ORIGINAL RESEARCH ARTICLE

To Study the Clinical Improvement with Standard Chemotherapy Regimen in Stage 3 and Stage 4 Non Small Cell Lung Carcinoma Patients

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DOI: http://dx.doi.org/10.21276/ijcmsr.2019.4.2.23

How to cite this article: Monica Singh, Sameer Singhal, Jai kishan, Parvinder Singh. To study the clinical improvement with standard chemotherapy regimen in stage 3 and stage 4 non small cell lung carcinoma patients. International Journal of Contemporary Medicine Surgery and Radiology. 2019;4(2):B102-B106.

ABSTRACT

Introduction: Paclitaxel and Cisplatin had shown promising activity in advanced non-small-cell lung cancer (NSCLC). We have studied the clinical improvement with standard chemotherapy regimen in stage III and stage IV non small cell lung carcinoma patients. Current research aimed to study the clinical improvement with standard chemotherapy regimen in stage III and stage IV non-small cell lung carcinoma patients

Material and methods: Thirty patients with NSCLC stage III or IV were treated with Cisplatin 75mg/m^2 day 1 and paclitaxel 175mg/m^2 days 1 every 21 days for a maximum of 5 cycles. The data collected was entered into Microsoft excel and analyzed using SPSS version 21 (IBM Chicago, USA). Proportions were calculated for qualitative data and mean ± SD for quantitative data. Chi-square and t-test will be used for finding significance. A value of less than 0.05 will be considered significant.

Results: The patients with good performance scale (KPS) responded better to chemotherapy and tolerated it well and there was significant improvement observed in performance score (KPS) of the patients post chemotherapy. Patients were also compared radio-logically and showed marked improvement.

Conclusions: Paclitaxel/Cisplatin has shown good antitumor activity in patients with advanced NSCLC and should be further evaluated in this disease. Early detection should further enhance the clinical value of this combination chemotherapy.

Keywords: Clinical Improvement, Standard Chemotherapy Regimen, Non Small Cell Lung Carcinoma

INTRODUCTION

Worldwide estimates of the incidence and mortality due to cancer published by GLOBOCAN an International Agency for Research on Cancer revealed that 12.7 million new cases and 7.6 million deaths occurred in 2008 due to cancer, with 56%of new cases and 63% of the deaths occurred in less developed regions of the world. Worldwide the most frequently diagnosed cancers are lung (1.61 million, 12.7% of the total), breast (1.38 million, 10.9%) and colorectal cancers (1.23 million, 9.7%). The most common causes of cancer death are lung cancer (1.38 million, 18.2% of the total), stomach cancer (738,000 deaths, 9.7%) and liver cancer (696,000 deaths, 9.2%).[1]

In the beginning of the century, lung cancer was considered to be rare.[2] Since, 1985 lung cancer is the most commonly diagnosed cancer annually and it has reached epidemic proportions.1In developed countries lung cancer is the leading cause of death and is rising at alarming pace in developing countries.[3] In India, approximately 63,000 new lung cancer cases are reported each year.[1]

Tobacco smoking is the most imperative risk factor for lung cancer, more than 80% or 1 in 9 smokers develops lung cancer.[4] The cumulative risk of lung cancer in lifelong heavy smokers is 30% and in non-smoker it is less than 1%.[5,6] Lung cancer risk is proportional to number of cigarettes consumption, the age of onset of smoking the degree of inhalation nicotine and tar content of cigarette and use of un-filter cigarettes, genetic predisposition and individual susceptibility is also a factor in carcinogenesis.[7] Other known significant risk factors in the pathogenesis of lung cancer include exposure to radon gas, asbestos and air pollution, as well as genetic factors.[8] One of the key factors initiating the pathogenesis of lung cancer is through direct exposure to reactive oxygen species (ROS) and via activation of polymorpho-nuclear neutrophils.[9] This leads to alterations in cell-signaling and mutations, and ultimately to carcinogenesis.

Staging has a key role for the decision of treatment in lung cancer patients. A system classifying lung cancer based on status of the primary tumor (T), regional lymph nodes (N) and metastases (M) was first proposed in 1946 by Denoix. The first edition of The TNM Classification of Malignant Tumors was published in 1968 by the Union International Controlee Cancer.[10] The TNM classification for lung cancer

was revised in 1986, 1997, 2009 and 2018. The diagnosis of lung cancer is usually made at the end stage of the disease, and is thus associated with poor prognosis. Modern diagnosis and staging includes computed tomography (CT) of the chest and upper abdomen. The use of fiber-optic bronchoscopy, tumor biopsy, positron-emission tomography and mediastino-scopy in the diagnosis and staging is often customized from patient to patient.[11]

The best chance for a cure is presently offered by complete surgical resection, while an incomplete resection will not improve survival at all.[12] A predicted post-resection FEV1 of more than 0.8 l is usually a pre-requisite for resection in the average-sized patient.[13] In relation to the extent of disease, patients with a completely resectable primary tumor who do not have preoperatively verifiable mediastinal metastases are candidates for surgery.[14] In cases of mediastinal metastases or a borderline resectable tumor, preoperative chemotherapy has shown promising preliminary results, after which the patients can be re-evaluated for surgery or radical radiotherapy.[15,16] Radiotherapy, combined with chemotherapy when feasible, should be considered for the patients who are definitely not suitable for a curative resection.[16] With the best available combinations of chemotherapy and radiotherapy, the five-year survival in locally advanced non-resectable disease has increased from 5% to as much as 20%. Chemotherapy for advanced non–small-cell lung cancer is often considered ineffective or excessively toxic. However, meta-analyses have demonstrated that, as compared with supportive care, chemotherapy results in a small improvement in survival in patients with advanced non–small-cell lung cancer.[17-19]

Over the past decade, a number of new agents have become available for the treatment of metastatic non–small-cell lung cancer, including the taxanes, gemcitabine, and vinorelbine. The combination of one or more of these agents with a platinum compound has resulted in high response rates and prolonged survival at one year in phase 2 studies.[20-23] However, there have been few comparisons of these newer chemotherapy regimens, which are now used frequently, with each other.

In the view of above observations and paucity of the data the present study was conducted with aim to study the clinical improvement with standard chemotherapy regimen in stage III and stage IV non-small cell lung carcinoma patients.

MATERIAL AND METHODS

The study was conducted in the department of Respiratory Medicine, MMIMSR. 30 patients admitted in department of Respiratory Medicine diagnosed non-small cell carcinoma of lung. The patients fulfilling the inclusion criteria and after verifying the exclusion criteria were finally taken up for the study.

Inclusion Criteria

Patients with diagnosed non small cell carcinoma of lung.

Exclusion Criteria

Patients with any cardiovascular impairment.
Patient with neutropenia.
Patient with any renal and hepatic dysfunction.
Non-cooperative patients who not giving consents.
KPS score less than 70

Investigations Required

A. CECT Chest was done on patients presenting with a mass on chest X-Ray and clinically suspicious of malignancy as it is useful for diagnosing and staging of the lung cancer and also in follow up
B. USG Abdomen was done to check for any metastasis in patients diagnosed as lung cancer
C. Transthoracic fine needle aspiration- TTFNA was used in appropriate clinical settings for investigation of patients with a lung mass lesion, usually peripheral and was used for histo-pathological diagnosis of lung cancer
D. Bronchoscopy- it was done in appropriate clinical case for confirming the diagnosis. Through bronchoscopy we have collected the BAL fluid and did its cytology, did Trans-bronchial needle aspiration (TBNA) which was sent for cytology and finally a biopsy of the mass also taken and sent for histopathology. Brushing, transthoracic needle aspiration was also done in lesions abutting chest wall.
E. Blood investigations mainly CBC, LFT, RFT were done before starting chemotherapy.

Variables to be used

Karnofsky performance score

The Karnofsky score runs from 100 to 0, where 100 is "perfect" health and 0 is death. Although practitioners occasionally assign performance scores in between standard intervals of 10. This scoring system is named after Dr. David A. Karnofsky in 1949. The primary purpose of it is to evaluate a patient's ability to survive chemotherapy.[24]

Preparing for Chemotherapy

Before starting chemotherapy complete blood counts of the patient was done and a close watch has to be kept on TLC as the drugs are immunosuppressive. The renal functions test was done as the drugs are nephrotoxic and hence requires strict monitoring of renal function tests. Patient was adequately hydrated before starting chemotherapy. A total of 2 liters of intravenous fluids mainly Normal saline and DNS should be given over 6 hours before starting of chemotherapy. An anti-emetic (inj. Ondansetron 4mg iv.) was also advised prior to start as the chemotherapeutic drugs induce a lot of nausea and vomiting. Patients were seen for alopecia, anemia, rashes, nausea, and emesis. Radiological improvement was noted on RECIST 1.0 criteria.[25]

STATISTICAL ANALYSIS

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages, means and standard deviations were calculated. The statistical tests applied for the analysis were Pearson's chi-square test (χ^2), confidence interval and p-value were set at 95% and ≤ 0.05 respectively

RESULTS

Table-1 Highest numbers of Patients were found in the age group 50-60 years which constituted 40% of the total

ISSN (Online): 2565-4810; (Print): 2565-4802 | ICV 2018: 86.41 |

Age in Years	Number of Patients	Percentage (%)
40-50 yr	5	16.7
50-60 yr	12	40.0
60-70 yr	11	36.7
70-80 yr	2	6.7
Mean±SD	55.16±3.36	
Gender		
Male	29	96.7
Female	1	3.3
Total	30	100.0

Table-1: Distribution of demographic characteristics of study population

Diagnostic Method	Frequency	Percentage (%)
FNAC	13	43.3
Bronchoscopy	17	56.7
Tumor staging		
Stage III	10	33.3
Stage IV	20	66.7
Total	30	100.0

Table-2: Distribution of patients studied according to diagnostic method and tumor staging

KPS Score	Mean	N	Std. Deviation	p-value
Pre intervention	79.33	30	5.07	0.007*
Post intervention	87.67	30	4.30	

Test applied: paired t-test. *indicates statistically significant

Table-3: Comparison of Pre and Post Chemotherapy mean KPS score

Radiographic Improvement	CR	PR	SD	PD	Total
	0	17	05	08	30

Table-4: distribution patients showing radiographic improvement

patients. Mean age group was found to be 55.16 years. (96.7%) were males and 1(3.3%) was female.

Table-2 Out of the 30 patients 17 (56.7) subjects were diagnosed with FNAC and rest 13 (43.3) subjects with Bronchoscopy. 20 (66.7%) presented with stage III tumor and remaining 10 (33.3%) presented with stage IV tumor.

Table-3 Depicted that post treatment the mean KPS (87.67) significantly increased in comparison to pre-treatment KPS mean value of (78.67) $p \leq 0.05$

Table 4 Revealed the radiographic improvement measured using the RECIST 1.0 criteria over course of treatment and it was observed that majority of the patients 17 out of total 30 showed persistent responses (PR) to treatment regimen.

DISCUSSION

Lung cancer is a leading cause of death worldwide and tobacco smoking is the most common risk factor for developing lung cancer. The incidence of smoking remained high in our study too however 19 of the total patients left smoking earlier. Only 5 patients were non-smokers. Out of which 36.7% had 15-50 pack years and only 6.7% had more than 150 pack years. In the present study out of all 85% are smokers. Tobacco smoking is the most important risk factor for lung cancer >80% of the lung cancers develop in smokers and approximately 1 in 9 develop lung cancer.[26] The cumulative risk of lung cancer in lifelong heavy smokers is 30% and in non smoker is <1%.[27,28] Lung cancer risk is proportional to number of cigarettes consumption, the age of onset of smoking the degree of inhalation nicotine and tar content of cigarette and use of unfiltered cigarettes, genetic predisposition and individual susceptibility is also a factor in carcinogenesis.

In developing country like India majority of the people live in rural areas, many living below poverty line lacks formal education and health awareness. Usually don't access health services because of poverty, illiteracy, lack of availability in peripheral health institutions. The services of diagnosis and treatment are mainly concentrated in the urban areas and are many times away from the reach of common man. Moreover despite of accessing health services early there is often delay in diagnosis by secondary or tertiary care centers.

In our setting patients came to us with IIIrd or IVth TNM stage of lung cancer mainly due to poverty, ignorance, illiteracy, lack of knowledge of disease and taking repeated treatment from quacks before the disease is diagnosed properly and by that time patient progress to extreme stages of lung cancer. With the help of CECT chest we staged the patients out of which 66.7% were in stage IV and 33.3% were in stage III. In a national cancer database survey of patients diagnosed with non small cell lung carcinoma, majority of the patients were at stage IV (38.1%) at time of initial diagnosis followed by stage III (27.6%), stage 1(26%) and stage II(8.3%).[29]

In our study we have studied 30 patients out of which 29 were males out of which 56% were in 40 to 60 years age group and 36.7% in 60 to 70 years age group and only 6.7% that is only 2 patients in age group of 70 -80 yrs.

In the present study the demographic distribution of factors like age and gender are discussed as, the mean age of the patients in the current study are 59.8 which are in accordance with study conducted by Prasad et al.[30] in a Clinico-pathological study of bronchogenic carcinoma where the mean age was found to be 58 years. But the number of female patients in the current study are only one rest are male patients. As discussed earlier mainly patients are from rural area and are below poverty line where females are taken less care, dependent on males for taking treatment from secondary or tertiary care centers. Similar gender distribution was observed by Bhattacharya et al.[31] his study conducted on Bronchogenic carcinoma in young adults.

The treatment of lung cancer has also evolved over the decades with development of newer therapies like molecular targeted therapy, advanced surgical techniques and radiotherapy leading to overall increase in 5 year survival rates in patients having lung cancer.

Randomized multinational trials have demonstrated the efficacy of various combination platinum based doublets.[32] Platinum-based chemotherapy leads to a small but statistically significant improvement in survival in patients with advanced non-small cell lung cancer. The superiority of a

two-drug combination over a single agent was demonstrated by the Cancer and Leukemia Group B (CALGB) 9730 trial[33] and further confirmed in a meta-analysis performed by Delblado.[34] Taken together, these results led to combination doublet chemotherapy becoming an accepted standard of care for stage IV disease.

The chemotherapy regimen chosen for this study consisted of cisplatin and palcitexal in management of stage III and IV NSCLC. It is less expensive and easily affordable for the low socioeconomic strata patients who formed a major bulk of the patient load of the hospital.

In this prospective study a total of 30 patients with advanced primary lung carcinoma who met the inclusive criteria were taken and chemotherapy regimen of cisplatin and etoposide was given. A total of 5 cycles each 21 days apart was given. At the end of 3 cycles the effectiveness of chemotherapy was determined on the basis of Karnofsky Performance scale (KPS). In the present study KPS score post chemotherapy score improves drastically that it is pre chemotherapy it was 78.67% post chemotherapy it touched the heights of 87.67% that is 9% improvement which was a great achievement. Post chemotherapy Radio-logically our patients shown improvement. 17 out of 30 patients showed partial response (PR) and 5 showed stable diseases which was quiet good number to consider. Similar results were seen by M Bhutani et al. in a Retrospective Cohort study conducted in AIIMS, New Delhi regarding Survival in small cell lung cancer in India with regard to Prognostic utility of clinical features, laboratory parameters and response to treatment.[35]

Radiotherapy can be offered to patients as single therapy or combination therapy along with chemotherapy in some specific stages and types of lung carcinoma but it was not included in our study as at the time if initiation of study radiotherapy was not available at our institution and has only recently been introduced so it was not included in the study. However, eligible patients were offered and advised for radiotherapy but as it's very costly per cycle, most of the patients could not afford it. Further studies should be done to evaluate the combination therapy of chemotherapy and radiotherapy rather than chemotherapy alone in appropriate patients

CONCLUSION

The present study concluded that the patients with good performance scale (KPS) responded better to chemotherapy and tolerated it well but there is marked improvement was observed in performance score (KPS) of the patients post chemotherapy. Chest X-Ray is a good modality for evaluation of the response of chemotherapy in patient's lung cancer that cannot afford or refused for post chemotherapy CECT chest. It is also seen that chemotherapy plays a very vital role in improving the quality of life of patients in case of advanced lung cancer and it should always be preferred over supportive care in all patients who are fit to receive chemotherapy.

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ISSN (Online): 2565-4810; (Print): 2565-4802 | ICV 2018: 86.41 |

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 22-03-2019; **Accepted:** 20-04-2019; **Published online**: 15-06-2019