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A PROSPECTIVE STUDY TO ASSESS THE TOXICITY PROFILE OF PACLITAXEL-CARBOPLATIN COMBINATION CHEMOTHERAPY IN ADVANCED NON SMALL CELL LUNG CANCER

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ABSTRACT
Systemic chemotherapy is the accepted standard of care for advanced NSCLC. Presently Cisplatin-Etoposide combination chemotherapy is most commonly used regimen for advanced NSCLC. Of late Paclitaxel-carboplatin combination has emerged as an encouraging regimen, with overall improvement in quality of life and modest survival advantage. Therefore the present study is designed to evaluate the toxicity profile of Paclitaxel-carboplatin regimen in advanced NSCLC. **Aims**: To study the different types of toxicities seen in patients on Paclitaxel-carboplatin regimen, to assess the severity of toxicity by grading them according to the WORLD HEALTH ORGANISATION (WHO) toxicity grading. **Patients and Methods:** Fifty patients with chemotherapy-naive advanced NSCLC were enrolled between February 2008 and December 2009. Additional criteria included karnofsky performance status ≥60, and adequate organ function. Patients received Paclitaxel 175mg/sq m and Carboplatin AUC=6mg/ml min as intravenous infusion repeated every 21 days. Such 6 cycles were given. **Results**: The predominant toxicities were grade 1 myalgia(64%), Arthralgia(62%) and peripheral neuropathy(52%),.. Nausea was reported in (68%) and alopecia in (96%) of the cases among hematological toxicities, leucopoenia was present in (34%) of the patients. **Conclusion:** The most common toxicities observed were nausea, alopecia, arthralgia myalgia and peripheral neuropathy.

KEYWORDS: Paclitaxel-carboplatin, Non-Small Cell Lung Cancer, Toxicity.

INTRODUCTION
Lung cancer, the most common cause of cancer-related death in men and the second most common in women,[1,2] is responsible for 1.3 million deaths worldwide annually.[3] The 2 main types of lung cancer are small cell lung cancer (SCLC) and non-SCLC (NSCLC); NSCLC accounts for approximately 85% of all cases of lung cancer.[4]

Most lung cancers develop systemic metastases, which, at the time of presentation, are associated with a very high risk of widespread metastases. Approximately 40% of patients present with advanced NSCLC.[4] Chemotherapy therefore plays a significant role in the treatment of NSCLC in light of the high probability of systemic metastasis. Many studies conducted in the past two decades have demonstrated superiority of platinum based doublets regimen.[5,6]

Presently cisplatin and etoposide are most commonly used regimen for advanced and metastatic disease. A recent retrospective analysis of phase III studies conducted between 1973 and 1994 in patients with advanced NSCLC concluded that gains in response and survival were modest at best, even with regimens that showed promise in earlier phase studies.[7] The 'optimal regimen' being sought was not identified in the studies included in that analysis. Nevertheless, options for treatment of NSCLC expanded tremendously throughout the 1990s with the development of new agents such as the taxanes, gemcitabine, and vinorelbine.[8] In addition, carboplatin began to replace cisplatin as the platinum compound of choice in combination doublet regimens as it had equivalent efficacy with lower toxicity compared with cisplatin. The carboplatin–paclitaxel combination has emerged as an encouraging regimen, with overall improvement in quality of life and modest survival advantage.[9] Therefore the present study is designed to evaluate the toxicity profile of carboplatin-paclitaxel regimen.

MATERIALS AND METHODS
This was a Prospective observational study in the Department of Radiotherapy, Government Medical

college, Thiruvananthapuram. Patients with histologically or cytologically confirmed stage IIIB/IV NSCLC who were > 20 years at the time of diagnosis and had not previously received chemotherapy were recruited for the study. Patients were also required to have a karnofsky performance status ≥60.Those receiving another chemotherapy regimen, those with inadequate hematopoetic, hepatic and renal function, and pregnant ladies were excluded from the study. The study was approved by the institutional research board and human ethics committee. Patients were required to provide written informed consent prior to entering the study. The patients were subjected to a complete blood cell count, a differential count, routine chemistry measurements, chest radiography before treatment onset.

Treatment Schedule

Patients received Paclitaxel 175mg/sq m and Carboplatin AUC=6mg/ml min as intravenous infusion repeated every 21 days. Such 6 cycles were given. All patients were premedicated with dexamethasone (8 mg i.v.), ranitidine(50 mg i.v.) and pheniramine (50 mg orally) to prevent severe hypersensitivity reactions induced by paclitaxel. Antiemetic (Granisetron 2mg iv) was also given before starting chemotherapy**.**

Patients were administered the scheduled chemotherapy and were observed for the occurrence of immediate toxicities. The patients were followed up during repeat visits and were assessed to detect the development of any toxicity during the course of chemotherapy and review visits on the 10^{th} day. All the toxicities that have occurred were recorded in the proforma sheet and graded according to the WHO guidelines.

Data analysis was done with the help of Excel 2007. The toxicity grades were entered in the Excel 2007 worksheet for each variable. The highest toxicity during any cycle was considered as the toxicity grade for that patient.

WHO grades toxicities into 4 grades (grade 0 to grade 4). Grade 0 represented absence of the toxicity and grade 4 is the maximum toxicity that can occur for a variable except alopecia where grade 2 is the highest toxicity (complete hair loss).

RESULTS

A total of 50 patients of histologically proven advanced Non Small Cell Lung Cancer, were studied. All the patients recruited for the study were males with Karnofsky performance status ≥60. The age range of patients (table 1) included in the study were between 45 and 70 with a mean age of 57 years. The maximum number of patients were in the age group of 56-65 years

Table 1: Age wise distribution of patients.

Age Group	Paclitaxel+Carboplatin n=50
35-45	2 (4%)
46-55	15 (30%)
56-65	29 (58%)
>66	4(8%)

Table 2: Treatment related toxicities (graded according to WHO toxicity grading).

	Grade 1	Grade 2	Grade 3	Grade 4	Aggregate toxicity
Toxicity					
Anemia	5 (10%)	1 (2%)	0	0	6(12%)
Leucopenia	11(12%)	5 (2%)	1 (2%)	0	17(34%)
Thrombocytopenia	6 (12%)	1 (2%)	0	0	7(14%)
Nausea	22 (44%)	12 (24%)		0	34(68%)
Vomiting	9(18%)	0	0	0	9(18%)
Stomatitis	6(12%)	0	0	0	6(12%)
Diarrhea	1(2%)	0	0	0	1(2%)
Alopecia	9(18%)	39 (78%)	0	0	48(96%)
Myalgia	32(64%)	0	0	0	32(64%)
Arthralgia	31(62%)	0	0	0	31(62%)
Per. Neuropathy	26(52%)	0	0	0	26(52%)

The most common toxicities encountered were arthralgia(62%) myalgia(64%) and peripheral neuropathy(52%), nausea(68%) and alopecia (96%) as listed in table 2.

Among Hematologic toxicities, leucopenia developed in 17 out of 50 patients enrolled for the study. A Majority of patients experienced grade 1 leucopenia. Furthermore only 7 patients developed Thrombocytopenia and anemia was seen in only 6 patients.

Nausea and Vomiting were most distressing symptomatic toxicities. 34 patients on Paclitaxel+Carboplatin regimen developed nausea and majority of them had grade 1 nausea whereas grade 1 vomiting was seen only in 9 patients. (96%) patients in the study developed complete alopecia during the course of chemotherapy.

The occurrence of other side effects was less common. Only 2 patients developed stomatitis, 4 patients developed grade 1 diarrhea. Myalgia of grade 1 was

experienced by six patients. Arthralgia and neuropathy developed in 3 patients each.

DISCUSSION

This study was undertaken to understand the toxicity profile of carboplatin–paclitaxel regimen used for chemotherapy in advanced Non Small Cell Lung Cancer. All the patients included in the study were males. The median age of patients was 57 years in both the regimens. Adverse events reported during the study were graded using WHO Toxicity criteria. Of 50 patients receiving Paclitaxel+Carboplatin, 49 patients (98%) experienced at least one adverse event during the course of chemotherapy.

The most prevalent toxicities were musculoskeletal in nature. Most patients in the study experienced grade 1 Myalgia and Arthralgia(>60%). These findings are consistent with study done by R.Rosell et al[10] in which 62% of patients on Paclitaxel+Carboplatin chemotherapy developed myalgia and arthralgia.

Peripheral neuropathy was a significant adverse effect of Paclitaxel+Carboplatin regimen developing in 52% of patients These findings are consistent with studies by C.P. Belani et al[9] which showed higher occurrence of grade 3 or 4 neurosensory adverse effects (20.7%) in taxane containing regimen. In another study done by R. Rosell et al,[10] the incidence of peripheral neuropathy was 59% in Paclitaxel+Carboplatin arm.

Among hematological toxicities, leucopenia developed in 34% of the patients but among them grade 3 leucopenia was seen only in 2% of the patients receiving Carboplatin-paclitaxel regimen. Thrombocytopenia(14%) and anemia(12%) were infrequent. These findings are consistent with the previous studies. In a study done by Karen Kelly et al,[11] leucopenia (31%) was more commonly reported than anemia (13%) and thrombocytopenia (10%) in patients receiving Paclitaxel+Carboplatin chemotherapy. In a study done by C.P. Belani et al,[9] occurence of neutropenia (30.3%) was more common than Anemia(7.9%) and thrombocytopenia(8%).

Different gastrointestinal adverse effects like nausea, vomiting, stomatitis and diarrhea were studied. patients developed more nausea (68%) and vomiting (18%). Stomatitis(12%) and diarrhea(2%) were very infrequent. In a study done by Karen Kelly et al,[11] grade 3 or 4 nausea and vomiting was only 7% and 4% respectively in patients receiving Paclitaxel+Carboplatin chemotherapy.

96% patients on Paclitaxel+Carboplatin regimen developed alopecia. In the study by Ashutosh Kumar Pathak et al,[12] alopecia was seen in all patients receiving Paclitaxel+Carboplatin regimen.

The occurrence of other side effects was less common in our study, this was consistent with findings of previous studies done by C.P. Belani et al,[9] and R. Rosell et al.[9]

CONCLUSION

This study was undertaken to assess the toxicity profile of Paclitaxel-Carboplatin regimen in advanced non small cell lung cancer. The most prevalent toxicities observed were arthralgia, myalgia, peripheral neuropathy, nausea and alopecia. Most of the data obtained in the study were consistent with the data available in the literature. The small differences between this data and the Western data could be due to the ethnic differences and needs to be evaluated. A drawback of the study is the small sample size. By increasing the sample size and the duration of the study the comparison of the toxicity profile, tolerability and survival rate can be assessed with a better possible outcome. Nevertheless this study will enable proper selection of the patients for undergoing chemotherapy with Paclitaxel-Carboplatin regimen as well as adequate implementation of countermeasures to avoid development of toxicities during the chemotherapeutic cycles.

DECLARATIONS

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REFERENCES

1. World Health Organization (2004). "Annex Table 2: Deaths by cause, sex and mortality stratum in WHO regions, estimates for 2002". The world health report 2004. Available at http:// www.who.int/whr/2004/annex/topic/en/annex_2_en. pdf. Accessed 29 May 2014.
2. American Cancer Society. Cancer Facts and Figures 2009. Atlanta: American Cancer Society; 2009. Available at http://www.cancer.org/Research/CancerFactsFigures /CurrentCancerFactsFigures /500809web-pdf. Accessed 29 May 2014.
3. Ferlay J. Cancer Incidence, Mortality and Prevalence Worldwide. Ann Oncol 2005; 16(3):481-88.
4. Alberg AJ, Brock MV, Samet JM. Epidemiology of lung cancer: looking to the future. J Clin Oncol 2005;23:3175-85.
5. Ramalingam S, Belani C. Systemic chemotherapy for advanced non-small cell lung cancer: recent advances and future directions. Oncologist. 2008;13:5–13.
6. Lilenbaum RC, Herndon J, List M. Single-agent (SA) versus combination chemotherapy (CC) in advanced non-small cell lung cancer (NSCLC): a CALGB randomized trial of efficacy, quality of life (QOL), and cost-effectiveness. Proc Am Soc Clin Oncol 2002; 21: 1-2.

7. Breathnach OS, Freidlin B, Conley B. Twenty-two years of phase III trial for patients with advanced non-small cell lung cancer: sobering results. J Clin Oncol 2001; 19: 1734–42.
8. Gunderson L, Tepper JE. Clinical Radiation Oncology. In: Bergman B, editors. Lung cancer management. 2nd ed. Philadelphia: Elsevier Churchill Livingston Publishers, 2007:827-949.
9. C. P. Belani, J. S. Lee, M. A. Socinski. Randomized phase III trial comparing cisplatin–etoposide to carboplatin–paclitaxel in advanced or metastatic non-small cell lung cancer. Ann Oncol 2005; 16: 1069–75.
10. R. Rosell, U. Gatzemeier, D. C. Betticher, U. Keppler, H. N. Macha, R. Pirker. Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: A cooperative multinational trial. Ann Oncol 2002; 13:1539-49.
11. Karen Kelly, John Crowley. Randomized Phase III Trial of Paclitaxel Plus Carboplatin Versus Vinorelbine Plus Cisplatin in the Treatment of Patients With Advanced Non–Small-Cell Lung Cancer: A Southwest Oncology Group Trial. J Clin Oncol 2001; 19:3210-18.
12. Ashutosh Kumar Pathak, Manisha Bhutani. Chemotherapy Alone *vs.* Chemotherapy Plus High Dose Multiple Antioxidants in Patients with Advanced Non Small Cell Lung Cancer. J Am Coll Nutr 2005; 24: 16-21.