

Immediate Versus Postponed Combination Chemotherapy (CAMP) for Unresectable Non-Small Cell Lung Cancer: A Randomized Trial¹

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SUMMARY

A randomized control trial was performed in good performance status patients with unresectable non-small cell lung cancer to test a strategy of early aggressive combination chemotherapy (CAMP [cyclophosphamide, doxorubicin, methotrexate, and procarbazine]) versus a strategy of delaying such treatment until clinical deterioration. Thirty-seven patients received immediate CAMP and 35 patients received initial low-dose single-agent CCNU (CAMP was postponed). Immediate CAMP therapy produced an objective response rate of 44% in patients with measurable lesions, and CCNU produced none. Median survival was 193 days for the immediate-CAMP group and 175 days for the postponed-CAMP group ($P = 0.26$). Measures of quality of life were made and no difference emerged between the two treatment strategies. This trial failed to show substantial benefit from immediate combination chemotherapy in minimally symptomatic patients with non-small cell lung cancer.

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Combination chemotherapy regimens containing doxorubicin can cause tumor regression in 30%-40% of patients with non-small cell lung cancer (1-7). The CAMP combination is one of these regimens and consists of cyclophosphamide, doxorubicin, methotrexate, and procarbazine (2-4). The benefit of these regimens has been assessed through the use of historic controls. When we compared survival times of our CAMP-treated patients with historic controls matched by age, stage, and performance status, we found no difference. A more rigorous method of treatment assessment is the randomized prospective control trial.

Our study design was a compromise among phy-

sicians with differing views of the lung cancer chemotherapy data available at the time. We agreed that radiation therapy had not provided significant clinical benefit for patients with lung cancer when tested against no treatment in the Veterans Administration randomized trial, since the survival difference was significant at 0.05 only by using a one-tailed test (8). A randomized trial of combination chemotherapy versus no treatment was not acceptable to all members of our group because of ethical considerations based, in part, on fear of an adverse psychologic effect in patients randomized to receive no treatment. Our study was designed to offer hope to all patients even though one half were to receive initial treatment (ie, low-dose CCNU as a single agent) considered by some to be little more than a placebo (1). Placebo effect, coupled with the promise of further possibly effective treatment, when necessary, may have great benefit for a patient with a serious illness. However, at the time of study design, we were not in agreement as to whether low-dose CCNU could be assumed to be either nontoxic or completely inactive.

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METHODS

The study population consisted of patients who fulfilled the following criteria: stage III M_0 or M_1 non-small cell lung cancer, a Zubrod performance score of 2 or better, and informed consent. To assure reproducibility of performance status assignment, performance status 3 was defined as housebound, not including visits to the clinic.

Over a 26-month period, 72 patients were randomized to receive initial treatment with either CAMP combination chemotherapy (4) or 50 mg/m² of CCNU as a single agent every 4 weeks. The CAMP-treated patients continued to receive CAMP until deterioration ("E₁," defined below) or death. Treatment after CAMP failure was at the discretion of the primary physician. CCNU-treated patients continued to receive CCNU until E₁, when they were crossed over to CAMP. E₁ was defined as one of four events: deterioration to housebound status (Zubrod performance score of 3), loss of 12% body weight, progression of tumor by volume doubling or appearance of new metastases, or death.

Patients were substaged at the time of randomization as having "limited" or "extensive" disease, as defined by the Veterans Administration Lung Cancer Study Group (9). Radiation treatment of the primary tumor was given only for palliation of symptoms. Primary radiation therapy was completed prior to randomization if given before chemotherapy. Twelve of the 34 patients with limited disease were treated in this manner. Response to chemotherapy was assessed according to Eastern Cooperative Oncology Group criteria (4). "Stable" patients were not considered responders.

Survival from the day of randomization was determined for each patient. Also determined were time to E₁ and time to housebound status (for patients whose E₁ was weight loss or tumor progression). These times were thought to reflect quality of life; thus, the influence of combination chemotherapy on the quality of life could be determined independent of survival. Balanced, nonstratified randomization was used. Our experience indicated that we would be able to enroll approximately 30 patients/year, and that median survival would likely be about 6 months. We then estimated that about 2.5 years would be necessary to enroll about 70 patients and that after 40 deaths the trial would have a power (type II risk) of about 0.5 for detecting a difference ("delta") of 0.37. In other words, we accepted a limited ability to detect a small benefit because of the toxicity and expense we felt inherent in CAMP treatment. The data were analyzed three times: once after 1 year (4), once when patient accrual ended (10), and here, when all but five patients

were dead. A total of four tests of significance comparing CAMP with CCNU were performed using the log-rank test (11). All significance levels were two-sided.

RESULTS

Of the 72 patients, 37 received CAMP and 35 received CCNU as initial treatment. Of the 37 patients, 23 subsequently received CAMP, and 14 patients (34% of the CCNU group) died while receiving CAMP. At the time of analysis five patients were alive, and two of these had reached a deterioration point (E₁). No patient was lost to followup. Table 1 shows the characteristics of the two groups. A trend toward unbalanced distribution of some prognostic variables is evident. None of these reached significance and tend to cancel each other in that some of the unbalancing favored one group and some the other.

Thirteen of the 43 patients with measurable disease receiving CAMP achieved an objective response, one of which was complete. The survival advantage of responders approached significance (median, 347 vs 153 days; $P = 0.11$). Of these patients, 25 received immediate CAMP (11 responders, 44%) and 18 received CAMP after reaching E₁ on CCNU treatment (two responders, 11%). Another five patients, who did not have measurable lesions, received CAMP after E₁. Three of the patients improved their performance status on CAMP. No response to CCNU was seen. Thus, of the 37 patients randomized to receive immediate CAMP achieved objective response (80%) and two of the 35 patients randomized to receive initial treatment with CCNU were responders (6%).

Despite the absence of objective response to CCNU, no differences existed in time to death, time to deterioration, or time to housebound status between the immediate-CAMP and initial-CCNU groups (figs 1-3).

Also, among patients with limited-stage disease, the survival difference was not significant between the two treatment groups (median, 385 vs 253 days; $P = 0.7$). Anatomic substage did not quite reach significance as a prognostic factor. Histologic type did not influence survival. CAMP was well-tolerated (table 2) and no drug-related toxicity was encountered from CCNU.

The size of this trial (67 deaths) gives an 80% chance of detecting a survival difference of about 40% between the two groups (ie, the type II risk is about 0.20 with a two-tailed type I risk of 0.05). A 40% difference roughly means that 70% of patients in the better treatment group would be alive when

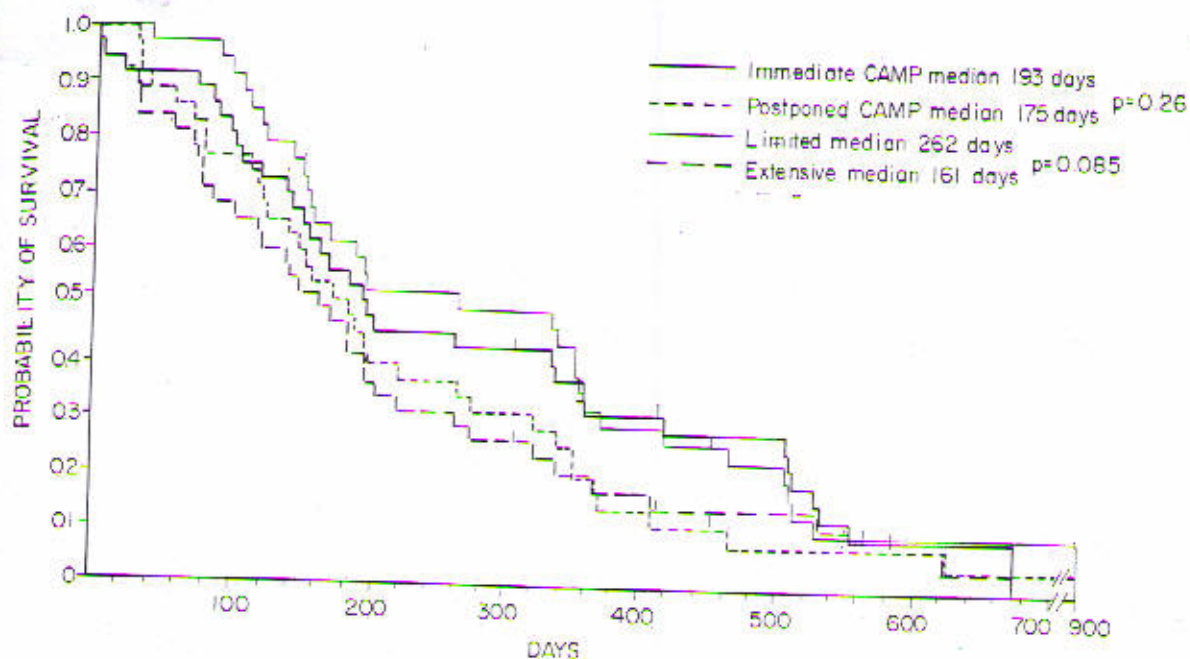


FIGURE 1.—Survival from randomization according to treatment assignment and stage. Small vertical marks = patients who remain alive at the time of analysis.

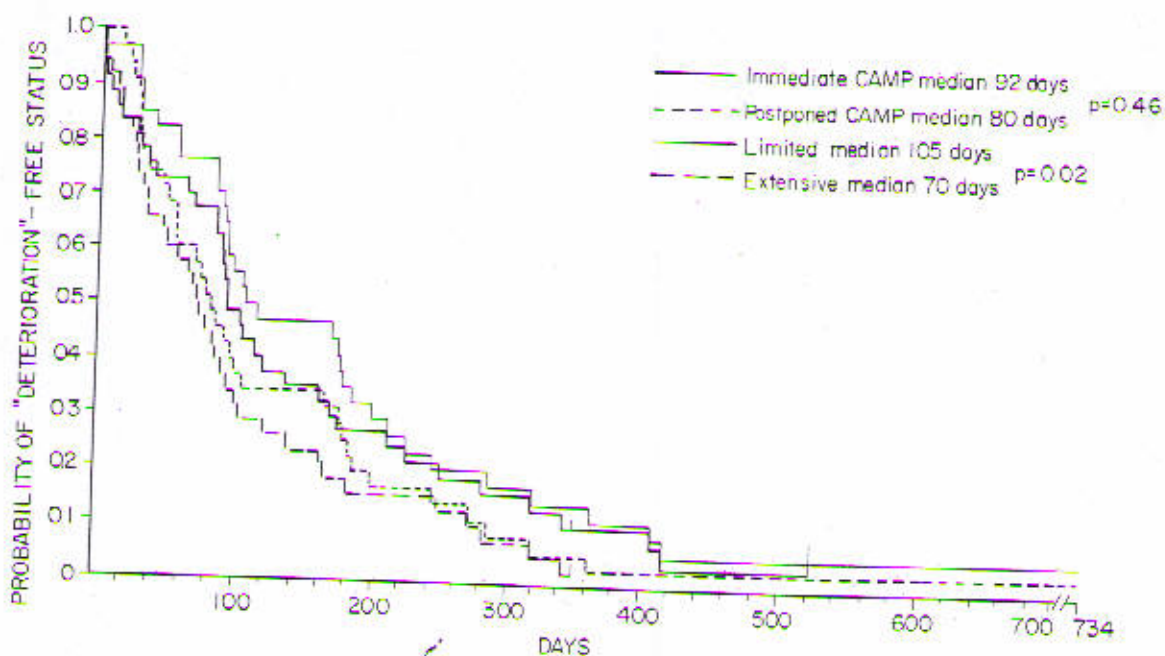


FIGURE 2.—Time from randomization to deterioration (E_1) according to treatment assignment and stage. Small vertical marks = patients who have not yet reached E_1 .

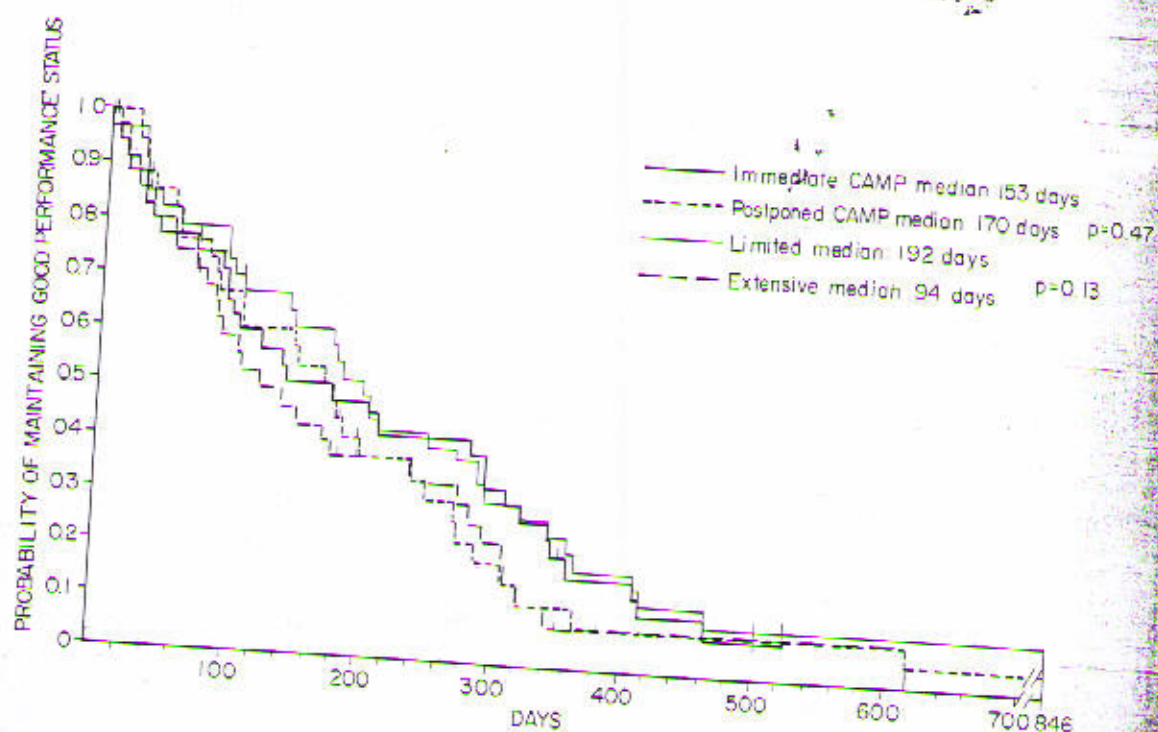


FIGURE 3.—Time from randomization to housebound status according to treatment assignment and stage. Small vertical marks = patients who have not yet reached poor performance status, including those who died without becoming housebound.

TABLE 1.—Randomization results*

Prognostic factor	Initial treatment		Total (100%)
	CAMP (%)	CCNU (%)	
Stage			
Limited	20 (59)	14 (41)	34
Extensive	17 (45)	21 (55)	38
P value†	0.84		
Cell type			
Squamous cell carcinoma	23 (55)	19 (45)	42
Adenocarcinoma	7 (47)	8 (58)	15
Large cell undifferentiated carcinoma	7 (47)	8 (53)	15
P value†	0.79		
Performance status			
0	5 (30)	12 (70)	17
1	22 (61)	14 (39)	36
2	10 (53)	9 (47)	19
P value†	0.10		
Prior radiotherapy (for symptomatic disease)			
Yes	8 (38)	13 (62)	21
No	29 (57)	22 (48)	51
P value†	0.23		
Total	37 (51)	35 (49)	72

* Unless otherwise specified, values = No. of patients.

† Chi-square test.

TABLE 2.—CAMP tolerance

No. of patients—	
Total	72
Randomized to receive immediate CAMP	37
Randomized to receive postponed CAMP	35
Died without receiving CAMP	12 (34%)
Receiving CAMP	60
Unable to tolerate procarbazine	8 (5%)
No. of CAMP cycles—	
Total	265
Mean/patient	4.4
At 100% dose	187 (63%)
Total dose of CAMP received	85%
Mean wks/CAMP cycle	4.2

the median survival of the poorer survival group is reached (11).

DISCUSSION

This study can be considered an "aggressive chemotherapy versus minimal treatment trial" for two reasons. First, nearly one third of the patients randomized to receive initial treatment with low-dose CCNU never received combination chemotherapy. Second, after cross-over of CCNU patients to CAMP the response rate was low, probably because of poor performance status. Poor performance status is known to predict poor response to treatment.

What appears to be a discrepancy between the survival advantage for CAMP responders and the lack of overall superiority of immediate CAMP deserves comment. The validity of retrospective comparisons by response and compliance can be questioned on logical and empiric grounds (12), and much of the evidence favoring combination chemotherapy is based on responder/nonresponder analysis. In addition, this trial was designed to quantitate the effect of combination chemotherapy on quality of life and survival rather than on tumor regression. Indeed, tumor measurability was not among the criteria for inclusion. The endpoints used in this trial (ie, death and other clinical deterioration) were easily determined, and thus suitable to the methodology of prospective, randomized trials.

Our survival curves are observations rather than predictions (ie, not heavily censored since all but five patients have died). In fact, our figures calculated at cessation of accrual to this study showed a significant survival advantage for limited-stage patients and CAMP responders (10). These significant differences did not persist. The fact that different conclusions may thus be reached within the same study depending on the length of followup illus-

trates the problems arising from early reporting of results (11).

The sensitivity, or power, of this small trial is not great (13), but three conclusions can be made. First, the magnitude of clinical benefit of CAMP combination chemotherapy for non-small cell lung cancer is not as large as historic control comparisons suggest (2). The median survival of our patients was about 6 months, whether they received immediate CAMP or not. Although this is almost double that observed for untreated patients in the Veterans Administration studies (9), our patients were selected for initially favorable performance status, as is the case in most cancer treatment trials. Second, CAMP combination chemotherapy at full doses does not have an adverse effect on survival of patients with non-small cell lung cancer, as was found in the Oxford trial with MVPP (14). In fact, combination chemotherapy is well-tolerated. Finally, care must be taken in the interpretation of chemotherapy experience citing survival differences between responders and nonresponders. Our CAMP results in terms of response rate and survival of responders are comparable to results from other studies using the same regimen. However, the survival and quality of life of our postponed-CAMP group (6% responders) and our immediate CAMP group (30% responders) were not different, although response was an indicator of a favorable prognosis. Future studies of combination chemotherapy should incorporate quality of life assessment in addition to the standard measurements of response rate and survival.

The survival and quality of life of patients with non-small cell lung cancer who have good performance status are quantitated in this study, and little benefit from immediate combination chemotherapy is evident. Such treatment for patients with unresectable non-small cell lung cancer with minimal symptoms should not be considered beneficial until well-controlled trials demonstrate improvement in the quality of life or a survival advantage.

REFERENCES

1. LIVINGSTON RB. Combination chemotherapy of bronchogenic carcinoma. I. Non-oat cell. *Cancer Treat Rev* 4:153-165, 1977.
2. BITTAN JD, DESSER RK, DEMESTER T, ET AL. Metastatic non-oat cell bronchogenic carcinoma therapy with cyclophosphamide, doxorubicin, methotrexate, and procarbazine (CAMP). *JAMA* 240:2743-2746, 1978.
3. VOGELZANG NJ, BONOMI PD, ROSSOF AH, ET AL. Cyclophosphamide, Adriamycin, methotrexate, and procarbazine (CAMP) treatment of non-oat cell bronchogenic carcinoma. *Cancer Treat Rep* 62:1595-1597, 1978.
4. LAD T, SARMA PR, DIEKAMP U, ET AL. "CAMP" combination chemotherapy for unresectable non-oat cell bronchogenic carcinoma. *Cancer Clin Trials* 2:321-326, 1979.

5. BUTLER TD, MACDONALD JS, SMITH FP, ET AL. 5-Fluorouracil, adriamycin, and mitomycin-c (FAM) chemotherapy for adenocarcinoma of the lung. *Cancer* 48:1183-1188, 1979.
6. CHAHINIAN AP, MANDEL EM, HOLLAND JF, ET AL. MACC (methotrexate, adriamycin, cyclophosphamide, and ccnu) in advanced lung cancer. *Cancer* 43:1590-1597, 1979.
7. EAGAN RT, INGLE JN, FRYTAK S, ET AL. Platinum-based polychemotherapy versus dihydrogalactitol in advanced non-small cell lung cancer. *Cancer Treat Rep* 61:1339-1345, 1977.
8. WOLF J, PATNO ME, ROSWIT B, ET AL. Controlled study of survival of patients with clinically inoperable lung cancer treated with radiation therapy. *Am J Med* 40:360-367, 1966.
9. GREEN RA, HUMPHREY E, CLOSE H, ET AL. Alkylating agents in bronchogenic carcinoma. *Am J Med* 46:516-525, 1969.
10. LAD T, NELSON R, DIERAMP U, ET AL. (Abstr) Early vs. late aggressive chemotherapy for unresectable non-small cell lung cancer: a randomized trial. In II World Conference on Lung Cancer (Hansen H, and Dombernowsky P, eds). Amsterdam, The Netherlands, Excerpta Medica, 1980, p 134.
11. PETO R, PIKE MC, ARMITAGE NE, ET AL. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 34:585-612, 1976, 35:1-39, 1977.
12. THE CORONARY DRUG PROJECT RESEARCH GROUP. Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project. *N Engl J Med* 1038-1041, 1980.
13. FRIEMAN JA, CHALMERS TC, SMITH H, ET AL. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *N Engl J Med* 299:890-894, 1978.
14. LAING AM, BERRY RJ, NEWMAN CR, ET AL. Treatment of inoperable carcinoma of the bronchus. *Lancet* 2:1161-1164, 1975.