

Induction Docetaxel and Cisplatin Followed by Weekly Docetaxel and Cisplatin with Concurrent Radiotherapy in Locally Advanced Stage III Non Small Cell Lung Cancer (LA-NSCLC)-A Phase II Study

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ABSTRACT

Purpose: The objective of this phase II study was to document the activity and to evaluate the toxicity of docetaxel and cisplatin as induction chemotherapy followed by concurrent docetaxel and cisplatin with thoracic radiation in locally advanced stage III non small cell lung cancer.

Patients and Methods: Twenty-seven patients with stage III locally advanced non-small cell lung cancer received induction chemotherapy with two cycles of docetaxel 75mg/m² and cisplatin 75mg/m² D1 every 3 weeks. Patients without disease progress after induction chemotherapy were assigned to concurrent chemoradiotherapy 20mg/m² docetaxel & 25mg/m² cisplatin administered on day 1 every week for 6 weeks along with concurrent radiotherapy at a dose of 60Gy in 30 fractions (2 Gy/fraction and 5 fractions per week). The primary endpoint was to determine the overall response rate (ORR), the secondary endpoint was to evaluate time to progression (TTP) and safety profile.

Results: After induction chemotherapy, the overall response rate (ORR) was 44.4%, 23 patients without disease progress were assigned to concurrent treatment with an overall response rate of 65%. Median survival time was 17 months, time to progression was 11.5 months and the one-year survival was 58%. Neutropenia was the most common toxicity during induction therapy (26% expressed grade 3-4) whereas esophagitis was the most common toxicity during concurrent phase (17.3% expressed grade 3-4); toxicities were manageable.

Conclusion: Induction chemotherapy by docetaxel and cisplatin followed by weekly docetaxel and cisplatin with concurrent thoracic radiation therapy is feasible and tolerable. These results warrant further large randomized studies to document and confirm the effectiveness of this regimen.

Key Words: Lung cancer – Docetaxel – Cisplatin – Concurrent chemoradiotherapy.

INTRODUCTION

Approximately 30% of patients with non-small-cell lung cancer (NSCLC) have unresectable locally advanced disease at diagnosis (mainly stage III B) [1]. While the roles for different treatment modalities are reasonably well established for stage I, II, and IV, the treatment of stage III disease remains challenging [2].

Since the majority of patients with locally advanced non-small-cell lung cancer (LA-NSCLC) develop distant metastases, the treatment outcomes of patients receiving surgery or radiotherapy alone are extremely poor. A combined modality approach to control local tumor and distant metastases is required to improve the treatment outcome [3]. Therefore, the standard treatment of locally advanced unresectable NSCLC is combined chemotherapy and radiotherapy [1,3,4,5] and their concurrent administration of both modalities has been reported to be superior to sequential therapy by several collaborative groups as Radiotherapy Oncology Group (RTOG) [4,6].

Cisplatin which is the cornerstone drug in the treatment of NSCLC, is also having potent radiosensitizing effect [3,7]. Docetaxel has proven efficacy in front line therapy of advanced NSCLC [6]. It also offers several potential advantages than other radiosensitizer chemotherapeutic agents. First, it inhibits microtubule depolymerization with high percentage and

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more prolonged duration and causes cell cycle arrest in the radiosensitive G₂-M phase [5,6]. Second, docetaxel aborts mitosis and causes cell death in the radioresistant S-phase, thereby exerting its cytotoxic effect at more than one point in the cell cycle [8,9]. Studies have indicated that a dose level of 75mg/m² is equally effective to other dose levels and is less toxic [10,11].

Many radiation oncologists continue to treat clinically uninvolved mediastinal and hilar nodes, a traditional technique that necessarily includes much of the esophagus. Restricting the volume of irradiation offers the possibility of reducing normal tissue exposure and allowing higher total dose of radiotherapy without increasing normal tissue toxicity [12,13]. The aim of the current work was to assess the effect of employing induction chemotherapy followed by concurrent chemoradiotherapy upon response rate as well as time to progression among patients with locally advanced non-metastatic stage III non small cell lung cancer (LA-NSCLC).

PATIENTS AND METHODS

Patients with histologically and/or cytologically documented locally advanced unresectable stage III NSCLC were eligible for the study. Each patient was required to meet the following criteria: Age between 18 and 65 years; World Health Organization (WHO) performance status (PS) ≤1; no previous chemotherapy or radiotherapy treatment; uni- or bidimensionally measurable disease; adequate hematological, hepatic, renal, cardiac and respiratory function were ensured prior to enrollment into study. No prior chemo or radiotherapy was allowed for any patient enrolled in the study. Uncontrolled concomitant medical illness was considered as a contraindication for inclusion. Also pretreatment pleural effusion and its treatment was not allowed.

Treatment plan:

The treatment plan is summarized in Fig. (1).

1- Induction chemotherapy:

Eligible patients received docetaxel 75mg/m² and cisplatin 75mg/m² one day treatment every 3 weeks for 2 cycles. Hydration and

adequate anti-emetic therapy were ensured for all patients. Growth factor (G-CSF) and antibiotic administrations were attempted in some cases, based upon clinical judgment.

2-Concurrent chemo-radiotherapy treatment:

It started 3 weeks after induction chemotherapy. Patients with progressive disease (PD) were withdrawn from the study. The remaining patients started to receive conventional radiotherapy delivered using Cobalt⁶⁰ (2Gy/day, 5 days/week for 6 consecutive weeks, for a total dose of 60Gy) with concurrent docetaxel 20 mg/m² and cisplatin 25mg/m² on D1,8,15,22,29 and 36. Computer tomography planning was mandatory.

The radiation dose was directed to the pre-chemotherapy clinical target volume. It was defined as the gross tumor volume and involved lymph nodes plus 1.5-2cm margin. An AP-PA parallel opposing technique was used to deliver radiation dose of 40-45Gy then a pair of oblique field arrangement was used to keep spinal cord dose <45Gy.

Patient evaluation:

The pretreatment evaluation was conducted before the start of treatment. It consisted of history, medical and physical examination, complete blood cell count, routine chemistry measurements, a chest computed tomography (CT) scan, abdominal ultrasound or CT scan, fiber optic bronchoscope, isotope bone scan and CT or MRI brain if clinically indicated. Laboratory investigations were repeated just before every induction chemotherapy, and weekly during concurrent chemoradiation treatment. Radiological imaging procedures were repeated after induction chemotherapy completion (D₅₆) and 4 weeks after concurrent chemoradiation treatment.

Response, survival, and toxicity assessment:

Tumor was assessed according to WHO criteria [14]. A complete response (CR) was defined as the disappearance of all measurable lesion for ≥4 weeks. A partial response (PR) was defined as a decrease of ≥50% of the sum of the products of the greatest perpendicular lesion diameters for ≥4 weeks with no evidence of new lesions. No change (NC) was defined as a <50% decrease or <25% increase in the product of the greatest perpendicular lesion

diameters with no evidence of new lesions for ≥ 4 weeks. Progressive disease (PD) was defined as an increase in any measurable lesions by $\geq 25\%$ or the detection of new lesions.

Survival time was defined as the period from the start of induction therapy to death or the last follow-up evaluation and time to progression (TTP) was defined as the time from the start of induction therapy until documented progression. Both were determined by using Kaplan-Meier method [15]. Statistical analysis was performed using SPSS Base system and statistics program (SPSS Inc., Chicago, IL, USA) [3].

Toxicity was assessed by the National Cancer Institute-Common Toxicity Criteria (NCI-CTC version 2.0, 1998).

RESULTS

Patient characteristics: From January 2003 to January 2005, 27 patients with stage IIIA and IIIB locally advanced non small cell lung cancer were enrolled in the study. Twenty-one patients were males (78 %), with a male: female ratio of 3.5:1 and a median age of 56 (range 48-69 years). Twenty patients (74%) had performance status of 1. Seventeen patients with stage IIIB patients represented the majority of cases (63%). The most predominant histopathological types were adenocarcinoma, present in 11 (41%) patients and squamous cell carcinoma in 9 (33%) patients. The patients' characteristics are listed in Table (1).

Response to treatment:

The majority of patients had experienced partial response and disease stability (11 and 11 patients, respectively) following 2 courses of induction chemotherapy, while only one patient achieved complete radiological remission. Four patients (14.6%) were withdrawn from the study due to disease progression with overall response rate of 44.4% after induction chemotherapy as shown in Table (2).

Twenty-three out of 27 patients were considered eligible to continue the pre-scheduled treatment plan via concurrent chemoradiation treatment. Response was re-assessed radiologically 4 weeks after completion of treatment schedule. Twelve out of 23 patients achieved partial response (52%), 3 patients (13%) & 3 (13%) had complete response and stable disease,

respectively, while 5 patients (21.7%) were documented to have progression disease and were considered for 2nd line salvage therapy. The overall response rate at the end of study had been proven to be 65%.

Overall survival:

The median overall survival time was 16 months (95% C I) with a range of 9.5 to 30 months, while 1 year survival was 58% (Fig. 2).

Time to progression:

Median time to disease progression was 10 months (95% C I) with a range of 7.5 to 16 months.

Safety & Toxicity:

Overall, only 26% of patients experienced grade 3-4 haematological adverse events in the form of neutropenia in the induction phase. Other haematological adverse events, such as anemia, thrombocytopenia, lymphocytopenia occurred in a lesser percentage of patients (Table 3).

As regards treatment-related non-hematological toxicities, only 2 patients (7.4%) experienced grade 3 vomiting in the induction phase, while in the concurrent phase grade 3-4 esophagitis was observed in 4 patients (17.3%), one patient suffered from grade III pneumonitis (4.3%) and 2 patients (8.6%) expressed grade III fatigue. Toxicities experienced during induction chemotherapy and the concurrent chemoradiotherapy are listed in Table (3).

Table (1): Clinico- epidemiological characteristics: Among 27 patients with LA-NSCLC (stage III) treated by induction chemotherapy.

Patients' characteristics	No. of patients (%)
No. of patients evaluated	27
<i>Median age (years):</i>	
Sex	56 (48-69)
Male	21 (78)
Female	6 (41)
<i>WHO performance status:</i>	
0	7 (26)
1	20 (74)
<i>Stage:</i>	
IIIA	10 (37)
IIIB	17 (63)
<i>Histology:</i>	
• Adenocarcinoma	11 (41)
• Squamous cell carcinoma	9 (33)
• Large cell carcinoma	4 (15)
• Anaplastic	3 (11)

Table (2): Response to treatment.

Response	After induction chemotherapy (n=27) n (%)	After concomitant chemoradiotherapy (n=23) n (%)
Overall response (ORR)	12/27 (44.4)	15/23 (65)
Complete response (CR)	1 (3.7)	3 (13)
Partial response (PR)	11 (40.7)	12 (52)
Stable disease (SD)	11 (40.7)	3 (13)
Progressive disease (PD)	4 (14.8)	5 (21.7)

Table (3): Treatment related toxicity.

Toxicity	Induction chemotherapy (n=27)				Concomitant chemoradiotherapy (n=23)			
	0,1 n (%)	2 n (%)	3 n (%)	4 n (%)	0,1 n (%)	2 n(%)	3 n(%)	4 n(%)
Neutropenia	7 (26)	5 (18.5)	5 (18.5)	2 (7.4)	3 (13)	2 (8.6)	–	–
Anemia	5 (18.5)	3 (11.1)	–	–	4 (17.3)	2 (8.6)	–	–
Thrombocytopenia	2 (7.4)	–	–	–	2 (8.6)	–	–	–
Lymphocytopenia	3 (11.1)	1 (3.7)	–	–	5 (21.7)	3 (13)	4 (17.3)	1 (4.3)
Fever	2 (7.4)	1 (3.7)	–	–	1 (4.3)	1 (4.3)	–	–
Esophagitis	3 (11.1)	2 (7.4)	–	–	10 (43.5)	6 (26)	4 (17.3)	1 (4.3)
vomiting	14 (52)	5 (18.5)	2 (7.4)	–	7 (30.4)	3 (13)	–	–
Pneumonitis	1 (3.7)	–	–	–	2 (8.7)	1 (4.3)	1 (4.3)	–
Fatigue	4 (14.8)	2 (7.4)	1 (3.7)	–	4 (17.3)	2 (8.6)	2 (8.6)	–
Peripheral neuropathy	11 (40.7)	4 (14.8)	1 (3.7)	–	5 (21.7)	2 (8.6)	–	–

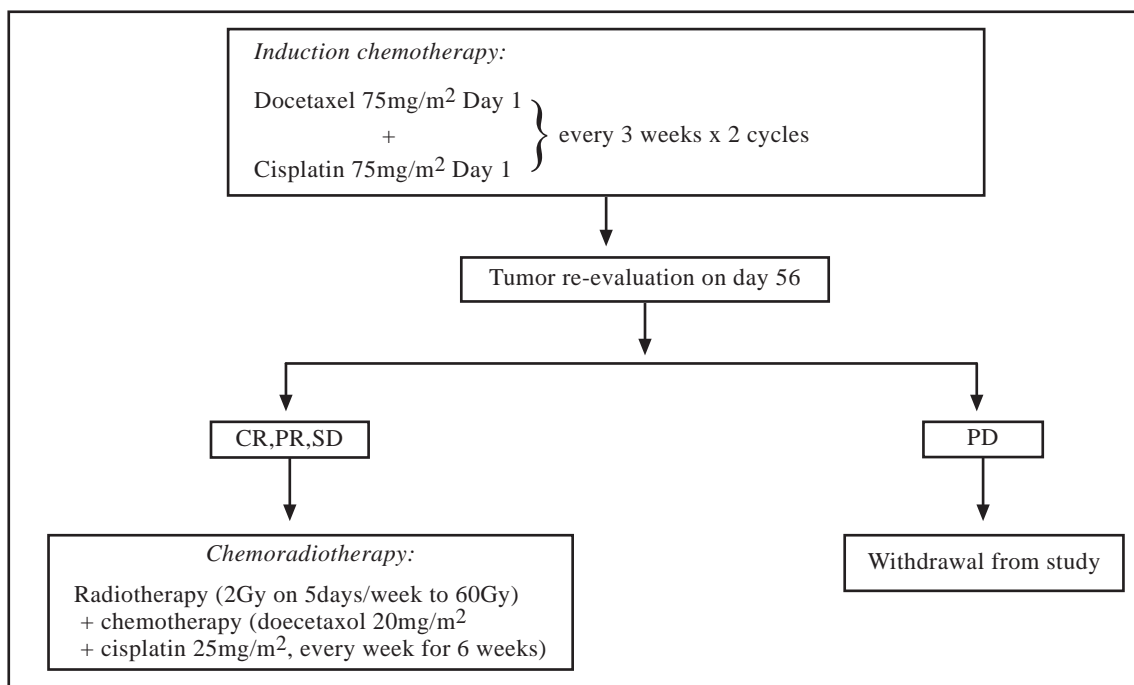


Fig. (1): The treatment plan.

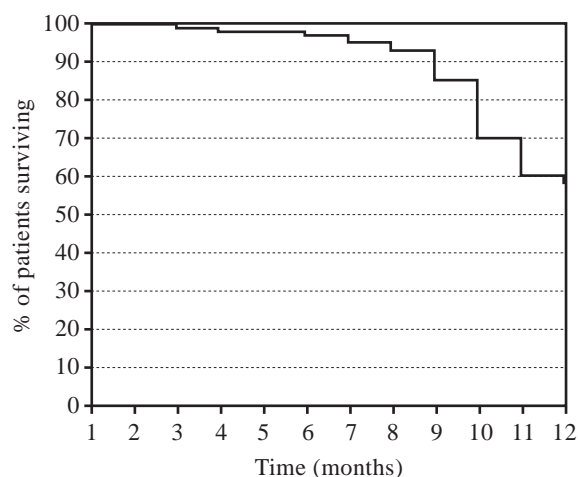


Fig. (2): One year survival.

DISCUSSION

The objective of this study was to investigate the feasibility and effectiveness of an induction chemotherapy regimen consisting of 2 cycles docetaxel and cisplatin followed by concurrent thoracic radiation with weekly docetaxel and cisplatin in patients with LA-NSCLC.

Following induction chemotherapy and concurrent chemoradiation schedule, the documented overall response rate among patients who completed the schedule was found to be 65%, a result found to be a little bit higher than those reported by Scagliotti and coworkers [4] and Huber et al. [16], 58% and 46.5% respectively, a difference that can be attributed to the smaller number of patients included in our study as well as the possibility of synergistic effect of adding cisplatin to weekly docetaxel with radiation therapy.

The two 21-day cycles of induction chemotherapy produced an ORR of 44.4%, similar to that reported by Scagliotti et al., [4] (44%) and by Biesma et al., [17] (45%) after induction with 3 cycles of docetaxel and cisplatin, and higher than that reported by Huber et al., [16] (36.6%) after induction by 2 cycles of paclitaxel and carboplatin. Reflecting the possible relative superiority of cisplatin over carboplatin in combination with either docetaxel or paclitaxel, a statement needs to be more verified via prospective studies to directly answer the question of which agent in combination needs to be adapted.

The toxicity profile reported in our study was accepted and tolerable. The incidence of

grade III and IV neutropenia (18.5% & 7.4%) during induction chemotherapy was less than that reported by Scaliotti et al., [4], this difference was due to the use of G-CSF and the smaller number of patients in our study.

The incidence of grade III & IV esophagitis during the concomitant phase was 21.7%, which was slightly higher than that observed by Scagliotti et al., [4] (17%) this may be due to the combination of the weekly cisplatin and docetaxel as a radiation sensitizer as well as the wide penumbra associated with the use of Cobalt-60 machines.

The median survival time in our study was 16 months, whereas Scagliotti et al. [4] reported 14.9 months and 15 months by Lori et al., [5]. The 1-year survival was 58% in our study matched to that reported by Scagliotti et al. (55.8%) [4] and Lori et al., (56%) [5]. Median time to progression was 10 months, which was slightly higher than 9 months reported by Lori et al., [5] and 7.5 months by Scagliotti et al., [4].

Our results confirmed that this combined modality was effective and well tolerated, although some recent studies are using up-front concurrent chemoradiotherapy and claimed better survival than induction chemotherapy followed by concurrent chemoradiation therapy [4,17]. Yet, future controlled randomized trials incorporating enough numbers of patients in both arms are mandatory to reach a firm conclusion about the strategy of choice. Another feature of using induction chemotherapy is to prognostically stratify patients into those who may benefit from combined modality treatment and hence become candidates for more lengthy exhausting, radical treatment regimens than might just benefit of palliative short course radiation therapy.

No significant difference could be proven regarding the survival issue nor response rates between patients having either stage III A or III B in our study due to the relatively small number (27 patients) enrolled in our work.

Larger randomized studies are suggested to document the benefit of the weekly combination of docetaxel and cisplatin plus concurrent radiotherapy after cisplatin-docetaxel induction therapy and also as upfront treatment followed

by docetaxel-cisplatin as consolidation therapy for patients with locally advanced NSCLC.

REFERENCES

- 1- Fournel P, Robinet G, Thomas P, Souquet PJ, Léna H, Vergnenégre A, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non small cell lung cancer: Group Lyon-Saint-Etienne d'Oncologie Thoracique-Group Francais de Pneumocancerologie NPC 95-01 Study. *J Clin Oncol.* 2005, 23 (25): 5910-17.
- 2- Rigas JR, Lara PN Jr. Current perspectives on treatment strategies for locally advanced, unresectable stage III non small cell lung cancer. *Lung Cancer.* 2005, 50 S2: S17-S24.
- 3- Katayama H, Ueoka H, Kiura K, Tabata M, Kozuki T, Tanimoto M, et al. Preoperative concurrent chemoradiotherapy with cisplatin and docetaxel in locally advanced non small-cell lung cancer. *Br J Cancer.* 2006, 90: 979-84.
- 4- Scagliotti GV, Szczesna A, Ramlau R, Cardenal F, Mattson K, Van Zandwijk N, et al. Docetaxel-based induction therapy prior to radiotherapy with or without docetaxel for non small cell lung cancer. *Br J Cancer.* 2006, 94: 1375-82.
- 5- Wirth LJ, Lucca J, Ostle P r, Fidias P, Lynch C, Jänne PA, et al. A phase I study induction docetaxel and carboplatin followed by weekly docetaxel and carboplatin with concurrent radiotherapy, then surgery in stage III non small cell lung cancer. *Clin Cancer Res.* 2003, 9: 1698-704.
- 6- Scagliotti GV, Turrise AT, III. Docetaxel-based combined-modality chemoradiotherapy for locally advanced non-small cell lung cancer. *Oncologist.* 2003, 8: 361-74.
- 7- Le Chevalier T, Berille J, Zalcberg JR, Millward MJ, Monnier A, Douillard JY, et al. Overview of docetaxel (taxotere)/cisplatin combination in non-small cell lung cancer. *Semin Oncol.* 1999, 26 (3 Suppl 11): 13-18.
- 8- Hennequin C, Giocanti N, Favaudon V. S-phase specificity of cell killing by docetaxel (taxotere) in synchronised hela cells. *Br J Cancer.* 1995, 71: 1194-8.
- 9- Valero V, Jones SE, Von Hoff DD, Booser DJ, Mennel RG, Randin PM, et al. A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. *J Clin Oncol.* 1998, 16: 3362-68.
- 10- Fosella F, De Vore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum containing chemotherapy regimens. *J Clin Oncol.* 2000, 18: 131-5.
- 11- Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol.* 2000, 18: 2095-103.
- 12- Hayman JA, Martel MK, Ten Haken RK, Normalle DP, Todd RF III, Littles JF, et al. Dose escalation in non-small cell lung cancer using three-dimensional conformal radiation therapy: Update of a phase I trial. *J Clin Oncol.* 2001, 19: 127-36.
- 13- Williams TE, Thomas CR Jr, Turrise AT 3rd. Counterpoint: Better radiation treatment of non-small cell lung cancer using new techniques without elective nodal irradiation. *Semin Radiat Oncol.* 2000,10: 315-23.
- 14- Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer.* 1981, 47: 207-14.
- 15- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958, 53: 457-81.
- 16- Huber RM, Flentje M, Schmidt M, Pöllinger B, Gosse H, Willner J. Simultaneous chemoradiotherapy compared with radiotherapy alone after induction chemotherapy in inoperable stage IIIA or IIIB non small cell lung cancer: Study CTRT99/97 by the bronchial carcinoma therapy group. *J Clin Oncol.* 2006, 24 (11): 4397-404.
- 17- Biesma B, Manegold C, Smit HJM, Willems L, Legrad C, Passiukov A, et al. Docetaxel and cisplatin as induction chemotherapy in patients with pathological-proven stage IIIA N2 non small cell lung cancer: A phase II study of the european organization for research and treatment of cancer (EORTC 08984). *Eur J Cancer.* 2006, 42: 1399-406.