

A PHASE II STUDY OF CISPLATIN AND 5-FLUOROURACIL COMBINATION CHEMOTHERAPY AND CONCURRENT THORACIC RADIATION IN SQUAMOUS CELL CARCINOMA OF LUNG

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ABSTRACT

Objective: To evaluate the efficacy and toxicity of cisplatin, 5-fluorouracil combination chemotherapy and concurrent thoracic radiation in squamous cell carcinoma of lung.

Methodology: A prospective, non randomized, quasi-experimental, phase II study which was conducted in the Department of Clinical Oncology Mayo Hospital / KEMC Lahore. This study was conducted from September 2002 to May 2004. Twenty two patients of histopathologically confirmed squamous cell carcinoma of lung were enrolled. Stage III B or stage IV patients requiring radiation therapy for control of local symptoms were included. These patients were treated with chemotherapy and concurrent chest radiation. The treatment regimen included cisplatin 80mg/m² on day one and day "28" and 5-FU 750mg/m² day 1-4 and day "28-31". Radiation was started on day one and a tumor dose of 50 Gy was delivered in 25 fractions. Common Toxicity Criteria and RTOG criteria were used to assess toxicities. Miller's criteria were used for response evaluation. Responses were evaluated two weeks after the completion of concurrent chemoradiotherapy.

Results: All the twenty two patients completed the planned treatment. Complete response was not achieved in any patient. Partial response was seen in 15 patients (68.18%), stable disease in five patients (22.73%) and progressive disease was seen in two patients (9.09%). CTC Grade-II nausea was seen in eight patients (36.36%), vomiting in five patients (22.73%) and mucositis in six patients (27.27%). Grade-III neutropenia was observed in three patients (13.64%) and Grade-III mucositis and diarrhea in five patients (22.72%) each. Grade-IV neutropenia was seen in two patients (9.09%).

Conclusion: Cisplatin and 5-Fluorouracil combination chemotherapy concurrent with 50 Gy radiation is an effective and well tolerated treatment modality for this subset of lung cancer patients.

KEYWORDS: Squamous cell carcinoma, Lung cancer, Chemo-radiotherapy, Concurrent.

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INTRODUCTION

Lung cancer is the leading cause of cancer death world wide.¹ The incidence of lung cancer is rising in Pakistan.² Non small cell lung cancer constitutes about 75% of lung cancers and 30%-40% of these are squamous cell type.³ For non-small cell lung cancer, surgery offers the best chance for long-term survival and cure, if the tumor is confined to the lung and is operable. Unfortunately the majority of patients

present at an advanced stage and are unresectable.

The primary treatment of locally advanced unresectable non-small cell lung carcinoma has been radiation therapy, but the results have been disappointing. Long-term survival has been poor in the range of 5%-10%^{4,5} with poor local control and early development of metastasis.⁶ Chemotherapy has been used in combination with radiotherapy. This combined therapy has shown a marked benefit in long-term survival.⁷⁻¹¹ However, the best way to combine chemotherapy & radiotherapy either sequentially or concurrently remains to be established.

The current approach is to explore the concurrent use of chemotherapy and radiotherapy, with the idea to treat both the distant and local sites at the same time. The concomitant chemo radiation shows synergism, that possibly enhances the local control.¹² It appears to be better than sequential administration in stage III non-small lung cancer.¹³ 5-FU and cisplatin have been used concurrently with radiotherapy in squamous cell carcinoma of head and neck. 5-Fluorouracil, is being used in squamous cell carcinoma of esophagus, anal canal and skin as well, with response rate of 10-30%¹⁴ 5-FU is also a radiosensitizer. This synergistic and radiosensitizing effect is due to increased DNA damage, inhibition of DNA repair and accumulation of cells in S phase.¹⁵

Cisplatin has been the back bone of most chemotherapies including those being used in lung cancer treatment. It has synergism with 5-FU¹⁶ as well as with radiotherapy.¹⁵ Cisplatin and 5-FU combination chemotherapy has been used alone¹⁷ and with radiotherapy in squamous cell carcinoma of head and neck with good results.¹⁸ Cisplatin and 5-FU combination chemotherapy has not been tested in advanced squamous cell carcinoma of lung. Therefore, with this background, the use of these drugs concurrent with radiotherapy in squamous cell carcinoma of lung seems appropriate.

PATIENTS AND METHODS

This was a prospective, single center, open label, non-randomized quasi-experimental

study of concurrent chemo-radiation in advance squamous cell carcinoma of lung. This study was carried out from September 2002 to May 2004 in the Department of Clinical Oncology Mayo hospital / KEMC Lahore. Eligibility criteria required histologically proven squamous cell carcinoma of lung. These patients were also required to have at least one bidimensionally measurable lesion. Stage III B patients and those stage IV patients were included, who required radiotherapy to chest for symptomatic disease. The patients having ECOG performance status of 0-2 and an adequate marrow function with white blood count of $\geq 3.5 \times 10^9/L$, platelet count of $\geq 100,000/cu\ mm$ and hemoglobin $\geq 10gm/dl$ were included. Adequate renal function with serum creatinine ≤ 1.25 times upper limit of normal or creatinine clearance of $\geq 45ml/min$ was required. An adequate liver function with serum bilirubin less than or equal to the upper limit of normal or AST ≤ 1.5 times upper limit of normal was required.

The patients with brain metastasis, second malignancy, previously treated or with massive pleural effusion were excluded from the study. The treatment included Injection cisplatin 80mg/m²I/V infusion on day one and day 28 and 5-Fluorouracil 750mg/m² as 12 hour infusion from day one to four and day 28-31. Radiation was delivered by cobalt- 60 starting from day one of chemotherapy. A total dose of 50 Gy was given in 25 fractions.

RTOG toxicity criteria were used for evaluation of toxicity induced by radiotherapy and NCI CTC criteria were used for documentation of other toxicities. Response rate was taken as a measure of efficacy and was evaluated by Miller's criteria, with the help of CT scan chest and upper abdomen, two to four weeks after completion of two courses of chemotherapy and concurrent radiation therapy.

RESULTS

From Sep 2002 to May 2004, twenty two patients of squamous cell carcinoma were enrolled in the study. Twenty one patients were male and only one was female. In 13 (59.09%)

patients the lesion was present in the right lung and remaining had disease on the left side. Patient characteristics are given in Table-I.

The most common presenting complaint was cough seen in (59.09%) patients. The duration of symptoms varied from three months to one year. Moderately differentiated squamous cell carcinoma was seen in majority of patients (50%). Eighteen patients (82%) had stage IIIB disease.

All the twenty two patients completed the planned treatment. Complete response was not achieved in any patient. Partial response was seen in 15 patients (68.18%), stable disease in five patients (22.73%) and progressive disease was seen in two patients (9.09%). Grade-II and III toxicity profile is given in Table-II. Common Toxicity Criteria Grade-II nausea was seen in eight patients (36.36%), vomiting in five patients (22.73%) and mucositis in six patients (27.27%). Grade-III neutropenia was observed in three patients (13.64%) and Grade-III mucositis and diarrhea in five patients (22.72%) each. Grade-IV neutropenia was seen in two patients (9.09%).

DISCUSSION

Squamous cell carcinoma of lung has not been separately studied as a disease entity different from other histologies. Furthermore, cisplatin and 5-FU combination chemotherapy has not been well studied in unresectable squamous cell carcinoma of lung in contrast to the squamous cell carcinoma of head and neck and other sites. However, in resectable disease a few studies have been reported. The Lung Cancer Study Group (LCSG) combined 5-FU, cisplatin

Table-I: Patient's characteristics (n=22)

Median age	62 years
Range	45-70 years
Male / Female ratio	21: 1
Laterality	
Right	13 (59.09%)
Left	09 (40.91%)
Sign and symptoms	
Cough	13 (59.01%)
Dyspnea	07 (31.81%)
Hemoptysis	06 (27.27%)
Stage	
III B	18 (81.82%)
IV	04 (18.18%)
Grade	
Well differentiated	05 (22.72%)
Moderately differentiated	11 (50.00%)
Poorly differentiated	06 (27.27%)

and 30 Gy of chest radiotherapy. Overall 42% of patients underwent complete surgical resection and median survival of 11 months was reported.¹⁹ The Cancer and Leukemia Group B (CALGB) tested the combination of 5-FU,vinblastine, cisplatin and 30 Gy of radiotherapy in 32 stage IIIA patients.²⁰ The complete resection rate was 62% and three treatment related deaths occurred.

In contrast to these studies, which were primarily designed for resectable NSCLC, this study was conducted in unresectable NSCLC. Although direct comparison of this study with these studies in terms of survival and DFI is not relevant but one can safely compare the response rate and toxicities of these studies. If the complete resection rate is taken as a surrogate of response, our response rate of 70% compares favourably.

Table-II: TOXICITY (n= 22)

Toxicity	Grade 2		Grade 3	
	Frequency	Percentages (%)	Frequency	Percentages (%)
Anemia	7	31.82	0	0
Neutropenia	8	36.36	3	13.64
Diarrhoea	7	31.82	5	22.73
Vomiting	5	22.73	0	0
Mucositis	6	27.27	5	22.73
Nausea	8	36.36	0	0

NB: Grade IV neutropenia was seen in 2 patients.

In advanced disease use of cisplatin, etoposide combination and concurrent radiotherapy produces significant toxicities. In a study by Radiation Therapy Oncology Group (RTOG) 66 inoperable NSCLC patients received two cycles of oral etoposide 100mg/day on days 1-4 of a 28 day cycle, intravenous cisplatin 50mg/m² on days 1&8, and hyperfractionated radiation therapy five days per week, total 69.6 Gy.²¹ Overall response rate was 72%, 21% had stable disease and 8% had progression, patients with squamous cell carcinoma tended to respond better than other histologic types.

Toxicity was significant, 57% developed Grade-IV haematologic toxicity, 53% Grade-III or IV oesophagitis, and 25% Grade-III or IV lung toxicity. There were three treatment related deaths.

An overall response rate of 68.18% has been achieved in our patients while another 27.73% achieved stable disease, and disease progression was seen in 09.09%. These results are also similar to the results seen in the above mentioned RTOG study. However, it is remarkable to note that in our small series of patients no Grade-IV toxicities were observed. Oral mucositis was the main side effect in our patients, which was manageable with local treatment. The higher toxicity reported in the above mentioned study is possibly related to the use of etoposide, a more powerful myelosuppressant than 5-FU used in our study. Despite these figures it is generally accepted that concomitant use of chemotherapy and radiation therapy is associated with more toxicity than what is seen with radiotherapy alone. Clinically this has not been documented in our study with cisplatin, 5-FU concurrent with chest radiation. This in part can be explained by the possibility that radiation sensitization due to cisplatin and 5-FU might be selective in tumour cells with little or no effect on normal cells. The present schedule of chemotherapy has been well tolerated. It is very difficult to have a meaningful interpretation of the response rates seen with chemoradiotherapy with cisplatin and 5-FU in our small series of patients. However; if the

larger studies are conducted a more significant evaluation of response rates with such chemoradiation may become available. But this small feasibility trial definitely indicates that cisplatin, 5-FU in conjunction with 50 Gy thoracic radiotherapy is well tolerated by stage IIIB/IV non-small cell lung cancer, squamous cell carcinoma, patients. It is recommended that further studies should be conducted with higher doses of radiotherapy.

Current standards of treatment for locally advanced non-small cell lung cancer patients include combination of chemotherapy and radiotherapy. Third generation cytotoxic agents like taxanes and gemcitabine are generally recommended but their cost effectiveness has not been worked out in Pakistan. The average cost per cycle with these drugs is Fifty thousand rupees. Therefore, there is a need for development of cheaper protocols for our patients. This protocol of cisplatin, 5-flourouracil therapy is a cheap protocol with the total cost of chemotherapy not exceeding Rs.2500-3000 per cycle.

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