The Combination of Cisplatin, Doxorubicin, and Mitomycin (PAM) Compared with the FAM Regimen in Treating Advanced Gastric Carcinoma

A Phase II Randomized Trial of the Italian Oncology Group for Clinical Research

Vincenzo De Lisi, M.D.
Giorgio Cocconi, M.D.
Francesco Angelini, M.D.
Francesco Cavicchi, M.D.
Francesco Di Costanzo, M.D.
Germana Gilli, M.D.
Carmelina Rodinò, M.D.
Marcello Soldani, M.D.
Maurizio Tonato, M.D.
Cecilia Finardi, Ph.D.

Medical Oncology Institutions of the GOIRC Group in Parma, Perugia, Terni, Ferrara, Piacenza, Latina, and Roma, Italy.

BACKGROUND. In a randomized Phase II study, the authors evaluated the activity and toxicity of the new cisplatin, doxorubicin, and mitomycin C (PAM) combination, that includes cisplatin (P) instead of 5-fluorouracil as in the 5-fluorouracil, doxorubicin, and mitomycin C (FAM) combination, in patients with advanced gastric carcinoma. FAM was utilized as a control treatment arm.

METHODS. Fifty eligible patients were assigned to the FAM (5-fluorouracil 600 mg/m^2 intravenous (i.v.) on Days 1, 8, 29, 36; doxorubicin 30 mg/m^2 i.v. on Days 1 and 29; mitomycin C 10 mg/m^2 i.v. on Day 1; every 8 weeks) and 52 to the PAM combination (cisplatin 60 mg/m^2 i.v. on Days 1 and 29; doxorubicin 30 mg/m^2 i.v. on Days 1 and 29; mitomycin C 10 mg/m^2 i.v. on Day 1; every 8 weeks). All eligible patients were included in the evaluation of response, toxicity and survival.

RESULTS. The PAM combination complete response (CR) rate was 8%, and the CR plus partial response (PR) rate was 21% (95% confidence interval [CI] from 10% to 32%). The median time to progression, duration of response, and duration of survival were 15, 26, and 29 weeks, respectively. The FAM combination CR rate was 2% and the CR plus PR rate was 26% (95% CI from 14% to 38%). The median time to progression, duration of response, and duration of survival were 17, 27, and 23 weeks, respectively. Hematologic and nonhematologic toxicity were mild with both regimens.

CONCLUSIONS. This study shows that this new combination, that does not include 5-fluorouracil, is active in patients with advanced gastric carcinoma. Since treatment with 5-fluorouracil alone is still considered the standard according to some authors, the PAM combination may be included among the sequential clinical options before or after treatment with 5-fluorouracil alone. ***Cancer* 1996; 77:245–50.** © *1996 American Cancer Society.*

KEYWORDS: gastric carcinoma, chemotherapy, FAM, PAM.

For many years a few single agents, such as 5-fluorouracil, doxorubicin, mitomycin C and nitrosoureas, have been considered to have significant antitumor activity in patients with gastric carcinoma.[1] More recently, even cisplatin has been reported to be very active.[2,3]

Among the so-called first generation combinations, FAM (5-fluorouracil, doxorubicin, and mitomycin C) became the conventional treatment after it was reported to be very active in nonrandomized Phase II studies.[4] However, the few randomized studies comparing this combination with 5-fluorouracil as a single agent failed to show significant superi-

This study was carried out by the Italian Group for Clinical Research (GOIRC) (G. Cocconi, Chairman), Parma, Italy.

The authors thank Dr. Sofia Di Sarra and Katherine Tonato for help in English translation and Mrs. Anna Quadretti for secretarial assistance.

Address for reprints: Vincenzo De Lisi, M.D., Medical Oncology Division, University Hospital, 43100 Parma, Italy.

Received June 13, 1995, revision received September 11, 1995; accepted October 11, 1995.

ority.[5,6] For that reason, an exploration of the activity of other combinations in this disease is warranted.

This trial, designed as a Phase II study, was aimed to assess the activity of a new three-drug combination, including cisplatin, doxorubicin, and mitomycin C (PAM). In order to have a control arm, the PAM combination was compared, in a prospective randomized fashion, with the conventional FAM combination.

PATIENTS AND METHODS

Patient Characteristics

Eligibility criteria required that patients have a biopsy-proven adenocarcinoma of gastric origin and either locally advanced disease beyond any hope of curative surgical excision or distant metastases. Patients with an expected survival of less than 1 month, with other tumors, with brain metastases, or who were previously treated with radiation therapy and/or chemotherapy were excluded. Other criteria for exclusion were active congestive heart failure or symptomatic ischemic heart disease.

Laboratory requirements at the start of treatment were a bilirubin level of < 1.5 mg/dL, a creatinine level of < 1.5 mg/dL, a leukocyte count of >4000/mL and a platelet count of $>100{,}000$/mL.

Treatment was assigned by telephone by the Trial Office in Parma and was performed in each of the participating medical oncology institutions of the Italian Oncology Group for Clinical Research (GOIRC). Patients were stratified according to sex, age ($\geq$ or $>$ 60 years), prior surgery (tumor resection or no), and Karnofsky performance status (100–80 vs. 70–50).

Treatment and Methods

Patients were randomized to receive either FAM (5-fluorouracil, 600 mg/m^2 intravenously [i.v.] bolus, Days 1, 8, 29, and 36; doxorubicin 30 mg/m^2, i.v. bolus, Days 1 and 29; and mitomycin C, 10 mg/m^2, i.v. bolus, Day 1. This course was repeated every 8 weeks) or PAM (cisplatin, 60 mg/m^2 i.v. bolus, Days 1 and 29; doxorubicin, 30 mg/m^2 i.v. bolus, Days 1 and 29; and mitomycin C, 10 mg/m^2 i.v. bolus, Day 1. This course was repeated every 8 weeks).

Cisplatin was administered, diluted in 250 mL isotonic saline as an infusion in 30 minutes after hydratation with 1000 mL intravenous fluid in 2 hours. Cisplatin administration was followed by 1000 mL i.v. fluid infusion. Urine volume was monitored from two hours before treatment to two hours after the end of cisplatin administration. Mannitol was administered as required to keep the output diuresis above 100–150 mL/hour. At the time of this study, the new 5-HT3 receptor antagonists were not available; antiemetic medication thus consisted of metoclopramide and steroids.

Both treatments had to be continued until progression or unacceptable toxicity. A total cumulative dose of 500 mg/m^2 of doxorubicin was allowed. Hemoglobin measurement and leukocyte and platelet counts were performed before each drug administration. Dose reductions were made, if there was hematologic toxicity, at Days 1, 8, 29, and 36, according to the indications reported below:

Leukocytes ($\times 10^3$)	Platelets ($\times 10^3$)	% dose
3.5	100	100%
2.5–3.5	75–100	50%
2.5	75	0%

If a treatment was withheld, blood counts were repeated weekly until the level required for at least 50% dosage was reached.

Assessment of Response

Assessment of tumor parameters was performed before treatment assignment using clinical examination, X-ray, endoscopy, computed tomography scan, and ultrasound, according to which method was most indicated. Both endoscopy and X-ray examination were required when stomach tumor was the only assessable parameter. Clinical examination was repeated prior to each drug administration. Tumor parameters were reassessed after the first eight weeks of treatment, and every eight weeks thereafter, until tumor progression. If the indicator lesion was primary or recurrent stomach tumor, evaluation of response required a repeated endoscopic examination, unless contrast radiography clearly showed progressive disease. Patients in whom primary gastric tumors were the only measurable area of response were considered only evaluable. Liver and renal function tests were repeated every four weeks.

Response was defined according to the World Health Organization (WHO) recommendations and side effects were graded using World Health Organization criteria.[7] Hematologic counts were performed on Day 1 of the first cycle and repeated prior to each injection of drugs and used for toxicity analysis.

Time to progression was measured in all patients from the beginning of chemotherapy to the first evidence of progression; duration of response was calculated in responding patients from the beginning of treatment to the date of relapse; duration of survival was dated from the beginning of treatment to the day of death. The curves were plotted with the Kaplan–Meier method[8] and compared using the log rank test.[9] Differences between patient characteristics and between response results were calculated using an adjusted chi-square test of proportions. All statistical comparisons were two-tailed.

This trial was designated as a Phase II study testing

TABLE 1
Characteristics of Eligible Patients

	FAM		PAM	
	No.	%	No.	%
Total no.	50	100	52	100
Sex				
Male	32	64	34	65
Female	18	36	18	35
Age (years)				
Median	60		61	
Range	40–75		34–74	
Performance status				
100–80	35	70	38	73
70–50	15	30	14	27
Resection				
Yes	25	50	29	56
No	25	50	23	44

FAM: 5-fluorouracil, doxorubicin, and mitomycin C; PAM: cisplatin, doxorubicin, and mitomycin C.

TABLE 2
Response Results

	FAM		PAM	
	No.	%	No.	%
Total	50	100	52	100
Insufficient treatment or response not attributed	4	8	2	4
Progression	20	40	16	31
No change	13	26	23	44
PR	12	24	7	13
CR	1	2	4	8
CR + PR	13	26	11	21
95% confidence limits	14–38		10–32	

FAM: 5-fluorouracil, doxorubicin, and mitomycin C; PAM: cisplatin, doxorubicin, and mitomycin C; PR: partial response; CR: complete response.

TABLE 3
Objective Response According to Patient Characteristics

	FAM		PAM	
	CR + PR/Total	(%)	CR + PR/Total	(%)
Age				
≤ 60 years	7/26	27	6/24	25
> 60 years	6/24	25	5/28	18
Sex				
Male	6/32	19	7/34	21
Female	7/18	39	4/18	22
Performance status				
100–80	11/35	31	8/38	21
70–50	2/15	13	3/14	21
Prior resection				
Yes	10/25	40	7/29	24
No	3/25	12	4/23	17
Disease extension				
Locoregional	3/20	15	4/23	17
Metastatic	10/30	33	7/29	24

FAM: 5-fluorouracil, doxorubicin, and mitomycin C; PAM: cisplatin doxorubicin, and mitomycin C; CR: complete response; PR: partial response.

the new PAM combination. Randomization versus PAM was intended to be a control measure. When the study was activated, we decided to randomize 100 evaluable patients in about 3 years, according to the previous accrual experience of the Italian Oncology Group for Clinical Research Group in other studies of advanced gastric carcinoma.

RESULTS

Between April 1984 and November 1987, 103 patients were entered into the trial from 8 participating institutions of the Italian Oncology Group for Clinical Research Group. One patient assigned to FAM was later found to be ineligible for the study, due to the absence of tumor parameters. Five patients received insufficient treatment, two were lost to follow-up after the first dose and before the first evaluation of response (FAM), two because of death within the first four weeks (one FAM, one PAM), and one because of rapidly progressive disease (FAM). In one additional patient randomized to PAM, response was not attributed due to protocol violation because he received FAM. All patients having insufficient treatment or nonattributed response were considered failures and included in the denominator of response rate calculation on the basis of the intention to treat analysis. All eligible patients were included in the calculation of toxicity and survival. A total of 50 eligible patients were assigned to FAM and 52 to PAM.

The characteristics of these 102 patients are reported in Table 1. Treatment allocation appears to have been well balanced between the two arms. Median age was 60 years (range, 40 to 75 years) in the FAM group and 61 years (range, 35 to 74 years) in the PAM group. Overall, 64% of the patients were male, 72% had a good performance status (100–80), 51% were older than 60 years of age, and 53% had resected primary tumor.

Response to Therapy

The median number of cycles of chemotherapy received was two for both groups (range, 1–7 and 1–6 in FAM and PAM, respectively). Nineteen patients in FAM and 16 in PAM completed 3 or more courses of chemotherapy.

The response results are shown in Table 2. Among patients treated with FAM, 1 achieved a complete re-

TABLE 4
Types and Levels of Toxicity

	FAM (Grade)					PAM (Grade)					
Hematologic	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**	***P*-value**
Leukocytes	34	7	6	2	1	33	10	9	0	0	0.12
Platelets	45	4	0	1	0	45	3	2	1	0	0.95
Hemoglobin	21	18	10	1	0	28	10	9	5	0	0.06
Nonhematologic											
Nausea/vomiting	24	12	12	1	1	22	13	14	3	0	0.80
Mucositis	50	0	0	0	0	52	0	0	0	0	
Diarrhea	50	0	0	0	0	50	1	1	0	0	
Renal	50	0	0	0	0	52	0	1	2	0	
Neurologic	49	0	1	0	0	52	0	0	0	0	
Cardiac	50	0	0	0	0	50	1	0	1	0	
Hearing	50	0	0	0	0	52	0	0	0	0	

FAM: 5-fluorouracil, doxorubicin, and mitomycin C; PAM: cisplatin, doxorubicin, and mitomycin C.

sponse (2%) and 12 a partial response (24%). Among patients treated with PAM, 4 achieved complete response (8%) and 7 partial response (13%). The objective response rate (complete response plus partial response) was 26% with FAM (95% confidence interval, 14% to 38%) and 21% with PAM (95% confidence interval, 10% to 32%).

The median time to progression was 16 weeks in FAM (range, 0 to 80) and 15 weeks in the PAM regimen (range, 2 to 88). Median duration of response was 27 weeks (range, 9 to 80) in the FAM regimen and 26 weeks (range, 11 to 53) in the PAM regimen. Median duration of survival was 23 weeks (range, 1 to 106) in the FAM group and 29 weeks (range, 2 to 356+) in the PAM group.

This trial was not meant to allow formal statistical comparison of both regimens. However, it may be commented that none of the differences in response and time parameters reached a statistical significance.

Objective response according to patient characteristics is reported in Table 3. There is no indication of superiority of one regimen over the other in any of the analyzed subgroups of patients. Overall, as expected, there were higher response rates considering patients with a higher (100–80) performance status over those with a lower (70–50) performance status (26% vs. 17%) and patients previously resected over those not previously resected (31% vs. 14%). Overall, seven patients had primary gastric tumor as the only assessable nonmeasurable area of response. None of the 3 patients in the FAM group and 2 of 4 patients in the PAM group showed an estimated greater than 50% tumor regression.

Table 4 reports toxicity levels in the two regimens. Leukocyte toxicity was moderate in both arms and only in the FAM regimen did 3 of the 50 patients report Grade III–IV leukopenia. Only slight and infrequent episodes of thrombocytopenia were observed in both treatments. Anemia was observed rather frequently in both treatments, but this was possibly due in part to the disease effects. Among the nonhematologic side effects, slight to moderate nausea/vomiting was unexpectedly observed not only in the PAM treatment but even in the FAM treatment. Nephrotoxicity was reported infrequently and was mild in the PAM treatment. Other types of nonhematologic toxicity were never or only sporadically reported. One patient treated with PAM died of septic shock 15 days after the first cycle.

DISCUSSION

When the present study was designed, there was no general agreement about which treatment should be considered as conventional in advanced gastric cancer. The reported response rates using the FAM regimen in nonrandomized studies were substantially higher than those expected administering 5-fluorouracil alone.[4] However, the few randomized comparisons were not able to show that differences in response rate between these two treatments achieved statistical significance.[5,6] Conversely, when using 5-fluorouracil as a single agent, a broad range of response rates was reported, probably because of differences in patient characteristics.[10] The median survival in advanced gastric carcinoma untreated with chemotherapy was reported to be around four months.[11] Administering chemotherapy, the figures of median survival ranged from around five to ten months, with no consistent survival advantages in administering combination chemotherapy versus administering 5-fluorouracil as a single agent.[12–15]

On the basis of these considerations, in general, the conventional chemotherapy of advanced gastric carcinoma, using survival as a meaningful endpoint, could possibly be no treatment or single agent 5-fluorouracil. Conversely, using response as an endpoint, the assessment of response rates in randomized Phase II or Phase III studies could give the clinician some suggestions about the expected probability of a significant tumor shrinkage, the expected toxicity, and, indirectly, the expected palliation using different types of chemotherapy.[16]

The main objective of this study was to assess achievable response and expected toxicity administering the new PAM combination. The FAM combination was used as a control arm. It must be remembered that the PAM combination did not include 5-fluorouracil, so it could be considered as a different sequential chemotherapy option before or after the use of 5-fluorouracil alone.

The response rate reported in this study with the PAM combination is lower than that reported administering the FAM combination but the difference is slight and statistically not significant. The response rate to PAM appears to be of the same order of that achievable with 5-fluorouracil alone. However, some favorable attention may be addressed to the 4 complete responses (8%) reported in the 52 patients treated with this new combination.

The results of this study could be considered as negative, in the sense that it did not demonstrate a high response rate achievable with the new combination. However, from another point of view the results could be considered positive, because they demonstrated that this chemotherapy, which does not contain 5-fluorouracil, is active with an acceptable toxicity.

In a clinical setting, the PAM combination may be suggested as a sequential clinical option in patients treated with 5-fluorouracil as a single agent. Indeed, 5-fluorouracil alone is still considered the standard treatment by some authors.[17] In this study, there were no formal suggestions on the second line treatment after failure of either combination. However, according to our results, the response rates achievable in a first and second line treatment using the sequence 5-fluorouracil followed by PAM or PAM followed by 5-fluorouracil, and assessing toxicity and quality of life, could be a design for a new exploratory Phase II study on the best palliation inducible in patients with advanced gastric carcinoma.

At present, the activity of other chemotherapy combinations different from FAM has been reported, including etoposide, doxorubicin, and cisplatin (EAP),[18,19] 5-fluorouracil, doxorubicin, and methotrexate (FAMTX),[20] and cisplatin, epirubicin, folimic acid, and 5-fluorouracil (PELF).[21] The first combination, similar to PAM, does not contain 5-fluorouracil and both FAMTX[22] and PELF[21] have been demonstrated to be superior in response rate compared with FAM. We hope that our study will also contribute to the scientific and clinical debate about the possible chemotherapy options in treating advanced gastric carcinoma.

REFERENCES

1. Wills J, Bleiberg H. Current status of chemotherapy for gastric cancer. *Eur J Cancer Clin Oncol* 1989;25:3–8.
2. Beer M, Cocconi G, Ceci G, Varini M, Cavalli F. A phase II study of cisplatin in advanced gastric cancer. *Eur J Cancer Clin Oncol* 1983 19:717–20.
3. Leichman L, Berry BT. Cisplatin therapy for adenocarcinoma of the stomach. *Semin Oncol* 1991;18:25–33.
4. Macdonald JS, Schein PS, Woolley PV, Smythe T, Veno W, Hoth D, et al. 5-Fluorouracil, doxorubicin and mitomycin (FAM) combination chemotherapy in advanced gastric carcinoma. *Ann Intern Med* 1980;93:533–6.
5. Beretta G, Arnoldi E, Beretta GD. A randomized study of fluorouracil versus FAM polychemotherapy in gastric carcinoma. Proceedings of the EORTC symposium in "Advances in Gastrointestinal Tract Cancer Research and Treatment." 1989 Nov 17; Strasbourg, France[Astract No. 48].
6. Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, et al. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs. fluorouracil and doxorubicin vs. fluorouracil, doxorubicin and mitomycin. *JAMA* 1985; 253:2061–7.
7. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–14.
8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
9. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;35:1–39.
10. Moertel CG. Chemotherapy of gastrointestinal cancer. *Clin Gastroenterol.* 1976;5:777–93.
11. Moertel CG. Carcinoma of the stomach: prognostic factors and criteria of response to therapy. In: Staquet MJ, editor. Cancer therapy: prognostic factors and criteria of response. New York: Raven Press, 1975:229–36.
12. The Gastrointestinal Tumor Study Group. Randomized study of combination chemotherapy in unresectable gastric cancer. *Cancer* 1984;53:13–7.
13. De Lisi V, Cocconi G, Tonato, Di Costanzo F, Leonardi F, Soldani M. Randomized comparison of 5-FU alone or combined with carmustine, doxorubicin and mitomycin (BAFMi) in the treatment of advanced gastric cancer. A phase III trial of the Italian Clinical Research Oncology Group (GOIRC). *Cancer Treat Rep* 1986;70:481–5.
14. Cocconi G, De Lisi V, Di Blasio B. Randomized comparison of 5-FU alone or combined with Mitomycin and Cytarabine (MFC) in the treatment of advanced gastric cancer. *Cancer Treat Rep* 1982;66:1263–6.
15. De Vita V, Hellman S, Rosenberg SA. Cancer of the stomach. In: Cancer principles and practice of oncology. 4th Edition. Philadelphia: J.B. Lippincott Co., 1983:818–48.
16. Cocconi G. Chemotherapy of advanced gastric carcinoma: to be completely rewritten? *Ann Oncol* 1994;5:8–11.
17. Cullinan SA, Moertel CG, Wieand HS, O'Connel MJ, Poon MA, Krook JE, et al. Controlled evaluation of three drug combination regimens versus fluorouracil alone for the therapy of advanced gastric cancer. *J Clin Oncol* 1994;12:412–6.

18. Preusser P, Wilke H, Achterrath W, Fink U, Lenaz A, Heinicke A, et al. Phase II study with the combination of etoposide, doxorubicin and cisplatin in advanced measurable gastric cancer. *J Clin Oncol* 1989;7:1310–7.
19. Kelsen D, Atiq OT, Saltz L, Niedzwiecki D, Ginn D, Chapman D, et al. FAMTX versus etoposide, doxorubicin and cisplatin: a random assignment trial in gastric cancer. *J Clin Oncol* 1992;10:541–8.
20. Wils J, Bleiberg H, Dalesio O, Blijham G, Mulder N, Planting A, et al. An EORTC Gastrointestinal Group evaluation of the combination of sequential methotrexate and 5-fluorouracil, combined with adriamycin in advanced measurable gastric cancer. *J Clin Oncol* 1986;4:1799–803.
21. Cocconi G, Bella M, Zironi S, Algeri R, Di Costanzo F, De Lisi V, et al. Fluorouracil, Doxorubicin, and Mitomycin combination versus PELF chemotherapy in advanced gastric cancer: a prospective randomized trial of the Italian Oncology Group for Clinical Research. *J Clin Oncol* 1994;12:2687–93.
22. Wils J, Klein H, Wagener DJTh, Bleiberg H, Reis H, Korsten F, et al. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin. A step ahead in the treatment of advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. *J Clin Oncol* 1991;9:827–31.