Pergamon

*European Journal of Cancer* Vol. 30A, No. 5, pp. 596–600, 1994

0959–8049/94 $7.00+0.00

0959-8049(93)E0002-L

# Etoposide, Doxorubicin and Cisplatin (EAP) Treatment in Advanced Gastric Carcinoma: a Multicentre Study of the Italian Trials in Medical Oncology (I.T.M.O.) Group

E. Bajetta, M. Di Bartolomeo, F. de Braud, F. Bozzetti, A.M. Bochicchio, P. Comella, D. Fagnani, G. Farina, C. Ferroni, R. Franchi, V. Gebbia, G. Ianniello, A. Iirillo, G. Pinotti, G. Schieppati, G. Ucci, M. Visini, A. Zaniboni, R. Buzzoni, C. Casartelli and P. Nelli

**Various reports have documented the efficacy of the combination of etoposide, doxorubicin and cisplatin (EAP) in the treatment of advanced gastric cancer, although other studies have not confirmed such results. This multicentre phase II study was designed to try to define the efficacy and tolerability of the original EAP regimen. From January 1990 to May 1992, 96 patients with locally advanced or metastatic gastric cancer were treated every 3 weeks with etoposide (120 mg/m$^2$) on days 4, 5 and 6, doxorubicin (20 mg/m$^2$) on days 1 and 7, and cisplatin (40 mg/m$^2$) on days 2 and 8. All of the patients had measurable lesions, and were to receive a maximum of six cycles. A total of 416 courses was given (median four/patient), 27% with a delay of ≥ 2 weeks. Objective responses were achieved in 34 of the 91 evaluable patients (37%: confidence interval 27–47%), with complete response (CR) in 11 (12%) and partial response (PR) in 23 (25%). The median duration of response was 6 months (range 1–19), and the median survival of the 96 eligible patients was 9 months. Side-effects (WHO grade 3–4) were leucopenia (30%), thrombocytopenia (9%) and mucositis (10%). We conclude that the EAP regimen is active in inducing major objective responses (12% of CR), and that treatment is feasible in patients with good performance status.**

**Key words: gastric cancer, etoposide, doxorubicin, cisplatin combination, chemotherapy**
*Eur J Cancer*, Vol. 30A, No. 5, pp. 596–600, 1994

## INTRODUCTION

SURGICAL RESECTION remains the usual approach for patients affected by gastric cancer. However, among the cases who undergo a potentially curative resection, relapse is common and the 5-year survival rate is unsatisfactory [1]. Greater emphasis has, therefore, been placed on the development of better systemic chemotherapy for patients who cannot be cured with surgery.

The most investigated drugs are fluorouracil (FU), mitomycin C, doxorubicin (ADM) and cisplatin. As single agents, these

drugs achieve a percentage of objective responses ranging from 10 to 30% [2, 3]. In the past, the most widely used polychemotherapeutic regimen was the combination of FU, ADM and mitomycin C (FAM). The results from studies in which a total of 760 patients received this regimen demonstrate that FAM was able to induce a response rate of 30%, but with few complete remissions [4, 5]. A new regimen which has recently been studied is the association of high dose methotrexate, FU and ADM (FAMTX) [6]. Cisplatin has been investigated in gastric cancer since 1983, and the cisplatin combination with FU and ADM or epirubicin has shown interesting activity [7–9].

Etoposide has been shown to be less active in gastric cancer. However, this agent has proved to be synergic with cisplatin in experimental tumour models, and a response rate of 28% was obtained when cisplatin and etoposide were combined in a phase II study on gastric cancer [10]. The activity of a combination of FU continuous infusion plus cisplatin appears promising [11].

Wilke and Preusser [12, 13] combined etoposide, cisplatin and ADM (the EAP regimen) delivered along an 8-day schedule. This regimen, which does not use FU, induced a major response in 64% of advanced gastric cancer patients with 21% achieving a complete response (CR). However, given that the same three-drug combination has been further investigated by other authors with discordant results [14, 15], we felt it necessary to assess the therapeutic role of the original EAP combination by means of a multicentre phase II study.

## PATIENTS AND METHODS

*Patients*

This study was conducted by the Italian Trials in Medical Oncology (I.T.M.O.) Group, with the Division of Medical Oncology B of Milan's Istituto Nazionale Tumori as the reference centre; the study patients came from 20 different centres. The inclusion criteria were a histologically confirmed diagnosis of gastric cancer; locally advanced or metastatic disease with measurable lesions; performance status (PS) $\leq 2$ (ECOG scale); age $\leq 65$ years; normal renal, hepatic and haematological functions [white blood cells (WBC) $\geq 4000/mm^3$ and platelet count $\geq 100000/mm^3$]; no concomitant severe illness; life expectancy $> 2$ months; and no previous chemotherapy, radiotherapy or immunotherapy.

The patients had to be ambulatory and to have had a minimum of 3 weeks since any major surgical procedures involving resection or bypass, or 2 weeks since any explorative laparatomy.

The nature of the program was explained to each patient, and their informed consent was obtained according to the standard procedures followed by each participating institution.

*Treatment and dose modifications*

The chemotherapy was administered as follows: doxorubicin (20 mg/m$^2$) was given as a rapid intravenous infusion on days 1 and 7; cisplatin (40 mg/m$^2$) by slow intravenous infusion on days 2 and 8, with a 500 ml saline solution being infused both before and afterwards; and intravenous etoposide (120 mg/m$^2$) on days 4, 5 and 6. No treatment was administered on day 3. The subsequent cycle was started on day 22. The dose of etoposide was reduced to 100 mg/m$^2$ in patients aged more than 60 years.

Correspondence to E. Bajetta.
The authors are at the Division of Medical Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via Venezian 1, 20133 Milan, Italy.
Revised 29 Sep. 1993; accepted 6 Oct. 1993

Toxicity was assessed by means of physical examination, hepatic and renal biochemistry, and haemography, and classified according to WHO criteria [16]. These procedures were performed at baseline and before the delivery of each new therapeutic cycle.

Drug dosages were modified as follows: in the presence of myelotoxicity WHO grades 1–4 at the moment of delivering a new cycle of therapy, a 1–2 week delay in treatment was required. In the presence of persisting myelotoxicity grades 1–2, the dose of all drugs was reduced by 25%; if grade 3 occurred, a 50% reduction was considered and in the case of persisting grade 4, the treatment was stopped.

*Evaluation of response*

Staging procedures were performed before starting treatment, and included physical examination, biochemical profile, chest X-ray, electrocardiogram (ECG) and abdominal ultrasound or computed tomography (CT) scan. In cases of locally advanced disease, the primary tumour was evaluated by endoscopy and CT scan.

Response was defined according to UICC criteria [16]. CR was defined as the complete disappearance of all known disease for a minimum of 1 month; partial remission (PR) as a $> 50\%$ decrease in the sum of the products of the two largest perpendicular diameters of all tumour lesions for at least 1 month; stable disease (SD) as a $< 50\%$ decrease or a $< 25\%$ increase in the size of measureable lesions; progressive disease (PD) as a $> 25\%$ increase in any tumour lesion or the appearance of new sites. The occurrence of pleural effusion or ascites was also considered as PD in the presence of positive cytology.

The first response evaluation was made after two cycles of therapy and, in the case of CR, the treatment was continued for two cycles and then stopped; in the case of PR or SD, the patients were kept on treatment until the sixth cycle; in the case of PD, a second-line treatment was considered according to the clinical condition of the patients.

*Statistical considerations*

According to the published data [10], an objective response is obtained in 57% of patients. To estimate the percentage of response with a precision of 10% (= 1/2 of confidence interval) and a 95% confidence interval, 94 patients were required.

Response duration was considered to be the time from the achievement of response to the assessment of PD; freedom from progression (FFP) as the time from the beginning of treatment to the first evidence of PD. The overall survival (OS) of all eligible patients was defined as the time from the beginning of treatment to death for any cause. The product limit method was adopted to estimate response duration, FFP and OS [17].

## RESULTS

From January 1990 to May 1992, 96 patients were sequentially enrolled in this multicentre trial, 91 of whom were evaluable. Of the 5 unevaluated patients, 1 was a major protocol violator; 1 dropped out because of an allergic reaction to etoposide during the first cycle; 2 died from stroke after the first cycle, without any evidence of progression; and 1 died from sepsis subsequent to myelosuppression after the first cycle of treatment administered at 100%. The 2 patients who died from stroke were in good general condition and they died after 21 and 18 days, respectively, so these events were classified as possibly but not definitely related to chemotherapy. The patient who died after 18 days was a 56-year-old man affected by metastatic disease, with a PS of 2 at the beginning of treatment; he died at home

*Table 1. Main patients' characteristics*

| | |
|---|---|
| No. evaluable | 91 |
| Male/female | 60/31 |
| Median age, years (range) | 56 (25–65) |
| Performance status (ECOG): 0–1/2 | 83/8 |
| Measurable lesions | 91 |
| Disease status | |
| Locally advanced | 16 |
| Local relapse after radical surgery | 3 |
| Metastatic | 72 |
| Without primary tumour | 41 |
| With primary tumour | 31 |
| Site of metastases | |
| Liver | 43 |
| Lung | 4 |
| Lymph nodes | 40 |
| Pelvic mass | 19 |
| Peritoneal carcinosis | 17 |

before he could be admitted to hospital. The main characteristics of the evaluable patients are summarised in Table 1. All of the patients had good PS; the great majority had metastatic disease (79%). Histological types according to Lauren's classification were intestinal in 30 patients (33%), diffuse in 20 (22%), diffuse plus intestinal in 5 (5%) and unspecified in 36 (40%). None of the patients had previously received chemotherapy, radiotherapy or immunotherapy. In the patients with locally advanced disease, exploratory laparotomy revealed a technically unresectable tumour, often combined with lymph node conglobate and infiltration of the retroperitoneal area. Of the 72 metastatic patients, 29 had been previously resected with radical gastrectomy, and the study chemotherapy was given at relapse. 17 patients with measurable lesions also had peritoneal carcinosis.

34 of the 91 evaluable patients (37%) achieved an objective response (95% confidence interval 27–47%) with 12% achieving CR (95% confidence interval 5–19%). Table 2 shows the response according to disease extension. No regression was observed in 3 patients with local relapse after radical surgery. In patients with locally advanced disease, the overall response rate was 6/16 (37%), with 1 CR. In 1 patient with partial response, second-look laparotomy was performed and the residual tumour was radically resected. The patient was alive and disease-free at 20 months. 28 of the 72 metastatic patients (39%) had objective regression, with 10 CR (14%). The overall response rate (CR+PR) varied slightly according to the site of disease: liver 42%, pelvic mass 37%, lymph nodes 35%, primary tumour 34%. However, the percentage of CR was higher in liver metastases (18%). These responses were documented by CT scan in 19

*Table 2. Response according to disease extension*

| | No. of patients | | |
|---|---|---|---|
| | Evaluable | CR+PR (%) | CR (%) |
| Total | 91 | 34 (37) | 11 (12) |
| Metastatic | 72 | 28 (39) | 10 (14) |
| Without primary tumour | 41 | 20 (49) | 9 |
| With primary tumour | 31 | 8 (26) | 1 |
| Locally advanced disease | 16 | 6 (37) | 1 |
| Local relapse after radical surgery | 3 | — | — |

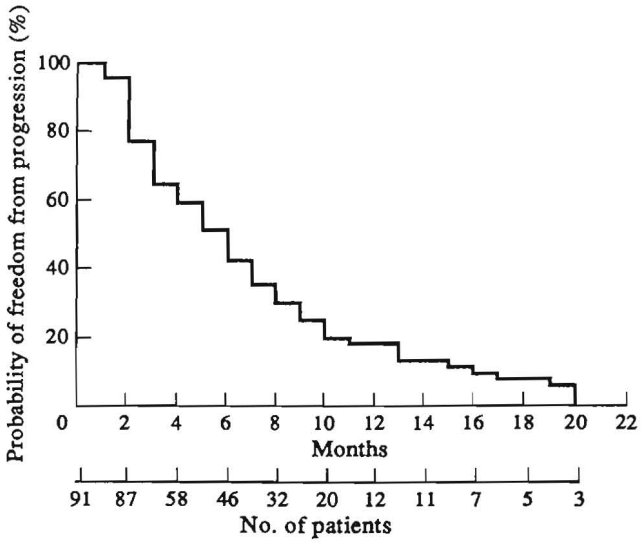


**Figure 1. The Kaplan–Meier curve for time free from progression.**

patients, by ultrasound in 17, by endoscopy in 13 and by laparoscopy in 2. Responses were achieved after a median of two cycles of therapy (range two to six), the median duration of response being 6 months (range 1–19+) and the median duration of complete remissions 5 months. The median time FFP was 8 months (Figure 1). The median OS for eligible patients was 9 months after a median follow-up of 18 months (Figure 2).

The effect of some pretreatment factors on therapeutic response were analysed (Table 3). The possible variables predictive of response were age, PS, tumour-related symptoms and resection status. The statistically significant factor in this analysis was resection status ($P = 0.04$). Of 50 symptomatic patients, 32 (64%) had their symptoms relieved during treatment.

A total of 416 courses were administered (median 4 per patient; range two to six), 27% of the cycles being given with an interval $\geq$ 5 weeks. This delay was due to myelosuppression. Eleven of the 416 (3%) courses were administered at 50% doses of all three drugs; in 35 courses (8%), the doses were reduced to 75%. Table 4 shows the haematological toxicity of the EAP regimen, based on the worst grade recorded for each patient at the third week. Overall, WHO grade 3–4 leucopenia was

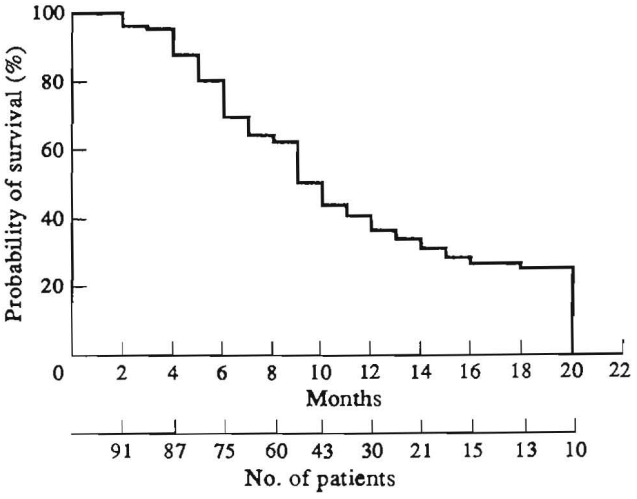


**Figure 2. Overall survival curve**

*Table 3. Response according to prognostic factors*

| | No. of patients | CR+PR | | |
|---|---|---|---|---|
| | Evaluable | (%) | CR | *P** value |
| Age (years) | | | | |
| ≤ 45 | 17 | 4 (24) | — | |
| > 45 | 74 | 30 (41) | 11 | 0.19 |
| Performance status | | | | |
| 0–1 | 83 | 32 (39) | 11 | |
| 2 | 8 | 2 (25) | — | 0.36 |
| Tumour-related symptoms | | | | |
| Yes | | | | |
| No | 50 | 16 (32) | 5 | |
| Resection status | 39 | 18 (46) | 6 | 0.17 |
| Prior gastrectomy | | | | |
| No gastrectomy | 44 | 21 (48) | 9 | |
| Histological type | 47 | 13 (28) | 2 | 0.04 |
| Diffuse | 20 | 8 (40) | 1 | |
| Intestinal | 30 | 12 (40) | 4 | |
| Diffuse plus intestinal | 5 | 1 (20) | 1 | |
| Unspecified | 36 | 13 (36) | 5 | 0.83 |

*Pearson's $X^2$ test and Fisher's exact test.

*Table 4. Haematological toxicity*

| | Cycles | | |
|---|---|---|---|
| | 1–2 | 3–4 | 5–6 |
| No. of patients | 91 (%) | 65 (%) | 36 (%) |
| Leucopenia | | | |
| Grade 0 | 24 (26) | 18 (28) | 6 |
| Grade 1 | 18 (20) | 12 (19) | 9 (25) |
| Grade 2 | 32 (35) | 20 (31) | 12 (33) |
| Grade 3 | 14 (15) | 13 (20) | 8 (22) |
| Grade 4 | 3 | 1 | 1 |
| Thrombocytopenia | | | |
| Grade 0 | 71 (78) | 50 (78) | 28 (77) |
| Grade 1 | 12 (13) | 9 (14) | 2 (5) |
| Grade 2 | 5 (5) | 2 | 2 (5) |
| Grade 3 | 2 | 2 | 2 (5) |
| Grade 4 | 1 | 1 | 2 (5) |

observed in 27 of 91 patients (30%), and WHO grade 3–4 thrombocytopenia in 8 (9%). The incidence of grade 3–4 leucopenia was 18% of 91 patients at the first and the second cycle, and 23% of 36 cases at the fifth and sixth cycle. In 4 patients, the treatment was stopped for grade 4 myelosuppression after 2, 3 and 4 cycles in 2, 1 and 1 patients, respectively.

Non-haematological toxicity was moderate, and included grade 2–3 alopecia in all cases, grades 3–4 mucositis in 10% and grade 1–2 nephrotoxicity in 2%.

## DISCUSSION

The role of chemotherapy in gastric cancer has been extensively investigated. Many reports show respose rates of 20–40% in advanced or metastatic disease, with no impact on survival [5]. This lack of benefit in terms of survival can be explained by the inability of the studied combinations to induce CR. The promising results of the EAP regimen reported by Wilke and Preusser has prompted many investigators to conduct phase II studies to evaluate its efficacy; Table 5 shows the results of the studies involving more than 11 patients. The conclusions drawn from such trials are contradictory, although it must be borne in mind that the drug administration schedules used were often different. Some authors have reported high toxicity and a low response rate for this combination [18–22]. Katz modified the dose of etoposide to reduce toxicity, and obtained 14% CR and 60% PR; but he still reported significant myelosuppression [23]. The groups of Taguchi and Lerner reported response rates of 45 and 33%, respectively, but at the cost of four treatment-related deaths [24, 25]. Possible explanations for these results may be inadequate sample sizes, different patient selection criteria or differences in the number of cycles administered. Only one phase III study comparing the efficacy and toxicity of EAP versus FAMTX has recently been published [26]. It reports that the EAP regimen had a response rate of 20%, less than the 33% reported for FAMTX; but no difference in terms of survival was observed.

For our study, the accrual of 91 evaluable patients was necessary in order to be able to make reliable comparisons with previous reports. We achieved objective responses in 37% of patients, with 12% of CR. It is worth noting that none of our patients had been previously treated with chemotherapy or radiotherapy, and that all had a good PS.

The good condition of the patients seems be the most important factor in allowing the administration of this regimen in an adequate fashion and with acceptable compliance, because we expected that the sequential administration of these three drugs to be myelotoxic.

Although our response rate is less exciting than that in Wilke's report, one-third of the responders obtained clinical or radiological CR with a median duration of 5 months. The different response rate between metastatic patients with a primary tumour (CR+PR: 26%) and those without (CR+PR: 49%) suggests that tumour burden is an important factor, and may be predictive of response if patients with a PS of ≤ 2 are selected.

Under the reported conditions, the regimen was feasible and well tolerated, most of the cycles being given in an out-patient setting. We would like to emphasise the fact that about 60% of the patients in our multicentre trial were treated in general community hospitals.

*Table 5. Results of studies on EAP regimen in gastric cancer*

| Studies [Ref] | No. of patients | % Response | | CI | Median survival |
|---|---|---|---|---|---|
| | | CR | CR+PR | | |
| Haim [28] | 13 | 7 | 46 | 19–75 | — |
| Tokunaga [22] | 14 | 7 | 29 | 8–58 | — |
| Willar Grimalt [15] | 15 | 7 | 7 | 0–32 | — |
| Shimada [20] | 19 | — | 42 | 20–64 | 7 |
| Gunzel [18] | 21 | 5 | 10 | 1–30 | 4 |
| Taal [21] | 26 | 3 | 15 | 4–35 | — |
| Katz [23] | 29 | 14 | 72 | 53–87 | 7 |
| Taguchi [24] | 29 | — | 45 | 27–63 | 5 |
| Kelsen [26] | 30 | — | 20 | 6–34 | 6 |
| Lerner [25] | 36 | 8 | 33 | 19–51 | 7 |
| Preusser [12] | 145 | 15 | 57 | 52–72 | 9 |
| Present series | 91 | 12 | 37 | 27–47 | 9 |

CI, confidence interval.

This is the first multicentre study of the use of the EAP regimen in a phase II trial, and we believe that the demonstration of its feasibility may have an important impact on everyday clinical practice.

The major toxicity of the regimen was grade 3 and 4 myelosuppression, which tended to occur more frequently as the number of given cycles increased. The administration of courses at full doses was more difficult after the first four cycles, and treatment delays were more frequent. Despite this fact, only 1 patient died from treatment-related toxicity.

On the basis of this experience, we consider that EAP is feasible in an out-patient setting (providing the selected patients are in good clinical condition), and that it is capable of inducing major objective responses. Because the length of the treatment (8 days every 3 weeks) proved to be a drawback, it may be useful to reduce the schedule.

For this reason, the data from Ajani's study are interesting [27]. The EAP regimen was given using a different schedule from that of the classic German scheme, and associated with granulocyte–macrophage colony-stimulating factor. We think that the combination of the three drugs in the EAP regimen may be worth pursuing in future studies, with different dosing schedules and with the use of colony-stimulating factor.


1. Noguchi Y, Imada T. Radical surgery for gastric cancer. *Cancer* 1989, **64**, 2053–2062.
2. Machover D, Goldschmidt E, Cholle T, Metzger G, Zittoun J, Marquet J. Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. *J Clin Oncol* 1986, **4**, 685–696.
3. Schabel FM, Trade MW. *Cis*-diamminedichloroplatinum: combination chemotherapy and cross-resistance studies with tumors of mice. *Cancer Treat Rep* 1979, **63**, 1459–1473.
4. Macdonald JS, Schein PS, Wolley PV, Smythe T, Ueno W, Hoth D. 5-fluorouracil, doxorubicin and mitomycin (FAM) combination. Chemotherapy for advanced gastric cancer. *Ann Intern Med* 1980, **93**, 533–536.
5. Macdonald J. Gastric cancer: chemotherapy of advanced disease. *Hematol Oncol* 1992, **10**, 37–42.
6. Wils J, Bleiberg M, Dalesio D. An EORT gastrointestinal group evaluation of the combination of sequential methotrexate and 5-fluorouracil combined with adriamycin (FAMTX) in advanced measurable gastric cancer. *J Clin Oncol* 1986, **4**, 1799–1803.
7. Vogl SE, Engstrom PF. Cisplatin, doxorubicin and 5-FU in combination for advanced gastric cancer. *Cancer Treat Rep* 1984, **68**, 1273–1275.
8. Cazap EL, Gisselbrect CN, Smith FP, Estevez RA, Alvarez CA, Lagarde C. Phase II trial of 5FU, doxorubicin and cisplatin in advanced measurable adenocarcinoma of the lung and stomach. *Cancer Treat Rep* 1986, **70**, 781–783.
9. Moertel CG, Rubin J, O'Connell MJ, Schutt AJ, Wieand HS. A phase II study of combined fluorouracil, doxorubicin and cisplatin in the treatment of advanced upper gastrointestinal adenocarcinoma. *J Clin Oncol* 1986, **4**, 1053–1057.
10. Elliott TE, Moertel CG, Wieand HS, Hahn RG, Gerstner JB, Tschetter LK. A phase II study of the combination of etoposide and cisplatin in the therapy of advanced gastric cancer. *Cancer* 1990, 65, 1491–1494.
11. Ducreux M., Rougier Ph, Lasser Ph, *et al.* Neoadjuvant chemotherapy in locally advanced gastric carcinoma: does it increase long-term survival? *Proc Am Soc Clin Oncol* 1993, 12 (abstract).
12. Preusser P, Wilke H, Achterrath W, Fink U, Lenaz L, Heinicke A. Phase II study with the combination etoposide, doxorubicin and cisplatin in advanced measurable gastric cancer. *J Clin Oncol* 1989, 7, 1310–1317.
13. Wilke H, Preusser P, Fink U, Gunzer U, Meyer HJ, Meyer J. Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: a phase II study with etoposide, doxorubicin and cisplatin. *J Clin Oncol* 1989, 7, 1318–1326.
14. Sparano SA, Wiernik PH. Toxicity of etoposide, doxorubicin and cisplatin in gastric cancer. *J Clin Oncol* 1990, **8**, 938–939.
15. Willar-Grimalt A, Candel MT, Garcia J, Bernacer B, Jimeno J. Combination of etoposide, adriamycin and cisplatin (EAP) in gastric cancer: association with severe toxicity. *Ann Oncol* 1991, **2**, 310–312.
16. WHO/UICC. *Handbook for Reporting Results of Cancer Treatment.* WHO Offset Publication No. 48. Geneva, World Health Organization, 1979.
17. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
18. Gunzel K, Flasshove M, Kath R, Hoffken K, Schmidt CG. Chemotherapy with etoposide, adriamycin and cisplatin (EAP) for patients with advanced gastric carcinoma. *Cancer Therapy Control* 1991, **1**, 327–332.
19. Merimsky O, Inbar M, Chaitchiks. Etoposide, doxorubicin and cisplatin in advanced or metastatic gastric cancer. *Eur J Cancer* 1991, 22, 944.
20. Shimada Y, Yoshida S, Ohtsu A, Saito D, Miyamoto K, Yoshido M, Fuji T. A phase II study of combination chemotherapy with etoposide, adriamycin and cisplatin (EAP) for advanced gastric cancer in Japan. *J Cancer Res Clin Oncol* 1990, **116**, 673 (abstract).
21. Taal BG. EAP in advanced gastric cancer. *J Clin Oncol* 1990, **8**, 939–940.
22. Tokunaga A, Onde M, Mizutani T, *et al.* Combination therapy with etoposide adriamycin and cisplatin in advanced primary and recurrent gastric cancer. *Gan to Kagaku Ryoho* 1989, **16**, 3713–3718.
23. Katz A, Gansl RC, Simon SD, Gama-Rodrigues J, Waiteberg D, Bresciani C. Phase II trial of etoposide, adriamycin and cisplatinum in patients with metastatic gastric cancer. *Am J Clin Oncol* 1991, **14**, 357–358.
24. Taguchi T. Combination chemotherapy with etoposide, adriamycin and cisplatin for advanced gastric cancer. *Proc Am Soc Clin Oncol* 1989, **8**, 108 (abstract).
25. Lerner A, Gonin R, Steele GD, Mayer RJ. Etoposide, doxorubicin, and cisplatin chemotherapy for advanced gastric adenocarcinoma. Results of a phase II trial. *J Clin Oncol* 1992, **10**, 536–540.
26. Kelsen D, Atiq O, Saltz L, Niedzwiecki D, Ginn D, Chapman D. FAMTX versus etoposide, doxorubicin, and cisplatin: a random assignment trial in gastric cancer. *J Clin Oncol* 1992, **10**, 541–548.
27. Ajani JA, Roth JA, Ryan B, Potnam JB, Pazdur R, Levin B. Intensive pre-operative CT with CSF for resectable adenocarcinoma of the esophagues or gastro-esophagues junction. *J Clin Oncol* 1993, **11**, 22–28.
28. Haim N, Robinson E. Combination of etoposide, adriamycin and cisplatin (EAP) in gastric cancer: association with severe toxicity. *Ann Oncol* 1992, **2**, 310–312.


**Acknowledgements**—We thank Dr J.S. Macdonald, Division of Medical Oncology, Temple University, Philidelphia, for reviewing the manuscript. Data management was performed by Italian Trials in Medical Oncology (I.T.M.O.) Scientific Service. This paper was presented in part at the Annual Meeting of the American Society of Clinical Oncology, San Diego, California, 17–19 May 1992.

## APPENDIX

The following investigators also participated in this study and are to be considered as co-authors: Giuseppina Arcangeli (Spedali Civili, Brescia), Paola Bertelli (Ospedale Fatebenefratelli, Milano), Carlo Floris (Ospedale Oncologico Businco, Cagliari), Pietro Masullo (Ospedale Civile, Vallo della Lucania, Potenza), Antonio Santoro (Ospedale San Gennaro, Napoli), Raffaella Taino (Ospedali Riuniti, Bergamo), Salvatore Tumulo (Ospedale C.R.O., Pordenone), and Eugenio Villa (Ospedale San Raffaele, Milano).