Efficacy of platinum agents for stage III non-small-cell lung cancer following platinum-based chemoradiotherapy: a retrospective study

Eriko Miyawaki1, Hirotugu Kenmotsu1*, Yasushi Shintani2, Ikuo Sekine3, Takehito Shukuya4, Koichi Takayama5, Akira Inoue6, Isamu Okamoto7, Katsuyuki Kiura8, Kazuhisa Takahashi9, Nobuyuki Yamamoto9, Tomoya Kawaguchi10, Etsuo Miyaoka11, Ichiro Yoshino12 and Hiroshi Date13

Abstract

Background: Platinum-based chemoradiotherapy is the standard treatment for unresectable stage III non-small-cell lung cancer (NSCLC). However, few studies have evaluated the efficacy of subsequent chemotherapy for relapsed NSCLC following platinum-based chemoradiotherapy. This study aimed to evaluate the efficacy of platinum-doublet chemotherapy as a second-line treatment for patients with unresectable stage III NSCLC.

Methods: We retrospectively evaluated patients with unresectable stage III NSCLC treated with cytotoxic chemotherapy following platinum-based chemoradiotherapy who were registered in a nationwide registry NSCLC database. Patients were divided into the platinum-doublet chemotherapy (platinum) group and single-agent chemotherapy (non-platinum) group based on the type of second-line chemotherapy.

Results: The platinum group (n = 119) showed significantly better overall survival (OS) than the non-platinum group (n = 201) (median OS: 21.5 vs. 10.5 months, hazard ratio [HR]: 0.54, 95% confidence interval [CI]: 0.40–0.73, p < 0.001). OS from the beginning of chemoradiotherapy was also significantly better in the platinum group than in the non-platinum group (median OS: 34.9 vs. 21.8 months, HR: 0.58, 95% CI: 0.43–0.79, p = 0.001). In the multivariate analysis, platinum-doublet chemotherapy as second-line therapy, female sex, clinical stage IIIA, and duration of ≥ 8.6 months from the beginning of first-line therapy to the beginning of second-line therapy were associated with significantly better OS.

Conclusion: Platinum-doublet chemotherapy as a second-line therapy may prolong survival in unresectable stage III NSCLC patients following platinum-based chemoradiotherapy. Thus, re-administration of platinum agents may be a promising treatment for unresectable stage III NSCLC treated with platinum-based chemoradiotherapy.

Keywords: Cytotoxic chemotherapy, Platinum-based chemotherapy, Second-line setting, Single-agent chemotherapy, Survival

*Correspondence: h.kenmotsu@scchr.jp
1 Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagazumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
Full list of author information is available at the end of the article

Background

Lung cancer is the leading cause of cancer-related deaths worldwide. Approximately one-third of patients with non-small-cell lung cancer (NSCLC) present with locally advanced nonmetastatic disease equivalent to...
stage III disease at the time of diagnosis [1]. Platinum-based chemoradiotherapy (CRT) with curative intent is the standard treatment modality for patients with unresectable stage III NSCLC [2, 3]. However, most patients show disease progression after CRT, with a median progression-free survival (PFS) of 10–21 months [4–7]. Durvalumab, a programmed death-ligand 1 (PD-L1) inhibitor, was recently proven to be effective for consolidation after platinum-based CRT and thus was approved as a new standard therapy for unresectable stage III NSCLC. However, many patients still show disease progression, with a 12-month PFS rate of approximately 50–60%, and consequently need second-line treatment [8, 9].

Non-platinum cytotoxic single-agent chemotherapy (e.g., docetaxel or pemetrexed) is currently one of the standard treatments in the second-line setting after first-line platinum-based chemotherapy for advanced NSCLC patients not harboring oncogenic drivers, such as mutations in the epidermal growth factor receptor (EGFR) gene or translocations of the anaplastic lymphoma kinase gene. However, patients treated with single-agent chemotherapy as a second-line treatment still have a poor prognosis, with a response rate of <10% and a median survival of only 6–8 months [10–12].

A pooled analysis of 10 studies on patients with advanced NSCLC who received platinum rechallenge showed that the objective response rate (ORR) to platinum doublets as a second-line therapy was 27.5%, with a median PFS of 3.9 months and a median overall survival (OS) of 8.7 months [13]. These results suggest that platinum doublets as subsequent chemotherapy may be an effective treatment option. Given that the previous studies mostly included patients with stage IV disease, there is limited data on the efficacy of subsequent platinum-based chemotherapy for relapsed stage III NSCLC patients previously treated with platinum-based CRT. Therefore, this study aimed to evaluate the efficacy of platinum-doublet chemotherapy as a second-line treatment for patients with unresectable stage III NSCLC previously treated with platinum-based CRT.

Methods
Study design and patients
This was a retrospective study on unresectable stage III NSCLC patients treated with cytotoxic chemotherapy following platinum-based CRT, registered in the Japanese Joint Committee of Lung Cancer Registry (JJCLCR) database. The JJCLCR has gathered the medical records of lung cancer patients from 314 Japanese educational institutions. The registry was opened between January 1, 2012, and December 31, 2012, and follow-up was completed on April 30, 2016. Participating institutions performed registration by accessing the website set up by the JJCLCR, as described in the registry survey [14].

The inclusion criteria for the registry were (1) pathological or cytological diagnosis of any type of lung cancer at a participating institution and (2) confirmation of diagnosis between January 1, 2012, and December 31, 2012. The staging was based on the Union for International Cancer Control version 7 [15], and the disease stage was assigned based on the findings of plain chest radiography, computed tomography (CT) of the chest and abdomen, positron emission tomography or bone scintigraphy, and CT or magnetic resonance imaging of the cranium.

The inclusion criteria for this retrospective cohort study were as follows: clinical stage IIIA or IIIB NSCLC, treatment with platinum (carboplatin or cisplatin)-based concurrent CRT as a first-line therapy, and cytotoxic chemotherapy administered as second-line therapy. We excluded patients harboring EGFR mutations and those receiving EGFR-tyrosine kinase inhibitors, such as gefitinib and erlotinib, as a second-line chemotherapy regardless of EGFR mutation status. Patients treated with chemotherapy including bevacizumab and non-platinum doublets were also excluded.

The included patients were divided into two groups according to the second-line chemotherapy regimen. The platinum group involved patients treated with platinum-doublet chemotherapy, while the non-platinum group involved those treated with non-platinum single-agent chemotherapy. The registry followed the ethical guidelines for epidemiologic studies. This study was approved by the Institutional Review Board of Osaka University Medical Hospital, where the registry office is located. Because this was a retrospective study, patient consent was waived, and anonymity was ensured.

Data collection and response evaluation
Data on age, sex, smoking status, the existence of respiratory comorbidities, Eastern Cooperative Oncology Group performance status (ECOG PS), histology, clinical stage at the start of CRT, type of platinum agent and radiation dose used in the first-line CRT, response to CRT, and duration from the start of the first-line CRT to the date of starting second-line chemotherapy were extracted from the master database. Clinicopathological profiles, OS, and tumor response were evaluated. The tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [16].

Statistical analyses
Patient characteristics were compared both descriptively and using Fisher’s exact test for categorical variables and the Mann–Whitney U test for continuous variables. OS was measured as the interval between the start of...
second-line chemotherapy and death or censored at the last follow-up date. Survival curves were plotted using the Kaplan–Meier method and compared using standard log-rank tests. Univariate and multivariate analyses were performed using Cox proportional hazard models to calculate the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) and to examine differences with respect to OS from the start of second-line chemotherapy in each group. Variables included age, sex, ECOG PS, smoking status, histology, clinical stage, the existence of respiratory comorbidity, tumor response to first-line therapy, and the duration from the start of the first-line CRT to the start of the second-line chemotherapy. The median value was used as a cut-off for the duration from the start of the first-line CRT to the start of the second-line chemotherapy. Information on the reasons for the termination of the first-line CRT was not available in this registry. Thus, subgroup analyses stratified by the duration from the start of the first-line CRT to the start of the second-line chemotherapy were performed, with a cut-off of 3 months to exclude the effect of patients terminating first-line platinum-based therapy early for reasons other than disease progression. All statistical analyses were performed using the SPSS software program, version 23.0 (SPSS Inc., Chicago, Illinois) for Windows. P-values (two-sided) less than 0.05 were considered statistically significant.

Results
Patient characteristics
Of the 320 patients included, 119 (37%) and 201 (63%) patients received platinum-doublet chemotherapy (platinum group) and single-agent chemotherapy (non-platinum group) in the second-line setting, respectively (Fig. 1). The median age was 64 years, 87% of the patients were male, and 94% were current or former smokers. Approximately 40% of patients had respiratory comorbidities, including pulmonary emphysema in 102 (32.5%) and interstitial lung disease in 14 (4%) patients. The most common histological types were adenocarcinoma and squamous cell carcinoma. The characteristics of the patients at the start of platinum-based concurrent CRT are shown in Table 1. There were no significant between-group differences in clinicopathological characteristics, such as age, sex, smoking status, respiratory comorbidity, and ECOG PS. There were also no significant differences in the type of platinum agents or radiation doses used for first-line platinum-based CRT (Table 2). The ORR of first-line CRT was not significantly different between the two groups (65.5% in the platinum group vs. 68.7% in the non-platinum group, \( p = 0.62 \)). The median time from the start of the first-line CRT to the start of the second-line chemotherapy was 8.6 months (range, 0.5–46.2 months). The interval between first-line CRT and second-line chemotherapy was significantly shorter in the platinum group than in the non-platinum group (median time: 6.6 vs. 8.7 months, \( p < 0.01 \)). The interval was < 3 months in 26% of patients in the platinum group and 4.5% of those in the non-platinum group.

Survival outcomes
At the time of data cut-off (April 30, 2016), the median follow-up duration from the start of second-line chemotherapy for censored cases was 14.0 months (range,
Of the 320 patients, 198 (61.8%) had died by the time of data cut-off. For the entire cohort, the median OS from the start of second-line chemotherapy was 12.5 months (95% CI, 10.8–14.2 months). The platinum group showed significantly better OS than the non-platinum group did (median OS: 21.5 vs. 10.5 months, HR: 0.54, 95% CI: 0.40–0.73, \( p < 0.001 \); Fig. 2). The 12-, 24-, and 36-month OS rates were 68.2%, 39.4%, and 33.4% in the platinum group and 39.3%, 23.6%, and 15.7% in the non-platinum group, respectively. OS from the start of the first-line CRT was also significantly longer in the platinum group than in the non-platinum group (median OS: 34.9 vs. 21.8 months, HR: 0.58, 95% CI: 0.43–0.79, \( p = 0.001 \)).

The median time interval between the start of CRT and the start of second-line chemotherapy was 8.6 months. With 8.6 months as the cut-off value, the platinum group showed significantly better OS than the non-platinum group (median OS: 21.5 vs. 8.5 months, HR: 0.38, 95% CI: 0.24–0.58, \( p < 0.001 \); Fig. 3A) in patients with an interval of < 8.6 months. However, there was no significant difference in OS from the start of CRT between the platinum and non-platinum groups (median OS: 20.5 vs. 12.5 months, HR: 0.69, 95% CI: 0.44–1.08, \( p = 0.09 \); Fig. 3B) in the subgroup with an interval of \( \geq 8.6 \) months.

Univariate analysis identified platinum-doublet chemotherapy in the second-line setting, female sex, and clinical stage IIIA as significant predictors of better OS. Multivariate analysis showed that platinum-doublet chemotherapy as second-line therapy (HR: 0.53, 95% CI: 0.39–0.73, \( p < 0.01 \)), female sex (HR: 0.55, 95% CI: 0.34–0.88, \( p = 0.01 \)), clinical stage IIIA (HR: 0.67, 95% CI: 0.50–0.90, \( p < 0.01 \)), and an interval of \( \geq 8.6 \) months from the start of the first-line CRT to the start of second-line chemotherapy (HR: 0.74, 95% CI: 0.55–0.997, \( p = 0.048 \)) were associated with significantly better OS from the start of second-line chemotherapy (Table 3).

### Table 1 Patient characteristics at the start of first-line chemoradiotherapy

| Characteristics | Platinum group | non-Platinum group | \( P \)-value |
|-----------------|----------------|--------------------|--------------|
| Overall         | n 119, % 55.5 | n 201, % 62.7 |              |
| Age (years)     |               |                    |              |
| Median (range)  | n 63, (33—81) | n 65, (44—80) |              |
| \( \geq 75 \)    | n 8, 6.7      | n 15, 7.4          | 1.0          |
| \(< 75 \)       | n 111, 93.3   | n 186, 92.5        |              |
| Sex             |               |                    |              |
| Female          | n 18, 15.1    | n 25, 12.4         | 0.50         |
| Male            | n 101, 84.9   | n 176, 87.6        |              |
| Smoking status  |               |                    |              |
| Current         | n 68, 57.1    | n 115, 57.2        | 1.0          |
| Former          | n 44, 37.0    | n 75, 37.3         |              |
| Never           | n 7, 5.9      | n 11, 5.5          |              |
| Respiratory comorbidity | | | |
| Yes             | n 43, 36.1    | n 78, 38.8         | 0.72         |
| No              | n 76, 63.9    | n 123, 61.2        |              |
| ECOG PS         |               |                    |              |
| 0               | n 66, 55.5    | n 100, 49.8        | 0.41         |
| 1               | n 49, 41.2    | n 97, 48.3         |              |
| 2               | n 4, 3.4      | n 4, 2.0           |              |
| Histology       |               |                    |              |
| Adenocarcinoma  | n 51, 42.9    | n 85, 42.3         | 0.99         |
| Squamous cell carcinoma | n 53, 44.5 | n 89, 44.3   |          |
| Other           | n 15, 12.6    | n 27, 13.4         |              |
| Clinical stage (UICC-TNM classification, 7th edition) | | | |
| IIIA            | n 60, 50.4    | n 95, 47.3         | 0.64         |
| IIIB            | n 59, 49.6    | n 106, 52.7        |              |

ECOG PS Eastern Cooperative Oncology Group performance status, UICC Union for International Cancer Control

All \( P \) values were calculated using the Fisher’s exact test.
The ORR of the second-line chemotherapy, assessed according to the RECIST, was significantly higher in the platinum group than in the non-platinum group (26.1% vs. 7.0%; \( p < 0.001 \)). In total, 67 (56.3%) patients in the platinum group and 101 (50.2%) in the non-platinum group received subsequent chemotherapy after

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### Table 2  Treatment and efficacies of first-line chemoradiotherapy

|                        | Overall   | Platinum group | non-Platinum group | \( P \)-value |
|------------------------|-----------|----------------|--------------------|--------------|
|                        | \( n = 320 \) | \( n = 119 \)  | \( n = 201 \)      |              |
| Platinum               |           |                |                    |              |
| CDDP                   | 189       | 68             | 121                | 0.21         |
| CBDOA                  | 129       | 49             | 80                 |              |
| Unknown                | 2         | 2              | 0                  |              |
| Radiation dose         |           |                |                    |              |
| \( \geq 60 \text{ Gy} \) | 271       | 96             | 175                | 0.10         |
| \(< 60 \text{ Gy} \)   | 47        | 23             | 24                 |              |
| Unknown                | 2         | 0              | 2                  |              |
| Response to chemoradiotherapy |   |                |                    |              |
| ORR (%)                | 67.5      | 65.5           | 68.7               | 0.62         |
| Duration from the start of first-line therapy to the start of second-line therapy | | | | |
| Median (range), (months) | 8.6 (0.5–46.2) | 6.6 (0.5–46.2) | 8.7 (0.5–38.0) | <0.01 |

CDDP cisplatin, CBDOA carboplatin, ORR objective response rate, Gy, gray

\( P \) values were calculated using the Fisher’s exact test for categorical variables and with Mann–Whitney U test for continuous variables.

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**Fig. 2** Kaplan–Meier curves of overall survival from the beginning of second-line chemotherapy until death or the last follow-up in patients treated with platinum-based chemotherapy and single agent in second-line setting. Tick marks represent data censored at the last time the patient was known to be alive. Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.
second-line chemotherapy. OS from the start of the third-line treatment was not significantly different between the platinum and the non-platinum groups (median OS: 12.7 vs. 8.7 months, HR: 0.78, 95% CI: 0.52–1.17, \(p = 0.24\)).

**Survival outcome in patients with an interval of ≥ 3 months between first-line CRT and second-line chemotherapy**

Among patients with an interval of ≥ 3 months between first-line CRT and second-line chemotherapy, the platinum group showed significantly better OS than the non-platinum group did (median OS: 20.5 vs. 10.5 months, HR: 0.57, 95% CI: 0.40–0.80, \(p = 0.001\)). The 12-month OS rate was 70.5% in the platinum group and 38.7% in the non-platinum group. The ORR of second-line chemotherapy, assessed according to the RECIST, was significantly higher in the platinum group than in the non-platinum group (23.9% vs. 7.3%; \(p < 0.001\)).

**Discussion**

The optimal regimen for patients with relapsed NSCLC previously treated with platinum-based CRT remains unclear. This retrospective cohort study found that platinum-doublet chemotherapy was an effective treatment modality in the second-line setting in patients with unresectable stage III NSCLC previously treated with platinum-based CRT, yielding a significantly good response and survival.

These findings were consistent with the findings from previous studies on small-cell lung cancer (SCLC) and ovarian cancer. Re-administration of platinum-based agents with etoposide and irinotecan prolonged the OS in patients with platinum-sensitive relapsed SCLC with a treatment-free interval of ≥ 90 days [17]. The treatment-free interval has been reported as a relevant prognostic factor and an important predictor of the probability of response to second-line chemotherapy in patients with SCLC [18]. In patients with ovarian cancer, a platinum-free interval of ≥ 6 months has been the most widely used and accepted clinical surrogate marker to predict chemotherapy response and prognosis [19–22]. Thus, in both SCLC and ovarian cancer, the length of the platinum-free interval is considered associated with platinum sensitivity and good prognosis. In contrast, this study did not show a contribution
of the platinum-free interval to the efficacy of platinum re-administration. In advanced NSCLC patients treated with a platinum agent in the second-line setting, the platinum-free interval was not associated with a survival benefit [23–25]. Arrieta et al. reported that a treatment-free interval of $\geq 9$ months was associated with a long PFS in patients receiving platinum-doublet chemotherapy in the second-line setting [26]. Therefore, the impact of the platinum-free interval on the efficacy of platinum re-administration is still unclear. However, a long platinum-free interval may be an independent prognostic factor rather than an indicator of platinum sensitivity in patients with stage III NSCLC. Larger studies are warranted to evaluate the association between platinum sensitivity and the platinum-free interval in patients with stage III NSCLC.

There have been few studies on second-line treatment after platinum-based CRT in patients with stage III NSCLC. In 10 studies suggesting the efficacy of platinum-based therapy as a second-line treatment [13], 0–66.7% of all patients had stage III NSCLC and 0–36.7% of all patients had been treated with CRT [23–32]. With respect to patients with stage III NSCLC previously treated with platinum-based CRT, only a small retrospective single-institution study showed that the efficacy of platinum-based chemotherapy was equivalent to that of docetaxel in relapsed patients, with an ORR of 31.2% (5/16) and an OS of 28.0 months [33]. There was no

| Variables                                      | Univariate HR (95% CI) | p-value | Multivariate HR (95% CI) | p-value |
|-----------------------------------------------|------------------------|---------|--------------------------|---------|
| Second-line chemotherapy                      |                        |         |                          |         |
| Platinum-doublet vs Single agent              | 0.54 (0.40 to 0.73)    | <0.01   | 0.53 (0.39 to 0.73)      | <0.01   |
| Age                                           |                        |         |                          |         |
| $\geq 75$ years vs $< 75$ years                | 0.79 (0.45 to 1.34)    | 0.41    | 0.82 (0.45 to 1.49)      | 0.51    |
| Sex                                           |                        |         |                          |         |
| Female vs Male                                 | 0.57 (0.36 to 0.91)    | 0.02    | 0.55 (0.34 to 0.88)      | 0.01    |
| ECOG PS                                       |                        |         |                          |         |
| 0/1 vs 2                                       | 2.15 (0.53 to 8.65)    | 0.28    | 2.59 (0.63 to 10.6)      | 0.19    |
| Smoking status                                 |                        |         |                          |         |
| Never or former smoker vs Current smoker       | 0.84 (0.63 to 1.12)    | 0.23    | 0.94 (0.70 to 1.27)      | 0.70    |
| Histology                                      |                        |         |                          |         |
| Adenocarcinoma vs Non-adenocarcinoma           | 0.98 (0.73 to 1.30)    | 0.87    | 1.14 (0.85 to 1.54)      | 0.38    |
| Clinical stage                                 |                        |         |                          |         |
| IIIA vs IIIB                                   | 0.62 (0.47 to 0.82)    | <0.01   | 0.67 (0.50 to 0.90)      | <0.01   |
| Respiratory comorbidity                        |                        |         |                          |         |
| No vs Yes                                      | 0.95 (0.71 to 1.27)    | 0.95    | 0.95 (0.70 to 1.29)      | 0.75    |
| Response to first-line chemoradiotherapy       |                        |         |                          |         |
| CR or PR vs not CR nor PR                      | 0.94 (0.70 to 1.28)    | 0.71    | 0.94 (0.68 to 1.30)      | 0.72    |
| Duration from the start of first-line therapy to second-line therapy | | | | |
| $\geq 8.6$ months vs $< 8.6$ months           | 0.82 (0.62 to 1.08)    | 0.16    | 0.74 (0.55 to 0.997)     | 0.048   |

CI: confidence interval, CR: complete response, ECOG PS: Eastern Cooperative Oncology Group performance status, HR: hazard ratio, PR: partial response
difference in patient characteristics such as age, sex, and PS between the two groups in the study, which is consistent with our study. To the best of our knowledge, our study is the largest to evaluate the efficacy of platinum-based chemotherapy in patients with relapsed stage III NSCLC after platinum-based CRT. Our study showed numerically longer survival in stage III NSCLC patients treated with second-line platinum-based CRT (ORR, 26.1%; OS, 21.5 months) than previous reports did, which mostly included stage IV patients (ORR, 27.5%; OS, 8.7 months) [34].

Durvalumab has been recently approved for maintenance therapy following platinum-based CRT in patients with stage III NSCLC with no progression after CRT [8, 9]. However, approximately 30% of patients receiving platinum-based CRT are not eligible for maintenance therapy with durvalumab in the real-world setting [34]. Moreover, many patients still show disease progression, with a 12-month PFS rate of approximately 50–60%, and consequently need a second-line treatment after durvalumab administration [8, 9]. Currently, the combination of platinum-based chemotherapy and PD-L1/PD-1 inhibitors [35–38] or the combination of docetaxel and angiogenesis inhibitors [39, 40] is also one of the options for second-line treatment after CRT. However, whether to use platinum-based chemotherapy or single-agent chemotherapy as a second-line treatment remains a fundamental clinical question even now that CRT followed by durvalumab has become the standard treatment. Therefore, the results of our study can be applied even for patients treated with current standard treatment.

This study has some limitations. First, because the data were retrospectively extracted from a registry and not from clinical trials, assessments were probably incomplete and not performed at fixed intervals. Second, this registry did not contain data on the date of disease progression, patient characteristics at the start of second-line chemotherapy, and subsequent cancer therapies. Although it was difficult to fully exclude selection bias, there was no difference in several recognized prognostic factors between the platinum and non-platinum groups in our study as well as in previous studies. These factors should be considered in future research by propensity score matching or other means. Third, details of chemotherapy, including types of agents, treatment cycles, and dosage at each stage, were also unknown. According to the Japanese guidelines, cisplatin plus docetaxel, carboplatin plus paclitaxel, cisplatin plus vinorelbine, and cisplatin plus S-1 are frequently used with concurrent radiotherapy for the first-line treatment of stage III NSCLC patients in the real-world setting. There are no significant differences in the effectiveness of these regimens [34]. Fourth, because there was no information about the reasons for the termination of the first-line therapy, we did not know the number of discontinuations due to disease progression and adverse events. In our study, the interval between first-line CRT and second-line chemotherapy was significantly shorter in the platinum group than in the non-platinum group, but the OS was reversed. The reasons for the shorter interval between first-line CRT and second-line chemotherapy in the platinum group may include not only disease progression but also discontinuation due to adverse events and consolidation therapy counted as a second-line therapy. Therefore, we analyzed subgroup with a duration of ≥3 months from the first-line CRT to second-line chemotherapy to exclude as many patients as possible whose platinum-based CRT was terminated prematurely due to adverse events or because of consolidation chemotherapy counted as a second-line chemotherapy. The analysis of this subgroup also showed that the platinum group had significantly better OS than the non-platinum group.

Conclusions

Platinum-doublet chemotherapy in the second-line setting yields significantly longer survival than single-agent chemotherapy in patients with unresectable stage III NSCLC previously treated with platinum-based CRT. Given the lack of standardized second-line treatments for stage III NSCLC patients showing relapse after platinum-based CRT, our results indicate that platinum re-administration is a promising treatment option for these patients. Although durvalumab maintenance therapy after platinum-based CRT is the current standard, our results are still meaningful for patients receiving durvalumab.

Abbreviations

CI: Confidence intervals; CRT: Chemoradiotherapy; CT: Computed tomography; ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR: Epidermal growth factor receptor; HRs: Hazard ratios; JJCCLCR: Japanese Joint Committee of Lung Cancer Registry; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; SCLC: Small-cell lung cancer.

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Authors’ contributions

E Miyawaki was a major contributor in conception and writing the manuscript. HK contributed conceptualization and writing. YS contributed data curation and supervision. IS, TS, KTakaya, AI, IO, KK, KTakahara, NY, TK, HY, and HD contributed substantially revised the work. EMiyawaki contributed formal analysis. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and analyzed during the current study are not publicly available due to participants of this study did not agree for their data to be shared publicly but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The registry followed the ethical guidelines for epidemiologic studies. This study was approved by the Institutional Review Board of Osaka University Medical Hospital, where the registry office is located. The Institutional Review Board of Osaka University Medical Hospital waived patient consent because this was a retrospective study and anonymity was secured.

Consent for publication
As this was a retrospective study, patient consent was waived, and anonymity was ensured.

Competing interests
HK reports grants and personal fees from Chugai Pharmaceutical Co., Ltd.; personal fees from Ono Pharmaceutical Co., Ltd.; personal fees from Boehringer Ingelheim; personal fees from Eli Lilly & K.K; personal fees from Kyowa Hakko Kirin Co., Ltd.; personal fees from Bristol-Myers Squibb, personal fees from MSD; grants and personal fees from Novartis Pharma K.K.; grants and personal fees from Daiichi-Sankyo Co., Ltd.; grants and personal fees from AstraZeneca K.K.; personal fees from Pfizer; and personal fees from Taiho Pharma, outside the submitted work. YS reports grants from Shionogi & Co., Ltd.; and ISHIHARA SANGYO KAISHA, LTD., outside the submitted work. IK reports personal fees from Nippon Boehringer Ingelheim, and grants and personal fees from Chugai, personal fees from Astra Zeneca, grants and personal fees from Daiichi-Sankyo, grants and personal fees from Ono, personal fees from Bristol-Myers Squibb, and grants and personal fees from Taiho, outside the submitted work. TS reports personal fees from Astra Zeneca, Chugai Pharmaceutical, Novartis, Taiho Pharma, Daiichi-Sankyo, Oho Pharmaceutical, Bristol-Myers Squibb, Nippon Kayaku, and Pfizer and grants and personal fees from Boehringer Ingelheim, and MSD, outside the submitted work. KTakaya reports personal fees from Eli Lilly Co., personal fees from Ono Pharmaceutical Co., personal fees from Astra Zeneca, personal fees from Chugai-Roche Co., personal fees from Boehringer-Ingelheim Co., personal fees from MSD Co., personal fees from Daiichi-Sankyo Co., grants from Chugai-Roche Co., grants from Boehringer-Ingelheim Co., and grants from Ono Pharmaceutical Co., outside the submitted work. AI reports personal fees from Astra Zeneca, Eli Lilly, Chugai, Daiichi-Sankyo, Boehringer Ingelheim, and Nippon Kayaku, outside the submitted work. IO reports grants from Boehringer Ingelheim, during the conduct of the study; grants and personal fees from AstraZeneca, grants and personal fees from Taiho Pharmaceutical, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Ono Pharmaceutical, grants and personal fees from MSD Oncology, and grants and personal fees from Lilly, grants from Astellas Pharma, and grants and personal fees from Bristol-Myers Squibb, grants from Novartis, grants and personal fees from Eli Lilly Japan K.K., personal fees from Pfizer, and personal fees from Abbvie, outside the submitted work. KK reports personal fees from AstraZeneca K.K., personal fees from Eli Lilly Japan K.K., personal fees from Novartis International AG, personal fees from Taiho Pharmaceutical Co., Ltd., personal fees from Chugai Pharmaceutical Co., Ltd., personal fees from Pfizer Japan Inc., personal fees from Ono Pharmaceutical Co., Ltd., personal fees from Bristol-Myers Squibb K.K., personal fees from MSD K.K., personal fees from Boehringer Ingelheim Co., Ltd., personal fees from Daiichi Sankyo Co., Ltd., grants from TEIJIN Pharma Limited, grants from Pfizer Japan Inc., grants from SHIONOGI & Co., Ltd., grants from Boehringer Ingelheim Co., Ltd., grants from Nippon Kayaku Co., Ltd., grants from Taiho Pharmaceutical Co., Ltd., grants from Ono Pharmaceutical Co., Ltd., grants from KYORIN Pharmaceutical Co., Ltd., grants from MSD K.K., grants from Chugai Pharmaceutical Co., Ltd., grants from Bristol-Myers Squibb K.K., grants from Merck Biopharma Co., Ltd., grants from Takeda Pharmaceutical Co., Ltd., grants from Daiichi Sankyo Co., Ltd., outside the submitted work. NY reports grants and personal fees from MSD K.K., grants and personal fees from Astra Zeneca, grants and personal fees from ONO PHARMACEUTICAL CO., LTD., personal fees from Thermo Fisher Scientific, grants and personal fees from DAICHI SANKYO CO., LTD., grants and personal fees from TAIHO PHARMACEUTICAL CO., LTD., grants and personal fees from Takeda Pharmaceutical Co., LTD., grants and personal fees from Chugai Pharmaceutical Co., LTD., grants and personal fees from Eli Lilly Japan K.K., grants and personal fees from Boehringer-Ingelheim, grants and personal fees from Novartis, grants and personal fees from Pfizer Inc., personal fees from Bristol-Myers Squibb, personal fees from Life Technologies Japan Ltd., personal fees from NIPPON KAYAKU, personal fees from Merk Biopharma, grants from Astellas Pharma Inc., grants from TSUMURA & CO., grants from SHIONOGI Co., Ltd., grants from AbbVie GK., grants from Amgen Inc., grants from KYORIN Pharmaceutical Co., Ltd., grants from Eisai Co., Ltd., grants from TERUMO CORPORATION, grants from Toppan Printing Co., Ltd., grants from TOSOH, outside the submitted work. TK reports grants and personal fees from Chugai Pharmaceutical Co., Ltd., grants from AstraZeneca K.K., grants from Eli Lilly Japan K.K., grants from Ono Pharmaceutical Co., Ltd., grants from Taiho Pharmaceutical Co., Ltd., personal fees from Nippon Boehringer Ingelheim Co., Ltd., outside the submitted work. EMiyaw, KTakaha, EMiyao, IF, and HD have nothing to disclose.

Author details
1 Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonomakaguko, Nagaizumi-cho, Suntogun, Shizuoka 411-8777, Japan. 2 Department of General Thoracic Surgery, Osaka University Graduate School of Medicine, Osaka, Japan 565-0871, Japan. 3 Department of Medical Oncology, Faculty of Medicine, University of Tsukuba, Tsukuba 305-8576, Japan. 4 Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo 113-8431, Japan. 5 Department of Pulmonary Medicine, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan. 6 Department of Palliative Medicine, Tokoh University School of Medicine, Miyagi 980-8574, Japan. 7 Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan. 8 Department of Allergy and Respiratory Medicine, Okayama University Hospital, Okayama 700-8558, Japan. 9 Internal Medicine III, Wakayama Medical University, Wakayama 641-8509, Japan. 10 Department of Respiratory Medicine, Graduate School of Medicine, Osaka Metropolitan University, Osaka 545-8586, Japan. 11 Department of Mathematics, Tokyo University of Science, Tokyo 162-8601, Japan. 12 Department of General Thoracic Surgery, Graduate School of Medicine, Chiba University, Chiba 260-8877, Japan. 13 Department of Thoracic Surgery, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan.

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References
1. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemo-therapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28:2181–90.
2. Yoon SM, Shaikh T, Hallman M. Therapeutic management options for stage III non-small cell lung cancer. World J Clin Oncol. 2017;8:1–20.
3. Majem M, Hernández-Hernández J, Hernando-Tranchos, Rodríguez de Dios N, Sotoca A, Trujillo-Reyes JC, et al. Multidisciplinary consensus state-ment on the clinical management of patients with stage III non-small cell lung cancer. Clin Transl Oncol. 2020;22:21–36.
4. Ozzelik M, Korkmaz T, Odbas H, Gemici C, Ercleop O, Yuksel S, et al. Comparison of efficacy and safety of three different chemotherapy regimens delivered with concomitant radiotherapy in inoperable stage III non-small cell lung cancer patients. Tumour Biol. 2016;37:8901–7.
5. Liew MS, Sai J, Starmans MH, Tafehri A, Harris S, Feigen M, et al. Comparison of toxicity and outcomes of concurrent radiotherapy with carboplatin/paclitaxel or cisplatin/etoposide in stage III inoperable non-small cell lung cancer. Cancer Med. 2013;2:916–24.
6. Eberhardt WE. Concurrent chemoradiotherapy in stage III non-small cell lung cancer: what is the best regimen? J Clin Oncol. 2015;33:532–3.
7. Senan S, Brade A, Wang LH, Vansteenkiste J, Dakhil S, Biema B, et al. PROCLAIM: randomized Phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. J Clin Oncol. 2016;34:953–62.
8. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemotherapy in Stage III non-small-cell lung cancer. N Engl J Med. 2017;377:1919–29.

9. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018;379:2342–50.

10. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol. 2000;18:2354–62.

11. Shepherd FA, Dancey J, Ramalho R, Mattson K, Gralla R, O’Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000;18:2095–103.

12. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non–small-cell lung cancer previously treated with chemotherapy. J Clin Oncol. 2004;22:1589–97.

13. Sekine I, Shintani Y, Shukuya T, Takayama K, Inoue A, Okamoto I, et al. A Japanese lung cancer registry study on demographics and treatment modalities in medically treated patients. Cancer Sci. 2020;111:1685–91.

14. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol. 2007;2:706–14.

15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–16.

16. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol. 2007;2:706–14.

17. Arzidzoni A, Tiseo M, Boni L. Validation of standard definition of sensitive versus refractory relapsed small cell lung cancer: A pooled analysis of topotecan second-line trials. Eur J Cancer. 2014;50:2211–8.

18. Friedlander M, Trimble E, Tinker A, Alberts D, Avall-Lundqvist E, Brady M, et al. Clinical trials in recurrent ovarian cancer. Int J Gynecol Cancer. 2011;21:771–7.

19. Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet. 2003;361:1099–106.

20. Pfisterer J, Plante M, Vergote I, du Bois A, Hirte H, Lacave AJ, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol. 2004;22:1846–50.

21. Friedlander M, Trimble E, Tinker A, Alberts D, Avall-Lundqvist E, Brady M, et al. Clinical trials in recurrent ovarian cancer. Int J Gynecol Cancer. 2011;21:771–7.

22. Pignata S, Cecere S, du Bois A, Harter P, Heitz F. Treatment of recurrent ovarian cancer. Ann Oncol. 2017;28:viii1–viii2.

23. Arzidzoni A, Tiseo M, Boni L, Vincent AD, Passalacqua R, Buni S, et al. Pemetrexed versus pemetrexed and carboplatin as second-line chemotherapy in advanced non-small-cell lung cancer: results of the GOIRC 02–2006 randomized phase II study and pooled analysis with the NVALT7 trial. J Clin Oncol. 2012;30:4501–7.

24. Metro G, Chian R, Mare M, Giannanni D, Tofanetti FR, Minotti V, et al. Carboplatin plus pemetrexed for platinum-pretreated, advanced non-small cell lung cancer: a retrospective study with pharmacoepidemiologic evaluation. Cancer Chemother Pharmacol. 2011;68:1405–12.

25. Yoh K, Kubota K, Kakinuma R, Ohmatsu H, Goto K, Nishi S, et al. Phase II trial of carboplatin and paclitaxel in non-small cell lung cancer patients previously treated with chemotherapy. Lung Cancer. 2007;58:73–9.

26. Arrieta O, Villareal-Garza C, Pachuca D, Michel Ortega RM, Martinez-Barerra L, Flores-Estrada D, et al. High response of second-line chemotherapy with pemetrexed or gemcitabine combined with carboplatin in patients with non–small-cell lung cancer experiencing progression following 6 months after concluding platinum-based chemotherapy. Med Oncol. 2011;28:300–6.

27. Palis AG, Ageidkai S, Ageidkaiou A, Varthalis I, Syrigos K, Kenteropodits N, et al. Randomized phase III study of the docetaxel/carboplatin combination versus docetaxel single-agent as second line treatment for patients with advanced/metastatic non-small cell lung cancer. BMC Cancer. 2010;10:633.

28. Kim HS, Lee GW, Kim JH, Kim HY, Kwon JH, Song HH, et al. Progression-free survival with durvalumab in patients with advanced NSCLC. Eur J Cancer. 2020;130:107–18.

29. Zhang GZ, Jiao SC, Meng ZT. Pemetrexed plus cisplatin/carboplatin in previously treated locally advanced or metastatic non-small cell lung cancer patients. J Exp Clin Oncol. 2010;29:8.

30. Numico G, Colantonio I, Gasco M, Bertelli G, Garone O, Occelli M, et al. Carboplatin and weekly paclitaxel in non-small cell lung cancer patients unfit for or pretreated with chemotherapy. Anticancer Res. 2005;25:5255–9.

31. Seto T, Takezaki Y, Nakamura H, Takeda K, Inoue F, Sembia H, et al. Doublet regimen of cisplatin plus docetaxel for second-line chemotherapy after prior therapy with cisplatin and irinotecan for non-small cell lung cancer: a phase II study. Int J Clin Oncol. 2004;9:378–82.

32. Stacpoole GS, Rigatos S, Malamos NA. Paclitaxel combined with cisplatin as second-line treatment in patients with advanced non-small cell lung cancers refractory to cis-platin. Oncol Rep. 1996;9:79–80.

33. Imai H, Kaia K, Moro K, Ono A, Akamatsu H, Taira T, et al. Comparison of platinum combination re-challenge therapy and docetaxel monotherapy in non-small cell lung cancer patients previously treated with platinum-based chemoradiotherapy. Springerplus. 2015;4:152.

34. Horinouchi H, Atagi S, Olzumi S, Ohashi K, Kato T, Kozuki T, et al. Real-world outcomes of chemotherapeutic regimens for unresectable Stage III non-small cell lung cancer: the SOLUTION study. Cancer Med. 2020;9:6597–608.

35. Gandhi L, Rodriguez-Arbeu D, Gadgil S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378:2078–82.

36. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med. 2018;379:2040–51.

37. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Strzykovskiy D, Nagani N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378:298–310.

38. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HV, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMPower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:924–37.

39. Reck M, Kaiser R, Mellemgaard A, Douillard J-Y, Orlov S, Krzakowski M, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol. 2014;15:13–55.

40. Garon EB, Ciuleanu TE, Arietta O, Prabhshak K, Syrigos KN, Goksel T, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Cancer. 2014;38:665–73.

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