Original Research Article

Clinicoradiological Profile of Lung Cancer

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Abstract

Objective: To study clinico-radiological profile of patients of lung cancer and to determine the response to Cisplatin and Irinotecan as chemotherapeutic regimen in appropriately staged IIIB/ IV cases of non small cell lung Cancer**Methods:** All consecutive patients of lung cancer more than 18 years of age were evaluated and staged using standard protocol .All patients with stage III-B and IV non small cell lung cancer were assessed. 20 patients with ECOG score 0, 1 or 2 in the study were enrolled and subjected to chemotherapy regimen .Controls were provided basic supportive care (BSC) including antibiotics, analgesics, bronchodilators and supportive measures.**Results**:Of 137 patients enrolled the mean age of patients was 57.16 .109 patients (79.6%) were males with Sex Ratio of 3.9:1.The commonest symptom was cough in 109 patients The mean duration of symptom was 5.52 months + SD 6.23. Smoking was found to be present in (85.4%) Majority of the patients were bidi smokers .The commonest sign observed was that of a mass lesion in 78 patients (56.93%) followed by that of collapse .On chest X ray, mass lesion was the most common finding (64.96%) followed by pleural effusion in 40 (29.19) .The commonest paraneoplastic syndrome observed was anorexia in 79 patients (57.66%), cachexia in 63 .Squamous cell carcinoma lung was the commonest histological subtype among male patients (42 out of 96— 43.8%), while adenocarcinoma was the commonest histological subtype among the female patients (10 out of 25-40%)**Conclusion**:Cisplatin and Irinotecan regimen showed improvement in the median survival and 1 year survival rates (57 weeks and 53% respectively) as compared to basic supportive care. The regimen is cheap; its side effects are mild,tolerable reasonable regimen in resource limited settings.

Keywords: Squamous cell carcinoma ,adenocarcinoma ,Cisplatin , Irinotecan

Introduction

Lung cancer is the most commonly diagnosed malignancy, and the leading cause of cancer-related death. Lung cancer has varied epidemiology depending on the geographic region. Globally, there have been important changes in incidence trends amongst men and women, histology, and incidence in non-smokers. Indian epidemiological data on lung cancer is scarce. Primary bronchogenic carcinoma is the number one cause of cancer mortality for both men and women. Approximately 85% of lung cancer occurs in smokers or former smokers Cigarette smoke is by far the most significant factor in the causation of lung cancer.The risk of developing lung cancer is related to the number of cigarettes smoked, age at which smoking started, and duration of smoking.In developing nations where smoking rates are high, the high mortality will continue to rise well into the century. Though tobacco use, especially cigarette smoking, accounts for up to 90% of all lung cancer deaths worldwide, fewer than 20% cigarette smokers, however, develop lung cancer, suggesting that other factors play a role in the development of disease.An Indian study suggested that ETS (Environmental Tobacco Smoke) exposure might be a strong risk factor for lung cancer in India also, a country with low prevalence of smoking and, therefore, with low rates of lung cancer[1-3].Other causes of lung cancer include environmental factors, such as tobacco smoke, radon, and various occupational exposures. Diet and pre-existent nonmalignant lung disease also have been associated with the risk for developing lung cancer.Various environmental and host factors also may affect the risk for lung cancer. About 90% of lung cancer cases are caused by smoking and the use of tobacco products. However, other factors such as radon gas, asbestos, air pollution exposures, and chronic infections can contribute to lung carcinogenesis. In addition, multiple inherited and acquired mechanisms of susceptibility to lung cancer have been proposed. Lung cancer is divided into two broad histologic classes, which grow and spread differently: small-cell lung carcinomas (SCLCs) and non-small cell lung carcinomas (NSCLCs). Treatment options for lung cancer include surgery, radiation therapy, chemotherapy, and targeted therapy. Therapeutic-modalities recommendations depend on several factors, including the type and stage of cancer. Despite the improvements in diagnosis and therapy made during the past 25 years, the prognosis for patients with lung cancer is still unsatisfactory. The responses to current standard therapies are poor except for the most localized cancers. The 5-year survival rate of this group of patients is <7% and therefore these patients are generally considered to be incurable . It is clear that new therapeutic modalities are required for the treatment of advanced lung cancer.

Cisplatin represents one of the most active chemotherapeutic agent for NSCLC. The combination of a platinum agent with a new generation cytotoxic agent has become the standard-line chemotherapy for advanced NSCLC.Newer chemotherapeutic agents have increased one-year survival upto 40% and median survival of about 8.9 months[4-6].These have become the standard of care for standard-line chemotherapy of advanced non-small call lung cancer. These include Gemcitabine, Irinotecan, and Newer Plantinum agents (Carboplatin, Oxaloplatin, etc)·Studies from India have also

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demonstrated that chemotherapy improves the overall survival rate in cases of unresectable NSCLC .Irinotecan is a cheap and well tolerated chemotherapeutic agent. There is a paucity of Indian literature on use of Irinotecan and cisplatin in patients of NSCLC. The present study was designed to determine the response of chemotherapeutic regimen comprising of cisplatin & irinotecan in appropriately staged IIIB/ IV cases of NSCLC.

Materials and Methods

All consecutive patients of lung cancer more than 18 years of age irrespective of sex, race or religion diagnosed over one calendar year were evaluated and staged using standard protocol mentioned in Annexure-I. All patients with stage III-B and IV non small cell lung cancer were assessed for performance status using Eastern Cooperative Oncology Group (ECOG) scale[33] (Annexure-II).). It was planned to enroll at least 20 patients with ECOG score 0, 1 or 2 in the study and subject them to chemotherapy regimen as per treatment protocol mentioned later. Patients who met enrolment criteria but did not agree to participate in the study served as inherent control group. These patients were followed up by personal contact or visit. They were provided basic supportive care (BSC) including antibiotics, analgesics, bronchodilators and supportive measures. The protocol was explained to all patients and an informed consent was taken for their willingness to participate[7-9].

Enrolment Criteria

All patients more than 18 years of age were enrolled if they met the following criteria:

1. Had a histologically documented NSCLC and an evaluated stage IIIB/IV
2. Did not receive any prior chemotherapy or immunotherapy
3. Had an ECOG performance status of 0,1 or 2
4. Did not have an associated malignant process of other type
5. Had an adequate organ function as documented by granulocyte count> 1500/mm^3, platelet count > 100000/mm^3, hemoglobin> 8g/dl, serum creatinine< 1.5 mg/mm^3, total bilirubin<2.0 mg/dl, serum glutamic pyruvate transaminase(SGPT)< 2 times and serum glutamic oxaloacetate transaminase(SGOT)< 2 times the institutional upper limit of normal

Exclusion Criteria

Patients were not eligible for study enrollment if they had any of the following criteria:

1. Uncontrolled brain metastases
2. Symptomatic neuropathy
3. Actively receiving radiation therapy
4. Significant cardiovascular disease
5. Pregnancy or lactation
6. Poor performance status

Patients were enrolled to the BSC arm treated with which ever therapy was judged to be appropriate by the treating physician. This treatment could have included treatment with antibiotics, analgesic drugs, transfusions.

Treatment Regimen :Chemotherapy Regimen

1. Injection Cisplatin 50 mg/m^2 was administered on day 1 and repeated every 28 days for 6 cycles.
2. Injection Irinotecan 70 mg/m^2 was administered on day 1 and repeated every 28 days for 6 cycles.
3. Premedication and hydration were administered as per standard protocol.

Follow Up Protocol The pretreatment evaluation included recording of weight, height, physical examination, laboratory tests(complete blood count with differential count, serum creatinine, blood urea nitrogen, serum electrolytes, serum glucose, serum alkaline phosphatase, SGOT, SGPT ,total and direct serum billirubin ,urine routine and microscopic examination, chest X ray, ultrasound examination and performance status (evaluated a day before the due cycle of chemotherapy as per Annexure-II).Grading of the toxicity features were done as per National Cancer Institute Toxicity Grading Criteria and dose modifications were done as per the recommendations .Evaluation for drug toxicity was done if patient self complained of side effect at given contact number of the doctor during the intervals between the chemotherapy cycles.

Response Criteria Following definitions were used for defining response .Response to therapy was defined as best response obtained for at least 1 month at any time during treatment. Complete response (CR) was defined as complete disappearance of all malignant lesions documented by radiological evaluation. Partial response (PR) was defined as a reduction of at least 50% of all evaluable lesions, without any new tumour lesion. No response (NR) or stable disease (SD) was defined as stabilization or less than 50% reduction of evaluable lesions. Progression was defined as an increase of more than 25% of all evaluable lesions or at least one lesion or appearance of a new tumour lesion. Response evaluation was also determined using Modified Response Evaluation Criteria in Solid Tumor (Modified RECIST Criteria) for same subset of patients

Consent

Written consent was obtained from the relatives of patients after explaining them the nature and purpose of the study. They were assured that confidentiality would be strictly maintained. The option to withdraw from the study was always open[9-11]

Observation Chart

The present study was carried out at LRS Institute of Tuberculosis and Respiratory Diseases, New Delhi in one calendar year with period of enrolment from May 2007 to May 2008 and a follow up of another year until May 2009.

Table 1: Patient Distribution According To Symptoms

Symptom	Frequency	Percent
Cough	109	79.6
Dyspnoea	91	66.4
Chest pain	103	75.2
Hemoptysis	37	27.0
Bone pain	12	8.7
Clubbing	21	15.3
Weakness	63	45.9
Weight loss	68	49.6
Dysphagia	7	5.1
Hoarseness	15	10.9
Wheeze & Stridor	7	5.1
Fever	54	39.4
S V C obstruction	10	7.2

Table 2: Smoking Frequency

	Frequency	Percent
Non smoker	20	14.6
Smoker	117	85.4
Total	137	100

Table 3: Patient Distribution According To Signs

Sign	Frequency	Percent
Mass	78	56.9
Mass collapse	42	30.65
Pleural effusion	36	26.27
S V O	10	7.29
Focal tenderness	7	5.10
Clubbing	21	15.32
HOA	3	2.18
Lymph node	19	13.8
Horner	3	2.18

Table 4: X Ray & C T Scan Findings

Findings	X Ray		C T Scan	
	Frequency	Percent	Frequency	Percent
Mass lesion	89	64.96	91	66.4
Mass lesion-collapse	38	27.7	43	31.3
Mediastinum wide- SVC	9	6.6	24	17.5
Mediastinum wide-LN	26	19.0	55	40.14
Rib erosion	7	5.1	7	5.1
Phrenic palsy	3	2.2	5	3.6
Pleural effusion	40	29.2	43	31.4
Cavitating Mass	4	2.9	9	6.5
Calcification			4	2.9
Chest wall involvement			9	6.6
Obstructive pneumonitis			10	7.3
Pleural thickening			9	6.6
Old-healed lesion &other			14	10.2
Lymphangitis			7	5.1

Table 5: Comparative Features Of Groups

Characteristic	Irinotecan Group (N=35)*	BSC (N=19)
Sex		
Male	30	13
Female	5	6
Stage		
IIIB	25	15
IV	10	4
Performance status		
0	2	1
1	24	7
2	9	11
Total	35	19

Table 6: Tumour Response Using WHO Criteria

Response	Frequency (N= 27)	Percent
Complete response	1	3.7
Partial response	2	7.4
Stable disease	27	70.4
Progression	5	18.5

However if the response rate was assessed by Modified RECIST criteria, it was observed that one patient had complete response (3.7%) and six patients had partial response (22.2%), while stable disease was observed in 15 patients (55.55%). The remaining 5 patients (18.51%) had progressive disease. (Table no.19, fig no.17)

Table 7: Tumour Response Using Modified Recist Criteria

Response	Frequency (N=27)	Percent
Complete response	1	3.7
Partial response	6	22.2
Stable disease	15	55.55
Progression	5	18.51

Survival Assessment:

(A) Median Survival A comparative assessment of survival was done using Kaplan Meier method for the chemotherapy and BSC groups. The median duration of survival for the chemotherapy arm was 57 weeks (95% confidence interval, 49.52 to 64.48 weeks) and was 11 weeks (95% confidence interval, 5.96 to 16.04 weeks) for the BSC group (log-rank $P < 0.001$).Three patients were still alive in the chemotherapy group at the time of assessment with an approx mean survival of 72 weeks.

(B) 1 -year survival The 1-year survival rate for chemotherapy group was 53%. All the patients of BSC group expired by the end of 35 weeks.

(C) Progression Free Survival Progression free survival was assessed in 27 patients. The median progression free survival in the chemotherapy arm was 27 weeks with a range of 5 to 54 weeks.

Toxicity and adverse events: Toxicities were generally mild (grade 1). Grade 2 toxicities were diarrhoea in 9 patients (26%), vomiting in 12 (34%), skin& hair loss 9(26%) and anaemia in 4 patients (11%). Grade 3 toxicity was rare .

Results

Of 137 patients enrolled majority (31.4%) were in the age group of 60-69 years followed by that in the 50-59 year age group (27.0%). The mean age of patients was 57.16 yrs + standard deviation (SD) of 10.693 with range from 30 to 88 years. 109 patients (79.6%) were males with Sex Ratio of 3.9:1.The commonest symptom was cough in 109 patients (79.6%) followed by chest pain in 103 (75.2%), dyspnoea in 91 (66.4%), weight loss in 68 (49.6%), weakness in 63 (45.9%), fever in 54 (39.4%), hemoptysis in 37 (27.0%), clubbing in 21 (15.3%), bone pain in 12 (8.75%), hoarseness in 15 (10.9%), superior vena caval obstruction in 10 (7.2%), wheeze and stridor in 7 (5.1%) and dysphagia in 7 patients (5.1%). The mean duration of symptom was 5.52 months + SD 6.23. Smoking was found to be present in 117 patients (85.4%) with a mean smoking index of 510.82 + SD 448.63. Majority of the patients were bidi smokers .The commonest sign observed was that of a mass lesion in 78 patients (56.93%) followed by that of collapse in 42 (30.65%), pleural effusion in 36 (26.27%), clubbing in 21 (15.32%), lymphadenopathy in 19 (13.86%), superior vena caval obstruction in 10 (7.2%), focal tenderness in 7 (5.10%) and hypertrophic osteoarthropathy (HOPA) in 3 patients (2.18%)On chest X ray, mass lesion was the most common finding in 89 patients(64.96%) followed by pleural effusion in 40 (29.19%), collapse in 38 (27.73%), mediastinal widening in 35 (25.54%), rib erosion in 7 (5.10%), cavitary mass in 4 (2.91%) and phrenic palsy in 3 .On C T chest , mass lesion was the most common finding in 91 patients (64.96%), followed by mediastinal widening in 79 (57.66%), pleural effusion in 43 (31.38%), collapse in 43 (31.38%) , old healed lesion in 14 (10.24%), obstructive pneumonitis in 10 (7.29%), cavitary mass in 9 (6.56%), chest wall involvement in 9 (6.56%), pleural thickening in 9 (6.56%), rib erosion in 7 (5.10%), lymphangitis in 7 (5.10%), phrenic palsy in 5 (3.6%) and calcification in 4 patients (2.91%). Commonest paraneoplastic syndrome observed was anorexia in 79 patients (57.66%), cachexia in 63 (45.98%), fever in 54 (39.41%), clubbing in 21 (15.32%), anemia in 7 (5.10%), neuropathy in 3 (2.18%), leucocytosis in 3 (2.18%), thrombocytosis in 5 (3.649%) , SIADH in 2 (1.45%), cutaneous lesion in 1 (.72%), and myopathy in 1 patient (0.72%).

Lung Cancer Type Squamous cell carcinoma lung was the commonest histological subtype among male patients (42 out of 96—43.8%), while adenocarcinoma was the commonest histological subtype among the female patients (10 out of 25—40%)

Statistical Analysis: Entire data was subjected to appropriate analysis. Median survival and one year survival were calculated from the date of registration. Partial and complete responses were evaluated after the first cycle and at least after every two cycles. Survival rate was calculated by Kaplan-Meier method and compared by the log rank test. Progression free survival was also assessed.

Discussion

Lung cancer was relatively uncommon at the turn of the 20th century, and has increased in prevalence at alarming rates, particularly because of the augmented trend in smoking, so that it is now the most common cause of cancer death in the world.The present study proposes to study the cisplatin and irinotecan combination in an Indian subset of patients in order to evaluate its safety and efficacyWe experienced lesser haematological or non – haematological toxicities as compared to most of the studies mentioned above. This could be due to a 4 weekly administration of drugs in our study.Noronha V et al while studied epidemiology of lung cancer in India in a single-centre experience which focussed on the differences between non-smokers and smokers **.** They set out to study the epidemiological patterns and clinical profile of lung cancer in India. Considerably higher numbers of Indian patients with lung cancer are non-smokers, compared to the West. The global trend of rise in adenocarcinoma is paralleled in India. Non-tobacco-related risk factors need further investigation.Dubey AK et al did a systematic review and analysis. also studied epidemiology of lung cancer and approaches for its management.Owing to the use of tobacco and the consumption of alcohol and adulterated food, worldwide cancer incidence is increasing at an alarming and frightening rate. Since the last decade of the twentieth century, lung cancer has been the most common cancer type. This study aimed to determine the global status of lung cancer and to evaluate the use of computational methods in the early detection of lung cancer.The findings provide an inclusive understanding of the incidences, mortalities, and survival rates of lung cancer in the UK, the US, India, and Egypt. The combined use of data mining and evolutionary algorithm can be efficient in lung cancer detection.Muhas C et al studied socio demographic characteristics of lung cancer patients in north malabar region of kerala, south india. Greenberg ER et al stressed on social and economic factors in the choice of lung cancer treatment[12-15].Large number of patients were reviewed and found that the treatment of patients varied according to their marital status, medical insurance coverage, and proximity to a cancer-treatment center. It was concluded that for non-small-cell lung cancer, socioeconomic as well as medical factors determine treatment. Lemjabbar-Alaoui H et al studied biology and treatment options of lung cancer. However, a better understanding of the biology pertinent to these challenging malignancies, might lead to the development of more efficacious and perhaps more specific drugs. The purpose of this review is to summarize the recent developments in lung cancer biology and its therapeutic strategies, and discuss the latest treatment advances including therapies currently under clinical investigation. Cooper S et al did a treatment review of small cell lung cancer.As almost a quarter of these cancers are of small cell in origin, it seems only appropriate that small cell lung cancer receives ample attention, rather than seemingly to have been overlooked over the last 10–15years. Despite its generally late presentation and high risk of dissemination, it is exceptionally sensitive to chemo-radiotherapy. This review looks at the diverse options of treatment that have been used over the last few years and tries to highlight the best available. As more than 50% of patients diagnosed with lung cancer are over 70 years of age and various studies have shown that older people respond just as well as their younger counterparts, with similar results in response rates, toxicity and outcomes.As cooper et al studied small cell ,Molina JR et al studied non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship.Lung cancer has become more predominant among former than current smokers. Yet in some countries which has experienced a dramatic increase in the cigarette smoking rate during the past 2 decades, a peak in lung cancer incidence is still expected. Non-small cell lung cancer accounts for 85% of all lung cancer cases in the United States. After the initial diagnosis, accurate staging of non-small cell lung cancer using computed tomography or positron emission tomography is crucial for determining appropriate therapy. When feasible, surgical resection remains the single most consistent and

successful option for cure. However, close to 70% of patients with lung cancer present with locally advanced or metastatic disease at the time of diagnosis. Chemotherapy is beneficial for patients with metastatic disease, and the administration of concurrent chemotherapy and radiation is indicated for stage III lung cancer. Rodin D et al stressed on radiotherapeutic management of non–small cell lung cancer in the minimal resource setting.Strategies are presented for maximizing the availability and impact of RT in settings with minimal resource availability, and areas for potential future innovation are identified. Priorities for LMICs involve increasing access to RT equipment and trained health care professionals, ensuring quality of care, providing guidance on priority setting with limited resources, and encouraging innovation to increase the economic efficiency of RT delivery. Several international initiatives are currently under way and represent important first steps toward scaling up RT in LMICs to treat lung cancer.European Organisation for Research and Treatment of Cancer recommendations for planning and delivery of high-dose, high-precision radiotherapy for lung cancer was used by De Ruysscher D et al **t**o derive recommendations for routine practice and clinical trials for techniques used in high-dose, high-precision thoracic radiotherapy for lung cancer.Recommendations were identified for each of the recommendation categories. Although most of the recommended techniques have not been evaluated in multicenter clinical trials, their use in high-precision thoracic radiotherapy and stereotactic body radiotherapy (SBRT) appears to be justified on the basis of available evidence.Recommendations to facilitate the clinical implementation of high-precision conformal radiotherapy and SBRT for lung tumors were identified from the literature. Pignon JP et al did a meta-analysis of thoracic radiotherapy for small-cell lung cancer.This meta-analysis was designed to evaluate the hypothesis that thoracic radiotherapy contributes to a moderate increase in overall survival in limited small-cell lung cancer.It included 13 trials and 2140 patients with limited disease. Conclusion was that thoracic radiotherapy moderately improves survival in patients with limited small-cell lung cancer who are treated with combination chemotherapy. Adaptive radiotherapy for lung cancer was coined by Sonke JJ et al .Lung cancer radiation therapy (RT) is associated with complex geometrical uncertainties, such as respiratory motion, differential baseline shifts between primary tumor and involved lymph nodes, and anatomical changes due to treatment response. Generous safety margins required to account for these uncertainties limit the potential of dose escalation to improve treatment outcome. Four dimensional inverse planning incorporating pretreatment patient-specific respiratory motion information into the treatment plan already improves treatment plan quality. More importantly, repetitive imaging during treatment quantifies patient-specific intrafraction, interfraction, and progressive geometrical variations. These patient-specific parameters subsequently can drive adaptive plan modification correcting for systematic errors while incorporating random errors. Adaptive RT therefore has the potential to considerably improve the accuracy of RT, reducing the exposure of organs at risk, facilitating safe dose escalation, and improving local control as well as overall survival.Schaake-Koning C et al studied effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancerSurvival was significantly improved in the radiotherapy—daily-cisplatin group as compared with the radiotherapy group (P = 0.009): survival in the radiotherapy—daily-cisplatin group was 54 percent at one year, 26 percent at two years, and 16 percent at three years, as compared with 46 percent, 13 percent, and 2 percent, respectively, in the radiotherapy group. Survival in the radiotherapy—weekly-cisplatin group was intermediate (44 percent, 19 percent, and 13 percent) and not significantly different from survival in either of the other two groups. Cisplatin, given daily in combination with the radiotherapy described here to patients with nonmetastatic but inoperable non—small-cell lung cancer, improved rates of survival and control of local disease at the price of substantial side effects. Lung cancer is the most common cancer worldwide and the fifth most common cause of death globally. Its incidence continues to increase, especially within low- and middle-income countries (LMICs), which have limited capacity to address the growing need for treatment. The standard of care for lung cancer treatment often involves radiation therapy (RT), which plays an important therapeutic role in curative-intent treatment of early-stage to locally advanced disease, as well as in palliation. The infrastructure, equipment, and human resources required for RT may be limited in LMICs. However, this narrative review discusses the scope of the problem of lung cancer in LMICs, the role of RT technologies in lung cancer treatment, and RT capacity in developing countries[16-19].

Conclusion

The study demonstrated that cisplatin and Irinotecan administered as a 4 weekly chemotherapy for stage IIIB/IV NSCLC is an acceptable regimen in terms of tumor response as assessed by WHO criteria and by the Modified RECIST criteria (11 % and 26% respectively). Also the regimen showed improvement in the median survival and 1 year survival rates (57 weeks and 53% respectively) as compared to basic supportive care. The regimen is cheap; its side effects are mild and tolerable. Thus it could be reasonable regimen in resource limited settings

What this Study Add to Existing Knowledge

The problems with chemotherapy in India include a large number of dropouts because of the cost and the side effects. Cost factor is an important consideration and constraint in resource limited countries. A relatively cheaper drug combination of irinotecan and cisplatin was used by us in patients of advanced lung cancer, which is safe, effective and increases median survival rate.

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