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Cyclic alternating combination chemotherapy for small cell lung cancer

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Summary. *Sixty-two patients with small cell carcinoma of lung received cyclic alternating non-cross-resistant combination chemotherapy. Radiation to the chest was given to all the patients. Patients were given a course of VP16, adriamycin and vincristine (VAV) followed by radiation (3,000 rads) to the chest and then a second course of VAV. Three weeks later, a course of cytoxan, CCNU, and methotrexate (CCM) was given (6 weeks). Subsequently, the treatment was cycled between two courses of VAV (6 weeks) and one course of CCM (6 weeks). Overall objective response rate of 73%, with 45% complete response, was noted. Overall median survival was 50 weeks, with 83 weeks for complete responders. Median survival for patients with regional disease was 58 weeks compared to 40 weeks for extensive disease. All the patients headed for complete response did so prior to receiving CCM. These results were not superior to conventional combination chemotherapy regimens.*

Introduction

Small cell carcinoma of the lung is highly sensitive to multiple chemotherapeutic agents and radiation therapy [4, 29]. The combination of multiple drugs appears to be superior to single-agent therapy, while three drugs appear to be superior to two [5, 13]. Continued improvement may be seen by the addition of more agents beyond three [14]. The combination of chemotherapy plus radiotherapy appears to improve tumor control in the thorax in limited disease, even though the advantage in terms of survival is not clear [8, 20–22]. The role of radiotherapy in patients with extensive disease remains to be clarified; it is, however, unlikely to improve survival [30].

Several chemotherapeutic agents are known to have significant activity against small cell lung cancer. Those single agents with over 20% response rate include cyclophosphamide, adriamycin, methotrexate, hexamethylmelamine, vincristine, procarbazine, the nitrosoureas (BCNU and CCNU), and VP-16 [6, 10, 17, 23, 25, 28]. VP-16, as a single agent, has been shown to have over 40% response rate in small cell lung cancer [6, 17]. Multiagent chemotherapy containing VP-16 yielded up to 80% objective response rate [1]. A combination of methotrexate, cyclophosphamide, and CCNU with radiation therapy to the chest achieved an objective response rate of 65% with median survival of 8.2 months in limited disease [26].

Despite significant progress in the treatment of small cell lung cancer, a vast majority of patients still succumb to their disease. Recently, there appears to be considerable interest in cyclic alternating combination chemotherapy with non-cross-resistant regimens [2, 7, 9, 18]. The superiority of these regimens over conventional combination chemotherapy is presently inconclusive. At Roswell Park Memorial Institute, an alternating non-cross-resistant combination was initiated and the results were published in 1981 [26]. Follow-up results are contained in this report.

Patients and methods

Sixty-two patients with histologically documented small cell carcinoma of lung were studied. Eligibility criteria included: (1) no previous chemotherapy or radiotherapy; (2) performance status of ≤ 3 (E.C.O.G.); (3) measurable or evaluable disease; (4) adequate bone marrow (WBC $\geq 4{,}000/mm^3$, platelets $\geq 100{,}000/mm^3$), renal (serum creatinine ≤ 1.5 mg%) and hepatic (serum SGOT ≤ 50 units, serum bilirubin ≤ 1.3 mg%) function.

The tumors were classified as either regional or extensive. Regional disease must be confined to one hemithorax, including extension to the mediastinum, ipsilateral hilum, pleura, thoracic wall or to ipsilateral scalene or supraclavicular nodes. Extensive disease includes all other patients. Standard criteria were used for assessing tumor response.

There were 38 males and 24 females. Median age was 62 (range: 37–76). One patient had a performance status (PS) of 0. Thirty eight patients had a PS of 1, 21 patients had a PS of 2, and two patients had a PS of 3. Fifty-five patients had small cell type, five patients had intermediate cell type, and 2 patients had mixed small and intermediate cell type. Thirty-two patients had regional disease and 30 patients had extensive disease (Table 1).

The quantities of all drugs, except vincristine, were reduced to two-thirds if the leukocyte count was $3{,}000–4{,}000/mm^3$. Amounts were reduced to half of the full dose if the leukocyte count was $2{,}000–3{,}000/mm^3$. Treatment was interrupted if the leukocyte count was $< 2{,}000/mm^3$ or if platelets were $< 50{,}000$. The methotrexate dose was modified if mucositis developed. The median total doses for various drugs were: VP-16 – 1,223 mg, vincristine – 15.8 mg, adriamycin – 230 mg, cyclophosphamide – 1,550 mg, CCNU – 80 mg, and methotrexate – 112.5 mg.

Patients with brain metastasis found at initial diagnosis were included in the study and treated with regional chemotherapy using various drugs with or without radiotherapy. One patient had surgical debulking in addition to chemotherapy.

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Table 1. The treatment program consisting of VAV + CCM + RAD

VAV =	VP-16	75 mg/m^2 IV days 1, 3, 5
	Vincristine	1.5 mg/m^2 (max. 2.0 mg) IV days 1, 5
	Adriamycin	45 mg/m^2 IV day 5
CCM =	Cyclophosphamide	600 mg/m^2 IV day 1, repeated for 21 days
	CCNU	50 mg/m^2 PO day 1, repeated for 6 weeks
	Methotrexate	30 mg/m^2 IM day 1, 8, repeated for 21 days
RAD =	Radiation therapy	3,000 rads to chest in 10 fractions over 2 weeks

VAV →	× RT →	VAV →	CCM →	VAV
1 course (3 weeks)	3,000 rads to chest	1 course (3 weeks)	1 course (6 weeks)	2 courses (6 weeks)

Duration of response was measured from day 1 of response until relapse. Survival was measured from day 1 of the treatment until death. Survival curves were derived using the method of Kaplan and Meier.

All patients were included in survival curves. However, six patients could not be evaluated for response (early deaths three; incomplete treatment – three).

Results

Twenty-five patients (45%) obtained complete response and 16 patients (29%) obtained partial response for an overall objective response rate of 73%. The median remission duration was 67 weeks for complete responders and 35 weeks for partial responders. The disease was stable in nine patients (16%) with median duration to progression of 23 weeks. The disease progressed in the remaining six patients (11%). Twenty-seven of 31 patients (87%) with regional disease responded to the treatment (CR = 61%, PR = 26%), whereas 14 of 25 patients (56%) with extensive disease responded (CR = 24%, PR = 32%). Median remission duration was 56 weeks for limited disease and 30 weeks for extensive disease (P = 0.00087).

Twenty of 37 patients (54%), with initial PS of 0 or 1, had a CR compared to five of 18 patients (28%) with a PS of 2, and none of one patient (0%) with a PS of 3.

Of the 25 complete responders, four patients are alive free of disease, three patients died of causes unrelated to their neoplastic desease and one patient was lost on follow-up. Seventeen of 25 complete responders have relapsed. Chest-only relapses were noted in three patients (18%); while in four other patients (24%), the relapse was noted in the chest as well as in the extrathoracic sites. Five patients (29%) had relapses only in the brain; one patient (6%) relapsed only in the liver; one patient relapsed only in soft tissue (pectoral area); and one patient relapsed only in axillary lymph node.

Overall median survival was 50 weeks. Complete responders achieved a median-duration survival of 83 weeks as compared to 40 weeks in partial responders, 36 weeks for patients with stable disease, and 12 weeks for nonresponders

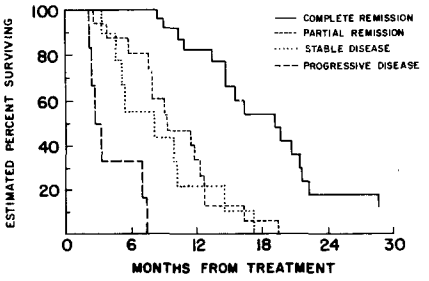

Fig. 1. Survival by response

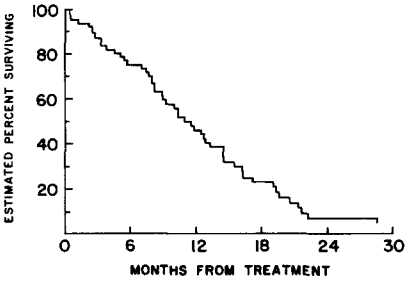

Fig. 2. Survival

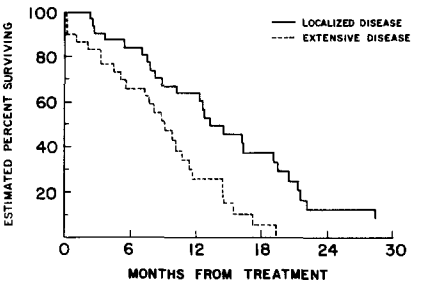

Fig. 3. Survival by extent of disease

($P < 0.0001$) (Fig. 1). Survival curves indicate that 20% of all patients were alive beyond 18 months (Fig. 2). There are two long-term survivors alive and free of disease at 4.8 years and 5.5 years, respectively. Both of these patients had regional disease and an initial PS of 1. Both achieved complete remission with treatment. The former patient underwent right lower lobectomy following four courses of VAV, one course of CCM, and radiation to the chest. No tumor was found in the surgical specimen. The latter received 2+ courses of VAV, one course of CCM, and radiation to the chest; then his chemotherapy was changed to a different protocol because of cardiac toxicity. Median survival for patients with regional disease was 58 weeks compared to 40 weeks for those with extensive disease (P = 0.0025; Fig. 3).

Among the patients with extensive disease, those with central nervous system and liver metastases discovered on initial evaluation had significantly lower survival of 25 weeks and 30 weeks, respectively, when compared to 40 weeks for patients with bone metastasis.

There were five treatment-related deaths. Three patients died of infections and two died of respiratory failure secondary to pulmonary fibrosis (no residual tumor). Of the three infection deaths, one patient had sepsis with *Pseudomonas* and *Klebsiella*. A second patient had sepsis with *E.coli* and *Streptococcus* pneumonia; in addition, *Candida* and herpes were identified in the esophagus and *Candida* in the larynx. A

third patient had bronchopneumonia. WBC counts in these patients were 1,200, 300, and 1,000/mm^3, respectively, just before death. The latter three patients had residual disease at autopsy. The cause of death could not be ascertained in two patients. No tumor recurrence was detected clinically. Both developed severe generalized weakness, with one of them also developing severe postural hypotension requiring high doses of mineralocorticoids. One patient died of erythema multiforme (Stevens-Johnson syndrome), which was attributed to phenytoin (Dilantin).

Hematologic toxicity was moderate, requiring modification of 37% of all courses of chemotherapy. Mild-to-moderate nausea and vomiting were noted in 42% of the patients, while diarrhea was noted in 11%. Paresthesias in varying degrees were evident in 50% of the patients, with severe impairment in three (5%) of them. Ten percent developed mild-to-moderate dysphagia following radiation to chest. Mucositis was noted in 13%, which was severe in two patients. Alopecia was seen universally.

Discussion

Over the past several years, treatment for small cell carcinoma of the lung of Roswell Park Memorial Institute has evolved from a single agent (methotrexate) to multiagents (cyclophosphamide, CCNU, and methotrexate), with the most recent treatment being cyclic alternating combination chemotherapy [26]. In this follow-up report on the latter treatment, a median survival of 50 weeks with 83 weeks for complete responders was noted. Sixty-one percent of the patients with regional disease showed complete response compared to 24% of patients with extensive disease. Survival curves showed that 20% of all patients were alive beyond 18 months. There were two (3%) long-term survivors.

Currently, most combination chemotherapy regimens produce 80% response rate (CR + PR) [2, 3, 11, 12, 15, 27]. Approximately 15%–20% of the patients with limited disease are expected to achieve long-term, disease-free survival ($\geq$ 3 years) [1].

Considerable improvement in response rate and in survival has been achieved with the cyclic alternating chemotherapy regimen compared to that of previous conventional combination chemotherapy (CCM) studied at Roswell Park Memorial Institute. However, the results do not appear to be superior to that of conventional combination chemotherapy, as generally reported. Since it is known that complete response yields longer survival, the goal is to increase the complete response rate. In this study, all the patients destined for complete response did so prior to receiving CCM; thus, it failed to increase the number of complete responses.

The most frequent site of relapse in complete responders was the primary (18% chest alone + 24% chest as well as extrathoracic site). Radiation therapy to the chest did not appear to prevent local recurrence [22]. Of the 17 patients who relapsed after complete response, 11 (65%) had relapse in their central nervous system (CNS) [CNS-only recurrences were noted in five (29%)], indicating a possible role of prophylactic therapy [19, 22].

Respiratory failure was the cause of death in at least two patients. Pulmonary fibrosis and interstitial pneumonitis were found at autopsy, and there was no residual disease. While this could be due to radiation to the chest, the possible contribution from chemotherapy cannot be ruled out [16]. Severe generalized weakness in two patients, with severe orthostatic hypotension in one of them, was particularly puzzling. Both of these patients were over 70 years of age (74 years and 76 years). No recurrence of disease was noted in them. These symptoms were attributed to severe neuropathy. While most of the patients tolerated this regimen well, the possible enhancement of vincristine neuropathy by VP-16 should be considered [24].

This study yielded results comparable to conventional combination chemotherapy regimens. To draw definite conclusions as to the superiority of cyclic alternating non-cross-resistant chemotherapy, a randomized trial is in order.

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