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Cyclophosphamide, vincristine, cisplatin, VP-16 and radiation therapy in extensive small-cell lung cancer*

A Southwest Oncology Group study

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Summary. Patients with extensive small-cell lung cancer were given induction chemotherapy consisting of cyclophosphamide, vincristine, cisplatin, and etoposide (COPE) every 3 weeks for four cycles. Responding patients then received chest and elective whole-brain irradiation. Patients presenting with brain metastases received therapeutic brain irradiation during the first cycle of chemotherapy. No maintenance therapy was given, but two late intensification cycles of COPE were given at weeks 24 and 48. Among the 34 evaluable patients, the response rate to induction chemotherapy was 59%, with 10% achieving a complete response (CR) and 49%, a partial response (PR). Of the 18 patients who completed chest irradiation, 3 achieved a CR, producing an overall CR rate of 18%. Five patients completed the projected course of treatment. The median duration of response for all patients was 8 months (range, 2–30+ months) and the median survival was 9 months (range, 1–30+ months). Complete responders had a median response duration of 9 months and a median survival of 11 months. This regimen produced significant myelosuppression, with 5 neutropenic deaths (13%) occuring in the 38 patients evaluable for toxicity; an additional 16% required hospitalization for fever while neutropenic. Only six patients (13%) had nadir platelet counts of $<50{,}000/mm^3$ with no episodes of thrombocytopenic hemorrhage. Nausea, vomiting, and neurotoxicity were mild to moderate in all patients. One patient with no evidence of disease died of radiation pneumonitis at 6 months. While producing significant toxicity, this regimen did not result in a CR rate or survival advantage that would suggest its superiority over standard regimens for small-cell lung cancer.

Introduction

It is generally agreed that the results achieved in the treatment of small-cell lung cancer are at a plateau of effectiveness. About 10% of patients with limited-stage disease and only 2% of those with extensive cancer achieve long-term disease-free survival with presently available therapy [17]; nearly all of the latter survivors are individuals who achieve a complete remission. A number of attempts have been made to develop better combinations of drugs through the addition of active compounds. The administration of VP-16 as a single agent in a series of phase II trials has produced response rates of 40%–60% [25]. In phase II clinical trials, the combination of VP-16 and cisplatin has produced overall response rates of >50% in patients with progressive small-cell carcinoma [8, 19, 29]. Since VP-16 is probably synergistic with cisplatin and cyclophosphamide is the most active single agent other than VP-16, it seemed logical to test the combination of cisplatin, VP-16, and cyclophosphamide as initial induction therapy in the treatment of small-cell lung cancer. As vincristine has demonstrated a useful additive effect and is nonmyelosuppressive, it was added at a time in the treatment cycle (day 14) when there should have been no possibility of an unfavorable kinetic interaction with VP-16. This is the report of a Southwest Oncology Group pilot study (SWOG 8460) using cyclophosphamide, vincristine, cisplatin, and VP-16 (COPE) as induction chemotherapy in extensive small-cell lung carcinoma. As a previous randomized SWOG study [10] demonstrated a decrease in the local relapse rate in complete responders with limited small-cell lung carcinoma who received thoracic irradiation, the latter was used as consolidation therapy in responding patients. Based on evidence that elective wholebrain irradiation can reduce the incidence of brain metastases, this was done concomitantly with the chest irradiation. Late intensification chemotherapy (COPE) was given because a previous, prospectively randomized SWOG study [18] demonstrated a survival advantage for responders with extensive small-cell lung cancer who received such treatment.

Materials and methods

Staging and eligibility. All patients with a histologic or unequivocal cytologic diagnosis of extensive small-cell carcinoma of the lung were eligible for study. Eligible patients showed evidence of tumor spread beyond the ipsilateral hemithorax and draining regional nodes. Staging evaluation included a history and physical examination, complete blood count (CBC), with differential and platelet counts, measurements of creatinine, alkaline phosphatase,

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lactic dehydrogenase (LDH), SGOT, bilirubin, sodium, potassium, and chloride, a chest X-ray, an ECG, computerized tomographic scans of the brain and abdomen, a radionuclide bone scan, unilateral bone marrow aspirate, and biopsy. Patients with a serum creatinine of > 1.6 mg/dl, an estimated creatinine clearance of < 60 ml/min, or uncontrolled heart failure were ineligible for study. Routine restaging was done at the end of the induction chemotherapy and again at weeks 24 and 48. After a detailed explanation, all patients signed a written informed consent form that had been approved by a human subjects review committee.

All patients received induction chemotherapy consisting of 750 mg/m^2 cyclophosphamide i.v. on day 1; 100 mg/m^2 VP-16 i.v. on days 1–3; 50 mg/m^2 cisplatin i.v. on day 2, only given in 250 cc normal saline with prior i.v. hydration of no less than 1,500 cc normal saline in 12 h; and 2 mg vincristine i.v. on day 14 only (COPE). Induction therapy was given every 3 weeks for 4 cycles delivered over 12 weeks. There were appropriate dose reductions in subsequent cycles for cyclophosphamide, VP-16, and cisplatin due to neutropenia and thrombocytopenia. Cisplatin was omitted on subsequent cycles if the serum creatinine was > 1.6 mg/dl. Cisplatin and vincristine were omitted for grade 3 or greater peripheral neuropathy. The vincristine dose was reduced to 1 mg if the bilirubin level was $\geqslant 2$ mg/dl.

At week 12, patients who had responded to induction chemotherapy with COPE were given 5,000 cG to the chest in 200-cG fractions 5 days a week. (AP/PA) fields were treated to 4,400 cG, followed by three final fractions delivered by tangential fields at 200 cG per fraction to a total dose of 5,000 cG. The target volume of the tumor was based on pretreatment tumor volumes and included the superior mediastinum, ipsilateral hilum, contralateral hilar nodes, and inferior mediastinum to at least 5 cm below the carina. Elective whole-brain irradiation (WBI) was given to all patients during chest irradiation, delivered in 10 fractions of 300 cG per fraction over 2 weeks to a total dose of 3,000 cG. Patients with brain metastases at the time of diagnosis were given WBI as outlined during the first cycle of chemotherapy.

Late intensification consisted of two additional courses of COPE given exactly as during the induction phase at weeks 24 and 48. No further therapy was given following the completion of late intensification. Patients with both partial (PR) and complete responses (CR) were followed until progressive or relapsed disease occurred; they were then removed from the study and further therapy was given at the discretion of their primary physician.

Patients characteristics. From May 1984 to October 1985, 40 patients were entered in the study. One patient with limited disease was ineligible. Of the 39 eligible patients, 32 were men, as outlined in Table 1. The median age was 60 years (range, 40–75 years). In all, 66% were fully ambulatory, with a SWOG performance status of 0-1. The median weight loss was 10.0 kg (range, 1–18 kg). A mean of 2.3 metastatic sites per patient was observed, including 9 patients with brain metastases, 7 with liver metastases, and 11 with bone marrow involvement. None of the six patients with a single extrathoracic disease site had an isolated pleural effusion. One patient presented with the syndrome of inappropriate antidiuretic hormone secretion, and another, with a superior vena caval syndrome, diabetes insipidus, and excess production of adrenocorticotropic hormone (ACTH).

Table 1. Clinical characteristics

Male:female	32:7
Age:	
Median	60 years
Range	40–75 years
Performance status:	
0–1	26 patients (66%)
2–4	13 patients (34%)
Average weight loss	6.5 kg
Sites of metastatic disease:	
Liver	7
Brain	9
Bone marrow	11
Distant adenopathy	11
Adrenal	8
Other[a]	17

[a] Skin, pericardial effusions, pleural effusions, spleen, contralateral lung

Response criteria. A CR was defined as the disappearance of all clinical evidence of active tumor for a minimum of 4 weeks, including objective signs and symptoms of disease; a PR was defined as a $\geqslant 50\%$ decrease in the sum of the products of all diameters of measured lesions for 4 weeks. Stable disease (SD) was defined as a steady state or response less than a PR. Progressive disease (PD) was defined as an unequivocal increase of at least 25% in the size of any measurable lesions, the appearance of new lesions, a worsening of symptoms, the occurrence of uncontrolled hypercalcemia, or any clearly progressive skeletal involvement manifested by an increasing number of lytic lesions.

Results

Response

Of the 39 eligible patients, 34 completed at least one cycle of chemotherapy and were evaluable for response. Four patients died during the first cycle of chemotherapy, and one patient refused further medical evaluation during the first cycle of chemotherapy. In all, 4 patients (10%) achieved a CR and 19 (49%) achieved a PR after induction chemotherapy, for an overall response rate of 59%. Eight patients (23%) had SD and three had PD. A total of 26 patients (67%) completed the 4 cycles of induction chemotherapy.

Nine patients received WBI for brain metastases concomitantly with the first cycle of chemotherapy; two patients received local irradiation to symptomatic extrathoracic bony metastases with initial treatment. Of the 23 patients who responded to induction chemotherapy, 18 subsequently received chest irradiation, including 3 with brain metastases. After induction chemotherapy, three partial responders achieved a CR after chest irradiation, including one patient who showed residual abnormalities on chest radiographic examinations; 30+ months after bronchoscopic biopsies revealed no malignancy, the latter patient still shows no evidence of disease. The CR rate after chest

radiation was 18%. Of the 18 patients completing WBI and chest irradiation, 16 received at least 1 cycle of late intensification chemotherapy at week 24 and 5 completed the projected course of treatment.

The median duration of response for the 34 evaluable patients was 8 months (range 2–30+ months), with a median survival of 9 months (range, 1–30+ months). Patients achieving a CR had a median duration of response of 9 months and a median survival of 11 months, with one complete responder still being free of disease at 30+ months.

Relapse data

Of the 18 patients completing chest irradiation, 1 is disease-free at 30+ months; 1 complete responder died of radiation pneumonitis at 6 months. All of the remaining 16 patients developed PD: 8 at systemic sites, 2 locoregionally, 4 systemically and locally, and 2 in the brain after WBI; therefore, 38% (6/16) of the patients suffered intrathoracic relapses after chest irradiation.

Toxicity

Of the 39 eligible patients entered on study, 38 were evaluable for toxicity; the only inevaluable patient died of PD on day 1 of chemotherapy. The majority of the patients experienced significant myelosuppression: 21 of 38 patients (55%) had nadir white blood cell counts of $<1{,}000/mm^3$; there were 5 neutropenic deaths (13%) secondary to pneumonia and/or sepsis. Four of the latter occurred during the first cycle of chemotherapy, and rapidly progressive disease was felt to be a significant contributing factor in three patients; the fifth patient died of *Pseudomonas aeruginosa* sepsis and meningitis during the fourth cycle of chemotherapy. An additional six patients (16%), none of whom had documented bacteremia, required hospitalization for the administration of broad-spectrum antibiotics during neutropenic nadirs, and all recovered uneventfully. Five patients (13%) had nadir platelet counts of $<50{,}000/mm^3$, but none required platelet transfusions and there were no episodes of thrombocytopenic hemorrhage. In all, 18 patients received appropriate dose reductions in subsequent cycles of chemotherapy.

Gastrointestinal toxicity was mild to moderate, with 19 patients (50%) experiencing grade 1–2 nausea and vomiting. There were five episodes of neuropathy, three of which necessitated the discontinuation of vincristine. One instance of significant nephropathy, with a serum creatinine of 2.8 mg/dl during induction chemotherapy, required the elimination of cisplatin in subsequent cycles of chemotherapy. There were four episodes of radiation pneumonitis, one of which was fatal in a complete responder at 6 months.

Discussion

A number of attempts have been made to develop better combinations of drugs through the addition of active compounds in the treatment of small-cell lung cancer. Several nonrandomized trials incorporating VP-16 in the treatment of extensive small-cell lung carcinoma have reported a wide range of objective response rates ranging from 50% to 90% [2, 3, 11, 13, 16, 22–24, 28]. In a prospectively randomized trial in the treatment of extensive disease [12], the substitution of VP-16 for methotrexate in addition to cyclophosphamide, vincristine, and CCNU produced a significantly superior duration of response and overall survival. The addition of VP-16 to the standard regimen of cyclophosphamide, Adriamycin, and vincristine (CAV) has been somewhat disappointing. In three prospectively randomized trials [13, 20, 32] the overall response rates, particularly the CR rates in extensive disease, have been significantly higher in the arm incorporating VP-16 in addition to CAV; however, this did not translate into an improvement in overall survival in any of these trials. Even very aggressive programs using these agents combined at "full-dose" levels with VP-16 have not translated into improved response duration or survival as compared with standard regimens [1, 10]. It has been shown in vitro that VP-16 may compete with anthracyclines and/or vinca alkaloids at the plasma membrane level for transport into the cell, possibly because a common carrier mechanism for the transport of complex, heterocyclic compounds is involved [27]. VP-16 is a drug with well-demonstrated phase specificity for maximal cytotoxicity within the cell cycle; G_2 appears to be the most sensitive [21]. The concomitant administration of agents such as methotrexate (S-phase-specific) or vincristine (S- and M-phase-specific), if the effects of these drugs were transient might, temporarily reduce the proportion of cells transversing through G_2, thereby decreasing the effectiveness of VP-16 by an unfavorable kinetic interaction. A final explanation for the lack of benefit from the simple addition of VP-16 to standard combinations may be the development of cross-resistance secondary to the phenomenon of multiple drug resistance, which has been demonstrated in a number of experimental tumor systems between a number of structurally unrelated "natural" compounds, including the podophyllotoxins and anthracyclines [5].

Although the single-agent activity of cisplatin in small-cell lung cancer appears to be relatively low [6], in vitro synergism has been demonstrated for the combination of VP-16 and cisplatin in both cell assay systems [7] and animal model systems [26, 30]. As a front-line therapy for small-cell lung carcinoma, this combination is highly active, with reported CR rates as high as 86% [9, 28]. However, the present results with the addition of cyclophosphamide and vincristine do not appear to represent an improvement over past experience with currently used standard chemotherapeutic regimens; they are similar to those reported by Greco et al. (personal communication) for the three-drug combination of cyclophosphamide, VP-16, and cisplatin. This may be partially explained by the substantial hematotoxicity of this regimen, with 13% of patients dying of neutropenic complications; it should be noted that four of the five deaths in the present study occurred in the first cycle of chemotherapy in patients with low performance status who were also felt to have rapidly progressive disease.

A previous SWOG study in limited small-cell lung cancer [15], randomized complete responders to induction chemotherapy for thoracic irradiation or the continuation of chemotherapy. Although the overall survival was not affected, 90% of the relapsing patients who did not receive radiation had intrathoracic recurrences, compared with an incidence of 56% in the relapsing patients who had received chest radiation therapy. The loco-regional relapse rate of 38% in the current study also demonstrates a re-

duced rate of local relapse in patients with extensive disease who receive chest radiation; however, there was no improvement in survival.

A dose-response relationship has been demonstrated in two randomized trials for limited small-cell lung cancer after moderate dose escalation [4, 31]. In a high-dose trial using cyclophosphamide (100 mg/kg), VP-16 (1200 mg/m^2), and cisplatin (120 mg/m^2) as induction chemotherapy, Johnson et al. [14] observed objective responses in 90% of patients with extensive disease, including a 65% CR rate. However, the median survival of this group of patients was 11 months, no substantial improvement over that found with standard dose regimens. It would appear that neither simple combinations of the most active drugs nor aggressive dose escalation on a classic intermittent schedule with the existing agents is capable of exerting a major impact on survival in extensive small-cell lung cancer. However, the delivery of weekly, "dose-intensive" programs dividing the dose of cisplatin into fractions 1 week apart or approaches aimed at the modulation of resistance to available agents may prove to be more successful.

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