ORIGINAL ARTICLE

A PILOT STUDY TO EVALUATE CARBOPLATIN / VINORELBIN COMBINATION CHEMOTHERAPY IN ADVANCED NON SMALL CELL LUNG CANCER

Shakeel Amanullah[1], Narjis Muzaffar [2], Imtiaz A. Malik[3].

ABSTRACT:

A pilot study in patients with stage IIIB/IV non-small cell lung cancer (NSCLC) was carried out to evaluate the clinical activity, survival and toxicity of the chemotherapeutic combination of Carboplatin + Vinorelbin. 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. Vinorelbin 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. 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. 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. It appears that Carboplatin/ Vinorelbin combination chemotherapy is an effective regimen for NSCLC with acceptable toxicity profile.

Keywords; NSCLC; Carboplatin; vinorelbine

Shakeel Amanullah[1]
Consultant Oncologist
Darul Sehat Hospital
Gulistan-e-Jauhar, Karachi

Narjis Muzaffar [2]
Consultant Oncologist
Department of Oncology
Ziauddin University, Karachi

Imtiaz A. Malik M.D.[3]
Consultant Oncologist
Dept. of Oncology
Loma Linda University, California, USA.

Correspondence:
Dr. Shakeel Amanullah
B-30, Block –N,
North Nazimabad,
Karachi.

INTRODUCTION

Lung cancer is the commonest cause of cancer death in United States [1]. Estimated incidence of lung cancer in the U.S. for 1996 is 1,77,000 cases and the estimated number of deaths is 1,58,700. Deaths from lung cancer have exceeded breast cancer deaths in females in U.S. since 1994 [2]. In a survey supported by Pakistan Medical Research Council in 1985, a review of 4277 male patients revealed that 12.7% had cancer of lung, making it the top most malignancy in the male population. These data were collected from four cancer registers based at Jinnah Postgraduate Medical Centre, Karachi; King Edward Medical College, Lahore; Liaquat Medical College, Jamshoro; Armed Forces Institute of Pathology, Rawalpindi. An update of the same study till 1992 has shown lung cancer to be the leading cancer in male population [3]. However, no population- based data to ascertain the present incidence of lung cancer in either male or female population of Pakistan are available. Major risk factor is cigarette smoking accounting for 75% to 80% of lung cancer mortality. Other risk factors include exposure to asbestos, radiation exposure, radon, dietary and genetic factors predisposition [4]. Non small cell lung cancer (NSCLC) comprises 2/3 of all lung cancers [5]. As the majority of patients present with locally advanced disease stage IIIa, stage IIIb, or stage IV disease, overall survival and prognosis is poor. Palliative therapy is often employed including use of cytotoxic therapy. Although single agent or combination chemotherapy produces modest response rates in NSCLC patients, no regimen has provided significant survival benefit or cure [6, 7]. Radiotherapy alone or followed by chemotherapy has again failed to show significant benefit [8, 9]. Five commonly employed single agents with the longest history of use in NSCLC (Clisplatin, Ifosfamide, Mitomycin, Vinblastine and Vindesine); generally give a 15% to 20 % response rate [10, 11]. These agents have demonstrated the best result in combination chemotherapy trials [12, 21].

Despite years of innumerable chemotherapy trials in advanced NSCLC, optimal regimen has not yet been identified[22]. Over the past couple of years FDA (USA) has approved number of new cytotoxic agents, which have shown significant activity as single agent in advanced NSCLC. Among them, Vinorelbine, (US patent number 4307100) a vinca alkaloid and tubulin inhibitor has shown 33% response rate as a single agent[23].

In Pakistan's perspective, there is a great need to define optimal treatment of NSCLC. As population-based tumour registries do not exist, it is not possible to ascertain exact facts and figures about NSCLC. In a pilot study conducted by Dr. Yasmeen A. Bhurguri it was learnt that 12.49% of the male patient registered during January 1995 – December 1996 were suffering from lung cancer making it the topmost malignancy in South of Karachi. However, it can be ascertained, keeping in view the large number of smokers in out society and tobacco companies investing heavily in marketing and advertising, that NSCLC is not only a major cause of cancer death, but also its incidence is going to rise in the coming years along with increase in number of deaths.

Keeping in view the above mentioned background, it is proposed that an effort should be made to define adequate treatment regimens for NSCLC.

Objectives:

1. To evaluate the response rates of Carboplatin / Vinorelbin combination chemotherapy and its impact on survival in patients with locally advanced and metastatic NSCLC.
2. To characterize the nature of toxicity according to WHO grading (Appendix I).
3. To evaluate time to progression and duration of response for responding patients.

MATERIAL AND METHODS

Study Design:

Prospective, non-randomized, open-label trial.

20 eligible patients were enrolled in study at Ziauddin Medical University, Cancer Hospital, and NCI Clifton, Karachi. Informed consent was obtained after explaining survival benefit, toxicity and expected life span. 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. The data was fed to the computer periodically for the analysis. EPI info package was used for analysis.

Inclusion Criteria:

1. Histologic/cytologic diagnosis of stage IIIb and IV NSCLC.
2. No prior chemotherapy.
3. Bi-dimensionally, radiologically measurable disease.
4. ECOG performance status of 0-2 (able to care for self and spend more than 50% of time out of bed) (Appendix II).
5. Adequate bone marrow reserve.
   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 CNS disease or metastases.
2. Abnormal LFT's
   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. Abnormal renal function.
   Serum creatinine > 1.5 mg / dl
5. Pregnancy

6. Breast feeding
7. Second primary malignancy

Twenty evaluable patients were enrolled after obtaining informed consent. Complete history, physical examination, laboratory and radiology work-up was done. 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].

Majority of clinical trials [11-21] have used Cisplatin in NSCLC. However, number of studies[25] have clearly demonstrated that there is very little difference in the efficacy of carboplatin, when compared with Cisplatin. Carboplatin is now being used instead of Cisplatin in ovarian [26] and head & neck cancers [27]. Carboplatin can be given as a 30 minutes infusion and it is less emetogenic and nephrotoxic than Cisplatin. Furthermore, it does not require extensive pre and post-chemo hydration, thereby needing a hospital stay of 3 hours compared to 4 days of Cisplatin.

The survival advantage gained by chemotherapy is usually around 5 months as evident from the review of literature [28-31].

Patients were placed on combination chemotherapy using. Vinorelbin 30 mg / m^2 and Carboplatin 400 mg/m^2. Cycles were repeated every 21 days and maximum of 6 cycles were administered. CBC was 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. Toxicity was recorded according to WHO grading and dose-modification were done accordingly. Patients showing radiological evidence of progressive disease were taken off the study. Response was judged as follows:

EVALUATION OF RESPONSE:

1. Complete response (CR)

Disappearance of all known disease determined by two observations not less than 4 weeks apart.

2. Partial Response (PR)

At least 50% decrease in tumour size of the target lesions by two observations not less than 4 weeks apart. In addition, there should not be appearance of any new lesions or progression of any previous lesion.

3. Progressive disease (PD)

Greater than 25% increase in the size of at least one measurable lesion or appearance of any new lesion.

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

In this study twenty patients (16 males, 4 females) were enrolled within the strict guidelines of inclusion and exclusion criteria. The mean age of study patients 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. Predominant histology was squamous cell carcinoma (7) followed by adenocarcinoma (6) with 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 termed 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. It appears that Carboplatin/ Vinorelbin combination chemotherapy is an effective regimen for NSCLC with acceptable toxicity profile.

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
Weakness	4
Febrile Neutropenia	1
Alopecia	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 themselves. 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.

Table 5 : Vinorelbin / cisplatin combination therapy for NSCLC

Author Country	Schedule (mg/m2)	Evaluable Patients	OR (%)	MS (months)	1YS (%)
DEPIERRE [32] France	NVB: 30/w CDDP*: 80 d1	116	43	7.7	34
LE CHEVALIER [33] International	NVB: 30/w CDDP: 120 d1, d29 then every 6 weeks	206	30	9.3	33
GIL DEZA [34] Argentina	NVB: 30/w CDDP: 80 d1	83	42	9.4	-
Wozniak [35] USA	NVB: 25/w CDDP: 100d1	206	26	8	36
BILACEROGLU [36] Turkey	NVB: 30 d1, d8 CDDP: d1 Q4w	70	41	8.5	-
MARTONI [37] Italy	NVB: 25 d1, d8 CDDP: 60 d1 Q3w	103	27	9.6	39
COMELLA [38] Italy	NVB: 30/w CDDP: 120 d1, d29 then every 6 weeks	60	25	8.1	34
GALETTA [39] Italy	NVB: 25 d1, d8 CDDP: 100 d1 Q4w	122	38	-	-
TAN [40] International	NVB: 25/w CDDP: 80d1	133	35	7	38
SCAGLIOTTI [41] Italy	NVB : 25/w CDDP: 100 d1	201	30	9.5	37
KELLY [42] USA	NVB: 25/w CDDP: 100d1	202	28	8.1	36

***** CDDP: Cisplatin

Table 6 : Carboplatin / Vinorelbin Combination Chemotherapy for NSCLC

Author Country	Schedule (mg/m2)	Evaluable Patients	OR (%)	MDR (months)	MS (months)	1YS (%)
MASOTTI [43] Italy	NVB: 25 d1 CBDCA*: 300 d1 Q4w	55	40	5	-	-
PRONZATO [44] Portugal	NVB: 25 d1, d8 CBDCA: 350 d1 Q4w	32	28	6	10	-
PARENTE [45] Portugal	NVB: 30 d1, d8 CBDCA: 300 d1 Q3w	75	45	7.2	7.9	-
SANTOMAGGIO [46] Italy	NVB: 30 d1, d8 CBDCA: 350 d1 Q4w	77	31	-	9.5	-
LENA [47] France	NVB: 30 d1, d8 CBDCA: 325 d1 Q3w	38	21	-	6.6	-
VINCENT [48] Canada	NVB: 25 d1, d8 CBDCA: AUC 6 Q3w	35	31	-	11	-
PARENTE* Portugal [49]	NVB: 30 d1, d8, d22 CBDCA: AUC 6 Q4w	41	45	11.7	6.7	-
VON [50] BULTZING-SLOWENGermany	NVB: 30 d1, d8, d22 CBDCA: AUC 5 Q3w	79	20	-	5.6	41
CREMONESI Italy [51]	NVB: 25 d1, d8, d8 CBDCA: 350 d1 Q3w	53	26	-	14.1	-

* CBDCA: Carboplatin

Table 7 : Selected Recent Phase III Randomized Trials in Advanced NSCLC

First Author (ref)	No. of Patients	Regimen	PS 0-1 (%)	Stage IV (%)	Male (%)	Cycles Planned (#)	Median of cycles delivered	RR (%)	Survival	
									Median (months)	1-year (%)
Lilenbaum [52]	561	P	82	72	68	6	4	17	6.7	33
		CbP					4	29	8.8	37
Kelly [53]	408	CV	100	88	70	6-10	3	28	8.1	36
		CbP					4	24	8.6	38
Schiller [54]	1207	CP	94	87	63	6	4	21	7.8	31
		CG					3	22	8.1	36
		CD					4	17	7.4	31
		CbP					4	17	8.1	34
Scagliatti [55]	607	CV	93	81	78	6	3	30	9.5	37
		CG					4	30	9.8	37
		CbP					4	32	9.9	43
Rodriguez [56]	1218	CV	96	68	73	6	4	NR	10	40
		CD					5	NR	10.9	46
		CbD					6	NR	9.1	38
Alberala [57]	562	CG	84	79		6	4	41	9.5	38
		CGV					4	40	8	33
		GV/IV					4	24	10.4	34
Van Meerbeck [58]	480	CP	88	80	67	6	5	31	8.1	36
		CG					5	36	8.8	33
		PG					4	27	6.9	27
Kubata [59]	311	C-VDS	97	100	66	> 2	2	21	9.6	41
		CD					3	37	11.4	48
Rosell [60]	618	CP	83	65	83	10	4	28	9.8	33
		CbP					4	25	8.2	33

Abbreviations: RR=response rate, CV=cisplatin/vinerolebine, CbP=carboplatin/ paclitaxel, CP=cisplatin/paclitaxel, CG=cisplatin/gemcitabine, CD=cisplatin/docetaxel, C-VDS=cisplatin/vindesine, P=paclitaxel, CbD=carboplatin/docetaxel, PG=paclitaxel / gemcitabine, CGV, cisplatin/gemcitabine/vinorelbine, GV/IV=gemcitabine/vinorelbine - ifosfamide/vinorelbine, NR=not reported.

* 10 cycles or treatment until progression was planned for responding patients.

Among the study 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. Of the twenty patients, one achieved complete response; eight achieved partial response, giving an overall response of 45%. All the 4 females achieved partial response. 5 patients had stable disease and 6 were non responders. Of the 9 responders, 8 received planned 6 cycles of chemotherapy. One patient had prolonged thrombocytopenia and her treatment had to be stopped after 5 cycles. All the 5 patients with stable disease received 6 cycles of chemotherapy. Of the non responders, 5 received 2 cycles each before they were taken off study. One non responder (presumptive) could received only 1 cycle, as he suffered pathological fracture of femur. . and he died probably due to fat embolism before the fracture could be surgically fixed. Among the responders, there was 1 non-cancer death — a female patient died of acute myocardial infarction after remaining in remission for 18 months.

Toxicity profile turned out to be encouraging. One patient suffered febrile neutropenia after the first cycle requiring hospitalization and i/v antibiotics. 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 Vinorelbin. Four patients developed generalized weakness and five patients developed alopecia.

The study had to be closed prematurely due to unavoidable circumstances*. At the time of closure of study 12 patients had died; five responders were alive in addition to 1 with stable disease and 2 with progressive disease. Median survival was 6 months and overall survival was 7.3 ± 4.5 months. Mean duration of response in responding patients was 7.1 months and time to progression was $6.9 \pm$ SD 4.9 months. Mean duration follow up and 1 year survival could not be calculated due to premature closure of the study.

Table 5 shows international studies[32-42] done with Cisplatin / Vinorelbin combination. The overall response in these studies ranged from 25% to 43%. Medial survival ranges from 7.7 months to 7 months. Compared to study under discussion, it matches the international studies in overall response. However, the results are inferior when comparison is made with median survival.

Table 6 shows international studies [43-51] done with Carboplatin Vinorelbin. The overall ranges from 21% to 45%. Mean duration of response ranges from 5 months to 11.7 months. Median survival ranges from 5.6 months to 14.1 months. It appears; that the study under discussion seems to be is comparable to other international studies.

Comparisons of Table-5[32-42] and Table-6 [43-51] suggest that Carboplatin and Cisplatin are almost equally efficacious. Moreover, Carboplatin can be given in day care setting; does not require hydration prior to and after the chemotherapy; has negligible ematogenic potential and is less nephrotoxic. As such, Carboplatin can be substituted in place of cisplatin in the management of advanced NSCLC.

Table 7 shows [52-60] abbreviated results from recent Phase III trials comprising various regimens currently in vogue. The overall responses in these trials range from 17% to 41% while median survival ranges 6.7 months to 10.9 months. It appears that the study under discussion is comparable to selected recent phase III trials.

The inferior median survival in this study may be attributed to the fact that study was closed while 8 patients were still alive 5 of them being in remission. Had those patients been followed till the eventual terminal events, the median survival would also have matched other international studies. Other attributable factor could be difference in the biology of our population compared to European and North American races, or the biology of the tumour. These questions could be addressed in a large randomized study.

*Institutional and administrative collapse of the group where study was being conducted. Study closure not related to treatment.

Conclusion

Carboplatin / Vinorelbin 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 / Vinorelbin 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

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