Cancer Chemother Pharmacol (1987) 19: 269–271

Cancer Chemotherapy and Pharmacology

5-fluorouracil, adriamycin, and mitomycin-C (FAM) chemotherapy in advanced adenocarcinoma of the lung: comparison of two dosage schedules

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Summary. Fifty patients with inoperable adenocarcinoma of the lung were randomized in a prospective study to receive either standard doses or high doses of 5-fluorouracil, adriamycin, and mitomycin-C (FAM versus Hi-FAM). The response/stabilization rate was 32% for FAM and 34% for Hi-FAM ($P > 0.05$), and the median survival was 27 weeks for FAM group and 24 weeks for Hi-FAM group ($P > 0.05$). Myelotoxicity was mild in FAM, but moderate to severe in Hi-FAM. It is concluded that Hi-FAM did not yield a higher response rate or median survival compared with FAM, but caused significantly more severe myelotoxicity.

Introduction

The incidence of adenocarcinoma as a proportion of all cancers of the lung has increased rapidly, from approximately 20% in the past to 32%–44% in some centres in the last decade [4, 14, 15]. In Hong Kong, lung cancer is the most common lethal malignant tumour in both sexes, and adenocarcinoma accounted for 22%–34% of male patients and 43%–55% of female patients with malignant tumours [8, 9]. The prognosis of inoperable, untreated disease is poor, with a median survival of 3–4 months only [5, 7].

The results of chemotherapy in advanced adenocarcinoma of the lung have been disappointing [1, 3, 6, 12, 13]. A review of 17 studies of combination chemotherapy [13] showed a poor overall response rate of 22%, with no single best combination. More recently, Rosi et al. reported [11] that a high-dose 5-fluorouracil, adriamycin and mitomycin-C (Hi-FAM) schedule produced a response rate of 50% in a subgroup of 18 patients with bronchial adenocarcinoma. We report here the results of a randomized, prospective study of two dosage schedules of 5-fluorouracil, adriamycin and mitomycin-C combination chemotherapy in 50 patients with inoperable adenocarcinoma of the lung, comparing the conventional FAM dosage schedule [2] with the Hi-FAM dosage schedule.

Patients and methods

Between July 1982 and February 1985, fifty patients suffering from inoperable adenocarcinoma of the lung were entered into the study. All patients were aged 65 years or below, had measurable disease, had a performance status of 60 or above on the Karnofsky scale, and had not received prior systemic chemotherapy or chest radiotherapy. They were randomized to two treatment groups. The FAM group received a schedule described by Butler et al. [2], which consisted of 5-fluorouracil 600 mg/m^2 i.v. on days 1 and 8 every 4 weeks, adriamycin 30 mg/m^2 i.v. every 4 weeks and mitomycin-C 10 mg/m^2 i.v. every 8 weeks. Patients in the Hi-FAM group were treated with high-dose FAM combination chemotherapy [11] consisting of two induction courses (28 days apart) of 5-fluorouracil 600 mg/m^2 i.v. on days 1, 2, 3, adriamycin 25 mg/m^2 i.v. on days 1, 2, 3, and mitomycin-C 10 mg/m^2 i.v. on day 1, followed by maintenance therapy every 21–28 days with 5-fluorouracil 600 mg/m^2 i.v. on days 1 and 2, adriamycin 25 mg/m^2 i.v. on days 1 and 2, and mitomycin-C 10 mg/m^2 i.v. on day 1 every third cycle.

The two groups of patients were comparable in age, extent of disease, and initial performance status (Table 1). 'Localized disease' was used to describe disease confined to the hemithorax (except pleural effusion). All patients in whom this was not the case were considered to have 'extensive disease'. A complete remission was defined as the disappearance of all clinical, roentgenographic, bronchoscopic, and laboratory evidence of cancer and a partial response, as a reduction by more than 50% in the sum of the products of the maximum perpendicular tumour diameters, maintained for at least 4 weeks. Stable disease was defined as a reduction in the size of tumour by less than 50%, or no increase in the size of the tumour for a period of at least 8 weeks.

Actuarial survivals were prepared by the life-table method, and comparisons of survival were made with reference to the Lee and Desu method [10].

Results

One patient in the Hi-FAM group was lost to follow-up after the first induction course and was excluded from the analysis. No patients in either group had a complete remission (Table 1). In the FAM group, four patients (16%) had partial response and a further four (16%) had stable disease for 4, 5, 6 and 11 months. In the Hi-FAM group, three patients (13%) had partial remission, and a further five (21%) had stable disease for 3, 4, 4, 5 and 9 months. The response/stabilization rates of the two groups were not

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Table 1. Patients characteristics and response to chemotherapy

	FAM group	Hi-FAM group
No of patients		
Total	25	24
Men (smokers)	15 (11)	17 (13)
Women (smokers)	10 (1)	7 (2)
Age		
Median	58	55.5
Range	32–65	30–65
Extent of disease		
Localized	5	5
Extensive	20	19
Performance status		
Karnofsky scale 80–100	14	16
Karnofsky scale 60–70	11	8
Response to chemotherapy		
No with complete response	0	0
No with partial response	4 (16%)	3 (13%)
No with stable disease	4 (16%)	5 (21%)
No with no response	17	16
Median survival (weeks)		
All patients	26.9	24.4
Responders/stable disease	129.3*	81*
Non-responders	24.1*	22*

* $P \leq 0.005$

statistically different ($P > 0.05$). In neither group was the median survival for partial responders and patients with stable disease statistically different, and these response classes are therefore combined (Table 1). Although responders and patients with stable disease survived longer than those with progressive disease in both groups, overall survival was not different for the two treatment schedules (26.9 weeks vs 24.4 weeks, $P = 0.3062$; Table 1). Median survivals of the responders and patients with stable disease were also not statistically different between the two groups (129.3 weeks vs 81 weeks, $P = 0.4404$).

The two regimens, however, differed markedly in toxicity. While the FAM regimen was well tolerated with grade 1–2 nausea and vomiting (WHO) [16] in 12 patients, the Hi-FAM regimen caused grade 1–2 nausea and vomiting in 11 patients and grade 3–4 nausea and vomiting in a further 11 patients, requiring intensive antiemetic treatment. Hi-FAM was also much more myelotoxic (Table 2). Severe leucopenia (WBC count $< 1 \times 10^9$/l) and thrombocytopenia ($< 50 \times 10^9$/l) occurred in 5% and 13% of FAM courses respectively and in 28% and 41% of Hi-FAM courses respectively. Two patients in the Hi-FAM group required platelet transfusions. There were two deaths due to leucopenia-related septicaemia in the Hi-FAM group but no thrombocytopenia-related deaths in either group (Table 2).

Table 2. Haematological toxicity of FAM and Hi-FAM schedules

	FAM group	Hi-FAM group
No of patients	25	24
No of chemotherapy cycles	77	63
Median leucocyte nadir ($\times 10^9$/l)	3.2	1.7
Median platelet nadir ($\times 10^9$/l)	141	69
Leucopenia-related septicaemia/severe pneumonia	3	15
Leucopenia-related deaths	0	2
Thrombocytopenia-related deaths	0	0

Discussion

The use of 5-fluorouracil, adriamycin and mitomycin-C (FAM) for the treatment of inoperable adenocarcinoma of the lung was first reported by Butler et al. [2], who obtained a remission rate of 36% in 25 patients. Rosi et al. [11], using an escalated dose of FAM (Hi-FAM) in 30 patients, obtained an overall response rate of 33% only, although in a subgroup of 18 patients who were less than 65 years of age, who had no prior treatment, and who had a performance status of greater than 60 on the Karnofsky scale the response rate was increased to 50%, with 1 complete and 8 partial responders. However, we are not aware of any randomized study comparing low- and high-dose FAM schedules in bronchial adenocarcinoma.

The results of our study are disappointing. We did not attain a higher response rate or a longer median survival with Hi-FAM than with the lower dose FAM. On the other hand, with the escalated dose of chemotherapy, we encountered moderate to severe toxicity in the majority of our patients, similar to that experienced by Rosi et al. [11]. All our patients in this study had the same good prognostic factors as Rosi et al.'s favourable subgroup (namely aged 65 or below, no prior specific treatment, and performance status 60 or above on the Karnofsky scale), and yet our response rate was significantly lower (partial response in 13%, stable disease in 21%, as against Rosi et al.'s 50% response). We cannot explain this disparity in response rates. Rosi et al. [11] found that none of their six patients with pleural effusion obtained a remission with Hi-FAM. In our study six patients receiving the Hi-FAM schedule had pleural effusion, and all six also failed to respond. Similarly, we cannot explain our lower response rate to FAM (16% partial response + 16% stable disease) compared with the 36% response rate reported by Butler et al. [2], except insofar as a higher proportion of our FAM group patients (20/25) than of Butler's patients (14/25) had extensive disease.

It is concluded that Hi-FAM chemotherapy as used by ourselves has added little to the response rate and median survival in patients with inoperable adenocarcinoma of the lung compared with the less toxic FAM regimen used by Butler et al., even though all our patients were younger than 65 years and had a good initial performance status. New drugs and regimens need to be tried in attempts to improve the poor response to chemotherapy of this disease, which currently has a dismally poor prognosis.

Acknowledgement. The authors wish to thank Dr M. Ng for statistical analysis.

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Received December 3, 1985/Accepted December 10, 1986