Cancer Chemother Pharmacol (2011) 68:1497–1505
DOI 10.1007/s00280-011-1642-8

ORIGINAL ARTICLE

Weekly docetaxel and cisplatin with concomitant radiotherapy in addition to surgery and/or consolidation chemotherapy in stage III non-small cell lung cancer

Fatma Sen · Esra Kaytan Saglam · Alper Toker · Sukru Dilege · Ahmet Kizir · Ethem Nezih Oral · Pinar Saip · Barkin Sakallioglu · Erkan Topuz · Adnan Aydiner

Received: 9 January 2011 / Accepted: 26 March 2011 / Published online: 17 April 2011

Abstract
Purpose The aim of this study was to evaluate efficacy and feasibility of a combination of weekly docetaxel and cisplatin administered concomitantly with radiotherapy followed by surgery in addition to consolidation chemotherapy with docetaxel and cisplatin administered every 3 weeks in stage III non-small cell lung cancer (NSCLC).
Methods A total of 31 histologically proven, locally advanced (stage IIIA-N2 = 9, stage IIIB-T4N0-2 = 22) NSCLC patients were investigated. After administration of 4–6 cycles of weekly docetaxel (20 mg/m^2) and weekly cisplatin (20 mg/m^2) concurrently with radiotherapy, patients underwent operation if their disease was appropriately downstaged. Combination chemotherapy with docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 every 3 weeks was administered as a consolidation regimen. The treatment response, toxicity, time to progression (TTP) and overall survival (OS) were evaluated.
Results After concomitant chemoradiotherapy, complete response and partial response occurred in 16.1 and 67.7% of patients, respectively. Thirteen percentage of patients progressed on treatment, and 3.2% had stable disease. Grade 3–4 hematologic and skin toxicities did not occur, whereas 17.9% of them experienced grade 3–4 oesophageal toxicity. Grade 3 pulmonary toxicity and grade 3–4 emesis developed in 9.7 and 6.4% of patients, respectively. Thirteen responsive patients (41.9%) underwent surgery. The toxicity of consolidation chemotherapy was tolerable. Median OS and TTP were 22 ± 5 (range 13–31) and 12 ± 3 (range 7–17) months, respectively. Median follow-up was 22 (range 2–57) months.
Conclusions Weekly administration of docetaxel and cisplatin concurrently with radiotherapy followed by consolidation chemotherapy is an effective treatment with acceptable toxicity for patients with locally advanced NSCLC especially in combination with surgery.

Keywords Cisplatin · Concomitant chemoradiotherapy · Consolidation · Docetaxel · Locally advanced disease · Non-small cell lung cancer · Surgery

F. Sen (✉) · P. Saip · E. Topuz · A. Aydiner
Department of Medical Oncology, Institute of Oncology, Istanbul University, Istanbul, Turkey
e-mail: fkaragoz_2000@yahoo.com

P. Saip
e-mail: pinarsaip@gmail.com

E. Topuz
e-mail: etopuz@istanbul.edu.tr

A. Aydiner
e-mail: adnanaydiner@superonline.com

E. K. Saglam · A. Kizir · E. N. Oral · B. Sakallioglu
Department of Radiation Oncology, Institute of Oncology, Istanbul University, Istanbul, Turkey
e-mail: esrasaglam@gmail.com

A. Kizir
e-mail: ahmkizir@gmail.com

E. N. Oral
e-mail: enoral@istanbul.edu.tr

A. Toker · S. Dilege
Department of Thoracic Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
e-mail: atoker@istanbul.edu.tr

S. Dilege
e-mail: sdilege@istanbul.edu.tr

Introduction

Patients with non-small cell lung cancer (NSCLC) usually present with locally advanced, unresectable disease

(stages IIIA and IIIB). Because distant metastases are not present macroscopically, treatment of these patients theoretically should be curative. However, patients with locally advanced NSCLC do not live beyond 5 years. Concomitant chemoradiotherapy is the standard treatment approach for patients with locally advanced, unresectable stage IIIA and IIIB NSCLC [1–3]. The approaches to locally advanced NSCLC and to chemoradiotherapy regimens remain heterogeneous among oncologists. The addition of further combination chemotherapy as induction or consolidation to concomitant chemoradiotherapy is the main field of research in this group of patients [4].

Improvements in radiation therapy are achieved through the independent cytotoxic action of drugs and their ability to sensitise tumour cells to radiation. Cisplatin is the standard radiosensitiser drug, although there are some potent newer generation agents, the radiosensitivity of which were investigated in vitro cultered cells and in vivo tumour cells [5]. Docetaxel and other taxanes are able to arrest cells in the radiosensitive G2/M phases of the cell cycle. Other mechanisms by which docetaxel and other taxanes enhance radiation are through the elimination of radioresistant S-phase cells, resulting in tumour reoxygenation, stimulation of antitumour immune resistance mechanisms and, possibly, inhibition of tumour angiogenesis [6]. Although docetaxel increases the tumour radioresponse, it does not increase radiation damage to normal tissue. However, concomitant chemotherapy regimens can result in the eradication of micrometastatic disease while providing a radiation-enhancing effect. Thus, docetaxel can significantly increase the therapeutic outcome when used concomitantly with radiation therapy.

Chemoradiation in the neoadjuvant setting is also expected to increase the resectability rate particularly for patients whose tumours are initially inappropriate for surgery. It has been postulated that the addition of a sequential chemotherapy component to concomitant chemoradiotherapy may further improve treatment outcomes [7]. The surgery has been included in this multimodality setting, and investigators tested either preoperative chemotherapy alone or combinations of preoperative chemotherapy and radiotherapy followed by definitive surgery in Stage III NSCLC [8, 9].

Our aim was to evaluate prospectively the outcome of concomitant chemoradiotherapy with weekly docetaxel and weekly cisplatin followed by surgery and/or combination chemotherapy with cycles of docetaxel and cisplatin administered every 3 weeks as consolidation therapy in unresectable, locally advanced NSCLC patients.

Materials and methods

Subjects

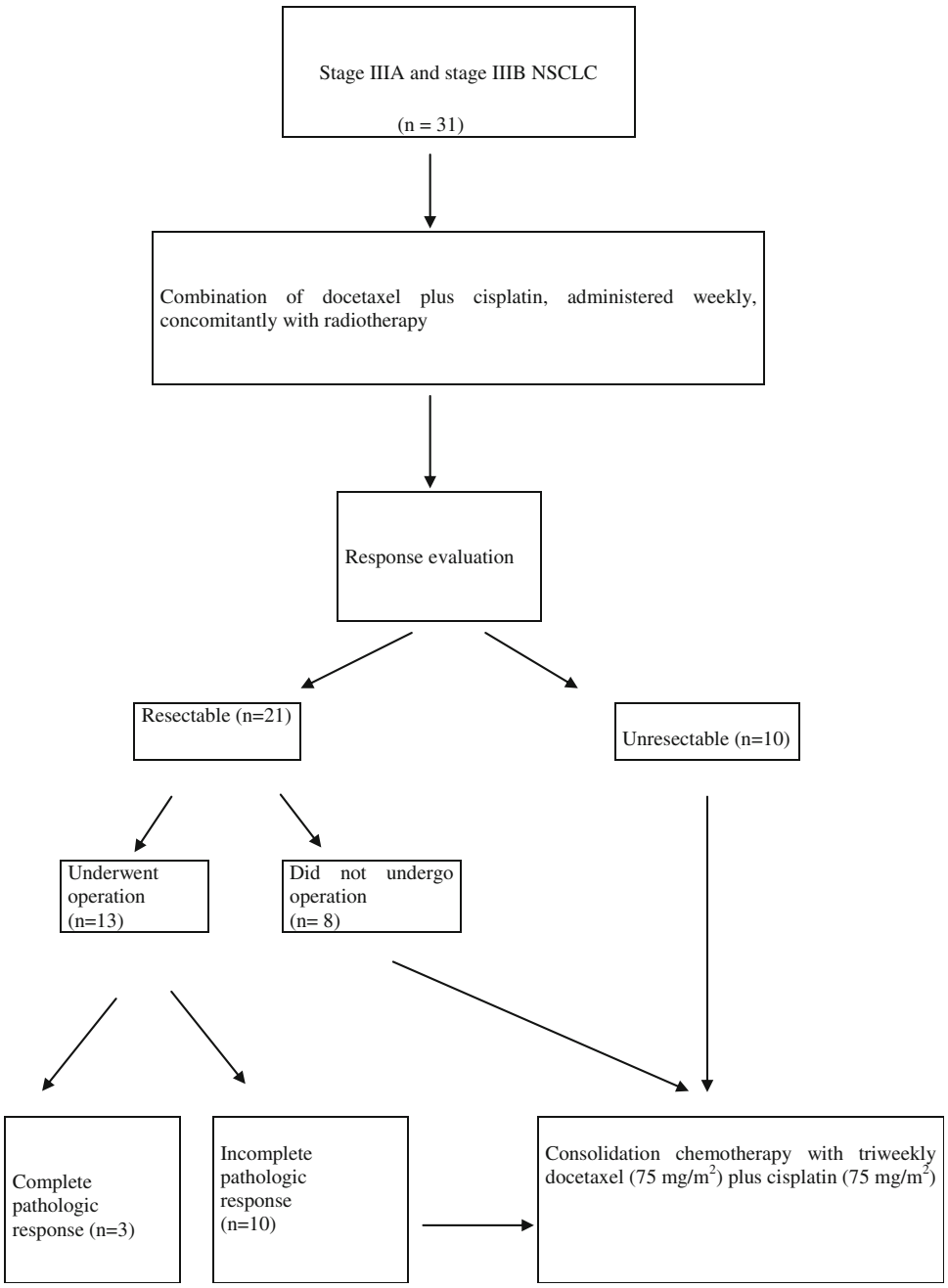
Patients with locally advanced NSCLC who were not previously treated with any modality were enrolled in this prospective study. A total of 31 patients with histologically proven stage IIIA and stage IIIB NSCLC were scheduled for treatment with concomitant chemoradiotherapy in our institute between February 2004 and December 2006. During that period, another study was initiated in which stage IIIA and IIIB locally advanced NSCLC patients were treated with induction chemotherapy followed by concomitant chemoradiotherapy with the same chemotherapy regimens. Patients were enrolled in these 2 studies according to the physicians' preferences. All patients were evaluated for operation before starting chemoradiotherapy and after chemoradiotherapy by an expert thoracic oncology surgeon (A.T. or S.D.). Inclusion criteria were a good performance status (Eastern Cooperative Oncology Group performance score 0–1), forced expiratory volume in 1s (FEV1) greater than or equal to 1.5 l, normal blood biochemistry and complete blood count. Exclusion criteria were major comorbidities, such as a history of congestive heart failure, ischaemic heart disease, uncontrolled arrhythmia, chronic renal failure, another malignancy or weight loss of more than 10% during the previous 3 months. Patients with malignant pleural or pericardial effusions or metastasis to the contralateral supraclavicular lymph nodes were excluded. The pretreatment assessment routinely included a medical history, physical examination, complete blood count, serum biochemistry, chest computed tomography (CT), abdominal CT and/or magnetic resonance imaging (MRI), bone scan, and/or positron emission tomography (PET/CT) and cranial MRI when indicated. Mediastinoscopy or transbronchial needle aspiration was performed for histopathological documentation of N2 or N3 disease. This study was approved by the local scientific committee, and all patients gave written informed consent before treatment was started.

Concomitant and consolidation chemotherapy

The study design is summarised in Fig. 1. Patients were evaluated for concomitant chemoradiotherapy followed by surgery and/or consolidation chemotherapy by the local tumour board.

The chemotherapy regimen used during radiotherapy was weekly docetaxel at 20 mg/m^2 and weekly cisplatin at 20 mg/m^2 starting on the first day of radiotherapy. Prophylactic antiemetics including a 5HT3 antagonist and dexamethasone 8 mg with a proton pomp inhibitor were

Fig. 1 Study design



administered with each chemotherapy cycle on the day before, the day of chemotherapy and the day after chemotherapy. Cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 were administered for 2–4 cycles every 3 weeks as consolidation therapy.

Radiotherapy

Radiotherapy (RT) was delivered with a linear accelerator (Simens/Oncor, Germany) with a 6-to 15-MV photon beam. All patients underwent three-dimensional treatment planning using a CMS—XIO (CMS Inc., St Louis, Missouri, USA). Treatment planning was based on CT scans with 5 mm section thickness and 5-mm intervals obtained in the treatment position. All patients were immobilised with customised devices. RT was administered with an angled field technique to include the entire planning volume (PTV) in the isodose 95% area. The median total dose was 60 Gy/2 Gy/d. Gross tumour volume (GTV) was defined as tumour extension and metastatic lymph nodes. The clinical target volume (CTV) was GTV plus a 1-cm margin. PTV consisted of CTV plus 1 cm in the superior–inferior direction and 0.5 cm in the anterior–posterior and left–right directions.

Toxicity and dose delay or dose modification

Complete blood count, serum biochemistry and physical examination were performed 1 day before each chemotherapy cycle. The common toxicity criteria (version 3.0) and European Organization for Research and Treatment of Cancer (EORTC)/Radiation Therapy Oncology Group (RTOG) criteria had been used for assessment of safety.

A dose reduction was not planned for grade I-III haematological toxicity, whereas treatment was delayed for 1 week if the granulocyte count was <1,500, the platelet count was <100,000, the serum creatinine was >1.5 times of upper limit of normal and/or a grade 2 non-haematological toxicity occurred. When a grade 3 non-haematological toxicity or a grade 4 haematological toxicity developed, the dose of chemotherapy was planned to be reduced 25%.

If grade 3/4 non-haematological toxicity occurred, radiotherapy was planned to be suspended until symptoms subsided to grade 1 of RTOG scale. If radiation had to be interrupted for more than 15 days, patient and physician decided whether continued treatment was warranted.

The complications related to surgery were classified into 2 groups: (1) major (haemorrhage requiring revision, leakage of cerebrospinal fluid, empyema, bronchopleural fistula, adult respiratory distress syndrome), (2) minor (pneumonia, prolonged air leak, atelectasia, wound infection and prolonged drainage).

Response evaluation

Response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria 4–6 weeks after the end of chemoradiotherapy and 4 weeks after the end of all treatments by chest and abdominal CT scans. Patients who were adequately downstaged were evaluated for surgery. However, 2 patients who became eligible for surgery did not choose to undergo operation, so consolidation chemotherapy was administered.

Overall survival was determined as the time elapsed between the time of histologic diagnosis and the date of death, the date of the last follow-up visit or the endpoint of the study if the patient was still alive at that time. Time to progression (TTP) of disease was recorded from the day of the histologic diagnosis to the first date of documented progressive disease, the date of death regardless of its cause or the date the study ended if the patient was alive with no disease progression at this point. Patient and disease characteristics including age, ECOG performance status, stage, response to therapy, gender, TTP and OS were obtained from the medical record.

The primary endpoint was response rate. Secondary endpoints were treatment toxicity and TTP and OS obtained with concomitant chemoradiotherapy with weekly docetaxel and cisplatin in addition to surgery and/or consolidation therapy every 3 weeks with docetaxel and cisplatin for patients with locally advanced NSCLC.

Statistical analysis

SPSS software (SPSS 16, Chicago, IL) was used for statistical analyses. Quantitative analyses included calculations of the mean, standard error, median, minimum and maximum values, and qualitative analyses were presented as frequencies and percentages. Survival analyses were performed using a Kaplan–Meier method. A $P \leq 0.05$ was considered statistically significant.

Results

Nine patients with stage IIIA and 22 patients with stage IIIB disease were enrolled in this study. The median age of patients was 52 years (range 37–70 years), and only one of them was woman (male/female: 30/1). The characteristics of patients are shown in Table 1. Median follow-up was 22 months with a range of 2–57 months.

Neoadjuvant chemoradiation

Neoadjuvant chemoradiotherapy was started in all patients. Thirty patients completed radiotherapy; one patient received only one cisplatin infusion and did not continue the treatment. The clinical responses of the 30 patients who completed the concomitant chemoradiotherapy were as follows: complete response in 5 patients, partial response in 20 patients, stable disease in 1 patient and progressive disease in 4 patients (Table 2). Two patients with progressive disease had bone metastases: one of them developed local progression and bone metastasis, and one had skin metastasis after completion of chemoradiotherapy.

Surgery

Although 25 patients responded to neoadjuvant therapy, only 13 of the responsive patients (IIIA = 2 patients, IIIB = 11 patients) underwent surgery [pneumonectomy ($n = 4$), lobectomy ($n = 8$) and wedge resection ($n = 1$)] following concomitant chemoradiotherapy. Eleven of the patients who underwent surgery had negative surgical margins (R0 resection). A pathologic complete response was achieved in 4 patients (12.9%; IIIA = 1 patient, IIIB = 3 patients). Patients whose tumours decreased in diameter but continued to be unresectable ($n = 5$) and/or who became medically inoperable due to poor performance status ($n = 5$) were not offered an operation. Two of the

Table 1 Characteristics of patients and tumours at initial diagnosis

Characteristics	Number of patients	%
	31	100
Age (years)		
Median	52	
Range	37–70	
ECOG performance status		
0	21	67.7
1	10	32.3
Histologic subtype		
Squamous cell cancer	12	38.7
Adenocarcinoma	8	25.8
Undifferentiated carcinoma	11	35.5
Stage at diagnosis		
Stage IIIA	9	29
Stage IIIB	22	71
Primary tumour location		
Right hemithorax	22	71
Left hemithorax	9	29
Mediastinoscopy		
Performed	24	77.4
Not performed	7	22.6
T staging		
T2	6	19.4
T3	5	16.1
T4	20	64.5
N staging		
N0	13	41.9
N1	2	6.5
N2	14	45.2
N3	2	6.5

responsive patients who were adequately downstaged refused to undergo operation.

There was no major complication after surgery, whereas 3 patients had minor complications (subtotal atelectasia in 1 patient, pneumonia in 1 patient, wound infection in 1 patient), which were treated without sequela.

Toxicity evaluation

In general, the concurrent use of weekly cisplatin and docetaxel with radiotherapy is well tolerated. Grade 4 haematologic toxicity was recorded in only 1 patient in whom thrombocytopenia developed during consolidation therapy. The five patients who experienced grade 3–4 oesophageal toxicity needed transient parenteral nutrition. Three patients developed grade 3–4 pulmonary toxicity, and 2 patients developed grade 3–4 emesis during concomitant chemoradiotherapy. Five of the patients who experienced grade 3–4 esophagitis and pulmonary toxicity became medically inoperable because of poorer performance status and lower lung capacity after concomitant chemoradiation compared with that prior to starting treatment. The toxicity associated with consolidation chemotherapy was tolerable. Acute toxicities during concomitant chemoradiotherapy and consolidation chemotherapy are summarised in Table 3.

Overall treatment response

The patients received a total of 152 weeks of concomitant chemotherapy and 68 cycles of consolidation regimen. Clinical and/or pathological complete response or complete resection was achieved in 13 patients with a partial response in 8 patients (Table 2). Neither of the patients who did not respond to initial concomitant chemoradiotherapy responded to further chemotherapy. In addition, 4 of the non-operative patients whose diseases initially partially responded and 1 of the post-operative patients experienced disease progression after the completion of all treatments. After the addition of consolidation chemotherapy, only one of the 12 patients who initially partially responded but did not undergo surgery achieved a clinical complete response. Eight patients who had partially responded to chemoradiotherapy and underwent surgery without residual disease were still macroscopically tumour-free after the completion of consolidation chemotherapy. Only one of the post-operative patients who had residual disease continued to be partially responsive to chemoradiotherapy. At this point, 6 patients (post-operative, $n = 4$ and non-operative, $n = 2$) are still alive.

Overall survival and progression-free survival

The median OS for all patients was 22 ± 5 (range 13–31) months, and TTP was 12 ± 3 (range 7–17) months with a median follow-up of 21.5 months (Fig. 2). Median TTP of non-operative patients and operated patients was 9 ± 3 (range 3–15) and 36 ± 19 (range 0–72) months, respectively (log-rank = 2.43, dif = 1, $P = 0.119$). Median OS of non-operative and operated patients was 17 ± 3 (range 10–24) and 36 ± 8 (range 19–53) months, respectively (log-rank = 3.02, dif = 1, $P = 0.082$). The three-year cumulative OS and PFS rates were 31.20 ± 8.61% and 29.51 ± 8.68%. Major sites of distant metastases were the bone and brain. OS and PFS were not statistically different between stage IIIA and stage IIIB patients.

Discussion

Patients with positive mediastinal lymph nodes or direct vascular invasion by the primary tumour should be

Table 2 Response to concomitant chemoradiotherapy and overall response of patients

	Number of inoperable patients		Number of post-operative patients		Total number of patients who completed treatment
	IIIA	IIIB	IIIA	IIIB	
After chemoradiotherapy					
Complete response	0	1	1	3	5
Partial response	6	6	1	8	20
Stabile disease	0	1	0	0	1
Progression	1	3	0	0	4
After full treatment course					
Complete response	1	1	2	9	13
Partial response	3	4	0	1	8
Stabile disease	0	1	0	0	1
Progression	3	5	0	1	9

Table 3 Safety profiles of chemoradiotherapy and consolidation chemotherapy

Side effects	Number of patients with toxicity (%)			
	Concomitant chemoradiotherapy		Consolidation chemotherapy	
	Grade 3	Grade 4	Grade 3	Grade 4
Haematological				
Anaemia	0	0	0	0
Leucopoenia	0	0	0	0
Neutropenia	0	0	0	0
Thrombocytopenia	0	0	1 (3.2)	0
Non-haematological				
Skin toxicity	0	0	1 (3.2)	0
Nausea/vomiting	1 (3.2)	1 (3.2)	2 (6.5)	1 (3.2)
Neurotoxicity	0	0	0	0
Esophagitis	4 (12.9)	1 (3.2)	0	0
Diarrhoea	1 (3.2)	0	0	0
Pulmonary toxicity	3 (9.7)	0	0	2 (6.5)
Nephrotoxicity	0	0	0	0

candidates for neoadjuvant treatment. The main goal of neoadjuvant chemotherapy and/or radiotherapy is to downstage preoperatively from N2 to N1–0 and to prevent early systemic metastasis. However, a complete pathologic response during neoadjuvant chemoradiotherapy in the primary tumour site and lymph nodes is approximately 5–10% [8].

During the last 2 decades, several approaches to multimodality treatment have been studied in patients with locally advanced, unresectable NSCLC. Several randomised phase II–III trials have demonstrated that starting treatment with concomitant chemoradiotherapy results in better survival rates with potential improvement in pathologic downstaging than starting with induction chemotherapy or sequential CRT [3, 9–13]. The rates of acute grade 3–4 non-haematological toxicities were reported to be higher in the concomitant treatment than in the sequential treatment group, but late toxicities were similar [3, 12, 14, 15]. In a very recently published meta-analysis by the NSCLC Collaborative Group, randomised trials that directly compared the concomitant versus sequential radiochemotherapy were investigated [10]. Concomitant chemoradiotherapy was shown to increase acute grade 3–4 oesophageal toxicity as compared with sequential chemoradiotherapy from 4 to 18% with a relative risk of 4.9 (95% CI, 3.1–7.8; $P < 0.001$). Acute grade 3–4 pulmonary toxicity was similar between the concomitant and thez sequential chemoradiotherapy groups [10]. Grade 3–4 haematologic toxicity rates were highly variable between the studies (20–90%).

The optimal schedule and dose of chemotherapy concurrently with radiotherapy has not yet been determined [16–19]. For the combination of cisplatin plus docetaxel administered concomitantly with radiotherapy, there are

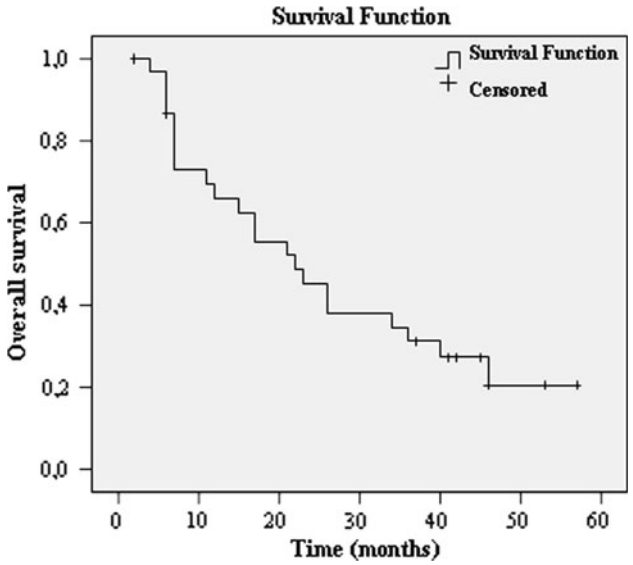


Fig. 2 Overall survival for the entire group

several studies in which modified dosing schedules were reported [20–22]. In general, phase I studies determined the weekly doses of cisplatin and docetaxel with CRT to be 20–40 mg/m^2 in locally advanced NSCLC [15, 21, 22]. We also used the doses based on these previously performed trials. A high incidence of oesophageal and pulmonary toxicities has been reported with concomitant chemoradiotherapy [3, 12, 14, 15, 23]. The frequency of severe oesophageal toxicity was reported to occur at an incidence of 8–25% for the patients treated with a combination of docetaxel plus cisplatin [17, 20, 22, 24]. Severe oesophageal toxicity was experienced in 16.1% of our study population during the concomitant phase. The frequency of severe pulmonary toxicity was 9.7%, which was similar to results in other reports using combinations of cisplatin plus docetaxel (0–11.8) [17, 20–22, 24, 25].

Although CT scans in 26 patients revealed tumour regression or stable disease after concomitant chemoradiotherapy, only 21 of them were adequately downstaged to be resectable, consistent with previous reports. Six of the adequately downstaged patients had poorer performance status due to grade 3–4 toxicities. Only 3 patients achieved pathologic complete response (10%). The Southwest Oncology Group (SWOG) trial 8,805 included 126 stage IIIA and IIIB patients treated with neoadjuvant cisplatin and etoposide concurrently with radiotherapy. Eighty-nine of them underwent surgery, and 15% of enrolled patients achieved a pathologic complete response [26].

The use of consolidation therapy after chemoradiotherapy to maximise the chemotherapy response is expected to improve overall survival [27]. A phase II trial performed by the SWOG (S9504) investigated concomitant chemoradiotherapy with cisplatin and etoposide followed by maintenance therapy with docetaxel [28]. The hypothesis was that the chemotherapy effect would be intensified using a different and non-cross resistant agent after concomitant therapy. One-, two- and three-year survival rates were impressive (76, 54 and 37%, respectively). However, a recent phase III trial by the Hoosier Oncology Group and the US Oncology Group showed no OS benefit in the consolidation group [29]. Consolidation treatment with docetaxel was associated with a significant increase in grade 3–4 toxicities and a 5.5% rate of toxicity-related deaths [29]. Although patient and disease characteristics of these 2 studies were similar, the baseline FEV1 of patients was higher in the S9504 trial than that in the Hoosier Oncology Group and the US Oncology Group trials (FEV1 $\geq$ 2 l or 800 ml in the contralateral lung compared with FEV1 $\geq$ 1 l, respectively). Baseline pulmonary function was reported to predict the outcomes [30]. Recently, Huber et al. [31] found that the maximally tolerated dose of docetaxel consolidation therapy after concomitant cisplatin/docetaxel CRT was 60 mg/m^2, although toxicity was considerable.

In our study, adding cisplatin to docetaxel as a consolidation therapy for patients who were not operative candidates added very little benefit: only one more patient experienced a clinical complete response. Moreover, 4 patients progressed under consolidation chemotherapy. We were not able to compare the efficacy of consolidation therapy in post-operative patients. We treated all the resected patients who did not achieve a pathologic complete response with consolidation therapy although eleven of them had already undergone an R0 resection. Post-operative patients tolerated the consolidation chemotherapy very well; only 1 patient experienced grade 3 emesis. Grade 4 pulmonary and grade 3 oesophageal and skin toxicities and thrombocytopenia developed in non-operative patients. Post-operative patients started the consolidation chemotherapy approximately 6 weeks after the concomitant chemoradiotherapy. A possible explanation of fewer incidences of grade 3–4 toxicity in the operative patients is that they had sufficient time to recover from the adverse effects of concomitant chemotherapy. Conversely, patients who did not undergo operation received consolidation chemotherapy without any delay. Thus, their tolerance was less than in post-operative patients. However, there were no toxic deaths in any group.

Albain et al., in a multicenter phase III trial [32], randomly assigned 396 patients with stage T1–3, pN2, M0 non-small-cell lung cancer in a 1:1 ratio to concurrent induction chemotherapy (two cycles of cisplatin (50 mg/m^2 on days 1, 8, 29, and 36) and etoposide (50 mg/m^2 on days 1–5 and 29–33) plus radiotherapy (45 Gy)). If there was no disease progression, then patients in group 1 underwent resection and those in group 2 continued radiotherapy uninterrupted

up to 61 Gy. Two additional cycles of cisplatin and etoposide were given in both groups. Median OS was 23.6 months (IQR 9.0 not reached) in group 1 versus 22.2 months (range 9.4–52.7 months) in group 2 (hazard ratio (HR) 0.87 (0.70–1.10); $P = 0.24$). Progression-free survival (PFS) was better in group 1 than in group 2, with a median 12.8 months (range 5.3–42.2 months) versus 10.5 months (range 4.8–20.6 months, HR 0.77 (0.62–0.96); $P = 0.017$), respectively.

In a recently published study performed by Kaya et al. [33], patients were treated with similar regimens in similar doses with those in our study during both the concomitant phase and the consolidation phase. Although in that study investigators did not provide the results of additional treatment responses and toxicity during consolidation therapy, the surgery added the major therapeutic benefit in terms of PFS and OS. One-year PFS and OS rates in operated patients were 71 and 92%, respectively. In our study, the results of initial partial and complete response rates (80.6%) after concomitant CRT were consistent with those in the literature. However, adequately downstaging without morbidity permitted surgery. Surgery with R0 resection may be one of the major determinants of the benefit of this trimodality treatment. Five of our patients who responded to neoadjuvant therapy became medically inoperable due to treatment-related severe oesophageal and pulmonary toxicities [34]. Adequately downstaged and medically operable patients tended to have improved overall survival compared with inoperable patients (36 ± 8 (range 19–53) months versus 17 ± 3 (range 10–24) months; $P = 0.082$); however, it did not reach statistical significance.

In conclusion, the combination of weekly docetaxel (20 mg/m^2) and weekly cisplatin (20 mg/m^2) used concurrently with radiotherapy, particularly when followed by surgery, and consolidation therapy every 3 weeks with docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) is a well-tolerated and effective trimodality approach in adequately downstaged patients. Further treatment with consolidation therapy in inoperable patients had no benefit to their overall response rate; additionally, it increased grade 3–4 toxicities and may increase the overall treatment-related morbidity.

Conflict of interest The authors have declared no conflicts of interest.

References

1. Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S Jr, Olak J, Stover D, Strawn JR, Turrisi AT, Somerfield MR (2004) American society of clinical oncology. American society of clinical oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 22:330–353
2. Sause W, Kolesar P, Taylor S IV, Johnson D, Livingston R, Komaki R, Emami B, Curran W Jr, Byhardt R, Dar AR, Turrisi A III (2000) Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: radiation therapy oncology group, eastern cooperative oncology group, and southwest oncology group. Chest 117:358–364
3. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, Katagami N, Ariyoshi Y (1999) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 17:2692–2699
4. Goodgame B, Stinchcombe TE, Simon G, Wozniak A, Govindan R (2009) Recent advances in lung cancer: summary of presentations from the 45th annual meeting of the American society of clinical oncology (2009). J Thorac Oncol 4:1293–1300
5. Baggstrom MQ, Stinchcombe TE, Fried DB, Poole C, Hensing TA, Socinski MA (2007) Third-generation chemotherapy agents in the treatment of advanced non-small cell lung cancer: a meta-analysis. J Thorac Oncol 2:845–853
6. Milas L (2002) Docetaxel/radiation combinations: rationale and preclinical findings. Clin Lung Cancer 3:29–36
7. Vokes EE, Crawford J, Bogart J, Socinski MA, Clamon G, Green MR (2005) Concurrent chemoradiotherapy for unresectable stage III non-small cell lung cancer. Clin Cancer Res 11:5045–5050
8. Pezzetta E, Stupp R, Zouhair A, Guillou L, Taffé P, von Briel C, Krueger T, Ris HB (2005) Comparison of neoadjuvant cisplatin-based chemotherapy versus radiochemotherapy followed by resection for stage III (N2) NSCLC. Eur J Cardiothorac Surg 27:1092–1098
9. Stinchcombe TE, Fried D, Morris DE, Socinski MA (2006) Combined modality therapy for stage III non-small cell lung cancer. Oncologist 11:809–823
10. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC, Uitterhoeve A, Wang X, Stewart L, Arriagada R, Burdett S, Pignon JP (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 28:2181–2190
11. Ulutin HC, Güden M, Oysul K, Sürenkök S, Pak Y (2000) Split-course radiotherapy with or without concurrent or sequential chemotherapy in non-small cell lung cancer. Radiat Med 18:93–96
12. Fournel P, Robinet G, Thomas P, Souquet PJ, Léna H, Vergnenégre A, Delhoume JY, Le Treut J, Silvani JA, Dansin E, Bozonnat MC, Daurés JP, Mornex F, Pérol M, Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Français de Pneumo-Cancérologie (2005) Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: groupe Lyon-Saint-Etienne d'oncologie thoracique-groupe français de pneumo-cancérologie NPC 95–01 study. J Clin Oncol 23:5910–5917
13. Zatloukal P, Petruzelka L, Zemanova M, Havel L, Janku F, Judas L, Kubik A, Krepela E, Fiala P, Pecen L (2004) Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer 46:87–98
14. Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, Curran WJ Jr (2005) Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multimodality protocol. J Clin Oncol 23:5883–5891
15. Onishi H, Kuriyama K, Yamaguchi M, Komiyama T, Tanaka S, Araki T, Nishikawa K, Ishihara H (2003) Concurrent two-dimensional radiotherapy and weekly docetaxel in the treatment of stage III non-small cell lung cancer: a good local response but

no good survival due to radiation pneumonitis. Lung Cancer 40:79–84
16. Harada H, Yamamoto N, Takahashi T, Endo M, Murakami H, Tsuya A, Nakamura Y, Ono A, Igawa S, Shukuya T, Tamiya A, Nishimura T (2009) Comparison of chemotherapy regimens for concurrent chemoradiotherapy in unresectable stage III non-small cell lung cancer. Int J Clin Oncol 14:507–512
17. Nakamura M, Koizumi T, Hayasaka M, Yasuo M, Tsushima K, Kubo K, Gomi K, Shikama N (2009) Cisplatin and weekly docetaxel with concurrent thoracic radiotherapy for locally advanced stage III non-small-cell lung cancer. Cancer Chemother Pharmacol 63:1091–1096
18. Beckmann G, Fietkau R, Huber RM, Kleine P, Schmidt M, Semrau S, Aubert D, Fittipaldo A, Flentje M (2006) Oral vinorelbine and cisplatin with concomitant radiotherapy in stage III non-small cell lung cancer (NSCLC): a feasibility study. Onkologie 29:137–142
19. Naito Y, Kubota K, Nihei K, Fujii T, Yoh K, Niho S, Goto K, Ohmatsu H, Saijo N, Nishiwaki Y (2008) Concurrent chemoradiotherapy with cisplatin and vinorelbine for stage III non-small cell lung cancer. J Thorac Oncol 3:617–622
20. Yamamoto N, Nishimura Y, Nakagawa K, Matsui K, Fukuoka M (2006) Phase I/II study of weekly docetaxel dose escalation in combination with fixed weekly cisplatin and concurrent thoracic radiotherapy in locally advanced non-small cell lung cancer. Cancer Chemother Pharmacol 58:285–291
21. Mudad R, Ramsey M, Kovitz K, Curiel TJ, Hartz R, Nedzi LL, Weiner RS, Zakris EL (2003) Concomitant weekly docetaxel, cisplatin and radiation therapy in locally advanced non-small cell lung cancer: a dose finding study. Lung Cancer 39:173–177
22. Kiura K, Ueoka H, Segawa Y, Tabata M, Kamei H, Takigawa N, Hiraki S, Watanabe Y, Bessho A, Eguchi K, Okimoto N, Harita S, Takemoto M, Hiraki Y, Harada M, Tanimoto M, Okayama Lung Cancer Study Group (2003) Phase I/II study of docetaxel and cisplatin with concurrent thoracic radiation therapy for locally advanced non-small-cell lung cancer. Br J Cancer 89:795–802
23. Koukourakis MI, Kourousis C, Kamilaki M, Koukouraki S, Giatromanolaki A, Kakolyris S, Kotsakis A, Androulakis N, Bahlitzanakis N, Georgoulias V (1998) Weekly docetaxel and concomitant boost radiotherapy for non-small cell lung cancer. A phase I/II dose escalation trial. Eur J Cancer 34:838–844
24. Iwasaki Y, Ohsugi S, Natsuhara A, Tsubokura T, Harada H, Ueda M, Arimoto T, Hara H, Yamada T, Takesako T, Kohno K, Hosogi S, Nakanishi M, Marunaka Y, Nishimura T (2006) Phase I/II trial of biweekly docetaxel and cisplatin with concurrent thoracic radiation for stage III non-small-cell lung cancer. Cancer Chemother Pharmacol 58:735–741
25. Wu HG, Bang YJ, Choi EK, Ahn YC, Kim YW, Lim TH, Suh C, Park K, Park CI (2002) Phase I study of weekly docetaxel and cisplatin concurrent with thoracic radiotherapy in Stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 52:75–80
26. Albain KS, Rusch VW, Crowley JJ, Rice TW, Turrisi AT III, Weick JK, Lonchyna VA, Presant CA, McKenna RJ, Gandara DR et al (1995) Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol 13:1880–1892
27. Guida C, Maione P, Rossi A, Bareschino M, Schettino C, Barzaghi D, Elmo M, Gridelli C (2008) Combined chemo-radiotherapy for locally advanced non-small cell lung cancer: current status and future development. Crit Rev Oncol Hematol 68:222–232
28. Gandara DR, Chansky K, Albain KS, Leigh BR, Gaspar LE, Lara PN Jr, Burris H, Gumerlock P, Kuebler JP, Bearden JD III, Crowley J, Livingston R, Southwest Oncology Group (2003) Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. J Clin Oncol 21:2004–2010
29. Hanna N, Neubauer M, Yiannoutsos C, McGarry R, Arseneau J, Ansari R, Reynolds C, Govindan R, Melnyk A, Fisher W, Richards D, Bruetman D, Anderson T, Chowhan N, Nattam S, Mantravadi P, Johnson C, Breen T, White A, Einhorn L, Hoosier Oncology Group, US Oncology (2008) Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and US Oncology. J Clin Oncol 26:5755–5760
30. Semrau S, Klautke G, Fietkau R (2011) Baseline cardiopulmonary function as an independent prognostic factor for survival of inoperable non-small-cell lung cancer after concurrent chemoradiotherapy: A single-center analysis of 161 Cases. Int J Radiat Oncol Biol Phys Int J Radiat Oncol Biol Phys 79:96–104
31. Huber RM, Borgmeier A, Flentje M, Willner J, Schmidt M, Manegold C, Bramlage P, Debus J (2010) Concurrent chemoradiation therapy with docetaxel/cisplatin followed by docetaxel consolidation therapy in inoperable stage IIIA/B non-small-cell lung cancer: results of a phase I study. Clin Lung Cancer 11:45–50
32. Albain KS, Swann RS, Rusch VW, Turrisi AT III, Shepherd FA, Smith C, Chen Y, Livingston RB, Feins RH, Gandara DR, Fry WA, Darling G, Johnson DH, Green MR, Miller RC, Ley J, Sause WT, Cox JD (2009) Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 374:379–386
33. Kaya AO, Buyukberber S, Benekli M, Coskun U, Sevinc A, Akmansu M, Yildiz R, Ozturk B, Yaman E, Kalender ME, Orhan O, Yamac D, Uner A, Anatolian Society of Medical Oncology (ASMO) (2010) Concomitant chemoradiotherapy with cisplatin and docetaxel followed by surgery and consolidation chemotherapy in patients with unresectable locally advanced non-small cell lung cancer. Med Oncol 27:152–157
34. D'Angelillo RM, Trodella L, Ciresa M, Cellini F, Fiore M, Greco C, Pompeo E, Mineo TC, Paleari L, Granone P, Ramella S, Cesario A (2009) Multimodality treatment of stage III non-small cell lung cancer: analysis of a phase II trial using preoperative cisplatin and gemcitabine with concurrent radiotherapy. J Thorac Oncol 4:1517–1523