ORIGINAL ARTICLE

TOXICITY PROFILE OF CARBOPLATIN / VINORELBINE COMBINATION CHEMOTHERAPY IN PATIENTS WITH ADVANCED NON SMALL CELL LUNG CANCER: A LOCAL EXPERIENCE

Shakeel Amanullah[1] ; Narjis Muzaffar [2]

[1]Darul Sehat Hospital and [2]Sindh Institute of Urology and Transplantation. Karachi

Correspondence to:

Dr. Shakeel Amanullah
Darul Sehat Hospital,
Gulistan-e-Johar, Karachi.

ABSTRACT:

Objective:
To evaluate the toxicity, response and survival of the chemotherapeutic combination of Vinorelbine / Carboplatin.

Design:
A prospective, non randomized and open label study in patients with stage IIIB/IV non-small cell lung cancer (NSCLC)

Patients and Methods:
Twenty patient (16 male, 4 female) with a mean age of 60.7 years ± SD. 7.2 (range 47-73) and ECOG performance status of 0-2 were enrolled into the trial. Eight patients had stage IIIB and 12 had stage IV NSCLC. Vinorelbine 30 mg /m^2 diluted in 50 cc of normal saline was given as i/v slow push. Carboplatin 400 mg/m^2 diluted in 200 CC of dextrose water was administered in 1 hour. Cycles were repeated every twenty one days.

Results:
One patient had a complete response, 8 had partial response (an overall response rate of 45%); 5 patients had stable disease and 6 were considered as treatment failures. Median survival was 6 months and overall survival was 7.3 ± SD 4.5 months. Mean duration of response in responding patients was 7.1 months and time to progression was 6.9 ± SD 4.9 months.
One patient experienced febrile neutropenia requiring hospitalization and one patient developed prolonged thrombocytopenia. Other than two adverse events, no remarkable toxicity was observed. There were no treatment related deaths.

Conclusion:
It appears that carboplatin/ vinorelbine combination chemotherapy has an acceptable toxicity profile with good tolerance.

INTRODUCTION

Lung cancer is the leading cause of cancer mortality in men and women accounting for an estimated 155,000deaths in the United States in 2003. Whereas lung cancer accounted for only 3% of all cancer deaths in women in 1950, in the year 2000, it accounted for an estimated 25% of cancer deaths. The average annual age-adjusted mortality rate per 100,000 (standardized to the 2000 US population) during 1992-2000 was 82.4 in men, and 40.2 in women. In the year 2000 nearly 27,000 more women died of lung cancer (67,600) than of breast cancer (40,800). 84% of all lung cancers is non small cell lung cancer [1, 2, 3].

The natural history of metastatic NSCLC is poor at best. The median survival is approximately 4 months, and only 10% of patients can be expected to be alive at 1 year[4, 5]. Several randomized studies in the late 1980s to early 1990s compared different chemotherapy regimens to best supportive care with mixed results [5-16].

Meta-analyses in the mid-1990s demonstrated a statistically significant benefit in survival with older chemotherapy regimens compared to best supportive care, although this benefit was modest at best. The mean potential gain in survival was only approximately 6 weeks, or 10% improvement in 1-year survival [4, 17-19]. In one meta-analysis, the only drug associated with an improved survival compared to best supportive care was cisplatin, whereas alkylating agents actually showed a detrimental effect compared to best supportive care [4]. An analysis of survival determinants in more than 2,500 patients with advanced NSCLC also found that the use of cisplatin was an independent predictor of improved out come [20]. Hence, platin has become the standard agent used in most modern chemotherapy regimens.

Based on clinical data demonstrating the survival advantage of chemotherapy over supportive care, the American Society of Clinical Oncology's (ASCO) clinical guidelines recognize that chemotherapy can prolong the survival of advanced NSCLC patients and is appropriate for those with good performance status, ECOG of 0-1 [21]. A subset analysis of a recent Cancer and Leukemia Group B (CALGB) trial suggested that patients with a performance status (PS) of 2 may also derive a benefit from chemotherapy[22].

Approximately 40% of NSCLC patients present with advanced or metastatic disease and are not candidates for potentially curative treatments; therefore management of these patients focuses on prolonging survival without compromising quality of life. Treatment decisions for patients with advanced NSCLC are determined by a variety of factors including performance status and the presence or absence of co-morbid illness. Systemic therapy is the only treatment modality proven to increase survival, decrease symptoms and improve quality of life among patients with advanced stage NSCLC [5]. During the 1990s several novel cytotoxic drugs such as docetaxel, paclitaxel, vinorelbine, gemcitabine and irinotecan were shown to exhibit impressive single agent activity in patients with advanced NSCLC, leading to evaluation of combination chemotherapy regimens consisting of a platinum compound and a cytotoxic agent [23], the combination regimens proved superior to therapy with cisplatin alone in randomized clinical trials for advanced NSCLC [24-28]. The drugs evaluated in combination with cisplatin or carboplatin included paclitaxel, vinorelbine, gemcitabine, and irinotecan. Doublet combination with a

platinum compound and a third generation cytotoxic agent have been accepted as "standard of care" for patients with advanced NSCLC. The platin combinations are associated with response rates of 30-40% and median survival of 8-11 months for advanced NSCLC patients with good performance status[5]. Docetaxel is the only agent that is approved for first – and second line therapy of NSCLC.

Chemotherapy has over the years shown to improve survival and exert beneficial effect on quality of life. However, it is not without toxic effects. Cisplatin is ematogenic, causes myelosuppression, alopecia, is ototoxic, highly nephrotoxic and causes peripheral neuropathy. Carboplatin, though less toxic, causes myelosuppression particularly thrombocytopenia. Vinorelbine is severely myelosuppressive.

OBJECTIVE

In this study we evaluated the toxicity profile of vinorelbine / carboplatin combination chemotherapy in advanced non-small cell lung cancer in addition to response and survival.

MATERIAL AND METHODS

Inclusion Criteria:

1. Histologic/ cytologic diagnosis of stage III-b and IV NSCLC,
2. No prior chemotherapy.
3. Bi-dimensionally, radiologically measurable disease.
4. Performance status of 0-2 (able to care for self and spend more than 50% of time out of bed) (Appendix II).
5. WBC > 3.5 x 10^9 / L; HB > 9.0 g/dl; Platelets > 1, 00,000 x 10^9 / L
6. Patients between 40 years to 75 years of both sexes.

Exclusion criteria:

1. Clinical / Radiological evidence of central nervous system disease or metastases.
2. Serum Bilirubin > 2 times the upper limit of normal; ALT & AST > 3 times the upper limit of normal.
3. Prior radiotherapy, if radiated area is the only source of measurable disease.
4. Serum creatinine > 1.5 mg / dl
5. Pregnancy
6. Breast feeding
7. Second primary malignancy

Study Design:

Prospective, non-randomized, open-level trial. 20 eligible patients were enrolled in study at Department of Oncology, Ziauddin University. Informed consent was obtained after explaining survival benefit, toxicity and expected life span.

Complete history, physical examination, laboratory and radiology work-up was done.

Patients were placed on combination chemotherapy using. Navelbine 30 mg / m^2 and Carboplatin 400 mg/m^2. Cycles were repeated every 21 days and maximum of 6 cycles

were administered. Blood counts were obtained at least 2 days before commencement of every cycle. CXR, PA view was obtained before the beginning of third cycle. LFTs and serum creatinine was monitored regularly and serum creatinine was done before the beginning of every cycle. Radiological response was judged after 2 cycles.
An effective contact was maintained with them for the entire duration of chemotherapy. Any patient showing progressive disease during chemotherapy was taken off the study. At the end of the treatment, patients were followed every four weeks in the clinic with the appropriate radiological and laboratory investigations. During follow up any clinical or radiological signs of progression of disease signaled the end point for the particular patient for the purpose of study. Toxicity profile was maintained in flow charts according to WHO toxicity criteria.

Data Analysis:

Initial findings and subsequent results were prospectively recorded in specially-designed forms. Data was analyzed by the Medical Statistician and analysis was done on Epi info system.

RESULTS

Twenty patients (16 males, 4 females) were enrolled within the strict guidelines of inclusion and exclusion criteria. The mean age was 60.7 years ± SD. 7.2 (range 47-73). Six patients had ECOG performance status of 0; ten patients had performance status of 1 and four patients had performance status of 2. Histology was squamous cell carcinoma (7), adenocarcinoma (6), while the remaining being large cell and undifferentiated carcinoma. The major metastatic site was bones (8). Eight patients had stage IIIB and 12 had stage IV NSCLC.
All patients received at least two cycles of chemotherapy with an average of 4.7 cycles of chemotherapy were delivered per patient.
One patient had a complete response and 8 had a partial response for an overall response rate of 45%. Five patients had stable disease and 6 were considered as treatment failures. At the time of closure of study twelve patients had died; five responders were alive in addition to 1 with stable disease and 2 with progressive disease at the time of closure of study. Median survival was 6 months and overall survival was 7.3 ± SD 4.5 months. Mean duration of response in responding patients was 7.1 months and time to progression was 6.9 ± SD 4.9 months.
One patient experienced febrile neutropenia requiring hospitalization after first cycle his dose was reduced by 25% for the second cycle. However, he developed febrile neutropenia even then and had to receive i/v antibiotics in house. Unfortunately he had progressive disease and died before the commencement of third cycle and can be term as treatment failure. One patient developed prolonged thrombocytopenia resulting in delay of at least one week for every of cycle of chemotherapy. She had to be taken of study after five cycles due to extremely late recovery i.e. more than two weeks for her platelet levels to recover. Four patients developed generalized weakness and five patients developed alopecia.

Table 1: Clinical characteristics of evaluable patients

Total No. of patients	20	Sites of involvement :	
Mean age in years	60.7 ± 7.2	Contra lateral lung	3
Male	16	Supraclavicular lymph node	2
Female	4	Mediastinal lymph node	8
Weight loss	9	Liver mets	2
ECOG performance status		Bone	8
0	6	Adrenals	2
1	10	Others	2
2	4		
Histological diagnosis		Stage of disease	
Adenocarcinoma	6	III B	8
Squamous cell	7	IV	12
large cell	4		
Undifferentiated	3		

Table 2: Response to therapy and survival

Total No. of Chemotherapy cycles	94
Mean number of chemo cycles	4.7
Response	
CR	1
PR	8
SD	5
NR	6
Overall response	45%
Mean duration of response in responding patients	7.1 months

Table 3: Clinical characteristics of evaluable patients

Status at the time of closure of study:	
Alive in remission	5
Alive with SD	1
Alive with PD	2
Dead	12
Overall survival	7.3 ± 4.5 months
Meantime to progression (TTP)	6.9 ± 4.9 months
Median survival	6 months

Table 4: Toxicity profile	Grade
WHO toxicity grading	3-4
Fatigue	4
Neutropenia (without fever)	5
Febrile Neutropenia	1
Alopecia (Grade 1 -2)	5
Prolonged thrombocytopenia	1

Discussion

The study was carried out from August 1996 to March 1999. During the period twenty eligible patients could be enrolled in the study. Of the twenty patients 16 were males and 4 were females. Interestingly all the 4 females were non smokers however their husbands were heavy smokers.

The accrual was slow; the primary reason being that potential patients remained with their primary physicians getting treated for pulmonary conditions like tuberculosis and pneumonia and, therefore, were diagnosed late for NSCLC; the other reason being that patients with diagnosed NSCLC preferred to seek unconventional methods of treatment like Homeopathy and Hikmat. As such, their performance status dropped below the study inclusion criteria and hence a sizeable number of patients were not eligible to be enrolled in the study.

The number of evaluable patient may seem small, but patients with performance status 0-2 comprise a very small percentage in patients with advanced NSCLC. Furthermore, recent North American and European studies have reported their results on similar number of patients[24].

There have been similar reports of toxicities in Vinorelbine and platin based chemotherapy studies. Kelly et-al[29] observed that grade 3 and 4 toxicities occurred in at least 5% of the study patients. One hundred and ninety seven patients on Cisplatin / Vinorelbine and 203 patients on Carboplatin / Paclitaxel were studied for toxicity. More patients in former group had grade 3 or 4 leucopoenia, nausea and vomiting and grade 3 or 4 infections; the latter group had more of peripheral neuropathy cases. Number of toxic deaths was 8 and 5 respectively.

Fossella and co-workers[30] compared Docetaxel-platinum combinations with Vinorelbine-Cisplatin. They observed that fewer patients in the former groups experienced grade 3 to 4 adverse events compared with the latter. No differences were seen among the three treatment groups with regard to grade 3 to 4 neutropenia, thrombocytopenia, or infection. More patients in Vinorelbine-Cisplatin group experienced anaemia, nausea or vomiting, hospitalization and discontinuation due to adverse events; whereas diarrhoea, oedema, nail disorders, hypersensitivity reactions and alopecia were reported more frequently in the Docetaxel-platinum combination groups.

In the Japanese Taxotere Lung Cancer Study[31], haematologic toxicities, anaemia, and leucopoenia were significantly more severe among patients receiving Vindisine/ cisplatin compared with those receiving Docetaxel/ Cisplatin ($P<.011$). However, the incidences of GI related adverse effects were commoner in latter group.

Among our patients, a total of 94 chemotherapy cycles were delivered. Mean number of chemotherapy cycles was 4.7. The duration of response was calculated from the time first sign of remission was noticed radiologically. All the responders achieved response between second and third cycle. Survival calculated from the date of start of chemotherapy.

Toxicity profile turned out to be encouraging. One patient suffered febrile neutropenia after the first cycle requiring hospitalization and i/v antibiotics. Five patients had

neutropenia without fever. His dose was reduced by 25% for the second cycle. However, he again developed febrile neutropenia from which he recovered. He was planned to be placed on growth factors. However, before the commencement of the third cycle, on evaluation he turned out to have rapidly progressive disease. He was taken off study and was sent for palliative radiotherapy. Unfortunately, he died of progressive disease before radiotherapy could be started.

One female patient had delayed recovery from thrombocytopenia, which delayed her chemotherapy cycles by one week. However, no dose reduction was done. After fifth cycle, her thrombocytopenia persisted for six weeks before eventual recovery. She was also taken off study. None of the patients developed Vinca Alkaloid associated neuropathy. None of the patients developed phlebitis associated with Navelbine. Four patients developed generalized fatigue and five patients developed alopecia.

Except for the patients with prolonged thrombocytopenia, all the responding patients and subjects with stable disease completed 6 cycles of chemotherapy delivered on scheduled time. There were no treatment related deaths.

Conclusion

Vinorelbine / Carboplatin combination chemotherapy appears to be an effective regimen for the treatment of advanced non-small cell lung cancer. It has a safe and acceptable toxicity profile. However, it cannot be designated as the standard of care for the treatment of advanced in NSCLC, as other regimens based on taxanes and gemcitabine have similar activity to Carboplatin / Navelbine combination. There is a need to focus on preventive aspect of Lung Cancer and need for development of newer and smarter drugs targeting the tumour at molecular level.

Declaration

No grant financial or otherwise was received from any source.

REFERENCE

1. Ries LAG, Kosary CL, Hankey BF, et al. SEER Cancer statistics Review 1975-2000. NIH Pub. No. 97-2789. Bethesda, MD: National Cancer Institute, 2003.
2. Jemal A, Chu KC, Tarone RE, Recent Trends in lung cancer mortality in the United States. J Natl Cancer Inst 2001; 93:277.
3. Shopland Dr, Eyre HJ, Pechacek TF. Smoking-attributable cancer mortality in 1991: is lung cancer now the leading cause of death among smokers in the United States. J Natl Cancer Inst 1991;83:1142.
4. Chemotherapy is non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 1995;311:899-909.
5. Rapp E, Pater J, Willan A, et al. Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer – Report of a Canadian multicenter randomized trial. J Clin Oncol 1988;6:633-641.
6. Woods RL, Williams CJ, Levi J, et al. A randomised trial of cisplatin and vindesine versus supportive care only in advanced non-small cell lung cancer. Br J Cancer 1990;61:608-611.
7. Cormier Y, Bergeron D, La forge J, et al. Benefits of polychemotherapy in advanced non-small-cell bronchogenic carcinoma. Cancer 1982;50:84-849.
8. Buccheri GF, Ferrigno D, Curcio A, et al. Continuation of chemotherapy versus supportive care alone in patients with inoperable non-small cell lung cancer and stable disease after two of three cycles of MACC. Results of a randomized prospective study. Cancer 1989;63:428-432.
9. Cellerino R, tummarello D, Guidi F, et al. A randomized trial of alternating chemotherapy versus best supportive care in advanced non-small-cell lung cancer. J Clin Oncol 1991;9:1453-1461.
10. Ganz PA, figlin RA, Haskell CM, et al. Supportive care versus supportive care and combination chemotherapy in metastatic non-small lung cancer. Does chemotherapy make a difference? Cancer 1989;63:1272-1278.
11. Kaasa S, Lund E, Thorud E, et al. Symptomatic treatment versus combination chemotherapy for patients with extensive non-small cell lung cancer. Cancer 1991;67:2443-2447.
12. Quoix E, dietemann A, Charbonneau J, et al. (Is chemotherapy with cisplatin useful in non small cell bronchial cancer at staging IV? Results of a randomized study). Bull Cancer 1991;78:341-346.
13. Cartei G, Cartie F, Cantone A, et al. Cisplatin-cyclophosphamide-mitomycin combination chemotherapy with supportive care versus supportive care alone for treatment of metastatic non-small-cell lung cancer. J Natl Cancer Inst 1993;85:794-800.
14. Thongprasert S, Sanguanmitra P, Juthapan W, et al. Relationship between quality of life and clinical outcomes in advanced non-small cell lung cancer: best supportive care (BSC) versus BSC plus chemotherapy. Lung Cancer 1999;24:17-24.
15. Cullen MH, Billingham LJ, Woodroffe CM, et al. Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. J Clin Oncol 1999;17:3188-3194.
16. Stephens R, Fairlamb D, Gower N. The big Lung Trial (BLT): determining the value of cisplatin-based chemotherapy for all patients with non-small cell lung cancer (NSCLC). Preliminary results in the supportive care setting. Proc Am Soc Clin Oncol 2002:21:291 (Abstract 1161).
17. Grilli R, Oxman A. Julian J. Chemotherapy for advanced non-small-cell lung cancer: how much benefit is enough? J Clin Oncol 1993;11:1866-1871.
18. Souquer PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non-small lung cancer: a meta-analysis. Lancet 1993;342:19-21.
19. Marino P Pampallona S, Preatoni A, et al. Chemotherapy vs supportive care in advanced non-small cell lung cancer: results of a meta-analysis of the literature. Chest 1994;106:861-865.
20. Albain KS, Crowley JJ, Le Blanc M, et al. Survival determinants in extensive –stage non-small-cell lung cancer: the southwest Oncology Group experience. J Clini Oncol 1991;9:1618-1626.
21. Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. Adopted on May 16, 1997 by the American Society of Clinical Oncology. J Clin Oncol 1997;15:2996-3018.

22. Lilenbaum R, 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;21:1a.
23. Ramalingam S, Belani CP. State-of-the-art chemotherapy for advanced non-small cell ung cancer. Semin Oncol 2004;31:68-74.
24. Kubota K, Watanabe K, Kunitoh H, et al. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer; the Japanese Taxotere Lung Cancer Study Group. J Clin Oncol 2004;22:254-61.
25. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 200321:3016-24.
26. Georgoulias V, papadakis E, Alexopoulos A, Et al. Platinum based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicentre trial. Lancet 2001;357:1478-84.
27. Fossella F, Belani CP: Phase III study (TAX 326) of docetaxel cisplatin and docetaxel-carboplatin versus vinorelbine cisplatin for the first-line treatment of advanced/metastatic non-small cell lung cancer: Analyses in elderly patients. Proc Am Soc Clin Oncol 2003;22:629. Abstract 2528.
28. Kubota K, Nishiwaki Y, Ohashi Y, et al. The four-Arm Cooperative study (FACS) for advanced non-small-cell lung cancer (NSCLC). J Clin Oncol 2004;22:618s. Abstract 7006.
29. Kelly K, Crowley J, Bunn PA, et al. Randomized phase 211 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;193210-3218.
30. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer; the TAX study group. J Clin Oncol 2003;21:3016-24.
31. Kubota K, Watanabe K, Kunitoh H, et al. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer study group. J Clin Oncol 2004;22:254-61.