Original Article-I

A Retrospective Non-Randomized Comparative Analysis of Experience with two Cisplatin Based Regimens in First Line Combination Chemotherapy for Advanced Non-Small Cell Lung Cancer

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ABSTRACT

Background : **There is no single-standard treatment for locally advanced non-small cell lung cancer (NSCLC), but platinum based chemotherapy with one of the new generation agents is regarded as most effective for patients with good performance status. The purpose of this study is retrospective comparative analysis of response, toxicity and survival of two chemotherapy regimens containing cisplatin, combined with gemcitabine (GP) or vinorelbine (VP) in previously untreated patients with advanced NSCLC.**

Patient & Methods: **Between 1998-2001 60 patients (51 males and 9 females) with stage III B-IV NSCLC received chemotherapy. Fifty two patients (86.7%) presented with locally advanced (stage IIIB – 11 patients, 18.3%) or metastatic (stage IV – 41 patients, 68.4%), and 8 patients (13.3%) had metastases after previous radical surgery. The choice of chemotherapy regimen was a matter of distinction of treating physician. 31 patients received chemotherapy GP and 29 patients were treated with VP regimen. The groups were comparable in terms of age, performance state and stage of disease. Chemotherapy regimens consisted of either intravenous (i.v.) gemcitabine 1250 mg/m2 given over 30 minutes on days 1 and 8, and i.v. cisplatin 80 mg/m2 given over 2 hours on day 8, both repeated every 3 weeks, or i.v. vinorelbine 30 mg/m2 given over 10 minutes on days 1, 8 and 15 and i.v. cisplatin 80 mg/m2 given over 2 hours on day 1, both repeated every 4 weeks. Both regimens were planned to 6 cycles. Treatment was terminated in case of disease progression or unacceptable toxicity.**

All patients were evaluable for response and toxicity.

Results: **A total of 157 cycles of GP and 142 cycle of VP were given. Therapy was well-tolerated without any life threatening event.**

Grade III-IV toxicities for GP and VP regimens included vomiting in 0% vs 13.8 % , neutropenia in 29% vs 68% (p=0.007), neutropenic fever 0% vs 10.3%, thrombocytopenia in 9.7% vs 0%, anemia in 3.2% vs 13.7% and peripheral neuropathy 0% vs 6.8% of patients respectively. Thirty one per cent of patients who received VP developed chemical phlebitis, that ultimated insertion of central venous access device.

No complete responses (CR) were documented. Partial response (PR) was

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achieved in 29% of patients who received GP as compared with 20.7% of those treated with VP, the disease remained stable (SD) in 32.3% and 31% of patients respectively.. There were no statistically significant difference in survival between GP and VP groups. The median progression free survival was 7 months vs 4 months, the median survival was 12.5 vs 8.3 months and one-year survival was 53% vs 45% respectively.

Conclusions: **To our experience, chemotherapy GP and VP for advanced NSCLC were both well tolerated. Though the rate of neutropenia was significantly higher in VP group, it wasn't life threatening. Response and survival analysis reveals no statistically significant difference between two regimens, that correspond with data reported in the literature. Both GP and VP regimens may be used as a standard of care for advanced NSCLC.**

INTRODUCTION

Lung cancer continues to be the leading cause of cancer-related deaths in the western world.[1] Approximately 75% to 80% of cases are of non-small cell histology.

At the time of initial diagnosis, almost 50% of patients with NSCLC have clinically detectable metastases outside the thorax and another 10-15% have locally advanced unresectable tumours. In addition, more than 50% of patients who undergo surgery recur with either localized unresectable tumour or extrathoracic dissemination.[2]

The prognosis for these patients is poor and the goals of therapy are palliation of symptoms and prolongation of survival. For many years, the treatment of NSCLC with cytotoxic agents remained controversial, given the unclear impact on patients survival. Support of treating patients with NSCLC came from an international collaborative meta-analysis of 52 randomized trials , which revealed clear advantage of platinum based chemotherapy over best supportive care in terms of survival.[3] Patients treated with cisplatin-containing regimens demonstrated a 27% reduction in the risk of death, that was equivalent to an absolute improvement in survival of 10% at 1 year with a modest improvement in median survival of 1.5 months. During the past decade, a number of new active agents like taxanes, gemcitabine, vinorelbine and irinotecan have been found to be effective against NSCLC. Those drugs combined with platinum analogues were investigated as first line chemotherapy of advanced NSCLC. Randomized controlled trials showed significant improvement in response and survival in patients treated with novel agents combined with cisplatin as compared with standard platinum based regimens.[4-8] The regimens, consisting of cisplatin with either gemcitabine, taxanes or vinorelbine were equally efficient and well-tolerated with slight differences in toxicity profiles.[9-11]

We here present retrospective comparative analysis of our single-institution experience with GP and VP in first line chemotherapy for advanced NSCLC.

PATIENTS AND METHODS

Sixty patients (51 males and 9 females) with histologically confirmed advanced NSCLC received first line chemotherapy GP or VP in 1998 - 2001.

Patients characteristics are shown in table 1. There was slight predominance of male patients in GP group (90.3%), compared with

Table 1. Patients characteristics and chemo-therapy parameters.

Variable	Gemcitabine – cisplatin n (per cent)	Vinorelbine - cisplatin n (per cent)
Total number	31 (100)	29 (100)
Males	28 (90.3)	23 (79.3)
Females	3 (9.7)	6 (20.7)
Median age (years)	59	61
Performance state (Karnofsky)		
60	4 (12.9)	4 (13.7)
70	14 (45.2)	11 (37.9)
80	7 (22.6)	7 (24.2)
90	6 (19.3)	7 (24.2)
Stage		
IIIB	3 (9.7)	5 (17.2)
IV	24 (77.4)	20 (68.9)
Relapse	4 (12.9)	4 (13.9)
Metastatic sites		
Mediastinal lymph nodes	19 (61.3)	16 (55.2)
Lung	11 (36)	9 (31)
Adrenal gland	7 (22.5)	5 (17.2)
Liver	4 (12.9)	2 (6.8)
Bone	4 (12.9)	7 (24.9)
Multiple sites	20 (64.5)	16 (55)
Chemotherapy schedule	Gemcitabine 1250 mg/m^2, days-1 and 8: cisplation 80 mg/m^2, day 8: q 21 days	vinorelbine 30 mg/m2, days 1, 8 and 15; cisplation 80 mg/m^2, day 1; q 28 days
Number of cycles given		
Total	157	152
Mean	5	5
Average relative dose intensity*	0.92	0.81

*p=0.02

VP group (79.3%). Karnofsky performance status of all patients was more than 60. The groups were comparable in terms of patient's age, performance state and stage of disease. Nineteen patients (61.3%) who received GP and 16 (55.2%) treated with VP, presented with mediastinal lymph node involvement. Metastases were found in lungs in 36% and 31%, adrenal glands in 22.5% and 17.2%, liver in 12.9% and 6.8%, and bones in 12.9% and 24.9% of patients in GP and VP groups, respectively. The percentage of patients who had metastases in more than one anatomic site was similar in both groups (64.5% vs 55%).

Pre-treatment evaluation included a complete medical history and physical examination, chest x-ray films, computed tomography (CT) of chest and abdomen and other appropriate scans. Blood count and chemistry, including liver function and serum creatinine, and 24-hour creatinine clearance were tested prior to therapy. Weekly blood counts were performed during therapy. Serum chemical values were assessed at the beginning of each treatment cycle.

Chemotherapy regimens consisted of either i.v. gemcitabine, 1250 mg/m2 given over 30 minutes on days 1 and 8, and i.v. cisplatin 80 mg/m2 given over 2 hours on day 8, both repeated every 21 days, or i.v. vinorelbine 30 mg/m2 given over 10 minutes on days 1, 8 and 15 and i.v. cisplatin 80 mg/m2 given over 2 hours on day 1, both repeated every 4 weeks. All patients received adequate i.v. hydration followed by i.v. diuretics before cisplatin administration. Both i.v. and oral serotonin receptor antagonists and steroids were used for prevention of vomiting. Patients received a total of 6 cycles.

Chest x-ray, CT and other relevant scans were repeated after every two cycles and at further follow up visits. Treatment was terminated in case of disease progression or unacceptable toxicity Patients were followed at two monthly intervals or till death. Response to therapy was assessed using standard criteria.[12] complete response was defined as a complete disappearance of all measurable and/ or evaluable lesions. Partial Response was defined as a reduction of at least 50% in the area of all measurable lesions. Tumor progression (TP) was defined as an increase of at least 20% in the overall area or the appearance of new lesions. The patients who did not meet the criteria of objective response or tumour progression were considered to have stable disease. Survival was calculated according to Kaplan-Meier method .[13]

RESULTS

Thirty one patients received GP chemotherapy and 29 patients received VP regimen. All patients were evaluable for response and toxicity. Total number of cycles administered was 157 (mean – 5) and 142 (mean – 5) , average given relative dose intensity was 0.91 and 0.82 (p=0.02) in GP and VP regimen, respectively.

Table 2. Acute grade III-IV toxicity.

Toxicity	Regimen	
	Gemcitabine - cisplatin (GP) n (per cent)	Vinorelbine - cisplatin (VP) n (per cent)
Nausea and vomiting	0	4 (13.8)
Neutropenia*	9 (29)	19 (68)
Neutropenic fever	0	3 (10.3)
Thrombocytopenia	3 (9.7)	0
Anemia	1 (3.2)	4 (13.7)
Peripheral neuropathy	0	2 (6.8)

*p=0.007

Toxicity analysis is given in table 2. The percentage of grade III-IV neutropenia was significantly lower for patients who received GP chemotherapy (29% vs 68%, p=0.007).

Grade III-IV thrombocytopenia was unique toxicity for GP group (9.7%). On the

other hand, grade III-IV neutropenic fever, vomiting and peripheral neuropathy were reported only in the VP group (10.3%, 13.8% and 6.8% relatively). Furthermore, the rate of grade III-IV anemia was slightly higher in VP group, but the difference was not statistically significant. In addition, 9 (31%) patients who received VP regimen, developed chemical phlebitis, that required insertion of central venous access device. In VP group vinorelbine administration was skipped on day 15 in 42 (29..5%) cycles due to toxicity. All toxicity episodes were well-manageable without any life-threatening event.

Table 3. Response Rates

Variable	Regimen	
	Gemcitabine - cisplatin (GP) n (per cent)	Vinorelbine - cisplatin (VP) n (per cent)
Complete response (CR)	0	0
Partial response (PR)	9 (29)	6 (20.7)
Stable disease (SD)	10 (32.3)	9 (31)

Response rates are given in table 3. No CR was observed. PR was seen in 29% and 20.7% of patients, and the disease remained stable in 32.3% and 31% patients respectively' for GP and VP regimens.

Survival curves are shown in fig. 1. The median follow up was 13 months for GP and 15 months for VP group. The one year survival was 53% and 47%, and the median survival was 12.5 months and 9.8 months respectively for GP and VP regimens, relatively (not significant). The one year progression-free survival was 29% and 18%, and the median progression free survival was 7 months and 5.5 months, respectively (p=ns).

DISCUSSION

The last decade has seen the introduction of several new cytotoxic agents, that have activity against NSCLC and produce single-agent response rates of >20% in the previously untreated patients with advanced tumours. The list of these agents includes taxanes, gemcitabine, vinorelbine and irinotecan.

Gemcitabine is a pyrimidine nucleoside antimetabolite. Vinorelbine is a semisynthetic vinca alkaloid, that acts by inhibiting tubulin polymerization. Both drugs have been studied in a variety of solid tumours. Randomized control study documented that gemcitabine, used alone as first line chemotherapy for advanced NSCLC was considerably superior over best supportive care in improving quality of life.[14] On the other hand, vinorelbine alone improved survival and quality of life of elderly patients with advanced NSCLC.[15] Furthermore, single agent chem-otherapy regimens with either gemcitabine or vinorelbine were at least as effective as platinum based combined schedules, were accepted as a standard of care in advanced NSCLC, and were better tolerated.[16-19] Those results promoted the use of both drugs in combination with cisplatin (GP or VP) in previously untreated patients with advanced NSCLC.

Both GP and VP chemotherapy demonstrated improvement of objective response rate (30-43%) and one-year (35-45%) and median (8-10 months) survival rates, that were considerably better than with standard cisplatin containing regimens.[4-7, 20-22] Efficacy of

GP was the same and similar to combinations of taxanes with cisplatin. The GP regimen was less toxic than VP in terms of grade III-IV neutropenia and neutropenic fever, but on the other hand the rate of thrombocytopenia was higher .[9-10]

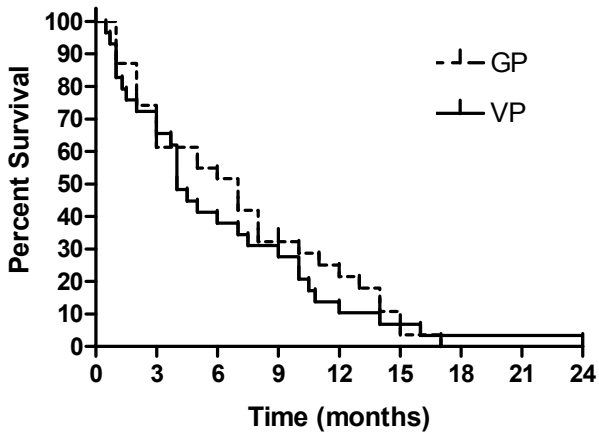
Two large randomized trials that were reported within the last two years compared several of new-generation regimens in the treatment of patients with advanced NSCLC.

The first trial, conducted by ECOG compared four therapeutic regimens (paclitaxel-cisplatin, GP, docetaxel-cisplatin and paclitaxel-carboplatin), given as first-line chemotherapy for advanced NSCLC.[11] No significant difference in response rates or survival was observed among the four arms, but there was a small statistically significant difference in progression-free survival in favour of patients receiving GP combination.

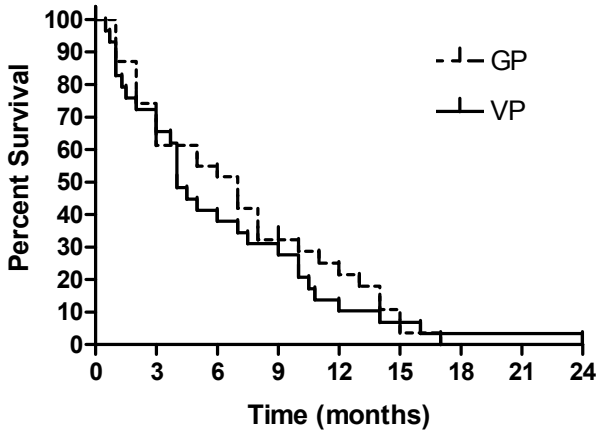
The second trial by SWOG compared the use of VP with paclitaxel-carboplatin also failed to report statistically significant difference in response and survival between two regimens.[23] Both trials also included comprehensive analysis of toxicity. In the first trial the GP regimen caused more thrombocytopenia, whereas the docetaxel-cisplatin combination produced more neutropenia. In the second trial, the combination of vinorelbine and cisplatin produced significantly more nausea and hematologic toxicity. In general, no one regimen has been demonstrated to be superior in the first-line chemotherapy for patients with advanced NSCLC. A cisplatin or carboplatin-based combination regimen, that includes one of novel agents remains the standard of care for first line chemotherapy in stage IV NSCLC .[24]

In our experience, both GP and VP regimens were well tolerated. Toxicity rates were not higher than those reported in the literature. Though the rates of neutropenia was significantly higher for VP regimen, it didn't cause any life threatening event. Response and survival rates correspond with those reported in the literature, providing further evidence in favour of use of GP or VP as appropriate option of first line chemotherapy in the patients with advanced NSCLC. Currently the choice between those regimens may be left to the discretion of treating physician. Any way, slight, though not statistically significant differences in survival in favour of GP warrant futher exploration in a larger sample size.

Figure 1. Survival after first line chemotherapy with gemcitabine and cisplatin or vinorelbine and cisplatin for advanced NSCLC



a – overall survival



b – progression-free survival

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