A Randomized Study of Gemcitabine Monotherapy versus Etoposide/Cisplatin in the Treatment of Locally Advanced or Metastatic Non-Small Cell Lung Cancer

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Abstract:

 Patients with stages IIIB and IV of non-small cell lung carcinoma (NSCLC) are treated with chemotherapy and radiotherapy. Platinum based combination chemotherapy is the mainstay of treatment, but response is not too promising. The objective of this study was to compare response rate and progression free survival of 2 chemotherapy regimens: gemicilabine monotherapy versus cisplatin and etoposide combination. This randomized, prospective study of 1 year included 48 patients, histologically proven cases of NSCLC belonging to stage IIIB or IV. These were randomized in two groups, A and B. The patients in arm A received gemcitabine and those in arm 'B' received cisplatin and etoposide repeated every 3 weekly. The evaluation of response during and after treatment was performed as per the WHO criteria. Overall 83.33% of patients were smokers, with majority having smoking history of 20-29 pack years. Evaluation of chemotherapy was performed in only 37 patients after excluding 11 dropouts. Mean progression free survival was 4.5 ± 2.3 (arm A 5.2±1.6, arm B 4.1±0.9) months. The overall mean survival was 6.37±1.05 months for arm A and 5.8±2.3 for arm B, which was not statistically significant (p=0.607). During the study period a total of 10 (20.8%) mortalities were seen. Both modalities of the chemotherapy regimens, gemcitabine monotherapy and cisplatin with etoposide seem to be equally effective. However, gemcitabine monotherapy is found to be more feasible to the patients as it can be administered on outpatient basis minimizing hospitalizations.

Keywords: *non-small cell lung cancer, chemotherapy gemcitabine, cisplatin, etoposide, response rate.*

Introduction:

Lung cancer is the leading cause of cancer deaths globally, and smoking is the established risk factor [1,2]. According to the current World Health Organization (WHO) estimates, there are around 1100 million smokers worldwide [3].Similar is the situation in India, although *bidi* smoking is more prevalent in this part of the world [4].Majority of lung cancer patients in our country present with advanced stages of the disease at tertiary care centers, the stages when they are inoperable. So chemotherapy and /or radiotherapy is the mainstay of treatment to these patients. Platinum -based chemotherapy regimens are commonly used in our set up, however, the response is not too good. So, there is need to develop new chemotherapy protocols. In view of this background, the presents study was conducted to compare the results of gemcitabine monotherapy and the platinum-based combination therapies. To our knowledge, this is the first study of its kind published from India so far.

Material and Methods:

This was a randomized prospective study conducted at the Kasturba Chest Hospital, Department of Pulmonary Medicine Chhatrapati Shahuji Maharaj (Erstwhile, King George's) Medical University, Lucknow, India, for one year from July 2005.

Study Population: The Study included 48 patients (34 males and 14 females) selected on the basis of histologically or cytologically confirmed stage III B or IV of non-small cell lung cancer (NSCLC). The patients were of ≤ 70 years of age having Karnofsky performance scale[5] of ≥ 70%, having stable hematologic profile, renal and liver functions. Prior complete history, physical examination, anthropometric measurements including body weight, height, body surface area, were conducted in all the selected patients. Besides, routine investigations, the diagnosis was obtained after fiberoptic bronchoscopy, computed tomography and the final histopathological study of the specimens.

Exclusion Criteria: These included: malignancy other than lung cancer, age >70 years, pregnancy, Kernofsky performance status <70%, history of previous chemotherapy or radiotherapy, total leucocyte count <4000/mm^3, platelet count< 1 lac/ mm^3, serum creatinine >1.25 times of its upper limit, serum bilirubin > twice of the normal and AST and/or ALT> thrice of the normal upper limit.

Staging: This was performed according to the prescribed TNM classification and staging [6], in all the selected subjects.

Treatment Regimens: **[1] Gemcitabine Monotherapy (arm A):** Each patient received gemcitabine in a dose of 1000 mg/m^2 on day 1 and 5 of the cycle and repeated after every 3 weeks, **[2] Cisplatin + Etoposide (arm B):** Each patient of this subgroup received cisplatin 25mg/m^2 on day 1,2 and 3 (75 mg/m^2 in total) with etoposide 100 mg/m^2 on same days and the cycle was repeated every 3 weekly.

Evaluation during and after treatment: This was done after following WHO criteria [7] indicating complete response, partial response, stable and progressive disease (Box 1), Kernofsky performance status[5] and WHO grading of toxicity[8] (Table 2).

All the findings including patient characteristics, investigations, treatment protocols, response, toxicity and mortality etc were meticulously entered in the master chart formulated for this purpose.

Statistical Analysis: The data were represented in proportions and percentages. For the purpose of statistical analysis, Statistical Package for Social Sciences (SPSS) version 10.0 was used. Differences between proportions were compared using Pearson's Chi-square test. For comparing the mean values between two groups, independent samples 't' test was used. The confidence level of the study was kept at 95%, hence a 'p' value <0.05 was considered significant.

Results:
Overall, there were 48 patients enrolled in this study. These included 34 (70.9%) males and 14 (29.1%) females in the age group of 30 to 69 years, randomized between arms A and B (24 patients each). Out of these, 11 patients were dropped out of the study (one was shifted to higher centre on will of attendants, 7 were lacking affordability, one did not feel the treatment satisfactory, and the remaining 2 patients were lost to follow up). Remaining thirty seven (77.0%) patients were analyzed during and after treatment. Out of these, 18 (37.5%) patients belonged to arm A and 19 (39.5%) to arm B. Among these, majority (60.0%) belonged to the rural set up. 58.33% patients were Hindus and 41.67% were Muslims by religion. 60% of patients in arm A had lesions on right side and the same side was predominantly involved in 75% patients of arm B, as well.

Smoking Status: In arm A, all patients were smokers, whereas 83.3% of patients in arm B were smokers. Fourty percent patients of arm A consumed 20-29 pack years, and 20% , each had 10-19, 30-39, and 40-49 pack year history. In the arm B, 30% patients consumed cigarettes for 20-29 pack years, and 20% each for 10-19, and 30-39 pack years, and 10% each for 1-9, 40-49 and 50-59 pack years, respectively. So majority of patients in both the arms had an average of 20-29 pack years smoking status. This association of smoking with the development of lung cancer was found statistically highly significant (P<0.05)

Symptomatology and clinico-radiological findings at presentation: In this study, anorexia and weight loss were the main symptoms in almost all of the patients. Cough was the commonest respiratory complaint present in 32 (86.4%) of the 37 patients selected for final study, followed by dyspnea (82.3%), chest pain (76.4%), fever (52.9%), expectoration of thick sputum

Box 1: WHO criteria of response to treatment

a. **Complete response:** the disappearance of all known disease determined by 2 observations not less than four weeks apart.

b. **Partial response:** 50% or more decrease in total tumor size of the lesions which have been measured to determine the effect of therapy by 2 observations not less than 4 weeks apart, with no appearance of new lesions or progression of the disease.

c. **Stable disease/no change**: a 50% decrease in total tumor size cannot be established nor has a 25% increase in the size of one or more measurable lesions been demonstrated.

d. **Progressive disease**: a 25% or increase in the size of one or more measurable lesions or the appearance of new lesions.

Table 1: Comparison of treatment response among the two arms

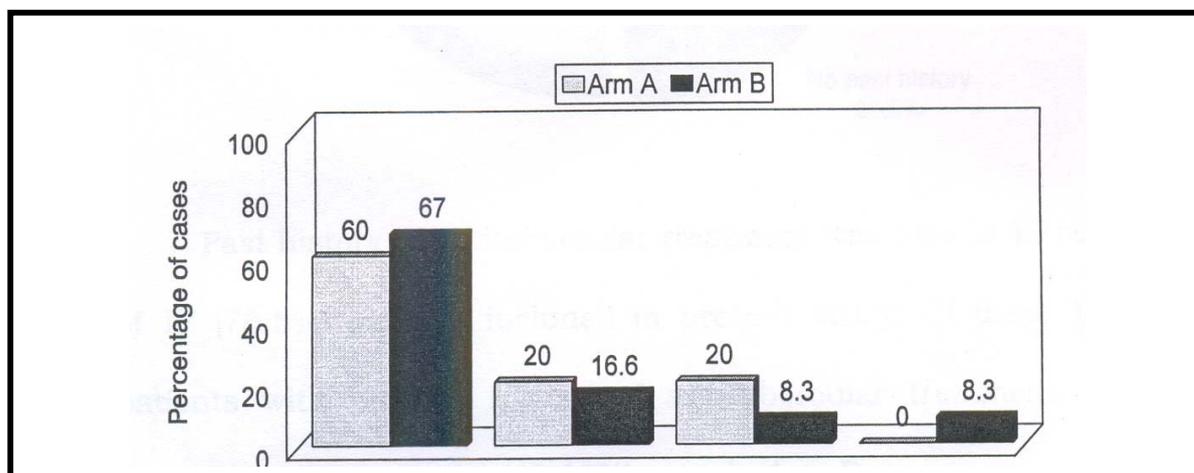| Response	Arm A (n=18) Number (%)	Arm B (n=19) Number (%)	'p' value
Complete Response	0(0)	1(5.2)	0.10
Partial Response	12(66.6)	10(52.6)	<0.05
Stable Disease	6(33.3)	6(31.5)	0.31
Progressive Disease	0 (0)	2(10.5)	0.75

Figure 1: Distribution of patients in two study arms according to histological type

(64.7%) and hemoptysis (29.4%). Compression symptoms included hoarseness of voice (23.5%), facial swelling (11.7%) and dysphagia in 17.6% patients. The commonest clinical findings on examination were pleural effusion (58.8%) clubbing (23.5%), superior vena caval obstruction (17.6%) and palpable lymph nodes (17.6%). The radiological profile revealed pleural effusion with mass lesion in the majority (64.7% in arm A and 58.8% in arm B) of patients. Other findings included associated

collapse (29.4%), hilar masses (11.7%) and cavities (5.8%). One patient presented with diffuse lesions, not classified in any of these categories.

Histopathology: On histopathological study, squamous cell carcinoma was the most frequent type (60% in arm A and 67% in arm B). No patient of adenosquamous cell carcinoma was seen in arm A while as 8.3% had this histologic type in arm B (Figure 1). 39.9% patients of arm A and 58.3% of arm B had stage III B of the disease at presentation whereas stage IV was present in 60.1% and 41.67% patients of the two arms respectively.

Response to treatment after completion of therapy: In arm A, no patient showed complete response, whereas in arm B complete response was observed in 1(5.2%) patient (Table 1). Partial response was seen in 66.6% and 52.6% patients among the two arms, respectively which was statistically significant (P<0.05). Again 33.3% and 31.5% of patients, respectively had the stable disease, whereas it was progressive in two patients in arm B, which was of no statistical significance (P= 0.759). After chemotherapy, the mean improvement in the value of Karnofsky performance status was 6.85 ± 1.4 in arm A and 6.20 ± 2.1 in arm B and was not statistically significant (p= 0.538), and the overall improvement in quality of life was upto our expectation.

Overall Survival Response: All the patients who received 6 cycles of chemotherapy were followed up with regular check ups, postal correspondence and phone calls, for over one year. Among the study group mean progression -free survival was 4.5 ± 2.3 (arm A 5.2±1.6, arm B 4.1±0.9) months. The overall mean survival was 6.37±1.05 months for arm A and 5.8±2.3 for arm B. The difference with 'p' value of 0.607 was not statistically significant.

Drug Toxicity: As per the WHO grading system, the toxicity of drugs was observed relatively more among the cases of arm B. Transient vomiting happened in 45.8% patients of arm A, and 29.1% of grade 3 vomiting required medical therapy; in arm B, in addition to the similar picture, one patient got intractable vomiting (Table-2). Anemia of grades 1 and 2 was more frequent amongst the patients of both arms. Leucopenia of grade 1 was observed in 66.6% patients of arm B and grade 2 was more (ie, 33%) in arm A patients. Similarly thrombocytopenia was more severe in arm B group. The profile of nephrotoxicity was almost similar among the two groups. Hematuria was not observed in either arm. Patchy hair loss was observed in 8 (16.6%) patients of arm A and 13 (68.4%) patients of arm B and complete alopecia in one patient only belonging to the later group.

Mortality: As, already mentioned, 10(20.8%) patients died during our study. The 4 patients who died at home, their cause of death could not be elucidated. Among the remaining 6 patients who died during hospital stay, 5 had concomitant severe infections, septicemia and subsequent cardio-pulmonary arrest, whereas one patient got sudden death while hospitalized.

Discussion:
Gemcitabine, a nucleoside analogue, has shown activity as a single agent in the treatment of metastatic NSCLC, producing response rates of 20% and above [9-12]. However, in a recent study published in 2010, response rate of only 9.4% with gemcitabine monotherapy has been observed [13]; a similar study revealed partial response of 32.8% and minimal response of 48% from gemcitabine monotherapy [4]. Because of its unique mechanism of action and non-overlapping toxicity with other active agents, gemcitabine is an attractive candidate for trials in combination with other cytotoxic agents.

Table 2: Profile of toxicity among the study population as per the WHO grading system

Toxicity	Grade	Level	Arm A (n=24) No. of patients (%)	Arm B (n=24) No. of patients (%)
Nausea/ vomiting				
	0	None	3 (12.5)	3 (12.5)
	1	Nausea	3 (12.5)	5 (20.8)
	2	Transient vomiting	11 (45.8)	9 (37.5)
	3	Vomiting requiring therapy	7 (29.1)	6 (25.0)
	4	Intractable vomiting	-	1 (4.1)
Anemia hemoglobin, g/dL				
	0	>11	-	-
	1	9.5-10.9	16 (66.6)	17 (70.8)
	2	8.0-9.4	7 (29.1)	5 (20.8)
	3	6.5-7.9	1 (4.1)	2 (8.3)
	4	<6.5	-	-
Leucopenia cells/mm^3				
	0	≥4000	9(37.5)	3 (12.5)
	1	3000-4000	5 (2.8)	16 (66.6)
	2	2000-3000	8 (33.3)	2 (8.3)
	3	1000-2000	2 (8.3)	1 (4.1)
	4	<1000	-	2 (8.3)
Thrombocytopenia platelets/ mm^3				
	0	>100000	17 (70.8)	15 (62.5)
	1	75000-100000	3 (12.5)	8 (33.3)
	2	50000-75000	2 (8.3)	1 (4.1)
	3	25000-50000	2 (8.3)	-
Nephrotoxicity serum creatinine x N				
	0	≤1.25	14 (58.3)	13 (54.1)
	1	1.26-2.5	7 (29.1)	9 (37.5)
	2	2.6-5.0	3 (12.5)	2 (8.3)
	4	>10.9	-	-

N, upper limit of normal

Because of synergistic action with cisplatin, response rates as high as 54% have been achieved with the combination therapy in stage III and IV NSCLC [14].In the present study partial response to the extent of 63.6% due to gemcitabine monotherapy was observed in arm A. In our study, majority of patients belonged to age group of 50 to 59 yerars. Jindal SK from India, also found long cancer patients presenting in 5th and 6th decade of life [15], and similar were the observations of Pathak AK from this country[16]. Smoking as a risk factor for lung cancer is now fully established [17-19]. Our study also demonstrated statistically significant relation between smoking of average 20-29 pack years in both arms. Similary, risk of lung cancer in India has been linked to smoking by Behera D[20], Prasad R[21], Gupta RC[22] and, several other studies as well. In our study, squamous cell carcinoma was the most histological type (60% in arm A and 67% in arm B). Similar has been the histologic result in previous studies of India.[15,21,23]. Among the toxic effects encountered during our study, the most significant finding was anemia of grade 1 to 2, in 66.6% and 29.1% respectively among patients belonging to arm B. The other toxicities like vomiting,

leucopenia, thrombocytopenia and nephrotoxicity were slightly higher among patents of arm B. In the study of Zwitter [5] only anemia of grade 3 was seen in one patient of arm A and 2 patients of arm B and no other toxic effect was observed, and similar study of the same workers, revealed anemia, thrompocytopenia, neutropenia, nausea/ vomiting more in arm B patients. Alopecia was seen in 54.5% patients in arm B compared to 9.7% in arm A [4]. Similar was the finding in our study. Majority (68.7%) of patients in arm B developed patchy hair loss and complete alopecia was seen in one patient belonging to same arm.

The overall status of response to treatment in our study was somehow encouraging. None of the patient in arm A got complete response, whiles it was seen among 5.2% of patients belonging to the arm B. Partial response rate was observed 66.6% and 52.6% among the arms A and B, respectively. Stable disease was found in 33.3% and 31.5% in arm A and B respectively where as two patients in arm B had progressive disease despite adequate therapy. In a pilot study conducted by Parikh and co-workers [24],using low dose prolonged infusion of gematabine in combination with carboplatin, a response rate of 80% was observed. In contrast to this, the response rate of gematabine monotherapy in recent studies was 32.8% [4] and 9.4% [5]' which were inferior to the response rates seen in combination therapy. Rodriguez and co-workers [25] used combination of paclitaxel, cisplation and gemcitabine to treat metastatic NSCLC and the over all response rate was 71.4% with grade 3-4 neutropenia and thrombocytopenia as the toxic effects of the combination observed among 39.9% and 11.4% of patients respectively. Ricci and co-authors, used gemcitabine and cisplatin in both arm A and arm B of their randomized study having different durations of administration

of the drugs in two arms, and the response rates were almost similar in both arm A and B (40.4%) and 45% respectively) [26]. In a similar study conduced on 92 patients by Rinaldi and co-workers [27], response rates were again almost similar (42% in arm A and 47% in arm B). Gemcitabine -cisplatin combination has been proved as a superior modality of treatment for advanced NSCLC by several other studies as well [28,29].

The average survival of population in our study was 6.37 months and the same has been to the extent of 4.3 and 10.1 in similar other studies [4,5].

The main limitations faced during our study were smaller sample size and financial constraints of the patients.

To conclude, gemcitabine monotherapy was almost equally effective as combination therapy in treatment of advanced NSCLC in our study, however, the combination therapy has been proved more superior than monotherapy by several other studies. Although as per our comments, gemcitabine monotherapy is the preferred choice for the patients because it can be administered on outpatient basis minimizing the hospitalization. For further substantiation of results, studies involving large sample sizes and longer durations with meticulous follow up are recommended in future.

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