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ORIGINAL ARTICLE

Comparison of efficacy and safety of three different chemotherapy regimens delivered with concomitant radiotherapy in inoperable stage III non-small cell lung cancer patients

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Abstract Concomitant administration of chemotherapy and radiotherapy is currently recognized as the standard of treatment in locally advanced inoperable non-small cell lung cancer (NSCLC). Our study aimed to compare the efficacy and toxicities of three different chemotherapy regimens delivered concurrently with radiotherapy. We retrospectively reviewed the clinical records of patients who received the PE (cisplatin, 50 mg/m^2, on days 1, 8, 29, and 36 plus etoposide, 50 mg/m^2, on days 1 to 5 and 29 to 33), PD (docetaxel, 20 mg/m^2, on day 1 plus cisplatin, 20 mg/m^2, on day 1, every week), and PC (carboplatin, AUC 2 plus paclitaxel, 45 mg/m^2, on day 1, every week) regimens concurrently with radiotherapy. A total of 227 patients were evaluated in the study. Median follow-up time was 13 months (2–101). There were 27 females (11.9 %) and 200 males (88.1 %) with a median age of 61 (38–82) years. The PD group had higher rates of esophagitis, mucositis, and anemia ($p < 0.05$). The PC group had higher rates of neuropathy ($p = 0.000$). The progression-free survival (PFS) time was 10 months for patients in the PC group, 15 months for patients in the PD group, and 21 months for the PE group ($p = 0.010$). Patients in the PC group had a median overall survival time of 23 months, those in the PD group 27 months, and those in the PE group 36 months ($p = 0.098$). Combination of cisplatin-etoposide with radiotherapy led to a more favorable outcome compared with the other two regimens. It shows generally manageable toxicity profile and compliance to treatment is noticeable.

Keywords Concurrent chemoradiation · Non-small cell lung cancer · Stage III

Introduction

Carcinoma of the lung remains one of the most devastating diseases worldwide, in terms of incidence and mortality rates [1]. Non-small cell lung cancer (NSCLC) constitutes up to 85 % of all cases of lung cancer, and about 35–45 % of these patients have stage III disease at diagnosis [2]. Stage III NSCLC is one of the most controversial areas in managing the lung cancer and gives clinicians chance to practice the art of medicine. Therapeutic strategies for stage III NSCLC include surgical resection with adjuvant therapy, preoperative chemotherapy, preoperative chemoradiotherapy, chemotherapy and radiotherapy (either sequentially or concurrently), chemoradiotherapy with induction, or consolidation chemotherapy. The role and timing of surgery, chemotherapy, and radiation therapy are best determined according to the patients' performance status and comorbidities, extent of nodal and tumoral involvement, and the experience of the centers.

To date, numerous trials were directed to find out which modality of treatment should be regarded as the mainstay of therapy for this group of patients. In 1980s, radiotherapy (RT) alone was used as standard therapy in stage III disease but results were disappointing. In order to improve tumor response, the addition of cytotoxic chemotherapy before,

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during, or after RT has been extensively investigated in later studies [3–6]. All of these studies have supported the use of chemotherapy in addition to RT. Phase III studies have also been done to assess the efficacy and the toxicity of concomitant chemoradiotherapy in comparison with that of sequential chemoradiotherapy [7, 8]. These have concluded survival advantage on concurrent chemoradiotherapy arms.

Thus, for stage IIIB and inoperable stage IIIA disease, combined modality of RT and chemotherapy has become the most widely used treatment. This approach can allow both the locoregional and micrometastatic disease control. But due to the lack of randomized phase III studies directly comparing the different chemotherapeutic agents in use with concomitant RT, the optimal regimen is unclear today. We designed this study to focus on this issue. The aim of the current study was to compare the efficacy and safety of three chemotherapy regimens used concurrently with RT in patients with stage III NSCLC.

Materials and methods

Patient selection

Patients with unresectable stage III NSCLC who received concurrent chemoradiotherapy admitted to Department of Oncology, Dr. Lutfi Kirdar Kartal Education and Research Hospital were retrospectively analyzed. Patients with histologically or cytologically proven NSCLC were included in this study. Staging was determined according to the TNM seventh edition. Inoperability and nodal status were defined on the basis of computed tomography (CT) and/or fluorodeoxyglucose positron emission tomography (PET) scan after discussion among radiologist, chest surgeons, and medical and radiation oncologists. As the information obtained from CT or PET scans is not necessarily reliable, confirmation of tumor involvement was done by biopsy of enlarged or metabolically active mediastinal, supraclavicular, or scalene lymph nodes. Presence of bulky N2 status involving multiple nodal stations was appreciated as unresectable disease. Bulkiness was defined as an evidence of extracapsular nodal involvement or a size of a lymph node greater than 3 cm in short-axis diameter. Patients with N3 disease were eligible if all disease could be encompassed in the radiation field. Clinical data including gender, age, weight loss, performance status, histological subtype, and chemotherapy regimen were recorded. Performance status was evaluated in accordance with an Eastern Cooperative Oncology Group (ECOG) performance status criteria [9].

Chemotherapy

During the concurrent chemoradiation phase, patients were administered:

Cisplatin-etoposide (PE) arm: cisplatin (50 mg/m^2) on days 1, 8, 29, and 36 and etoposide (50 mg/m^2) on days 1 to 5 and 29 to 33.

Cisplatin-docetaxel (PD) arm: docetaxel (20 mg/m^2) and cisplatin (20 mg/m^2) on day 1, every week.

Carboplatin-paclitaxel (PC) arm: carboplatin (AUC 2) and paclitaxel (45 mg/m^2) on day 1, every week.

Some patients were administered induction and/or consolidation chemotherapy in each group, according to the physicians' individual discretion.

Radiotherapy

Radiotherapy was delivered with 6-MV photons with three-dimensional conformal planning. The gross tumor volume (GTV) included the primary disease as well as any involved regional lymph nodes was either detected by CT or by fluorodeoxy-glucose PET-CT scan. The primary tumor was contoured using pulmonary window tomography settings and nodal tumor using mediastinal window. Planning target volume (PTV) was obtained by adding 0.5- to 1-cm margin to clinical target volume (CTV) which was obtained by adding 1-cm margin to GTV. Total dose for GTV was 60 Gy delivered with 2 Gy daily fractions, 5 days per week for 6 weeks. Boost was planned after 46 Gy in order to keep 20-Gy dose receiving pulmonary parenchyma below 35 %, and spinal cord dose below 46 Gy. Radiotherapy was started on the first day of concomitant chemotherapy.

Toxicity and follow-up

National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used in order to define toxicities [10]. The first evaluation of response was performed following the completion of concurrent chemoradiotherapy. Subsequently, follow-up visits including laboratory findings and thoracic CT were conducted every 3–4 months. After 2–3 years, this interval was extended to 6 months. Imaging studies were repeated whenever recurrence was suspected. Response Evaluation Criteria in Solid Tumors (RECIST) was used for to evaluate the response [11].

Statistical analysis

Overall survival (OS) was defined as the time from the beginning of concurrent chemoradiotherapy to death from any cause or to last follow-up evaluation (censored). Progression-free survival (PFS) was defined as the time between the beginning of concurrent chemoradiotherapy and the earliest date of disease progression or death, or censored (as for OS). OS and PFS were estimated by the Kaplan-Meier method and were compared by the log-rank test. All statistical

calculations were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software. Results were evaluated at a significance level of $p < 0.05$.

Results

Patients

Between January 2004 and February 2014, a total of 227 patients were evaluated in the study. No patients were lost to follow-up. There were 27 females (11.9 %) and 200 males (88.1 %) with a median age of 61 (range, 38–82) years. Characteristics of study patients by treatment arms are shown in Table 1. The groups were well balanced with respect to median age, clinical stage, weight loss, histopathology, maintenance chemotherapy, and response to treatment. There were more female patients ($p = 0.049$) and ECOG performance status of II patients ($p = 0.000$) in the PC group than the other groups. Significantly fewer patients were given induction chemotherapy in the PE group (18 %) with respect to the PC group (55.2 %) and the PD group (64.4 %) ($p = 0.000$).

Table 1 Characteristics of study patients by treatment arms

	PC ($n = 87$) n (%)	PE ($n = 50$) n (%)	PD ($n = 90$) n (%)	p value
Median age	64 [42–82]	60 [38–80]	60 [46–74]	0.080
Gender				0.049
Female	16 (18.4)	5 (10)	6 (6.7)	
Male	71 (81.6)	45 (90)	84 (93.3)	
Weight loss				0.425
Absent	39 (44.8)	20 (40)	46 (51.1)	
Present	48 (55.2)	30 (60)	44 (48.9)	
Clinical stage				0.199
IIIA	44 (50.6)	28 (56)	37 (41.1)	
IIIB	43 (49.4)	22 (44)	53 (58.9)	
ECOG PS				0.000
PS 0	34 (39.1)	29 (58)	41 (45.6)	
PS 1	27 (31)	20 (40)	44 (48.9)	
PS 2	26 (29.9)	1 (2)	5 (5.6)	
Histopathology				0.058
Squamous cell	54 (62.1)	20 (40)	52 (57.8)	
Adenocarcinoma	22 (25.3)	17 (34)	28 (31.1)	
NOS	11 (12.6)	13 (26)	10 (11.1)	
Induction chemotherapy				0.000
Yes	48 (55.2)	9 (18)	58 (64.4)	
No	39 (44.8)	41 (82)	32 (35.6)	
Consolidation chemotherapy				0.364
Yes	22 (25.3)	10 (20)	15 (16.7)	
No	65 (74.7)	40 (80)	75 (83.3)	
Response of treatment				0.140
Complete response	10 (11.5)	8 (16)	16 (17.8)	
Partial response	45 (51.7)	31 (62)	47 (52.2)	
Stable disease	11 (12.6)	8 (16)	15 (16.7)	
Progressive disease	21 (24.1)	3 (6)	12 (13.3)	

ECOG PS Eastern Cooperative Oncology Group performance status, *NOS* not otherwise specified, *PC* carboplatin-paclitaxel, *PE* cisplatin-etoposide, *PD* cisplatin-docetaxel

Nodal staging

Pathologic documentation of clinical N2 or N3 status on imaging modalities was performed in 163 patients (71 %). Lymph node staging was confirmed by endobronchial ultrasonography (EBUS)-guided biopsy in 59 patients, by transbronchial blind biopsy in 47 patients, by supraclavicular/scalene lymph node biopsy in 32 patients, and by transthoracic percutaneous fine needle aspiration under CT guidance in 25 patients.

Treatment delivery

Fifty-seven patients (25.1 %) were not able to get the whole preplanned dose of chemotherapy, due either by dose reduction ($n = 33$) or chemotherapy cessation ($n = 24$). Dose reductions were undertaken in 11 (12.6 %), six (12 %), and 16 (17.8 %) patients in the PC, PE, and PD arms, respectively as a result of toxicity ($p = 0.530$). Chemotherapies of nine patients (10.3 %) in the PC arm, three patients (6 %) in the PE arm, and 12 patients (13.3 %) in the PD arm were cessated ($p = 0.399$). The reason was toxicity in 16 patients. The remaining eight patients refused to continue the treatment without having obvious toxicity. Radiotherapy doses were not reduced, as the serious side effects were occurred after completion of therapy; instead medical therapy were applied to these patients thereafter.

Forty-eight of 87 patients (55.2 %), nine of 50 patients (18 %), and 58 of 90 patients (64.4 %) received induction chemotherapy in the PC, PE, and PD groups, respectively ($p = 0.000$). The median number of cycles given in the PE group was two while was three in each of the PD and PC groups. Commonly used regimens of induction chemotherapy were carboplatin-paclitaxel (40.4 %) and cisplatin-docetaxel (45.6 %). Less frequently used regimens included cisplatin-gemcitabine ($n = 7$), cisplatin-etoposide ($n = 4$), cisplatin-vinorelbine ($n = 2$), carboplatin-gemcitabine ($n = 2$), and cisplatin-pemetrexed ($n = 1$).

The number of patients received consolidation chemotherapy were 22 (25.3 %), 10 (20 %) and 15 (16.7 %) in the PC, PE, and PD groups, respectively ($p = 0.364$). Mostly used consolidation chemotherapy schedules were carboplatin-paclitaxel (45.7 %) and cisplatin-docetaxel (28.3 %), followed by cisplatin-gemcitabine ($n = 4$), single agent of docetaxel ($n = 4$), cisplatin-etoposide ($n = 3$), and single agent of gemcitabine ($n = 1$). The median number of cycles administered for each group was two.

Toxicity

Treatment-related fatal adverse events occurred in four patients. The causes of rare cases of toxic deaths were acute kidney injury ($n=2$), cardiac failure ($n=1$), and febrile neutropenia ($n=1$). Twelve, four, and ten patients in the PC, PE, and PD arms were hospitalized during treatment, respectively ($p=0.586$).

The PD arm had higher rates of radiation esophagitis, mucositis, and anemia than those of the PC and PE arms ($p<0.05$ for both). Neuropathy occurred more often with the PC than with the PD and PE ($p=0.000$). More patients in the PC arm than in the PD and PE arms experienced thrombocytopenia and liver toxicity which were not significant ($p=0.202$ and $p=0.567$, respectively). Treatment-related grade II or more toxicities, hospitalization, and death are listed in Table 2.

Survival

Median follow-up time was 13 months (2–101). The sum of complete and partial response rates was 63.2, 78, and 70 %, among the PC, PE, and PD arms, respectively ($p=0.140$). The median OS time was 27 months (95 % CI 20–34), and the median PFS time was 14 months (95 % CI 11–17) for all the patients. Patients in the PC arm had a median survival time of 23 months (95 % CI 16–30), those in the PD arm had 27 months (95 % CI 14–41), and those in the PE arm had 37 months (95 % CI 9–65). The difference was not statistically significant ($p=0.098$). The overall survival time for patients in each of the treatment arms is shown in Fig. 1.

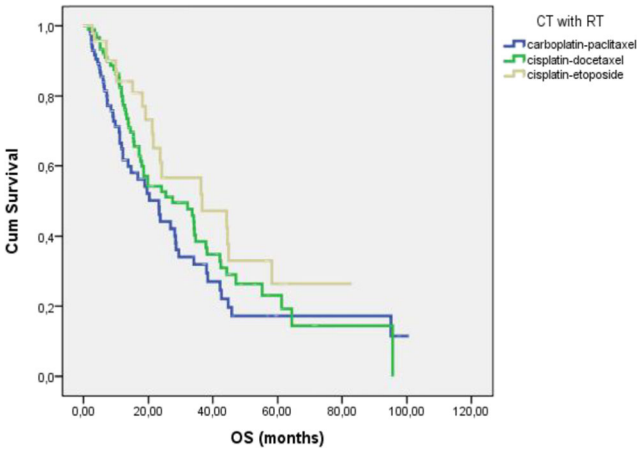

Fig. 1 The overall survival time for patients in each of the treatment arms

The PFS time was 10 months (95 % CI 7–13) for patients in the PC arm, 15 months (95 % CI 12–18) for patients in the PD arm, and 21 months (95 % CI 17–25) for the PE arm. The difference was statistically significant ($p=0.010$). The progression-free survival time for patients in each of the treatment arms is shown in Fig. 2.

Table 2 Treatment-related grade II or more toxicities, hospitalization, and death

	PC ($n=87$) n (%)	PE ($n=50$) n (%)	PD ($n=90$) n (%)	p value
Esophagitis	9 (10.3)	8 (16)	22 (24.4)	0.044
Pneumonitis	5 (5.7)	2 (4)	2 (2.2)	0.486
Mucositis	4 (4.6)	4 (8)	16 (17.8)	0.014
Neutropenia	7 (8)	4 (8)	15 (16.7)	0.136
Anemia	14 (16.1)	4 (8)	22 (24.4)	0.045
Thrombocytopenia	9 (10.3)	2 (4)	4 (4.4)	0.202
Neuropathy	23 (26.4)	1 (2)	1 (1.1)	0.000
VTE	2 (2.3)	1 (2)	4 (4.4)	0.627
Liver toxicity	3 (3.4)	1 (2)	1 (1.1)	0.567
Renal toxicity	2 (2.3)	1 (2)	8 (8.9)	0.071
Cardiac toxicity	1 (1.1)	1 (2)	1 (1.1)	0.893
Ototoxicity	0 (0)	1 (2)	1 (1.1)	0.462
Nausea/vomiting	24 (27.6)	10 (20)	29 (32.2)	0.302
Fatigue	26 (29.9)	9 (18)	33 (36.7)	0.069
Febrile neutropenia	7 (8)	3 (6)	8 (8.9)	0.831
Anaphylaxis	1 (1.1)	0 (0)	0 (0)	0.446
Hospitalization	12 (13.8)	4 (8)	10 (11.1)	0.586
Death	1 (1.1)	1 (2)	2 (2.2)	0.854

VTE venous thromboembolism, *PC* carboplatin-paclitaxel, *PE* cisplatin-etoposide, *PD* cisplatin-docetaxel

Discussion

This retrospective study of comparing three chemotherapy regimens commonly used concurrently with radiotherapy in unresectable NSCLC showed an improved outcome associated with the use of cisplatin-etoposide. We found that PFS was significantly increased in this subset of patients without an excess of toxicities. However, improvement in PFS did not translate into an OS advantage. A possible explanation for this may be the confounding effect on OS of postprogression therapies.

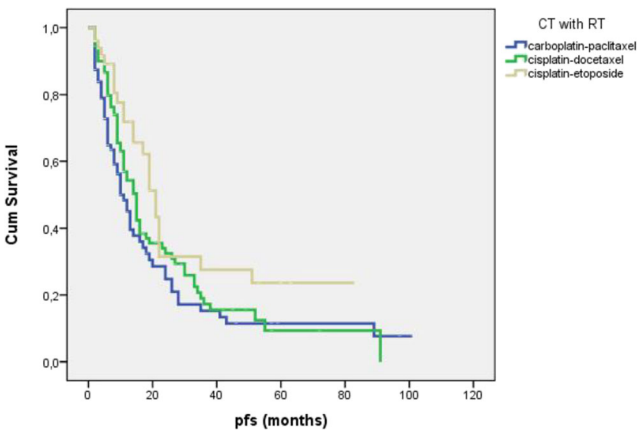

Fig. 2 The progression-free survival time for patients in each of the treatment arms

The therapeutic outcome in the treatment arms of the current study was at the upper range of reported values in conventional trials. Median OS ranged from 15 to 35 months for the PE [12, 13], 12 to 22 months for the PC [14, 15], and 23 to 27 months for the PD regimen [16, 17] in earlier studies. In our study, the median OS time was 23 months in the PC arm, 27 months in the PD arm, and 37 months in the PE arm. This supports the suggestion that cisplatin-based regimens are superior in terms of survival over carboplatin-based regimens. There are two possible factors that may contribute to the favorable survival times in the PE arm. Firstly, compliance with chemotherapy was better in the PE arm compared to other treatment arms indicating that the PE regimen did not adversely affect the timely completion of definitive radiotherapy. Secondly, patients in the PE arm belong to better performance status than the other two groups.

The superiority of concurrent chemoradiotherapy approach over radiotherapy alone or sequential chemoradiotherapy is well established [18–20]. Current investigations have now aimed to identify more ideal chemoradiotherapy schedules with the hope of pronouncing efficacy without enhancing toxicity. In this area, head-to-head comparisons of different chemotherapeutic agents are rare, and to our knowledge, none have compared the carboplatin-paclitaxel, cisplatin-etoposide, and cisplatin-docetaxel regimens with each other in the same setting. Cisplatin-docetaxel and carboplatin-paclitaxel are more recently developed regimens. And trials were designed to compare these with the older regimens to find out survival or safety advantage, if any.

A phase III trial by Segawa et al. [21] compared PD with an older regimen, MVP (mitomycin-vindesine-cisplatin). The median survival time for the PD and MVP arms were 26.8 and 23.7 months, respectively. Although the overall and progression-free survival rates tended toward the PD arm, the differences were not statistically significant. The OS in the PD arm was similar with that in our study. However, there are some differences regarding the toxicity rates. The rate of esophagitis was higher (24.4 vs. 14 %) whereas febrile neutropenia was lower (8.9 vs. 22 %) in our study. This discordance about the rates of toxicities could be due to the administration schedule of chemotherapy (a weekly regimen of 20 mg/m^2 throughout radiotherapy vs. 40 mg/m^2 on the first and last 2 weeks of radiotherapy) as the thoracic radiotherapy dose was 60 Gy in both studies.

Another phase III trial [22] which was conducted by the West Japan Oncology Group compared the MVP, carboplatin-irinotecan, and PC regimens. The median survival time was 22 months for the PC arm which is consistent with that in our study. Differences in survival among the treatment groups were not statistically significant. Many toxicities other than neuropathy were seen fewer in the PC arm than the other two arms. The authors concluded that although the efficacy was not better, PC had a more favorable toxicity profile making it a strong candidate for standard of care.

A prospective trial by Wang et al. [23] compared the PE-based with PC-based chemoradiotherapy. Median OS was 20.2 and 13.5 months for the PE and PC arms, respectively ($p = 0.04$). The study favored the PE arm similarly to our study, but the median OS in our study was significantly higher for both the groups. Fewer patients discontinued preplanned complete dose chemoradiotherapy in our study (PE, 24.2 vs. 18 % and PC, 28.1 vs. 22.9 %). This may possibly made gains in the increment in survival time.

More recently published retrospective trial by Liew et al. [24] compared the efficacy and toxicities of the PC regimen with that of the PE. The PC arm was found to achieve similar survival outcomes compared to the PE arm. Although statistically insignificant, the median OS favored the PC group (PC, 20.7 months vs. PE, 13.7 months, $p = 0.989$). The contrast between the outcomes of this study and the current study could be explained by differences in compliance to treatment, performance status of patients, and incorporation of consolidation and/or induction chemotherapy. Patients were able to get the full dose radiotherapy in our study, and more patients have completed the overall preplanned chemoradiotherapy particularly in the PE group (PE, 82 vs. 58 % and PC, 77.1 vs. 50 %). Performance status proved to be an independent prognostic factor in stage III NSCLC [25, 26], and more patients were of performance status 0 in our study for both the groups (PC, 39.1 vs. 18 % and PE, 58 vs. 35 %).

Other possible explanation about favorable outcome in our study is the potential role of induction and/or consolidation chemotherapy in combination with chemoradiotherapy. Remarkably, some patients received induction chemotherapy in our study (PC, 55.2 % and PE, 18 %) while none were given in the trials of Liew et al. and Wang et al. Although induction chemotherapy seems to add little benefit according to previous studies [27], it could indirectly improve compliance to chemoradiotherapy via decreasing the radiation induced toxicity in case of high tumor volumes. There is some evidence that chemotherapy following chemoradiotherapy is more efficacious than chemoradiotherapy alone [28]. The numbers of patients who received consolidation treatment are higher in our study than those reported by Liew et al. (PE, 20 vs. 16 % and PC, 25.3 vs. 0 %). In our institution, we used to deliver consolidation chemotherapy with full systemic doses, in an attempt to further control the micrometastatic disease, especially when doses reduced during concurrent chemoradiotherapy phase.

Toxicities are an important concern about concurrent chemoradiotherapy. These lead to treatment breaks and limit the improvement gained in efficacy. Radiation eosaphagitis and mucositis were more prominent in the PD arm whereas radiation pneumonitis was more common in the PC arm in the present study. These confirm the data from the literature. Previous trials [23, 24] comparing the PE and PC regimens generally concluded that serious hematological toxicities were

higher in the PE arm compared to the PC arm. In contrast, hematological toxicities were the lowest in the PE arm with anemia being statistically significant in our study.

Several limitations of the current study exist. The first and foremost is that the evaluation of cases was retrospective, and there was unavoidable selection bias. Assessment of stored data rather than real-time evaluation can confound one's judgment of the efficacy and toxicity of each treatment. For instance, grade 1 toxicities found generally not to be reported in the records. Thus, we collected data about only grade 2 or more toxicities. Second, prognostic factors were not well arranged in the treatment groups. Performance status of patients in the PC arm was poorer compared to the rest. Weight loss was reported as absent or present rather than estimation in detail, due to the insufficient information in the existing data. Third, the numbers of patients in the PE arm were less than the other groups. Lastly, overall sample size is relatively small.

In conclusion, concurrent chemoradiotherapy involving the combined use of three commonly used chemotherapy regimens with thoracic radiotherapy did not prove a statistically significant difference in OS among the treatment groups. But we highlight the prolonged PFS and considerably tolerable toxicity profile for cisplatin-etoposide arm. We hope that improvements in this area will expand, and stage III NSCLC will not be a significant clinical challenge anymore.

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Compliance with ethical standards

Conflicts of interest None

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