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Research Article

A comparison of toxicity profile of gemcitabine monotherapy versus etoposide/cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer

Ved Prakash[1], Arpita Singh[2], Surya Kant[1]*, Ajay K. Verma[1], Prachi Saxena[1], Ankit Bhatia[1]

[1]Department of Pulmonary Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India, [2]Department of Pharmacology, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India

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***Correspondence to:**
Dr. Surya Kant,
Email: dr.kantskt@rediffmail.com

ABSTRACT

Background: Lung cancer is the leading cause of cancer deaths globally in which about 40% patients reporting in advanced stage disease. Both platinum and non platinum combinations have been shown to be equally efficacious as initial first-line treatment of advanced non-small cell lung cancer (NSCLC), however because of the toxicity of cisplatin, combination treatment can only be administered to a minority of patients in good general health. Gemcitabine could be combined with one of the other new agents to create novel non-platinum-doublet combinations with efficacy and/or toxicity profile superior to that of standard platinum based combinations. Hence, this study was conducted to compare the toxicity profiles of gemcitabine monotherapy and the cisplatin/etoposide combination therapy.

Methods: This was a randomized prospective study, which included 96 patients selected on the basis of histologically or cytologically confirmed Stage III B or IV of NSCLC. Study was divided into two arms-Arm A received gemcitabine monotherapy in a dose of 1000 mg/m^2 on day 1 and 5 of the cycle and repeated after every 3 weeks while Arm B received cisplatin (25 mg/m^2 on day 1, 2 and 3) + etoposide (100 mg/m^2). Patient were evaluated for adverse events by following World Health Organization grading of toxicity.

Results: Out of the 96 patients enrolled in the study, 74 (77.0%) patients were eligible and were analyzed. Of these, 36 (37.5%) patients belonged to Arm A and 38 (39.5%) to Arm B. Transient vomiting (45.8% vs. 37.5%), leukopenia (33.3% vs. 8.3%) were seen more in Arm A, while thrombocytopenia (33.3% vs. 12.5%), patchy hair loss (68.4% vs. 16.6%) was seen more in Arm B. Nephrotoxicity was seen almost similarly in both the groups.

Conclusions: Single-agent gemcitabine appears to have a safer toxicity profile than the combination cisplatin-etoposide in the first-line chemotherapy of advanced NSCLC. With less toxic anticancer drugs like gemcitabine, the physician now has greater choice in choosing treatment, which can have better effect on the patients concerned.

Keywords: Non-small cell lung cancer, Chemotherapy, Toxicity

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] Approximately 40% of patients with non-small cell lung cancer (NSCLC) present at an advanced stage, including patients with metastatic disease and those with locally advanced disease with malignant pleural or pericardial effusion.[5]

Both platinum-based two-drug regimens and non-platinum combinations have been shown to be efficacious in the first-line treatment of advanced NSCLC. Because several chemotherapy regimens have similar degrees of efficacy in advanced NSCLC, the choice of which to use is often made after considering factors such as schedule, toxicity profile, and cost. The systemic treatment currently recommended in patients with advanced NSCLC is cisplatin-based combination chemotherapy.[6] However, because of the toxicity of cisplatin, combination treatment can only be administered to patients in good general health, which is the case only for a minority of Stage IV patients.[7]

Gemcitabine is a new nucleoside analogue with major antitumor efficacy in various solid tumors in contrast to cytosine-arabinoside which is not active in solid tumors. Several Phase II studies have also shown that gemcitabine is well tolerated, is easy to administer on an outpatient basis, and is effective in NSCLC, with activity in a range that can be expected for cisplatin-containing combination regimens. Gemcitabine can be particularly beneficial for the therapy of elderly and unfit patients as well as for the palliation of tumor-related symptoms.[8] Three Phase II trials have suggested that single-agent gemcitabine can produce response rate and survival outcomes equivalent to the combination regimens of cisplatin-etoposide or cispaltin-vindesine, but with considerably less toxicity.[7,9-10] Therefore, it can be hypothesized that gemcitabine could be combined with one of the other new agents to create novel non-platinum-doublet combinations with efficacy and/or toxicity profile superior to that of standard platinum based combinations. It therefore seemed logical to compare gemcitabine as a single agent with a standard combination chemotherapy (such as cisplatin-etoposide) to establish whether better tolerated treatment could be given to patients who could not receive cisplatin-containing chemotherapy because of its toxicity.

In view of this background, the present study was conducted to compare the toxicity profiles of gemcitabine monotherapy and the cisplatin/etoposide combination therapy.

METHODS

This was a randomized prospective study conducted at the Kasturba Chest Hospital, Department of Pulmonary Medicine King George's Medical University, Lucknow, India, for 1-year from July 2005.

Study population

The study included 96 patients selected on the basis of histologically or cytologically confirmed Stage III B or IV of NSCLC. The patients were of 70 years of age having Karnofsky performance scale[5] of 70%, having stable hematologic profile, renal and liver functions.

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 25 mg/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 treatment

This was done after following WHO grading of toxicity[8] (Table 1).

Statistical analysis

The data were represented in proportions and percentages. 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 $p<0.05$ was considered as significant.

RESULTS

Overall, there were 96 patients enrolled in this study. These included 68 (70.9%) males and 28 (29.1%) females in the age group of 30-69 years, randomized between Arms A and B (48 patients each). Out of these, 22 patients were dropped out of the study (two were shifted to higher center on will of attendants, 14 were lacking affordability, one did not feel the treatment satisfactory, and the remaining 5 patients were lost to follow-up). Remaining 74 (77.0%) patients were analyzed during and after treatment. Of these, 36 (37.5%) patients belonged to Arm A and 38 (39.5%) to Arm B. 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 1).

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 (i.e., 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 16 (16.6%) patients of Arm A and 26 (68.4%) patients of Arm B and complete alopecia in two patients only belonging to the later group. Leukopenia of Grade 1 was observed in 66.6% patients of Arm B and Grade 2 was more (i.e., 33%) in Arm A patients.

DISCUSSION

Approximately 40% of patients with NSCLC present at an advanced stage, including patients with metastatic disease and those with locally advanced disease with malignant pleural or pericardial effusion. Treatment options for these subgroups are chosen based on patient performance status

Table 1: Profile of toxicity among the study population as per the WHO grading system.

Toxicity	Grade	Level	Arm A (n=36) number of patients %	Arm B (n=38) number of patients %	Odds ratio (Chi-square for trend)	p value
Nausea/vomiting	0	None	4 (12.5)	5 (12.5)	1.00 (Ref)	0.39
	1	Nausea	5 (12.5)	8 (20.8)	0.78	
	2	Transient vomiting	16 (45.8)	14 (37.5)	1.43	
	3	Vomiting needing therapy	11 (29.1)	9 (25.0)	1.53	
	4	Intractable vomiting	-	2 (4.1)	NA	
Anemia Hb (g/dl)	0	>11	-	-	NA	0.88
	1	9.5-10.9	24 (66.6)	27 (70.8)	1.00 (Ref)	
	2	8.0-9.4	10 (29.1)	8 (20.8)	1.41	
	3	6.5-7.9	2 (4.1)	3 (8.3)	0.75	
	4	<6.5	-	-	NA	
Leukopenia (cells/mm^3)	0	≥4000	20 (55.6)	5 (12.5)	1.00 (Ref)	0.60
	1	3000-4000	2 (2.8)	25 (66.6)	0.02	
	2	2000-3000	12 (33.3)	3 (8.3)	1.00	
	3	1000-2000	3 (8.3)	2 (4.1)	0.38	
	4	<1000	-	3 (8.3)	NA	
Thrombocytopenia (cells/mm^3)	0	>1,00,000	25 (70.8)	24 (62.5)	1.00 (Ref)	0.55
	1	75,000-1,00,000	5 (12.5)	12 (33.3)	0.40	
	2	50,000-75,000	3 (8.3)	2 (4.1)	1.44	
	3	25,000-50,000	3 (8.3)	-	NA	
Nephrotoxicity serum creatinine X N	0	≤1.25	21 (58.3)	21 (54.1)	1.00 (Ref)	0.99
	1	1.26-2.5	11 (29.1)	14 (37.5)	0.79	
	2	2.6-5.0	4 (12.5)	3 (8.3)	1.33	
	3	>10.9	-	-		

WHO: World Health Organization, NA: Not applicable

(PS), because it is an important determinant of outcome.[12] Combination chemotherapy is considered the standard of care for patients with advanced NSCLC and a PS score of 0 or 1.[13] Both platinum-based two-drug regimens and non-platinum combinations have been shown to be efficacious in the first-line treatment of advanced NSCLC. Because several chemotherapy regimens have similar degrees of efficacy in advanced NSCLC, the choice of which to use is often made after considering factors such as schedule, toxicity profile, and cost.

We initiated a randomized study to compare gemcitabine with cisplatin-etoposide in order to determine whether single-agent gemcitabine would be better tolerated, so that it could be used in patients in which cisplatin-based chemotherapy would be too toxic.

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 such as vomiting, leukopenia, thrombocytopenia and nephrotoxicity were slightly higher among patients of Arm B. In a Phase II randomized study, done in 1997 by Manegold et al.,[7] hematological toxicity was more pronounced with cisplatin-etoposide compared with gemcitabine.

Anemia was usually mild in both treatment arms, although red cell transfusions had to be administered to twice as many cisplatin-etoposide patients (compared with gemcitabine). Furthermore, there was no neutropenic fever or sepsis with gemcitabine, whereas 8% of patients on cisplatin-etoposide had to be hospitalized for neutropenic sepsis. Thrombocytopenia was generally mild in both treatment arms.

The incidence of alopecia was minimal with gemcitabine (97% of patients had no hair loss, whereas 60% and 2% of cisplatin-etoposide patients had Grade 3 and 4 hair loss. The majority of cisplatin-etoposide patients reported nausea and vomiting with about 30% Grade 3 and 4 toxicity; only 11% of cisplatin-etoposide patients experienced no nausea and vomiting. With gemcitabine, Grade 3 nausea and vomiting was only 11% with no Grade 4 toxicity; as many

as 45% of the patients had no nausea and vomiting. In the study of Zwitter[14] 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.[15] 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. Rodriguez et al.[16] used combination of paclitaxel, cisplation and gemcitabine to treat metastatic NSCLC and the overall 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. Ceribelli et al. conducted a Phase II randomized study in 112 chemonaıve patients with advanced NSCLC of two different 4 weeks schedules of gemcitabine at 1000 mg/m^2 as 30 mins infusion or at a fixed dose rate of 10 mg/m^2/mins for 100 mins on days 1, 8, 15, in association with cisplatin at a dose of 80 mg/m^2 on day 15.[17] Novello et al. presented the results of a noninferiority Phase III randomized trials where chemonaive advanced NSCLC patients with responsive or stable disease after two 3 weeks cycles of GC (cisplatin 75 mg/m^2 day 2 and gemcitabine 1250 mg/m^2 days 1 and 8) were randomly assigned to three additional cycles of the GC combination (Arm A) or gemcitabine alone (Arm B) at the same doses and schedules.[18] The experimental arm showed to be not inferior to Arm A in terms of median and 1-year survival, with considerably less hematologic and non-hematologic toxicity. Cardenal et al. in their randomized Phase III trial explored a 3 weeks schedule delivering 1250 mg/m^2 gemcitabine on day 1 and 8, and CDDP 100 mg/m^2 on day 1.[19] In this study, no substantial reduction of the gemcitabine planned dose intensity was observed, and toxicity (Grade 3 and 4 neutropenia and alopecia) was significantly more pronounced in the comparator CDDP-etoposide regimen.

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

In conclusion, single-agent gemcitabine appears to be less toxic than the combination cisplatin-etoposide in the first-line chemotherapy of advanced NSCLC. With less toxic anticancer drugs like gemcitabine, the physician now has greater choice in choosing treatment. In patients where quality of life is particularly important and patients are unable to tolerate the toxicities of traditional cisplatin-based chemotherapy, gemcitabine offers lower toxicity yet activity, which is equivalent to that of other single agents.

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