. Despite this, the survival advantage is modest with approximately 5% at 5 years. Cisplatin-based chemotherapies are recommended as the adjuvant chemotherapy in patients with completely resected NSCLC. The combination of cisplatin and vinorelbine is the most well-studied regimen, but current consensus for patients with advanced-stage NSCLC is to use four cycles of any of the platinum-based chemotherapy regimens commonly used as front-line therapy.

Despite the survival benefit, severe toxicities are occasionally observed in patients treated with cisplatin-based chemotherapies. According to the LACE meta-analysis, at least 33% of the patients in the chemotherapy arm did not complete the planned three or four cycles of treatment.

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as the rate of overall grade 3 or 4 toxicity reached 66% [5]. Accordingly, the development of a novel therapeutic strategy that is both safe and efficient is essential for patients with completely resected NSCLC.

A phase III study, weekly nab-paclitaxel, a nanoparticle formation of paclitaxel bound to human albumin (nab-P), plus carboplatin every 3 weeks (q3w) vs. standard q3w paclitaxel plus carboplatin, produced a significantly higher overall response rate (overall response rate, primary end point; 33% vs. 25%, P = 0.005), a 1-month increase in median overall survival (OS) (12.1 vs. 11.2 months, P = 0.271), and an improved safety profile with significantly less grade ≥3 neuropathy, neutropenia, arthralgia, and myalgia in the first-line treatment of patients with advanced NSCLC [8]. In a phase II trial that we conducted and previously reported, the feasibility of an adjuvant chemotherapy regimen with nab-P and carboplatin in patients who underwent complete resection of pathological stage IB/II/IIIA NSCLC was assessed [9]. Twenty-two (75.9%) of the 29 patients enrolled completed four cycles of this regimen. The most common grade 3 or 4 adverse event experienced during the nab-P plus carboplatin was neutropenia (34.5%), followed by anemia (13.8%). No grade 3 or 4 nonhematological adverse event was observed during this chemotherapy.

Finally, we postulated that this safe and well-tolerated regimen may be an attractive alternative postoperative adjuvant chemotherapy for completely resected NSCLC. Therefore, the purpose of this study was to evaluate the survival efficacy of the adjuvant administration of nab-P plus carboplatin for patients with completely resected stage IB, II, and IIIA NSCLC compared with consecutive patients with a similar disease stage and who received other postoperative chemotherapy regimens during the same period as a histological control group.

Methods

Patients

Between July 2013 and November 2015, a total of 29 patients with pathologically confirmed completely resected stage IB, II, and IIIA NSCLC by lobectomy, bilobectomy, or pneumonectomy were enrolled in this study as the experimental group.

These patients received modified 3-week cycles of nab-P (30-min infusion) at a dose of 100 mg/m² on days 1 and 8, followed by carboplatin [area under the curve (AUC) = 6 mg/min/ml (per the Calvert formula)] given on day 1 every 3 weeks, and a maximum of four cycles as a postoperative adjuvant chemotherapy [9]. Other inclusion criteria were age 20–79 years, Eastern Cooperative Oncology Group performance status ≤2, adequate hematological (absolute neutrophil count ≥ 1500/ml, platelet count ≥ 100 000/ml, hemoglobin ≥9.0 g/dl), hepatic functions [aspartate and alanine aminotransferases <2.5 x upper limit of normal, serum bilirubin (≤1.5 mg/dl)], and renal functions (serum creatinine ≤1.5 mg/dl). In addition, surgery should have been completed within 4–8 weeks before enrollment.

Controls

Between January 2009 and December 2013, a total of 83 consecutive patients with primary lung cancer with pathological stage IB/IIA/IIB/IIIA who underwent curative lobectomy or more with mediastinal lymph node dissection at our hospital were retrospectively enrolled as controls in this study. Among them, 55 (66.2%) patients with primary lung cancer received any postoperative adjuvant chemotherapy including UFT, cisplatin plus vinorelbine, cisplatin plus docetaxel, cisplatin plus gemcitabine, cisplatin plus etoposide, carboplatin plus paclitaxel, carboplatin plus docetaxel, carboplatin plus pemetrexed, carboplatin plus TS-1, carboplatin plus etoposide, and carboplatin plus irinotecan. After excluding four patients with small cell lung cancer, two patients with carcinoids and two patients with pleomorphic carcinoma because of different biological prognosis, the remaining 47 patients were enrolled as the control group. We analyzed the survival efficacy of the 47 controls in comparison with the 29 experimental patients in this study.

Assessment of patients

Pathological stages of NSCLC were determined using the 7th edition of the Union for International Cancer Control Manual of Clinical Oncology [10]. Histologic subtypes of lung cancer were determined according to the WHO classification [11]. After pulmonary resection, the patients were followed up at 3- to 6-month intervals for 3 years, then at 6- to 12-month intervals for the next 2 years, and thereafter at 1-year intervals as necessary. The follow-up evaluations included physical examination, routine laboratory tests including tumor marker, chest roentgenogram, and chest and abdominal computed tomography. FDG-PET and brain imaging were requested upon presentation of clinical symptoms.

Statistical analysis

OS and recurrence-free survival (RFS) were estimated using the Kaplan–Meier method, and differences in survival rates were determined by log-rank analysis. OS was defined as the time elapsed from the date of pulmonary resection to the date of death from any cause or last follow-up when alive. RFS was defined as the time elapsed from the date of pulmonary resection to the date of the first recurrence or last follow-up showing no recurrence. The last follow-up observation was censored if the patient was alive or lost to follow-up. Categorical and continuous variables were analyzed using Fisher’s exact test and Student’s t-test, respectively. The interaction terms of variables selected in the final model were evaluated by the likelihood ratio test. All tests were two-sided and P values <0.05 were considered statistically significant. All statistical calculations were performed using the SPSS statistical software package (version 24.0; SPSS, Inc., Chicago, Illinois, USA).
Ethics
This study was approved by the Institutional Review Board and Ethics Committee of St. Marianna University School of Medicine (No. 2233) and conducted in accordance with the Declaration of Helsinki. All patients in the experimental group were required to sign a study-specific informed consent form to be included in the study. This prospective study is also registered with the University Hospital Medical Information Network in Japan (UMIN000011225). Furthermore, the requirement for informed consent from the historical control patients was waived because of the retrospective study design.

Results
Patient characteristics
The patient characteristics showed no statistically significant differences in various clinicopathological factors, including age, gender, smoking and performance status, surgical procedure, tumor histology, and pathological stage, between the two groups (Table 1). Seemingly, more pathological stage IB and II populations in the control and experimental groups were noted, respectively, due to the conventional UFT used in patients with pathological stage IB in a practical setting in Japan.

Survival efficacy
The median follow-up for all 76 patients was 47.5 (range 5.4–118.2) months; and it was 32.6 (range 7.3–58.4) and 60.9 (range 5.4–119.2) months for the 29 experimental and 47 control patients, respectively. No treatment-related death was observed during these regimens in this study. The cumulative OS rates at 5 years of the experimental and control groups in pathological stage IB–IIIA were 85.4% and 63.9%, respectively (P = 0.598) (Fig. 1a), while the RFS rates in these groups at 5 years were 61.1% and 37.3%, respectively (P = 0.460) (Fig. 2b). Consequently, there was no significant difference in survival between the two groups.

Discussion
Surgical resection is the most effective treatment for early-stage NSCLC, and despite this, up to 60% of patients with IB–IIIA NSCLC relapse after surgery and die, with the situation remaining unchanged over the past decade [12–14]. The presence of micrometastases at the time of resection is the most likely cause of recurrence, even after complete surgical removal of all macroscopically recognizable disease. Therefore, adjuvant chemotherapy was hypothesized to be a rational treatment, leading to its use to reduce the risk of relapse and death from lung cancer.

The LACE meta-analysis of data from five large randomized trials — [Adjuvant Lung Project Italy (Alpi) [15]; International Adjuvant Lung Cancer Trial (IALIT) [16]; National Cancer Institute of Canada JBR.10 trial (JBR.10) [3]; Adjuvant Navelbine International Trialist Association (ANITA) [4]; and Big Lung Trial (BLT)] [17] – revealed a significant advantage in OS [hazard ratio (HR) = 0.89, 95% confidence interval (CI) 0.82–0.96; P = 0.005], corresponding to a 5-year absolute benefit of 5.4% from chemotherapy [5]. In view of this benefit, cisplatin-based adjuvant chemotherapy, especially vinorelbine plus CDDP, was adopted for pathological stage II or IIIA NSCLC. Despite the survival benefit, compliance and toxicity cannot be ignored.

The compliance rates that we reported previously in a phase II feasibility study of adjuvant chemotherapy using a modified 3-week cycle of either nab-P (100 mg/m²) on days 1 and 8, followed by carboplatin area (AUC = 6) on day 1 from a standard regimen in a metastatic NSCLC...
setting, 3-week cycles of either nab-P on days 1, 8, and 15 followed by carboplatin on day 1 [8] was more favorable than that of cisplatin-based adjuvant chemotherapy. About 75% of patients completed four cycles, and over 80% of patients completed three cycles of the modified weekly nab-P and carboplatin chemotherapy regimen.

Anemia was the most frequent hematological toxicity, occurring in 62.1% of the patients, followed by neutropenia (48.2%) and grade 3 or 4 neutropenia (34.5%), while grade 3 or 4 anemia was experienced by 13.8% of the patients [9]. Considering the results of these trials, a phase III clinical trial in a multi-institutional setting to
Adjuvant TKIs generally decrease the risk of recurrence in patients with NSCLC harboring an EGFR mutation, but have not improved OS. With approvals in advanced-stage disease, multiple programmed death 1/programmed death ligand 1 ICIs are now being studied in the adjuvant setting; however, no data remain exciting: Impower010 (chemotherapy, then atezolizumab vs. placebo), BR31 (chemotherapy or no chemotherapy, then durvalumab vs. placebo), and KEYNOTE-091 (chemotherapy or no chemotherapy, then pembrolizumab vs. placebo). Trials for adjuvant targeted therapy including adjuvant EGFR-TKI trials and trials of immunotherapy drugs are ongoing and will define the role of these agents as adjuvant therapy. Recently, KEYNOTE-407, a phase III trial, showed that in patients with previously untreated metastatic, squamous NSCLC, the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-P resulted in significantly longer OS and PFS than chemotherapy alone [21]. Therefore, our results showed that carboplatin plus nab-P presented relatively low toxicity and moderate survival outcomes as a postoperative adjuvant chemotherapy, and will encourage this regimen plus pembrolizumab as a postoperative adjuvant chemotherapy for completely resected squamous NSCLC.

This study is not without limitations. First, the study design involved the comparison of a retrospective control group, small sample size, and was conducted at a single institution. Second, the treatment bias of the control group may have influenced poor prognostic outcomes in patients with completely resected early-stage NSCLC.

Conclusion
We aimed to confirm the survival outcomes of adjuvant chemotherapy with modified nab-P plus carboplatin after a complete standard resection in patients with NSCLC. The cumulative OS and RFS rates at 5 years in prospectively enrolled patients receiving adjuvant nab-P plus carboplatin were 85.4% and 65.2% in pathological stage IB–IIIA, respectively, and 83.5% and 61.1% in pathological stage II–IIIA, respectively (the median follow-up was 32.6 months). There was no significant difference in survival between experimental and retrospective control groups. This new regimen was considered an attractive alternate postoperative adjuvant chemotherapy regimen with relatively low toxicity and moderate survival outcomes for completely resected NSCLC.

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Conflicts of interest
There are no conflicts of interest.
References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68:394–424.

2 Shimizu H, Endo S, Tatsugoe S, Doki Y, Hiraoka K, Koyabashi J, et al.; J.J.A.I.T.S. Committee for Scientific Affairs, Thoracic and cardiovascular surgery in Japan in 2016: annual report by The Japanese association for thoracic surgery. Gen Thorac Cardiovasc Surg 2019; 67:377–411.

3 Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, et al.; National Cancer Institute of Canada Clinical Trials Group; National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005; 352:2589–2597.

4 Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramaulu R, Gonzales-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (adjuvant navelbine international trialist association [ANITA]): a randomised controlled trial. Lancet Oncol 2006; 7:719–727.

5 Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al.; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE collaborative group. J Clin Oncol 2008; 26:3552–3558.

6 Strauss GM, Hendon JE, Maddaus MA, Johnstone DW, Johnson EA, Harpole DH, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 93333 with the cancer and leukemia group B, radiation therapy oncology group, and north central cancer treatment group study groups. J Clin Oncol 2008; 26:5043–5051.

7 Douillard JY, Tribodet H, Aubert D, Shepherd FA, Rosell R, Ding K, et al.; LACE Collaborative Group. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the lung adjuvant cisplatin evaluation (LACE) trial. J Clin Oncol 2010; 5:220–228.

8 Socinski MA, Bondarenko I, Karaseva NA, Makhsan AM, Vynnychenko I, Okamoto I, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol 2012; 30:2065–2072.

9 Saji H, Marushima H, Miyazawa T, Sakai H, Kimura H, Kurimoto N, Nakamura H. Feasibility study of adjuvant chemotherapy with modified weekly nab-paclitaxel and carboplatin for completely resected non-small-cell lung cancer: FAST-nab. Anticancer Drugs 2017; 28:795–800.

10 Sobin LH, Gospodarowicz MK, Wittekind C; International Union against Cancer, ebrary Inc. TNM Classification of Malignant Tumours. Chichester, West Sussex, UK; Hoboken, NJ: Wiley-Blackwell, 2009. p. 310.

11 Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011; 6:244–285.

12 Asamura H, Goya T, Koshishii Y, Sohara Y, Eguchi K, Mori M, et al.; Japanese Joint Committee of Lung Cancer Registry. A japanese lung cancer registry study: prognosis of 13,010 resected lungs cancers. J Thorac Oncol 2008; 3:46–52.

13 Searabada N, Miyaoa E, Asamura H, Nakaisyi Y, Eguchi K, Mori M, et al.; Japanese Joint Committee for Lung Cancer Registration. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. J Thorac Oncol 2011; 6:1229–1235.

14 Okami J, Shintani Y, Okumura M, Ito H, Ohtsuka T, Toyooka S, et al.; Japanese Joint Committee of Lung Cancer Registry. Demographics, safety and quality, and prognostic information in both the seventh and eighth editions of the TNM classification in 18,973 surgical cases of the japanese joint committee of lung cancer registry database in 2010. J Thorac Oncol 2019; 14:212–222.

15 Scagliotti GV, Fossati R, Toni V, Crinò L, Giaccone G, Silvano G, et al.; Adjuvant Lung Project Italy/European Organisation for Research Treatment of Cancer-Lung Cancer Cooperative Group Investigators. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. J Natl Cancer Inst 2003; 95:1453–1461.

16 Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J; International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004; 350:351–356.

17 Waller D, Peake MD, Stephens RJ, Gower NH, Milroy R, Parmar MK, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the big lung trial. Eur J Cardiothorac Surg 2004; 26:173–182.

18 Hirsch FR, Suda K, Wiens J, Bunn PA Jr. New and emerging targeted treatments in advanced non-small-cell lung cancer. Lancet 2016; 388:1012–1024.

19 Kelly K, Altorki NK, Eberhardt WE, O’Brien ME, Spigel DR, Crinò L, et al. Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung cancer (RADIANT): a randomized, double-blind, phase III trial. J Clin Oncol 2015; 33:4007–4014.

20 Zhong WZ, Wang G, Mao WM, Xu ST, Wu L, Shen Y, et al.; ADJUVANT investigators. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-III (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol 2018; 19:139–148.

21 Paz-Ares L, Luijt A, Vicente D, Tafreshi A, Gümüş M, Mázieres J, et al.; KEYNOTE-407 Investigators. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018; 379:2040–2051.