Randomized Study of Concurrent Carboplatin, Paclitaxel, and Radiotherapy with or Without Prior Induction Chemotherapy in Patients with Locally Advanced Non-Small Cell Lung Cancer

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ABSTRACT

**Background:** Multiple concepts of combined modality therapy for locally advanced inoperable non-small cell lung cancer have been investigated. These include induction chemotherapy, concomitant chemo-radiotherapy, and radiation only. To date, combined modality therapy specially the use of concomitant chemo-radiotherapy has led to promising results and was shown to be superior to radiotherapy alone in phase II studies. However the optimum chemo-therapeutic regimen to be used as well as the benefit of induction chemotherapy before concomitant chemo-radiotherapy are yet to be determined. Based on these observations, we investigated the use of paclitaxel and carboplatin concomitantly with radiotherapy and the benefit of prior two cycles induction chemotherapy.

**Materials and Methods:** In this trial 60 patients with locally advanced inoperable non small cell lung cancer, good performance status and minimal weight loss have been randomized into 3 groups each of 20 patients. Group A received induction 2 cycles paclitaxel (175 mg/m²) and carboplatin (AUC 6) on day 1 and 28th followed by concomitant paclitaxel (45 mg/m²) and carboplatin (AUC 2) weekly with radiotherapy. Group B received concomitant carboplatin, paclitaxel (same doses as in group A) and radiotherapy with no prior induction chemotherapy. Group C received only radiotherapy to a total dose of 60 Gy in conventional fractionation.

**Results:** A total of 60 patients were enrolled in this study between 1998 and 2000. Pretreatment characteristics, including age, gender, performance status, histological features and stage were comparable in each group.

The incidence of oesophagitis was significantly higher in group A and B than in group C (75%, 79%, and 40% respectively) (p=0.020). The time to in-field progression was significantly higher in group B as compared to group A (48% vs. 32% failure in 2 years respectively) (p=0.000).

The median 2 year survival was significantly higher in group A and B than in group C (p=0.039) but no statistical difference was seen between group A and B.

**Conclusion:** Combined chemo-radiotherapy resulted in better response and survival as compared to conventional radiotherapy in the treatment of locally advanced non-small cell lung cancer.

Early initiation of radiation with concomitant chemotherapy resulted in prolonged time to infield progression. On the other hand, two cycles of induction chemotherapy did not show any significant difference regarding the response or survival.

Weekly paclitaxel and carboplatin plus radiotherapy is a well tolerated regimen for outpatients with encouraging results.

**Key Words:** Induction chemotherapy – NSCLC – Carboplatin – Paclitaxel.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death for both men and women [1]. It constitutes approximately 75% of all lung cancer cases [2]. Approximately 40% of patients will present with stages IIA and IIB which are usually treated by primary surgery, radiotherapy or combined chemotherapy and radiotherapy.

Despite the great improvement of surgical and radiation techniques, few patients achieve a complete response [3,4].
Due to the limited benefits provided by radiation therapy alone, the use of combined chemoradiotherapy in patients with locally advanced, unresectable NSCLC has been explored.

Recent years have seen several new approaches to the combined modality treatment of locally advanced NSCLC. These approaches include induction chemotherapy, concomitant chemotherapy, and intensified schedules of radiation therapy. Induction chemotherapy has been compared with radiotherapy alone in randomized prospective trials and has been shown to improve survival [5-7]. Concomitant chemoradiotherapy achieved promising results when combination drug regimens were used in the phase II setting, and has been shown to be superior to induction chemotherapy by direct comparison [8-10].

By 1994, it was clear that several new cytotoxic agents were active in stage IV NSCLC, both when given individually and administered in combination [11-21]. It was argued that these agents should be investigated in stage III disease.

Recent meta analyses have demonstrated a statistically significant survival benefit for patients receiving cisplatin-based chemotherapy combined with radiotherapy compared to those receiving radiotherapy alone [22-25]. Chemotherapy produced a 3-6 month improvement in the median survival rate and 5-15% improvement in 3- to 5-year survival rates.

Despite the substantial gains in long-term survival rates, the overall survival of patients is still unacceptably low. Clearly, new treatment strategies are needed.

The addition of paclitaxel and carboplatin to radiation represents an extension of these chemoradiation principles.

The interactions of chemotherapy and radiation therapy are complex. The taxanes interact with radiation at many levels. Cell cycle synchronization through mitotic arrest has been consistently shown to play a major role in radiation enhancement [26-34], however, increased apoptosis [35] and tumor reoxygenation [36] may constitute additional mechanisms.

In the current study, we attempted to improve local control rates by using concomitant chemoradiotherapy and to improve systemic control by adding two cycles of induction chemotherapy.

The objectives of this study were to determine the response rate and the relapse-free and overall survival rate, and to evaluate the qualitative and quantitative toxicity of the combination of paclitaxel, carboplatin and radiotherapy in patients with locally advanced NSCLC.

**Aim of the work:**

The aim of this study was to evaluate the results of combination of carboplatin and paclitaxel concomitantly with radiotherapy in the treatment of locally advanced inoperable non-small cell lung cancer. Also to evaluate the benefit of prior two cycles induction chemotherapy.

**MATERIAL AND METHODS**

**Eligibility criteria of the patients:**

- All patients included in this study should have histologically documented stage IIIa or IIIb. Patients with malignant pleural effusion were not eligible.
- All patients should have measurable or assessable disease.
- Further eligibility criteria included: age greater than 18 years; ECOG performance status ≤1; weight loss less than 10% during the 6 months preceding diagnosis; no prior chemotherapy or lung radiation therapy. Platelet count >100,000/uL; absolute neutrophil count >1,800 uL; hemoglobin >10 g/dL; BUN <1.5 times the upper limit of normal; creatinine level <1.5 mg/dL; bilirubin <1.5 times upper limit of normal (ULN); AST <2 times ULN and no other serious medical or psychiatric illness.

All patients signed an informed consent. Height, weight, performance status and tumor stage were recorded. All patients underwent complete physical examination, lab work up, chest x-ray, CT scan of the chest and upper abdomen, CT scan of the brain and isotopic bone scan.

**Treatment plan:**

In this trial 60 patients with locally advanced NSCLC have been randomized into 3 groups.

Group A received induction 2 cycles paclitaxel (175 mg/m²) and carboplatin (AUC6) on
day 1 and 28th followed by concomitant paclitaxel (45 mg/m²) and carboplatin (AUC2) weekly with radiotherapy.

Group B received concomitant carboplatin, paclitaxel (same doses as in group A) and radiotherapy with no prior induction chemotherapy.

Group C received only radiotherapy to a total dose of 60 Gy in conventional fractionation.

The initial large-field target volume of radiation included the primary tumor, the mediastinum at least 5 cm below the carina, and the ipsilateral supraclavicular region.

The boost target volume encompassed the primary tumor with 2-cm margin. Heterogeneity corrections were not used in the definitions of total doses. The maximal dose in any part of either target volume should not have exceeded the prescribed dose by more than 15%.

Responses were assessed using the modified World Health Organization criteria.

Toxicities were assessed using the RTOG/EDRTC acute radiation toxicity criteria [37].

SPSS software ver 11 was used to perform the statistical analysis in the present study using the non-parametric statistics (Kruskal-Wallis) and Kaplan Meier survival analysis, 5% level of significance was considered.

RESULTS

This study included 60 patients with stage IIA and IIIB NSCLC seen in the Department of Clinical Oncology at Medical Research Institute as well as at University Hospital of Alexandria between 1998 and 2000.

Table (1) represents the pretreatment patient’s characteristics. No statistically significant differences were found among patients in the 3 treatment groups.

Table (2) represents the treatment toxicities in the three groups. The incidence of oesophagitis was significantly higher in group A and B than in group C. Haematological toxicities were also significantly higher in group A & B than in group C.

Table (3) represents the response to treatment among the 3 studied groups.

Table (1): Median age, gender, performance status, histology, stage of the tumor and smoking habit in the three studied groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
<th>Group C (n=20)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (year)</td>
<td>61 (55%)</td>
<td>62 (55%)</td>
<td>59 (55%)</td>
<td>p=0.814</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (90%)</td>
<td>15 (75%)</td>
<td>19 (95%)</td>
<td>X²=3.75</td>
</tr>
<tr>
<td>Female</td>
<td>2 (10%)</td>
<td>5 (25%)</td>
<td>1 (5%)</td>
<td>p=0.153</td>
</tr>
<tr>
<td>* Performance status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3 (15%)</td>
<td>1 (5%)</td>
<td>3 (15%)</td>
<td>X²=1.29</td>
</tr>
<tr>
<td>1</td>
<td>17 (85%)</td>
<td>19 (95%)</td>
<td>17 (85%)</td>
<td>p=0.523</td>
</tr>
<tr>
<td>Histology:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>11 (55%)</td>
<td>14 (80%)</td>
<td>9 (45%)</td>
<td>X²=2.818</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>7 (35%)</td>
<td>5 (25%)</td>
<td>8 (40%)</td>
<td>p=0.235</td>
</tr>
<tr>
<td>Large cell</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
<td>3 (15%)</td>
<td></td>
</tr>
<tr>
<td>Stage:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>6 (30%)</td>
<td>3 (15%)</td>
<td>2 (10%)</td>
<td>X²=2.89</td>
</tr>
<tr>
<td>IIIB</td>
<td>14 (70%)</td>
<td>17 (85%)</td>
<td>18 (90%)</td>
<td>p=0.153</td>
</tr>
<tr>
<td>Smoking:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>18 (90%)</td>
<td>16 (80%)</td>
<td>19 (95%)</td>
<td>X²=2.26</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>2 (10%)</td>
<td>4 (20%)</td>
<td>1 (5%)</td>
<td>p=0.332</td>
</tr>
</tbody>
</table>

p>0.05 is not significant * Performance status was assessed based on ECOG scale
Randomized Study of Concurrent Carboplatin, Paclitaxel

Table (2): Treatment toxicities encountered in the three studied patients.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
<th>Group C (n=20)</th>
<th>Kruskal-Wallis test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade I, II n (%)</td>
<td>Grade III, IV n (%)</td>
<td>Grade I, II n (%)</td>
<td>Grade III, IV n (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14 (70%)</td>
<td>11 (55%)</td>
<td>10 (50%)</td>
<td>11.781</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (55%)</td>
<td>10 (50%)</td>
<td>7 (35%)</td>
<td>8.226</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (40%)</td>
<td>9 (45%)</td>
<td>5 (25%)</td>
<td>22.293</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>7 (35%)</td>
<td>9 (45%)</td>
<td>5 (25%)</td>
<td>7.549</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (60%)</td>
<td>10 (50%)</td>
<td>8 (40%)</td>
<td>1.712</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>15 (75%)</td>
<td>13 (65%)</td>
<td>3 (15%)</td>
<td>21.758</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (15%)</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
<td>4.484</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>5 (25%)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>8.732</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (20%)</td>
<td>3 (15%)</td>
<td>0 (0%)</td>
<td>3.085</td>
</tr>
<tr>
<td>Alopecia</td>
<td>7 (35%)</td>
<td>8 (40%)</td>
<td>0 (0%)</td>
<td>10.727</td>
</tr>
</tbody>
</table>

Toxicities were assessed using RTOG/EDRTC acute radiation toxicity criteria [37]. p>0.05 is not significant.

Table (3): Response to the treatment among the 3 studied groups.

<table>
<thead>
<tr>
<th>Response</th>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
<th>Group C (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Complete response</td>
<td>4</td>
<td>(20%)</td>
<td>5</td>
</tr>
<tr>
<td>Partial response</td>
<td>11</td>
<td>(55%)</td>
<td>10</td>
</tr>
<tr>
<td>No response</td>
<td>3</td>
<td>(15%)</td>
<td>4</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>(10%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Kruskal-Wallis test X²=7.794, p=0.020*

The response rate (partial and complete response) was significantly higher in group A and B than in group C (75%, 79% and 40% respectively).

The time to in-field progression as shown on Table (4) was significantly higher in group B as compared to group A at 24 months (48% vs. 32% failure in 2 years respectively).

The median two-year survival was significantly higher in group A and B than in group C but no statistical significant difference was seen between group A and B (Table 5, Fig. 1).

Table (4): Time to in-field progression.

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
<th>Group C (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>(0%)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>(16%)</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>(31%)</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>(31%)</td>
<td>5</td>
</tr>
<tr>
<td>24</td>
<td>9</td>
<td>(48%)</td>
<td>6</td>
</tr>
</tbody>
</table>

Kruskal-Wallis test X²= 15.804, p=0.000*
Table (5): Overall survival at two years.

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
<th>Group C (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
<td>(100%)</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>(80%)</td>
<td>18</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>(55%)</td>
<td>13</td>
</tr>
<tr>
<td>18</td>
<td>9</td>
<td>(45%)</td>
<td>10</td>
</tr>
<tr>
<td>24</td>
<td>8</td>
<td>(40%)</td>
<td>9</td>
</tr>
</tbody>
</table>

Kruskal-Wallis test $X^2 = 6.513, \ p=0.039^*$

Fig. (1): Overall survival after treatment.

Fig. (2): A patient with complete response.

Before treatment

After two cycles of chemotherapy

Sub pleural thickening proved negative by FNA

After completion of treatment
DISCUSSION

The optimal therapy for stage III NSCLC continues to evolve. No single modality has proven effective.

It is now established that induction chemotherapy followed by radiotherapy is superior to radiotherapy alone [38-40] for patients with minimal to moderate symptoms and weight loss <10%.

Although the incidence of distant metastasis may be reduced by chemotherapy, there is no suggestion that induction chemotherapy has any effect on control of the locoregional tumor, [41] which is the most immediately life threatening component of the disease [42]. Around the same time, Schaake-Koning and colleagues [4] from the European Organization for Research and Treatment of Cancer (EORTC) demonstrated that cisplatin concurrent with Radiotherapy significantly improved both locoregional control and survival compared with radiotherapy alone, which supports a strategy that aims to improve locoregional control and subsequently improve survival.

The results of the Cancer and Leukemia Group B (CALGB) trial reported by Dillman et al. [38] combined with the EORTC results support the combination of the induction cisplatin/vinblastine followed by Radiotherapy with concurrent low-dose cisplatin, which was the background of Radiotherapy Oncology Group (RTOG) 88-08 [43].

Fig. (3): A patient with partial response.
Concurrent cisplatin/etoposide with hyperfractionated radiotherapy without induction chemotherapy was the background for RTOG 91-06 [44]. With a minimal follow-up of 21 months for the 56 patients in RTOG 91-06 with <15% weight loss, the median survival was 21.1 months, and the 2 year survival rate was 42%. However, 57% of patients developed Grade 3 and 7% of patients had Grade 4 toxicity.

Reboul et al. [45] reported similar median and 2 year survival rates using concurrent cisplatin and I.V. etoposide with once-daily radiotherapy.

In our study, we evaluated the role of paclitaxel in the combined-modality approach for the treatment of advanced non-small cell lung cancer, particularly because of the profoundly high radiation sensitizing property of paclitaxel at low concentration, [30,31] and relatively high response rate in the phase I study [46].

The lower in-field progression rate in group B is in keeping with the hypothesis that epithelial tumors behave like acute responding normal tissues which might be expected to result in improved survival because the distant metastases are nearly identical.

**Conclusion:**

Combined chemo-radiotherapy resulted in better response and survival as compared to conventional radiotherapy in the treatment of locally advanced non-small cell lung cancer.

Early initiation of radiation with concomitant chemotherapy resulted in prolonged time to infield progression. On the other hand two cycles of induction chemotherapy did not show any significant difference regarding the response or survival.

Weekly paclitaxel and carboplatin plus radiotherapy is a well tolerated outpatient regimen with encouraging results.

**REFERENCES**


