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Short Communication

Cisplatin, Doxorubicin and Etoposide (PAV) in Advanced Gastric Carcinoma: The SAKK Experience

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EAP (etoposide, doxorubicin, cisplatin), a chemotherapeutic combination given over 8 days, proposed by German investigators in cancer of the stomach, has been considered to be too toxic by others. A positive experience with a similar regimen (PAV) developed by the SAKK given over 3 days in small cell lung cancer led us to test it in gastric adenocarcinoma. 41 patients with metastatic gastric cancer were enrolled in the study and 38 were evaluable for response and toxicity. One complete response and 12 partial responses were recorded, giving a response rate of 34% (95% confidence interval (CI) 20–51%). Median progression-free and overall survival were 3.4 and 6.3 months, respectively. Haematotoxicity was the leading toxicity with 34 (90%) and 17 (45%) grade III–IV neutropenia and thrombocytopenia, respectively. Despite this high rate of granulocytopenia, only six episodes of non-fatal febrile neutropenia were observed. Other toxicities were relatively easy to manage with infrequent grade III–IV occurrences. We conclude that PAV is active in gastric cancer and seems to be better tolerated than EAP.

Key words: gastric cancer, metastatic, chemotherapy
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INTRODUCTION

GASTRIC CARCINOMA has always been considered as a poorly chemoresponsive disease. More effective so-called 'second generation' cytotoxic regimens were recently proposed for advanced disease [1–4]. Among them EAP (etoposide, doxorubicin, cisplatin) has been shown to be very effective in metastatic disease and as primary therapy for advanced locoregional disease [5, 6]. However, this regimen, which was administered over 8 days, was considered by others to be too toxic and, thus, difficult to recommend for general use [7, 8].

During the past 10 years, the Swiss Group for Clinical Cancer Research (SAKK), for small cell lung cancer, used a regimen with the same drugs at similar dose levels (PAV), but administered over 3 days [9]. This regimen was proven to be very well tolerated and, therefore, suitable for testing in the advanced gastric cancer setting.

PATIENTS AND TREATMENT

41 patients with metastatic adenocarcinoma of the stomach not previously treated by systemic therapy and not amenable to curative resection were enrolled in this study. The patients had to have bidimensionally measurable disease, a performance status ≤ 1, normal blood counts, creatinine clearance ≥ 60 ml/min, normal liver function tests and a left ventricular ejection fraction $\geq 50\%$ estimated by echocardiography or Mugascan. Written consent was obtained from each patient.

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The treatment consisted of cisplatin 30 mg/m^2 days 1–3, doxorubicin 45 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1–3 given every 4 weeks for up to six cycles. In case of delayed resolution of toxicity, the next cycle of treatment could be postponed up to disappearance of the symptoms, but for no more than 2 weeks, otherwise the treatment was discontinued. No dose modification was planned except for grade III–IV mucositis, which led to a 50% dose reduction of doxorubicin.

Response was assessed according to WHO criteria at the end of every other cycle of treatment. After completion of the treatment programme or discontinuation of chemotherapy, disease status was re-evaluated every 3-months. Toxicity was assessed according to WHO grading.

The study was designed as a two-stage phase II study [10]. The lower limit for the response rate was 20%, with the probability to conclude that the treatment was promising being less than 5% (significance level). If the response rate was at least 40% (upper limit), then the probability of rejecting the treatment would be less than 20% (power 80%). 13 consecutive patients were enrolled in the first stage. An additional 28 cases were then recruited, for a total of 41.

RESULTS

41 patients were enrolled in the study. There were 40 males, 15 (38%) whose performance status was 0 and 25 (63%) whose performance status was 1. 25 (61%) of the patients had previously undergone surgical resection of their primary tumour (total or subtotal gastrectomy). 3 patients did not receive PAV treatment due to refusal (1 patient) and rapid deterioration of performance status precluding chemotherapy administration (2 patients). All remaining 38 patients received at least one cycle of treatment and were considered in the evaluation of the study for response, toxicity and survival.

One complete and 12 partial responses were recorded, giving a response rate of 34% (95% confidence interval (CI) 20–51%). The median progression-free survival was 3.4 months. The median overall survival from registration was 6.3 months.

One hundred and thirty cycles of treatment were administered with a median of two cycles per patient, 105 (81%) without any dose reduction or delay. The median delivered doses was greater than 90% of the planned dose of each drug. Haematotoxicity was the leading side-effect with grade III–IV neutropenia and thrombocytopenia occurring in 34 (90%) and 17 (45%) of the patients, respectively (Table 1). Despite this high rate of granulocytopenia, only 6 cases of febrile neutropenia were observed. The duration of haematoxicity was not assessed.

Grade III–IV non-haematological toxicities were infrequent, apart from alopecia (38; 100%) nausea/vomiting (9; 24%) and fatigue (11; 29%). Other severe toxicities consisted of 1 case of grade III diarrhoea, 1 case of upper gastrointestinal bleeding, 1 episode of reversible apnoea without cardiac arrest and 1 episode of convulsion. Discontinuation of treatment due to unacceptable toxicity occurred in 6 patients (16%) after one to five cycles of treatment. No toxic death was recorded.

Table 1. *Haematological toxicity* (38 *patients*)

	WHO grade (*n*, %)			
	1	2	3	4
Anaemia (*n* = 38)	7 (18)	11 (29)	8 (21)	6 (16)
Leucocytes (*n* = 38)	0 (0)	6 (16)	19 (50)	12 (32)
Granulocytes (*n* = 28)	0 (0)	0 (0)	3 (11)	22 (79)
Thrombocytes (*n* = 38)	6 (16)	3 (8)	6 (16)	11 (29)

DISCUSSION

The results of this study confirm that the association of PAV is active in the treatment of gastric cancer. The response rate, time to disease progression and overall survival observed are in the range of those obtained with EAP in stage IV disease [8]. Our results are similar to those observed with EAP and other second generation regimens, such as 5-FU, doxorubicin, methotrexate (FAMTX), etoposide, 5-FU, leucovorine (EFL) or (5-fluorouracil) 5-FU–cisplatin, tested in confirmatory studies and in a randomised multicentric setting [3, 4, 11]. These reports seem to be confirmed by recent modest data obtained with FAMTX versus epirubicin, cisplatin, 5-FU (ECF), a new effective combination based on 5-FU given in continuous protracted infusion developed in the U.K. [12].

Despite its high haematotoxicity with grade III–IV leucopenia observed in 82% of the patients, we had only six episodes of febrile neutropenia and no toxic death. This contrasts with what has been reported with EAP by others [7, 8]. It is possible that PAV, which is given in 3 days instead of 8 days for EAP, induces a neutropenia of shorter duration which minimises the occurrence of septic complications, although we did not assess the duration of neutropenia in this study so cannot confirm that this is the case. Since PAV is a regimen well known by the SAKK group, the experience of the participating centres might also play a role in the patient tolerance observed.

The median progression-free and overall survival obtained in this study, which are comparable to that observed with the other second generation regimens for metastatic gastric cancer, emphasise the limitations faced with combinations using classic drugs given in a standard manner. The development of innovative regimens using prolonged infusional delivery of 5-FU, such as ECF [12] or weekly drug administration such as platine, etoposide, leucovorin, 5-FU (PELF) as proposed by the Italians [13], as well as the emergence of new drugs showing activity in gastric cancer, such as docetaxel, might help in the progress of treatment of this disease in the coming years [14–16].

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