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ORIGINAL ARTICLE **CME**

Three-week Cycles of Paclitaxel-Carboplatin Administered Concurrently with Radiotherapy for Inoperable Stage III Non-small Cell Lung Cancer: 10-Year Single-Centre Experience

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ABSTRACT

Introduction: *We reviewed the efficacy, toxicities, and prognostic factors of two 3-week cycles of paclitaxel-carboplatin administered concurrently with radiotherapy for treatment of unresectable stage III non-small cell lung cancer (NSCLC).*

Methods: *Cases of unresectable stage III NSCLC treated with chemoradiotherapy using paclitaxel 175 mg/m² and carboplatin area under the curve=5 on day 1 of a 21-day cycle concurrently with 6 weeks of radiotherapy (60-66 Gy) from 2007 to 2017 were retrieved.*

Results: *A total of 65 patients (median age=63 years) were included. At a 29.5-month median follow-up, the median overall survival was 35.0 months (95% confidence interval [CI]=17.5-52.5 months). Multivariable Cox regression analyses showed that gross tumour volume (p = 0.001), mean heart dose ≥5 Gy (p = 0.007), and more than four cycles of chemotherapy administered (p = 0.006) were independent negative prognostic factors. The maximum grade toxicity was Grade 2 in 27 patients (41.5%), grade 3 in 13 patients (20.0%) and grade 4 in five patients (7.7%). No grade 5 events were observed. The most common grade 3 or 4 toxicity was neutropenia, which occurred in nine (13.8%) and five (7.7%) patients, respectively. Three patients (4.6%) had neutropenic fever. Grade ≥2 pneumonitis and oesophagitis were seen in five (7.7%) and nine (13.8%) patients, respectively.*

Conclusion: *Two 3-week cycles of paclitaxel-carboplatin given concurrently with radiotherapy for unresectable stage III NSCLC was well-tolerated, with outcomes comparable to historical data, and fewer hospital visits.*

Key Words: *Carcinoma, non-small-cell lung; Positron-emission tomography*

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Data Availability: Research data are stored in an institutional repository and will be shared by the corresponding author on reasonable request.

Ethics Approval: This study was approved by the Kowloon West Cluster Research Ethics Committee, Hospital Authority [Ref KW/EX-20-054(146-03)]. The Ethics Committee waived the need for patient consent for this retrospective study.

中文摘要

紫杉醇-卡鉑三週週期及同步放射治療方案治療不宜手術的第III期非小細胞肺癌：十年單中心經驗

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引言：回顧每3週為一週期，共兩週期的紫杉醇-卡鉑及同步放射治療用於治療不可切除的第III期非小細胞肺癌的療效、副作用和預後因素。

方法：我們將2007年至2017年期間同步使用紫杉醇-卡鉑（每21天的第1天注射紫杉醇175 mg/m^2，卡鉑曲線下面積=5）和6週放射治療（60-66 Gy）醫治不可切除的第III期非小細胞肺癌病例進行回顧性研究。

結果：研究共納入65名患者（年齡中位數63歲）。在29.5個月的中位跟進期中，總存活期中位數為35.0個月（95%置信區間=17.5-52.5個月）。多變量Cox 迴歸分析顯示，腫瘤體積（p = 0.001）、平均心臟劑量≥5 Gy（p = 0.007）和多過四個化療週期（p = 0.006）為獨立的負面預後因素。27例（41.5%）的最大副作用級別為第2級、13例（20.0%）為第3級、5例（7.7%）為第4級，未有發現患者出現第5級副作用。最常見的第3或第4級副作用為嗜中性白血球低下症，分別9例（13.8%）和5例（7.7%）。3例（4.6%）出現嗜中性白血球低下症伴隨發燒。分別有5例（7.7%）和9例（13.8%）出現第2級或以上放射治療引起的肺炎和食道炎。

結論：對於不可切除的第III期非小細胞肺癌，放射治療期間同步使用每3週一次的紫杉醇-卡鉑副作用可接受，效果與文獻數據相若，在醫院接受化療次數也較少。

INTRODUCTION

Concurrent chemoradiotherapy (CCRT) with platinum-based agents is preferred over a sequential treatment approach for fit patients with unresectable stage III non-small cell lung cancer (NSCLC) for optimal survival rates.[1,2] However, overall outcomes still remain poor, with a 5-year overall survival (OS) rate of approximately 15% to 30%.[2-4] No major recent advances had been made until the publication of the PACIFIC trial, which established the role of durvalumab after CCRT.[5]

There have been multiple studies evaluating the efficacy of different chemotherapy regimens in combination with radiotherapy (RT) since the 2000s, including etoposide-cisplatin (EP), weekly paclitaxel-carboplatin (PC), vinorelbine-cisplatin, and pemetrexed with either cisplatin or carboplatin.[6-10] Trials comparing these regimens were not available until after 2012, and there has not been a conclusion as to which is superior. For example, a phase III randomised trial showed a higher 3-year OS with EP compared with weekly PC with an absolute difference of 15%.[11] In contrast, one meta-analysis and two other large-scale retrospective analyses showed the opposite effect, with comparable efficacy using either EP or PC.[12,13] Earlier guidelines from The European Society of Medical Oncology (ESMO) for early unresectable NSCLC published in 2010 recommended that 'etoposide-cisplatin (or vinblastine or vinorelbine) and PC both at systemic doses should be considered as reference regimens'.[14] No recommended schedule or doses of the agents were suggested.

From 2007, our institution adopted paclitaxel 175 mg/m^2 and carboplatin area under the curve [AUC]=5 administered on day 1 of a 21-day cycle as one option given concurrently with RT for inoperable stage III NSCLC because of its convenient schedule requiring only one in-patient day in the chemotherapy centre every cycle. The chemotherapy component is well-described for palliation in advanced NSCLC[15-17] but data combining the chemotherapy as part of CCRT for unresectable stage III disease are limited. Movsas et al[18] established the safety of this regimen with RT using paclitaxel 175 mg/m^2 and carboplatin AUC=5 in a dose escalation study in 2001. A small retrospective study of 43 patients (15 patients given PC, 28 patients given EP)

in China showed that there was no statistical difference in response rates, progression-free survival (PFS), or OS compared with the EP group.[19]

This study aimed to review the survival outcomes, toxicities, and prognostic factors of giving 3-week cycles of PC during RT and compare with another cohort receiving EP at our institution.

METHODS

Patients

The case cohorts were identified from the list of NSCLC patients treated with RT from the treatment planning system from January 2007 to April 2017. Inclusion criteria were diagnosis of inoperable stage III (restaged based on the TNM American Joint Committee on Cancer 7th edition) NSCLC treated with CCRT of curative intent with 3-week cycles of PC. Histological diagnosis was preferred, but radiological diagnosis with a positive positron emission tomography–computed tomography (PET-CT) scan was allowed if obtaining histology was not feasible. Patients were excluded if no chemotherapy was administered concurrently with RT and/or total RT dose was <60 Gy. Patients administered more than two cycles of chemotherapy before RT were considered as having received sequential treatment and were also excluded. Cases were included if they had received at least one of their cycles of chemotherapy beginning on day 1 of RT. A case cohort with the same inclusion and exclusion criteria but receiving EP was identified for comparison. This study was approved by the local clinical research ethics committee with permission waived due to its retrospective nature. The STROBE reporting guidelines were implemented in this manuscript.

Procedures

RT was administered 5 times per week (Monday to Friday with weekend rests) in 2 Gy fractions using 6 to 15 MV photons. Free-breathing contrast-enhanced simulation computed tomography (CT) with 5 mm thickness was acquired with a scan range from neck to the upper abdomen including the entire liver. All treatments were administered using three-dimensional conformal RT. Dose constraints were as follows: lung V20 <30%, whole heart <40 Gy, spinal cord Dmax <45 Gy, and oesophagus V55 <30% or mean oesophageal dose <34 Gy. RT doses of 60 to 66 Gy were prescribed to the planning target volume (PTV). Contouring of treatment volumes was done on simulation contrast CT and assisted by PET imaging if available. Gross tumour volume (GTV) was defined as the primary tumour and any involved regional lymph nodes with short axis >1 cm on diagnostic CT or fluorodeoxyglucose avid on pretreatment PET-CT. Clinical target volume (CTV) was defined as the GTV with a 0.6- to 0.8-cm margin for the primary tumour and was the same as the GTV for the regional involved lymph nodes. CTV of the primary tumour was trimmed off from the chest wall and vertebral bodies unless there was tumour involvement. Elective nodal irradiation was not given. PTV of the primary tumour was defined as the CTV with a 1.0 cm margin axially and 1.0 to 1.5 cm in the superior-inferior direction to account for respiratory motion. PTV of the lymph nodes was defined as the CTV with a 1.0 cm margin. PTV coverage was achieved if 95% of the PTV was covered by 95% of the prescribed dose. Treatment verification was carried out with online kV portal images on the first day, mid-treatment, and, if needed, as determined by the treating radiotherapist at any time during treatment without the use of fiducial markers.

Chemotherapy consisted of either PC regimen (paclitaxel 175 mg/m^2 and carboplatin AUC=5 given every 3 weeks on day 1 of the cycle) or EP regimen (etoposide 100 mg/m^2 and cisplatin 30 mg/m^2 days every 3 weeks on days 1 to 3 of the cycle). Patients were scheduled to receive a total of four cycles of chemotherapy, in which two were concurrent with RT. A maximum of up to six chemotherapy cycles were allowed at the treating clinicians' discretion. RT had to commence concurrently with the first three cycles of chemotherapy. No prophylactic granulocyte-colony stimulating factor was used. In the case of Grade 3 or 4 toxicities, chemotherapy was withheld until toxicities improved to Grade 1 or less and a 25% dose reduction was applied to the subsequent cycle. Chemotherapy was stopped if toxicities failed to return to Grade 1 or the treating clinician decided that the risks of further chemotherapy outweighed the benefits. Paclitaxel infusion was given over 3 hours after premedication with intravenous dexamethasone 20 mg, intravenous chlorpheniramine 10 mg, an H2 blocker (oral or intravenous), and standard anti-emetics, followed by carboplatin infusion given over 30 minutes.

Assessments

Baseline clinical, serological, and pathological parameters within 4 weeks prior to the first cycle of chemotherapy were documented. Clinical parameters including TNM stage based on the American Joint Committee on Cancer 7th edition, Eastern Cooperative Oncology Group performance status, smoking history, use of PET-CT for

staging, medical co-morbidities, and serological levels of haemoglobin, platelets, neutrophils, and albumin. RT and dosimetric details including treatment dose, GTV (cc), mean lung dose, mean oesophageal dose, and mean heart dose were retrieved from the treatment planning system. Treatment-related toxicities were graded based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Patients were followed up every 3 to 4 months in the first year, every 6 months in the second to third year and 6 to 8 months in the fourth and fifth year, then once every year. Routine follow-up assessments included assessment of symptoms and signs of recurrence, Eastern Cooperative Oncology Group performance status, and CTCAE grading of adverse events. Plain chest radiograph was done at every follow-up visit, while CT scans were acquired within the first year after treatment and if clinically indicated as determined by the treating physician. Response was assessed using the RECIST (Response Evaluation Criteria in Solid Tumors) criteria.

Statistical Analyses

Baseline characteristics and dosimetric parameters were compared with the Chi-squared test or Fisher's exact test for categorical variables and Student's *t* test for continuous variables between patients with or without high-grade treatment-related toxicities. PFS was defined as the duration from the commencement of the first cycle of chemotherapy to the time when there was radiological or clinical evidence of disease progression or patient death. OS was calculated from the time of commencement of the first cycle of chemotherapy to the time of death. PFS and OS were estimated using the Kaplan–Meier method. Patients lost to follow-up were censored. Cox regression analysis was used to determine the prognosticators for PFS and OS. Statistically significant parameters in the simple analysis were included in the multivariable Cox regression analysis to determine independent prognostic factors. The toxicities of the EP and PC case cohorts were compared using Chi-squared or Fisher's exact tests. Median PFS and OS of the cohorts were estimated with the Kaplan–Meier method and compared with log rank tests. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the SPSS (Windows version 21.0; IBM Corp, Armonk [NY], US).

RESULTS

Case Characteristics

A total of 65 cases (median age 63 years, range 45-74) who received 3-week cycles of PC with RT were analysed (Table 1). Molecular tests were done on all non-squamous cell cancers except for four patients because of inadequate tissue. One patient with squamous cell carcinoma also received molecular tests. Only a small number of patients had epidermal growth factor receptor or anaplastic lymphoma kinase genomic aberrations (16.9%). PET-CT was available in 73.8% of patients as part of the staging workup. The distribution of staging was similar among stage IIIA (53.8%) and stage IIIB (46.2%). Most patients received four cycles of chemotherapy (83.1%) in total. Almost all patients (96.9%) received 60 Gy of concurrent RT and 41.5% (n=27) had RT started concurrent with the first two cycles of chemotherapy.

Treatment Delivery and Acute Toxicities

The majority of cases (89.2%) received RT treatment without interruption, with 96.9% completing the planned number of chemotherapy cycles. Dose reduction was required in 40.0% of cases and deferral of chemotherapy was required in 36.9%.

The maximum grade toxicity observed per patient was grade 1 in 20 (30.8%) patients, grade 2 in 27 (41.5%), grade 3 in 13 (20.0%) and grade 4 in five (7.7%); there were no grade 5 toxicities observed (Table 2). No pretreatment clinical characteristics or dosimetric parameters were associated with higher-grade toxicities (Table 3).

Treatment Outcomes

Overall Survival

At a median follow-up of 29.5 months (interquartile range=13.3-56.3), the median OS was 35.0 months (95% confidence interval [CI] = 17.5-52.5) [Figure 1]. The 1-, 3- and 5-year OS rates were 76.9%, 48.3% and 29.7%, respectively. Simple analysis identified five parameters associated with poorer OS: GTV, mean heart dose ≥5 Gy, more than four cycles of chemotherapy administered, omission of planned chemotherapy cycles, and chemotherapy deferrals. Multivariable regression analyses showed that GTV (hazard ratio [HR] = 1.005, 95% CI = 1.002-1.008; p = 0.001), mean heart dose ≥5 Gy (HR = 2.507, 95% CI = 1.293-5.108; p = 0.007), and more than four cycles of chemotherapy administered (HR = 3.830, 95% CI = 1.479-9.921; p = 0.006) were independent prognostic parameters (Table 4).

Progression-free Survival

The median PFS for this cohort was 12.2 months (95% CI = 9.0-15.4) [Figure 2]. The 1-, 3-, and 5-year

Table 1. Baseline characteristics.*

	PC (n = 65)	EP (n = 17)	p Value
Age, y			
≥65	24 (36.9%)	7 (41.2%)	0.747†
<65	41 (63.1%)	10 (58.8%)	
Sex			
Male	55 (84.6%)	14 (82.4%)	1.000‡
Female	10 (15.4%)	3 (17.6%)	
ECOG performance status			
0	42 (64.6%)	13 (76.5%)	0.608†
1	22 (33.8%)	4 (23.5%)	
2	1 (1.5%)	0	
Smoking history			
Current and ex-smoker	49 (75.4%)	15 (88.2%)	0.337‡
Non-smoker	16 (24.6%)	2 (11.8%)	
Histology			
Squamous	25 (38.5%)	7 (41.2%)	0.566†
Adenocarcinoma	27 (41.5%)	9 (52.9%)	
Poorly differentiated/ undifferentiated	12 (18.5%)	1 (5.9%)	
Radiologic diagnosis	1 (1.5%)	0	
Actionable target (*EGFR/ ALK/ROS1* mutation)			
EGFR	10 (15.4%)	3 (17.6%)	0.631†
ALK	1 (1.5%)	0	
ROS1	0	0	
Negative	25 (38.5%)	4 (23.5%)	
Test not done	29 (44.6%)	10 (58.9%)	
Chronic obstructive pulmonary disease			
Yes	3 (4.6%)	2 (11.8%)	0.275‡
No	62 (95.4%)	15 (88.2%)	
Cardiac disease			
Yes	7 (10.8%)	1 (5.9%)	1.000‡
No	58 (89.2%)	16 (94.1%)	
Dose of radiotherapy			
>60 Gy	2 (3.1%)	1 (5.9%)	0.507‡
60 Gy	63 (96.9%)	16 (94.1%)	
T stage AJCC 7th edition			
T1	5 (7.7%)	1 (5.9%)	0.951†
T2	23 (35.4%)	5 (29.4%)	
T3	13 (20.0%)	4 (23.5%)	
T4	24 (36.9%)	7 (41.2%)	
N stage AJCC 7th edition			
N0	8 (12.3%)	1 (5.9%)	0.757†
N1	2 (3.1%)	0	
N2	37 (56.9%)	11 (64.7%)	
N3	18 (27.7%)	5 (29.4%)	
Overall staging AJCC 7th edition			
IIIA	35 (53.8%)	8 (47.1%)	0.618†
IIIB	30 (46.2%)	9 (52.9%)	
PET-CT staging			
Yes	48 (73.8%)	11 (64.7%)	0.455†
No	17 (26.2%)	6 (35.3%)	

Abbreviations: AJCC = American Joint Committee in Cancer; ECOG = Eastern Cooperative Oncology Group; EP = etoposide-cisplatin; PC = paclitaxel-carboplatin; PET-CT = positron emission tomography–computed tomography.
* Data are shown as No. (%), unless otherwise specified.
† Chi-squared test.
‡ Fisher's exact test.

Table 1. (cont'd)

	PC (n = 65)	EP (n = 17)	p Value
No. of chemotherapy cycles before radiotherapy			
0	11 (16.9%)	4 (23.5%)	0.686†
1	16 (24.6%)	5 (29.4%)	
2	38 (58.5%)	8 (47.1%)	
No. of chemotherapy cycles after radiotherapy			
0	35 (53.8%)	8 (47.1%)	0.861†
1	15 (23.1%)	5 (29.4%)	
2	12 (18.5%)	4 (23.5%)	
3	2 (3.1%)	0	
4	1 (1.5%)	0	
Total No. of cycles of chemotherapy			
1	1 (1.5%)	0	0.260†
2	0	1 (5.9%)	
3	2 (3.1%)	1 (5.9%)	
4	54 (83.1%)	15 (88.2%)	
5	2 (3.1%)	0	
6	6 (9.2%)	0	

PFS rates were 52.3%, 19.5% and 12.7%, respectively. RT interruption, chemotherapy deferrals, chemotherapy dose reduction, grade 2 oesophagitis or above, less than four cycles of chemotherapy completed, and GTV were noted to be prognostic factors in simple analysis, while grade 2 oesophagitis or above was the only independent adverse factor for PFS (HR = 2.563, 95% CI = 1.031-6.370; p = 0.043) [Table 5].

Comparison with Historical Cohort of Patients Treated with Etoposide-Cisplatin

There were no differences in the baseline characteristics between the PC and EP case cohorts (Table 1). Compared with the PC case cohort, the 17 patients who received EP had significantly more grade 3 or 4 neutropenia (EP 82.4% vs. PC 21.5%; p < 0.01), grade 3 or 4 thrombocytopenia (EP 11.8% vs. PC 0.0%, p = 0.04), any grade nausea or vomiting (EP 64.7% vs. PC 33.8%; p = 0.02), but less of any grade of peripheral neuropathy (EP 0.0% vs. PC 41.5%; p < 0.01). There were no significant differences between any grade pneumonitis, grade 3 or 4 anaemia, and any or grade 3 or 4 oesophagitis between the two regimens (Table 6). There were also no statistically significant differences in the median PFS (EP 10.3 months, 95% CI = 9.0-15.4 months vs. PC 12.2 months, 95% CI = 3.3-17.3 months; p = 0.29) and median OS (EP 25.3 months, 95% CI = 14.0-36.6 months vs. PC 35.0 months, 95% CI = 17.5-52.5 months; p = 0.36).

Table 2. Treatment-related toxicities by grade (n = 65).*

Toxicity	CTCAE 4.0 Grade	No. (%)
Fatigue	Grade 0	38 (58.5%)
	Grade 1	22 (33.8%)
	Grade 2	5 (7.7%)
	Grade 3	0
	Grade 4	0
Nausea and vomiting	Grade 0	43 (66.2%)
	Grade 1	18 (27.7%)
	Grade 2	4 (6.2%)
	Grade 3	0
	Grade 4	0
Skin reaction	Grade 0	51 (78.5%)
	Grade 1	9 (13.8%)
	Grade 2	4 (6.2%)
	Grade 3	1 (1.5%)
	Grade 4	0
Oesophagitis	Grade 0	26 (40.0%)
	Grade 1	30 (46.2%)
	Grade 2	6 (9.2%)
	Grade 3	3 (4.6%)
	Grade 4	0
Peripheral neuropathy	Grade 0	37 (56.9%)
	Grade 1	22 (33.8%)
	Grade 2	6 (9.2%)
	Grade 3	0
	Grade 4	0
Pneumonitis	Grade 0	60 (92.3%)
	Grade 1	0
	Grade 2	5 (7.7%)
	Grade 3	0
	Grade 4	0
Increase in alanine aminotransferase	Grade 0	45 (69.2%)
	Grade 1	19 (29.2%)
	Grade 2	1 (1.5%)
	Grade 3	0
	Grade 4	0
Neutropenia	Grade 0	32 (49.2%)
	Grade 1	5 (7.7%)
	Grade 2	14 (21.6%)
	Grade 3	9 (13.8%)
	Grade 4	5 (7.7%)
Anaemia	Grade 0	3 (4.6%)
	Grade 1	43 (66.2%)
	Grade 2	17 (26.2%)
	Grade 3	2 (3.1%)
	Grade 4	0
Thrombocytopenia	Grade 0	47 (72.3%)
	Grade 1	17 (26.2%)
	Grade 2	1 (1.5%)
	Grade 3	0
	Grade 4	0

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.
* Data are shown as No. (%).

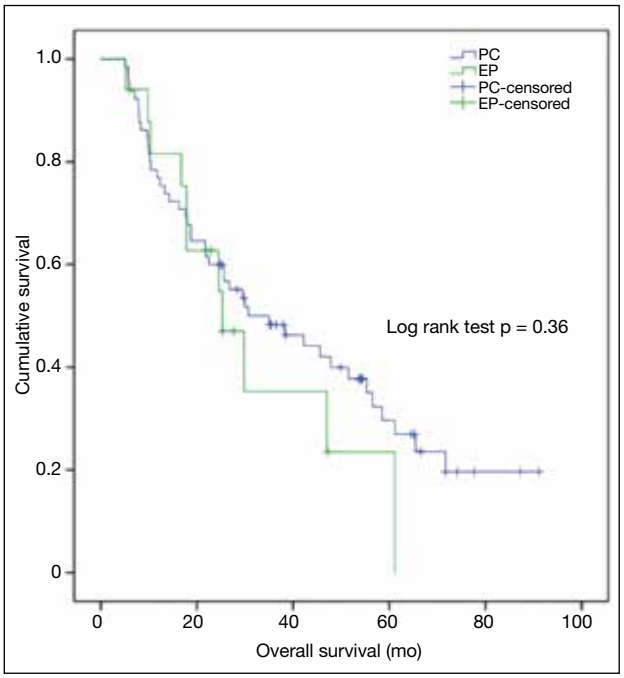

Figure 1. Overall survival for stage III unresectable non-small cell lung cancer treated with 3-week cycles of paclitaxel-carboplatin (PC) versus etoposide-cisplatin (EP) concurrent with radiotherapy from 2007 to 2017.

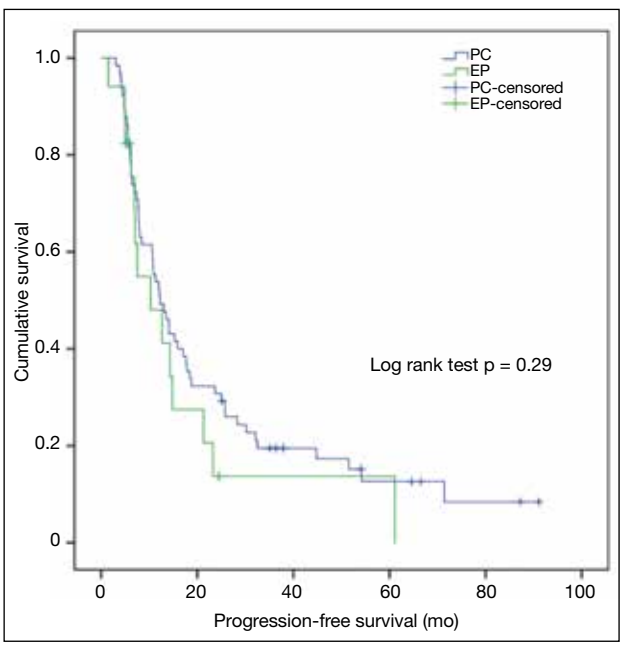

Figure 2. Progression-free survival for stage III unresectable non-small cell lung cancer treated with 3-week cycles of paclitaxel-carboplatin (PC) versus etoposide-cisplatin (EP) concurrent with radiotherapy from 2007 to 2017.

Table 3. Predictors of selected toxicities.*

	Grade ≥2 peripheral neuropathy	Grade <2 peripheral neuropathy	p Value
Age, y			
≥65	1 (1.5%)	23 (35.4%)	0.400†
<65	5 (7.7%)	36 (55.4%)	
Sex			
Male	5 (7.7%)	9 (13.8%)	1.000†
Female	1 (1.5%)	50 (76.9%)	
ECOG performance status			
1-2	1 (1.5%)	22 (33.8%)	0.411†
0	5 (7.7%)	37 (56.9%)	
Diabetes mellitus			
Yes	0	14 (21.5%)	0.327†
No	6 (9.2%)	45 (69.2%)	
Albumin, mg/dL			
<35	3 (4.6%)	13 (20.0%)	0.154†
≥35	3 (4.6%)	46 (70.8%)	
	Grade ≥2 oesophagitis	Grade <2 oesophagitis	p Value
Age, y			
≥65	2 (3.1%)	22 (33.8%)	0.466†
<65	7 (10.8%)	34 (52.3%)	
Sex			
Male	6 (9.2%)	49 (75.4%)	0.135†
Female	3 (4.6%)	7 (10.8%)	
ECOG performance status			
1-2	1 (1.5%)	22 (33.8%)	0.142†
0	8 (12.3%)	34 (52.4%)	
Albumin, mg/dL			
<35	3 (4.6%)	13 (20.0%)	0.678†
≥35	6 (9.2%)	43 (66.2%)	
Mean oesophageal dose	27.8 Gy	24.2 Gy	0.146‡
	Grade ≥2 pneumonitis	Grade <2 pneumonitis	p Value
Age, y			
≥65	4 (6.2%)	20 (30.8%)	0.058†
<65	1 (1.5%)	40 (61.5%)	
Sex			
Male	3 (4.6%)	52 (80.0%)	0.166†
Female	2 (3.1%)	8 (12.3%)	
ECOG performance status			
1-2	3 (4.6%)	20 (30.8%)	0.337†
0	2 (3.1%)	40 (61.5%)	
Albumin, mg/dL			
<35	0	16 (24.6%)	0.322†
≥35	5 (7.7%)	44 (67.7%)	
Chronic obstructive pulmonary disease			
Yes	0	3 (4.6%)	1.000†
No	5 (7.7%)	57 (87.7%)	
Mean lung dose	14.6 Gy	12.4 Gy	0.056‡
Volume of lung receiving ≤20 Gy	25.22%	20.81%	0.060‡

* Data are shown as No. (%), unless otherwise specified.
† Fisher's exact test.
‡ Student's *t* test.
§ Chi-squared test.

Table 3. (cont'd)

	Grade ≥3 neutropenia	Grade <3 neutropenia	p Value
Age, y			
≥65	7 (10.8%)	17 (26.2%)	0.252§
<65	7 (10.8%)	34 (52.3%)	
Sex			
Male	12 (18.5%)	43 (66.2%)	1.000†
Female	2 (3.1%)	8 (12.3%)	
ECOG performance status			
1-2	5 (7.7%)	18 (27.7%)	1.000§
0	9 (13.8%)	33 (50.8%)	
Albumin, mg/dL			
<35	2 (3.1%)	14 (21.5%)	0.487†
≥35	12 (18.5%)	37 (56.9%)	

DISCUSSION

The optimal choice of chemotherapy for CCRT remains debatable for unresectable stage III NSCLC. However, there are limited data on the efficacy and toxicities of the convenient schedule of PC given every 3 weeks in the existing literature. To our knowledge, this is the largest review of using this regimen for this disease stage.

Results of our 3-week cycle PC cohort (median OS 35.0 months, 3-year OS 48.3%, 5-year OS 29.7%) are comparable to data reported using other regimens. In the RTOG 0617 study,[20] patients treated with weekly PC concurrent with standard dose RT (60 Gy) had a median survival of 28.7 months, and a 5-year OS of 32.1%. In the control arm of the PACIFIC trial, patients had a median survival of 29.1 months and a 3-year OS of 43.5%.[21] Although statistically significant conclusions cannot be drawn across trials, our similar survival results suggest that PC given every 3 weeks is a feasible alternative.

Treatment with this regimen was well-tolerated in our study. Grade ≥2 pneumonitis and Grade ≥3 oesophagitis occurred in <10% of patients. Moreover, no grade 5 toxicities were observed. Treatment interruption due to intercurrent illness or adverse events occurred in 10.8% of patients, which was less than the 19.7% in the RTOG 0617 trial.[20] This is of particular advantage in the era of maintenance durvalumab, where timely administration of the drug after patients have recovered from acute toxicities of CCRT is crucial.

Table 4. Prognostic factors for overall survival.

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p Value*	Hazard ratio	95% CI	p Value*
Age, y						
≥65	0.783	0.419-1.465	0.445			
<65	1					
Sex						
Male	0.934	0.414-2.106	0.869			
Female	1					
ECOG performance status						
1-2	0.639	0.337-1.215	0.172			
0	1					
Smoking						
Yes	0.795	0.398-1.591	0.518			
No	1					
Chronic obstruction pulmonary disease						
Yes	1.580	0.486-5.133	0.447			
No	1					
Cardiac disease						
Yes	1.337	0.563-3.178	0.510			
No	1					
Histology						
Squamous	1.298	0.710-2.374	0.397			
Non-squamous	1					
Druggable target						
Yes	1.156	0.536-2.495	0.712			
No/unknown	1					
Staging PET-CT performed						
Yes	0.676	0.357-1.279	0.228			
No	1					
Albumin, mg/dL						
<35	1.392	0.723-2.680	0.323			
≥35	1					
Cycle of chemotherapy given concurrent with radiotherapy						
Cycle 1-2	1.257	0.685-2.305	0.460			
Cycle 3-4	1					
Radiotherapy interruption						
Yes	2.245	0.938-5.374	0.069			
No	1					
More than 4 cycles of chemotherapy given in total						
Yes	2.507	1.105-5.687	0.028	3.830	1.479-9.921	0.006
No	1			1		
Chemotherapy deferrals						
Yes	2.029	1.116-3.689	0.020	1.528	0.811-2.879	0.190
No	1			1		
Chemotherapy dose reduction during treatment						
Yes	1.656	0.904-3.033	0.102			
No	1					
Admission during treatment						
Yes	1.323	0.705-2.481	0.383			
No	1					
≥Grade 2 oesophagitis						
Yes	1.634	0.725-3.684	0.237			
No	1					
Received <4 cycles of planned chemotherapy						
Yes	3.316	1.141-9.634	0.028	0.968	0.297-3.156	0.957
No	1			1		
Mean lung dose, Gy	1.002	0.910-1.103	0.967			
Mean oesophageal dose, Gy	1.020	0.979-1.063	0.341			
Gross tumour volume, cc	1.005	1.002-1.007	<0.001	1.005	1.002-1.008	0.001
Mean heart dose				1		
≥5 Gy	2.029	1.078-3.820	0.028	2.507	1.293-5.108	0.007
<5 Gy	1			1		

Abbreviations: 95% CI = 95% confidence interval; ECOG = Eastern Cooperative Oncology Group; PET-CT = positron emission tomography–computed tomography.

* Cox proportional hazards model.

Table 5. Prognostic factors for progression-free survival.

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p Value*	Hazard ratio	95% CI	p Value*
Age, y						
≥65	0.883	0.512-1.522	0.655			
<65	1					
Sex						
Male	0.621	0.308-1.251	0.182			
Female	1					
ECOG performance status						
1-2	0.823	0.469-1.446	0.499			
0	1					
Smoking						
Yes	0.626	0.341-1.148	0.130			
No	1					
Chronic obstruction pulmonary disease						
Yes	2.067	0.630-6.781	0.231			
No	1					
Cardiac disease						
Yes	0.839	0.359-1.960	0.685			
No	1					
Histology						
Squamous	1.011	0.591-1.730	0.968			
Non-squamous	1					
Druggable driver mutation present						
Yes	1.720	0.878-3.367	0.114			
No/unknown	1					
Staging PET-CT performed						
Yes	0.977	0.537-1.778	0.939			
No	1					
Albumin, mg/dL						
<35	1.077	0.582-1.992	0.813			
≥35	1					
Cycle of chemotherapy given concurrent with radiotherapy						
Cycle 1-2	1.509	0.883-2.579	0.132			
Cycle 3-4	1					
Radiotherapy interruption						
Yes	2.852	1.260-6.458	0.012	1.518	0.560-4.113	0.412
No	1			1		
More than 4 cycles of chemotherapy given in total						
Yes	2.152	0.962-4.817	0.062			
No	1					
Chemotherapy deferrals						
Yes	1.772	1.023-3.068	0.041	1.319	0.671-2.592	0.421
No	1			1		
Chemotherapy dose reduction during treatment						
Yes	1.736	1.007-2.993	0.047	1.273	0.681-2.381	0.449
No	1			1		
Admission during treatment						
Yes	1.588	0.914-2.759	0.101			
No	1					
≥Grade 2 oesophagitis						
Yes	3.558	1.686-7.509	0.001	2.563	1.031-6.370	0.043
No	1			1		
Received <4 cycles of planned chemotherapy						
Yes	6.446	2.250-18.468	0.001	2.301	0.633-8.359	0.206
No	1			1		
Mean lung dose, Gy	0.520	0.891-1.060	0.520			
Mean oesophageal dose, Gy	1.00	0.965-1.040	0.927			
Gross tumour volume, cc	1.003	1.001-1.006	0.003	1.002	0.999-1.005	0.169
Mean heart dose				1		
≥5 Gy	1.306	0.735-2.321	0.362			
<5 Gy	1					

Abbreviations: 95% CI = 95% confidence interval; ECOG = Eastern Cooperative Oncology Group; GTV = gross tumour volume; PET-CT = positron emission tomography–computed tomography.

* Cox proportional hazards model.

Table 6. Comparison of toxicities between EP and two 3-week cycles of PC concurrent with radiotherapy for stage III inoperable NSCLC.*

	EP	PC	p Value
Grade 3 or 4 neutropenia	14/17 (82.4%)	14/65 (21.5%)	< 0.01†
Grade 3 or 4 thrombocytopenia	2/17 (11.8%)	0/65	0.04†
Grade 3 or 4 anaemia	2/17 (11.8%)	2/65 (3.1%)	0.19†
Any grade nausea/vomiting	11/17 (64.7%)	22/65 (33.8%)	0.02‡
Any grade oesophagitis	10/17 (58.8%)	38/65 (58.5%)	0.98‡
Grade 3 or 4 oesophagitis	0/17	3/65 (4.6%)	1.00†
Any grade peripheral neuropathy	0/17	27/65 (41.5%)	< 0.01†
Any grade pneumonitis	0/17	5/65 (7.7%)	0.58†

Abbreviations: EP = etoposide-cisplatin; NSCLC = non-small cell lung cancer; PC = paclitaxel-carboplatin.
* Data are shown as No. (%), unless otherwise specified.
† Fisher's exact test.
‡ Chi-squared test.

Neutropenia was the most common grade 3 or 4 toxicity in our 3-week cycle PC cohort, occurring in 21.5% of patients, but only 4.6% had neutropenic fever. This was similar to the grade 3 or 4 neutropenia rate of 24% in the standard dose RT arm of the RTOG 0617 trial.[20] Prophylactic granulocyte colony-stimulating factor may be indicated to prevent chemotherapy delays and dose reductions, which were negative prognostic factors for worse PFS at univariate analysis.

Comparison with the historical cohort of EP at our institution showed that patients treated with 3-week cycles of PC had no significant difference in survival outcomes but less grade 3 or 4 neutropenia and thrombocytopenia, which suggests 3-week cycles of PC is a safer regimen compared with EP. These comparisons should be interpreted with caution due to the imbalance in patient numbers between the two cohorts. Besides, the 3-week cycle EP regimen used in our institution is different from the 4-week cycle used in other randomised trials (etoposide 50 mg/m^2 days 1-5, cisplatin 50 mg/m^2 day 1 and 8 every 4 weeks).[6,11,22]

Analysing dosimetric parameters revealed that a mean heart dose of ≥5 Gy was an independent negative prognostic factor for OS. In the RTOG 0617 study, heart V40 was associated with worse OS after adjusting for other prognostic factors.[23] Retrospective analyses also demonstrated that there is a continuous increase in risk of cardiac events with each Gy increase in mean heart dose.[24,25] Our results confirmed the association between high cardiac radiation exposure and worse OS.

Strategies have to be constructed to reduce cardiac dose in order to lower cardiac complications and related deaths, as NSCLC patients have better survival from nonchemotherapeutic systemic treatment options, which can carry cardiac toxicities, e.g., prolonged QT interval from crizotinib and osimertinib and immune-related myocarditis from immunotherapy.[26] The use of four-dimensional CT and intensity-modulated RT for treatment planning, which has been shown to reduce cardiac dose,[23,27,28] should be reviewed to see whether clinical benefit can be derived from those techniques.

In our series, all patients were designated to receive four cycles of chemotherapy, with two given with RT. An additional two cycles after the fourth was allowed depending on patient's fitness, response and tolerance to treatment, and presence of any poor prognostic factors, e.g., large tumours, N3 disease and neuroendocrine component. The worse OS in patients receiving more than four cycles of chemotherapy suggests that continuing chemotherapy beyond four cycles does not alter the poor prognosis of these patients. Instead, they should be considered for adjuvant durvalumab as soon as possible after recovering from CCRT based on the recent PACIFIC trial.[5]

The ongoing coronavirus disease 2019 pandemic has changed how oncologic care is delivered, as cancer patients are more vulnerable to infections and its complications. ESMO highlights minimising hospital attendance with alternative treatment schedules as an important strategy in preventing this highly contagious virus.[29] PC given every 3 weeks has the merit of only requiring 1 day of admission in 3 weeks, compared with 6 days of admission for the SWOG 9019 EP regimen[6] and 3-day admissions for weekly PC every 3 weeks. The fewer doses of high-dose dexamethasone (20 mg once every 3 weeks) required for premedication compared

with the weekly regimen (10 mg once every week) reduces the risk of immunosuppression.

Another chemotherapy regimen which would reduce day admissions is the pemetrexed-platinum combination, similarly, only requiring one infusion every 3 weeks. The PROCLAIM trial demonstrated that there was no statistically significant survival difference between pemetrexed-cisplatin and EP with RT, but the former was associated with fewer Grade 3 or 4 events, including neutropenia.[30] PC given every 3 weeks has two potential advantages compared with the pemetrexed-platinum combination. First, pemetrexed-platinum requires slightly more dexamethasone as premedication (4 mg twice daily for 3 days for a total of 24 mg every 3 weeks). Besides, as intramuscular vitamin B12 injections and daily folic acid supplementation are required, drug compliance may be an issue for some patients.

In the era of precision oncology, there are emerging data regarding use of neoadjuvant oral targeted treatment before surgery for borderline operable stage III-N2 tumours with driver mutations.[31,32] This strategy is also favourable during the pandemic as patients can receive treatment at home and avoid multi-day RT treatment. However, many questions still have to be answered in prospective studies before routine application of this approach, including the total duration of perioperative treatment, patient selection, and its benefit can be compared with definitive CCRT.

A major limitation of this study is that it is a single-centre retrospective study, and hence prone to selection bias. Inoperable stage III lung cancer is a heterogeneous group with varying treatment strategies employed depending on the size and location of tumours as well as patient's age, performance status and co-morbidities. In our cohort, >60% of our patients had performance status score 0 and most did not have significant cardiopulmonary co-morbidities. Therefore, patients may have had better tolerance of treatment and hence a better prognosis. Moreover, as intensity-modulated RT technique was not used for treatment planning, tumours with poorer prognostic factors, for example, larger bulky disease, contralateral nodal involvement, or close proximity to critical organs like the spinal cord were excluded as dosimetric limits cannot be met with three-dimensional conformal technique for a dose of 60 Gy. These two reasons could have resulted in better treatment outcomes in our cohort.

Another limitation is lack of consistency in progress imaging interval for response assessment due to resource constraints. Only 31 patients (47.7%) had a follow-up CT or PET-CT within the first 6 months after CCRT. Patients with asymptomatic disease progression or with extrathoracic metastases not detected on a follow-up chest radiograph were possibly missed. Therefore, the PFS may have been overestimated. On the other hand, only a small number of patients in the cohort had brain imaging for staging prior to treatment (magnetic resonance imaging: two patients [3.1%], contrast-enhanced CT: seven patients [10.8%]). Small asymptomatic brain metastases could have been missed for some patients and hence underestimated the PFS.

In summary, PC given every 3 weeks concurrently with RT is a well-tolerated option for stage III inoperable NSCLC with comparable outcomes to those of other chemotherapy regimens reported in the literature. Its schedule, with fewer day admissions for chemotherapy infusions, may be an advantage during the ongoing coronavirus disease pandemic. Future studies should evaluate whether this regimen in combination with more sophisticated RT techniques (e.g., intensity-modulated RT, four-dimensional CT) could further improve the therapeutic ratio of treatment in this group of patients in the era of consolidative durvalumab.

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