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VP16-213 in Combined Modality Treatment of Small Cell Carcinoma of the Lung

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Abstract—*Thirty-four previously untreated patients with histologically proven small cell carcinoma of the lung were treated with a combined modality therapy program that incorporated VP16-213, an epipodophyllotoxin derivative, into the chemotherapy regimen. Initial therapy for two cycles was with V-CAM, VP16-213, cyclophosphamide, doxorubicin and methotrexate. Following two cycles of V-CAM each patient received radiation therapy consisting of 4000 rads to the primary site, both hila and the mediastinum, as well as 2000 rads as prophylaxis to the whole brain. After a one-week rest period the patients received monthly cycles of V-CAM until death. Of 10 patients with stage III_{M0} disease, 7 had a complete response (CR), 1 a partial response (PR) and 2 had progressive disease. The median survival was still not reached by approximately 18 months. Of 24 patients with supraclavicular and/or metastatic disease there were only 5 patients with a CR, 11 with a PR and 8 with progressive disease. Their median survival was approximately 9 months. The 70% overall response rate and 9.3-month median survival of the entire group are essentially the same results as those in previously reported studies. There appears to be no additional benefit when VP16-213 is incorporated into our combined modality program.*

INTRODUCTION

SMALL cell carcinoma (SCC) of the lung is a highly malignant tumor which presents as advanced regional or metastatic disease in over 80% of cases. Aggressive combination chemotherapy in conjunction with radiation therapy has changed the natural history of this disease. We recently reviewed our five-year experience with combined modality treatment of SCC [1]. The epipodophyllotoxin derivative VP16-213 has been found to have antineoplastic activity in the treatment of SCC and has been used both alone and in combination with other agents in this disease [2]. We incorporated VP16-213 in our combined modality treatment program in an effort to improve the response rate and overall survival of our patients. We report on our recent experience with VP16-213 in SCC.

MATERIALS AND METHODS

Patients

Between July 1979 and December 1980, 34 consecutive previously untreated patients with histologically proven SCC of the lung were entered into a combined modality treatment program at the University of Chicago (18 patients) or at Michael Reese Medical Center (16 patients). They included 22 men and 12 women with a median age of 57 years and an age range of 39–80 years of age. Their performance statuses ranged from 20 to 100, with a median of 70 on the Karnofsky scale. All patients were evaluated with complete history and physical examination, CBC, SMA-12, liver function tests, liver–spleen scan, bone scan, gallium tumor scan, bone marrow aspirate and core biopsy. Staging was done according to the TNM system of the Task Force on Carcinoma of the Lung [3]. Patients with disease confined to the hemithorax and mediastinal lymph nodes were classified as stage III_{M0}; those in whom disease outside the chest was evident only in the ipsilateral supraclavicular lymph node were designated as stage II_{M0} SCN+ and those with distant metastases as stage II_{M1} [4].

Chemotherapy was given as follows: VP16-213 (V), 100 mg/m^2 i.v. over 30 min, on days 1 and 8; cyclophosphamide (C), 1000 mg/m^2 i.v.

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on day 1; doxorubicin (A), 40 mg/m^2 i.v. on day 1; and methotrexate (M), 30 mg/m^2 i.v. on day 22. Cycles of V-CAM were repeated every 28 days. The dose reduction schedule for all drugs was as follows: for white blood count (WBC) > 4000/mm^3 and platelets (PLT) > 150,000/mm^3 we gave 100% dose; for WBC < 4000 > 3000 and/or PLT < 100,000 > 75,000, 75% dose; for WBC < 3000 > 2000 and/or PLT < 75,000 > 50,000, 50% dose; for WBC < 2000 or PLT < 50,000 chemotherapy was withheld. Following two cycles of V-CAM each patient received radiation therapy consisting of 4000 rads to the primary site, both hila and the mediastinum, as well as 2000 rads as prophylaxis to the whole brain. After a one-week rest period the patients received monthly cycles of V-CAM until death. Four of the patients received chest and brain radiation as initial therapy followed by monthly V-CAM treatment. During follow-up patients had a chest X-ray each month and a gallium tumor scan every 3 months or as indicated clinically.

Response was designated as: complete (CR) if there was disappearance of all tumor as documented by initial radiographic and scintographic studies without the appearance of new disease for at least two months; partial (PR) for greater than 50% decrease in all measurable tumor with no new additional sites of involvement; and no response (NR) for patients not fulfilling either of these criteria. Survival was calculated from the date of first treatment until death or until the close of the study. Statistical analysis was performed by the Gehan modification of the generalized Wilcoxon analysis [5].

RESULTS

Staging

Ten patients (29%) had disease limited to the chest (III_{M0}), four patients (12%) had disease in the chest and ipsilateral supraclavicular lymph node (III_{M0} SCN+), and 20 patients (59%) had metastatic disease at the time of diagnosis (III_{M1}). Sites of metastases included bone (7 pts), bone marrow (4 pts), liver (3 pts), skin and soft tissue (2 pts), lung (1 pt), brain (1 pt) and multiple sites (2 pts).

Response and survival

Patient response and survival according to initial stage are shown in Table 1. The median survival for all 34 patients was 9.3 months. Those initially staged as III_{M0} had a significantly longer median survival than those in the III_{M0} SCN+ and III_{M1} groups ($P < 0.05$). Responders (CR + PR) had a significantly longer median survival than non-responders (10.3 months vs 7.5 months; $P < 0.02$), regardless of the initial stage.

Table 1. Response and survival by initial stage

Response	CR	PR	NR	Median survival (months)
Stage				
III_{M0}	7	1	2	*
III_{M0}–SCN+	2	1	1	9.3
III_{M1}	3	10	7	9.0

*Median not reached at 18.6 months.
Survival times through 3/30/81.

Cause of death

At the time of reporting, 20 of the 34 patients have died. Nineteen deaths were directly related to progressive SCC, and one patient died of a myocardial infarction four months after entering into the study. The sites of progression in those patients who died of SCC were local disease confined to the chest (9 patients), metastatic disease without local progression (8 patients), and both local and metastatic progression (2 patients). The metastatic sites were liver (3 patients), bone and bone marrow (2 patients), and multiple metastatic sites (5 patients).

Toxicity

All patients experienced some degree of nausea and vomiting after the day 1 injection of cyclophosphamide, doxorubicin and VP16-213. The day 8 VP16-213 injection was associated with mild to moderate nausea and vomiting in most patients, but few experienced any nausea with the day 22 methotrexate injection. All patients experienced some degree of alopecia. There were no episodes of hypotension associated with infusion of VP16-213.

The median nadir of the WBC for the entire group was 1900/mm^3 and occurred at 7–10 days. The median platelet nadir was 140,000/mm^3. All patients became anemic (hematocrit less than 34%) during the course of therapy, and 26 patients required red blood cell transfusion at some time. The number of patients requiring a reduction in the dose of VP16-213 on day 8 was significant. Over the entire number of V-CAM cycles for all patients treated, VP16-213 was omitted on day 8 46% of the time. Half the calculated dose was given 22% of the time, 75% of the dose 14% of the time and the full calculated dose only 18% of the time.

Six patients required hospitalization because

of fever associated with a WBC less than $1000/mm^3$ during the course of treatment. There were two documented episodes of bacterial sepsis; however, no deaths were attributable to the complications of therapy.

DISCUSSION

Although the exact mechanism of action of VP16-213 is not known, it is believed to cause a metaphase arrest possibly by impairing mitochondrial electron transport at the NADH dehydrogenase level [6]. The drug has also been reported to cause lysis of cells entering mitoses and to impair DNA synthesis by inhibiting thymidine uptake [7]. Issell and Crooke reviewed the literature on VP16-213 monotherapy in SCC and found that the reported response rates ranged from 20 to 65% in groups including previously treated and untreated patients [2]. Those investigators reporting the highest response rate gave the drug daily for 3–5 days, repeating the cycle every 14–21 days. Aisner *et al.* [8] and Tenczynski *et al.* [9] used VP16-213 in combination with doxorubicin and cyclophosphamide or ifosphamide respectively, and both reported overall response rates (CR + PR) of 90%. The median survival, however, was approximately 11 months in these studies. More recently Jackson *et al.* [10] reported on 39 patients with SCC who were randomized to treatment with doxorubicin, vincristine and cyclophosphamide, with or without VP16-213. He found similar response rates (~80%) in both groups, with slightly greater myelosuppression in those receiving VP16-213.

The 70% overall response rate (CR + PR), 9.3-month median survival of the entire group and survival times evaluated according to initial stage are essentially the same as those in our previously reported experience with other combined-modality treatment regimens [1, 3]. These results compare favorably with those in other large series reviewed by Livingston [11]. Patterns of local and metastatic relapse in patients with progressive disease were also unaffected by the addition of VP16-213. In view of the impressive single-agent activity in SCC, one might ascribe the lack of benefit seen in this group of patients to an error in the study design. The rationale for the day 1 and 8 schedule was to enhance patient convenience and compliance. The cumulative myelosuppression caused by the day 1 cyclophosphamide, doxorubicin, and VP16-213, however, precluded giving any VP16-213 on day 8 46% of the time and less than the calculated full dose 82% of the time. Therefore, in any given 28-day cycle, patients usually received less VP16-213 than is considered optimal in the treatment of SCC [7, 12]. We conclude from this that if VP16-213 is to be used effectively in combination with cyclophosphamide and doxorubicin it should be administered either as a large single dose on day 1 only, or in smaller doses over the first 3–5 days of each cycle [3, 8, 9].

In summary, although VP16-213 has been demonstrated to have single-agent antineoplastic activity in SCC of the lung and has been used successfully in combination with other agents in the treatment of this disease, we found no additional benefits in terms of response rate or overall survival when this drug was incorporated into our combined-modality program. In addition, it had no demonstrable effect on sites or rate of relapse. Although hematologic toxicity was somewhat greater with this regimen than in our previous programs without VP16-213, there was no significant increase in therapy-related morbidity or mortality.

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