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Metastatic Non-small Cell Bronchogenic Carcinoma: a Randomized Trial of Sequential vs Combination Chemotherapy

PHILIP C. HOFFMAN,* STEVEN B. NEWMAN,* HARVEY M. GOLOMB,*† TOM R. DEMEESTER,‡† RICHARD R. BLOUGH§ and CORINNE A. SOVIK||

*Chest Oncology, Departments of *Medicine, ‡Surgery, §Biostatistics and ||Nursing, The University of Chicago, IL 60637, U.S.A.*

Abstract—*In order to determine whether combination chemotherapy offered any advantage over single-agent therapy in cases of metastatic non-small cell bronchogenic carcinoma, we performed a randomized study in* 56 *patients comparing combination chemotherapy (cyclophosphamide, doxorubicin, methotrexate, procarbazine, leucovorin—CAMP-L) with a regimen in which the same drugs were given sequentially (methotrexate/leucovorin followed by cyclophosphamide/doxorubicin at progression). Of the patients receiving the combination,* 52% *(*14 *of* 27*) had either a partial response or stable disease, compared to* 17% *(*5 *of* 29*) in the sequential group. Of the patients with adenocarcinoma, those in the combination group had a significantly longer survival than those treated in the sequential group (medians,* 10.0 *vs* 2.8 months; $P < 0.01$*); such a difference could not be demonstrated for patients with squamous carcinoma. Patients who achieved a partial response had a median survival of* 15.3 months; *those with stable disease survived a median of* 10.0 months; *and those with no response survived a median of* 2.5 months ($P < 0.0001$). *Four patients died from chemotherapy-related complications: three from methotrexate toxicity and resultant infection and one from pneumonia associated with neutropenia. We conclude that the short survival of non-responding patients and the survival benefit accompanying response or stabilization make early aggressive combination therapy useful for patients with metastatic non-small cell lung cancer.*

INTRODUCTION

METASTATIC non-small cell bronchogenic carcinoma has continued to present a difficult therapeutic problem despite the use of combination chemotherapy regimens. Response rates have generally been lower than those of patients with small cell carcinoma and survival has not been prolonged significantly. We recently reported on 54 patients with metastatic non-small cell lung cancer who were treated with a combination of cyclophosphamide, doxorubicin, methotrexate and procarbazine (CAMP). Of these patients, 55% showed a response or stabilization of their disease and their survival was prolonged [1]. In 1977 we began a randomized study to examine whether combination chemotherapy offered any advantage over sequential therapy with single agents in this disease. We now report our findings.

MATERIALS AND METHODS

Patients

Between June 1977 and August 1980, 74 patients diagnosed as having metastatic non-small cell carcinoma of the lung were seen at The University of Chicago Hospitals and Clinics. All of the patients to be described here had distant metastases (Stage III_{M1}). For our randomized study we excluded patients whose tumor spread outside the chest appeared to be confined to the ipsilateral supraclavicular nodes and whom we classified as Stage III_{M0} SCN+.

In all of the 74 patients lung cancer was demonstrated by pathology studies and the cell type was confirmed either by biopsy of primary or

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Reprint requests to: Dr. Hoffman, University of Chicago Hospital, Box 420, 950 E. 59th St., Chicago, IL 60637, U.S.A.
†Co-directors, Chest Oncology Program.

metastatic lesions or, in rare cases, by cytology studies. Cytology findings alone were accepted only if a specific cell type (i.e. at least non-small cell) could be inferred. Staging evaluation included physical examination, screening blood studies for renal and hepatic function, chest radiograph and tomographic gallium-67 scanning [2]. Most patients did not have routine bone, liver or brain scans except as required to confirm or clarify abnormal findings on the gallium scan. Patients were staged according to the TNM classification of the Task Force on Carcinoma of the Lung [3].

Of the 74 patients, 14 did not enter the study. Some refused to participate or requested to be treated elsewhere; for others high-dose methotrexate might have been particularly hazardous, e.g. for patients with large pleural effusions or uncertain ability to comply with instructions for taking oral leucovorin. The remaining 60 patients consented to participate and were randomly assigned by the 'sealed opaque envelope' tehnique to receive either combination chemotherapy or sequential chemotherapy. Four of these patients were later dropped from the protocol, however, because we discovered that they had been ineligible at the time of inclusion: three had had prior treatment and one was found not to have metastatic disease. Thus a total of 56 eligible patients are reported on here.

Combination chemotherapy consisted of CAMP-L (cyclophosphamide, 300 mg/m^2 i.v., days 1 and 8; adriamycin, 20 mg/m^2 i.v., days 1 and 8; methotrexate, 180 mg/m^2 i.v., days 1 and 8; procarbazine, 100 mg/m^2 p.o., days 1–10; and leucovorin, 150 mg/m^2 p.o., in 4 divided doses every 6 hr starting 24 hr after methotrexate; these cycles were repeated evey 28 days). Sequential therapy consisted of methotrexate with leucovorin rescue (same dose and schedule as above) until disease progression occurred. At that point cyclophosphamide and adriamycin (same doses as above) were substituted, which were continued until disease progression, at which time procarbazine was substituted. In some cases the doses of cyclophosphamide and adriamycin were increased by 25% each cycle if no mylesuppression was noted and the disease was progressing. Some patients in the combination group received only 15 mg/m^2 methotrexate if the nausea and vomiting caused by the other drugs prevented absorption of the leucovorin tablets. One patient with adenocarcinoma in the combination group was transferred to a nursing home after receiving only one dose of chemotherapy; she survived 9.7 months with no further therapy.

Adriamycin was discontinued when the cumulative dose of 450 mg/m^2 was reached. Dose modifications for the myleosuppressive drugs were made as follows: 75% of the calculated dose was given if the WBC count was between 3000 and 4000/mm^3 and the platelet count between 75,000 and 100,000/mm^3; 50% of the calculated dose was given if the WBC count was between 2000 and 3000/mm^3 and the platelet count between 50,000 and 74,000/mm^3. No drugs were given if blood counts were below these levels.

Responses were designated as complete if measurable tumor disappeared at all sites for at least two months; partial if all measurable tumor regressed by 50% or more, with no additional sites of involvement, for at least two months; stable disease if tumor regression of less than 50% occurred, but no progression of disease was noted for at least two months; and none if the tumor progressed within two months.

Patients received radiation therapy before beginning chemotherapy only if metastatic disease was present in critical or severely painful sites. Randomization was done on the day the chemotherapy was to begin, and survival was calculated from the first day of chemotherapy until death or, for the one current survivor, until the last day on which the patient was seen in our clinic, 7 July 1982.

Data were entered and stored in the University of Chicago's DEC System-20 computer with System 1022 data base management. Some preprocessing of the data, such as conversion of site names to numerical codes and conversion of dates to survival days, was also done with the System 1022. All survival computations were carried out with the SURVIVAL programs of SPSS release 8.1 on the DEC-20. The SPSS computes cumulative survival probabilities by the life-table method and compares survival curves by using the Lee–Desu statistic. All survival probabilities were computed at monthly intervals and median survival times (in months) were derived by linear interpolation from these probabilities.

RESULTS

Patient characteristics

At the time of diagnosis the 56 patients ranged in age from 34 to 78 yr, with a median of 55 yr. There were 33 men and 23 women. Forty-eight of the 56 patients had a performance status of 0, 1 or 2 (ECOG) [3]. Characteristics of the two groups are shown in Table 1. There were no significant differences between the groups with respect to the parameters listed.

Cell types of the patients were squamous carcinoma (19 patients), adenocarcinoma (32), large cell undifferentiated (2), poorly differentiated (2) and mixed adenocarcinoma and squamous

Table 1. *Characteristics of treatment groups*

	Combination	Sequential
No. of patients	27	29
Median age (yr)	58	55
Males/females	16/11	17/12
PS 3 or 4 (ECOG)	3	5
Cell type		
Squamous	9	10
Adenocarcinoma	14	18
Large cell	2	0
Poorly differentiated	1	1
Mixed	1	0
Prior radiotherapy	15	16
(Brain metastases)	(10)	(6)
(Squamous)	(5)	(6)
(Adenocarcinoma)	(10)	(10)

carcinoma (1). Initial dominant sites of metastases in the 56 patients were brain (15), bone (15), lung parenchyma (10), skin and soft tissue (6), liver (4) and multiple sites (6).

Response rates and survival

The response rates and median survival for the two groups are shown in Table 2. None of the patients had complete responses. All patients with a partial response or stable disease in the sequential group attained the response with the first element of the treatment sequence, methotrexate with leucovorin; no additional responses were noted when cyclophosphamide/adriamycin was given to patients in whom methotrexate/leucovorin had failed.

The response rates are grouped according to major sites of metastases in Table 3. The median survival of patients with lung, skin or brain metastases was longer than that for patients with liver, bone and multiple sites of metastases, but the difference was not significant. Table 4 shows the response rates according to cell type; here, also, the differences were not statistically significant.

The median survival times for the sequential and combination groups, whose survival curves are given in Fig. 1, were 3.5 months and 7.3 months respectively ($P = 0.13$). Figure 2 shows the survival curves according to response to therapy. Patients who achieved a partial response had a median survival of 15.3 months; those with stable disease survived a median of 10.0 months; and those with no response survived a median of 2.5 months ($P < 0.0001$). In both groups there was no statistically significant difference in survival between patients with a partial response and those with stable disease. Non-responding patients in the combination group ($n = 13$) had a median survival of 1.9 months, compared to 2.8 months for the sequential group ($n = 24$). This difference is not statistically significant.

In order to examine response to treatment in more detail, we computed survival functions for subgroups of the data. For the two predominant cell types, squamous carcinoma and adenocarcinoma, the results differed considerably. Within the adenocarcinoma group the overall survival of the 14 patients assigned to combination therapy appeared to be longer than that of the 18 patients assigned to the sequential group (medians, 10.0 and 2.8 months respectively; $P = 0.0047$). In the squamous group there was little difference (medians, combinations 4.3 months, sequential 6.5 months; $P = 0.84$). The

Table 2. *Response rates and median survival according to treatment regimen*

Regimen	Partial response	Stable disease	PR and SD	Median survival (months)
Sequential ($n = 29$)	1 (3)*	4 (14)	5 (17)	3.5
Combination ($n = 27$)	4 (15)	10 (37)	14 (52)	7.3
Overall ($n = 56$)	5 (9)	14 (25)	19 (34)	4.5

*Percentage of patients in group with given response.

Table 3. *Response rates and survival according to initial site of metastasis*

Site	Partial response	Stable disease	PR and SD	Median survival (months)
Skin ($n = 6$)	0	1 (17)*	1 (17)	6.0
Lung ($n = 10$)	2 (22)	3 (33)	5 (56)	5.0
Brain ($n = 15$)	3 (21)	4 (29)	7 (50)	6.5
Liver ($n = 4$)	0	0	0	1.5
Bone ($n = 15$)	0	3 (27)	3 (27)	3.8
Multiple ($n = 6$)	1 (13)	4 (50)	5 (63)	3.5

*Percentage of patients in group with given response.

Table 4. Response rates and survival according to cell type

Cell type	Partial response	Stable disease	PR and SD	Median survival (months)
Squamous carcinoma ($n = 19$)	1 (5)*	6 (32)	7 (37)	4.8
Adenocarcinoma ($n = 32$)	4 (13)	6 (19)	10 (31)	5.0
Large cell, undifferentiated ($n = 2$)	0	0	0	1
Poorly differentiated ($n = 2$)	0	1 (50)	1 (50)	4.0
Mixed squamous/adenocarcinoma ($n = 1$)	0	1 (100)	1 (100)	7.4

*Percentage of patients in group with given response.

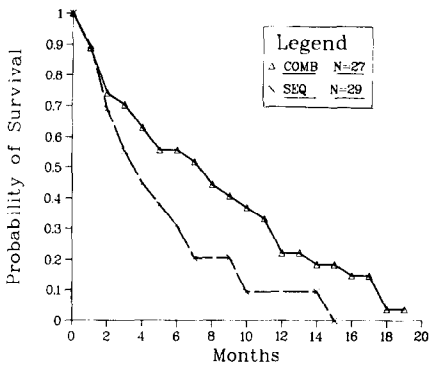

Fig. 1. Actuarial survival of 56 patients with metastatic non-small cell lung cancer according to treatment regimen. COMB, patients treated with combination chemotherapy; SEQ, patients treated with sequential chemotherapy.

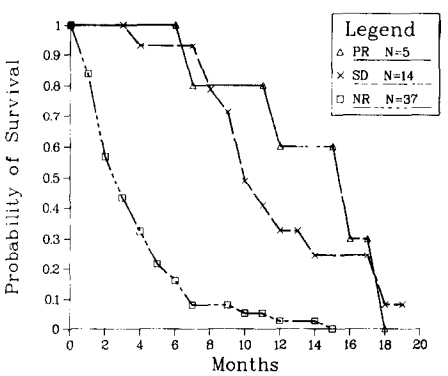

Fig. 2. Actuarial survival of all 56 patients according to response to therapy. PR, partial response; SD, stable disease; NR, no response.

respective curves, shown in Figs 3a and 3b, indicate that the difference between the two curves of Fig. 1 can be accounted for almost entirely by the differences between survival of the two treatment regimens in the adenocarcinoma group alone. Chance differences in composition of the two therapy groups which might have accounted for the observed differences in survival experience were sought through tables, graphs and survival computations based on subgroupings of age, sex, performance status and site of metastasis, but none were found.

Toxicity

Most patients who received cyclophosphamide and adriamycin experienced moderate nausea and vomiting, and all had alopecia. There was little or no nausea with methotrexate alone given on the sequential treatment program. Half of the patients on the combination program had to discontinue procarbazine because of intolerable nausea.

Three patients died of methotrexate toxicity and resultant infection; two were in the combination group and one was in the sequential group. One patient in the combination group died of bacterial pneumonia associated with granulocytopenia. In the sequential treatment group myelotoxicity was absent or minimal. In the combination treatment group the lowest WBC count was generally between 1000 and 2000/mm^3 and the lowest platelet count was generally above 100,000. Except if complications occurred, all chemotherapy was administered on an outpatient basis.

DISCUSSION

Our purpose in this randomized study was to determine whether improved response and survival similar to those which we achieved with our CAMP regimen could be attained with less overall toxicity if the drugs were administered sequentially. The results demonstrate that combination treatment offered rates of response and disease stabilization that were superior to those for the sequential regimen, although the increase in survival was not statistically significant. However, when the two treatment groups were compared for each of the two major cell types a significantly improved survival was noted for those patients with adenocarcinoma who received the combination treatment, compared to their counterparts who received sequential therapy

(Fig. 3a). No such difference could be demonstrated for the squamous carcinoma patients (Fig. 3b). The sequential regimen appeared to select out the group of patients whose tumors were sensitive to methotrexate. Although we had

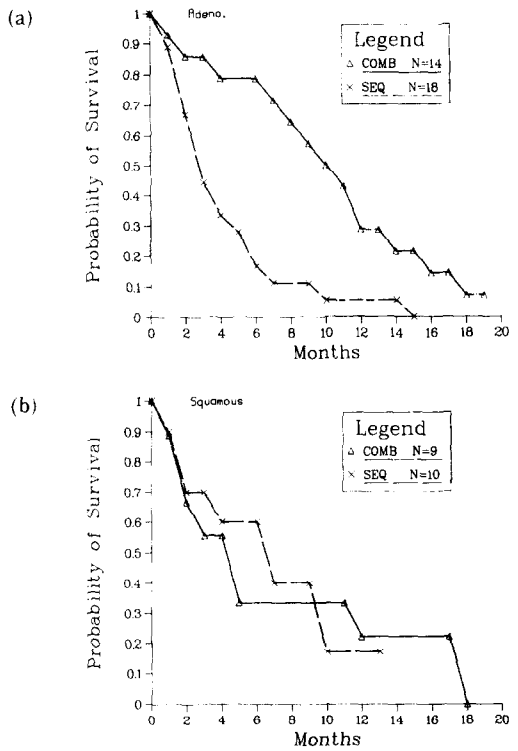

Fig. 3(a). Actuarial survival according to treatment regimen of patients with adenocarcinoma; (b) actuarial survival according to treatment regimen of patients with squamous carcinoma. COMB, patients treated with combination chemotherapy; SEQ, patients treated with sequential chemotherapy.

planned to move to the next phase of the sequence if a patient did not respond to methotrexate, this generally was done only after two cycles (2 months) of methotrexate. Of the patients who failed to respond to methotrexate, none responded to cyclophosphamide/adriamycin. It would appear that non-small cell bronchogenic carcinoma does not lend itself to such a sequential approach. If the median survival of non-responders is 3 months, it is not feasible to wait two months to seek a response to the first phase of the sequential program.

This study serves to confirm our earlier conclusions regarding response rates and survival with the CAMP regimen [1]. Although the partial response rate to CAMP-L in this study was only 15%, compared to 35% in the earlier study, an additional 37% of the patients achieved disease stabilization with prolonged survival. The combined response and stabilization rate was 55% in the earlier study, compared to 52% in the present study.

In contrast to our previous results with CAMP, in which bone, brain and skin as the initial sites of metastases signaled the shortest survival, the best response and survival results in this study were seen in patients whose initial site of metastatic disease was the brain, lung parenchyma or skin. This may be related in part to the preponderance of patients with adenocarcinoma (57%) in this study compared to the earlier group (41%). Patients with adenocarcinoma appear to be at higher risk for early brain metastases [4]; in the present series, of 15 patients with brain metastases, 10 (67%) had adenocarcinoma and only 4 (27%) had squamous carcinoma. Because the brain metastases were treated initially with radiation therapy, often there was little other measurable disease to follow during chemotherapy, leading to a higher percentage of patients with stable disease and with longer survival. The differences in survival according to site of metastasis between our previous study and the current one, however, point to the fact that metastatic disease is often widespread and that the dominant site of metastasis is not necessarily a precise indicator of the exact extent of disease.

The improved response and stabilization rates for patients treated with combination chemotherapy in this study, along with the significantly increased survival times for patients with adenocarcinoma, emphasizes the need for early aggressive treatment in cases of metastatic non-small cell carcinoma. Responding patients who might achieve longer survival can be selected out early with combination chemotherapy, instead of waiting for one or more single agents to work or fail. As in our earlier report, this study did not show a statistically significant difference in metastatic non-small carcinoma between partial response and stable disease in terms of survival benefit obtained.

Although some improvement has been noted in the effectiveness of chemotherapy in metastatic non-small cell lung cancer, the results are still often disappointing [5]. The results of using the CAMP regimen have been reported by other groups [6, 7], with results similar to ours. Recent studies suggest that cisplatin-containing combinations may have significant activity against non-small lung cancer [8–11]. We have designed our current studies to compare these with our experience using CAMP.

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