

## **Induction Chemotherapy Followed by Concomitant Chemoradiotherapy in Patients with Locally Advanced Non Small Cell Lung Cancer**

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### **ABSTRACT**

Between January 1996 and May 1997, 25 patients with stage III inoperable non-small cell lung cancer were planned to receive induction chemotherapy consisting of cisplatin (100 mg/m<sup>2</sup> day 1) and etoposide (100 mg/m<sup>2</sup> days 1-3), every 28 days for three cycles. Patients responding to induction chemotherapy received concomitant chemoradiotherapy whereas non-responsive patients received the planned radiotherapy alone and/or palliative treatment. Radiation dose was 50 Gy, delivered in 2 Gy daily fractions, over 5 weeks. Concomitant chemotherapy consisted of cisplatin (15 mg/m<sup>2</sup>, days 1-5) and etoposide (50 mg/m<sup>2</sup>, days 1-5) given on weeks 1 and 4 of irradiation. Response rate to induction chemotherapy was 60% including 8% complete response. Toxicity ( $\geq$  grade 3) of induction chemotherapy was mostly hematological (56%). Out of the 15 patients who received concomitant chemoradiotherapy, 8 had complete response and 5 had partial response. Toxicity ( $\geq$  grade 3) of concomitant chemoradiotherapy was mostly hematological (26.7%) and esophageal (20%). With a median follow-up of 17 months (range, 12-28), the estimated 1- and 2-year survival rates were 60% and 35%, respectively. Median survival for all patients was 13 months. Responding patients had a 2-year survival of 53% compared to 10% in non-responders ( $p < 0.01$ ). During follow-up, 17 of 25 patients (68%) had disease progression: 5 local, 7 distant (5 in brain) and 5 had both. Of the 15 patients who received concomitant chemoradiotherapy, 8 (53%) had disease progression (4 local, 2 distant and 2 both). Four of 10 patients alive at the time of analysis without evidence of disease were complete responders to concomitant chemoradiotherapy. This treatment approach was feasible with an acceptable toxicity, resulted in a high response rate and in a survival benefit for responsive patients.

**Key Words:** *Chemotherapy - Radiotherapy - Small cell lung cancer.*

### **INTRODUCTION**

Cancer of the lung continues to be the most

frequent cause of death among adult malignancies. Non-small-cell lung cancer (NSCLC) constitutes more than 75% of all lung cancer cases [31]. For the approximately one-third of NSCLC patients who present with locally advanced inoperable disease, radiotherapy has been the mainstay of treatment. However, the overall outcome of these patients has been invariably poor, with 5-year survival rate less than 10% [22].

Efforts to improve these results have included radiation dose escalation, altered fractionation [17,28] and combined chemoradiation approaches [6,7,14,30]. With incorporation of cisplatin-based chemotherapy regimens in the combined modality programs, promising survival results were reported in several studies [6,7,10,14]. Some studies [6,14] showed an advantage for induction chemotherapy over the radiotherapy alone, while other studies [10,30] showed advantage for concomitant chemoradiotherapy. Although, induction chemotherapy studies showed improvement in survival due to a reduction in distant metastasis, studies of concomitant chemoradiotherapy showed improvement in survival due to improved local control.

To treat patients with locally advanced NSCLC, therefore, we have selected a cisplatin/etoposide regimen and combined it with radiotherapy. The cisplatin/etoposide regimen has been shown to have synergistic antitumor effects against NSCLC [16]. The potentiation of radiation effects by cisplatin [32] and by etoposide has been reported [12]. The objective of this

prospective study was to evaluate the efficacy and toxicity of cisplatin/etoposide induction chemotherapy, followed by concomitant cisplatin, etoposide and radiotherapy in the treatment of stage III inoperable NSCLC.

## PATIENTS AND METHODS

### *Selection criteria and pretreatment evaluation:*

Eligibility criteria included the following: age up to 70 years; histologically or cytologically confirmed NSCLC; inoperable stage IIIA or IIIB [21]; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2 [25]; normal renal, liver and hematological functions; no pleural effusion and no prior chemotherapy or radiotherapy.

Pretreatment evaluation included medical history, physical examination, complete blood count, biochemical tests, posteranterior and lateral chest radiography, computed tomography (CT) of the thorax (including the upper abdomen) and bronchoscopy. Liver CT scan or ultrasound, radionuclide bone scan and brain CT scan (if indicated) were also performed.

### *Treatment plan:*

Eligible patients were planned to receive induction chemotherapy. Patients responding to induction chemotherapy (group A) received concomitant chemoradiotherapy. Non-responsive patients (group B) received the planned radiotherapy alone and/or palliative treatment.

### *Chemotherapy:*

Induction chemotherapy consisted of cisplatin (100 mg/m<sup>2</sup> intravenous, day 1) and etoposide (100 mg/m<sup>2</sup> intravenous, days 1-3), every 28 days for three cycles. Before and after cisplatin infusion, all patients received 2 liters of 5% dextrose and 0.9% saline with potassium chloride (10-20 mEq/liter) and magnesium sulphate (4-8 mEq/liter) as well as 250 ml of mannitol 10%. Vomiting was controlled with a combination of ondansetron, dexamethasone and metaclopramide. Prior to each cycle of chemotherapy, complete blood count and serum creatinine were determined. Concomitant chemotherapy consisted of cisplatin (15 mg/m<sup>2</sup> intravenous, days 1-5) and etoposide (50 mg/m<sup>2</sup> intravenous, days 1-5) given on weeks 1 and 4 of irradiation.

### *Radiotherapy:*

Radiotherapy was administered using Co-

balt-60 teletherapy machine. The initial target volume included primary tumor, ipsilateral hilum and entire mediastinum (from the suprasternal notch to 5 cm below the carina) plus 2-cm margin. Lower lobe lesions required mediastinal irradiation to the diaphragm and upper lobe lesions required irradiation of the ipsilateral supraclavicular area. Radiation dose was 50 Gy, delivered in 2 Gy daily fractions, 5 days a week over a period of 5 weeks. Treatment was started with two opposing anteroposterior-posteroanterior fields. The spinal cord was excluded from the irradiated volume at 40 Gy by using oblique or lateral off-cord fields.

### *Treatment evaluation:*

Patients were followed on weekly basis during treatment. Subsequently, patients were examined every one-month for 1 year and every 3 months thereafter. Patients were evaluated for initial response 4 weeks after induction chemotherapy. Final evaluation of response was performed 3 months after radiotherapy. Among the criteria for treatment response, complete response (CR) was defined as complete disappearance of all measurable disease for a minimum of 4 weeks. Partial response (PR) was defined as a 50% or more decrease in the sum of the products of diameters of measurable disease for a minimum of 4 weeks. Stable disease (SD) was defined as a less than 50% decrease in the sum of the products of measurable disease or a less than 25% increase. Progressive disease (PD) was defined as a 25% or more increase in the size of measurable disease or appearance of new lesions. Toxicity was evaluated according to the World Health Organization criteria [18].

### *Statistical analysis:*

Frequencies were compared using chi-square or Fisher's exact test. Overall survival was measured from the start of treatment to death or last follow-up evaluation and estimated by the method of Kaplan-Meier. Differences in survival estimates between groups of patients were evaluated using a log-rank test. A *p*-value of < 0.05 was considered significant [27].

## RESULTS

### *Patient characteristics:*

Between January 1996 and May 1997, 25 patients with stage III inoperable NSCLC referred to Radiation Oncology Unit at Zagazig University Hospitals were included.

Pretreatment characteristics of the patients are listed in Table (1). There were 20 males (80%) and 5 females (20%), with a median age of 60 years (range, 30 to 70%). Seventeen (68%) patients had ECOG performance status 0-1. Fourteen (56%) patients had squamous cell carcinoma and 11 (44%) nonsquamous cell carcinoma. Fifteen (60%) patients had stage IIIA and 10 (40%) stage IIIB disease.

#### Initial response:

Fifteen of 25 (60%) patients were responders (2 CR and 13 PR) to induction chemotherapy (group A). There was no significant association between response and PS (65% for PS 0-1 and 50% for PS 2), histology (64% for squamous cell carcinoma and 55% for nonsquamous cell carcinoma) and stage (67% for stage IIIA and 50% for stage IIIB) (Table 2). Of the 10 non-responders (group B), 5 had SD and 5 had PD.

#### Final response:

Of 15 patients' in-group A, 8 had CR, 5 had PR and 2 had PD. Among the 8 complete responders, 4 were squamous cell carcinoma (all stage IIIA) and 4 non-squamous cell carcinoma (2 stage IIIA and 2 stage IIIB). Of the 5 patients' with SD (received radiotherapy alone) in-group B, one had PR, one had SD and 3 had PD. The 5 patients with PD in-group B received palliative radiotherapy for the primary and metastatic sites (brain, bone) except one patient with liver metastasis had bad general condition received only supportive measures.

#### Toxicity:

Toxicity of induction chemotherapy (Table 3) was mainly hematological, grade  $\geq 3$  was noticed in 14 patients (56%) including leukopenia in 7 (28%), thrombocytopenia in 4 (16%) and anemia in 3 (12%). Nine patients (36%) had grade 3 alopecia. Seven patients (28%) developed grade  $\geq 3$  nausea/vomiting. No grade  $\geq 3$  nephrotoxicity or neurotoxicity was observed.

Toxicity of concomitant chemoradiotherapy is shown in Table (4). Grade 3 hematologic toxicity was noticed in 4 patients (26.7%) including leukopenia in 3 (20%) and thrombocytopenia in one (6.7%). Three patients (20%) had esophagitis grade  $\geq 3$ . No grade  $\geq 3$  radiation pneumonitis was observed. Of the 5 patients who received radiotherapy alone, only one patient had grade 2 esophagitis. Late treatment

toxicity was infrequent. Lung fibrosis was observed in one patient who had grade 2 radiation pneumonitis, 6 months later. No esophageal stricture or radiation myelitis has been identified.

#### Survival and patterns of failure.

With a median follow-up of 17 months (range, 12-28), the estimated 1- and 2-year survival rates were 60% and 35%, respectively (Fig. 1). Median survival for all patients was 13 months. Responding patients had a 2-year survival of 53% compared to 10% in non-responders ( $p < 0.01$ ). During follow-up, 17 of 25 patients (68%) had disease progression: 5 local, 7 distant (5 in brain) and 5 both. Median time to disease progression was 9 months (range, 2-24). Four of 5 patients who developed brain metastases had non-squamous cell carcinoma (brain was the sole site in 2). Of the 15 patients in group A, 8 (53%) had disease progression (4 local, 2 distant and 2 both). Among the 8 complete responders, 4 had disease progression (2 local, one distant and one both). Three of them were squamous cell carcinoma (2 local and one both). At June 1998, 15 patients had died of their disease and 10 patients were alive. Four of 10 patients alive without evidence of disease were complete responders to concomitant chemoradiotherapy.

Table (1): Pretreatment patient characteristics (n=25).

Characteristics	No.	%
<i>Age (years):</i>		
Median	60	
Range	30-70	
<i>Sex:</i>		
Male	20	80
Female	5	20
<i>ECOG performance status:</i>		
0	1	4
1	16	64
2	8	32
<i>Histologic type:</i>		
Squamous cell carcinoma	14	56
Non-squamous cell carcinoma	11	44
<i>Tumor stage:</i>		
IIIA	15	60
IIIB	10	40
<i>Tumor extent:</i>		
T1	1	4
T2	5	20
T3	11	44
T4	8	32
<i>Nodal extent:</i>		
N0	7	28
N1	7	28
N2	9	36
N3	2	8

Table (2): Response rate to induction chemotherapy (n=25).

Variable	No.	Response				Response rate (%)	p-value
		CR	PR	SD	PD		
Overall	25	2	13	5	5	60	
<i>Performance status:</i>							
0-1	17	2	9	3	2	65	NS
2	8	-	4	2	3	50	
<i>Histology:</i>							
Squamous cell carcinoma	14	1	8	3	2	64	NS
Non-squamous cell carcinoma	11	1	5	2	3	55	
<i>Stage:</i>							
IIIA	15	2	8	4	1	67	NS
IIIB	10	-	5	1	4	50	

Table (3): Toxicity of induction chemotherapy (n=25).

	Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Leukopenia	6	24	9	36	5	20	2	8
Anemia	7	28	4	16	3	8	-	-
Thrombocytopenia	3	12	4	16	3	12	1	4
Nausea/vomiting	6	24	7	28	6	24	1	4
Alopecia	4	16	8	32	9	36	-	-
Nephrotoxicity	1	4	1	4	-	-	-	-
Neurotoxicity	5	20	4	16	-	-	-	-

Table (4): Toxicity of concomitant chemoradiotherapy (n=15).

	Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Leukopenia	4	26.7	4	26.7	3	20.0	-	-
Anemia	3	20.0	4	26.7	-	-	-	-
Thrombocytopenia	1	6.7	2	13.3	1	6.7	-	-
Esophagitis	6	40.0	6	40.0	2	13.3	1	6.7
Pneumonitis	2	13.3	1	6.7	-	-	-	-
Nausea/vomiting	3	20.0	2	13.3	-	-	-	-

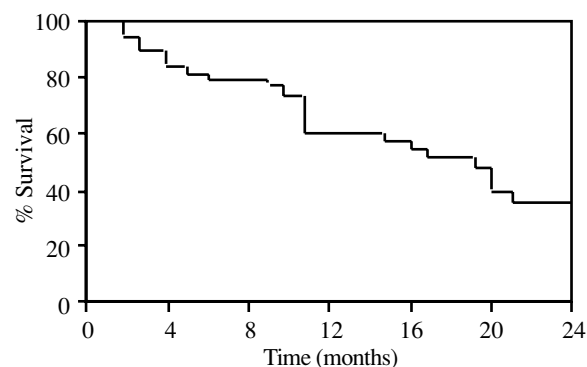


Fig. (1): Overall survival in all patients (n=25).

## DISCUSSION

In locally advanced NSCLC, radiotherapy alone results in disappointing long-term disease control. Several randomized trials have demonstrated that radiotherapy in combination with cisplatin-based chemotherapy, delivered either sequentially or concomitantly, improves survival over radiotherapy alone [6,7,14,30]. What is the apparent in all of these trials is that both local and distant failures remain impediments to long-term disease control.

Dillman et al. [6] reported a doubling in 2-

year survival (26% versus 13%) for induction chemotherapy (two cycles of cisplatin and vinblastine) followed by radiotherapy (60 Gy) compared to radiotherapy alone. The median survival time for the combined chemoradiation arm was 13.8 months as compared with 9.7 months for radiotherapy arm ( $p = 0.007$ ). The 5-year survival of the patients who were treated with combined treatment was 19% versus 7% among those who were treated by radiotherapy alone [7]. Le Chevalier et al. [14], randomized patients to receive radiotherapy alone (65 Gy) or three cycles of vindesine, cyclophosphamide, cisplatin and lomustine followed by the same radiotherapy. The 3-year and median survival time significantly improved with combined treatment compared with radiotherapy alone, 12% versus 4%, 12 months versus 10 months, respectively. The improvement in survival in this trial was attributed to a decreased rate of distant metastases from 70% to 49% in the chemoradiation arm, while chemotherapy had no impact on local control that was poor in both study arms (17% at one year in the radiotherapy arm versus 15% in the combined arm) [14]. Obviously, low rates of complete response and persistence of macroscopic residual tumor after induction chemotherapy are the rule in these patients and late radiotherapy may be unable to ultimately eradicate such resistant residuum [20]. Concomitant administration of chemotherapy and radiotherapy may be a way to overcome this problem.

In the study by Shaake-Koning et al. [30], radiotherapy (55 Gy) and concomitant cisplatin (6 mg/m<sup>2</sup>/daily) arm showed an improved significant 2-year survival, 26% compared with 13% among the patients who received radiotherapy alone ( $p = 0.009$ ). The survival benefit in this study was attributed to improvement of local control from less than 10% to 30% with concomitant administration of daily cisplatin. Sause et al. [29] randomized patients to be treated with two cycles of vinblastine and cisplatin followed by concomitant cisplatin and radiotherapy (63 Gy) versus radiotherapy alone. The median survival time was 13.7 months and the 2-year survival was 33% for combined treatment compared with 11.4 months and 21% among the patients who received radiotherapy alone ( $p = 0.03$ ). Fursue et al. [10] randomized patients to either concomitant or sequential mitomycin, vindesine and cisplatin with 60 Gy of

radiotherapy. Median survival time and 2-year survival were longer in the concomitant group, 16.5 months and 37% compared to 13.3 months and 25.6% for sequential group ( $p = 0.473$ ).

In the present study, we attempted to reduce both local and distant failures by using 3 cycles of cisplatin/etoposide induction chemotherapy followed by concomitant cisplatin, etoposide and radiotherapy. Median survival time was 13 months and overall survival rates were 60% at 1 year and 35% at 2 years. These survival outcomes were nearly similar to those reported in other chemoradiation trials [10,29].

Eberhardt et al. [8] reported that brain relapse at 3 years for patients without prophylactic cranial irradiation (PCI) was 54%, whereas, it was 13% for those who received PCI. The hypothesis that PCI can improve survival is based on the assumption that isolated brain failures occur commonly and can be effectively prevented by irradiation. However, randomized trial by Mira et al. [19] have not demonstrated improved survival with PCI for patients with locally advanced NSCLC. In the present study, 4 of 5 patients who developed brain metastases were non-squamous cell carcinoma (brain was the sole site in 2). The higher risk of brain metastasis with non-squamous cell carcinoma justifies a new evaluation of prophylactic cranial irradiation [5].

Pattern of failure analysis of our series showed that out of the 8 patients who developed disease progression after concomitant chemoradiotherapy, 4 were squamous cell carcinoma (all of them had isolated local failure). Of the 4 patients who progressed after complete response, 3 were squamous cell carcinoma (2 had isolated local failure and one had both local and distant). These data suggest that a total dose of 50 Gy may be inadequate for local control of squamous cell carcinoma, with no or little potentiation effects provided by concomitant chemotherapy.

Hyperfractionated radiotherapy (HFRT) may have also contributed to improving local control as suggested by some studies [17,28]. Other pilot studies had evaluated HFRT and concomitant chemotherapy [1,11,15,23]. These pilot studies obtained promising results [1,11,15,23]. One of these studies reported by Lee et al. [15], in which HFRT (69.6 Gy, 2 Gy twice daily) was combined with cisplatin (50 mg/m<sup>2</sup>,

days 1,8,29 and 36) and oral etoposide (50 mg bid, days 1-14 and 29-43). Median survival time was 18.9 months and 1- and 2-year survivals were 67% and 35%, respectively. This was achieved at the expense of significant toxicity, because 57% of patients had grade 4 hematological toxicity, 53% had grade  $\geq 3$  esophagitis and 25% grade  $\geq 3$  bronchopulmonary toxicity [14]. Komaki et al. [13] reported a randomized study that compared induction and concomitant chemoradiotherapy. The induction arm consisted of vinblastine and cisplatin followed by conventional fractionated radiotherapy (63 Gy) and the concomitant arm consisted of HFRT (69.6 Gy) plus cisplatin and oral etoposide: median survival time and 1-year survival (15.5 versus 14.4 months, respectively; 65% versus 58%, respectively) were not significantly different. The induction arm had significantly more grade 4 hematological toxicity (62% versus 33%,  $p = 0.021$ ) and acute nonhematological toxicity grade  $\geq 3$  was greater in the concomitant arm, mainly due to esophagitis (38% versus 6%,  $p = 0.0001$ ).

In the present study, toxicity ( $\geq$  grade 3) of induction chemotherapy was mostly hematological (56%). With concomitant chemoradiotherapy grade 3 hematological toxicity occurred in 25%, grade  $\geq 3$  esophagitis in 20% and no grade  $\geq 3$  pneumonitis was observed. In a trial by Blanke et al. [3], 21 patients were treated with radiotherapy (60.4 Gy) concomitantly with cisplatin and etoposide, grade  $\geq 3$  pneumonitis occurred in 25% of the patients leading to early closure of the study. The inclusion of the contralateral hilar nodes plus a margin in Blanke et al. [3] trial may have resulted in a sufficiently large volume of irradiated lung that lead to an increased rate of severe pneumonitis.

Local progression of locally advanced inoperable NSCLC continues to be a problem with current radiation doses given. Three - dimensional (3-D) conformal radiotherapy as a means of dose escalation for tolerance and local tumor control is being explored in several studies [2,4]. Despite the importance of effective local therapies, systemic progression is the rule in most patients and more effective systemic therapies are needed. Preliminary studies that used platinum compounds with a number of newer agents, including paclitaxel, vinorelbine, gemcitabine and docetaxel are encouraging [9,24,26].

### Conclusion:

Cisplatin/etoposide induction chemotherapy followed by concomitant cisplatin, etoposide and radiotherapy was feasible with an acceptable toxicity, resulted in a high response rate and in a survival benefit for responsive patients.

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