TREATMENT OF SMALL CELL LUNG CANCER WITH CYCLOPHOSPHAMIDE, ADRIAMYCIN AND VINCRISTINE (CAV)COMBINATION THERAPY: EXPERIENCE AT UNIVERSITY HOSPITAL, KUALA LUMPUR, MALAYSIA

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ABSTRACT

Seventeeen patients with small cell lung cancer (SCLC) were treated with cyclophosphamide, adriamycin and vincristine (CAV) combination chemotherapy. The overall response rate was 76.5% with 47% achieving complete response and 29.5% partial response. In limited and extensive stage disease, complete response was achieved in 67% and 36.5% respectively. Chinese were the predominant ethnic group affected (82%). Six patients presenting with superior vena cava obstruction responded significantly to CAV chemotherapy alone. Median survival for patients with extensive disease was 7.4 months. All patients with limited disease were still alive. Two relapsed patients with limited disease achieved significant response to VP-16/Cisplatin combination chemotherapy.

Keywords: CAV combination therapy, small cell lung cancer.

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INTRODUCTION

Lung cancer is the predominant fatal cancer of our time and small cell lung cancer (SCLC) which accounts for about 25% of all lung cancer, if untreated is rapidly fatal with a median survival of 3 months in patients with limited disease and 1.5 months in patients with extensive disease and overall survival of less than 0.5% following the use of localized treatment with surgery or radiotherapy [1-3].

Since the early 1970s, it has been known that SCLC are highly chemo-sensitive tumours and combination chemotherapy has been the cornerstone of therapy for SCLC. Currently employed aggresssive combination chemotherapy has allowed a four- to five-fold improvement in median survival over untreated patients and response rate exceeding 80% are regularly being achieved in all stages of the disease. The median survival is about 14 months in patients with limited disease and about 7 months in patients with extensive disease following chemotherapy [1]. Approximately 15 to 20% of patients with limited disease can be expected to have long term survival [1,2]. Poor prognosis is associated with extensive stage disease and poor performance status [2].

The combination chemotherapy consisting of cyclophosphamide, adriamycin and vincristine (CAV) is an effective first-line regimen for SCLC [4]. More recently, the combination consisting of VP-16 and cisplatin [5] has been shown to be an effective second-line treatment for relapsed SCLC following CAV chemotherapy. We describe our experience in the use of CAV chemotherapy as first-line treatment in our local population with SCLC.

MATERIALS AND METHODS

Seventeen consecutive patients with previously untreated SCLC were treated with CAV chemotherapy since January 1988 at University Hospital, Kuala Lumpur.

All patients had histologically or cytologically confirmed SCLC with measurable or evaluable disease. Baseline investigations were performed including a complete history and physical examination, full blood count with differential, BUSE, liver function tests, chest X-ray, bone scan, bone marrow aspiration and trephine biopsy, bronchoscopy and liver ultrasound if liver function tests were abnormal. Patients were then staged into either limited disease or extensive disease.

Limited disease was defined as disease confined to one lung, the mediastinum excluding malignant pleural effusion or pericardial effusion and ipsilateral supraclavicular lymph nodes. Extensive disease was defined as evidence of spread of tumour beyond the boundary of one lung, mediastinum and ipsilateral

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supraclavicular lymph nodes.

Chemotherapy for all patients consisted of cyclophosphamide (1000 mg/m2), adriamycin (45 mg/m2) and vincristine (2 mg.), all given on day 1 and repeated every 3 weeks for a total of six courses. Patients were required to complete two courses of CAV chemotherapy to be considered evaluable. Patients achieving complete response were referred for radiotherapy to chest and prophylactic cranial irradiation.

At relapse following CAV chemotherapy, patients who achieved complete response were treated with second-line chemotherapy consisting of VP-16 (etoposide) (100 mg/m2) day 1 to day 3 and cisplatin (100 mg/m2) day 1 with hydration and diuresis; repeated every 3 weeks for a total of 3 courses.

A complete reponse (CR) was defined as the complete disappearance of all clinically and radiologically evident disease. A partial response (PR) as a decrease of at least 50% in the product of the cross-sectional diameters of well-defined lesions. Any response less than this or not evaluable was considered to be no response.

Survival was measured from time of first treatment until death and survival curve plotted as recommended by Peto et al [6].

RESULTS

Patients' characteristics are summarised in Table I. Of the 17 patients, 6 (35%) were classified as limited disease and 11 (65%) as extensive disease. The majority were male (82%; 14 patients) with a male to female ratio of 4.7:1. Chinese were the predominant ethnic group affected and comprised 82% of all patients (14 patients). The median age of all patients was 60 years (range 45-75). 9 patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 and 2, and 8 patients with ECOG performance status of 3 and 4.

Table I
Patients' Characteristics

	Limited disease	Extensive disease	Total
Number of patients	6 (35%)	11 (65%)	17 (100%)
Age (yr.)			
Median	59	61	60
Range	45-75	45-75	45-75
Race			
Chinese	5	9	14 (82%)
Malay	0	1	1 (6%)
Indian	1	1	2 (12%)
Performance status (ECOG)			
1	1	1	2
2	4	3	7
3	1	5	6
4	0	2	2
Died	0	6	6

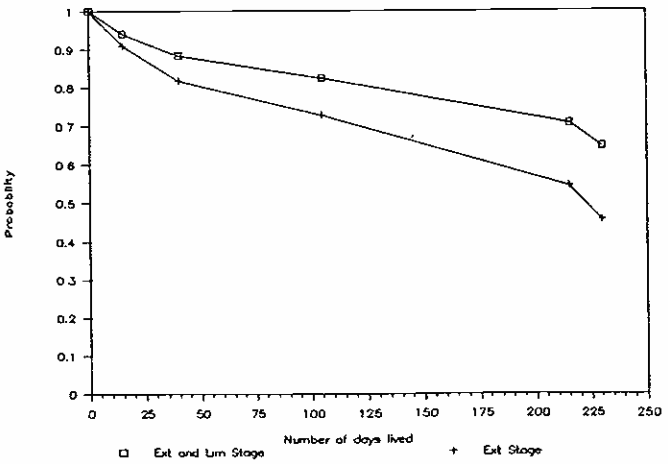
The therapeutic response is summarised in Table II. The overall response rate was 76.5% with 47% achieving CR and 29.5% PR. No response was seen in 23.5%. CR was achieved in 4 of the 6 patients (67%) with limited disease and 4 of the 11 patients (36.5%) with extensive disease. The majority of patients with extensive disease (8 out of 11 patients) had significant relief of haemoptysis, dyspnoea, weight loss and superior vena cava obstruction (SVCO). All 6 patients (2 limited-staged and 4 extensive-staged) presenting with SVCO responded to primary CAV chemotherapy without requiring radiotherapy.

Table II
Response

	Stage of Involvement		
	Limited (n = 6)	Extensive (n = 11)	Total
Complete	4 (67%)	4 (36.5%)	8 (47%)
Partial	1 (16.5%)	4 (36.5%)	5 (29.5%)
None	1 (16.5%)	3 (27%)	4 (23.5%)
	6 (100%)	11 (100%)	17 (100%)

The survival curve for all patients is shown in Fig. 1. All patients with limited disease are still alive (range 93-323 days). The survival curve for patients with extensive disease is also shown in Fig. 1 and the median survival for this group is 222 days (range 61-497 days). The 6 deaths in extensive-staged disease have an average ECOG performance score of 3.3 and median age of 65.5 years.

Fig 1
Survival Curve



Since entry into the study, 7 patients had relapse after achieving significant response, 3 patients with limited disease and 4 patients with extensive disease. The sites of relapse were 3 in the chest alone, 3 in both chest and liver and 1 in the brain alone. Two relapsed patients with limited disease refused chest irradiation and prophylactic cranial irradiation after achieving CR. This is summarised in Table III. These 2 relapsed patients with limited disease were treated with VP16/cisplatin chemotherapy and achieved significant response (1 CR and 1 PR).

Treatment was generally well tolerated. Alopecia, nausea and vomiting occurred in all patients receiving CAV chemotherapy. Systemic infection occurred in 3 patients and all responded to systemic antibiotics. 6 courses of chemotherapy were delayed due to haematological toxicity.

Table III
Sites of Relapse

Sites of relapse	Stage of Involvement: Limited (n = 3)	Extensive (n = 4)
Chest only	1	2
Brain only	1	0
Chest, nodes and liver	1	2

DISCUSSION

The results of our experience with CAV chemotherapy are very similar to results reported in the western institutions [2,4]. The overall response rate was 76.5% with 47% achieving complete response and 29.5% partial response. For limited and extensive stage disease, complete response was achieved in 67% and 36.5% respectively. This was encouraging as pointed out by Greco et al [7] that attainment of a complete response is essential for long-term survival. Chinese were the predominant (82%) ethnic group affected with SCLC in our treated population. 6 patients presenting with SVCO have had significant resolution of their symptoms following CAV chemotherapy without receiving radiotherapy. Experience with VP-16/cisplatin chemotherapy as second-line salvaged treatment proved this to be an effective regimen confirming the experience of others [5]. Generally the treatment was well-tolerated with manageable toxicities.

Overall, despite the high initial response to chemotherapy, the cure rate remains low [1,2]. After a period of rapid progress in the 1970s and early 1980s, the therapeutic results appear to have reached a plateau. Maintenance chemotherapy, alternating 'non cross-resistant' combinations and intensive chemotherapy with the currently available drugs appear not to make much impact to the survival rate [2].

In patients with extensive disease, chest radiotherapy does not improve survival [2,8] and mainly confined to a palliative role. The role of radiotherapy in patients with limited disease remains controversial [8]. However as about 75% of all limited disease patients achieving complete response with chemotherapy will relapse within the first 2 years and overwhelming majority do so in the chest and brain, local chest radiotherapy and prophylactic cranial irradiation are generally recommended here [2,8]. However we noticed our SCLC population are reluctant to undergo radiotherapy after achieving significant response following CAV chemotherapy. Only 5 patients received radiotherapy.

The major challenge in the therapy of SCLC remains the achievements of more durable complete remission after induction chemotherapy. Development of new chemotherapeutic agents and combinations offer a more promising approach [9,12]. One centre reported a 2-year survival of over 30% using new chemotherapy combination [10]. In addition, with the availability of haematopoietic growth factors in the future, more patients can be treated with more intensive combination for a shorter period of time with reduction of risks of haematological toxicities [11] and postponement of chemotherapy schedule and the added benefit of reduction of morbidity associated with prolonged chemotherapy. There may be also the possibility that allowing more intensive dose escalation beyond those currently employed dosage may result in more durable remission and increased survival.

In summary, our experience shows that CAV combination chemotherapy is an effective first-line chemotherapy for the treatment of SCLC in our local population, inducing high response rate and should be offered to all patients with SCLC. Despite cure being achieved in only 15-20% [1] of patients with limited disease, the majority of our patients with extensive disease have had significant relief of their presenting symptoms (haemoptysis, SVCO, cough, weight loss, malaise) making chemotherapy a worthwhile treatment with its benefit far outweighing the potential side-effects. There is also prolongation of their life-span up to five-fold as seen in one of our patients with extensive disease, still alive 17 months after CAV chemotherapy.

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