COMBINATION CHEMOTHERAPY USING CYCLOPHOSPHAMIDE, VINCRISTINE, METHOTREXATE, 5-FLUOROURACIL, AND PREDNISONE IN SOLID TUMORS

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Three hundred and ninety-eight patients with disseminated solid tumors other than breast cancer, were treated with a combination chemotherapy protocol utilizing cyclophosphamide, vincristine sulfate, methotrexate, 5-fluorouracil, and prednisone. Three hundred and eighty were evaluable (95.5%). Partial or complete tumor regressions were noted in 73 of 380 (19%) evaluable patients. Response to therapy was associated with a prolongation and survival. The largest tumor categories were lung, ovary, and gastrointestinal. The proportion of complete plus partial responses in evaluable lung cancer patients was 40/236 (17%), compared to 20/44 (45%) for ovarian cancer patients and 6/39 (15%) for gastrointestinal tumors. Of the patients who could be evaluated for toxicity, 47% had minimal or no toxicity, 51% had moderate to severe toxicity, and 2% had life threatening toxicity. Virtually all patients were treated and managed as outpatients.

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The combination of cytoxan, vincristine sulfate, methotrexate, 5-fluorouracil, and prednisone was initially reported by Cooper in the therapy of 60 patients with disseminated breast carcinoma.[3] Eighty-eight percent of the patients achieved a complete response lasting an average of 10 months. The dosage of these drugs was such that 45% of the patients had marked leukopenia and two drug deaths were reported.

A number of studies have been published using various modifications of the original regimen in breast cancer. Ansfield used a modified Cooper regimen to test whether the same degree of effectiveness could be achieved with less toxicity.[1] Seventeen of the 18 patients could be evaluated and 11/17 had objective responses (3 complete), a 65% response rate. The average duration of response was 6 months; less toxicity was evident with no drug deaths. Spigel *et al.*, using the same modified 5 drug combination, treated 23 patients with disseminated breast carcinoma.[10] Ten of 23 responses (4 complete) were obtained. The median duration of response was 8 months.

Kaufman *et al.*, using another modified Cooper regimen, reported on 42 patients with disseminated breast carcinoma with 23 responders (55%).[7] There were 3 deaths attributed to drugs. The median survival of the patients who

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TABLE 1. Hematopoietic Toxicity Criteria

	None	Mild	Moderate	Severe	Life threatening
Hemoglobin (m%)	≥ 10.0	9.0–9.9	7.0–8.9	5.0–6.9	< 5.0
White blood cells (granulocytes/L)	> 4,000 (1500)	3,000–3,999 (< 1500)	2,000–2,999 (< 1,000)	1,000–1,999 (< 500)	< 1,000 (25)
Platelets/L	≥ 1,000,000	75,000–99,999	50,000–74,999	25,000–49,999	< 25,000

similar regimen in 32 breast cancer patients with 6 complete and 9 partial responses (42%).[8]

The most recent modification used four drugs in combination (vincristine was excluded). Canellos *et al.* reported that 17 of 25 patients with advanced breast cancer achieved a response.[4] Seven of 25(28%) were complete responders. The median duration of response was 9 months. At the time of publication, the median survival of the responders had not been reached but was calculated in excess of 13 months.

In view of the extensive positive experience with these various combinations in breast cancer, the present study was designed to examine the influence of the modified five-drug program in disseminated tumors other than breast cancer.

MATERIALS AND METHODS

Between November 1970 and October 1973, 398 patients with disseminated tumors other than breast cancer were treated with cytoxan, vincristine, methotrexate, 5-FU, and prednisone by the Southwest Oncology Group.

The drug dosages were: cyclophosphamide 100 mg, daily, orally; vincristine sulfate, 0.025 mg/kg, or a maximum of 1 mg, intravenously, weekly; methotrexate, 0.5 mg/kg, intravenously, weekly; 5-fluorouracil, 10 mg/kg, or a maximum of 500 mg, intravenously, weekly; and prednisone 45 mg/day for two weeks, 30 mg/day for two weeks, and 15 mg/day for the remainder of an 8-week period with a reduction of 5 mg/day each week until the dosage was 0.

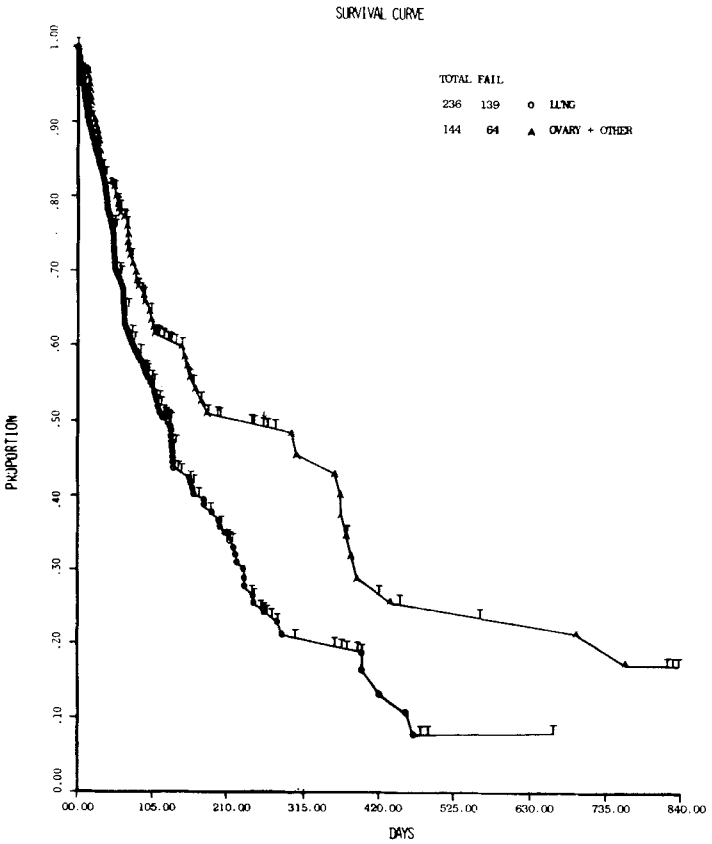

FIG. 1. Cumulative survival curves comparing lung vs ovary and other tumor types.

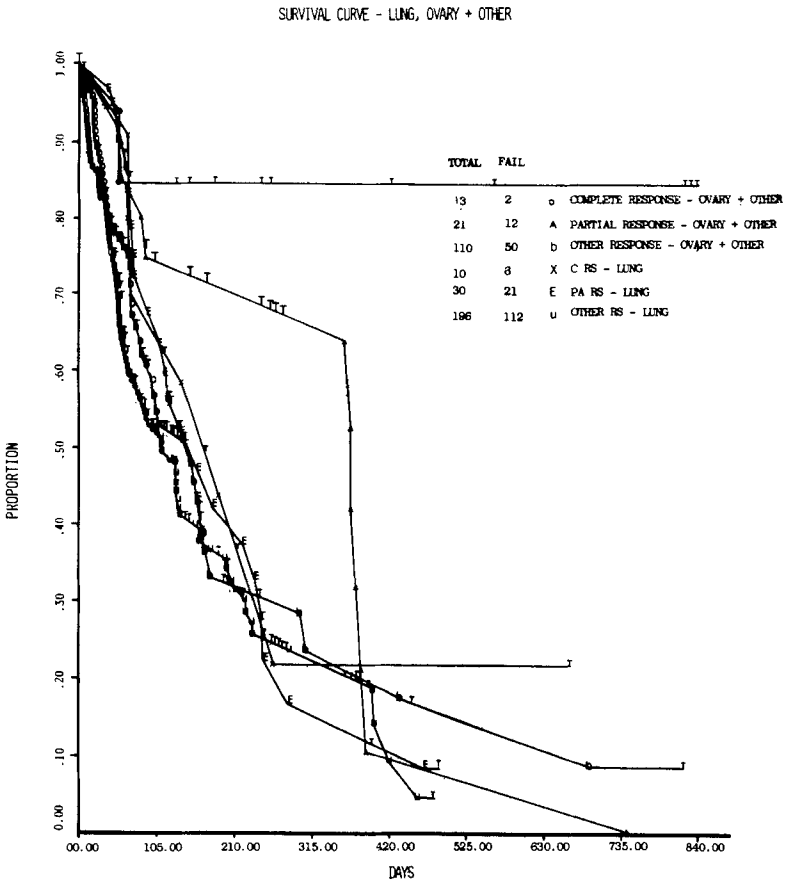

FIG. 2. Cumulative survival curves by response comparing lung cancer vs ovary and other tumor types.

Following eight weeks of therapy, vincristine was given every other week while methotrexate and 5-fluorouracil were administered on a weekly basis. Cyclophosphamide therapy was also continued at 100 mg/day orally.

Tumor measurements, complete blood cell and platelet counts were performed once weekly. Renal and hepatic function, metastatic bone survey, and liver scan were monitored every two months. Progressive disease or death were endpoints for chemotherapy.

Toxicity criteria are those established by the Southwest Oncology Group. Hematopoietic toxicity criteria are shown in Table 1. If the white blood cell (WBC) fell below 3,000/cu mm or platelet count below 100,000/cu mm, therapy with the cytotoxic drugs was discontinued for one or more weeks until recovery of counts above these levels occurred. Vincristine therapy was discontinued when patellar reflex was lost. No formal antacid regimen was specified.

Criteria for response are defined as follows: increasing disease—50% increase in the size of measured lesions; no response—no change in size of measured lesions after three courses; mixed response—at least a 50% decrease in size of one or more lesions with increase in size of others; partial response—at least a 50% decrease in the sum of the products of two perpendicular diameters of all measured lesions; complete response—disappearance of all lesions A new lesion was regarded as progressive disease.

Chi-square tests were used in testing for the difference in response rates. Survival curves were calculated using the method of Kaplan and Meier.[6] The statistical significance of differences between survival curves was tested by the generalized Wilcoxon test.[6]

RESULTS

Three hundred and eighty of the 398 patients are considered in this report. Eighteen were not evaluable; 12 due to insufficient data, five because they were not treated according to the protocol, and one patient committed suicide after being on study two weeks.

TABLE 2.

Tumor type	Evaluable	Complete remission	Partial remission	Response	Improvement	No response	Increasing disease	Early death	Inadequate trial due to toxicity	Lost to follow up	Refused further treatment
Lung	236	10(4%)	30(13%)	40(17%)	9(4%)	90(38)%	97(41%)	40	0	7	1
Squamous	63	4(6%)	7(11%)	11(17%)	3(5%)	25(40%)	24(39%)	16	—	—	—
Adeno	64	1(2%)	8(13%)	9(14%)	3(5%)	22(34%)	30(47%)	8	0	4	1
Oat	36	3(8%)	4(11%)	7(19%)	2(6%)	14(39%)	13(36%)	4	—	2	—
Anaplastic	10	0(0%)	2(20%)	2(20%)	0(0%)	1(0%)	7(70%)	1	—	—	—
Alveolar	3	1(33%)	0(0%)	1(33%)	0(0%)	2(66%)	0(0%)	0	—	—	—
Undiff	36	0(0%)	7(19%)	7(19%)	0(0%)	14(39%)	15(42%)	8	0	—	—
Unclassified	3	0(0%)	0(0%)	0(0%)	0(0%)	2(67%)	1(33%)	1	—	—	—
Other	21	1(5%)	2(10%)	3(14%)	1(5%)	10(48%)	7(33%)	2	0	1	—
Ovary	44	6(14%)	14(32%)	20(45%)	2(5%)	8(18%)	14(32%)	3	—	2	—
Colon	19	2(11%)	3(16%)	5(26%)	0(0%)	6(32%)	8(42%)	0	—	—	—
Pancreas	13	0(0%)	0(0%)	0(0%)	1(8%)	6(46%)	6(46%)	0	—	—	—
Stomach	7	0(0%)	1(14%)	1(14%)	0(0%)	2(29%)	4(47%)	1	—	1	—
Other	61	5(8%)	3(5%)	7(11%)	2(3%)	10(16%)	42(69%)	14	4	2	1
	280	23	51	73	14	122	171	58	4	12	2

TABLE 3. Overall Toxicity

Severity	Number	%
None	80	(25)
Mild	68	(22)
Moderate	133	(42)
Severe	28	(9)
Life threatening	6	(2)
Unknown	65	

Table 2 shows the response rates of the different tumor types. There is not a statistically significant difference in the proportions of complete response or complete plus partial responses among the different lung cell types. However, the proportion of complete plus partial responses in lung patients is 40/236 (16.8%) compared to 20/44 (45.4%) for ovary patients. This is a statistically significant difference (P = .01). There were six complete and 11 partial responses in the 25 (68%) ovarian carcinoma patients who had no prior alkylator therapy while only 3/19 (16%) with prior alkylator therapy showed response.

The median time from onset of treatment to maximum response is 45 days for complete responders and 29 days for partial responders. The median duration of complete response is 194 days compared with 153 days for partial responders. The difference between these curves is not statistically significant (P = .46). Figure 1 shows the survival of all lung patients (236) compared to the survival of all patients without lung cancer (144 patients with ovary and other disease sites). The median survival of all lung cancer patients was 124 days or 4.13 months and 221 days or 7.37 months for all other patients. There was a statistically significant difference between these two survival curves (P = .02). The survival by response for all patients without lung cancer is shown in Fig. 2. While no median survival has been reached for the patients achieving a complete response (CR), median survivals of 367 days and 146 days were obtained for partial responders and patients obtaining less than a partial response (other re-

TABLE 4.

Ovary + Other	Lung	P-Value
Complete response	C RS	.17
Complete response	PA RS	.02
Complete response	OTH RS	.01
Partial response	C RS	.37
Partial response	PA RS	.10
Partial response	OTH RS	.01

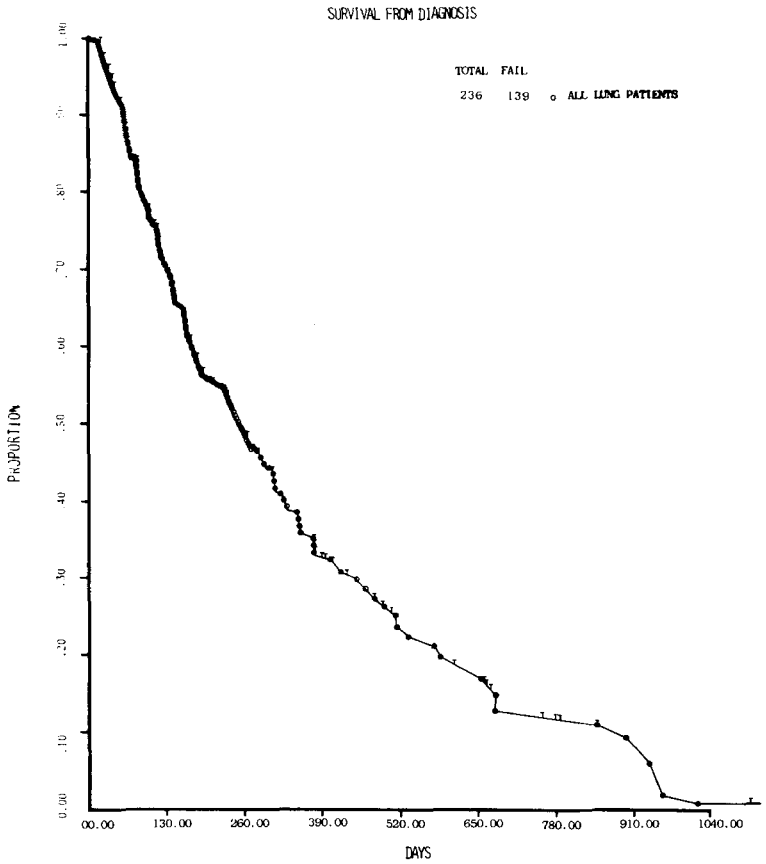

FIG. 3. Cumulative survival curve for all lung cancer patients calculated from date of diagnosis.

sponse). There is a significant difference between the survival for complete responders and other responders (P = .02) as well as the difference between partial responders and other responders (P = .04). The survival of complete responders and partial responders in Fig. 2 is not significantly different (P = .20).

The survival by response for lung cancer patients and ovary plus other patients is shown in Fig. 2. The median survival of 167, 145 and 112 days was computed for lung cancer patients who obtained a complete response, partial response, or other response, respectively. The following pair-wise comparison of survival curves was performed, and the associated P = values are depicted in Table 4. Although the survival curves for complete responders from the ovary plus other cancer group appear to be substantially better than that of the complete responders from the lung cancer group, the associated P = value is only .17. This P value (as all P values) is directly related to the small number of patients in each group.

The survival from *diagnosis* to last follow-up or death of all lung patients is shown in Fig. 3. The median survival from diagnosis is 251 days or 8.37 months.

Survival curves for each of the different lung cell types are shown in Fig. 4. Note that survival is slightly better for patients with oat cell carcinoma compared with the other lung cell types. There is no evidence of a difference between these curves except for the difference between oat cell carcinoma and squamous cell carcinoma (P = .09).

Table 3 outlines the degree of toxicity in the subjects in which data is available. Two hundred and eighty-one (89%) of the patients had no worse than moderate toxicity, 28 (9%) patients had severe toxicity, and 6 (2%) patients experienced life-threatening toxicity. Of interest is the fact that in the 13 patients who had carcinoma of the pancreas, six of them (46%) had severe toxicity.

DISCUSSION

In the present study, the median survival from diagnosis to last follow-up or death of all lung patients is 251 days or 8.37 months. The average

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