Cancer Chemother Pharmacol (1985) 14 : 282–283

Cancer Chemotherapy and Pharmacology

Short communication

Cyclic combination chemotherapy in advanced adenocarcinoma of the lung: Comparison of two FAM schedules

W. K. Lam, S. Y. So, Mary Ip, and Donald Y. C. Yu

Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

Summary. *Forty patients with advanced adenocarcinoma of the lung were treated by two FAM chemotherapy schedules. Group A (20 patients) received Futraful, adriamycin, and mitomycin C, and group B (20 patients) received 5-fluorouracil, adriamycin, and mitomycin C. The response/stabilization rate was greater for group B (4 partial responses + 4 cases of stable disease) than for group A (no responders + 5 cases of stable disease), and the median survival was longer for group B (32 weeks) than for group A (22 weeks), although the differences did not reach statistical significance in either case ($P > 0.05$). Myelotoxicity was mild in both schedules. Furth[illegible] studies of the two FAM schemes at an escalated dose wo[illegible] while.*

Cancer Chemotherapy and Pharmacology
© Springer-Verlag 1985

Introduction

The incidence of adenocarcinoma of the lung has been rising rapidly in the past decade or so, to such an extent that it has become the most frequent cell type found in both men and women in some centres [11, 12]. In Hong Kong, lung cancer is the most common lethal malignant tumour in both sexes, and adenocarcinoma accounted for 22% of male and 43% of female patients in one study [7]. The prognosis is poor. In a clinicopathological study, only 14% of patients had curative surgery [9], and the median survival of patients with inoperable disease ranged from 3 months to 7 months [3, 9].

The results of chemotherapy in advanced adenocarcinoma of the lung have been disappointing [4, 10]. A review of 17 studies of combination chemotherapy showed a poor overall response rate of 22%, with no single best combination [10]. One of the more satisfactory schemes was that of Butler et al. [2], who used cyclical 5-fluorouracil, adriamycin, and mitomycin C (FAM) in 25 patients with bronchial adenocarcinoma and obtained a response rate of 36% with a significant survival benefit for responders. We report here the result of 5-fluorouracil, adriamycin, and mitomycin C (FAM) combination chemotherapy in 40 patients with inoperable adenocarcinoma of lung, comparing 5-fluorouracil and 1.2-tetrahydrofuryl-5-fluorouracil (Futraful), its oral derivative, in two FAM schedules.

Offprint requests to: W. K. Lam

Materials and methods

Forty patients suffering from inoperable adenocarcinoma of lung were treated with monthly cycles of FAM combination chemotherapy. Group A (Table 1) consisted of 20 patients referred to us between January 1980 and March 1981. They received FAM according to a schedule which consisted of 1.2-tetrahydrofuryl-5-fluorouracil (Futraful) 800 mg PO daily for 5 days every 4 weeks, adriamycin 30 mg/m^2 IV every 4 weeks, and mitomycin C 10 mg/m^2 IV every 8 weeks. Group B included 20 patients referred to us between April 1981 and [illegible]hey received FAM according to a schedule [illegible]utler et al. [2], which consisted of 5-fluorouracil [illegible] on days 1 and 8 every 4 weeks, adriamycin every 4 weeks, and mitomycin C 10 mg/m^2 IV [illegible]. All patients had measurable disease, and none [illegible] prior specific treatment apart from radiotherapy to the brain in two patients in group A and three patients in

Table 1. Patients characteristics and response to FAM chemotherapy

	Group A	Group B
No. of patients:		
Total	20	20
Men (smokers)	12 (9)	13 (10)
Women (smokers)	8 (4)	7 (3)
Age: Median	61	55.5
Range	20–69	27–70
Extent of disease		
Localized	7	6
Extensive	13	14
Performance status		
Karnofsky scale 80–100	8	11
Karnofsky scale 40– 70	12	9
Response to FAM chemotherapy:		
No. with complete response	0	0
No. with partial response	0	4 (20%)
No. with stable disease	5 (25%)	4 (20%)
No. with no response	15	12
Median survival (weeks)		
All patients	22	32
Responders/stabile disease	100$^+$ *	48 *
Non-responders	15	19

* $P < 0.01$

group B. Localized disease was defined as disease confined to the thorax (except pleural effusion). All others were described as having extensive disease. The two groups of patients were comparable in age, extent of disease, and initial performance status (Table 1). The disappearance of all clinical, roentgenographic, and laboratory evidence of cancer constituted a complete remission. A partial response was a reduction by more than 50% in the sum of the products of the maximum perpendicular tumour diameters, maintained for at least 4 weeks; and stable disease was a reduction in the size of tumour by less than 50%, or no increase in 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 [8].

Results

In groups A (Futraful group), no patient had complete or partial response (Table 1). Five patients had stable disease lasting for 5, 7, 8, 12, and 17 months, respectively. In groups B (5-fluorouracil group), four patients (20%) had partial remission, and a further four (20%) had stable disease that lasted for 5, 5, 6, and 8 months, respectively. The response/stabilization rates of the two groups, however, were not statistically different ($P > 0.05$). For group B, the median survival times for partial responders (45 weeks) and patients with stable disease (65 weeks) are not statistically different, and they are therefore combined in one group. Although responders and patients with stable disease survived better than those with progressive disease in both groups, overall survival was not different for the two treatment groups (22 weeks vs 32 weeks; $P > 0.05$).

Both FAM regimens were well tolerated. Toxicity, primarily haematological and gastrointestinal, was mild. Nausea with occasional vomiting occurred in 13 patients in group A and 15 patients in group B, but was easily managed with anti-emetics. Despite the age of the patients, no definite adriamycin cardiotoxicity was observed. Myelosuppression was mild. Severe leukopenia (WBC count $< 2{,}000/mm^3$) and thrombocytopenia ($< 100{,}000/mm^3$) occurred in 15% and 14% of patients in group A, respectively and in 10% and 26% of patients in group B, respectively. There were no leukopenia-or thrombocytopenia-related deaths.

Discussion

In our group A patients, oral 1.2-tetrahydrofuryl-5-fluorouracil (Futraful) was used in place of the IV 5-fluorouracil in Butler's FAM scheme [2]. Futraful is a 5-fluorouracil derivative, and is converted to 5-fluorouracil in vivo [5]. It gave a response rate of 37%–47% in breast cancer and 20%–30% in gastric adenocarcinoma, with generally lesser overall toxicity than 5-fluorouracil [5]. By combining oral Futraful with cyclophosphamide and mitomycin, a response rate of 22% was obtained in 23 patients with adenocarcinoma of the lung [6]. However, we are not aware of any study comparing oral Futraful and IV 5-fluorouracil in the same combination chemotherapy in the English medical literature.

The result of our Futraful FAM chemotherapy is disappointing however. There were no responders, and only five patients (25%) had stabilization of their disease. Our group B (5-fluorouracil group) treatment schedule gave a partial response in four patient (20%) and stabilization of disease in a further four patients (20%). We cannot explain this low response rate compared with the 36% response rate reported by Butler et al. [2] using the same FAM (5-fluorouracil) scheme, except that a higher proportion of our group B patients had extensive disease (14/20) than in Butler's study (14/25). The median survival of our eight patients (40%) with partial response or stable disease, however, was comparable to that of responders in Butler's series (48 weeks versus 50 weeks).

Although we did not find any statistically significant difference in the response rate and overall survival between the two treatment groups, there appeared to be a trend towards better response and survival in the 5-fluorouracil group. As the three drugs in the FAM scheme have produced response rates of 15%–25% when used as single agents against bronchial adenocarcinoma [2] and the combination of 5-fluorouracil and mitomycin C had shwon a synergistic effect in vivo [1], and as our current FAM schemes involved only mild myelotoxicity, it may be worthwhile to devise new FAM schemes at an escalated dose to determine first whether the response rate could be improved, and secondly whether the Futraful FAM schedule could still compare favourably with 5-FU FAM schedule in larger studies.

Ackknowledgements. The autors thank Dr M. M. T. Ng for help with the statistical analysis of survival data.

References

1. Buroker TR, Kim PN, Baker LH, Ratanatharathorn V, Wojtasak B, Vaitkevicicius VK (1978) Mitomycin-C alone and in combination with infused 5-fluorouracil in the treatment of disseminated gastrointestinal malignancies. Med Pediatr Oncol 4 : 35
2. Butler TP, MacDonald JS, Smith FP, Smith LF, Woolley PV, Schein PS (1979) 5-Fluorouracil, adriamycin and mitomicyn-C (FAM) chemotherapy for adenocarcinoma of the lung. Cancer 43: 1183
3. Green RA, Humphrey E, Close H, Patro ME (1969) Alkylating agents in bronchogenic carcinoma. Am J Med 46: 516
4. Hoffman PC, Bitran JD, Golomb HM (1983) Chemotherapy of metastatic non-small cell bronchogenic carcinoma. Semin Oncol 10: 111
5. Inuyama Y, Horiuchi M, Kohno N, Mashino S, Ozu R, Asaoka K (1981) Clinical trials with oral Futraful (INN: tegafur) in cancer of the head and neck. Clin Oncol 7: 131
6. Konno K, Nakai Y (1977) Treatment of lung cancer with FT-207 (Futraful). Proc III Conf Tohoku District Cancer Chemother Soc, Japan, January 1977
7. Lam WK, So SY, Yu DYC (1983) Clinical features of bronchogenic carcinoma in Hong Kong: Review of 480 patients. Cancer 52 : 369
8. Lee E, Desu M (1972) A computer program for comparing K-samples with right-censored data. Comput Prog Biomed 2: 315
9. Marabella P, Takita H (1975) Adenocarcinoma of the lung: Clinicopathological study. J Surg Oncol 7: 205
10. Taylor RE, Smith IE, Ford HT, Bryant BM, Casey AJ, Smyth JF (1980) Failure of intensive combination therapy (cyclophosphamide, adriamycin, 5-fluorouracil) to control adenocarcinoma or large cell anaplastic carcinoma of lung. Cancer Chemother Pharmacol 4: 271
11. Valaitis J, Warren S, Gamble D (1981) Increasing incidence of adenocarcinoma of the lung. Cancer 47: 1042
12. Vincent RG, Pickren JW, Lane WW, Bross I, Takita H, Houten L, Gutierrez AC, Rzepka T (1977) The changing histopathology of lung cancer – a review of 1682 cases. Cancer 39: 1647

Received August 8, 1984/Accepted August 29, 1984