Cancer Chemother Pharmacol (1982) 7: 187–193

Cancer Chemotherapy and Pharmacology

Doxorubicin, Cyclophosphamide and VP16-213 (ACE) in the Treatment of Small Cell Lung Cancer*

Joseph Aisner, Margaret Whitacre, David A. VanEcho, Margaret Wesley, and Peter H. Wiernik

Section Medical Oncology, Baltimore Cancer Research Center, University of Maryland Hospital, 22 South Greene Street, Baltimore, Maryland 21201, USA

Summary. *Small cell lung cancer requires aggressive combination chemotherapy. The three active agents, doxorubicin (A) 45 mg/m² i.v. day 1, cyclophosphamide (C) 1.0 mg/m² i.v. day 1 and VP16-213 (E) 50 mg/m²/day i.v. days 1–5 were given together. The combination (ACE) was given every 21 days without chest irradiation. One hundred and seventy-four patients have been stratified for extent of disease and randomized on three sequential studies testing ACE vs ACE + MER immunotherapy (38 patients), or ACE vs ACE alternating with CCNU, methotrexate, vincristine and procarbazine (109 patients), or ACE vs ACE II (ACE with continuous VP16-213 – 100 mg/m²/day × 5 days – 27 patients – ongoing). The immunotherapy and the alternating non-cross resistant combination have not proven beneficial with respect to response or survival. The ACE combination, regardless of additional treatments, has produced greater than 90% response overall. In limited disease the complete response (CR) frequency is 65%. The median survival for limited disease overall is 14 months and 18 months for patients achieving CR. In extensive disease the CR frequency is 40% with a median survival of 9 months overall and 13 months for patients achieving CR. Response frequency and survival are identical in the first two studies and 20–30% of patients with limited disease are long-term survivors with one late relapse (> 3 years). Patients who achieved CR had a significantly longer survival regardless of other factors such as performance status or extent of disease. Prophylactic cranial irradiation was demonstrated to be useful in prevention or delaying CNS metastases in patients who achieved CR. The third generation study of high-dose VP16-213 infusion seeks to increase the CR frequency. ACE chemotherapy without chest irradiation is a highly effective treatment for all patients with small cell lung cancer and compares favorably with all other studies with or without adjuvant radiotherapy.*

Send offprints requests to J. Aisner at the above address

* This investigation was supported in part by PHS Grant Number 1 P50CA 32107-01 awarded by the National Cancer Institute, DHHS

Introduction

Small cell carcinoma of the lung is a distinct clinical and pathological entity with a high labeling index, short doubling time and aggressive biological behavior which is expressed clinically by the rapid progression of the disease, the short symptomatic period and early dissemination [7, 9, 10, 25]. It has been appreciated for some time that localized forms of therapy such as surgery or radiotherapy or both are inadequate to produce prolonged disease free survival even among selected patients with limited disease [2, 7, 9, 10, 25, 32]. In addition, the usual staging system for lung cancer was found not to correlate with end results in treatment and the VALG recognized the utility of staging patients according to limited and extensive disease where limited disease includes the hemithorax with or without mediastinal and ipsilateral supraclavicular nodes [34].

Combination chemotherapy has proven to be highly effective in this disease with many reports now showing improved response rate, prolongation of median survival and occasional long-term disease free survivors [3, 5–6, 8, 11–12, 15–17, 19, 21, 23, 30, 33]. In 1975, the Baltimore Cancer Research Center identified a highly active combination of doxorubicin, cyclophosphamide and VP16-213 given without adjuvant chest irradiation [3]. The three drug combination (ACE) was based on available single drug activity data as well as suggestions from animal studies that there were multiple synergistic pairs. All patients with small cell carcinoma of the lung seen at the BCRC were evaluated for extent of disease, stratified

0344-5704/82/0007/0187/$01.40

and randomized on three sequential studies testing ACE vs ACE plus additional therapy. The purpose of this paper is to review the accumulated experience with these combination chemotherapies utilizing ACE with nearly 3 years of average followup.

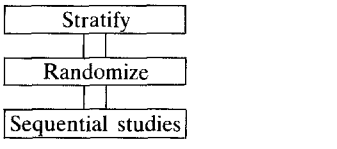
Patients and Methods

All patients admitted to the Baltimore Cancer Research Center with histologically or cytologically (more than 3 consecutive specimens) proven small cell carcinoma of the lung were extensively staged using history and physical examination; bronchoscopy with brushings, washings and biopsies; whole-lung tomography, CAT scan or both; isotopic liver and bone scans (with roentgenograms of suspicious bone lesions), bilateral iliac crest bone marrow aspirations and biopsies; CT brain scan; complete blood count, platelet count and differential; serum chemistries including electrolytes, liver function studies (SGOT, SGPT, LDH, and alkaline phosphatase), uric acid; and biomarkers such as ACTH and ADH where clinically indicated. Following staging patients were clinically stratified according to extent of disease, performance status and randomized on one of the three sequential ACE protocols. Limited disease was defined as disease confined to one hemithorax with or without bilaterial mediastinal lymph node involvement and with or without ipsilateral supraclavicular lymph node involvement (single irradiation port). Extensive disease was defined as any involvement beyond the confines of the definitions of limited disease. There were no age restrictions and all patients were considered eligible for study if they gave informed consent and did not have any history of any other primary or concurrent malignancies.

Drug Administration. After evaluation for extent of disease and performance status, patients were stratified and randomized on one of three sequential studies. The study design, drug doses and scheduling are given in Table 1. The first study, BCRC 7510, randomized between ACE and ACE plus MER, the methonol extracted residue of BCG [8]. The second study, BCRC 7705 was conducted between August 1977 and September 1980 and patients were randomized between ACE followed by a non-cross resistant second combination of CCNU, vincristine, methotrexate and procarbazine (COMP), and ACE given for a minimum of three courses or until maximal response occurred then alternating ACE with COMP according to the 21 and 42 day cycles respectively. The third study randomizes between ACE and ACE II in which ACE II utilizes 100 mg/m^2 of Etoposide (VP16-213) given by continuous infusion for 5 days. The first study, 7510, did not utilize prophylactic cranial irradiation. The second generation study, 7705, randomized all patients who achieved complete remission to prophylactic cranial irradiation or observation, and the third study includes prophylactic cranial irradiation for all patients who achieve complete remission.

Dosage modifications were made according to the hematologic nadir counts, primarily leukopenia except where bone marrow metastases were documented. If the white count had not recovered by the 21st day (first day of next cycle), then treatment was delayed a week. All patients were routinely followed on a weekly basis to determine counts and potential toxicities. Patients were completely re-evaluated for any change in clinical status such as apparent complete remission or progression. This re-evaluation included history and physical examination and repeat of all

Table 1. Sequential randomized studies in small cell lung cancer



Study	#7510 ACE + MER	#7705 ACE/COMP alternating	#8020 ACE-II
Dates	6/75–7/77	8/77–9/80	10/80 -
PCI	None	Randomize CR	all CR

Each Cycle = 21 days

A	= Doxorubicin	45 mg/m^2 i.v. day 1
C	= Cyclophosphamide	1,000 mg/m^2 i.v. day 1
E	= Etoposide (VP 16–213)	50 mg/m^2 days 1–5
MER	= Methanol extracted residue of BCG 200 g in 5 sites intradermally	
ACE-II	= ACE with etoposide	100 mg/m^2/day continuous infusion days 1–5

Each Cycle = 42 days

C	= CCNU	75 mg/m^2 i.v. day 1
O	= Vincristine	1 mg/m^2 i.v. days 1 and 21
M	= Methotrexate	40 mg/m^2 i.v. days 1 and 21
P	= Procarbazine	75 mg/m^2 p.o. days 1–5 and 21–25
PCI	= "Prophylactic" cranial irradiation 3,000 R/10 fractions	

previously positive suspicious tests including whole-lung tomography, CT scan, bronchoscopy, isotopic liver and bone scans, CT brain scan, and bilateral iliac crest bone marrow aspirates and biopsies. No patient was judged as having complete remission unless all of the repeat evaluation revealed no evidence of disease. Standard criteria for response were used. Complete remission (CR) was defined as the disappearnace of all signs and symptoms of disease, including normalization or all abnormal biomarkers lasting a minimum of 30 days. Partial response (PR) was defined as a minimum of 50% decrease in the cross perpendicular dimensions of each lesion with a subjective improvement and no evidence of progression lasting a minimum of 30 days. Objective response (OR) was defined as any tumor regression which did not fulfill the criteria of complete or partial response. No response (NR) was defined as disease stabilization (no objective regression) or increased tumor growth during therapy. Radiotherapy to primary distal sites was not used during protocol treatment.

Results

Patient Characteristics

Between June 1975 and August 1981, 174 patients were entered onto the three sequential randomized studies and the patient characteristics are shown in Table 2. Each of the indivdual studies contains both the experimental and control arms but are considered together because of the lack of differences shown between the control and experimental arms in each of the first two studies. For each study, the regimens are well matched for the numbers of patients, age, sex, and performance status among both limited and extensive disease patients for each of the respective comparative arms. There were no age limitations but in general this was an ambulatory group of patients only six of whom had received any prior therapy. The majority of patients had identifiable lesions in the lung and regional nodes. The most common extrathoracic sites of metastases were bone, liver, and bone marrow. None of the patients with bone lesions had single isolated lesions detected only by bone scan. The details of the patient characteristics according to the component arms of each study (which are balanced within the study) have been previously published [3, 5].

Response and Survival

The overall response to ACE (plus or minus other therapies) is shown in Table 3 according to study. Six of the 38 patients in study 7510 [3] had received prior therapy and five of these six had measurable disease. Three of these five patients failed to respond to chemotherapy and 2 had objective response but died toxic during neutropenia and infection. All patients with measurable disease among the 32 previously untreated patients had objective tumor regression, 8 of 11 patients with limited disease achieved CR as did 10 of 19 patients with extensive disease. MER as used in that study had no appreciable effect on response or survival but did produce fever during periods of granulocytopenia which confused the management of these patients. The median number of courses to complete remission was 2 and ranged from 1–5. Patients who had received prior radiotherapy to the primary tumor had a significantly shorter survival than the patients who had no prior therapy measured either from the time of onset of chemotherapy or from the time of diagnosis. The median survival for the previously untreated patients with limited disease was 14 months and the median survival of patients with extensive disease was 9.5 months. Three of the 14 patients with limited disease survived beyond 2 years when all treatment was discontinued. One patient, however, subsequently died from a myocardial infarction and another died from a late (48

Table 2. Patient characteristics for ACE (± additional chemotherapy)

Study	7510	7705	8020[a]	Total[a]
No. patients	38	109	27	174
No. prior treatments	6	0	0	6
Median age years	57	59	60	59
(Range)	(48–67)	(29–73)	(48–69)	(29–73)
Male/Female	27/11	77/32	16/11	120/54
Lim/Ext disease	14/24	44/65	11/16	69/105
Performance status				
0–1	21	55	14	90
2–3	13	48	11	72
4	4	6	2	12

[a] As of July 15, 1981

Table 3. Summary of overall results of ACE ± other therapies

n	38[a]	109	27
% CR Limited	77	64	≥ 64
% CR + PR Limited	90	90	≥ 90
% CR Ext	52	40	≥ 40
% CR + PR Extensive	90	86	≥ 90
Median No. of courses to CR	2	2	TE
(Range)	(1–5)	(1–6)	
Survival (Mos) Limited	14	14	TE
Median Survival (Mos) Extensive	$9^1/_2$	10	TE
% Limited 2 year survival	30[b]	29[c]	TE
3 years survival	21[b]	20	TE

[a] 35 patients had measurable disease
[b] 1 Patient subsequently died from M.I., 1 patient died from late (48 months) relapse
[c] 2 Patients died of CNS only disease proven at necropsy (no. prophylactic cranial irradiation)

month) relapse leaving one of the 14 patients still alive at greater than 6 years (Fig. 1). All patients with extensive disease eventually relapsed and died and the longest survival was 26 months.

There were no significant differences in the response frequency between the continuous or alternating regimens for either limited or extensive disease in study 7705 [9]. Overall 28 of the 44 patients (64%) with limited disease achieved CR and 11 of 44 (26%) achieved PR for an overall response rate of 90%. Only three patients with limited disease failed to respond to therapy with at least a PR and eight patients with limited disease remain in CR from 15 + to 48 + months. Overall for extensive disease, 26 of the 65 (40%) patients achieved CR and 28 (46%) achieved PR for an overall response rate of 86%. The median number of courses to CR was 2 and ranged from 1–6. Six patients with extensive disease failed to respond to induction therapy and all patients with extensive disease have eventually relapsed and died. The longest survival was 28 months. There were no statistically significant differences in the survival curves between the two regimens for either limited or extensive disease. The median survival for all limited disease patients is 14 months and the median duration of survival for patients with extensive disease is 10 months. The overall survival for patients with limited disease is significantly better than for extensive disease ($P < 0.001$). Two patients with limited disease who did not receive prophylactic cranial irradiation (see below) relapsed with CNS disease and died with necropsy proven CNS only disease (Fig. 1).

Twenty-seven patients have thus far been entered onto study 8020 as of July 15, 1981. It is far too early to determine if there are any differences between the two treatment regimens. As of the analysis date, 7 of 11 patients with limited disease and 7 of 16 patients with extensive disease have achieved complete remission. Ten of the 11 patients with limited disease and 15 of the 16 patients with extensive disease have had an objective tumor regression. Since the study has been accruing patients for less than a year and the average followup on the study is less than 6 months, it is much too early to determine median number of courses to complete response or median survival for any category.

Patients who achieved complete remission in the first two studies survived significantly longer than patients who did not. The median duration of survival for patients with limited disease who achieved complete remission is 18 months compared to 10.5 months for patients who did not achieve complete remission ($P < 0.0001$). If one excludes the patients who died with CNS disease only (see below), approximately 40% of all patients who achieved complete remission are long-term disease free survivors. Similarly in patients with extensive disease, the median survival for patients with complete remission is 14 months compared to 7 months for patients who do not achieve complete remission ($P < 0.0001$). For both studies, no patient with extensive disease has survived beyond 28 months.

In order to evaluate the impact of complete response, a multivarite step-down analysis was performed for all patients (161) with more than 6 months of followup from treatment using the variables: response, performance status, extent of disease, sex, and age. Using this model the response is the single best "prognostic" factor ($P = 0.02$) and performance

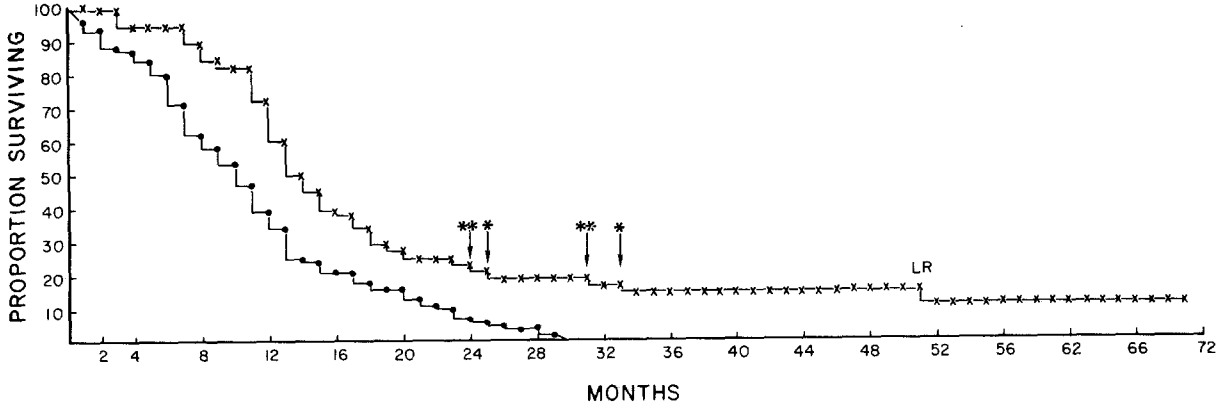


Fig. 1. Actuarial survival for 174 patients with small cell carcinoma of the lung treated with ACE combination chemotherapy plus or minus additional treatments (see text). Average followup for these studies is in excess of 32 months and a small number of patients have been recently entered. LR at 48 months indicates a late intrathoracic relapse which failed to respond to subsequent therapy. * Indicates patients who died of myocardial infarction after completion of all therapy. Both patients had received maximal cumulative dose (540 mg/m^2 of doxorubicin). ** Indicate patients who died with CNS only disease proven at necropsy. (●——●) Extensive disease $n = 101$; (×——×) limited disease $n = 73$

status is the next most important factor ($P = 0.04$). Thus response and performance status are the best pair. Once response and performance status are in the model, extent of disease adds marginally for overall survival ($P = 0.06$) but is important in long-term survival.

Prophylactic Cranial Irradiation

Eighteen patients presented with brain metastases and were treated with 3,000 rad whole brain irradiation in ten fractions. The median duration of survival for patients who presented with brain metastases is 5.5 months ranging from 1–10 months. Whole brain irradiation was not used "prophylactically" in the first study because it was unclear whether the epipodolphylotoxin derrivative etoposide (VP16-213) might be effective in preventing or delaying CNS involvement. In addition to the four patients who presented with brain metastases, nine patients eventually developed evidence of CNS metastases including two patients who relapsed first in the CNS. In the second study, BCRC 7705 patients who achieved complete remission were randomized to receive or not receive "prophylactic" cranial irradiation (PCI). Forty patients were eligible for this randomization, 29 were randomized and 11 refused randomization. At the time of the first analysis of these randomization, none of 15 patients randomized to prophylactic cranial irradiation had relapsed in the CNS, whereas 5 of the 14 randomized to the observation group developed intracranial metastases ($P < 0.02$) and 4 of the 11 patients who refused randomization (not irradiated) also developed intercranial metastases. Further randomization was halted and the third study (BCRC 8020) included PCI for all patients who achieved CR. Among the 26 patients who did not receive prophylactic cranial irradiation on the randomized study, two of the patients with CNS relapsed and eventually died of this CNS disease and at autopsy were shown to have CNS metastases with no evidence of systemic disease. As of July 15, 1981, 21 patients in complete remission have received PCI and one of the 21 have relapsed first in the CNS and two relapsed in the CNS after systemic relapse. So far PCI has not shown any change in the survival curves and censoring patients who developed metastases also does not effect the survival curves except for the plateau.

Eighteen patients, only one of whom received prophylactic cranial irradiation, developed documented leptomeningeal carcinomatosis and an additional two patients were suspected of having this disease which could not be confirmed by either cytology or necropsy (refused in both). Sixteen of the patients had extensive disease at presentation and two had limited disease. The cytological, clinical, pathological and therapeutic aspects of leptomeningeal carcinomatosis in these patients has been previously described [4, 27, 29].

Toxicity

The toxicity from ACE chemotherapy with or without additional treatments was moderately severe myelosuppression. The majority of myelosuppression occurred during the first few courses of chemotherapy which was later ameliorated by dosage modification according to nadir counts. Leukopenia, the major hematologic toxicity, ranged in the early courses from a white count nadir of 100–2,000/μl. Neither MER in the first study nor the alternating chemotherapy in the second study produced a significant difference in the degree of myelosuppression which was more severe in extensive disease patients then in those with limited disease. In general, the white count suppression correlated well with performance status with a correlation coefficient of 0.89. There have been a total of 57 febrile episodes among 35 patients. Thirty-six of the 57 febrile episodes were associated with clinically or microbiologically documented infections. The most frequent site of infection was the lower respiratory tract. There were eight drug related deaths, four in the first study, and four in the second study. All drug related deaths occurred in patients with pretreatment performance status of 3 or 4. Non-hematologic toxicity included alopecia in all patients; nausea and vomiting, primarily on the first day after cyclophosphamide; and mild mucositis in approximately 15% of patients. MER toxicity in the first study included fever, chills, local pain and occassionally weeping ulcers. Four patients died of myocardial infarction. Two patients died while on study and two patients died after completion of all chemotherapy. The latter two patients had received 540 mg/m^2 of doxorubicin and all four patients had preexisting arteriosclerotic cardiovascular disease. Congestive heart failure was seen in 4 patients, none of whom had exceeded the usually recommended doxorubicin recommended dose. No patient refused treatment because of the side effects or toxicities.

Discussion

Three sequential studies conducted at the Baltimore Cancer Research Center utilizing a combination of doxorubicin, cyclophosphamide, and VP16-213

(ACE) without radiotherapy to the local disease and plus or minus additional treatments designed to improve response and survival, have demonstrated that the three drug combination, ACE, is highly effective therapy against small cell carcinoma of the lung. The overall complete remission rate for limited disease (65%) and for extensive disease (40%) have been very consistent in all three studies and compare favorably with any combination chemotherapy treatment program or combined modality treatment program that has been published or reported [1, 6, 8, 11–17, 19, 21, 23, 24, 26, 29–31, 33]. The median duration of survival for limited and extensive disease (14 and 10 months respectively) and the percentage of long-term survivors with limited disease are also entirely comparable between the first two studies and compare favorably with any reported treatment program for small cell lung cancer [1, 6, 8, 11–17, 19, 21, 23, 24, 26, 29–31, 33]. These results indicate that the ACE combination chemotherapy regimen alone is a highly effective treatment for small cell carcinoma of the lung regardless of extent of disease. The first two studies sought to improve the complete response and survival by additional therapies such as MER or alternating non-cross resistant chemotherapy respectively. These approaches, however, have not shown any improvement upon the three drug combination. These studies, similar to other reports, show that patients who achieve complete remission have a significantly improved survival compared to those who do not. Multivariate analysis suggest that complete response is the single most important factor in determining survival and analysis of the survival data shows only patients who achieve complete remission can achieve long-term disease free survival. Thus, further studies need to address the possibility of improving the complete response rate among both limited and extensive disease patients. The current BCRC study, therefore, tests dose and schedule of VP16-213 in order to determine maximal treatment with this highly active agent.

One of the more serious complications of small cell lung cancer continues to be CNS disease [1, 19, 22]. The first study did not incorporate prophylactic cranial irradiation because of the possibility that the epipodophyllotoxin derivative VP16-213 might prevent or delay CNS involvement. Nine patients (24%) however, developed CNS metastases and thus VP16-213 did not prevent or delay such involvement. The second study sought to determine the most appropriate timing for prophylactic cranial irradiation (PCI) since there was uncertainty regarding the utility of PCI especially with respect to patient survival [20]. Patients who do not achieve CR do not always survive sufficiently long to have clinically manifest disease and patients who complete prophylactic cranial irradition while they still have active systemic disease may still develop CNS metastases after completion of the PCI. The second study therefore randomized patients who achieved CR to receive or not receive PCI. The results of this aspect of the study confirm the value of PCI in either preventing or delaying the clinical onset of intracranial metastases [9]. One of 21 patients who received PCI relapsed in the CNS and two CNS or relapse of these patients eventually developed leptomeningeal metastases after systemic. In the three sequential studies, 18 of 53 patients who did not receive PCI (including 5 of 14 patients randomized to observation) developed intracranial metastases and two of these patients died with CNS only disease proven at necropsy. No patients developed cranial metastases in the interval between the initiation of chemotherapy and the achievement of complete remission. Although cranial irradiation of micrometastases was effective in reducing the incidence of overt intracranial metastases, an effect on the overall survival of patients was not demonstrable. This lack of effect was likely not shown because of the relatively small percentage of patients who achieve long-term survival and the fact that most patients relapsed systemically and died of systemic metastases. With further improvement in long-term survival however, it is likely that PCI may become a progressively more important part of the treatment.

Our studies indicate that the three drug combination of doxorubicin, cyclophosphamide and VP16-213 (etoposide) combined with prophylactic cranial irradiation for presumed cerebral micrometastases is a highly effective treatment modality for small cell carcinoma of the lung regardless of the extent of disease. Regardless of the high response rate, however, the majority of patients still return with local or systemic tumor and further studies are necessary to improve both the frequency of complete remission, the duration of response and survival.

References

1. Abeloff MD, Ettinger DS, Khouri NF, Lenhard RE jr (1979) Intensive induction therapy for small cell carcinoma of the lung. Cancer Treat Rep 63: 519–524
2. Aisner J (1982) Is combined modality treatment of small cell carcinoma of the lung necessary. In: Wiernik PH (ed) Controversies in oncology. J Wiley and Sons, New York, pp 155–173
3. Aisner J, Wiernik PH (1980) Chemotherapy vs. chemoimmunotherapy for small cell undifferentiated carcinoma of the lung. Cancer 46: 2543–2549
4. Aisner J, Ostrow S, Govindan S, Wiernik PH (1981) Leptomeningeal carcinomatosis. In: Small cell carcinomatosis of the lung. Med Ped Oncol 9: 47–59

5. Aisner J, Whitacre MY, VanEcho DA, Slawson R, Wiernik PH (1982) Combination chemotherapy for small cell carcinoma of the lung: continuous vs. alternating non-cross resistant combination. Cancer Treat Rep 66: 221–230
6. Brereton HD, Kent CH, Johnson RE (1979) Chemotherapy and radiation therapy for small cell carcinoma of the lung: A remedy for post therapeutic failure in lung cancer. In: Muggia FM, Rozencweig M (eds) Prog Ther Res. Raven Press, New York, pp 575–586
7. Bunn PA, Cohen MH, Ihde DC, Fossieck BE, Matthews MJ, Minna JD (1977) Advances in small cell bronchogenic carcinoma. Cancer Treat Rep 61: 333–342
8. Bunn PA, Nugent JL, Matthews MJ (1978) Central nervous system metastases in small cell bronchogenic carcinoma. Semin Oncol 5: 314–322
9. Cohen MH (1975) Signs and symptoms of bronchogenic carcinoma. Semin Oncol 1: 183–189
10. Cohen MH, Matthews MJ (1978) Small cell bronchogenic carcinoma: A distinct clinicopathologic entity. Semin Oncol 5: 234–243
11. Cohen MH, Ihde DC, Bunn PA jr, Fossieck BE jr, Matthews MJ, Shackney SE, Early AJ, Makuch R, Minna JD (1979) Cyclic alternating combination chemotherapy for small cell bronchogenic carcinoma. Cancer Treat Rep 63: 163–170
12. Cohen MH, Lichter AS, Bunn PA jr, Glatstein EJ, Ihde DC, Fossieck BE jr, Matthews MJ, Minna JD (1980) Chemotherapy-radiation therapy versus chemotherapy in limited small cell lung cancer. Proc Am Soc Clin Oncol 21: 448
13. Daniels JR, Chak L, Alexander M, Kohler M, Friedman M, Torti F, Carter S (1980) Oat cell carcinoma. Alternating compared with sequential combination chemotherapy. Proc Am Soc Clin Oncol 21: 346
14. Dombernowsky P, Hansen HH, Sorensen S, Osterlind K (1979) Sequential versus non-sequential combination chemotherapy using six drugs in advanced small cell carcinoma. A comparative trial including 146 patients. Proc Am Assoc Cancer Res 20: 277
15. Einhorn LH, Bond WH, Hornbach M, Beng-Teh J (1978) Long term results in combined modality treatment of small cell carcinoma of the lung. Semin Oncol 5: 309–313
16. Ginsberg SJ, Comis RL, Gottlieb AJ, King GB, Goldberg J, Zamkoff A, Meyer JA (1979) Long term survivorship in small cell anaplastic lung carcinoma. Cancer Treat Rep 63: 1347–1349
17. Greco FA, Chardson RL, Snell JN, Stromp SL, Oldham RK (1979) Small cell lung cancer. Complete remission and improved survival. Am J Med 66: 625–630
18. Hansen HH (1973) Should initial treatment of small cell carcinoma include systemic chemotherapy and brain irradiation? Cancer Chemother Rep Part II 4: 239–241
19. Hansen HH, Dombernowsky P, Hansen HS, Rorth M (1979) Chemotherapy vs. chemotherapy plus radiotherapy in regional small cell carcinoma of the lung. A randomized trial. Proc Am Assoc Cancer Res 20: 277
20. Hansen HH, Dombernowsky P, Hirsch FR, Hansen M, Rygard J (1980) Prophylactic irradiation in bronchogenic small cell anaplastic carcinoma. Cancer 46: 279–284
21. Holoye PY, Samuels ML, Smith T, Sinkovics JG (1978) Chemoimmunotherapy of small cell bronchogenic carcinoma. Cancer 42: 34–40
22. Kato Y, Fergusson TB, Bennett DE, Burford TH (1969) Oat cell carcinoma of the lung. A review of 138 cases. Cancer 23: 517–524
23. Livingston RB, Moore TN, Heilbrun L, Bottomley R, Lehane D, Rivkin SE, Thigpen T (1978) Small cell carcinoma of the lung: Combined chemotherapy and radiation. Ann Int Med 88: 194–199
24. Livingston R (1980) Non-cross resistant combinations in patients with extensive small-cell lung cancer. Proc Am Soc Clin Oncol 21: 449
25. Muggia FM, Krezoski SK, Hansen HH (1974) Cell kinetic studies in patients with small cell carcinoma of the lung. Cancer 34: 1683–1690
26. Natale R, Hilaris B, Wittes R (1980) Prolonged remission of small cell lung carcinoma (SCLS) with intensive chemotherapy induction and high dose radiation therapy without maintenance. Proc Am Soc Clin Oncol 21: 452
27. Nugent JL, Bunn PA jr, Matthews MJ, Ihde DC, Cohen MH, Gazdar A, Minna JD (1979) CNS metastases in small cell bronchogenic carcinoma: Increasing frequency and changing pattern with lengthening survival. Cancer 44: 1885–1893
28. Pendergrass KB, Abeloff MD, Ettinger DS, Burke PT, Order SE, Khouri N (1980) Intensive timed sequential combination chemotherapy and adjunctive radiotherapy in extensive stage small cell carcinoma of the lung (SCCL). Proc Am Soc Clin Oncol 21: 447
29. Rosen ST, Aisner J, MaKuch RW, Matthews MJ, Ihde DC, Whitacre M, Glatstein EJ,Wiernik PH, Lichter AS, Bunn PA jr (1981) Carcinomatous meningitis in small cell lung cancer: A clinicopathologic review of the National Cancer Institute Experience. Medicine (in press)
30. Stevens E, Einhorn L, Rohn R (1979) Treatment of limited small cell lung cancer. Proc Am Clin Oncol 20: 435
31. Vincent RG, Wilson H, Lane W, Raza S, Chen T (1980) Sequential chemotherapy of small cell carcinoma of the lung. Proc Am Soc Clin Oncol 21: 453
32. Weiss RB, Minna JD, Glatstein E, Martini N, Ihde D, Muggia F (1980) Treatment of small cell undifferentiated carcinoma of the lung: Update of recent results. Cancer Treat Rep 64: 539–548
33. Williams C, Alexander M, Glatstein EJ, Daniels JR (1977) Role of radiation therapy in combination with chemotherapy in extensive oat cell cancer of the lung: A randomized study. Cancer Treat Rep 61: 1427–1431
34. Zelen M (1973) Keynote address in biostatistics and data retrieval. Cancer Chemother Rep 4: 31–42

Accepted July, 1981