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Failure of Intensive Combination Therapy (Cyclophosphamide, Adriamycin, 5-Fluorouracil) to Control Adenocarcinoma or Large-cell Anaplastic Carcinoma of Lung

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Summary. *Eleven patients with advanced adenocarcinoma of lung and six patients with large cell anaplastic carcinoma of lung were treated with combination chemotherapy using cyclophosphamide 1 g/m² i. v., adriamycin 30 mg/m² and 5-FU 500 mg/m² i. v. on days 1 and 8, of a 28 day cycle. In neither group did any patient achieve a complete remission; 1 patient achieved a partial response in each group, and the rest showed no evidence of response. The duration of survival of the responding patients in each group was not significantly longer than those of the non-responders. Toxicity and side effects were considerable in all patients. This study demonstrates that these tumour types are refractory to this form of intensive combination chemotherapy. A literature review suggests that other forms of combination chemotherapy are usually equally ineffective.*

Introduction

Adenocarcinoma and large-cell anaplastic carcinoma of lung (WHO types 3 and 4) are relatively rare tumours for which effective chemotherapy is not so far available. Single-agent treatment is associated with a low response rate and no evidence of prolonged survival [12]. Recently two sequential combination chemotherapy regimens using cyclophosphamide and 5-FU, or, cyclophosphamide, 5-FU and adriamycin, have been reported as showing no evidence of response in patients with either of these tumour types [4].

For the last 2 years we have been investigating the use of a similar chemotherapy regimen, using the same three drugs (cyclophosphamide, adriamycin and 5-FU) but with a larger dose of cyclophosphamide, in patients with adenocarcinoma and large-cell anaplastic carcinoma of lung. Our results are reported here.

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Patients and Methods

Seventeen patients with histologically proven advanced carcinoma were included in this study; 11 had adenocarcinoma of lung (age range 33–74 years, median 66 years) and 6 had large cell anaplastic carcinoma (age range 38–72, median 61 years).

All patients were treated with cyclophosphamide 1 g/m² IV adriamycin 30 mg/m² and 5-FU 500 mg/m² IV, given by bolus injection on days 1 and 8 of each 4-week cycle, as toxicity allowed.

No patient had received previous chemotherapy.

Sites of disease for patients with each of the two histological types are given in Table 1.

Complete response (CR) was defined as disappearance of all clinical and radiologically measurable disease for at least one month. Partial response (PR) was defined as a greater than 50% reduction in the product of the two largest perpendicular diameters of any measurable lesion, in the absence of any new lesions developing elsewhere, or further progression of known lesions, for at least 1 month.

Results

Ten of the 11 patients with adenocarcinoma were evaluable for response; the eleventh patient died of progressive disease within 1 week of starting treatment. None of the ten patients achieved a CR, one achieved a PR in a subcutaneous mass, and nine showed no evidence of response.

Five of the six patients with large-cell anaplastic carcinoma were evaluable for response; the sixth died of progressive disease 10 days after starting treatment. One patient showed a PR in the lung and four showed no evidence of response.

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The responding patient with adenocarcinoma of lung survived 7 months after starting chemotherapy; this compared with a median survival in non-responders of 6 months (range 1 week to 25 months). The responding patient with large-cell anaplastic carcinoma survived 5 months after starting treatment compared with a median survival of 3 months (range 3–18 months) for non-responders.

Significant toxicity was seen in all patients and included nausea and anorexia (100%), vomiting (67%), alopecia (100%), leucopenia of less than 2,000 cells/mm^2 (33%), neutropenic infection (12%), thrombocytopenia of less than 100,000/mm^2 (33%). Nine patients (60%) developed anaemia sufficiently severe to require blood transfusion. Mouth ulcers, bladder symptoms and diarrhoea were also seen in a minority of patients.

Discussion

These results confirm the findings of Brugarolas et al. [4] and show that this form of intensive combination chemotherapy, even with the larger dose of cyclophosphamide used in this study, is unlikely to achieve a response in patients with adenocarcinoma or large-cell carcinoma of lung. Furthermore, even where partial responses were achieved in two patients, their duration of survival was not significantly longer than that of non-responders.

Table 2 lists the results obtained with other chemotherapy combinations used in the treatment of adenocarcinoma of lung. Although one group [1] reports a 50% response rate, this was achieved in a series of only six patients, and overall results are similar to our own, whatever combination is used.

Table 3 lists the results of different chemotherapy combinations in the treatment of large cell anaplastic carcinoma. Although one group [1] report eight responders out of nine, these results appear to be unique; other groups using the same or similar combinations have found this tumour to be extremely resistant to combination chemotherapy.

Our conclusion therefore is that intensive combination chemotherapy based on cyclophosphamide, adriamycin and 5-FU is unlikely to be of benefit in controlling advanced adenocarcinoma and large-cell carcinoma of lung, and their use does not justify the considerable toxicity encountered. Other chemotherapy combinations appear to be equally unpromising. At present, chemotherapy for these tumour types should therefore be aimed at finding more effective single-agent therapy which might eventually form the basis of more active drug combinations.

Table 1. Sites of disease

Site	Large-cell anaplastic		Adenocarcinoma	
	No. of patients	%	No. of patients	%
Lung	6	100	11	100
Nodes	2	33	2	18
Liver	3	50	4	36
Bone	1	16	2	18
CNS	1	16	1	9
Marrow	–	–	1	9
Subcutaneous	1	16	1	9

Table 2. Response to combination chemotherapy of adenocarcinoma of lung

Reference	Treatment[a]	Patients treated	Responders %	Median response duration
1	F.A.M.	6	3 (50%)	not given
2	C.F.Cc.	23	5 (22%)	5.5 months
3	F.V.Cc.	16	0 (0%)	–
4	CF	6	0 (0%)	–
4	C.A.F.	6	0 (0%)	–
5	F.A.Mc.	25	9 (36%)	7 months
6	C.A.M.Cc.	17	6 (35%)	6 months
7	C.Cc.	83	10 (12%)	4
8	C.M.	12	1 (6%)	–
8	C.M.Cc.	21	8 (38%)	4
9	F.A.M.	11	5 (36%)	not given
10	M.C.Cc.	28	7 (25%)	not given
10	A.F.	26	4 (15%)	not given
11	C.A.M.	18	7 (39%)	4 months
13	F.A.M.	16	6 (38%)	not given
14	A.Cc.	14	4 (29%)	not given
15	C.A.M.Cc.	16	1 (6%)	4 months
Total		349	76 (22%)	

[a] Coding: C, cyclophosphamide; A, adriamycin; M, methotrexate; F, 5-fluorouracil; Cc CCNU; V, vincristine; Mc, mitomycin C

Table 3. Response to combination chemotherapy of large-cell anaplastic carcinoma

Reference	Treatment[a]	Patients treated	Responders %	Median response duration
1	M.A.F.	9	8 (89%)	not given
4	C.F.	14	0 (0%)	–
4	C.A.F.	19	1 (5%)	not given
10	M.C.Cc/A.F.	27	0 (0%)	–
11	C.A.M.	7	1 (14%)	not given
Total		76	10 (13%)	

[a] Coding as in Table 2

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