PRELIMINARY EXPERIENCE WITH MITOMYCIN, VINBLASTINE AND CISPLATIN (MVP) COMBINATION CHEMOTHERAPY IN THE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER AT UNIVERSITY HOSPITAL, KUALA LUMPUR

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ABSTRACT

Twelve patients with advanced inoperable non-small cell lung cancer (NSCLC) were treated with mitomycin, vinblastine and cisplatin (MVP) combination chemotherapy. The overall response rate was 33% (4 partial responses and no complete response) with a median survival of seven months. One responder above subsequently achieved complete remission following successful resection of his tumour and is still alive 14 months after initial chemotherapy. Responses were observed in patients with good performance status and limited disease. Side-effects were generally well tolerated and manageable. MVP is an effective regimen and the low response rate achieved here as compared to other centres is also discussed.

Keywords : Non-small Cell Lung Cancer (NSCLC), MVP combination chemotherapy.

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INTRODUCTION

Treatment of advanced inoperable non-small cell lung cancer (NSCLC) is one of the most frustrating areas in oncology. Limited yet inoperable disease (Stage III, MO, see Table on Mountain classification) traditionally has been managed with radiotherapy which, although effective palliatively, has little impact on long term survival. Five-year survival data show only about 6% of patients remain alive and well with radiotherapy alone (1). Most died from distant metastasis, outside the local radiotherapy field. Successful management therefore will clearly require some form of systemic treatment.

Recently combination chemotherapy especially cisplatin-based regimens have produced significant response rates in advanced inoperable NSCLC (Stage III, MO disease). In one series of 58 patients with stage IIIA disease with mediastinal node involvement treated with MVP, 74 percent response rate was achieved (2). Major response rate in the region of 50 to 70% are frequently observed in other studies as well (3-5).

In an attempt to increase response rate and hopefully survival in patients with advanced inoperable NSCLC, we commenced a preliminary study of MVP chemotherapy in our local population to assess response rate and survival. Patients achieving significant response were subjected to surgery and/or radiotherapy if this was feasible in an attempt to obtain long term survival.

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MATERIALS AND METHODS

Twelve patients with histologically documented advanced, inoperable NSCLC were entered in the study from May 1988. All had endobronchial lesions seen on bronchoscopy.

Consent was obtained from all patients. Measurable disease was required of each subject. Patients had to be less than 70 years of age, had normal renal function, normal marrow function and normal liver function. Those with intracerebral metastasis were excluded.

Limited disease is defined as tumour confined to one hemithorax with or without ipsilateral node involvement or pleural effusion. Extensive disease refers to any patient with evidence of tumour beyond these limits.

The treatment schedule consisted of mitomycin C (6mg/m^2 i.v.), vinblastine (6mg/m^2 i.v.) and cisplatin (100mg/m^2 i.v. with hydration and mannitol diuresis). Courses were repeated every four weeks up to a maximum of six courses. Response was assessed after each course clinically and with chest X-ray using WHO criteria (6). If no objective response was detectable after two courses, the therapy was discontinued. Patients achieving significant responses will be subjected to surgery and/or radiotherapy if this was feasible.

Survival time were computed from start of treatment and actuarial survival was estimated by the method of Kaplan and Meier (7).

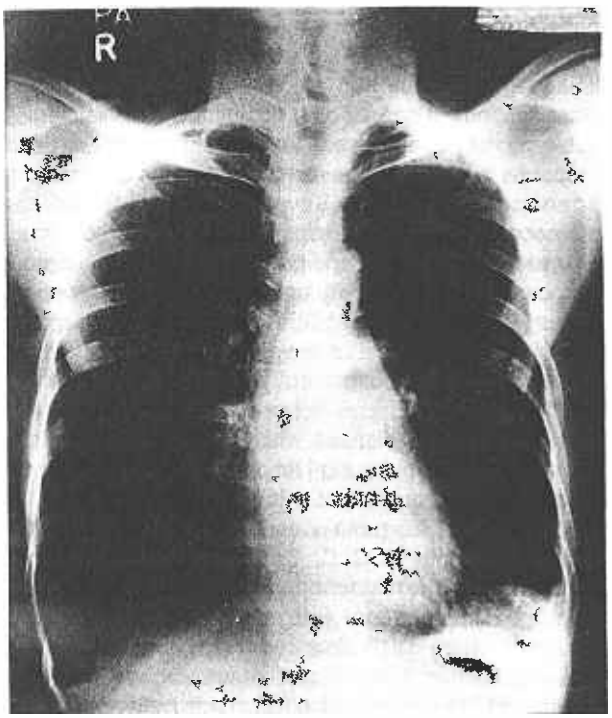
Table I
Patients' Characteristics

	No. of patients
Total	12
Male/Female	7/5
Age, year	
Median	51
Range	39-65
Performance status (ECOG)	
1-2	6
3-4	6
Histological Type	
Adenocarcinoma	7
Squamous cell carcinoma	4
Large cell carcinoma	1
Limited/Extensive	7/5
Previous treatment	
Radiotherapy	1
Chemotherapy	0

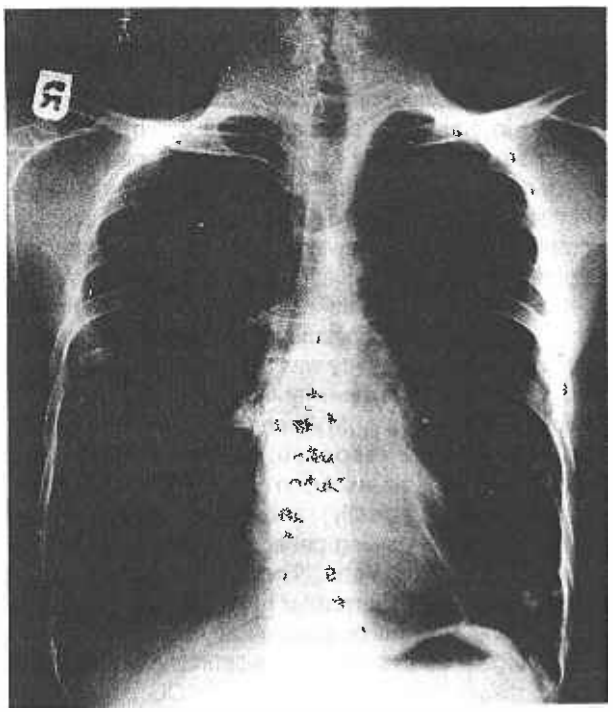
RESULTS

Patient characteristics are summarized in Table I. The median age of all patients was 51 years with a range of 29 to 65 years. Five patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 and 2 and seven patients with ECOG performance status of 3 and 4. The average performance status for all patients was 2.6. Seven patients had adenocarcinoma, four had squamous cell carcinoma and one had large cell carcinoma. Of the twelve patients, seven had limited disease and five had extensive disease. In the extensive group, three had malignant pericardial effusion, one had contralateral supraclavicular lymphadenopathy and bone metastasis and one had diffused lymphadenopathy outside the mediastinum.

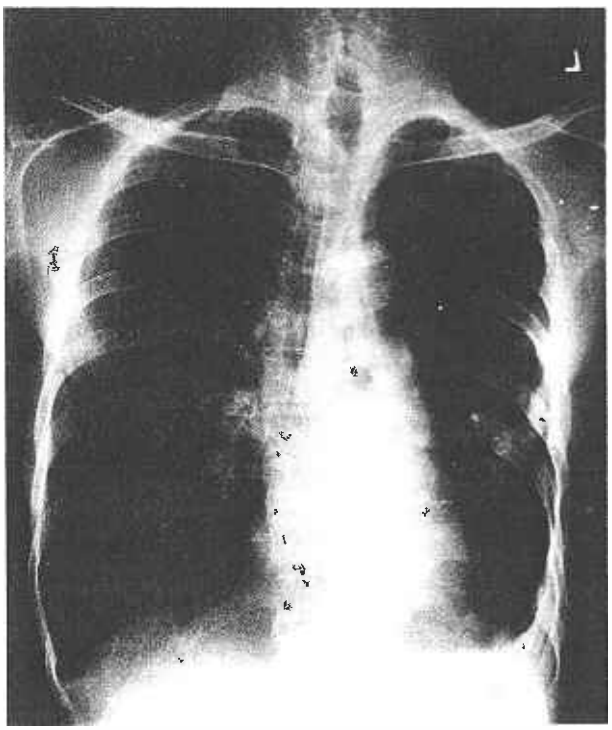
Fig 1: Chest X-rays showing
(a) before chemotherapy, a large nodular capacity at left lung base



(b) a significant reduction of lung capacity.



(c) after surgery, no evidence of tumour recurrence six months after lung resection.



The therapeutic response is summarised in Table II. The overall response rate was 33% (4 out of 12 patients with partial responses). No complete response was seen. In the four responders, two had squamous cell carcinoma and two had adenocarcinoma. Activity was particularly marked in squamous cell carcinoma which had a 50% response rate (2 out of 4 patients) as compared to 30% in adenocarcinoma (2 out of 7 patients). One responder with squamous cell carcinoma subsequently achieved complete response following a second thoracotomy and segmental lung resection (Fig 1(a), 1(c)). Histological review showed complete resection of tumour with the surgical margin free of tumour. The initial thoracotomy showed the pleural cavity was studded with secondaries and the lung tumour was adherent to the diaphragm. Following 6 courses of MVP chemotherapy in which he achieved partial response (Fig 1(b)), a second thoracotomy showed resolution of the pleural secondaries (confirmed histologically) and shrinkage of the lung tumour. The 2 remaining patients were not operable on re-staging investigations. They had residual pleural effusion and were referred for radiotherapy. One patient refused any surgical or radiotherapy treatment. It was interesting to note that the 4 responding patients had limited disease and their average ECOG performance status score was 1.5.

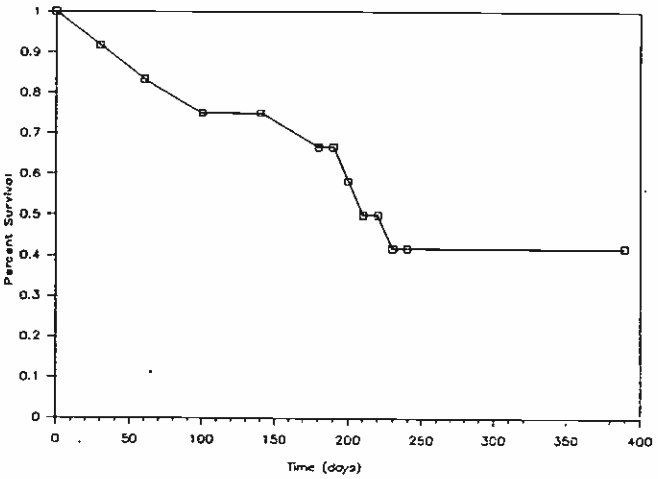
The survival time for all patients is shown in Fig 2. Median survival time was 212 days (7.0 months). Five patients are still alive and the longest survival patient is 14 months (patient above with complete response following chemotherapy and surgery). Significant difference in response was apparent between patients with limited disease and extensive disease (<0.05). No response was seen in our patients with extensive disease. Performance status was also an important factor in predicting response. The 4 responders had an average ECOG performance score of 1.5 compared to 3.1 for non-responders.

Table II
Response Characteristics

	No. of patients
Total	12
Partial response	4 (33%)
Complete response	0 (0%)
No response	8 (67%)
Responders	
Adenocarcinoma	2/7 (30%)
Squamous cell carcinoma	2/4 (50%)
Large cell carcinoma	0/1 (0%)

Toxicity generally was mild and all patients received high-dose metoclopramide to counteract the cisplatin-induced nausea and vomiting. One patient developed neutropaenia-related septicaemia. There were no serious instances of nephrotoxity. Three patients developed mildly elevated serum creatinine level from their baseline level (range 10 - 23µol/1 elevation). Three patients developed paraesthesiae of their fingers and toes. No mitomycin lung injury was seen.

Fig 2
Overall Survival Curve



DISCUSSION

Our preliminary study showed MVP combination chemotherapy is active in the treatment of advanced inoperable NSCLC. However the response rate of 33 percent was not as high as compared to other centres. There may be several reasons for this. Many of our patients had poor performance status. Also five out of the twelve patients studied had extensive disease. In the limited group, four had stage IIIB disease (Mountain classification). It can also be postulated that histological sub-type may affect response. One study showed better response with squamous cell carcinoma as compared to adenocarcinoma (8). Seven of our patients had adenocarcinoma. In the responding patients in our study all had limited disease and preponderance of squamous cell carcinoma (Table II) and also good performance status (average score of 1.5). I suspect that the response rate for MVP combination chemotherapy would be much higher if we confined our entry criteria to patients with good performance status (0,1 or 2) and inoperable limited disease (stage III disease with no distant metastasis). Most centres achieving high response rates confined their studies to this group of patients (2-4).

Few questions remain unanswered in the role of chemotherapy in NSCLC. Can chemotherapy prolong survival in patients with advanced disease either advanced locoregional (stage III, MO) or metastatic disease (stage IV)? One recent trial conducted by National Cancer Institute of Canada showed improved survival (9) but no separation was made between patients with advanced locoregional inoperable and metastatic disease. In contrast, an Australian group showed no apparent survival benefit when the two treatment arms were compared (10). Another study looking at metastatic

NSCLC alone (stage IV Mountain classification), showed no survival advantage in patients treated with chemotherapy arm as compared to supportive arm (11). The data suggest the appropriate role of chemotherapy in treatment of advanced NSCLC (stage IIIB and stage IV, Mountain classification) remains uncertain and cannot be enthusiastically supported outside the investigational setting. What is the role of combined modality approach combining surgery, radiotherapy and chemotherapy? Is there any role for adjuvant chemotherapy following surgical resection in NSCLC? These questions are not fully resolved and will require well-controlled clinical studies to address this.

However, I believe the role of chemotherapy in NSCLC is of greatest benefit if used as initial therapy in patients with advanced locoregional disease (Stage III, Mountain classification) in an attempt to shrink the tumour followed by surgical resection and or radiotherapy. In one study addressing this issue of combined modality approach at Memorial Sloan-Kettering Cancer Centre, New York, MVP significantly reduces the tumour burden in the majority of patients with stage IIIA (74%) and 75% of these patients were successfully resected of their tumour as compared to 14% resection rate in their earlier study with similar stage disease treated with surgery alone. Patient survival was 82% at 1 year and 54% at 3 years (12). This data and elsewhere (2-4) indicate combined modality approach with chemotherapy as initial therapy may be the most ideal approach in treating patients with locoregional advanced NSCLC (stage IIIA, Mountain classification).

In summary, MVP chemotherapy is an effective therapy in NSCLC although the complete response rate is still unsatisfactory. Further studies are warranted and should be confined to patients with good performance status and advanced locoregional disease (stage III), specially in a neoadjuvant setting as described above.

Table III
Mountain classification in the New System of Lung Cancer Staging

Stage	TNM Components
I	T1N0
	T2N0
II	T1N1
	T2N1
IIIA	T3N0
	T3N1
IIIB	N3 (any T)
	T4 (any N)
IV	M1

Abbreviations: T1 : tumour <3 cm ; T2 : tumour >3 cm or visceral pleural involvement >2 cm from carina; T3 : circumscribed extrapulmonary e.g. chest wall or superior sulcus but resectable; T4 : SVC obstruction, malignant effusion, unresectable soft tissue invasion; N1 : ipsilateral peribronchial and hilar nodes; N2 : ipsilateral mediastinal or subcarinal nodes; N3: supraclavicular or contralateral hilar mediastinal nodes; M1 : metastasis beyond scope of T4 or N3 classification. Ref. (13).

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