Europ. J. Cancer, Vol. 15, pp. 331–335

0014-2964/79/0301-0331 $02.00/0

Results of Two Sequential Chemotherapy Studies in WHO Types I, III and IV Lung Cancer: Cyclophosphamide–5-Fluorouracil(CF)and Cyclophosphamide–5-Fluorouracil–Adriamycin (CAF)

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Abstract—*From June* 1974 *to February* 1976, 2 *sequential Phase* II *studies tested combination chemotherapy in Types* I, III *and* IV *lung cancer.*

CF was given to 43 *evaluable patients. There were* 5/23 *objective responses in Type* I, 0/6 *in Type* III *and* 0/14 *in Type* IV. *Median survival time (MST) for all patients was* 25.4 weeks *and MST for responders was* 90 weeks.

CAF was given to 43 *evaluable patients. Objective responses were observed in* 4/18 *Type* I, 0/6 *in Type* III *and* 1/19 *in Type* IV. *MST for all patients was* 23.5 weeks, *and MST for responders was* 82 weeks.

It was concluded that both chemotherapy regimens were minimally active in Type I *lung cancer.*

INTRODUCTION

LUNG cancer of the Types I, III and IV of the WHO Classification, that is epidermoid carcinoma, adenocarcinoma and anaplastic large cell carcinoma respectively, is relatively resistant to chemotherapy compared to Type II, small cell carcinoma. Several drugs considered minimally active did not prolong the overall dismal survival when given as single agent therapy [1]. Combination chemotherapy, as recently reviewed by Livingston suggested a very modest improvement in the overall survival [2–5]. Comparative trials, however, failed to confirm a sustained prolongation of survival [6, 7]. More recently, the CAP regimen (cyclophosphamide, adriamycin and *cis*-diammine-dichloro-platinum) was reported to induce a high response rate [8–10].

During 1973–1974 a comparative trial of cyclophosphamide and 5-fluorouracil given as single drugs was done in Oviedo [11]. The MST for all patients was 12.7 weeks. Following that trial, two studies were designed to test the effectiveness of combination chemotherapy. The results obtained in these sequential studies are presented.

Accepted 21 August 1978.

MATERIALS AND METHODS

Selection of patients was done according to the following criteria: 1. Histology proven bronchogenic carcinoma of Types I, III and IV of the WHO Classification [12]. 2. Measurable progressive disease, 3. UICC stage III, or Stages I and II if there was a contraindication for surgery [13]. 4. The exclusion factors were senility, central nervous system lesions, Karnofsky scale status less than 50%, expected difficulties for follow-up and a history of a second different primary malignancy.

Definite histologic diagnosis was required. Whenever the tumor type could not be satisfactorily assessed by exfoliative cytology and endoscopic biopsy, the convenience of obtaining adequate samples by needle aspiration biopsy or surgical biopsy of the tumor was directly discussed with the referring pathologists.

Drug regimens

Cyclophosphamide–5-fluorouracil (CF) combination consisted in cyclophosphamide (C) 600 mg/M^2 i.v. on day 1 and 5-fluorouracil (F) 600 mg/M^2 i.v. on days 1–3 every 3 weeks.

Cyclophosphamide-adriamycin-5- fluorouracil (CAF) combination consisted in C 600 mg/M^2 i.v. on day 1, adriamycin (A) 40 mg/M^2 i.v. on day 1 and F 400 mg/M^2 i.v. on days 1–3 every 4 weeks. When a total dose reached 550 mg/M^2 this drug was discontinued and patients continued on CF therapy.

The response to therapy was evaluated according to objective remission criteria as has been defined elsewhere [14]. Duration of response was considered from day one of treatment. Patients with an interstitial or alveolar pattern in the chest X-ray were given one week treatment with antibiotics or digitalis before the proper baseline films were obtained.

RESULTS

Ninety-one patients were studied. CF was given from June 1974 to March 1975 to 45 patients. Two patients were not evaluable for the final analysis. CAF was given from April 1975 to February 1976 to 46 patients. Three patients were not evaluable and were excluded from the final analysis. All patients entering the study are dead at the time of this report.

Characteristics of the patients

CF. The characteristics of the 43 evaluable patients are analysed in Table 1. Sixteen patients (37%) received prior chemotherapy. Five patients (11%) received extensive chemotherapy (2–5 drugs) not including the drugs used in this study and 11 patients received 4–6 weekly doses of vincristine. Two of the latter patients, both with an adenocarcinoma, presented a previous objective response. Finally, three patients received prior radiation therapy. Definite histologic diagnosis was established by sputum cytology in 13 patients (11 epidermoid and 2 adenocarcinoma), by needle aspiration biopsy in 9 patients (3 epidermoid, 1 adenocarcinoma and 5 anaplastic large cell carcinoma), and by tissue biopsy in 21 patients (9 epidermoid, 3 adenocarcinoma and 9 anaplastic large cell carcinoma).

CAF. Characteristics of patients are shown in Table 1. Six patients (14%) received prior chemotherapy: 3 patients extensive chemotherapy and 3 patients 4–6 weekly doses of vincristine. None had a previous chemotherapy response. Six patients received radiation therapy previously. Define histologic diagnosis was established by sputum cytology in 9 patients (5 epidermoid, 2 adenocarcinoma and 2 anaplastic large cell carcinoma), by needle aspiration biopsy in 11 patients (2 epidermoid, 3 adenocarcinoma and 6 anaplastic large cell carcinoma) and by tissue biopsy in 23 patients (11 epidermoid, 1 adenocarcinoma and 11 anaplastic large cell carcinoma).

Table 1. Patient characteristics according to treatment given (CF and CAF)

Patients	Treatment CF	CAF
Number	43	43
Male/female	39/4	42/1
Age: Mean	56.5	58
Range	44–76	35–74
Karnofsky: 50–60	7 (15%)	11 (23%)
Above 60	36 (84%)	32 (76%)
Type: Epidermoid	23	18
Anaplastic large cell	14	19
Adenocarcinoma	6	6
Stage II	2	2
III limited	16 (37%)	23 (53%)
extensive	25	8 (41%)

Toxicity. (Table 2)

CF. Median number of treatment cycles per patient was 3, ranging from 1 to 23 cycles per patient. Ten patients required a 25% dose reduction due to hematologic toxicity. There were no toxic deaths in this group.

CAF. The median number of treatment cycles per patient was 3, ranging from 1 to 18 cycles per patient. Nine patients required a 25% dose reduction due to hematologic toxicity. One patient with hepatic insufficiency required twice a dose reduction. One patient might have had a toxic death. He refused further therapy when his leukocytes were 800/mm^3, and he died at home 3 days later. No heart or other organ toxicity could be identified.

Response

CF. (*Table* 3). Five of 23 patients (21%) with epidermoid carcinoma demonstrated an objective response: 1 complete and 4 partial. No responses were observed in 14 patients with anaplastic large cell carcinoma and 6 patients with adenocarcinoma. The overall response rate was thus 11.6%. Duration of

Table 2. *Toxicity*

Therapy	Patients	Median number of cycles	Hematologic toxicity				Mucositis	Alopecia
			Mild	Moderate	Severe	Lethal		
CF	43	3	25	12	0	0	2	36
CAF	43	3	27	13	1	1	2	43

Table 3. *Distribution of patients according to cell type, therapy given and response to therapy*

Treatment	Tumor type	Response to therapy			Objective response Total patients	
		CR	PR	P	No.	(%)
CF	Epidermoid	1	4	18	5/23	(21.7)
CAF	Epidermoid	1	3	14	4/18	(22.2)
CF	Anaplastic	0	0	14	0/14	
CAF	Anaplastic	0	1	18	1/19	(5.2)
CF	Adeno	0	0	6	0/6	
CAF	Adeno	0	0	6	0/6	

response ranged from 165 to 445 days, with a median duration of response of 295 days. Responses according to the tumor site were in epidermoid carcinoma: primary tumor and mediastinum 4/11 (36.3%), liver 1/5, bone 1/5, supraclavicular lymph nodes 1/6 and skin soft tissues 0/4. Two patients with an epidermoid carcinoma presented a second response to chemotherapy (both with a combination of adriamycin and methotrexate) which lasted 181 and 320 days respectively.

CAF. (*Table* 3). Four of 18 patients (22%) with epidermoid carcinoma presented an objective response: 1 complete and 3 partial. One of 19 patients (5.2%) with anaplastic large cell carcinoma presented an objective partial remission. This patient had a clear cell carcinoma of the left hilum with supraclavicular metastases. No other responses were observed in 6 patients with adenocarcinoma. The overall response rate was then 11.6%. Duration of response ranged from 135 to 475 days, with a median duration of response of 310 days. Response according to the tumor site in patients with epidermoid carcinoma were: primary tumor and mediastinum 4/12 (33%), liver 1/5, supraclavicular lymph nodes 1/3, bone 0/4 and skin soft tissues 0/3. No subsequent chemotherapy responses were observed upon progression to CAF.

Survival time

MST was 25.4 weeks for CF and 23.5 weeks for CAF, Survival times according to treatment given and category of response are shown in Table 4.

Table 4. *Survival time in days according to therapy given and response*

Therapy	Patients	Survival time	
		Median	Range
CF	All	178.5	27–992
CAF	All	165.5	24–727
CF	Responders	635	343–992
CAF	Responders	578	428–730

DISCUSSION

These sequential studies were performed in similar patient populations regarding the most important prognostic factors, that is performance status and extension of the disease for each cell type, thus, the results can be discussed with the same criteria. In general both regimens had a low activity. No responses were observed in anaplastic large cell carcinoma, and the response rate was very low in epidermoid carcinoma.

Two recognizable factors might have contributed to the relatively long survival obtained in these studies: one was probably the low toxicity of the combination chemotherapy employed, and the other was the patient selection criteria.

An interesting point was the identical survival obtained with CF and CAF. These results might suggest that adriamycin added

no further benefit to the CF combination. This is not clearly understood since according to the review of Selawry adriamycin gave 15% objective responses as a single drug, and large group studies confirmed this activity [15–17]. It might probably represent that chemotherapy has a very little impact on the overall survival of non small cell lung cancer.

Another point of this study is the absence of responses in anaplastic large cell carcinoma. This tumor type is the one in which more contradictory results are found [2–5, 10, 19–22]. It might reflect general difficulties involving the identification and the assessment of results in Type IV lung cancer. From the pathologic point of view, Type IV lung cancer includes tumors with distinct morphologic traits which have not been adequately defined in terms of biologic behaviour and response to therapy. Furthermore, a chemotherapy sensitive tumor such as the intermediate cell carcinoma, actually considered in the small cell category could be included in Type IV carcinoma which might add to the differences observed.

In conclusion, the reported sequential studies failed to demonstrate a higher activity in terms of response rate as compared to a past immediate controlled trial using single agents. A minimal prolongation of MST was observed from what should be expected, and it requires a controlled trial confirmation. A higher level of activity might be needed for the single agents to obtain a significant improvement by combination chemotherapy.

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