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Phase II Study of a Modified Combination of Etoposide, Doxorubicin, and Cisplatin for Patients With Advanced Gastric Cancer

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SYNOPSIS: Etoposide, doxorubicin, and cisplatin combination chemotherapy in a modified combination was an effective treatment in advanced gastric cancer, with an overall response rate of 40.5%. Disease extension and pretreatment performance status had significant effects on survival.

ABSTRACT: Background: Based on the promising results of EAP (etoposide, doxorubicin, and cisplatin) combination, a phase II study of modified EAP combination was performed in patients with advanced gastric cancer to evaluate the response, toxicity, and survival.

Method: Fifty-two consecutive patients with measurable or evaluable advanced gastric cancer, who had no prior therapy except surgery, were treated every 28 days with etoposide 120 mg/m^2/day, doxorubicin 25 mg/m^2/day, and cisplatin 40 mg/m^2/day on days 1 and 8, intravenously. Forty-seven patients were evaluable for response and toxicity.

Results: Overall response rate was 40.5% (95%CI = 37–54.7%), including 12.8% complete response. Responses were higher in patients with locally advanced disease (57.89%) as compared to those with distant metastases (28.57%) ($P = 0.044$). The median overall survivals of the entire group and the responders were 7 months and 11 months, respectively. Complete responders had significantly longer response duration and overall survival (31.5 months and 45,5 months, respectively), as compared to partial responders (6 months and 9 months, respectively). Six of the responders (31.6%) were alive at 2 years. Disease extension and pretreatment performance status had significant effects on survival. Grade 3–4 toxicity was observed in 33% of patients. There were no deaths related to toxicity.

Conclusion: EAP as used in this trial is an effective treatment in advanced gastric cancer. The effect is more pronounced in patients with locally advanced disease. *J. Surg. Oncol. 64:318–323, 1997.*

KEY WORDS: **etoposide; doxorubicin; cisplatin; chemotherapy; advanced gastric cancer**

INTRODUCTION

Gastric cancer is the most common type of gastrointestinal cancer in Turkey [1]. At diagnosis more than 75% of all patients have unresectable locally advanced and/or metastatic disease. The prognosis of these patients is very poor. Some single agents, such as cisplatin, 5-fluorouracil, mitomycin-C, doxorubicin, and etoposide produce about 15–20% partial response rates of short dura-

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tion [2]. The combination of 5-fluorouracil, doxorubicin, and mitomycin-C (FAM) which results in 25–40% response rates with a few complete responses, has been the most commonly used treatment until recently [2,3]. In 1989, Preusser et al. [4] reported an impressive 64% overall response rate, including 21% complete responders, with the combination of etoposide, doxorubicin (Adriamycin), and cisplatin (EAP) chemotherapy. However, it was found to have a high hematologic toxicity in most subsequent studies [5–8]. Moreover, these high response rates could not be confirmed by others; some investigators concluded that EAP cannot be a standard treatment in gastric cancer [5–7]. The present study was undertaken to evaluate the efficacy of a different schedule of EAP administration in advanced gastric cancers.

PATIENTS AND METHODS

Between May 1990 and February 1992, 52 consecutive patients diagnosed with locally advanced and/or metastatic gastric adenocarcinoma were treated in a phase II trial of EAP combination. All patients had histologically proven, measurable, or evaluable inoperable disease. The biopsy and the gastric resection materials were reviewed by at least two pathologists. Patients with performance status 4 and/or life expectancy of less than 2 months were excluded. Likewise, patients with cardiac problems were not entered in the protocol. No prior chemotherapy or prior radiation therapy was allowed. All patients were required to have normal liver and renal function tests and adequate bone marrow reserve (white blood cell count $\geq 4000/mm^3$, platelet count $\geq 100.000/mm^3$).

The diagnosis was obtained by endoscopic biopsies in all patients. Extent of disease was evaluated by exploratory laparotomy in 32 cases (68%) and by computed tomography (CT) of the abdomen in 8 patients (17%). Chest radiography and abdominal ultrasound were performed in all patients. Staging was done according to the International TNM system developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) [9]. Eastern Cooperative Oncology Group (ECOG) criteria were used to assess the performance status [10]. Response and hematologic toxicity were evaluated according to World Health Organisation (WHO) criteria [11].

Etoposide was given 120 mg/m^2/day intravenously (iv) on days 1 and 8, doxorubicin 25 mg/m^2/day iv on days 1 and 8, and cisplatin 40 mg/m^2/day iv on days 1 and 8. Treatment was repeated every 28 days on an outpatient basis. Adequate hydration with 2–3 L of intravenous fluids was given to all patients with the treatment. Antiemetics were routinely given before administration of cisplatin and doxorubicin. Blood counts and liver and renal function tests were repeated before each treatment. In the case of grade 1–3 hematologic toxicity, treatment was delayed until blood counts attained normal levels. Likewise, the dosage of etoposide was lowered by 20 to 25% in patients with grade 4 hematologic toxicity. A total of 161 cycles of chemotherapy was administered (median 3 cycles per patient, range 1-6).

TABLE I. Characteristics of Patients With Advanced Gastric Cancer

	N	%
No. of entered patients	52	
No. of evaluable patients	47	
Median age in years (range)	53 (26–76)	
Male : Female	27 : 20	
Histopathologic grade		
Well differentiated	13	27.7
Moderately differentiated	1	2.1
Poorly differentiated	26	55.3
Unknown	7	14.9
Disease status		
Locally advanced disease	19	40.4
Distant metastases	28	59.6
Performance status		
0–1	32	68.1
2–3	15	31.9
Previous treatment		
No treatment	23	49.0
Surgical treatment		
Palliative	16	34.0
Curative	8	17.0

Tumor response to treatment was evaluated by endoscopy in 14 patients, CT of the abdomen in 22 patients, and abdominal ultrasound in all patients. Response to treatment was recorded every 4–8 weeks. Discontinuation of the chemotherapy after the first cycle, was permitted for patients with rapidly progressive disease. Likewise, treatment was stopped in patients with stable disease after two consecutive cycles.

Statistical significance of the difference in response rates was calculated by chi-square test [12]. Survival analysis was done according to the Kaplan–Meier method; statistical significance was assessed using the log-rank test [13]. Prognostic factors were assessed using Cox-regression analysis [14].

RESULTS

Patient characteristics are shown in Table I. Forty-seven of 52 patients were evaluable for response and toxicity. Three patients were lost to follow-up following the first cycle of chemotherapy, and two patients refused further treatment after the first day application because of nausea and vomiting. Median age was 53 years (range 26–76 years). The most common histological type was poorly differentiated adenocarcinoma (55.3%). Nineteen patients (40.4%) had locally advanced disease and 28 (59.6%) had distant metastases. ECOG performance status (PS) was 0–1 in 32 patients (68.1%). While one-half

TABLE II. Advanced Gastric Cancer: Response to Etoposide, Doxorubicin, and Cisplatin Treatment and Relative Dose Intensity ± SEM According Response (n = 47 Patients)

Response	N	%	Relative dose intensity
Responders	19	40.5	0.92 ± 0.02*
Complete response	6	12.8	
Partial response	13	27.7	
Nonresponders	28	59.5	0.85 ± 0.03*
Stable disease	16	34.0	
Progression	12	25.5	

*$P = 0.081$.

TABLE III. Advanced Gastric Cancer: Response to Etoposide, Doxorubicin, and Cisplatin Treatment According to Extent of Disease

	Locally advanced disease (n = 19)		Distant metastasis (n = 28)	
Response type	n	%	n	%
Responders	11	57.89*	8	28.57*
Complete response	5	26.31	1	3.57
Partial response	6	31.58	7	25.00
Nonresponders	8	42.10	20	71.43
Stable disease	4	21.05	12	42.86
Progression	4	21.05	8	28.57

*$P = 0.044$.

TABLE IV. Median Response Duration and Survival in Months According to Response Types in Patients Treated With Etoposide, Doxorubicin, and Cisplatin Combination Chemotherapy for Advanced Gastric Cancer

Response type	Overall survival[a] (mo)	Response duration[a] (mo)	DFS[a] (mo)	No. of patients with 2-year survival	
				n	%
Complete response	45.5 (16–61)	31.5 (11–54)	27 (8–52)	5	83.3
Partial response	9.0 (5–33)	6.0 (4–21)	—	1	7.7
Stable disease	6.0 (3–11)	—	—		—
Progression	3.5 (2–8)	—	—		—

[a]Range given in parentheses.
DFS, disease-free survival.

of patients had no treatment before chemotherapy, 16 patients (34%) underwent palliative surgery, and 8 other patients (17%) had relapsed disease following curative surgery before chemotherapy.

The first two cycles were given without any delay in 27 patients (57.5%) with a mean relative dose intensity of 0.96 ± 0.02. In 14 patients (29.8%), chemotherapy cycles were administered with a 1-week delay.

Complete response (CR) was achieved in 6 patients (12.8%) and partial response (PR) was observed in 13 others (27.7%) (Table II). All CRs were confirmed by endoscopic biopsies. Total response rate was 40.5% (95% confidence interval: 37–54.7%). All complete responders had PS 0-1, and five had locally advanced disease. Only three responders (1 with CR and 2 with PR) accepted and underwent partial or total gastrectomy following chemotherapy. The patient with CR was found to have no residual tumor at histopathologic examination of the resection material. However, he relapsed 11 months following the gastrectomy.

The relative dose intensity (RDI) of the drugs used in the treatment was not significantly higher in the responders when compared to nonresponders ($P = 0.081$) (Table II). While the total response rate in patients with locally advanced disease was 57.89%, it was 28.57% in those with distant metastases ($P = 0.044$) (Table III).

Response duration and survival according to response types are shown in Table IV. The median response duration of complete responders was significantly longer than that of the partial responders (31.5 months vs 6 months, respectively; $P = 0.019$).

While the median survival of the entire group was 7 months (range 2–61+ months), it was significantly longer for the chemotherapy responders than for the nonresponders ($P = 0.0000$) (Fig. 1). Likewise, the median survival of complete responders was 45.5 months and was only 9 months for partial responders ($P = 0.0006$) (Table IV). Two patients with CR are still alive at 54 and 61 months. One patient in PR died of a cerebrovascular accident at 8 months, while the response was continuing. The median survivals of patients with stable (SD) and progressive disease (P) were 6 and 3.5 months, respectively.

The median survival of the patients with locally advanced disease was 10 months (range 3–61+ months) and 4 of them (21%) were alive at 2 years, but it was only 6 months (range 2–54+ months) for patients with disseminated disease ($P = 0.0127$). Overall survival of the three patients who underwent surgery following chemotherapy was 16, 16, and 33 months. Multivariate analysis showed the survival to be significantly influenced by performance status and disease extension (Table V).

Chemotherapy toxicity is depicted in Table VI. There were no deaths due to toxicity. The most common tox-

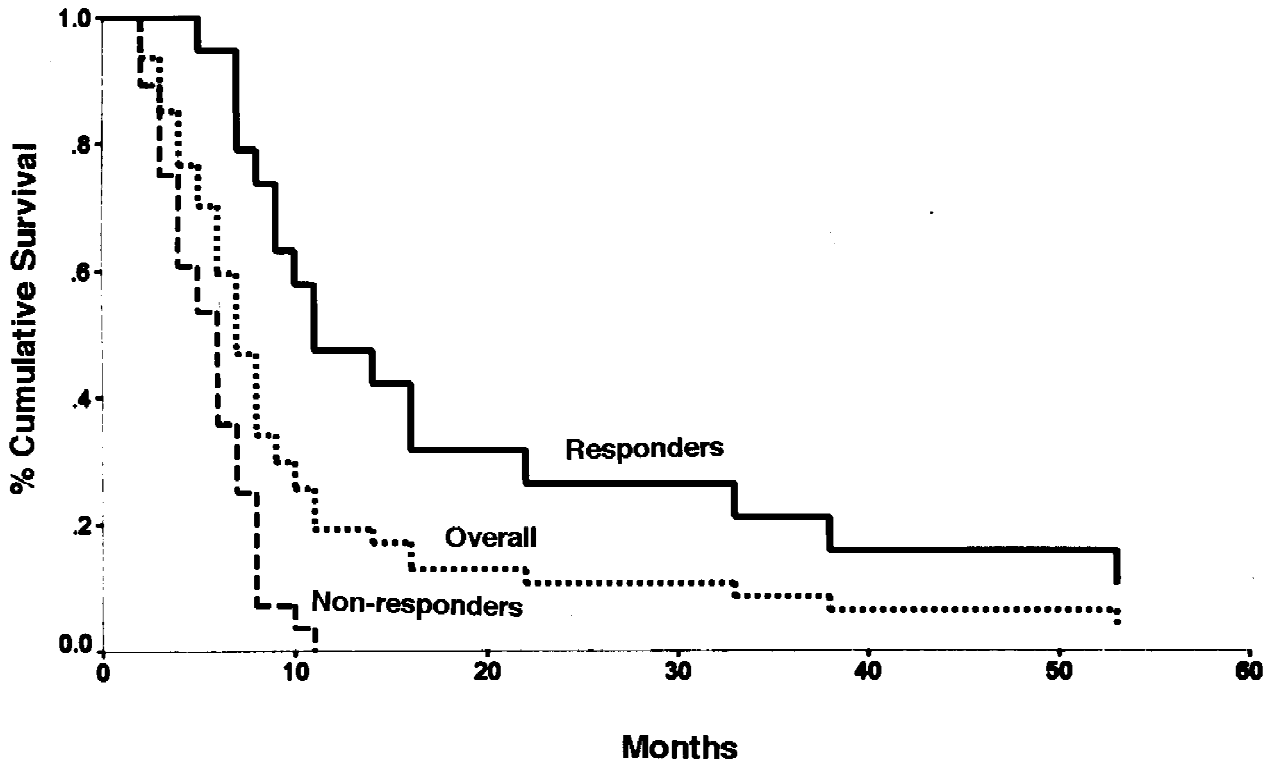

Fig. 1. Overall survival of the entire group of patients with advanced gastric cancer included in the study and comparison of survival of responders and nonresponders to etoposide, doxorubicin, and cisplatin combination chemotherapy ($P = 0.0000$).

TABLE V. Cox's Proportional Hazards Model Regression Analysis of Performance Status, Disease Extension, and Age on Survival in Patients With Gastric Cancer

Variable	Relative risk	95% CI	*P*
Performance status	0.6399	0.4525–0.9050	0.0116
Disease extent	0.7008	0.5132–0.9570	0.0253
Age	0.9526	0.9526–1.0104	0.2042

CI, confidence interval.

TABLE VI. Toxicity of Etoposide, Doxorubicin, and Cisplatin Combination Chemotherapy

	No. of patients		WHO grade 1–2	WHO grade 3	WHO grade 4
	n	%	(%)	(%)	(%)
Hematotoxicity					
Leukopenia	28	59.6	27.7	17.0	14.9
Anemia	5	10.6	6.4	—	4.2
Thrombocytopenia	2	4.2	—	2.1	2.1
Gastrointestinal					
Nausea–vomiting	37	78.7	61.7	17.0	—
Diarrhea	5	10.6	8.5	2.1	—
Stomatitis	7	14.9	8.5	6.4	—
Transaminase elevations	1	2.1	2.1	—	—
Cardiac arrhythmia	1	2.1	2.1	—	—
Nephrotoxicity	3	6.4	6.4	—	—
Alopecia	18	38.3	31.9	6.4	—
Peripheral neuropathy	2	4.2	4.2	—	—
Ototoxicity	1	2.1	—	—	—
Infections	2	4.2	4.2	—	—
Vascular toxicity	1	2.1	—	—	—
Death due to toxicity	0	—	—	—	—

WHO, World Health Organization.

icity was nausea and vomiting followed by leukopenia. Grade 3–4 leukopenia was observed in 32% of patients.

DISCUSSION

There have been several trials of EAP combinations for the treatment of advanced gastric cancer (Table VII). The high response rates of 57-70% reported by Preusser and colleagues [4,15,16] could not be confirmed in the subsequent studies other than that by Katz et al [17]. However, response rates of 15-52% in eight other studies with at least 25 evaluable patients give the impression that EAP is an active combination in the treatment of advanced gastric cancer [5–8,18–21]. On the other hand, a high rate of hematologic toxicity with an associated average 5.1% mortality rate was observed in almost all trials [5–8,15,17,19–21] other than those reported by Preusser et al. [4], Wilke et al. [16], and Rath et al. [18]. In view of these dismal toxicity rates, O'Connell [22] from the Mayo Clinic indicated in an editorial that the ''EAP regimen should not be used in clinical practice for the treatment of gastric cancer at all.''

Because of the inconvenience of the original EAP

TABLE VII. Published Results With Etoposide, Doxorubicin, and Cisplatin Combination in Gastric Cancer

Investigators/year	No. of patients	% response		Median survival (mo)	Grade 4 hematologic toxicity (%)	Death due to toxicity (%)
		Total	Complete response			
Preusser et al. 1989 [4]	67	64.0	21.0	9.0	19.0	0
Wilke et al. 1989 [16]	33	70.0	21.0	18.0	18.0	0
Wilke et al. 1990 [15]	145	57.0	15.0	10.0	19.0	2.1
Taal et al. 1990 [5]	26	15.4	3.8	—	—	11.5
Rath et al. 1990 [18]	45	18.0	0	9.0	22.2	0
Katz et al. 1991 [17]	29	72.5	14.0	7.2	26.0	10.3
Lerner et al. 1992 [7]	36	33.0	8.0	7.5	97.0	11.0
Kelsen et al. 1992 [8]	30	20.0	0	6.1	50.0	13.0
Ajani et al. 1993 [19]	48	31.0	12.0	15.5	31.0	2.0
Haim et al. 1994 [20]	25	52.0	4.0	8.0	26.0	2.3
Bajetta et al. 1994 [21]	96	37.0	12.0	9.0	5.5	1.1
Clark et al. 1995 [6]	31	23.0	0	9.0	55.0	12.9
Present study	47	40.5	12.8	7.0	14.9	0

regimen, we changed the schedule so that all the drugs were administered on days 1 and 8, every 4 weeks. Likewise, we lowered the dose intensity of etoposide by 33% and increased the dose intensity of doxorubicin by 25% in the current study when compared to the original EAP regimen of treatment every 4 weeks. Our trial with a convenient schedule of EAP resulted in a 40.5% response rate, excluding those patients with minimal responses (Table II). The response rate was twice as high in the locally advanced disease group as compared to those with distant metastases (57.89% vs 28.57%; $P = 0.044$). While only one patient (3.57%) with distant metastases achieved a CR, it was observed in five patients (26.31%) with locally advanced disease (Table III). In the present study, the dose intensity seems to have no significant effect on the response rates (Table II). Median overall survival, response duration, and disease-free survival of the patients with complete response were remarkable (45.5, 31.5, and 27.0 months, respectively). The survival rate of the complete responders, the overall responders, and the whole group at 2 years were 83.33%, 31.58% and 12.77%, respectively (Table IV). However, the median survival of all the patients in our study is similar to that of most of those reported previously (Table VII). When we compare our results to previous reports, we can assume that relatively high response rates and long survival of responders, obtained in our trial, could be related to the modified schedule. But the role of the other factors, such as virulence of the disease in different countries, younger age in our study (median 53 years), and other patient selection differences, cannot be totally disregarded.

In this trial, only three responders (1 with CR and 2 with PR) were operated following chemotherapy with complete resection of the residual disease. Overall survival in this group was 16, 16, and 33 months, and disease-free survival was 8, 11, and 17 months, respectively. Therefore, the improvement in survival of the responders in the present study cannot be related to surgical treatment. Likewise, the results of the surgical resection following chemotherapy in a small group of similar patients with locally advanced disease reported by Lerner et al. [7] were not very rewarding. In that trial, only one out of five patients with surgical resection after chemotherapy had a complete pathological response lasting 12 months.

We observed somewhat lower hematologic toxicity compared to most of the previous reports using the original EAP combination (Table VII). In a recent trial, a similar decrease in hematologic toxicity was observed by changing the schedule of EAP without even reducing the dosage of the original combination [20]. The modified EAP combination in that trial scheduled administration of the drugs in 3 consecutive days instead of in 7 days of the original EAP scheme. Only 1 patient (2.3%) was lost because of toxicity. In addition, the overall response rate for patients in the above trial was very impressive (52%). Moreover, in an another phase II study of the original EAP combination in advanced gastric cancer, Bajetta et al. [21] reported a response rate of 37% and grade 4 leukopenia in only 3.3% of patients at one or two cycles and with one death due to toxicity.

In view of all these trials, we can state that it is not fair to consider EAP combination as contraindicated in gastric cancer. Our results suggest that EAP, at the dose and schedule used in the present study, is effective in patients with good performance status and locally advanced disease, with acceptable toxicity. Moreover, the CR achieved in one-fourth of patients with locally advanced disease resulted in encouraging overall survival.

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