

Combination Chemotherapy for Small Cell Lung Cancer

A.W. Sufarlan, MRCP

B.M.Z. Zainudin, MRCP

Respiratory Unit, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur

Summary

Small cell lung cancer (SCLC) disseminates early and has poor prognosis. However, SCLC is highly chemosensitive, thus chemotherapy has been established as the primary mode of treatment. Seventeen patients (15 males and 2 females) with median age of 60 years (range 49 to 74 years) were treated with combination cyclophosphamide 750 mg/m², adriamycin 40 mg/m², vincristine 1.4 mg/m² on day 1 and etoposide (VP 16) 75 mg/m² on days 1 to 3 (CAVE). This combination was given in 6 courses at 3 weekly intervals. The response to the chemotherapy and the quality of life of patients was assessed at the third cycle and after the completion of therapy (sixth cycle). The overall response rate was 76.4%; 52.9% achieved complete response and 23.5% had partial response. The survival rate at 6 months was 70.8% and 4 patients (23.5%) were still alive after 1 year of chemotherapy. The median survival after therapy was 36 weeks. There was a 30% overall improvement in the Karnofsky performance score at the completion of chemotherapy.

This study illustrated that the CAVE regimen is effective and beneficial in the majority of our patients with small cell lung cancer.

Key words: Combination chemotherapy, small cell lung cancer, response rate and survival.

Introduction

Lung cancer is now the commonest cause of death from malignant diseases in men in the Western hemisphere and second only to that of breast cancer in women^{1,2}. There is evidence to suggest that the incidence is also rising in developing countries^{3,4}.

Clinical presentation, response to treatment and prognoses are different between the 2 groups of lung cancer, i.e., non small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)^{2,5}. SCLC accounts for approximately 25% of lung cancer and has a comparatively worse prognosis. Without treatment, the overall median survival for patients with SCLC is only 10 weeks and less than 5% of patients are alive at 1 year¹. SCLC is characterised by rapid growth with a doubling time on only 30 to 40 days⁶. Distant metastasis develops early and the disease is usually already disseminated at diagnosis^{2,7}. However, SCLC is highly chemosensitive to a large number of agents^{1,8}. Several studies have shown improvement in patient survival with chemotherapy, establishing it as the most important therapeutic modality^{1,8,9}. It has also been established that the drug combination is superior to single agents¹⁰.

We started a chemotherapy programme for SCLC in our unit in late 1988, using a combination of cyclophosphamide, adriamycin, vincristine and etoposide (CAVE) in the patients presented here.

This study was carried out to assess the response rate, survival and quality of life of our patients with SCLC treated with the CAVE regimen.

Patients and Methods

Seventeen patients with histologically confirmed SCLC were enrolled into this prospective trial. Prior consent was obtained from the patients before enrolment. There were 15 males and 2 females, with ages ranging from 49 to 74 years. All of them had no vascular, renal or neurological diseases which would preclude chemotherapy and none had previous malignancy.

Comprehensive assessment including chest radiograph, bronchoscopic examination and blood biochemistry was performed in all patients. Chest CT, bone and liver scans were done when indicated prior to the therapy. A simplified staging system was employed: limited disease (LD) was defined as disease confined to 1 hemithorax or involving ipsilateral supraclavicular nodes, extensive disease (ED) was when there was more widespread intrathoracic disease, pleural effusion or metastasis¹².

All patients received combination chemotherapy with cyclophosphamide, adriamycin, vincristine and etoposide in 6 cycles. For every cycle of therapy, patients were admitted to the general medical ward for the intravenous administration of drugs over 3 consecutive days at 3 week intervals. Details of the protocol are shown in Table I. Clinical assessment and baseline blood investigations were checked before each course of chemotherapy. Intravenous maxolon (metachlorpromide hydrochloride) 10 mg 3 times a day was used as an antiemetic. Immediate toxic and side effects of drugs were monitored closely both clinically and biochemically. Patients were discharged home after the third day of chemotherapy. Full blood picture was checked on the tenth day after each course of chemotherapy to detect early marrow suppression. The next course of chemotherapy was delayed for a week if the white cell count was less than $3.0 \times 10^9/L$, or platelet count less than $100 \times 10^9/L$.

Response to treatment was assessed at the third course and at completion of chemotherapy (sixth course). This included clinical, biochemical, radiological and repeat bronchoscopy if necessary. The objective response to chemotherapy was recorded as complete response (CR) when there was radiologic disappearance of all tumour mass for at least 1 month during or after chemotherapy. Partial response (PR) was defined as reduction of tumour mass by more than 50% without the appearance of new lesions. No response (NR) denoted a reduction of tumour mass by less than 50% without the appearance of new lesions, and progressive disease (PD) when there was an increase in the tumour size or the appearance of new lesions.

Table I
Treatment schedule for SCLC with CAVE regimen

Cyclophosphamide	750 mg/sqm	60 mins infusion	Day 1
Adriamycin	40 mg/sqm	IV bolus (slow)	Day 1
Vincristine	1.4 mg/sqm	IV bolus (slow)	Day 1
Etoposide (VP16)	75 mg/sqm	30 mins infusion	Days 1 - 3
Maxolon 10 mg tds as antiemetic during the course of therapy			

* Given in 6 courses at 3 weeks interval

IV=intravenous; sqm=square meter; tds=three times a day.

The survival rate of our patients was determined at 6 months and 1 year after the commencement of chemotherapy. The median survival was calculated according to the Kaplan Meier Method¹⁵. The quality of life of patients before and after therapy was measured by the Karnofsky performance status scale (KPS) which is an 11 point rating ranging from a normal functioning patient (100%) to death (0%)¹⁴. After the completion of 6 courses of chemotherapy, all of the patients were followed-up at the Chest Clinic regularly. No maintenance or further chemotherapy was given.

Results

Of the 17 patients with SCLC studied, 12 were in the stage of extensive disease and 5 had limited disease. Nine patients achieved complete response (52.9%), 4 partial (23.5%) and 4 (23.6%) failed to show any response, of whom 3 died before the third course of chemotherapy. The overall response rate (CR+PR) to CAVE regimen was 76.4%. In most cases, the initial response occurred in the first or second cycle of chemotherapy. Nausea and vomiting were experienced by a majority of the patients but this was easily controlled with maxolon (metachlorpromide) 10 mg 3 times a day. Hair loss occurred in all patients. Three patients needed postponement of their chemotherapy due to leucopaenia but completed all the cycles. No other side effects were recorded.

Twelve patients survived at 6 months and 4 patients were still alive after 1 year, giving the survival rate of 70.5% and 23.5% at 6 months and 12 months respectively. Median survival based on Kaplan Meier survival curves was 36 weeks. The quality of life measured by KPS before chemotherapy ranged between 40% to 70%, with the median of 50%. There was a significant improvement in the quality of life in the majority of our patients after chemotherapy. The overall improvement of KPS was about 30% among the survivors. The overall results showed a better response in patients with limited disease in all aspects (Table II).

Table II
Detailed characteristics of 17 patients with SCLC before and after chemotherapy

Characteristics	Limited disease	Extensive disease	Overall/total
Number	5(M4 F1)	12(M11 F1)	17
Age median (yrs)	55	62	60 (49 - 74)
Karnofsky Performance Score (KPS median)			
Before treatment	70%	40%	48.8%
After treatment	90%	70%	77.5%
Improvement of KPS	20%	30%	26.2%
Response rate			
Complete response	80% (4)	41.69% (5)	52.9% (9)
Partial response	20% (1)	25.9% (3)	23.5% (4)
No response of disease progress	0%	35.5% (4)	23.6% (4)
Overall response	100% (5)	66.6% (8)	76.4% (13)
Survival at 6 mths	80% (4)	66.6% (8)	70.5% (12)
Survival at 1 year	40% (2)	16.6% (2)	23.5% (4)
Overall median survival : 36 weeks			

Discussion

Chemotherapy has a central and well-established role in the management of small cell lung cancer. Combination chemotherapy gives better results than single drug therapy¹⁰. Various combinations of drugs such as cyclophosphamide, doxorubicin, etoposide (VP 16), vincristine and cisplatin were able to induce initial objective response in 50% to 60% of patients^{15,16}. The response usually occurs within 3 to 4 weeks of treatment. Response rates of 80% or more have been reported with current combination chemotherapy for SCLC and complete clinical response is achieved in approximately 50% of patients with limited disease⁸. The Lung Oncology Group from University of Toronto reported an overall response of induction chemotherapy with cyclophosphamide, adriamycin, cisplatin and vincristine or etoposide which was as high as 80% (complete response 38% and partial response 42%)¹⁷.

In our study, we treated 17 patients with SCLC (5 limited and 12 extensive) with a combination of 4 drugs regimen, namely cyclophosphamide, adriamycin, vincristine and etoposide (CAVE), in 6 courses at 3 weeks interval. The majority of our patients started with a poor KPS score (50% or less), especially those with extensive disease. Despite that, our preliminary result was very encouraging, with an overall response of 76.4%, with 9 patients (52.9%) achieving complete response and 4 (23.5%) partial response. The quality of life of our patients also improved and they seemed to tolerate the therapy well. The survival rate of 70.5% and 23.5% at 6 months and 1 year respectively, with a median survival of about 36 weeks, is comparable to the results of Macchiarini *et al*¹³. In their study of 34 previously untreated patients with limited disease the overall response rate was 74% with 53% of patients achieving complete response after 6 courses of etoposide, epirubicin and cyclophosphamide alternating with cisplatin and etoposide.

The optimal duration of chemotherapy has also been addressed recently. One such study came from the Research Campaign Trial in the United Kingdom, which studied 616 patients who were randomised to receive either 4 or 8 courses of chemotherapy and at relapse to receive either symptomatic treatment or further chemotherapy using agents other than used for the initial induction chemotherapy. The overall response rate was 61% with no significant increase in patients receiving 8 courses (63%)¹². There was no advantage in further chemotherapy at relapse if 8 courses were given at initial treatment. However, there was slight improvement with further chemotherapy in those who originally received only 4 courses. The United Kingdom Lung Cancer Working Party also addressed the same issue; they studied 497 patients by giving them 6 cycles of a 4 drug regimen¹⁸. Additional radiotherapy for responding patients with limited disease was given between the second and third courses of chemotherapy. At the completion of the initial 6 cycles, patients whose disease remained controlled were randomly allocated to 6 further courses of maintenance chemotherapy or to no maintenance chemotherapy. The overall response was 63% and the median survival was 39 weeks. There was no overall advantage for patients who received the maintenance treatment. Based on these 2 studies, it has been suggested that about 6 courses of chemotherapy is a reasonable optimal duration for initial chemotherapy and that maintenance therapy is not useful¹⁹.

Functional status assessment is frequently used to complement medical information in evaluating the impact of disease to an individual patient. Loss of function is generally related to the cumulative physical, physiological and psychological effect of disease process and drug side effect. In cancer therapy clinical trials, performance status scale has been shown to be an important predictor of response to therapy and survival rate^{20,21}. The Karnofsky performance status scale (KPS) is the most widely used method quantifying the functional status of cancer patients^{4,22}. In our study we found that the response to chemotherapy and survival rate was poorer in patients with poor KPS at diagnosis. In those patients who survived after 6 courses of chemotherapy performance status had improved significantly as compared to before treatment.

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In conclusion, our study substantiates the combination of cyclophosphamide, adriamycin, vincristine and etoposide as an effective regimen for small cell lung cancer. Six courses of combination chemotherapy at 3 weekly intervals is optimal in the majority of such patients.

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