Acta Medica Okayama

Volume 37, *Issue* 2 1983 *Article* 7

APRIL 1983

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Abstract

Forty-one patients with small cell carcinoma of the lung were treated with a four-drug combination of cyclophosphamide, vincristine, methotrexate, and procarbazine. The response rate was 68% (28 responded among 41 patients), with 10 complete responses (24%) and 18 partial responses (44%). The median survival time from the initiation of chemotherapy was 11 months for patients with limited disease and 8 months for those with extensive disease. Patients who achieved complete response survived significantly longer than those who did not; the median survival time for complete responders was 14.5 months, compared to 8.5 months for partial responders and 6 months for non-responders. Myelosuppressive toxicity remained within acceptable limits, with 5% incidence of leukocytopenia (less than 1,000/microliter) and 7% incidence of thrombocytopenia (less than 50,000/microliter) following the first course of the regimen.

KEYWORDS: small cell lung cancer, combination chemotherapy

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*PMID: 6307001 [PubMed - indexed for MEDLINE]

Acta Med. Okayama 37, (2), 147–153 (1983)

COMBINATION CHEMOTHERAPY FOR SMALL CELL CARCINOMA OF THE LUNG: EVALUATION OF FOUR-DRUG COMBINATION OF CYCLOPHOSPHAMIDE, VINCRISTINE, METHOTREXATE, AND PROCARBAZINE

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Received November 4, 1982

Abstract. Forty-one patients with small cell carcinoma of the lung were treated with a four-drug combination of cyclophosphamide, vincristine, methotrexate, and procarbazine. The response rate was 68 % (28 responded among 41 patients), with 10 complete responses (24 %) and 18 partial responses (44 %). The median survival time from the initiation of chemotherapy was 11 months for patients with limited disease and 8 months for those with extensive disease. Patients who achieved complete response survived significantly longer than those who did not; the median survival time for complete responders was 14.5 months, compared to 8.5 months for partial responders and 6 months for non-responders. Myelosuppressive toxicity remained within acceptable limits, with 5 % incidence of leukocytopenia ($<1{,}000/\mu l$) and 7 % incidence of thrombocytopenia ($<50{,}000/\mu l$) following the first course of the regimen.

Key words: small cell lung cancer, combination chemotherapy.

Although untreated small cell carcinoma of the lung (SCC)has a worse clinical course than other histologic types of lung carcinoma, this disease is sensitive to a viriety of chemotherapeutic agents. Several clinical trials have revealed that combination chemotherapy produced more remissions and longer survival than single drug therapy. Consequently, combination chemotherapy is the principal therapy for this disease (1).

Based on data regarding the effectiveness and toxicity of single drug therapy (2, 3), we designed studies in 1975 to evaluate the effectiveness of a four-drug combination (COMP) of cyclophosphamide, vincristine, methotrexate, and procarbazine in patients with SCC. We have previously reported preliminary results with this regimen (4). This paper reports response and survival data, and toxocity in 41 patients.

MATERIALS AND METHODS

Forty-one patients (37 males and 4 females) with histologically or cytologically documented SCC were included in this study from October 1975 to December 1980. None of the patients had received chemotherapy or radiotherapy. The median age of the patients at diagnosis was 64 years (range, 44-76).

Prior to therapy, a complete history was taken and a physical examination, chest X-ray examinations, fiberoptic bronchoscopy with biopsy, bone marrow aspiration and biopy, and liver and bone scan were performed. Computerized tomography was introduced for the detection of metastases in the brain, liver and abdominal lymph nodes in 1978.

After completion of staging, 23 patients were defined as having limited disease, *i.e.*, disease confined to one hemithorax with or without bilateral mediastinal and ipsilateral supraclavicular lymph nodes, and 18 as having extensive disease (disease beyond these limits). Twenty-one patients had a Zubrod (5) performance status (PS) of 0 or 1, 16 patients had a PS of 2 or 3, and four patients had a PS of 4.

Chemotherapy was given initially according to the following schedule (Table 1): Cyclophosphamide, 270 mg/m^2, intravenously (iv), day 1-5; vincristine, 1 mg/m^2, iv, day 1; methotrexate, 6.5 mg/m^2, intramuscularly, day 1-5; and procarbazine, 65 mg/m^2, orally, day 1-5. Cyclophosphamide and methotrexate were given orally to out-patients. Courses of treatment were repeated every 3-4 weeks from day 1 of the first course. Hematologic profiles were obtained on a weekly basis to assess toxicity and to adjust subsequent drug dosages. When the WBC count nadir reached $< 2{,}000/\mu l$ or the platelet count nadir $< 100{,}000/\mu l$, a 25 % reduction in cyclophosphamide was used as the standard dose in subsequent courses. Responders continued receiving chemotherapy until disease progression occurred. In 14 of the 23 patients with limited disease, radiation therapy (4,000 rads) of the thorax covering the primary site, hilum, mediastinum and ipsilateral supraclavicular area was given for the consolidation of the chemotherapy effect for four weeks between the second and the third course of the chemotherapy.

A complete remission (CR) was defined as the total disappearance of the tumor in physical examination and chest roentgenogram. CR also required disappearance of tumor cells in tissue from bone marrow aspiration and biopsy as well as normalization of the liver scan or computerized tomogram. However, fiberoptic bronchoscopy for the assessment of CR was not performed routinely. A partial response (PR) was defined as > 50 % reduction in the product of two perpendicular diameters of the tumor as agreed upon by two investigators. For patients with evaluable but unmeasurable lesions, CR was as defined above. Duration of response was calculated from the time of the CR or PR determination, and survival was calculated from the first day of the chemotherapy.

TABLE 1. DOSE AND SCHEDULE OF COMP REGIMEN

Drug	Dose (mg/m^2)	Route	Schedule	
Cyclophosphamide	270	i.v. (p.o.)*	Day 1-5	
Vincristine	1	i.v.	Day 1	Courses repeated
Methotrexate	6.5	i.m. (p.o.)*	Day 1-5	every 3-4 weeks
Procarbazine	65	p.o.	Day 1-5	

( )*: Route for out-patients

RESULTS

Of 41 patients, 28 (68 %) responded to chemotherapy including 10 (24 %) CRs (Table 2). There are no differences in the total response rate between patients with limited disease and those with extensive disease, but the CR rate in the former (35 %) is much higher than in the latter (11 %). The maximal tumor response generally occurred during the first two courses of the treatment. No patients who had a PR at the end of the third course of the treatment subsequently developed a CR. The duration of response in complete responders is longer than in partial responders. The median duration of response is 6.5 months (range, 2-41 months) for CR and 3.5 months (range, 1.5-10 months) for PR. Ono of the patients with limited disease is currently in remission 26 months following the initiation of therapy.

Patient survival according to the extent of disease is shown in Fig. 1. The median survival time of the total population from the initiation of therapy was 9 months. Patients with limited disease had a somewhat better median survival (11 months) than those with extensive disease (8 months). Of 23 patients with limited disease, 10 (43 %) survived over one year, while only three of the 18 patients (17 %) with extensive disease lived over one year. Radiation therapy did not

TABLE 2. RESPONSE TO CHEMOTHERAPY ACCORDING TO EXTENT OF DISEASE

Extent of disease	No. of patients	No. (%) of		
		CR*	PR**	CR + PR
Limited	23	8 (35)	8 (35)	16 (70)
Extensive	18	2 (11)	10 (56)	12 (67)
All	41	10 (24)	18 (44)	28 (68)

*CR = Complete response, **PR = Partial response

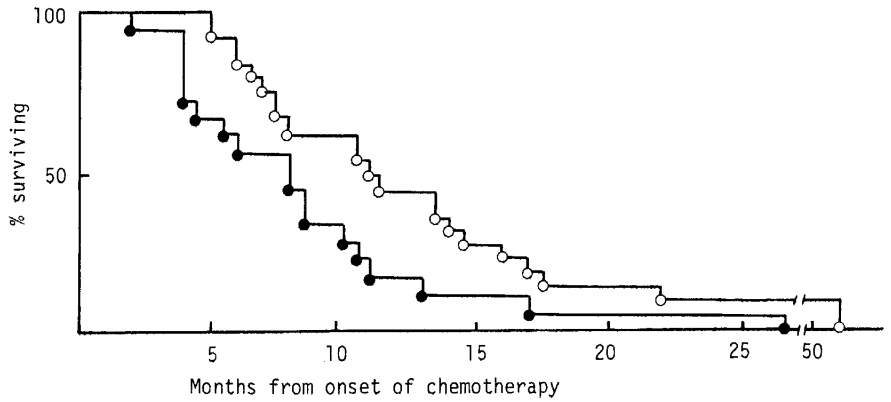

Fig. 1. Patient survival according to the extent of disease. ○: Limited disease (N = 23). ●: Extensive disease (N = 18).

affect the median survival time of patients with limited disease; a group of 14 patients who received chest radiation had a median survival of 11 months, compared with 11 months for a group of nine patients who received no chest radiation. However, both of the two patients with limited disease who survived over two years had received chest radiation during chemotherapy as a part of the primary treatment program.

As shown in Fig. 2, patients who achieved CR survived significantly longer than those who did not; the median survival for complete responders was 14.5 months, compared with 8.5 months for partial responders and 6 months for non-responders. Of 13 complete responders, three survived more than 2 years form the initiation of therapy. One of these patients with extensive disease relapsed on maintenance therapy and died at 25 months. The other two patients had limited disease and received concomitant chest radiation therapy. One had a relapse at the primary site and, consequently, in the brain 21 months after cessation of all treatment and died at 51 months. The other is disease-free at 26 months, having been off all treatment for 12 months.

Three patients with limited disease achieved CR with chemotherapy followed by chest radiation for a minimal tumor residue at the primary site. They had an identical survival time with those achieving CR with chemotherapy alone. The initial PS tended to correlate with survival; patients with a PS of 0 or 1 had a median survival of 11 months, compared with 7.8 months for those with a PS of 2, 3 or 4.

The principal toxicity of this regimen was myelosuppression. As shown in Table 3, leukocytopenia $< 3{,}000/\mu l$ occurred in 59 % of the patients and thrombocytopenia $< 100{,}000/\mu l$ occurred in 15 % of the patients in the first course of the regimen. However, severe cytopenias were noted only in a few patients. Blood count nadirs were seen between day 8 and day 19 (median, day 14) in the

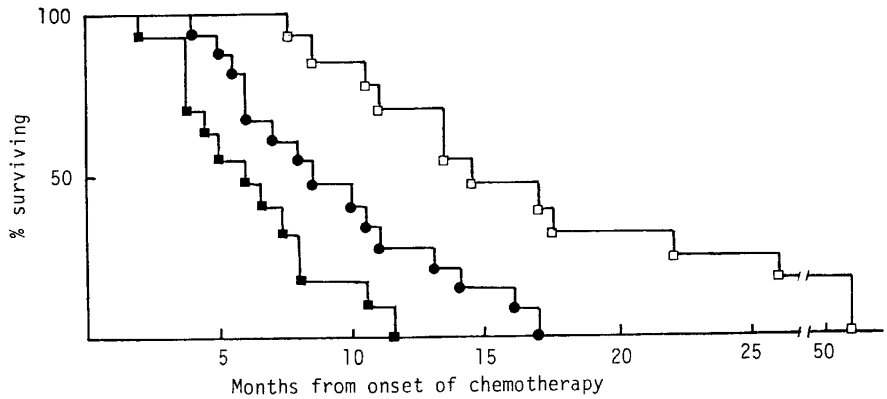

Fig. 2. Patient survival according to response category. □: Complete responders (N = 13), including three patients who received radiation therapy of the thorax for residual disease at the primary site. ●: Partial responders (N = 15). ■: Nonresponders (N = 13).

TABLE 3. MYELOSUPPRESSIVE TOXICITY SEEN IN THE FIRST COURSE OF COMP

WBC count nadir ($\times 10^3/\mu l$)	No. of patients (%)	Platelet count nadir ($\times 10^3/\mu l$)	No. of patients (%)
≥ 3.0	17 (41)	≥ 100	35 (85)
2.9-2.0	13 (32)	99-50	3 (7)
1.9-1.0	9 (22)	< 50	3 (7)
< 1.0	2 (5)		

WBC count and between day 7 and day 17 (median, day 10) in the platelet count. The median time to recover was approximately 7 days. Although myelosuppression was relatively mild, it tended to accumulate during repeated courses resulting in infectious complications in some instances. There were severe infections documented in two neutropenic patients with a poor PS; one patieht developed septicemia after three courses and the other bacterial pneumonia after two courses of the regimen. Both of the patients, however, improved with an intensive antimicrobial chemotherapy.

Although most patients experienced anorexia and/or upper abdominal discomfort during drug administration, nausea and vomiting occurred only in 27 % of the patients. Mild to moderate mucositis was noted in 10 % of the patients. Elevation of s-GOT and/or s-GPT which was noted in 20 % of the patients was transient and returned to normal before the start of the subsequent course in most patients. Alopecia, either partial or total, was experienced by almost all patients. Although vincristine neuropathy with mild acral paresthesia occurred in approximately one-third of the patients, dose reduction was required in no patients.

DISCUSSIONS

Small cell carcinoma of the lung is a highly malignant disease with a rapid progression, and untreated patients have a median survival of a few months (6). However, this disease is the most susceptible to chemotherapy among the four major histological types of lung carcinoma. It is generally accepted that combination chemotherapy is superior to single-agent chemotherapy in response rate, including percentage of CR, and in median survival time (1, 7).

The four-drug combinarion regimen, COMP, utilized in this study resulted in a relatively high response rate of 68 %, including a CR rate of 24 %, in patients with SCC. The therapeutic results are more than twice in the CR rate as well as in the median survival time than were obtained through single-agent treatment (6, 8), and comparable to other combinations reported in the literature (1, 7, 9). This study also reaffirms that a lasting complete response is the major determinant of patient survival. As for toxicity, the COMP regimen was well tolerated. The degree of myelosuppression and the incidence of infection were not any higher

than has been reported with other combinations (1, 7-9). There were no treatment-related deaths among our patients.

We consider the COMP only an initial step in the control of SCC. Although the regimen produced responses in a significant proportion of the patients, the CR rate was still too low to gain a significant prolongation of the median survival for the total population. Moreover, the majority of the complete responders relapsed and only a few patients, who had received radiation therapy of the thorax, enjoyed continued response. These facts stress the need for more effective therapy. In the present study, all patients responding had their maximal tumor response by the end of two courses of the regimen, as has been observed in other studies of SCC (8). Since prolonged survival generally requires attainment of a CR, and since several active agents potentially non-cross-resistint to those in the COMP, such as VP-16-213 (10) and adriamycin (11), are available today, alternate administration of two non-cross-resistant combinations appears reasonable. On the basis of the therapeutic results obtained through the present study, we started a new therapy in which the COMP was alternated with a combination of VP-16-213, adriamycin and ACNU.

Although the patients with limited disease who received radiation therapy of the thorax had a similar median survival with those who did not, and the majority of relapses initially occurred within the thorax regardless of irradiation, it is important to note that only a few patients among those who received radiation therapy survived over two years with a lasting response. Thus, a randomized trial of combination chemotherapy alone or with radiation therapy may better define the role of combined therapy in the treatment of SCC, especially in patients with limited disease.

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