CISPLATIN AND VINORELBINE IN THE TREATMENT OF LOCALLY ADVANCED AND METASTATIC NON-SMALL CELL LUNG CANCER

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ABSTRACT: From August 1999 to January 2001, twelve chemotherapy naive patients with locally advanced and metastatic non-small cell lung cancer (NSCLC) in our hospital received vinorelbine and cisplatin. Ten patients had stage IV disease while two had stage III disease. Patients' performance status (PS) were as follows: four had PS 1, six had PS 2, and one each PS 3 and 4. A total of 46 cycles were given as scheduled.

Only major haematological toxicities were noted; one patient each with Grade 3 anaemia, Grade 3 and Grade 4 leucopenia, two had Grade 3 neutropenia and 5 had Grade 4 neutropenia without associated mortality. Three patients had Grade 3 alopecia and one had Grade 3 phlebitis. After three cycles, three patients demonstrated partial response and two had stable disease. For the four patients who completed 6 cycles, two demonstrated stable disease and two partial response. Symptom improvement was reported in all but one patient. Performance status was better in four, stable in six but declined in two patients. In conclusion, in patients with locally advanced and metastatic NSCLC, vinorelbine/cisplatin is a well-tolerated and active regimen, offering symptom palliation and improved performance status in a significant proportion of patients. *(JUMMEC 2001; 1:20-23)*

KEYWORDS: Vinorelbine, lung cancer, chemotherapy.

Introduction

Bronchogenic carcinoma is the most common cancer diagnosed in recent years and accounts for the majority of cancers in both female and male patients (1,2). The majority of cases present late and are not resectable (3). Chemotherapy, neoadjuvant or concurrent, with radiotherapy is now the primary mode of therapy for these patients (3). To date, many newer agents have been introduced and have been reported to be efficacious for non-small cell lung cancer (NSCLC), which accounts for 80% of the histological type of lung cancer. Vinorelbine used in combination with cisplatin have been purported to be an agent with better efficacy than the standard cisplatin/mitomycin and cyclophosphamide regime with acceptable side effects (4). We need to better define the activity and toxicity of vinorelbine/cisplatin as first line chemotherapy in Malaysian patients with locally advanced and metastatic NSCLC. Therefore, a descriptive analysis of a preliminary group of patients treated with this regime was carried out to evaluate these parameters.

Materials and Methods

Patient population

From August 1999 to January 2001, patients newly diagnosed with NSCLC in the University of Malaya Medical Centre were considered for chemotherapy if they had stage III or IV inoperable disease. Diagnosis of NSCLC was made by histological and/or cytological examination of sputum cytology, the primary tumour mass, involved lymph nodes or other involved organs. Clinical staging was done according to the International staging system for lung cancer (5), based on physical findings, computed tomography (CT) scan of the thorax and upper abdomen and bronchoscopy. Patients had CT scan of the brain or bone scans if they had symptoms or biochemical results suggestive of involvement. Those who consented to chemotherapy with cisplatin plus vinorelbine were recruited prospectively for analysis. This regime involved administering intravenous cisplatin

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80 mg/m^2 on day 1 and vinorelbine 25 mg/m^2 on days 1and 8, every 3 weeks. Pre-chemotherapy evaluation included haemoglobin levels, white blood count and differential counts, renal function and liver function as well as bone chemistry with chest radiographs and CT scan thorax and upper abdomen. At each cycle, the haemoglobin and absolute white blood counts were checked on day 8, 15 and whenever necessary. Chemotherapy was delayed if the absolute neutrophil count was less than 1.5x 109/L or if the platelet counts were less than 100x 109/L. Chemotherapy was resumed upon recovery of the counts. If the haemoglobin was less than 8g/l, blood tranfusion was given but chemotherapy was administered as scheduled. The drugs were diluted in normal saline; cisplatin infused over an hour while vinorelbine was given in 10 minutes.

The hydration regime for cisplatin included one litre of dextrose 5% and one litre of normal saline with 2 grams of potassium chloride (KCL) and 2 grams of magnesium sulphate. Antiemetics (granisetron 3 mg), 10 mg dexamethasone and 10 grams of mannitol were routinely given 1/2 hour before the commencement of cisplatin infusion. This was followed by one litre of dextrose 5% and one litre of normal saline with 2 grams KCL and 10 grams of mannitol post-cisplatin. Postchemotherapy medications included oral maxolon 10mg TID as necessary. Patients were evaluated for performance status according to World Health Organization (WHO) criteria (6), symptoms clinical signs, toxicity profile (Common Toxicity Criteria)(7) and tumour response every cycle.

A CT scan thorax was done after three cycles of chemotherapy to evaluate tumour response. A complete response was defined as the disappearance of all measurable or assessable disease, signs, symptoms and biochemical changes related to the tumour. Partial response meant a greater than 50% reduction in measurable lesions. Stable disease indicates <50% reduction and <25% increase in measurable lesions without new lesions. Disease progression was defined least 25% increase in tumour size or the appearance of new or metastatic lesions.

Results

Twelve patients with the median age of 53.5 (range 24-68) years received chemotherapy as scheduled, totaling 46 cycles. Seven patients had adenocarcinoma, four squamous carcinoma and one poorly differentiated carcinoma. Ten patients had stage IV disease while one patient each had stage IIIa and IIIb disease, respectively. One patient received radiotherapy to the brain for symptomatic brain metastasis. The patients' performance status (PS) were as follows: four had PS 1, six PS 2, and one each PS 3 and 4 (Table 1).

Table 1. Patient clinical profil.

• Total number of patients:		12
• Sex:	10 Male	2 Female
• Age(years):	range: 24-68	median: 53.5
• WHO performance status (Stage) (no. patients)		
	1	4
	2	6
	3	1
	4	1
• TMN staging:	Stage IIIa	1
	Stage IIIb	1
	Stage IV	10
• Histology :Squamous cell carcinoma		4
:Adenocarcinoma		7
:Poorly differentiated carcinoma		1

Table 2. Toxicity Evaluation.

	Grades				
Toxicity	0	1	2	3	4
Anaemia	5	4	2	1	0
Leukopenia	5	3	2	1	1
Neutropenia	3	2	0	2	5
Thrombocytopenia	12	0	0	0	0
Nausea/vomiting	5	1	6	0	0
Alopecia	6	2	1	3	0
Phlebitis	0	0	1	0	0
Neurotoxicity	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0
Mucositis	0	0	0	0	0
Nephrotoxicity	0	0	0	0	0
Hepatotoxicity	0	0	0	0	0

The regime was well-tolerated without any chemotherapy-related deaths. The major toxicities were haematological; one patient each with Grade 3 anaemia, Grade 3 and Grade 4 leucopenia, two had Grade 3 neutropenia and five had Grade 4 neutropenia but not associated with fever. Non-haematological toxicities were only significant (Grade 3 or 4) in the following; three had Grade 3 alopecia and one had Grade 3 phlebitis (Table 2). Chemotherapy was stopped after one cycle in one patient due to progression. After three cycles (total 34 cycles), three of the remaining eleven patients demonstrated partial response, two stable disease and the rest progressed. One patient who had partial response opted to continue treatment elsewhere. For the four patients who completed 6

cycles, two demonstrated stable disease and two partial response (Table 3). Time to disease progression and survival data were not available.

Table 3. Patient response.

Cycles completed	Complete response	Partial response	Stable disease	Disease progression
3	0	3	2	7
6	0	2	2	0

At the time of chemotherapy completion, symptom improvement was reported in all but one patient. Similarly, PS was better in four, stable in six but declined in two patients whose disease progressed.

Discussion

Lung cancer is a worldwide health problem and has now exceeded all other cancers in the Western world. It is the commonest reported cause of cancers in the United States of America as well as Europe (1,2); with around 170,000 new cases (90,000 in men and 80,000 in women) estimated annually and at least 157,000 deaths predicted in 2001 in the United States alone (1).

The overall cure rate remains around 10-14% and non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases with adenocarcinoma occurring most commonly. The majority have advanced, poor prognosis stage III and IV disease and fewer than 20% of NSCLC patients are deemed resectable, due to late presentation, and since this is the primary curative mode of treatment, it means that the majority will need chemotherapy, radiotherapy and supportive care (6). Cures are achieved in less than 20% for the locally advanced disease and are only anecdotal in the metastatic group of patients.

In unresectable or inoperable locally advanced and metastatic NSCL cancer, chemotherapy for good performance patients is an appropriate mode of therapy and is usually combined with definitive thoracic radiotherapy for selected stage III patients (6,7). For this group of patients, since the influential CALGB 8433 trial (8,9), which demonstrated a 5-year survival that tripled in the combined modality group (17% v 6%), numerous other studies have shown that induction (or neoadjuvant) cisplatin-based chemotherapy with definitive radiotherapy is superior to thoracic radiotherapy alone (10,11). Modern chemotherapy regimes may provide absolute benefits of about 5% in the surgical and 2% in the definitive radiotherapy setting at 5 years (11). For metastatic disease, trials indicate median survival improvement of 6-8 weeks and absolute 1-year survival improvement of 10% (from 15% to 25%)(11, 14) for those patients on cisplatin-based chemotherapy. More importantly, quality of life (15) and symptom improvements (16) have also been demonstrated in patients on chemotherapy.

Chemotherapy therefore is an integral part of combined treatment modalities for non-small cell lung cancer (17) and the search for newer agents with better efficacy and less toxicities have resulted in the development of recent chemotherapeutic agents. Vinorelbine; the antimetabolite gemcitabine; the taxanes, paclitaxel and doxetaxel; and the topoisomerase I inhibitors, irinotecan and topotecan have come into use in the last few years. These newer agents have demonstrated superior activities compared to older agents in lung cancer treatment with single agent response rates of between 20-27% and combinations with cisplatin have shown response rates of between 22 to 47% with improved survival (18, 19).

Vinorelbine is a semi synthetic vinca alkaloid with good activity in non small cell lung cancer and in clinical settings have been effective as first line agent in stage III and IV disease. Trials have demonstrated that cisplatin combined with vinorelbine is better than either agent alone and has an objective response rate of 30% with a median survival of 40 weeks and 1- and 2- year survival reaching 33% and15%, respectively (20,21). Vinorelbine as monotherapy plus best supportive care proved to be as efficacious with improved quality of life as well as improved survival (median survival of 28% and 21% with one year survival of 32% and 14% for stage III and IV, respectively for these patients above 70 years of age (22).

With the increasing need to administer chemotherapy in our NSCLC patients, vinorelbine was chosen as the newer agent to be paired with cisplatin for our chemotherapy regime based on the above evidence for its clinical usage. Our 12 patients were all deemed inoperable with the majority in the stage IV group. Due to poor lung reserve, definitive radiotherapy was judged by our radiotherapist to be inappropriate and could not be administered for those in the stage III category. Performance status for the majority was in the recommended WHO stage 1 and stage 2 categories and chemotherapy was administered to the other two patients due to their young age; 24 and 35 years old, respectively. We achieved a response rate of 25% after 3 cycles and 17% after 6 cycles, which are comparable to the published data.

Toxicity data for vinorelbine (20) cited myelosuppression as the major dose-limiting toxicity. Grade 3 or 4 neutropenia occurred in 53.2% of patients on monotherapy with only 3.4% complicated by sepsis. Generally, toxicity is tolerable and acceptable in published reports.

In our patients group, myelosuppression was also the commonest severe toxicity noted. There were no cases of related sepsis or mortality. Grade 3 alopecia and

phlebitis were the only other significant toxicity and occurred in 3 and one patients, respectively. These figures are similar to the published data.

From the point of performance status, 25% of our patients reported improvement, while half reported stable condition, and decline occurred in two patients whose disease was progressive. This is encouraging when combined with the report of symptom relief in all but one patient.

The role of chemotherapy as a palliative modality is worthwhile in metastatic cancers (24) and our patients demonstrated the viability of utilizing the newer agent vinorelbine as a chemotherapeutic agent with promising results in patients with locally advanced and metastatic NSCLC. Vinorelbine and cisplatin is a well-tolerated and active combination regimen, offering symptom palliation and improved performance status in a significant proportion of patients.

Apart from demonstrating comparable results in our patient population, we have also learnt that to provide good quality care in our lung cancer patients, a dedicated oncological day care service is crucial and should be given the necessary consideration in any future planning for hospital services.

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