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Research Article

A COMPARISON OF TWO CHEMOTHERAPY REGIMENS FOR NON SMALL CELL LUNG CANCER IN A MEDICAL COLLEGE

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ABSTRACT

A study was conducted in Department of Pulmonary Medicine, King George's Medical University, Lucknow to evaluate the efficacy and toxicity of combination therapy of Mitomycin, Ifosfamide, Cisplatin (MIC) and Cisplatin, Etoposide (CE) in the treatment of Non-Small Cell Lung Cancer (NSCLC). The objectives were response rates and evaluation of toxicity. The response rate in MIC group was 75%; no change in disease was observed in 25% (3/12 pts) and partial response in 50% (6/12 pts). The response rate in CE group was 55.6% (5/9 pts); no change in disease was observed in 33.4% (3/9 pts) & partial response in 22.2% (2/9 pts). Mitomycin, ifosfamide, cisplatin was found to be superior combination therapy compared to cisplatin and etoposide.

INTRODUCTION

Despite advances in diagnosis and management, lung cancer remains the leading cause of cancer related deaths worldwide.[1] Chemotherapy has an established role in the management of patients with advanced non small cell lung cancer. Mitomycin, ifosfamide and cisplatin are three most active single agents for non-small cell lung cancer and widely used as chemotherapy regimen in Europe whereas cisplatin and etoposide are the most commonly used regimen for lung cancer in United States of America. Previous results of studies comparing mitomycin, ifosphamide and cisplatin regimen with cisplatin and etoposide regimens have been contradictory.[2] We did this study to determine the superior regimen with acceptable toxicity.

MATERIAL AND METHODS

The study was conducted over one year period. Patients were required to have histological confirmed, previously untreated NSCLC with measurable or evaluable lesions. Patients of stage III or stage IV NSCLC with Karnofsky performance status score greater than 60, normal renal function (with creatinine clearance >50 ml/min), Hb > 10 gm%, TLC > 4000/cc, Platelet count >1, 00,000/cc and age 70 yrs or under were the eligibility criteria. Staging procedure included investigations like chest x-ray PA view, CT scans, bronchoscopy, brain and bone scans. Before each course of treatment a complete physical examination and a chest radiograph was repeated.

The evaluation of the chemotherapeutic response was done at the end of 5th cycle. A complete response (CR) was defined as the disappearance of all clinical and radiological evidence of disease with subjective improvement of symptoms. A partial response (PR) was defined as a greater than 50% decrease in the total area for all measurable disease with no evidence of new lesions, lasting for at least 4 weeks. Unchanged disease after three courses was accepted as treatment failure.

Patient enrolled in this study was randomly divided into two Groups. In group A (MIC group), 12 patients received Mitomycin (6mg/m^2 I.V. bolus on day 1), Ifosfamide (3 gm/m^2 I.V. infusion with Mesna on day 1-5) and Cisplatin (80 mg/m^2I.V infusion on day 1). In group B (CE group), 9 patients received Cisplatin 80 mg/m^2I.V infusion on day 1 after hydration and Etoposide 100mg/m^2 I.V. infusion on day 1, 3 and 5. Both regimens were administered in three weeks interval if patient had recovered from toxicities related to previous dose. Patients who had not recovered from toxicities related to previous course had dosing delayed up to 2 weeks. Criteria for removal from the study were progression of disease, development of intolerable toxicity or withdrawal of consent for further treatment. Results were evaluated at the end of 5 cycles.

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RESULTS

Over one year, 21 patients were enrolled in this study and were randomized between the two treatment groups, Group A and group B. Relevant prognostic factors were equally distributed between the two groups. (Vide Table-1).

Table 1 Patients Characteristics

Characteristics		Total	Group A	Group B
Median Age in Years		59	60	59
Male / Female		18/3	10/2	8/1
Stage	III	15(71.4 %)	9(75%)	6(66.7%)
	IV	6(28.6%)	3(25%)	3(33.3%)
Prevalence Of Tobacco Smoking	Smoker	18(85.7%)	11(91.7%)	7(77.8%)
	Non-Smoker	3(14.3%)	1(8.3%)	2(22.2%)
Previous ATT History		18(85.7%)	11(91.7%)	7(77.8%)
Associated with COPD	Yes	17(81%)	10(83.3%)	7(77.8%)
	No	4(19%)	2(16.7%)	2(22.8%)
Weight Loss		21(100%)	12(100%)	9(100%)
Karnofsky Status	≥ 70	14(66.7%)	8(66.7%)	6(66.7%)
	< 70	7(33.3%)	4(33.3%)	3(33.3%)
Histologic Type	Squmous Cell Carcinoma	9(42.8%)	6(50%)	3(33.3%)
	Adenocarcinoma	12(57.2%)	6(50%)	6(66.7%)
Site of Lesion	Upper Zone	11(52.4%)	7(58.3%)	4(44.4%)
	Middle Zone	7(33.3%)	3(25%)	4(44.4%)
	Lower Zone	3(14.3%)	2(16.7%)	1(11.2%)

The median age of the patients was 59 years and there were 18 males and 3 females. There were 9 patients with squamous cell carcinoma and 12 with Adenocarcinoma. Response rate are shown in Table 2.

Table 2

Response	Group A	Group B
Total Response(CR+PR)	6(50%)	2(22.2%)
CR*	0	0
PR**	6(50%)	2(22.2%)
No change	3(25%)	3(33.4%)
Progressive Disease	2(16.7%)	2(22.2%)
Deaths	1(8.3%)	2(22.2%)

* CR – Complete Response, ** PR – Partial Response

The response rate in group A (MIC) was 50% (6/12 pts), no change in disease observed in 25 % (3/12 pts) and progressive disease in 16.7% (2/12 pts). The response rate in Group B was 22.2% (2/9 pts), no change in disease was observed in 33.4% (3/9 pts) & progressive disease in 22.2% (2/9 pts).The overall response rate in the Group A was better as compared to Group B and was statistically significant ($Z=2.001$, $p<0.05$). Toxicities in both groups were generally moderate and manageable. Nausea, vomiting and myelosuppression were the observed side effects. One patient in Group A died during chemotherapy due to nephrotoxicity and two patient in Group B died due to severe anemia and leucopenia.

DISCUSSION

Lung cancer is the most common cancer worldwide with an estimated annual incidence of 1.2 million.[3] It is also the most common cause of cancer deaths worldwide and accounted for 1.69 million deaths in 2015.[3] Non-small cell lung cancer comprises 85% of all lung cancer cases. Clinical trials, as well as meta-analyses, have confirmed that platinum based combination chemotherapy improves survival in NSCLC compared with single agent, second-generation cytolytic agents and best supportive care alone.[4] Platinum-based combinations are the currently agreed standard regimens for NSCLC resulting in improved survival and symptom control for patients with good performance status. In this study, we have evaluated the efficacy & toxicity of two platinum combinations of Mitomycin, Cisplatin & Ifosfamide (Group A) and Cisplatin & Etoposide (Group B) in the treatment of NSCLC.

Mitomycin, ifosfamide, and cisplatin are three of the most active single agents in NSCLC, and phase II data for the MIC combination were first reported in the late 1980s. Mitomycin, ifosfamide and cisplatin have been associated with response rates of 20, 36 and 20% respectively.[5] MIC is a standard regimen for patients with advanced NSCLC in the United Kingdom and Europe.[6] The cisplatin-etoposide regimen was developed in the early 1980s and has been one of the standard chemotherapy regimens most extensively used in the clinical practice until a few years ago.[7]

The overall response rate with MIC regimen were 50 % and CE regimen 22.2% with no complete response in either regimen which was statistically significant ($Z=2.001$, patients<0.05).

The patients in the MIC arm of our study fared better than in the study by Urban *et al* in French patients. The response rate was only 37% in the study because of possibly larger cohort of stage IV NSLC patients (58%) as compared to our study (28.6%).[8] However, the response rate in our study is similar to previous trials on this regimen. Cullen *et al* in a cohort of 74 patients of NSCLC found response rate of 56% with the MIC regimen.[9] Currie *et al* in a study of 45 patients found a response rate of 56%.[10] Girón CG found a response rate of response rate of 68.8% in 32 patients of NSCLC administered MIC regimen. The higher response rate maybe due to all patients being stage III in the study.[11] Cullen *et al* undertook two multicenter randomized trials of mitomycin, ifofamide and cisplatin, (MIC1 and MIC2) to assess response rate in localized and advanced disease respectively. The overall response rate in the MIC 1 trial was 52% and the MIC 2 trial was 42%.[12]

In a study by Belani *et al*, the response rate for cisplatin etoposide regimen was 15%.[13] The European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Working Party in a RCT comparing cisplatin and carboplatin in combination with etoposide, found a response rate of 27% in the cisplatin etoposide arm.[14]

Our study demonstrates a statistically significant difference between response rates of Mitomycin Ifosfamide Cisplatin and Cisplatin Etoposide regimen. The mitomycin ifosfamide cisplatin regimen demonstrated superiority over cisplatin etoposide regimen.

The results indicate that the combination of mitomycin, ifosfamide & cisplatin was more efficacious and safe than cisplatin & etoposide in the treatment of NSCLC.

Nausea, vomiting and myelosuppression were the major side effects. Most patients in both groups suffered from cisplatin induced nausea and vomiting which were controlled with anti emetic therapy. One patient in MIC regimen died during chemotherapy due to nephrotoxicity and two patients in group B died due to severe anemia and leucopenia. This study confirms that MIC is an effective regimen for treatment of NSCLC, with acceptable toxicity.

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