Cancer Chemother Pharmacol (1985) 15 : 86–87

Short communication

Cancer Chemotherapy and Pharmacology

Phase II trial of 5-fluorouracil, adriamycin and cisplatin (FAP) in advanced gastric cancer

D. J. Th. Wagener[1], S. H. Yap[2], T. Wobbes[3], J. T. M. Burghouts[4], F. E. van Dam[5], H. F. P. Hillen[6], G. J. Hoogendoorn[7], H. Scheerder[8], and S. G. L. van der Vegt[9]

[1] Division of medical Oncology, University Hospital St. Radboud, Nijmegen
[2] Division of Gastroenterology, University Hospital St. Radboud, Nijmegen
[3] Department of General Surgery, University Hospital St. Radboud, Nijmegen
[4] Groot Ziekengasthuis, 's-Hertogenbosch
[5] St. Jozef Ziekenhuis, Eindhoven
[6] Catharina Ziekenhuis, Eindhoven
[7] St. Geertruiden Ziekenhuis, Deventer
[8] Ziekenhuis Venlo-Tegelen, Venlo
[9] Ziekenhuis Oudenrijn, Utrecht

Summary. *Twenty patients (15 male, 5 female) with nonresectable gastric adenocarcinoma were treated with FAP (5-fluorouracil 300 mg/m² IV on days 1–5, adriamycin 50 mg/m² IV on day 1, cisplatin 20 mg/m² IV on days 1–5). Each course was repeated every 21 days. Eighteen patients were evaluable for response. The median age was 51 years, the range extending from 34 to 68. None had undergone chemotherapy. The median Karnofsky performance score was 80%. Nine (50%) partial responses (PR) and eight (44%) cases of stable disease (SD) were observed. One patient showed progression of the disease and died after 6 months. The median duration of response was 6+ months for PR and 6 months for SD. The median survival was 12 months. FAP toxicity was moderate, with the median WBC nadir 3.2 × 10⁹/l (range 0.7–4.2). One patient in PR died of septicemia. Nausea and vomiting were not dose-limiting. Neuropathy was mild in four and moderate in two patients. This FAP combination appears to be as effective with respect to response rate and duration as reported for 5-fluorouracil, adriamycin and mitomycin C (FAM).*

Introduction

Cytostatic drugs known to have some effect in the treatment of advanced gastric carcinoma include 5-fluorouracil (5-FU), mitomycin C, BCNU, methyl-CCNU, and adriamycin (ADM). The objective response rate to these drugs is 18–36% and the duration of response 2.7–5 months [6]. Combination chemotherapy regimens have improved response rates over those obtained with single-agent chemotherapy [4, 7, 8]. The combination of 5-FU, ADM, and mitomycin C (FAM) introduced by MacDonald et al. [5] has been reported to give better results than any other combination previously used. An objective response rate of 42% was achieved in 62 patients with advanced gastric cancer. The median survival of responding patients was 12.5 months. This result has been confirmed by several other groups [1, 2, 9].

In 1980 we noted the occasional effect of cisplatin (CDDP) on stomach cancer, and we have started a phase II trial using 5-FU, ADM, and CDDP (FAP-5). Recently, results showing the efficacy of CDDP as monotherapy in stomach cancer have been published [3].

Offprint requests to: D. J. Th. Wagener, Department of Internal Medicine, Division of Medical Oncology, University Hospital St. Radboud, Postbox 9101, 6500 HB Nijmegen, The Netherlands

Materials and methods

Twenty patients with a diagnosis proven by biopsy of metastatic or nonresectable gastric adenocarcinoma and who had not received prior chemotherapy have received treatment with the FAP combination since April 1980. The patients had at least one area of measurable or evaluable disease to serve as an objective indication of response to treatment. The characteristics of the patients are shown in Table 1. The FAP

Table 1. Patient characteristics and treatment results

Number of patients	20
Total evaluable	18
Sex	
Male	13
Female	5
Median age in years (range)	51 (34–68)
Performance status	
80–90	11
60–70	7
Response	
Partial remission	9 (50%)
Stable disease	8 (44%)
Disease progression	1
Predominant sites of disease and response	
Stomach	8
4 PR, 4 SD	
Abdominal mass	3
2 SD, 1 PD	
Abdominal nodes	2
2 PR, 0 SD	
Peripheral nodes	2
2 PR, 0 SD	
Liver	2
1 PR, 1 SD	
Skin	1
1 SD	
Median duration of response (range)	
Partial	6+ months (4–14+)
Stable	6 months (3–14)
Median survival (range)	
Total	12 months (4–29+)
Partial	12 months (4–29+)
Stable	11 months (5–23)

Table 2. Dose attenuation schedule for bone marrow depression

Leukocytes $\times 10^9$/l	Thrombocytes $\times 10^9$/l	5FU	ADM	CDDP
> 4	> 150	100%	100%	100%
3–4	100–150[a]	75%	50%	100%
2–3	100–150[a]	50%	25%	75%
< 2	< 100	0	0	0

[a] Postpone for 1 week, adjust thereafter

regimen consisted of 5-FU 300 mg/m^2 IV on days 1–5, ADM 50 mg/m^2 IV on day 1, and CDDP 20 mg/m^2 IV on days 1–5. The course was repeated on day 22. After six courses the cycles were given once every 6 weeks until progression of disease occurred. Drug dosage was modified for subsequent courses according to the degree of hematologic toxicity (Table 2). The dose of ADM was reduced by 50% for a bilirubin level of 35–50 mmol/l. No ADM was given if the bilirubin was > 50 mmol/l.

Patients were evaluated for response using the following system. Objective response was determined by physical examination, roentgenograms, computer tomograms, ultrasonograms, and endoscopy. A complete response was defined as no objective signs of residual cancer. A partial response (PR) was defined as reduction of ≥ 50% in the sum of the products of the longest perpendicular diameters of all measurable lesions. In addition, a PR required that there be no increase in the size of any lesion and no new metastasis. Stable disease (SD) was defined as either no regression reaching 50% or no increase of ≦ 25% in any lesion and no new metastasis. Disease progression (PD) was defined as ≦ 25% increase in any lesion or a new metastasis. The results had to be observed at a minimum of 4 weeks after the initiation of treatment. Duration of response and survival were measured from the start of chemotherapy.

Toxicity was assessed using a 0–4 grading system according the World Health Organization [11].

Results

Of the 20 treated, one patient died after one course due to perforation of the stomach and one patient, who had clinically improved after 3 cycles, died for unknown reasons at home, leaving 18 patients evaluable for response (Table 1). All these patients received at least four cycles. Of the 18 patients, nine (50%) achieved PR, with median duration of response of 6+ months, while eight patients (44%) had SD with a median duration of 6 months. Only one patient had progression of disease. He died after 6 months. The median survival for the whole group was 12 months, with a range of 4–29+ months. The patients who achieved PR had a median survival of 12 months, and those with SD had a median survial of 11 months. Two patients had complete disappearance of the tumor but X-rays of the stomach still showed hyperrugosity. Deep endoscopic biopsies were performed but no malignant infiltration could be found. These patients were classified as having achieved PR.

The dose-limiting toxic effect was myelosuppression. The median WBC nadir was 3.2 × 10^9/l (range 0.7–4.2). Only 26 of 111 cycles could be given as planned. One patient in PR died of septicemia. Nausea and vomiting were not dose-limiting. Alopecia was seen in 100%. Four patients developed signs of mild neuropathy (WHO grade 1), and in two patients there was moderate neurotoxicity (WHO grade 2).

Discussion

In this study an effect with respect to response rate and duration of response of the combination of FAP was found, which was comparable with that obtained with FAM regimen [5]. The results are superior to the results obtained in the study of Woolley et al. [10], who found a PR rate of 29% for FAP with a median response duration of 5 months and a median survival of 7 months for responders and 2.5 months for nonresponders in a multicenter trial. The difference in results between the studies could be due to the dose schedule. In our study 5-FU and CDDP were given on 5 consecutive days and the total dose of the drug was higher than in the study of Woolley et al., who gave 5-FU 600 mg/m^2 IV on days 1 and 8, CDDP 75 mg/m^2 IV on day 1, and ADM 40 mg/m^2 IV on day 1. Moreover, in our study the courses were intented to be administered every 3 weeks, whereas in Woolley et al.'s study the cycle was repeated after 4 weeks. This is probably less important, since only 26 of 111 courses could be given on the appropiate days, because of myelosuppression.

The results of the study suggest that CDDP in the FAP combination is as effective as mitomycin C in the FAM combination.

References

1. Bitran JD, Desser RK, Kozloff MF, Billings AA, Shapiro CM (1979) Treatment of metastatic pancreatic and gastric adenocarcinomas with 5-fluororouracil, adriamycin, and mitomycin C (FAM). Cancer Treat Rep 63: 2049
2. Gastrointestinal Tumor Study Group (1981) A comparative clinical assessment of combination chemotherapy in the management of advanced gastric carcinoma. Cancer 49: 1362
3. Leichman L, McDonald B, Dindogru A, Samson M, Vaitkevicius VK (1984) Cisplatin, an active drug in the treatment of disseminated gastric cancer. Cancer 53: 18
4. Levi JA, Dalley DN, Aroney RS (1979) Improved combination chemotherapy in advanced gastric cancer. Br Med J II: 1471
5. MacDonald JS, Schein PS, Woolley PV, Smythe T, Ueno W, Hoth D, Smith F, Boiron M, Gisselbrecht C, Brunet R, Lagarde C (1980) 5-Fluorouracil, doxorubicin and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. Ann Intern Med 93: 533
6. Moertel CG (1975) Clinical management of advanced gastrointestinal cancer. Cancer 36: 675
7. Moertel CG, Lavin PT (1979) Phase II–III chemotherapy studies in advanced gastric cancer. Cancer Treat Rep 63: 1863
8. Moertel CG, Mittelman JA, Bakemeier RF, Engstrom P, Hanley J (1976) Sequential and combination chemotherapy of advanced gastric cancer. Cancer 38: 678
9. Pannetierre F, Heilbrun L (1979) Comparison of two different combinations of adriamycin, mitomycin C and 5-fluorouracil in the management of gastric carcinoma. Proc Am Soc Clin Oncol *20: 315*
10. Woolley P, Smith F, Estevez R, Gisselbrecht C, Alvarez C, Boiron M, Machado C, Lagarde C and Schein P (1981). A phase II trial of 5-FU, adriamycin and cisplatin (FAP) in advanced gastric cancer. Proc Am Soc Clin Oncol 481: 455
11. World Health Organization (1979) Handbook for reporting results of cancer treatment. WHO, Geneva, p. 16 (Offset publication no. 48)

Received May 31, 1984/Accepted November 2, 1984