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Phase I study of concurrent and consolidation cisplatin and docetaxel chemotherapy with thoracic radiotherapy in non-small cell lung cancer

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ABSTRACT

Background We designed a phase I study of concurrent chemoradiotherapy (CCRT) with docetaxel (D) and cisplatin (C), followed by consolidation DC, for unresectable stage III non-small cell lung cancer (NSCLC).

Methods Patients with histologically proven and unresectable stage III NSCLC were eligible. During CCRT, C was given every 3 weeks (75 mg/m^2) and D given weekly. The starting dose of D was 20 mg/m^2, escalated in cohorts of 3 to define the maximum tolerated dose (MTD). Radiotherapy was prescribed to a dose of 60 Gy in 30 fractions. This was followed by 2 cycles of consolidation DC, which were dose escalated if CCRT was tolerated.

Results Twenty-six patients were enrolled, with 1 excluded following evidence of metastatic disease. Nineteen patients completed both phases of treatment. There were 7 grade 3 events during CCRT (5 esophagitis, 2 nausea), and 8 grade 3 events during consolidation (2 neutropenia, 2 leukopenia, 1 esophagitis, 2 nausea, and 1 pneumonitis). Three patients had grade 4 neutropenia. No patients died due to toxicities. The MTD of concurrent weekly D was 20 mg/m^2. Consolidation D and C were each dose escalated to 75 mg/m^2 in 8 patients. The median overall survival (OS) and progression-free survival (PFS) of all patients were 33.6 months and 17.2 months, respectively, with median follow-up of 26.6 months (range 0.43–110.8).

Conclusions The use of docetaxel 20 mg/m^2 weekly and cisplatin 75 mg/m^2 every 3 weeks concurrent with thoracic radiotherapy, followed by consolidation docetaxel and cisplatin, both given at 75 mg/m^2 every 3 weeks, appears to be safe in this phase I trial.

Key Words Non-small cell lung cancer, docetaxel, cisplatin, chemoradiotherapy, consolidation

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INTRODUCTION

Concurrent chemoradiotherapy (CCRT) is considered the standard treatment for locoregionally advanced non-small cell lung cancer (NSCLC) that is surgically unresectable and/or medically inoperable. Concurrent chemoradiotherapy has been shown to be superior to sequential chemotherapy and radiation therapy in randomized trials but at an increased risk of acute esophagitis[1-5]. Although chemotherapy usually consists of platinum-doublet therapy, there is no established consensus for the optimal regimen. Locoregional failure after CCRT occurs in over 30% of cases at two years, with distant failure occurring in close to 50% of patients[6]. As a result, more effective therapy is needed to reduce the risk of both locoregional disease and metastatic spread.

Docetaxel is a semi-synthetic taxane that has been shown in preclinical studies to be a more effective radiosensitizer than paclitaxel[6,7]. Mechanisms include inducing G_2/M phase arrest and reoxygenation of radioresistant

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hypoxic cells[8,9]. Previous phase I trials of docetaxel given weekly or bi-weekly concurrently with radiation have been reported, with the maximum tolerated dose (MTD) in the range of 20–30 mg/m^2 [10-13]. Some studies investigating concurrent docetaxel and cisplatin with radiation have demonstrated feasibility mostly with each drug given weekly[14-17]. However, taxanes have an association with radiation pneumonitis when given concurrently with radiation, and therefore caution is warranted[13,18-20].

Although both docetaxel and cisplatin can be given weekly, an alternative approach is to deliver cisplatin every three weeks and administer docetaxel weekly. A randomized phase II trial evaluating neoadjuvant carboplatin and paclitaxel followed by maintenance paclitaxel for advanced or metastatic NSCLC demonstrated that carboplatin given every four weeks with weekly paclitaxel resulted in better outcomes than weekly administration[21].

To our knowledge, there has never been a dose-finding study for CCRT and consolidation chemotherapy completed using cisplatin and docetaxel. The goal of this phase I trial was to evaluate a regimen of CCRT consisting of cisplatin 75 mg/m^2 given every three weeks and docetaxel given weekly, for a total of two cycles concurrent with six weeks of radical radiation treatment prescribed to 60 Gy, followed by two consolidation cycles of cisplatin and docetaxel given every three weeks. Dose-limiting toxicity (DLT) is expected to arise mainly from the acute toxicity of the two initial cycles of chemotherapy administered with thoracic radiotherapy (RT). Although the consolidation regimen is known to be tolerable when given alone[22], toxicity could also arise in the two consolidation cycles of chemotherapy as a result of exacerbation from the prior CCRT. Our primary objectives were to recommend phase II/III doses for weekly docetaxel during concurrent radiation treatment and for cisplatin and docetaxel during consolidation chemotherapy. Our secondary objective was to characterize toxicities, especially DLTs.

METHODS AND MATERIALS

Patient Selection

Patients with histologically or cytologically proven and unresectable stage IIIA/B NSCLC were eligible for this study. Inclusion criteria were: patients over the age of 18; performance status 0–2 by the Eastern Cooperative Oncology Group (ECOG) scale; creatinine clearance ≥ 50 mL/min; baseline forced expiratory volume in 1 second (FEV1) ≥ 1.5 L or, if <1.5 L, the predicted FEV1 of the contralateral lung must be greater than 800 mL based on quantitative split function; absolute neutrophil count ≥ 1.5 x 10^9/L; adequate hepatic function with bilirubin ≤ 1.5 times the upper limit of normal (ULN) and serum glutamic-oxaloacetic transaminase level (SGOT) or serum glutamic-pyruvate transaminase (SGPT) ≤ 2.5 times the ULN. Exclusion criteria included: resectable stage IIIA disease with planned trimodality therapy; malignant pleural/pericardial effusions; uncontrolled comorbidities precluding safe completion of the regimen; pre-existing cancers other than non-melanoma skin cancer, cervical carcinoma-in-situ or inactive malignancies treated only by surgery and/or hormone therapy that do not confuse the diagnosis of NSCLC; known hypersensitivity to drugs formulated with polysorbate 80 or to platinum-containing compounds.

This study was approved by the local research ethics board and scientific committee, and re-approved for each year patients were followed on protocol. This trial was registered under the Ontario Institute for Cancer Research with Protocol ID OCT1164, CIS/DOC/RT.

Chemotherapy

Chemotherapy consisted of cisplatin given every three weeks and docetaxel given weekly during CCRT. Chemotherapy and RT began within 24 hours of each other. Two cycles of consolidation cisplatin and docetaxel were given after the completion of CCRT. Cisplatin dose during CCRT was fixed at 75 mg/m^2. Docetaxel was administered prior to cisplatin, and given over one hour, followed by intravenous dexamethasone, ondansetron, 1,000 mL normal saline, and furosemide. Cisplatin was then administered in 500 mL normal saline over one hour. Ondansetron was given after cisplatin administration and for three days after. Dexamethasone was given for three to five days starting the day before chemotherapy during both CCRT and consolidation.

Radiotherapy

Patients were treated using 6 to18 MV photon beams. The radiation dose was 60 Gy in 30 fractions, prescribed daily excluding weekends. The maximal doses to the spinal cord, heart, and esophagus were 47 Gy, 45 Gy, and 60 Gy, respectively. The maximum V20 (volume of lung receiving 20 Gy or more) was 33%. Target volumes were defined with clinical tumour volume (CTV) being a 1 cm margin around the gross tumour volume (GTV). Initially, elective nodal irradiation (ENI) was permitted, which prophylactically treated clinically and radiographically uninvolved lymph nodes at the discretion of the treating radiation oncologist. However, after treating the initial eight patients, it became clear that concurrent docetaxel at a lower dose of 15 mg/m^2 was not tolerable. The protocol was then modified to omit ENI, which is consistent with more modern protocols[6].

Patients were treated with any combination of coplanar or non-coplanar (preferred) three-dimensional conformal or intensity-modulated fields. Antero-posterior and postero-anterior (APPA) arrangements followed by off-cord fields were permitted, but were used primarily during the early years of the study. While arc-based therapy (Rapid Arc or Helical Tomotherapy) was not allowed, gated radiotherapy was permitted.

Dose-Limiting Toxicity, MTD, and Response Evaluation

Evaluation for toxicity was performed on a weekly basis during treatment, through clinical exam, complete blood count (CBC), as well as biochemistry tests and chest X-ray every three weeks. Electrocardiogram and wall motion studies were performed after cycle 2. Computed tomography (CT) of the chest and CT or ultrasound of the abdomen were performed after CCRT and within one month after the last cycle of consolidation chemotherapy. Patients were then monitored every three months with a clinical visit, CBC, biochemistry, and chest X-rays. Computed tomography

imaging was performed every three months for one year then every six months thereafter.

Dose-limiting toxicity was defined as any of the following, during or within six weeks after CCRT: febrile neutropenia; life threatening bleed due to grade 4 thrombocytopenia; grade 3/4 neutropenia or thrombocytopenia causing an omission of weekly docetaxel; grade 4 esophagitis; grade 3 esophagitis causing more than 2-day interruption in radiotherapy, or an omission of one of the weekly chemotherapies, or requiring any of hospital admission, enteral feeding, or more than one day of fluid administration or is severe enough to make treatment undeliverable according to the principal investigator; grade 4 pneumonitis; any grade 4 toxicity mandating greater than 7-day break in RT; toxic death. Dose limiting toxicity related purely to cisplatin consisted of: grade 3/4 renal impairment; grade 2/3 peripheral neuropathy; grade 3/4 nausea and vomiting (despite maximal antiemetics). Dose-limiting toxicity related to consolidation cisplatin and docetaxel also included grade 3/4 diarrhea despite use of loperamide.

The procedure for determining MTD is shown in a schematic in Figure 1. Patients were accrued in cohorts of three, starting at a dose of weekly docetaxel 20 mg/m^2 for six weeks during CCRT. Tolerability was defined as the dose at which docetaxel did not cause DLT in ≥ 33% of a cohort of at least three patients. If one DLT instance occurred in a cohort of three, then the cohort was expanded to up to six patients. If a dose was deemed to be intolerable, then another three to six patients were accrued to a new cohort at a lower docetaxel dose. Before the MTD of concurrent docetaxel was determined, patients received consolidation cisplatin and docetaxel, dosed at 60 mg/m^2 each, given every three weeks.

Once the MTD of concurrent docetaxel was established, at 20 mg/m^2 or less, the consolidation cisplatin dose was escalated to 75 mg/m^2. If this was tolerated, the dose of consolidation docetaxel was escalated to 75 mg/m^2. Finally, if all of the above were tolerated, the concurrent docetaxel dose was escalated to 25 mg/m^2. The last cohort was expanded to at least 12 patients to ensure tolerability.

Response and progression were evaluated using RECIST (Response Evaluation Criteria in Solid Tumours) guidelines[23]. Overall survival (OS) was defined as the time from date of registration to date of last follow-up and/or death, whichever came first. Progression-free survival (PFS) was defined as the time from date of registration to date of last follow-up, death and/or progression, whichever came first.

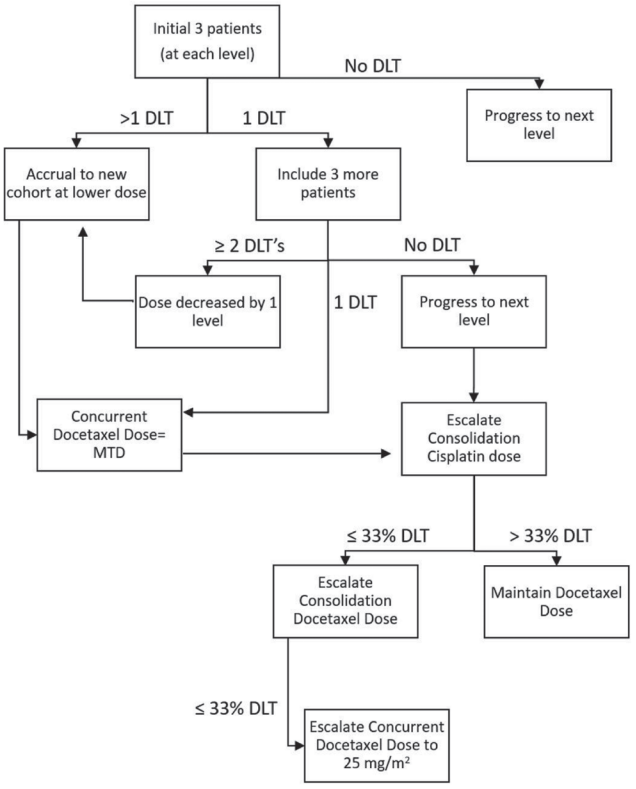

FIGURE 1 Study design and flow. DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

Statistical Analysis

Descriptive statistics were generated for baseline patient and tumour characteristics, as well as the type of DLT for all patients. Kaplan–Meier estimates of OS and PFS were generated.

RESULTS

Patient Characteristics

Between September 2004 and June 2014, 26 patients were enrolled in the study. One patient was excluded following evidence of metastatic stage IV disease on baseline CT imaging and was not treated on protocol. Patient characteristics are shown in Table I.

Treatment Delivery

Of 26 patients, 19 (73%) were able to complete concurrent chemoradiotherapy and receive consolidation chemotherapy. Seven patients did not complete both phases of treatment: one patient was not treated on study protocol due to metastatic disease; one patient withdrew consent for treatment; one did not complete CCRT due to grade 3 esophagitis; one had disease progression prior to completion of CCRT; one had disease progression prior to the initiation of consolidation; two could not receive consolidation due to toxicities from grade 3 esophagitis and nausea.

It became clear after recruiting the initial eight patients that docetaxel at 15 mg/m^2 (concurrent level -1) was intolerable due to esophageal toxicity. Radiotherapy was then modified to exclude nodal irradiation (ENI). New cohorts of patients were recruited to start at concurrent -1 and consolidation level 0 chemotherapy with new radiotherapy planning. Doses were then escalated as per the original protocol (Figure 1 and Table II).

Toxicity

In the initial cohort of three patients, a weekly docetaxel dose of 20 mg/m^2 was given (concurrent level 0), and two of the three patients had DLTs of grade 3 esophagitis. Thus, another cohort was recruited with docetaxel dose reduced to 15 mg/m^2 (level -1). One of the five patients accrued to this cohort developed grade 3 esophagitis and was unable complete treatment. After modification of radiotherapy

TABLE I Summary of patient characteristics

Characteristic	Total group (*N*=26)
Age	
Median	61
Range	47–75
Sex	
F	12
M	14
Performance Status	
ECOG 0	18
ECOG 1	7
ECOG 2	1
T stage	
1	1
2	11
3	8
4	5
N stage	
0	1
1	2
2	20
3	2
Stage	
IIIA	18
IIIB	7
Histology	
Adenocarcinoma	6
Squamous cell carcinoma	8
Large cell carcinoma	2
Not otherwise specified	10

TABLE II Dose level of chemotherapy

Concurrent chemotherapy			Consolidation chemotherapy		
Level	Docetaxel dose weekly (mg/m^2)	Cisplatin dose q3 weeks (mg/m^2)	Level	Docetaxel dose (mg/m^2)	Cisplatin dose (mg/m^2)
-2	10	75	-1	45	60
-1	15	75	0	60	60
0	20	75	+1	60	75
+1	25	75	+2	75	75

technique to exclude ENI, docetaxel was tolerated at 20 mg/m^2 (level 0) for six patients (Tables III–IV). A total of five patients (20%) developed grade 3 esophagitis and no patients had grade 2 or higher pneumonitis or hematological toxicities during CCRT. Consolidation levels of chemotherapy were then escalated to cisplatin 75 mg/m^2 (levels +1 and +2) for eight patients, and to both cisplatin and docetaxel 75 mg/m^2 (level +2) for five patients. Grade 3 and 4 hematological toxicities occurred only during consolidation chemotherapy. Three patients (12%) developed grade 4 neutropenia at levels +1 and +2 of consolidation chemotherapy. However, there was no significant increase in esophagitis or pneumonitis (Table V). Most patients (7 of 8) treated with levels +1 and +2 of consolidation completed treatment, with one not completing due to disease progression. The concurrent docetaxel dose of 25 mg/m^2 (level +1) was not reached. Details of incidences of toxicities during CCRT and consolidation chemotherapy are shown in Tables III, IV, VI, VII.

Response and Survival

Radiological complete response to treatment was observed in 1 of 26 analyzed patients. Partial response and stable disease were achieved in 16 and 4 patients, respectively. Two patients had progressive disease: one patient prior to and one after completion of CCRT. In three patients, disease was not evaluable due to the presence of metastatic disease on baseline imaging before initiation of treatment, patient refusal, and grade 3 esophagitis during treatment (Tables VIII–IX).

Although planned trimodality therapy was one of the study exclusion criteria, 5 of the 11 patients who achieved partial responses were re-evaluated and underwent surgical resection; one patient underwent a pneumonectomy, two patients underwent lobectomies, one patient underwent lobectomy and a wedge resection, one patient underwent bi-lobectomies and wedge resection. No residual disease was seen in pathological specimens of three of five patients.

Patients were followed to a median of 26.6 months, with a range of 0.43 to 110.8 months. At this time, nine patients are living (post-operative, *n*=2, and non-operative, *n*=7). Two patients have no evidence of residual disease currently (post-operative, *n*=1), while seven patients are living with disease recurrence. Sixteen patients died of their disease, and one patient died of another cause.

The median OS for all patients was 33.6 months (95% confidence interval [CI] 15.8–71.6). Median progression-free survival was 17.2 months (95% CI 9.2–30.3) followed over a range of 0.43 to 110.8 months (Figure 2). To assess the impact of surgery on PFS, a sensitivity analysis was done censoring at the time of surgery. This resulted in median PFS of 20.1 months (95% CI 11.0–N/A).

DISCUSSION

This phase I trial is, to our knowledge, the first to examine optimal doses for cisplatin and docetaxel in the setting of concurrent chemoradiotherapy followed by consolidation chemotherapy for patients with locally advanced and unresectable NSCLC. The MTD and recommended phase II dose (RP2D) of docetaxel was determined to be 20 mg/m^2 given weekly with cisplatin 75 mg/m^2 given every three weeks concurrent with thoracic radiotherapy prescribed to 60 Gy without ENI. Doses of consolidation docetaxel and cisplatin given every three weeks were escalated to 75 mg/m^2 each, the RP2D for consolidation. Main DLTs were esophagitis during the concurrent phase and neutropenia during the consolidation phase. Pulmonary toxicities were minimal. There was one complete radiological response

and three complete pathological responses in five patients who underwent surgery. Results of OS and PFS, 33.6 months and 17.2 months, respectively, are promising considering the results of the standard arm of the recent RTOG 0617 trial, in which median OS and PFS were 28.7 and 11.8 months, respectively[6]. These results are hypothesis-generating only given that trials with different design and treatment approaches cannot be compared directly.

Currently, several concurrent chemotherapy regimens are accepted, with none being shown to be superior to others[24-26]. A phase III trial did not show any difference in survival, response rate, and toxicity between docetaxel, paclitaxel, and gemcitabine when combined with cisplatin given concurrently with radiotherapy, with median survival being 27.6 months in the cisplatin and docetaxel arm[27]. The role and safety of docetaxel given concurrently with radiotherapy, with or without cisplatin, has been evaluated in previous studies, with each drug usually administered weekly[10-17]. The recommended dose for weekly docetaxel ranged from 20 to 30 mg/m^2 and for weekly cisplatin 20 to 25 mg/m^2. A selection of these studies is summarized in Table X[11-17].

TABLE III Hematological toxicities during concurrent chemotherapy with radiation (highest grades reported)

Dose Level	Nodal RT (Y/N)	Patients (*n*)	Grade							
			Leukopenia		Neutropenia		Anemia		Thrombocytopenia	
			1	2–4	1	2–4	1	2–4	1	2–4
0	Y	3	0	0	0	0	0	0	0	0
-1	Y	5	0	0	0	0	0	0	0	0
-1	N	3	0	0	0	0	0	0	0	0
0	N	14	2	0	2	0	1	0	1	0
	Total	25	2	0	2	0	1	0	1	0

Note: 1 patient was excluded due to metastatic disease and was not treated on trial.
Nodal RT = elective nodal radiotherapy; Y = received, N = not received.

TABLE IV Non-hematological toxicities during concurrent chemotherapy with radiation (highest grades reported)

Dose Level	Nodal RT (Y/N)	Patients (*n*)	Grade							
			Esophagitis			Nausea			Pneumonitis	
			1	2	3	1	2	3	1	2–4
0	Y	3	0	1	2	0	0	2	0	0
-1	Y	5	2	2	1	0	3	0	0	0
-1	N	3	0	3	0	1	0	0	0	0
0	N	14	10	2	2	10	0	0	1	0
	Total	25	12	8	5	11	3	2	1	0

Note: 1 patient was excluded due to metastatic disease and was not treated on trial.
Nodal RT = elective nodal radiotherapy; Y = received, N = not received.

TABLE V Incidences of toxicities during concurrent chemoradiotherapy and consolidation chemotherapy

Toxicity	Grade							
	Concurrent (*n*=25)				Consolidation (*n*=25)			
	1	2	3	4	1	2	3	4
Hematologic								
Leukopenia, *n* (%)	2 (8)	0	0	0	0	0	2 (8)	0
Neutropenia, *n* (%)	2 (8)	0	0	0	0	0	2 (8)	3 (12)
Anemia, *n* (%)	1 (4)	0	0	0	0	2 (8)	0	0
Thrombocytopenia, *n* (%)	1 (4)	0	0	0	1 (4)	0	0	0
Non-hematologic								
Esophagitis, *n* (%)	12 (48)	8 (32)	5 (20)	0	8 (32)	6 (24)	1 (4)	0
Nausea, *n* (%)	11 (44)	3 (12)	2 (8)	0	6 (24)	4 (16)	2 (8)	0
Pneumonitis, *n* (%)	1 (4)	0	0	0	2 (8)	1 (4)	1 (4)	0

A previous study showed that when weekly docetaxel at 20 mg/m^2 was combined with thoracic radiotherapy, three patients (9%) died of chemoradiation-induced pneumonitis with a 47% incidence of grade 3 or higher pneumonitis[13]. However, this study was conducted using 2D radiotherapy planning and also employed the use of granulocyte colony-stimulating factor (G-CSF). In fact, several studies summarized in Table X also utilized 2D radiotherapy planning and many patients received ENI. In contrast, we ultimately employed the use of 3D radiation planning and more modern 3D-conformal or intensity-modulated fields. Furthermore, we discontinued the practice of ENI, in keeping with current treatment methods. We also did not use G-CSF. We believe that this contributed to minimal observed pneumonitis in our study, with no patients having grade 2 or higher pneumonitis during CCRT and only one having grade 3 pneumonitis after consolidation.

The findings of this study must be considered in the context of its limitations. Patients who were enrolled had excellent performance status and were either ECOG 0 or 1.

TABLE VI Hematological toxicities during consolidation chemotherapy (highest grades reported)

Dose Level	Nodal RT (Y/N)	Patients *(n)*	Grade								
			Leukopenia		Neutropenia			Anemia		Thrombocytopenia	
			1–2	3	1–2	3	4	2	3–4	1	2–3
0	Y	6	0	0	0	0	0	0	0	0	0
+1	Y	2	0	0	0	0	0	0	0	0	0
0	N	9	0	0	0	1	0	1	0	0	0
+1	N	3	0	2	0	0	2	1	0	1	0
+2	N	5	0	0	0	1	1	0	0	0	0
	Total	25	0	2	0	2	3	2	0	1	0

Note: 1 patient was excluded due to metastatic disease and was not treated on trial.
Nodal RT = elective nodal radiotherapy; Y = received, N = not received.

TABLE VII Non-hematological toxicities during consolidation chemotherapy (highest grades reported)

Dose Level	Nodal RT (Y/N)	Patients *(n)*	Grade								
			Esophagitis			Nausea			Pneumonitis		
			1	2	3	1	2	3	1	2	3
0	Y	6	0	3	1	1	0	1	0	0	0
+1	Y	2	1	0	0	0	0	0	0	0	0
0	N	9	3	4	0	3	1	0	0	0	0
+1	N	3	2	0	0	1	1	0	0	1	1
+2	N	5	2	1	0	1	2	0	2	0	0
	Total	25	8	6	1	6	4	1	2	1	1

Note: 1 patient was excluded due to metastatic disease and was not treated on trial.
Nodal RT = Elective Nodal Radiotherapy; Y = Received, N = not received.

TABLE VIII Best response to treatment

Dose Level		Nodal RT (Y/N)	Patients *(n)*	CR	PR	SD	PD	NE	Surgery	cPR
Concurrent	Consolidation									
0	0	Y	3	0	1	2	0	0	0	-
-1	0	Y	3	1	2	0	0	0	1	1
-1	+1	Y	2	0	0	1	0	1	0	-
-1	0	N	3	0	3	0	0	0	1	0
0	0	N	7	0	4	0	1	2	1	1
0	+1	N	3	0	3	0	0	0	0	-
0	+2	N	5	0	3	1	1	0	2	1
		Total	26	1	16	4	2	3	5	3

Nodal RT = Elective Nodal Radiotherapy, Y = received, N = not received; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; cPR = complete pathological response post surgical resection

In addition, although we included patients with initially unresectable stage IIIA/IIIB NSCLC, five patients had surgical resection after their treatment, which may have impacted outcomes. We also did not have a control group. Ideally, the efficacy of docetaxel with cisplatin would be assessed in a future randomized controlled trial comparing with other chemotherapy regimens.

This study extends the published knowledge base in several important ways. We demonstrate that weekly docetaxel and cisplatin given every three weeks concurrently

TABLE IXa Best response to treatment after concurrent chemotherapy and radiation

Dose Level	Nodal RT (Y/N)	Patients (n)	CR	PR	SD	PD	NE
0	Y	3	0	0	3	0	0
-1	Y	3	0	1	2	0	0
-1	Y	2	0	0	1	0	1
-1	N	3	0	1	2	0	0
0	N	7	0	1	3	1	2
0	N	3	0	1	2	0	0
0	N	5	0	2	2	1	0
	Total	26	0	6	15	2	3

Nodal RT = Elective Nodal Radiotherapy, Y = received, N = not received; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable

TABLE IXb Best response to treatment after consolidation chemotherapy

Dose Level	Nodal RT (Y/N)	Patients (n)	CR	PR	SD	PD	NE
0	Y	3	0	1	0	0	2
0	Y	3	1	2	0	0	0
+1	Y	2	0	0	1	0	1
0	N	3	0	3	0	0	0
0	N	7	0	4	0	0	3
+1	N	3	0	3	0	0	0
+2	N	5	0	3	1	0	1
	Total	26	1	16	2	0	7

Nodal RT = elective nodal radiotherapy, Y = received, N = not received; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable

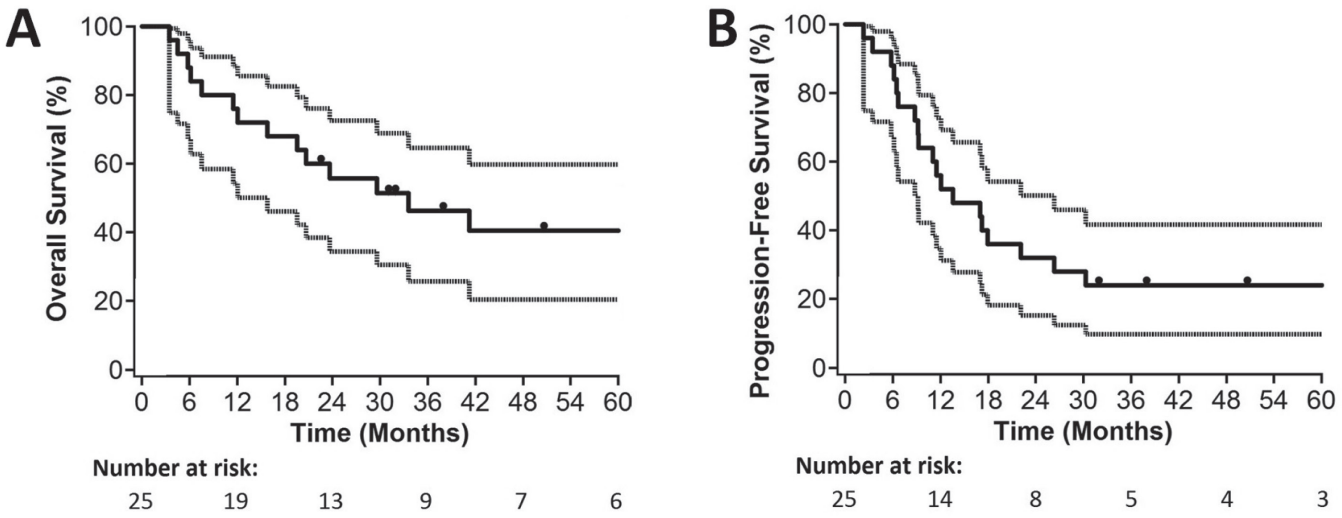

FIGURE 2 Kaplan–Meier plots for A) overall survival and B) progression-free survival (*n*=25).

TABLE X Summary of previous Phase I/II CCRT studies using docetaxel with or without cisplatin

Study	Study population	Docetaxel dose weekly (mg/m^2)	Cisplatin dose (mg/m^2)	RT dose (Gy)	RT technique	Median OS/PFS (months)
Koukourakis 1998	NSCLC, stage III–IV	30[a]	N/A	60–64 + ENI	3D planning, APPA fields	Stage IIIB: 7.5 / NR
Mauer 1998	NSCLC, esophageal cancer, stage III–IV	20[a]	N/A	45–70	NR	NR
Wu 2002	NSCLC, stage III	20[a]	20, weekly	54 + ENI, tumour boost to 63	APPA fields	NR
Mudad 2003	NSCLC, stage III	25[a]	25, weekly	60 + ENI	APPA fields	10.5 / NR
Onishi 2003	NSCLC, stage III	20	N/A	44 + ENI, tumour boost to 60–66	2D planning, APPA fields	12.4 / NR
Yamamoto 2006	NSCLC, stage III	20[a]	25, weekly	60 + ENI	2D planning, APPA fields	23.1 / NR
Nakamura 2009	NSCLC, stage III	20[b]	80, days 1 & 29	60 + no ENI	3D planning, APPA fields	26.4 / 16

[a] dose-escalation study.
[b] 1 week chemotherapy break during CCRT.
CCRT = concurrent chemoradiotherapy; NSCLC = non-small cell lung cancer; ENI = elective nodal irradiation; APPA = antero-posterior and postero-anterior; OS = overall survival; PFS = progression-free survival; NR = Not reported.

with radiation followed by consolidation chemotherapy is a feasible option with promising results. We had the benefit of a relatively long follow-up for a phase I study, with median follow-up of 26.6 months up to a maximum of 9.17 years of follow-up, and nine patients are still currently living. The relatively strong PFS of 17.2 months suggests that the results are dependent on the presented regimen rather than on therapies that patients may have received later on which could influence OS results. Furthermore, we had the advantage of assessing pathological response due to patients who were able to undergo surgery after treatment, with three of five demonstrating complete pathological response.

We also incorporated the use of consolidation chemotherapy using docetaxel and cisplatin in this phase I study. The role of consolidation chemotherapy after CCRT is still controversial. The Southwest Oncology Group 9504 trial showed promising results for consolidation docetaxel following CCRT with cisplatin and etoposide, with a median PFS and OS of 16 and 26 months, respectively[28]. Randomized phase II trials using platinum-based chemotherapy in the concurrent and consolidation settings have shown possible trends in favour of the use of consolidation chemotherapy[29,30]. A Hoosier phase III trial evaluating consolidation docetaxel following cisplatin and etoposide CCRT was terminated early on the basis of futility, with no improvement in survival and an increased rate of toxicity[31]. A pooled analysis of 41 studies showed that consolidation chemotherapy did not offer survival advantages[32]. However, individual patient data were not used and there was significant patient heterogeneity and variability in treatment regimens, with some arguing for better candidate selection for consolidation chemotherapy[33,34].

A randomized phase III trial by the Korean Cancer Study Group evaluated CCRT with cisplatin and docetaxel, both given weekly at 20 mg/m^2 with and without consolidation chemotherapy with 3 cycles of cisplatin and docetaxel, each dosed at 35 mg/m^2 every 3 weeks. Consolidation failed to prolong median PFS and OS (8.1 vs. 9.1 months, and 20.6 vs. 21.8 months in the observation vs. consolidation arms, respectively), but may have significant benefits for patients over 60 on subset analysis[35]. However, 31.6% of patients did not receive any consolidation due to death, progression of disease or toxicity, and 57.9% of patients did not complete consolidation. There were 15 (3.6%) treatment-related deaths during CCRT and 5 deaths during consolidation. In comparison, 19 of our patients (73%) were able to complete both phases of treatment. There were also no treatment-related deaths, suggesting that patient selection or dosing schedules may play a role. Nevertheless, our findings also support that patients treated on this regimen should be highly selected, given potentially encountered toxicities.

A previous study demonstrated significant differences in chemotherapy-related toxicities between trials conducted in Japan and the United States for NSCLC, despite similar study design and treatment regimens[36]. In addition to the Korean phase III trial, many of the phase I/II studies were conducted in Asia[13,15-17]. We postulate that potential differences in allelic distribution in genes involved in chemotherapy disposition and DNA repair between the two regions may also address the varying grades of toxicities observed between our study and previous studies. Differences in toxicity levels may affect survival outcomes in trials in different patient populations. Interestingly, a more recent meta-analysis which included five eligible studies indicated that consolidation chemotherapy improved OS, but not PFS or overall response rate[37]. There was no significant increase in grade 3 or higher radiation pneumonitis but there was an increase in infection risk.

Furthermore, the role of immunotherapy as consolidation treatment after CCRT has been highlighted by the interim results of the PACIFIC trial, in which patients were randomized to durvalumab/MEDI4736, a *PD-L1* inhibitor or placebo, following CCRT with platinum-based

chemotherapy. Planned interim analysis showed that there was significantly improved PFS in patients receiving durvalumab compared with placebo[38]. Newer generations of clinical trials integrating chemotherapy with novel approaches such as immunotherapy should be a priority to further improve the therapeutic ratio of this challenging patient population.

The potential efficacy of combining chemotherapy and immunotherapy was demonstrated in the KEYNOTE-021 study, in which patients with stage IIIB/IV non-squamous NSCLC had superior response when receiving pembrolizumab in addition to platinum-based chemotherapy compared with chemotherapy alone[39]. Docetaxel is a chemotherapy agent which is thought to have additional mechanisms of immune-modulation leading to immunogenic cancer cell death[40,41]. In contrast, etoposide, a frequently used agent in platinum-doublets, has not demonstrated immunogenic properties[42,43]. It is possible that immunogenic agents such as docetaxel may have a synergistic effect when integrated with immunotherapy. Further research should be conducted on the use of combination chemotherapy and immunotherapy in the consolidation setting as well as on the selection of the most optimal drug combinations.

The totality of evidence suggests that consolidation chemotherapy may still be considered for select patients. Specific chemotherapy regimens in both concurrent and consolidation settings warrant further investigation, especially if used in combination with immunotherapy. We believe that this phase I study forms a basis for further trials in the North American and European population using cisplatin and docetaxel in the concurrent or consolidation setting.

CONCLUSIONS

Cisplatin and docetaxel chemotherapy with concurrent radiation treatment followed by consolidation cisplatin and docetaxel appears to be safe, with results suggesting treatment efficacy. Randomized trials are needed to compare this regimen with current widely used chemotherapy agents.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest and declare the following interests: AVL has received speaking honoraria from Varian Medical Systems Inc. There are no other conflicts of interest.

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