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Efficacy and Tolerability for Neoadjuvant Chemotherapy in Locally Advanced Non-Small Cell lung Cancer

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Abstract

The objective of this study is to assess Efficacy and tolerability for neoadjuvant chemotherapy in Locally advanced non-small Cell lung cancer. This research is a retrospective study. Between May 2011 and April 2013, 20 patients with stage III A,B Non-small cell lung cancer (NSCLC) referred to Oncology department, Salmanyia Medical Complex (SMC) were treated with combined induction chemotherapy consisting of 3 cycles of cisplatin (80 mg/m2) day I, and Gemcitabine 1250 mg/m2 by intravenous infusion day 1 and 8. Cycles were repeated every 3 weeks. The chemotherapy was followed with thoracic irradiation starting 4-6 weeks after induction chemotherapy up to 60 Gy/6weeks. Patients were assessed for the response and tolerability.

The overall response rate was 40% with no complete response obtained. At a median follow up of 18 months, the overall survival was 75% and median survival was 12 month.

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Treatment toxicity was mainly hamotological in 75% of patients. No grades III or IV toxicity were registered. Nausea and vomiting Grade III was reported in 15 patients (75%), esophagitis grade I in 3 patients (15%), radiation pneumonitis grade I, II in 5 patients (25%), alopecia in 6 patients (30%), nephrotoxicity in 3 patients (15%). As a conclusion we can say that the combination chemotherapy of cisplatin and gemcitabine is a tolerable and active induction chemotherapy regimen for patients with locally advanced NSCLC. Sequential radiotherapy given after induction chemotherapy is tolerable with potential improvement in both locoregional control and survival.

Keywords: neoadjuvant ; non-small cell lung cancer; chemotherapy.

1. Introduction

Cancer is the leading cause of death in many countries and Bronchogenic carcinoma is a major cause of death from cancer [1]. It is generally accepted that surgical resection can be effective in stage I, II and in some cases of stage III patients with non-small cell lung cancer (NSCLC). Unfortunately, more than 75% of NSCLC patients are inoperable because of either distant metastatic disease or disease confined to one hemithorax with one or more criteria of unresectability at the time of presentation. The prognosis of such inoperable patients is poor. The high proportion of disseminated disease in such inoperable patients has justified the numerous attempts to improve systemic treatment for several years [1,2].

There were also many previous studies that showed prolongation of median survival of locally advanced or metastatic NSCLC by cisplatin-based chemotherapy, when compared with best supportive care [2].

Gemcitabine (GEM) is a nucleoside analog with confirmed activity against several solid tumors, especially NSCLC [1,3]. It is well tolerated when given in doses of 1,000 to 1,250 mg/m2 weekly for 3 weeks followed by a 1-week rest. Single drug response rates of 17% to 28% have been reported for NSCLC [1,2, 7]. Several trials have demonstrated significant benefit to induction chemotherapy in reducing the distant failure rate, however, poor local control remains a major issue in the locally advanced disease [5].

This retrospective study was conducted to evaluate neoadjuvant chemotherapy (Gemcitabine plus cisplatin) in treatment of locally advanced NSCLC patients followed by radiotherapy.

Response rate and toxicity profile were assessed as well as quality of life (QOL) and time to disease progression.

2. Patients and methods

Patient selection and pretreatment evaluation:

Between May 2011 and April 2013, 20 patients with stage III A,B Non-small cell lung cancer (NSCLC). were entered into the study.

2.1 Eligible patients should have

- histological or cytological diagnosis of NSCLC,
- stage III (A-B) according to TNM staging [6].
- 18 and up to 65 years of age.
- Eastern cooperative oncology group (ECOG) performance status of 0-2[7],
- life expectancy of more than 12 weeks.
- normal renal, liver, and hematological profile.
- no prior radiation therapy or chemotherapy.

Pretreatment evaluation included patient history, clinical examination, laboratory investigations (blood count, liver function tests, renal function tests) radiological studies (chest x-ray, computerized tomography of the chest, pelvi-abdominal ultrasound) Bone scan and CT of the brain when indicated.

2.2 Treatment methods

Eligible patients were stratified according to sex, performance status, disease stage and histopathological types and were treated as follow:

Twenty patients were treated with induction chemo-therapy in the form of 3 cycles of the following combination: cisplatin (80 mg/m2) given by intravenous infusion over 30-60 minutes day 1, and Gemcitabine 1250 mg/m2 intravenously infused over 30 minutes day 1, 8. Cycles were repeated every 3 weeks. Before and after administration of cisplatin, patients were hydrated with 2 liters of 5% dextrose and 0.9% saline, and 250m1 of manitol 10%. A combination of intravenous dexamethasone and ondansetrone were given before chemotherapy to control vomiting .

2.3 Radiation Therapy Planning

Thoracic irradiation was started 4-6 weeks after induction chemo-therapy using 18 MV LINAC machine.

2.3.1 Position

All patients were treated in supine position.

2.3.2 Localization

CT-based treatment planning was done in the same position as simulation.

2.3.3 Fields arrangements

We used of complex; multiple field arrangement utilizing wedges filters, tissue compensators, field weighting, and bolus to achieve an adequate coverage of the target volume.

2.3.4 Gross target volume (GTV)

Accurate delineation of gross tumor volume of lung cancer depends on positive findings obtained from all diagnostic modalities used in pretreatment evaluation, including computed tomography whichever was positive or magnetic resonance imaging (MRI) scans.

2.3.5 Planned target volume (PTV)

The treatment volume encompasses the primary tumor with a 2cm safety margin around and the entire width of the mediastinum including ipsilateral and contralateral hilum, and extends from sternal notch to at least 5-6 cm below the level of the carina in upper or middle lobes, or hilar tumors, and to the levels of the diaphragm in lower lobe lesions. In undifferentiated tumors or upper lobe lesions, the supraclavicular regions were also included in the treatment volume.

2.3.6 Dose

Patients were treated with 18 MV LINAC machine. A tumor dose of 60 Gy/6 weeks, 5 fractions/week was delivered with exclusion of the spinal cord after 40 Gy.

2.3.7 Dosemetric evaluation

The 3-D computer planning system was used to have the best dose homogenicity to cover the target volume into the 95 % isodose curve. Doses to the spinal cord, heart, lungs, liver, and kidneys were kept within the tolerance limits to reduce sequelae and morbidity. Weekly verification of the target volume was done. Patients were assessed on daily bases for proper repositioning and tolerance to radiation therapy. Also weekly CBC was done for any hematological toxicity detection.

2.4 Post-treatment evaluation

All patients had regular weekly follow up visits during treatment and monthly after treatment, in each visit complete physical examination was performed. Laboratory investigations (CBC, liver functions, kidney functions) were done before each chemotherapy cycle and every two weeks during radiotherapy and radiological investigations (chest X-ray and pelvi-abdominal sonar) was done every 2 months, CT chest was done 2 months after end of treatment and then every 4 months, other investigations were done (e.g bone scan) when indicated.

Patients were assessed for local control, distant metastasis, time to recurrence, quality of life and treatment toxicity.

The final evaluation for response was performed 2-3 months after end of treatment. Response and toxicity were evaluated according to WHO criteria[8] as follows

- Complete response (CR): was defined as complete disappearance of all measurable lesions for a minimum of 4 weeks.

- Partial response (PR): was defined as a 50% or more decrease in the sum of the products of perpendicular diameters of all measurable lesions for a minimum of 4 weeks.

- Stable disease (SD): was defined as a less than 25% decrease in the sum of products of measurable lesions or a less than 25% increase.

- Progressive disease (PD): was defined as a 25% or more increase in the size of measurable lesions or the appearance of new lesions.

All toxic reactions are graded 0-5 implying: none (0), mild (1), moderate (2), sever (3), life threatening (4); and fatal (5) [9].

2.5 Statistical Analysis

Statistical package for social sciences (SPSS) version 16 was used for data base construction and analysis. Quantitative variables were summarized using mean and SD, median minimum and maximum values. Qualitative data were summarized using frequencies and percentage. The starting point was the date of diagnosis for survival and response while it was the end of treatment for the time to relapse. Immediate local failure was counted whenever residual tumor is detected.

Survival analysis was done using Kaplan- Meier, comparisons between survival curves was done using Log-rank test. Differences were considered significant when p was <0.05 and highly significant when $p<0.01$. (16).

3 . Results

3.1 Patient characteristics

Table 1 shows pretreatment characteristics in both groups. A total of 20 patients were included in the study. Thirteen patients (65%) were under 40 year old while 7 (35%) were over 40 year old. The mean age was 44.2 □6.3 (Range 25
only 2 patients.

Eleven patients (55%) had ECOG performance status 0-1, and 9 patients (45%) had ECOG performance status 2. Squamous cell carcinoma was reported in nine (45%) patients, adenocarcinoma in seven patients (35%) and large cell carcinoma in four (20%) patients.

Table 1: Patient characteristics in both study groups.

Characteristics	No	%
Age (years)		
≤ 40	13	65
>40	7	35
Range	25-65	
Mean±SD	45.3±6.7	
Sex		
Male	18	90
Female	2	10
Performance Status		
0-1	11	55
2	9	45
Histopathological types		
Squamous cell	9	45
Adenocarcinoma	7	35
Large cell carcinoma	4	20
Tumor stage		
IIIA	11	55
IIIB	9	45
Tumor grade		
Moderate differentiated tumors	13	65
Poorly differentiated tumors	7	35

Moderately differentiated tumors were reported in 13 (65%) of patients, while 7 (35%) had poorly differentiated tumors in both groups. stage IIIA was documented in eleven patients (55%) while 9 patients (45%) had stage IIIB.

3.2 Response

None of our patients achieved a complete response (CR). There were 13 patients with partial response (65%). Two patients (10%) had progressive disease and 5 patients (25%) had stable disease. See (table 2).

Response rate analysis based on prognostic factors.

Table 2: Response rate

Response rate	No	%
Partial Response (PR)	13	65
Stable disease (SD)	5	25
Progressive disease (PD)	2	10

NB: none of our patients had complete response

Table 3: Response rate analysis based on prognostic factors

Prognostic factor			RESPONSE						P V
			PR (N 13)		SD (N 5)		PD (N 2)		
	No	%	No	%	No	%	No	%	
Age (years)									0.68
≤ 40	13	65	8	61.5	3	23	2	15.5	
>40	7	35	5	71.4	2	28.5	0	0	
Sex									0.35
M	18	90	12	66.66	4	22.22	2	11.11	
	2	10	1	50	1	50	0	0	
Performance Status									0.07
0-1	11	55	7	63.67	3	27.23	1	9	
2	9	45	6	66.66	2	22.22	1	11.11	
Tumor stage									0.07
IIIA	11	55	8	72.72	3	27.27	0	0	
IIIB	9	45	5	55.55	2	22.22	2	22.22	
Tumor grade									0.08
MDT	13	65	9	69.23	3	23.07	1	7.69	
PDT	7	35	4	57.14	2	28.57	1	14.28	

PV: P Value, M: Male, F: Female MDT: Moderate differentiated tumors PDT: Poorly differentiated tumors Partial Response (PR), Stable disease (SD) and Progressive disease (PD)

NB: none of our patients had complete response

It was observed that younger patients with better performance status had a better response to treatment in comparison to the older patients and performance status less than one. The difference was not significant statistically. Table (3) is showing the response rate analysis based on prognostic factors.

3.3 Time to disease progression

The median time to progression was 8 months. The probability of the tumor response lasting at least 6 months, was estimated to be 81%. Time to disease progression free survival curve is shown in (Figure 1).

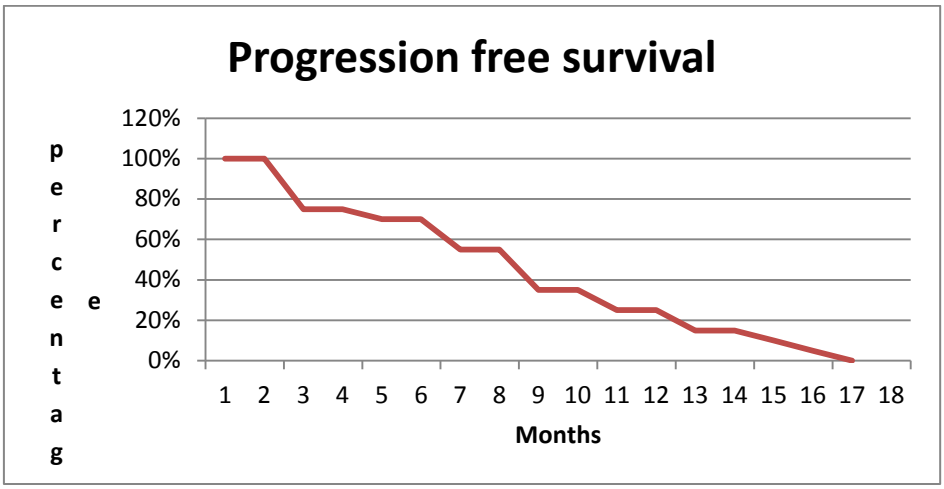

Figure 1: progression free survival curve

3.4 Survival time

Overall survival time curves are shown in Figure (2). The overall survival rate was 65% at 15 months and the median survival time was 16 months.

3.5 Change of performance status after treatment

Eight patients (40%) shifted to better scale but 3 patients (15%) showed worsening of their performance status dropping to performance status (PS) 3. Two patients had PS 2 and three patients had PS 1. None of our patients deteriorated to a PS 4.

3.6 Treatment toxicity

None of patients were graded as grade IV or V all-through the course of treatment.

3.6.1 Hematological toxicity

The hematological toxicities were mild . Leucopenia grade I&II were represented in 2 (10%) and 3 (15%) patients respectively. Anemia was reported in 7 patients as grade I or II while thrombocytopenia was reported in 4 patients (20%) at same grades (G1 and GII).

3.6.2 Gastrointestinal toxicity

All patients had experienced different grades of Nausea and vomiting. One patient (5%)had grade I Nausea and

vomiting while 15 patients (75%) had grade II.

Grade I esophagitis was observed in two patients (10%) while one patient (5%) had Grade II .

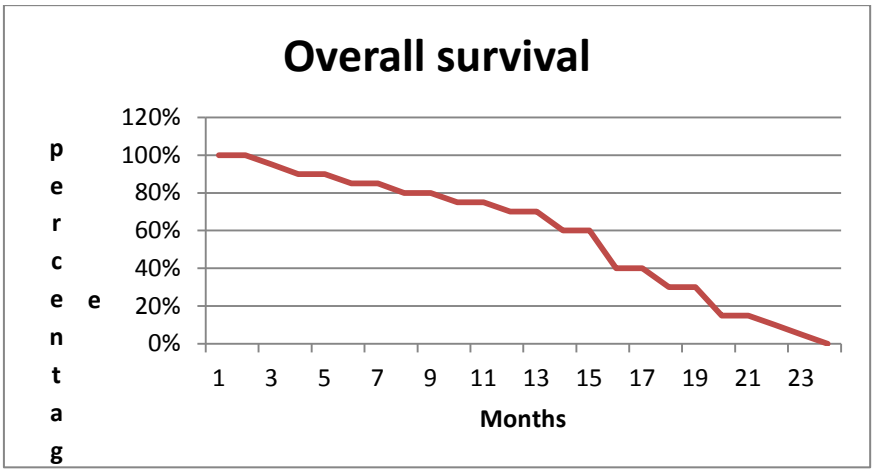

Figure 2: The overall survival

Table 3: shows patient's performance status before and after treatment

Before		After			
Scale		0	1	2	3
	No of pts				
0	4	4	0	0	0
1	8	4	2	1	1
2	8	4	1	1	2
Total		12	3	2	3

3.6.4 Skin toxicities

Skin reactions were reported in two patients only as one for each grade I and II. This was the same situation for Radiation pneumonitis.

3.6.5 Alopecia

Alopecia reported in 6 (30%) patients. Stomatitis observed in 3 (15%) patients as grade I and in one (5%) patient as grade II. Nephrotoxicity was reported only in one (5%) patient as grade I and II. Table (4) si showing the toxicity profile for all patients.

Table 3: Change of performance status of patients in both study groups before and after treatment.

Toxicity	Grade	No	%
Haematological toxicity			
Leucopenia	Grade I	2	10
	Grade II	3	15
Anaemia	Grade I	3	15
	Grade II	4	20
Thrombocytopenia	Grade I	3	15
	Grade II	1	5
Gastrointestinal toxicity			
Nausea and vomiting	Grade I	1	5
	Grade II	15	75
	Grade III	3	15
	Grade IV	1	5
Oesophogitis	Grade I	2	10
	Grade II	1	5
Skin Reactions	Grade I	1	5
	Grade II	1	5
Alopecia		6	30
Stomatitis	Grade I	3	15
	Grade II	1	5
Nephrotoxicity	Grade I	1	5
	Grade II	1	5
Radiation pneumonitis	Grade I	1	5
	Grade II	1	5

Table (4): toxicity profile for all patients according WHO grading

4. Discussion

Approximately 30% of NSCLC patients present with locally advanced inoperable disease [11].

Long-term results for these patients after radiotherapy alone are dismal with only 15% surviving beyond 2 years [11,12]. Both poor local control and a high rate of early distant dissemination contribute to the poor outcome.

At present there is a strong rationale for combining chemotherapy and radiotherapy as the primary treatment of locally advanced NSCLC. In addition to early effective systemic chemo-therapy, concurrent radiotherapy should result in enhanced local control where additive or synergistic effects with chemotherapy can be expected. The mechanisms of interaction between drugs and radiation have been extensively studied during the past years[17]. They include radiosenstization of hypoxic cells, inhibition of tumor cell repopulation and cellular repair processes, and improved drug penetration [17].

Obviously low rate of complete response and persistence of macroscopic residual tumor after induction chemotherapy are the rule in these patients and late radiation therapy may be unable to ultimately eradicate such resistant residium. Concurrent administration of chemotherapy and radiotherapy may be a way to overcome this problem.

Hopefully, these interactions should lead to significant activity against the radioresistant and/or chemoresistant population in the bulk of the primary tumor, and to an improved therapeutic gain if toxicity remain acceptable.

Cisplatin is not only one of the most effective drugs for metastatic or locally advanced NSCLC, but exihibits radiosensitizing proper-ties. Similarly, gemcitabine was recognized as an effective radiosensitizing agent. So combining cisplatin and Gemictabine and concurrent radiotherapy is highly effective in locally advanced NSCLC [18].

At the present time, eradication of micrometastases can only be achieved through the use of early effective systemic therapy, and clearly, definitive eradication of the primary tumor is a pre-requisite for long-term disease control[13].

Induction combination chemo-therapy regimen mostly used for locally advanced NSCLC has been the two-drug combination of cisplatin and Gemcitabine. The overall response rates were 26% - 67% with no or few complete responses[13,14,].

In the present study, patients received induction chemotherapy followed by radiotherapy. The partial response rate was 65% and the stable disease rate was 25 %.

In a trial by Crino et al., (1999)[14], 42 patients with stage III unresectable NSCLC received 4 cycles of induction chemotherapy with gemicitabine (1000 mg/m2 day 1-8-15); cisplatin (100 mg/m2 day 2) every 28 days followed by radiotherapy (54-66 Gy). The response rate was 62% with 4.7% complete remissions.

In a retrospective study [13], 60 patients with advanced stage III NSCLC treated with 4 courses of gemcitabine (1000-1250 mg/m2 day 1,8) and cisplatin (70-100 mg/m2 day 2), every 28 days. After chemotherapy all patients received thoracic irradiation (at a median dose of 56 Gy). The response rate was 67% with 1.6% complete response and 65% partial response and stable disease was 20%.

Bretti & his collogues [15], treated 45 patients with locally advanced NSCLC with induction chemotherapy, cisplatin (80 mg/m2 day 1) and Gemictabine (1000 mg/m2 day 1 and 8), to be repeated every three weeks for

two or three cycles followed by thoracic irradiation (56-62 Gy). The response rate was 23% and increased to 45% when the chemotherapy courses were completed to six courses.

In the present study, the median time to disease progression for patients was 8 months. Overall survival rate was 65% at 15 months and median survival was 16 months. In a trial comparing induction chemotherapy followed by radiotherapy to radiotherapy alone, a small but statistically significant gain in survival at 2 years, in the range of 12-38%, was demonstrated[19].

On the other hand, some studies have failed to show a benefit from chemotherapy added to radiotherapy, but most of these negative studies used non-platinum-containing regimens or older less active chemotherapy combinations[20].

In the present study there had been slightly increased toxicity rates in the combined treatment group than in the radiotherapy only group.

Haematological toxicity were mild. None of patients were graded as III, IV all through the course of treatment.

As regards to non haematological morbidity, nausea and vomiting were the most common and occurred in 100% of patients. Nephrotoxicity, alopecia and stomatitis were observed. Other side effects including esophagitis, skin reaction, radiation pneumonitis, were mild.

In trial of induction chemo-radiotherapy [14], grade 1-2 dysphagia occurred in 5% of patients, pneumonitis in 2.3% of patients. Hematological toxicity was the main side effect with 29% and 24% grade III, IV thrombocytopenia and leukopenia.

While in another trial [13], treatment toxicity included leucopenia, grade III, IV in 20% of patients, thrombocytopenia grade III, IV in 30% of patients, esophagitis grade II in 9% and pneumonitis grade II in 3% and alopecia in 10%.

5. Conclusion

For patients with locally advanced NSCLC; combination chemotherapy with cisplatin and Gemcitabine is a tolerable and active induction chemotherapy regimen. Sequential radiotherapy given after induction chemotherapy is tolerable and may offers the hope of improved locoregional control and survival over radiotherapy alone.

6. Recommendations

From our study we recommending neoadjuvant combination chemotherapy followed by radiotherapy to be considered as an effective tolerable treatment strategy for patients with locally advanced non-small cell lung cancer.

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