JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH

**How to cite this article:**
MEERA S, PHILIPJ, RADHESHYAM, ULLA I. A COMPARATIVE CLINICAL STUDY OF DOCETAXEL-CARBOPLATIN AND GEMCITABINE- CARBOPLATIN IN PATIENTS WITH NON SMALL CELL LUNG CANCER. Journal of Clinical and Diagnostic Research [serial online] 2008 August [cited: 2008 August 4]; 2:946-951.
Available from
http://www.jcdr.net/back_issues.asp?issn=0973-709x&year=2008&month=August &volume=2&issue=4&page=946-951&id=200

## ORIGINAL ARTICLE

# A Comparative Clinical Study of the Docetaxel-Carboplatin combination and the Gemcitabine- Carboplatin combination in Patients with Non Small Cell Lung Cancer

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## ABSTRACT

**Back Ground:** Non small cell lung cancer (NSCLC) constitutes about 75-80% of all lung cancer cases. In the chemotherapy of NSCLC, a platinum drug can be combined with taxanes or Gemcitabine.

**Aim:** To compare the Docetaxel-Carboplatin (DC) and Gemcitabine-Carboplatin (GC) treatment regimen in patients with NSCLC.

**Setting And Design:** Prospective, Randomized, Open labeled double arm study

**Methods:** Thirty patients with stage IIIB/IV NSCLC were randomly divided into two groups. The patients of the DC group were treated with Docetaxel (75 mg/m$^2$, day one) and Carboplatin (calculated to give an AUC of 6 mg/ml, day one) and those of the GC group were treated with Gemcitabine (1200 mg/m$^2$, day one and eight) and Carboplatin (day one). Treatment cycles were repeated every 21 days for a period of three cycles. Response and toxicity were assessed using WHO criteria.

**Results:** The patients in both the groups were well balanced for demographics and disease. Objective responses were similar in the two groups; DC group: 20% partial response, 60% stable disease and 20% of progressive disease. GC group: 33.3% partial response, 53.3% stable disease and 13.3% progressive disease. The only significant toxicity was anemia in the DC group. The evaluation of the quality of life of patients in both the groups showed significant change in the incidence of anemia, dysphagia and peripheral neuropathy in the DC group. Alopecia was significantly higher among the patients of the GC group.

**Conclusion:** The toxicity profiles of the Docetaxel-Carboplatin and Gemcitabine-Carboplatin combinations were similar. The Docetaxel-Carboplatin treatment regimen is cost effective for patients. Global quality of health is not improved in either combination, although advantages in some components of ten QOL were apparent.


**Key Words:** Non small cell lung cancer (NSCLC), Docetaxel, Gemcitabine, Carboplatin, Quality of life, tumour response, haematology.

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## Introduction

Uncontrolled multiplication and spread of abnormal forms of cells within the body is termed as Cancer. It is one of the major causes of death in the developed nations [1]. Lung cancer has a death rate, greater than that attributed to colorectal, breast and prostate cancers combined [2].Non small cell lung cancer (NSCLC) constitutes about 75-80% of all lung cancer cases, and accounts for 1.2 million cases world wide each year[3]. The role of platinum-based chemotherapy has now been clearly established in advanced stage NSCLC. Chemotherapy improves survival rate in patients with stage IV disease as compared to best supportive care, in patients with inoperable stage III, when combined with thoracic radiation and compared to radiation alone. Chemotherapy improves survival rate in patients with stage IIIA (N2) also, when given before radical surgery as compared to surgery alone [3]. One of the chemotherapeutic treatments of NSCLC is, combining a platinum agent with one of the two taxanes (Docetaxel, Paclitaxel), vinorelbine or gemcitabine[4]. The possible haematological and non haematological toxicities of these treatments include anemia, neutropenia, thrombocytopenia, nausea/vomiting, mild skin rash, diarrohea, mucositosis, constipation, neurotoxocity, asthenia, neutropenia, fluid retention, asthenia, alopecia, hypersensitivity reactions, and skin and nail toxicities [5],[6].

The assessment of a cancer patient broadly includes two sets of endpoints - cancer outcome and patient outcome. Cancer outcome measures the response of a patient to treatment, duration of response, symptom free period, and early recognition of relapse. Patient outcome, on the other hand, assesses the survival benefit attained after treatment as measured by the increase in life span, and the quality of life before and after therapy. Quality of life (QOL) is a broad, subjective, and multidimensional concept that includes: (a) Physical health and symptoms (b) Functional status and activities of daily living [7]. The present study was taken up with the aim of comparing Docetaxel-Carboplatin and Gemcitabine-Carboplatin treatment regimens in patients with non small cell lung cancer.

## Materials and Methods

A prospective, randomized, open labeled, double-arm study of a total duration of eight months, was taken up from November 2006 to June 2007, at the Curie Centre of Oncology, St. Johns Medical College and Hospital campus, Bangalore. Thirty patients of NSCLC of both sexes with an age range of 35-65 years, from different strata of society, were included in the study. The institutional Ethics Committee's permission was obtained before starting the studies.

## Inclusion and exclusion criteria

Patients suffering from cytologically or histologically confirmed stage III/IVB non small cell carcinoma, with no prior chemotherapy treatment given, were included in this study. Patients having a WHO performance status of <3 and adequate liver, kidney and bone marrow functions, were included in the study. All patients signed informed consent before enrollment into the study.

Patients with active infection, symptomatic central nervous system metastases, pregnancy, second primary malignancy, or serious concomitant systemic disorders, inadequate liver function (bilirubin >1.5 times upper limit of normal), with alanine transaminase or aspartate transaminase less than three times normal or inadequate renal function, HIV/HbSAg +ve, or with life threatening systemic diseases were excluded from the study.

## Treatment Regimen

Hospitalized patients were centrally randomized according to age, performance status and stage of disease to receive either Docetaxel-Carboplatin (DC group) or Gemcitabine-Carboplatin (GC group) treatment. DC group patients received Docetaxel 75 mg/ $m^2$ as a one-hour i.v.

infusion, immediately followed by, Carboplatin, calculated to give an AUC of 6 mg.min/ml according to the Calvert formula. The GC group patients received 1200 mg/$m^2$ Gemcitabine intravenously over 30 minutes on days one and eight, and Carboplatin on day one. Standard WHO toxicity and response criteria were used. To access the toxicity during treatment, differential leucocyte count and platelet count were done weekly. In the event of grade three or four neutropenia, febrile neutropenia, or grade four thrombocytopenia, the complete blood-cell count was done daily until the absolute granulocyte count was greater than 1200/μL and the platelet count was greater than $50\times10^3$/μL. A detailed medical history was recorded, and a complete physical examination was done before each course of treatment, to assess symptoms of the disease and treatment toxicity. Biochemical tests, electrocardiogram and chest radiographs were done at the beginning of the Ist course and after completion of the IIIrd course.

The quality of life (QOL) was assessed with the English or Kannada version of EORTC QLQ-C30 and QLQ-LC 13 questionnaires. The patients answered the questionnaire before and during the treatment. QOL scores were assessed according to the EORTC-QLQ scoring manual. The scores were transferred to a scale of 0 to 100. A high score for a functional or global QOL scale represents a relatively high/healthy level of functioning or global quality of life, whereas a high score for a symptom scale represents the presence of a symptom or problem(s).

## Statistical Analysis

Values were expressed as mean ± SEM or as percentages, and were analyzed using the Fisher exact test. The quality of life questionnaires were analyzed by the Wilcoxon signed rank test.

## Results

Demographics of the thirty patients (15 patients each in both the groups) enrolled in the study are shown in [Table/Fig 1], which indicates that incidence of NSCLC is less in females.

(Table/Fig 1) Patient Characteristics

| Group | DC | GC |
|---|---|---|
| Age in years | 50.53±11.53 | 56.60±6.95 |
| Sex<br>Male<br>female | 13(86.7%)<br>2(13.3%) | 12(80.0%)<br>3(20%) |
| Histology<br>Adenocarcinoma<br>Bronchocarcinoma<br>Epidermal carcinoma | <br>10(66.7%)<br>5(33.3%)<br>- | <br>8 (53.3%)<br>6 (40.0%)<br>1 (6.7%) |
| Performance status (WHO)<br>0<br>1<br>2 | <br>6(40.0)<br>7(46.7)<br>2(13.3%) | <br>8 (53.3%)<br>6 (40.0%)<br>1 (6.7%) |
| Tumour stage<br>IIIB<br>IVB | <br>8(53.3%)<br>7(46.6%) | <br>7 (46.6%)<br>8(53.3%) |

## Toxicity

As shown in [Table/Fig 2a] and [Table/Fig 2b], incidence of anaemia was statistically significant (P=0.065) in patients treated with the DC combination as compared to patients treated with the GC combination. Incidence of neutropenia, leucopenia, nausea/vomiting and alopecia, was higher in patients treated with the GC combination than in those treated with the DC combination, while incidence of thrombocytopenia and diarrohoea was slightly higher in patients treated with DC combination.

(Table/Fig 2a) Comparison of haematological toxicity in patients treated with DC and GC regimen.

| Parameters | DC-Group | GC-Group | P value |
|---|---|---|---|
| Anaemia | 12.34±2.15 (6.90-14.20) | 10.47±3.09 (6.10-14.20) | 0.065 |
| Neutropenia | 1.98±1.05 (0.40-3.40) | 2.23±1.09 (0.60-3.40) | 0.535 |
| Leucopenia | 2.74±0.69 (0.40-3.60) | 2.86±0.62 (0.90-3.80) | 0.626 |
| Thrombocytopenia | 2.62±0.45 (1.79-3.20) | 2.54±0.72 (0.90-3.80) | 0.717 |

(Table/Fig 2b) Comparison of Nonhaematological toxicities in patients treated with DC and GC regimen.

| Complications | DC-Group | GC-Group | P value |
|---|---|---|---|
| Nausea and Vomitting | 7 (46.7%) | 10 (66.7%) | 0.269 |
| Diarrhea | 9 (60.0%) | 6 (40.0%) | 0.273 |
| Alopecia | 11 (73.3%) | 13 (86.7%) | 0.651 |
| Total | 15 | 15 | - |

## Response

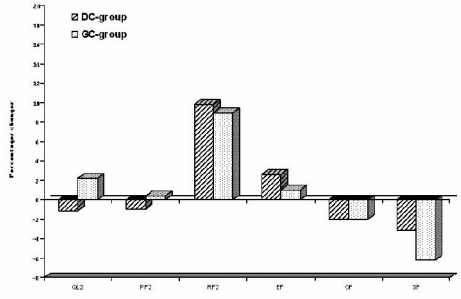
As shown in [Table/Fig 3], incidence of partial response and progressive disease was seen more in the GC group, and the incidence of stable disease was more in the DC group. On comparison of the tumour size pre and post chemotherapy, no significant difference was seen between the DC group (P= 0.078) and the GC group (P=0.070)

**(Table/Fig 3) Comparison of tumour response in patients treated with DC and GC regimen.**

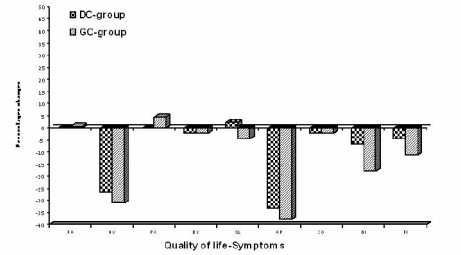
| Tumor response | DC-Group | GC-Group |
|---|---|---|
| Progressive | 3 (20.0%) | 2 (13.3%) |
| Partial | 3 (20.0%) | 5 (33.3%) |
| Stable | 9 (60.0%) | 8 (53.3%) |
| Total | 15 | 15 |

## QOL

As shown in [Table/Fig 4]and[Table/Fig 5], the functional scale of patients treated with the DC combination showed a decline in the physical and social functioning, while the patients treated with GC combination showed a decline in role, emotional and cognitive functioning.

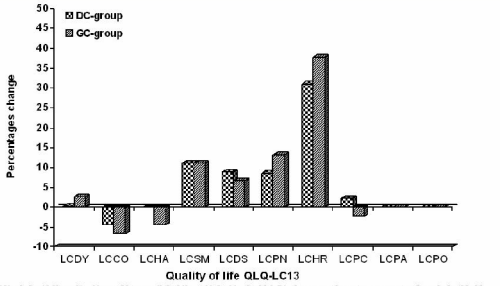



**(Table/Fig 4 ) Quality of Life (Global and Functional) in patients treated with DC and GC regimen.**




**(Table/Fig 5) Quality of Life (Symptoms) in patients treated with DC and GC regimen.**

When the symptom scales of patients were assessed using the EORTC QLQ-LC13 questionnaire, it was found that incidence of dysphagia and peripheral neuropathy was significantly more in the patients treated with the DC combination. The incidence of alopecia significantly increased in the patients treated with the GC combination as seen in [Table/Fig 6] .




**(Table/Fig 6) Quality of Life (QLQ-LC13) in patients treated with DC and GC regimen.**

## Discussion

New strategies are required in the treatment of NSCLC for clinically significant progress. The emergence of new generations of chemotherapeutic agents with anticancer activity in NSCLC, has generated interest in the development of platinum based treatment regimens. Various studies have substantiated the combined use of Docetaxel-Carboplatin and Gemcitabine-Carboplatin [8],[9].

The present clinical study indicates a higher incidence of NSCLC in males. This may be due to various reasons like smoking, occupational hazards etc. The toxicity profiles of the DC and GC regimens are similar. Patients treated with the DC regimen showed a higher incidence of anemia, whereas nausea/vomiting was severe in the patients treated with the GC arm. These toxicities may be due to the platinum based drug, Carboplatin, as indicated by a randomized study [10] conducted by some scientist, earlier. It is also reported that carboplatin-based chemotherapy develops the risk of grade 3 or 4 thrombocytopenia, anemia, neutropenia and neurotoxicity [11].

## QOL

Platinum based chemotherapy regimens are the standard treatment for patients with NSCLC. The present clinical study is the first of its kind, which attempts to assess the QOL of NSCLC patients treated with the

GC and DC combination regimens using EORTC guidelines. The results showed that there was no significant improvement in the quality of life of patients treated with either regimen. The incidence of alopecia was significantly increased in the patients treated with the GC regimen, and the incidence of dysphagia and peripheral neuropathy was significant in the patients treated with the DC regimen. There was no significant advantage of either of the treatment arm over the other, but for cost effectiveness.

## Cost Effectiveness of the Treatment

The cost of the GC combination treatment regimen for a patient of NSCLC for three treatment cycles is in the range of Rs. 45,500-66,780. The cost of the DC combination treatment regimen for a patient of NSCLC after three treatment cycles is about of Rs. 43,500. It is evident that from the patient's point of view, the DC combination treatment regimen is cost effective. Also, it is interesting to note that there is no significant advantage of the gemcitabine treatment over the docetaxel treatment regimen [12].

## Conclusion

Both the DC and GC combination regimens are effective in the treatment of NSCLC. The toxicities due to both drug combinations are similar. The global quality of health is not improved by either combination.

From the patient's point of view, the DC combination treatment regimen is cost effective.

## Limitation of the Study

Because of the short term nature of study, survival rate, time to progressive disease and response duration could not be evaluated. Emphasis was given to the tumour response, toxicity profiles and quality of life of the patients.

## Suggestion to Oncologists

Since the toxicity profile of the both the combinations is the same, and the DC combination being cost effective, it may be recommended that the DC (Docetaxel-Carboplatin) combination is a better treatment option as compared to the GC (Gemcitabine-Carboplatin) combination, to treat NSCLC.

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