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Histologic Subtypes of Small Cell Carcinoma of the Lung: Response to Therapy

STEPHEN DAVIS* and HAROLD SOBEL†

**Oncology–Clinical Immunology Section and †Pathology Service, Veterans Administration Medical Center, East Orange, New Jersey and College of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey, U.S.A.*

Abstract—*Seventy-seven patients with extensive small cell carcinoma of the lung were initially treated with the same combination chemotherapy consisting of cyclophosphamide and doxorubicin. All cases were retrospectively subdivided according to their histological subtype as proposed by the World Health Organization Lung Cancer Classification (WHO): the classic lymphocyte-like (oat cell), type* 21, *and intermediate cell, type* 22. *Type* 21 *has an objective response rate of* 43% *and type* 22 *a response rate of* 23%. *Analysis of the data revealed that the median survival for WHO type* 21 *was* 30.4 *weeks; whereas median survival for type* 22 *was* 17.2 *weeks* ($P=0.04$). *This difference in subtype response was also seen when response was corrected for Karnofsky initial performance status* 40–70 *but not for performance status* 80–100. *Type* 21 *small cell carcinoma appears to offer a higher response rate to chemotherapy and a longer survival than type* 22.

INTRODUCTION

SMALL cell cancer of the lung is now considered as a well-recognized clinical pathologic entity distinct from other histologic types of lung cancer. It has become apparent from its rapid growth rate and propensity for early widespread metastases that radiotherapy and chemotherapy, rather than surgery, offer the greatest chance for extended survival. Using radiotherapy and chemotherapy, the median response duration has improved from a dismal two months to approximately six months for extensive disease in most studies [1]. The present World Health Organization (WHO) classification designates three subtypes of small cell carcinoma: (1) classic lymphocyte-like (oat cell, type 21); (2) an intermediate cell type (type 22); and (3) a combined form (type 23). In the past, most reports on the efficacy of chemotherapy and radiotherapy have consolidated subtypes into one group. Our present report analyses the response rate of 77 consecutive, unselected patients with extensive small cell carcinoma of the lung according to WHO subtype using a single chemotherapy protocol. These data reveal that WHO subclassification type 22 behaves in a more aggressive fashion and is less responsive to therapy.

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MATERIALS AND METHODS

A total of 77 consecutive patients with histologically confirmed extensive (detectable disease not confined to one hemithorax) small cell carcinoma of the lung were evaluated in this study. Every attempt was made to exclude non-small cell histologies. All patients were untreated, and the diagnosis was confirmed by bronchoscopy, mediastinoscopy, or open lung biopsy of the initial lung tumor seen at presentation. Two pathologists reviewed the slides retrospectively. In 17 cases disagreement occurred; in these cases the opinion of Veterans Administration Lung Pathology Panel members was used. To be entered on the therapy protocol all patients were required to have a Karnofsky performance status greater than 40. Patients had clinically detectable disease measurable by physical examination of masses or by roentgenographic techniques. The group consisted of 67 men ranging in age from 37 to 82 (mean:61) and 10 women ranging in age from 48 to 74 (mean:59). Initial performance status (IPS) and extent of disease have long been documented as prognostic factors for survival

in bronchogenic carcinoma [2]; therefore, survival within subtypes was corrected for IPS. All patients had extensive disease.

Pre-treatment evaluation consisted of history and physical examination, blood counts, liver function tests, BUN, creatinine, urinalysis, chest X-ray, liver, brain and bone radionuclide scans, and a bone marrow biopsy and gallium^{67} nuclide scan.

Response was evaluated every three weeks. The response was considered complete when there was no detectable evidence of any disease either by physical examination and/or roentgenographic or radionuclide techniques. A partial response was categorized by a decrease of over 50% in all measurable disease without new evidence of malignant disease being present. Patients who had a subjective response, i.e., decrease in pain, weight gain, but no associated decrease in measurable tumor burden, were considered non-responders.

Patients received the following courses of chemotherapy: cyclophosphamide 700 mg/m^2 given every three weeks along with doxorubicin 50 mg/m^2 given every three weeks. Doxorubicin was continued until a cumulative dose of 500 mg/m^2 was reached or tumor progression occurred. When large tumor bulk was seen within the mediastinum or hilar area, radiation was given if there was no response following six weeks of chemotherapy or when further response could not be obtained in a partial responder. No patient received prophylactic brain irradiation as it does not influence survival. Survival was calculated in the various subgroupings in all patients regardless whether radiation was given. Chemotherapy was continued until disease progression was documented (increase of 25% of measurable tumor burden). At the time of progression, patients were continued on cyclophosphamide therapy as described, doxorubicin was discontinued, and CCNU (CeeNu®) 70 mg/m^2 was then given every six weeks. A similar change was instituted when maximum doxorubicin dose (500 mg/m^2) was reached. No alternate chemotherapy was given at any time. Adjuvant irradiation was used as necessary to the brain, bone and other visceral organs.

Significance (P value) of the data was determined by the model of Cox [3].

RESULTS

Seventy-seven patients with biopsy-proven extensive small cell carcinoma are the subject of this report. Fifty-five patients were classified into WHO type 21, and 22 patients were classified into WHO classification 22. There were too few cases of WHO classification 23 to evaluate. There are recognizable difficulties in histologic classification of small cell carcinoma [4]. In addition, it is unknown to what extent primary and metastatic sites differ histologically; therefore, only the primary biopsy was used in classification. Table 1 shows the objective response rates of the two small cell carcinoma subgroups. Patients with type 21 showed an objective response rate of 43% from our chemotherapeutic regimen whereas the response rate in type 22 was 23% (Table 1) ($P=0.03$). Seventy-four percent of patients in type 21 eventually received radiotherapy for control of local disease, i.e., mediastinum, brain, bone and other viscera, and 79% in type 22 received radiotherapy for similar local control of disease. The objective response rate showed in Table 1 actually represents the effect of our chemotherapeutic regimen on the small cell variants; a radiation-induced reduction in tumor bulk was not considered 'a response'.

Table 1. Objective tumor response of small cell carcinoma patients by WHO classification*

WHO classification	Responding patients	Total patient number
21	24 (43%)	55
22	5 (23%)	22
All patients	29 (38%)	77

*A complete or partial response following initiation of chemotherapy.

Table 2 shows the median survival by WHO classification. As can be seen, median survival for all patients was 26.6 weeks; whereas survival for type 21 was 30.4 weeks, median survival for type 22 was 17.2 weeks. The difference in median survival between the

Table 2. Median survival of small cell carcinoma patients by WHO classification

WHO classification	Median survival (weeks)	Total patient number
21	30.4	55
22	17.2	22
All patients	26.6	77

The difference in median survivals between type 21 and 22 was significant at the 4% level ($P<0.04$).

two subgroups is significant at the P value of 0.04. Table 3 reveals the median survival by WHO classification corrected for initial performance status. Median survival of patients who presented with a Karnofsky status of 80 or greater had a higher survival in each type than those patients with a performance status between 40 and 70 (34.6 vs 22.5; $P<0.05$). The median survival of type 21 patients whose performance status ranged between 40 and 70 was 26.3 weeks, whereas those with a performance status of 80 or greater had a median survival of 39.4 weeks ($P<0.03$). Similar figures for type 22 were 13.6 weeks as compared to 23.8 weeks ($P<0.01$), respectively. When patients with an initial performance status of 80 or greater were considered, those grouped in type 21 had a greater median survival (39.4 weeks) than those patients in type 22 (23.8 weeks). However, the difference did not reach statistical significance ($P=0.1$). For patients with an initial performance status 40–70 in type 21, median survival was 26.3 weeks compared to 13.6 weeks in type 22 ($P<0.01$).

Table 3. Median survival of small cell carcinoma patients by WHO classification and initial Karnofsky performance status

WHO classification	Median survival (weeks)	Total patient number
Initial performance status 40–70		
21	26.3	37
22	13.6	14
All patients	22.5	51
Initial performance status 80–100		
21	39.4	18
22	23.8	8
All patients	34.6	26

DISCUSSION

It has been clearly established that small cell carcinoma of the lung is a highly malignant tumor with a tendency to have widespread metastasis at time of diagnosis. For this reason, surgery is genrally contraindicated as a primary therapeutic modality. Untreated, this cancer has a median survival of approximately two months. Combination chemotherapy seems to be the superior means of producing remissions especially in patients with documented extrathoracic disease (extensive). Together with radiotherapy, chemotherapy produced the most complete remission inductions with prolongation of survival [5]. However, despite therapeutic advances, survival of extensive small cell carcinoma of the lung is poor.

The overall objective response rate seen in our group of patients (38%) is very similar to the data achieved by the Cancer and Leukemia Group B, in their multiple drug chemotherapy and radiotherapy program using cyclophosphamide, vincristine, methotrexate and radiotherapy. In their study, the median survival of those patients with extensive disease was six months [6]. Again, median survival in our study was 26.6 weeks. Similar combined therapeutic regimens have shown a wide range of induction response percentages; however, the median survival is remarkably similar and is the most reliable indicator of efficacy [5]. It appears that no one combined radiation–chemotherapeutic modality program appears to have noticeable advantage over others. It is possible that our objective response rate and subsequent survival would be altered if a more intensive therapy, e.g. 3 or 4 drug regimen, were employed, thus negating a selective survival preference for type 21. This assumption requires further study.

It must be emphasized that type 21 and type 22 are commonly present in the same biopsy specimen and a designation, from a pathologist's view point, may depend on which type predominates. Still another factor in determining subtype is the magnitude of the fusiform cell component. In the revised 1977 WHO classification fusiform was discarded as a growth pattern common to other cell types.

Important in our data is that classification of patients into WHO types 21 and 22 revealed an increase in survival amongst those patients with type 21. Similarly, an enhanced objective response rate to chemotherapy is elicited in type 21 when compared to those patients who presented with cell type 22. Our findings are at variance with those of Matthews *et al.* [7]. These investigators, reporting on a similar number of patients and using a single pathologist, found no differences in objective response rate or median survival in types 21 or 22. Nixon *et al.* [9] analysed 61 patients with small cell carcinoma accumulated from two different institutions. Histologically, four histologic subgroups were analysed: (1) lymphocyte-like; (2) fusiform; (3) polygonal; and (4) other. This histological classification does not conform with the 1977

WHO classification used by Matthews *et al.* [7] and ourselves so that direct extrapolation and comparison of data is not entirely possible. However, Nixon *et al.* [8] found that survival in the lymphocyte-like and fusiform categories were superior to the polygonal and 'other' types. These data seem to be simlar to ours. Hansen *et al.* [1] analysed their cases of small cell carcinoma in a fashion identical to that of Nixon *et al.* [8]; Hansen found no survival advantage with any of the four histologic classifications they used. It must be stressed that different therapy regimens were employed.

From the available data it would appear that the prognostic role of histologic subtyping in small cell carcinomas is uncertain. Larger studies will be needed conclusively to answer the question. In this regard one of us (S.D.) has analysed this question in 620 patients entered into the randomized studies of the Veterans Administration Lung Cancer Study Group [9]. The data from the VA study showed that patients with type 21 small cell carcinoma offers a better prognosis in extensive disease.

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REFERENCES

1. H. H. Hansen, P. Dombernowsky, M. Hansen and F. Hirsch, Chemotherapy of advanced small cell anaplastic carcinoma. *Ann. intern Med.* **89,** 177 (1978).
2. J. H. Edmonson, S. Lagakos and O. S. Selawry, Cyclophosphamide and CCNU in the treatment of inoperable lung cancer. *Cancer Treat. Rep.* **60,** 925 (1976).
3. D. R. Cox, Regression models and lifetables, *J. roy. Statist. Soc. B.* **34,** 187 (1972).
4. A. R. Feinstein, N. A. Gelfman, R. Yesner, O. Auerbach, D. B. Hackel and P. C. Pratt, Observer variability in the histopathologic diagnosis of lung cancer. *Amer. Rev. Resp. Dis.* **101,** 671 (1970).
5. R. B. Weiss, Small-cell carcinoma of the lung: Therapeutic management. *Ann. Int. Med.* **88,** 522 (1978).
6. L. H. Maurer and M. Tulloh, Combination chemotherapy and radiation for small cell carcinoma of the lung. Protocol No. 7283. Minutes of the Cancer and Leukemia Group B Meeting, March 1977.
7. M. J. Matthews, A. F. Gazdar, D. C. Ihde *et al.* Histologic subtypes of small cell carcinoma of the lung and their clinical significance. In *Lung Cancer, Progress in Therapeutic Research.* (Edited by F. Muggia and M. Rozencweig) p. 155. Raven Press, New York (1979).
8. D. W. Nixon, G. W. Murphy, C. W. Sewall *et al.*, Relationship between survival and histologic type in small cell anaplastic carcinoma of the lung. *Cancer (Philad.)* **44,** 1045 (1979).
9. S. Davis, K. Stanley, Y. A. Yesner, D. Kuang and J. Morris, Small cell carcinoma of the lung: Survival according to histologic subtype. *Cancer*, in press.