Surgery Today (2019) 49:678–685
https://doi.org/10.1007/s00595-019-01791-z

ORIGINAL ARTICLE

Phase II trial of induction chemotherapy with carboplatin and paclitaxel plus bevacizumab in patients with stage IIIA to IV nonsquamous non-small cell lung cancer

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Received: 7 January 2019 / Accepted: 1 February 2019 / Published online: 2 March 2019

Abstract

Purpose Surgery remains the best curative treatment option for non-small cell lung cancer (NSCLC), but is of benefit only to patients with localized disease. A meta-analysis showed a significant beneficial effect of induction chemotherapy on survival, but there is still no clear evidence. This phase II study was conducted to establish whether induction chemotherapy with carboplatin (CBDCA) and paclitaxel (PTX) plus bevacizumab prior to surgery reduces the risk of progression.

Methods The subjects of this study were 29 patients with treatment-naive nonsquamous NSCLC (clinical stages IIIA to IV). Patients received PTX (200 mg/m^2), CBDCA (area under the curve, 5), and bevacizumab (15 mg/kg) followed by surgery. Chemotherapy was repeated every 3 weeks for up to six cycles.

Results The overall response rate was 72.4%. Of the 29 patients, ten underwent surgery after the induction chemotherapy and complete resection was achieved in 7 (70%). The median progression-free-survival (PFS) time and the 3-year PFS rate were 0.92 years and 16.2%, respectively. The median overall survival (OS) time and the 3-year OS rate were 1.96 years and 44.9%, respectively.

Conclusion Combined modality therapy with surgery after induction chemotherapy with CBDCA and PTX plus bevacizumab is clinically feasible and tolerable for patients with unknown or negative molecular profiles.

Keywords Carboplatin · Paclitaxel · Bevacizumab · Induction chemotherapy · Lung cancer

Introduction

Lung cancer is the leading cause of cancer-related death globally. Surgery remains the best option for a potential cure of non-small cell lung cancer (NSCLC); however, this radical surgery benefits only patients with localized disease and no evidence of mediastinal lymph node involvement or distant metastasis. The best treatment strategy for patients with perioperative advanced NSCLC, including stage III-N2 disease, remains controversial [1, 2].

Adjuvant chemotherapy is now standard treatment for patients with completely resected stage II–III NSCLC. Randomized trials and meta-analyses have shown better survival outcomes when patients are treated with adjuvant or induction chemotherapy and surgery than with surgery alone [3, 4]. Induction chemotherapy has the potential to reduce tumor size, increase its operability, and eradicate micro-metastases. An update of an earlier systematic review [5, 6] and a

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meta-analysis of 15 randomized controlled trials [4] revealed a significant benefit of preoperative chemotherapy on survival, based on an analysis of 2385 patients (hazard ratio = 0.87, $p = 0.007$), with a 13% reduction in the relative risk of death. This represents a 5% improvement in survival at 5 years, from 40 to 45% [4]. Most of the patients who received induction chemotherapy in the randomized trials had clinical stage IB-IIIA tumors (93%), although there were three patients with stage IV tumors. These were predominantly squamous cell carcinomas (50%) or adenocarcinomas (29%), and there is no clear evidence that the beneficial effect of induction chemotherapy on survival was affected by age, sex, performance status, clinical stage, histology, or chemotherapy regimen [4].

Bevacizumab, a humanized monoclonal antibody targeting the vascular endothelial growth factor (VEGF), combined with the standard platinum doublet-based chemotherapy was approved as first-line treatment for NSCLC, based on data from two randomized phase III clinical trials: the open-label Eastern Cooperative Oncology Group (ECOG) 4599 study and the double-blind Avastin in the Lung (AVAiL) BO17704 trial [7, 8]. Chemotherapy plus bevacizumab significantly improved the response rate and extended progression-free survival (PFS) versus a placebo. Moreover, a later meta-analysis indicated that this regimen extended the overall survival (OS) of patients with advanced NSCLC [9], particularly adenocarcinoma. Standard platinum-based chemotherapy combined with bevacizumab chemotherapy thus offers important clinical benefits for patients with advanced nonsquamous NSCLC. Importantly, although an improvement in the response rate was not anticipated a priori since antiangiogenic drugs are not considered to have a cytotoxic effect [10], the addition of bevacizumab resulted in a significant 34.1–35% improvement in the response rate over standard chemotherapy.

We hypothesized that chemotherapy with a higher response rate, such as carboplatin (CBDCA) and paclitaxel (PTX) plus bevacizumab, would have increased potential to reduce tumor size, increase operability, and eradicate micro-metastases. Moreover, because the VGEF blockade will prevent the development of new blood vessels, these agents should inhibit tumor growth. This effect may help prevent adhesion to adjacent tissues or shrink metastatic lymph nodes, thereby simplifying the surgery and exfoliation. We conducted this phase II study to find out if induction chemotherapy with CBDCA + PTX plus bevacizumab followed by surgery reduces the risk of cancer progression in patients with stage IIIA to IV nonsquamous NSCLC.

Methods

Study design

This clinical trial was an open-label, multicenter, single-arm study involving four institutions in Akita, Japan. It was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review boards at each institution, including Akita University Hospital (Permit number: 836), and written informed consent was obtained from each patient before enrollment. This study was registered at the University Hospital Medical Information Network (UMIN) Clinical Trial Registry as UMIN000006809 (http://www.umin.ac.jp/ctr/index.htm).

Patient population

Patients with cytologically or histologically confirmed stage IIIA (including bulky and/or multiple N2 and pm 1,2) to IV nonsquamous NSCLC not amenable to surgical resection or radiation with curative intent were eligible for inclusion in this study. The enrolled patients had disease staged according to the 8th edition of the TNM classification for lung cancer [1]. All participants were chemotherapy/radiation-naïve and > 20 years of age, with an ECOG performance status of 0 to 1 and adequate hematologic, hepatic, and renal function.

Exclusion criteria included CNS metastases with symptoms; a history of thrombotic or hemorrhagic disorders (> 2.5 ml fresh hemoptysis); therapeutic anticoagulation at enrollment; current or recent use of aspirin (325 mg/day); clinically significant cardiovascular disease; medically uncontrolled hypertension; a non-healing wound, ulcer, or bone fracture; palliative radiotherapy for bone lesions outside the thorax within 2 weeks before treatment; surgery within 4 weeks before treatment; and pregnancy or lactation. Patients with tumors invading or abutting major blood vessels (based on assessment by a radiologist and thoracic surgeon) were also excluded. Although guidance about the trial protocol was provided, the expertise of the investigators and radiologists/surgeons was relied upon for establishing tumor location and interpreting scans.

Treatment plan

Eligible patients were given PTX, 200 mg/m^2, intravenously over 3 h; CBDCA, as area under the curve (AUC) of 5, given intravenously over 30 min, after PTX; and bevacizumab, 15 mg/kg given intravenously on day 1. Chemotherapy was repeated every 3 weeks for up to six cycles unless there was evidence of disease progression or unacceptable toxicity.

Toxicities were graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 4.0. Chemotherapy was modified for toxicity and adverse effects as necessary. Within 2 weeks after every second cycle of chemotherapy, patients were re-evaluated for surgery based on physical examination, chest X-ray, CT, PET/CT, electrocardiography, pulmonary function tests, and laboratory tests. Radiographic responses were assessed using RECIST ver 1.1 [11]. The trial allowed for eligible patients to receive radical surgery if the thoracic surgeons and diagnosticians decided the tumor was completely resectable, especially for patients with clinical stage IIIA-bulky and/or multiple N2 tumors.

Restaging

After every two cycles of chemotherapy, all patients underwent restaging based on CT and/or PET/CT. The restaging procedures were performed within 2 weeks to allow for the start of the same or another chemotherapy cycle or the selection of another treatment, including additional irradiation, if resection was not considered possible. Figure 1 summarizes our phase II study schema.

Surgery after induction chemotherapy

Radical surgery was performed within 4–8 weeks after the last chemotherapy. In general, surgery was either lobectomy, bilobectomy, or pneumonectomy, with systematic lymph node dissection. Wedge resection was discouraged. Patients found to have unresectable disease intraoperatively, or whose resection was found to be incomplete after the operation, could receive radiation therapy. Moreover, all patients who underwent surgery were allowed to undergo any adjuvant therapy, and treatment for recurrence was not restricted.

Evaluation and statistical analysis

The primary endpoint of this study was the overall response rate (ORR). Secondary endpoints were the best response rate; the PFS, defined as the time from the treatment initiation day to the date of disease progression; recurrence; death from any cause; OS, defined as the time from the treatment initiation day to death or date when last seen; the maximum tumor response; surgery rate after induction therapy; and toxicity profiles. Tumor responses were assessed every two cycles using chest radiography, CT, and PET/CT.

Briefly, the planned sample size was 29 patients, taking into consideration withdrawals, which were calculated using the Southwest Oncology Group (SWOG)'s one-arm binominal design based on an expected ORR of 35% for CBDCA + PTX plus bevacizumab and a threshold ORR of 15% for CBDCA + PTX. This was based on the results of a randomized phase III trial AVAiL, E4599 [8], with an alpha error of 0.05 (two-side) and 80% statistical power.

The Kaplan–Meier curve method was used to estimate PFS and OS and the log-rank test was used to assess the impact of surgery on PFS and OS. P values were two-sided and considered significant if less than 0.05. Statistical

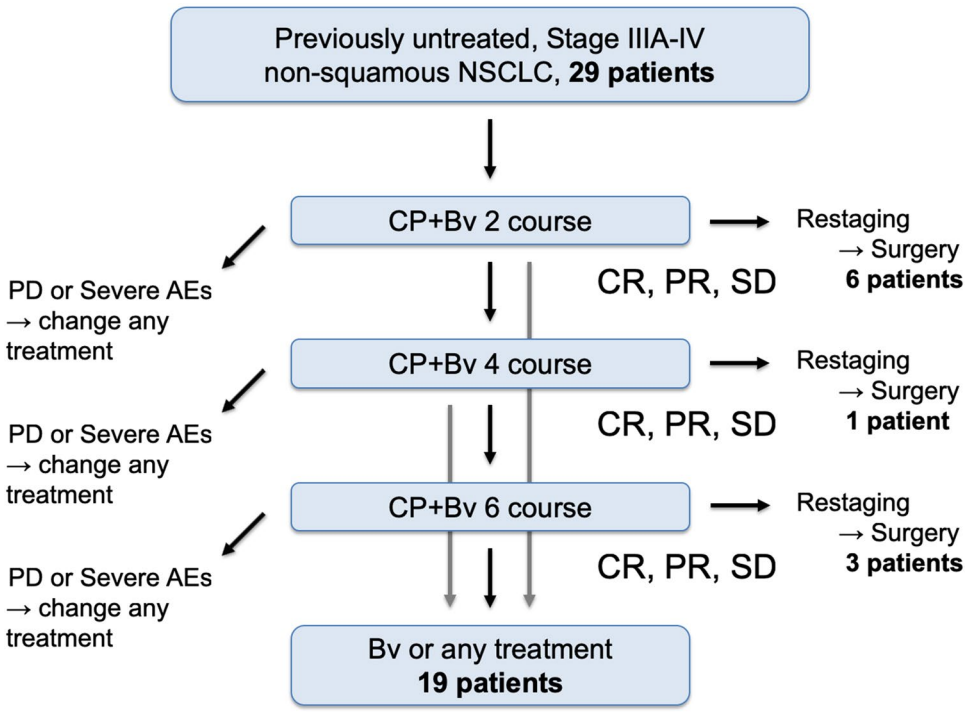

Fig. 1 Study schema. *CP* carboplatin and paclitaxel, *Bv* bevacizumab, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

analysis was performed using Stata 14.0 (StataCorp LP, College Station, TX, USA) and JMP IN 11.0.0 software (SAS Institute, Cary, NC, USA).

Results

Between April, 2012 and October, 2017, a total of 29 patients from four centers were enrolled in this study. Table 1 summarizes their clinical characteristics. Patients received a median of four cycles of CBDCA + PTX plus bevacizumab and the median length of follow-up for all patients was 2.05 years (range, 0.45–4.51 years), as of March 31, 2018.

Table 1 Patient characteristics

No. of patients	29
Age (years)	63.5 ± 9.2
Sex (*n*)	
Male	19
Female	10
Tumor location (*n*)	
RUL	11
RML	0
RLL	7
LUL	8
LLL	2
Multiple	1
Tumor size	
Mean (mm)	42.58 ± 24.29
Range (mm)	10–119
Type (*n*)	
Adeno	29
Clinical stage (*n*)	
IIIA	12
IIIB	4
IIIC	0
IV	13
EGFR mutation site (*n*)	
Del 19	2
L858R	3
Minor	0
Negative/unknown	24
ALK rearrangement	
Positive	1
Negative/unknown	28
PDL1 (22C3)	
> 50%	2
> 1%, < 50%	0
Negative/unknown	27

RUL right upper lobe, *RML* right middle lobe, *RLL* right lower lobe, *LUL* left upper lobe, *LLL* left lower lobe, *adeno* adenocarcinoma

The overall response rate was 72.4%: none of the patients exhibited progressive disease, eight exhibited stable disease, 21 had a partial response, and none had a complete response. Figure 2 shows the greatest percentage change from the baseline in the sum of target lesions for each evaluable patient, based on the relative change of tumor size from the baseline. The median PFS time and 3-year PFS rate for all patients were 0.92 years (95% CI 0.60–1.32; Fig. 3a) and 16.2% (95% CI 4.5–34.5%) and for 19 patients who did not receive surgery, they were 0.92 years (95% CI 0.39–1.11) and 8.51% (95% CI 0.6–30.5%), respectively. For ten patients who underwent surgery, the 3-year recurrence-free survival time and rate were 1.11 years (95% CI 0.47 to not evaluated [N/E]) and 29.6% (95% CI 5.2–60.7%), respectively. The log-rank test showed no significant difference between patients who underwent surgery and those who did not.

The median OS time and 3-year OS rate for all patients were 1.96 years (95% CI 1.26–3.7, Fig. 3b) and 44.9% (95% CI 24.4–63.5%), respectively. These statistics for those patients who did not undergo surgery were 1.76 years (95% CI 1.24–3.7) and 34.4% (95% CI 12.7–57.6%), while those for patients who underwent surgery were 3.02 years (95% CI 0.54 to not evaluated [N/E]) and 64.8% (95% CI 25.3–87.2%), respectively. The log-rank test showed that surgery did not have a significant effect on OS. Moreover, the median OS time for patients with R0 disease alone who underwent surgery was 3.725 years.

Ten patients, being 9 of 16 with clinical stage III disease (56.25%) and 1 with stage IV disease with clinical M1a/pm3, underwent surgery after induction chemotherapy. Table 2 lists the procedures performed. The surgical approach was posterolateral thoracotomy with resection, including lymph node dissection 2a–2. The levels and numbers of the resected lymph nodes were documented. Complete resection was

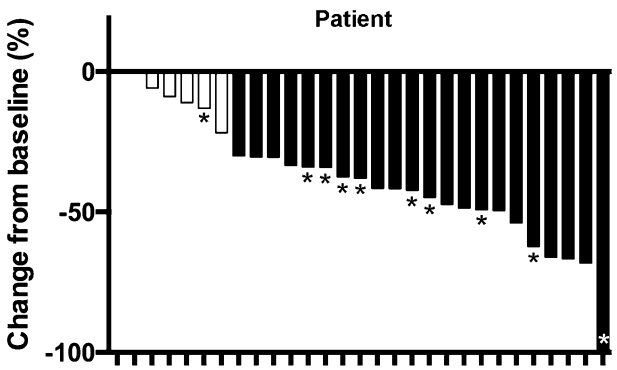

Fig. 2 Waterfall plot showing the greatest percentage change from the baseline in the sum of the target lesions elicited by carboplatin (CBDCA) and paclitaxel (PTX) plus bevacizumab. *Patients who underwent surgery. Percentages were calculated based on the relative change in tumor size from the baseline

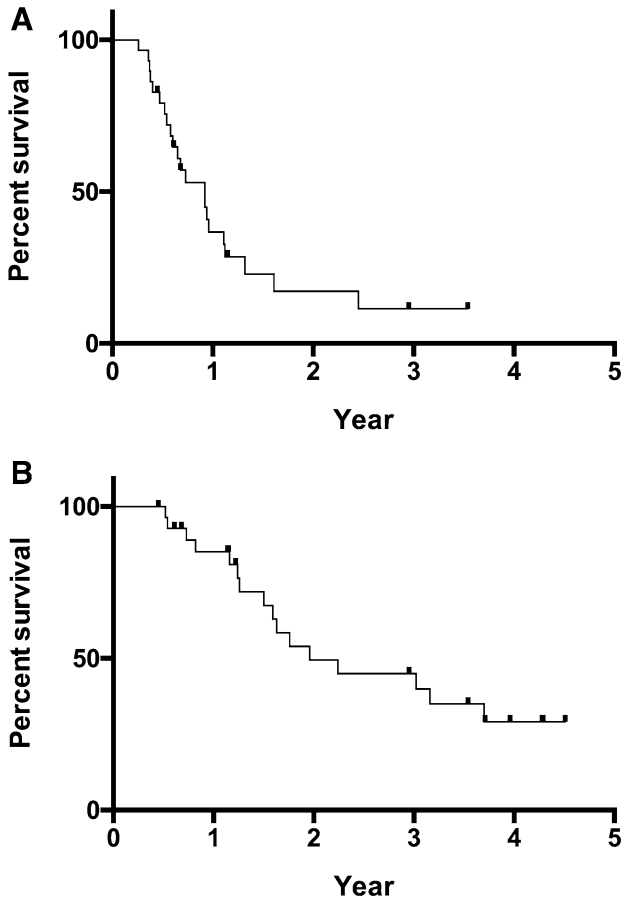

Fig. 3 Progression-free survival (**a**) and overall survival (**b**) of all the patients (median follow-up, 2.05 years)

achieved in seven of these ten patients (70%). The bronchial stump and anastomoses were buttressed with a pericardial flap or intercostal muscle flap in some patients. The 30-day hospital mortality rate was 0% for patients who underwent surgery, but one suffered the surgical complications of stump fistula and empyema after right lower lobectomy, despite an intercostal muscle flap. This patient did not receive any adjuvant chemotherapy and died 4 months after surgery from sepsis arising from the empyema. Another patient had late-onset pneumothorax after discharge and yet another had early onset postoperative empyema but was completely cured by only chest drainage. Two of three patients with R2 disease received radiation therapy for unresectable swollen mediastinal lymph nodes.

Table 3 lists the toxicities. Grade 3 or 4 adverse events (AEs) occurred in 72.4% (21 of 29) of the patients, 18 of whom had grade 3 or 4 neutropenia. Dose modifications were necessary in 20.7% (6) of patients. All patients experienced grade 1 or 2 AEs, particularly anorexia and/or hair loss. Greater pulmonary hemorrhage and GI bleeding were observed in only one patient.

Discussion

This multicenter phase II study conferred with previous reports that the addition of bevacizumab to the CBDCA + PTX regimen improved the response rate for the primary endpoint [7, 9]. Notably, ten patients (9 of 16 with clinical stage III disease (56.25%) and 1 with stage IV disease with clinical M1a/pm3) were able to undergo lobectomy with lymph node dissection after induction chemotherapy, and complete resection R0 was achieved in 7 (70%).

Table 2 Patients who underwent surgery after induction chemotherapy

Age (years)	Sex	Histology	Clinical stage	Cycle no. before	Response/yStage	pStage	Surgery	Complication	Curability	Adjuvant therapy	Survival (y)/DOA
70	F	Adeno	T4N1M0 IIIA	2	PR/IB	IA	LLL	–	R0	UFT	3.02/D
60	F	Adeno	T1cN3M0 IIIB	4	PR/IA	IA	RLL	–	R0***	–	3.16/D
71	M	Adeno	T2aN2M0 IIIA	6	PR/IIIA	IIIA	RUL	–	R2***	RT 60 Gy	1.50/D
59	M	Ad→Sq*	T3N2M0 IIIA	6	PR/IIIA	IA	LUL	–	R0	–	4.29/A
74	F	Adeno	T2bN2M0 IIIA	2	SD/IIA	IV	RLL+	Fistula	R2	–	0.54/D
59	F	Adeno	T1cN1M1a IV	2	SD/IV	IIA**	RUL	–	R0	CP + Bv	3.71/A
52	M	Adeno	T2bN2M0 IIIA	6	PR/IA	IA	LUL	–	R0	–	2.95/A
72	M	Adeno	T2aN2M0 IIIA	3	PR/IIIA	IIIA	RMLL+	Pneumothrax	R2	CP	0.73/D
72	F	Adeno	T3N2M0 IIIA	2	PR/IIB	IA	RUL	–	R0	–	1.14/A
73	M	Adeno	T2aN2M0 IIIA	3	PR/IB	IIB	RUL	Empyema	R0	Bv	0.45/A

adeno adenocarcinoma, *PR* partial response, *SD* stable disease, *LLL* left lower lobe, *RLL* right lower lobe, *LUL* left upper lobe, *RMLL* right middle and lower lobe, *RT* radiotherapy, *CP* carboplatin + paclitaxel, *Bv* bevacizumab, *A* alive, *D* death

*By surgical pathology, **denied pm histologically and diagnosed double primary cancer, ***mediastinal radiotherapy

+Bronchial stump reinforcement

Table 3 Summary of severe (Grade ≥ 3) adverse events and severe adverse events of interest

AE	No. of patients ($n=29$)
Severe (Grade ≥ 3) AE	
Neutropenia	18
Anemia	0
Nausea and vomiting	6
Hypertension	1
Severe AEs of interest	
Bleeding	1
Proteinuria	0
GI perforation	0
Ischemic events and venous thromboembolic events	0
Hemoptysis (including pulmonary hemorrhage)	1

AE adverse events, *GI* gastrointestinal

Thus, induction chemotherapy using CBDCA + PTX plus bevacizumab appears feasible and tolerable.

Radiotherapy provided no added benefit to induction chemotherapy followed by surgery with respect to surgical mortality or toxic effects. Consistent with that finding, one definitive local treatment modality combined with induction chemotherapy is reportedly adequate to treat resectable stage III NSCLC [12]. The fact that trimodality treatment was of no benefit may relate to the high death rate after pneumonectomy, which is mainly attributable to acute respiratory distress syndrome and other respiratory causes. Trimodality treatment may be beneficial if complete resection with lobectomy can be done after chemotherapy and/or radiotherapy, or if mortality from pneumonectomy can be prevented [13]. We also used induction chemotherapy to avoid the need for pneumonectomy in most patients with N1 in the present study. If we can achieve a higher response rate through more effective chemotherapy, the use of one local treatment; namely, definitive surgery, in combination with effective chemotherapy (without radiation) would be sufficient for patients with local advanced NSCLC and should be considered as standard treatment. The CBDCA + PTX plus bevacizumab regimen had a response rate of 72.4% in the present study. This higher response rate could potentially increase the likelihood of complete resection.

According to a recent meta-analysis [9], bevacizumab significantly increases the risk of grade ≥ 3 proteinuria, hypertension, hemorrhagic events, neutropenia, and febrile neutropenia. Although the majority of these events were controlled with standard clinical management, grade 4 neutropenia occurred significantly more frequently with CBDCA + PTX plus bevacizumab than with CBDCA + PTX alone (73% vs 57%; $p=0.0395$) [14]. Because the incidence of neutropenia, which is a major concern for surgical infection and healing, is dose-dependent [15], we set an AUC of 5 as the CBDCA dose in the present study. Nonetheless, 62% of our patients suffered grade 3 or 4 neutropenia, and dose modifications were necessary in 20.7%. Therefore, we may need to modify the chemotherapy interval, dose, and regimen with bevacizumab if the patient is to undergo radical surgery after induction chemotherapy.

No new toxicities or adverse events of bevacizumab were identified in the present phase II study. The favorable tolerability profile for bevacizumab is reflected by the observation that 41.4% of patients were able to continue on bevacizumab monotherapy for a median of five cycles (1–37) following CBDCA + PTX plus bevacizumab chemotherapy with or without surgery. Concerns have been raised that induction chemotherapy increases surgical morbidity and mortality. The most severe surgical complications after induction chemotherapy are empyema and bronchial fistula, which may be prevented by special surgical procedures. In the present study, the 30-day mortality rate was 0% for the ten patients who underwent surgery. However, there was no clear evidence that the bevacizumab chemotherapy shortened the operation time, or made surgery or exfoliation easier. Minimizing treatment-related deaths is imperative and physicians must be careful when choosing a chemotherapy regimen in the setting of preoperative treatment.

One patient who underwent radical surgery had a solitary pulmonary nodule in a different ipsilateral lobe, simultaneously with the primary tumor (clinical pm 3). However, the patient's pathological stage was eventually changed from cStage IV to pStage IIA, as the nodule's response to chemotherapy was different from that of the primary tumor. The solitary nodule, which was suspected preoperatively to be pm3, was diagnosed as double primary lung cancer after partial resection of the lung following the chemotherapy. Although it is essential for clinicians and diagnosticians to distinguish between separate primary lesions and metastases, the histopathologic features of surgical samples are the current standard used to guide staging of NSCLC and to provide the rationale for classifying lesions as intraparenchymal metastasis (pT3-pm1/T4-pm2 and M1a-pm3) or as synchronous primary lung cancer. Providing accurate histological tumor information through surgery after induction chemotherapy, as in the present study, is a positive feature of this regimen.

Complete resection was achieved in 70% of our patients who underwent surgery after induction chemotherapy. The prognosis of patients with R0 and yStage I disease may be better, with longer survival and fewer complications. In the present study, four of seven R0 patients had yStage I disease. The median OS for patients with R0 alone is 3.725 year, which is clearly better than that of those with R2. Interestingly, two of three patients with R2 had postoperative complications; however, the small sample size in this study

makes it difficult to define the characteristics of patients with R0 after induction CBDCA + PTX plus bevacizumab.

The role of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in induction or adjuvant chemotherapy for NSCLC with EGFR activating mutations has not been established and validated [16–18]. The ongoing randomized trials of CTONG1103 and CTONG1104 for induction TKI therapy to treat perioperatively confirmed advanced NSCLC with EGFR mutation in exon 19 or 21 may contribute to the validating the combined modality therapy of surgery and induction chemotherapy with TKIs [16]. Antibodies that block programmed death 1 (PD-1) protein improve the survival of patients with advanced NSCLC, but have not been validated in an induction setting. In a pilot study (ClinicalTrials.gov number NCT02259621), induction therapy with nivolumab was associated with few immediate adverse events, did not delay surgery, and induced a major pathological response in 45% of resected tumors [19]. Long-term follow-up of these studies will be necessary to define the role of induction therapy from the standpoint of their biological impact. CBDCA + PTX plus bevacizumab may be an effective strategy for induction chemotherapy in patients whose molecular profiles such as EGFR mutation, ALK rearrangement, and PD-L1 are unknown or negative.

Durvalumab is a high-affinity, human IgG1 monoclonal antibody that blocks programmed death ligand 1 and CD80, enabling T cells to recognize and kill tumor cells. The PFS of patients with stage III unresectable NSCLC, who had already received chemoradiotherapy, was significantly longer for those given durvalumab than for those given a placebo [20]. Although the response rate was significantly higher with durvalumab than with the placebo (28.4% vs. 16.0%), the incidences of pneumonitis or radiation pneumonitis of any grade were 33.9% and 24.8%, respectively, for those who received durvalumab and those who received the placebo. Although durvalumab may be considered effective adjuvant therapy for patients with stage III NSCLC after standard chemoradiotherapy, it does increase the risk of radiation pneumonitis. The combination of salvage surgery after induction chemotherapy and durvalumab may be an alternative choice.

This trial has several limitations. First, because of recent advances with a similar chemotherapy regimen [4, 18–20], it was hard to find eligible patients with stage IIIA–IV NSCLC for this phase II trial. Second, because of the small sample size, we were unable to demonstrate the survival benefit of adding surgery after induction chemotherapy. Third, this trial included patients with stage IV disease who would not benefit from surgery. Surgery would be indicated for only a very small percentage of patients with advanced NSCLC after induction chemotherapy.

In summary, this phase II trial showed that combined modality therapy with surgery after induction chemotherapy with CBDCA + PTX plus bevacizumab for patients with advanced nonsquamous NSCLC is feasible and clinically tolerable, taking into consideration the higher response rate and acceptable toxicity. However, a randomized phase III study will be needed to confirm the survival benefit of CBDCA + PTX plus bevacizumab as induction chemotherapy for locally advanced lung cancer.

Acknowledgements We thank Prof. Akiteru Goto (Department of Cellular and Organ Pathology, Akita University Graduate School of Medicine) for suggesting pathological diagnoses.

Funding None.

Compliance with ethical standards

Conflict of interest We have no financial conflicts of interest to declare.

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