Pergamon

European Journal of Cancer, Vol. 34, No. 7, pp. 1128–1130, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10140-X

Short Communication

Treatment of Advanced Gastric Cancer with Oral Etoposide, Leucovorin and Tegafur: Experience with an Oral Modification of the Etoposide, Leucovorin and 5-Fluorouracil (ELF) Regimen

M. Raderer, G.V. Kornek, M.H.L. Hejna, J. Miholic, G. Weinlaender, T. Brodowicz, W.C.C. Fiebiger, J.B. Valencak and W. Scheithauer

Department of Internal Medicine I, Division of Oncology, University of Vienna, Vienna, Austria

Recent data have suggested enhanced therapeutic activity with prolonged administration of both etoposide as well as fluoropyrimidines in the treatment of gastrointestinal malignancies. Based on this rationale, we investigated the clinical effectiveness and tolerance of an oral modification of the widely applied etoposide, leucovorin and 5-fluorouracil (ELF) regimen in patients with advanced gastric cancer. 32 patients with advanced gastric cancer were treated with oral etoposide (100 mg), leucovorin (3×100 mg), and tegafur (3×200 mg) over 14–21 days for a maximum of six cycles. Objective response was seen in only 5 patients (16%), stable disease was documented in 7 (22%), while the remaining patients progressed during therapy. The median time to progression was 2.8 months (range 0.7–12 months) and median overall survival was 6 months (range 1–18+ months). Due to grade 3 nausea/emesis, 8 patients discontinued treatment prematurely, while 12 patients experienced anorexia and progressive weight loss. Haematological toxicity was modest, with 4 patients developing asymptomatic grade 3–4 granulocytopenia. We conclude that this oral combination regimen cannot be recommended for the treatment of advanced gastric cancer. © **1998 Elsevier Science Ltd. All rights reserved**

Key words: gastric cancer, etoposide, tegafur, leucovorin, chemotherapy
Eur J Cancer, Vol. 34, No. 7, pp. 1128–1130, 1998

INTRODUCTION

Despite its declining incidence in the Western world, gastric cancer is still amongst the most common malignancies [1]. Single agents with modest, yet documented activity include 5-fluorouracil (5-FU), mitomycin C, BCNU, the anthracyclines, etoposide and cisplatin [2]. In addition, numerous drug combinations have been investigated. One of these regimens, consisting of intravenous (i.v.) etoposide, leucovorin and 5-FU (ELF), is commonly applied to patients with disseminated disease, due to the relatively good response rates along with an acceptable toxicity profile [2, 3]. Taal and coworkers have recently reported an increase in objective responses when i.v. etoposide was replaced by an oral formulation over a prolonged period of time [4]. The concept of continuous administration of low drug doses has also become a focus of interest for the use of fluoropyrimidines [5]. Based on this rationale, various oral 5-FU prodrugs have been developed. One of these agents which has already undergone extensive clinical investigation is tegafur, which is converted to 5-FU by hepatic microsomal enzymes [6]. Based on these biochemical and pharmacokinetic considerations, and because of recent demonstration of preference for oral chemotherapy in cancer patients [7], we initiated the present trial using oral formulations of etoposide, tegafur and leucovorin.

PATIENTS AND METHODS

32 consecutive chemotherapeutically naive patients with histologically ascertained, unresectable locally advanced and/or metastatic gastric cancer were enrolled in the trial. Eligibility criteria also included the presence of at least one bidimensionally measurable target lesion documented by computed

Correspondence to M. Raderer.
Received 5 Aug. 1997; revised 10 Nov. 1997; accepted 3 Dec. 1997.

tomography (CT) scan, WHO performance status ≤ 2, age 18–75 years, adequate bone marrow (leucocyte count > 4000/μl, platelet count > 100 000/μl), renal (serum creatinine < 1.5 mg/dl) and hepatic functions (total bilirubin < 1.5 mg/dl, transaminase levels less than twice the upper normal limits). Only subjects with the ability to swallow normally were included in the trial. All patients gave informed consent according to institutional guidelines.

Treatment consisted of etoposide 100 mg/day, leucovorin 3×100 mg/day (Calciumfolinat® 100 mg capsules were kindly provided by Ebewe Arzneimittel Ges.m.b.H, Unterach, Austria), and tegafur 3×200 mg/day (Ftoralon®, Schöller Pharma, Austria), given orally from day 1 to day 14. In the absence of haematological or non-haematological side-effects ≥ WHO grade 2, treatment was continued for a total of 21 days. Premedication with daily oral tropisetron was given routinely during the intake of the cytotoxic agents. The next treatment cycle was started 2 weeks after the last intake of chemotherapy. A maximum of six cycles was given unless progressive disease was documented earlier. In case of WHO grade 4 haematotoxicity or any other severe (grade 3 or 4) organ toxicity, except alopecia, the daily dose of both etoposide and tegafur was reduced by 50%.

Pretreatment evaluations included medical history and physical examination, performance status, complete blood cell count (CBC), biochemical profile, chest radiograph, electrocardiogram, and abdominal CT scan. CBCs were performed at weekly intervals during chemotherapy, and all baseline investigations, including tumour measurements, were repeated every 8 weeks. Toxicity and treatment effects were evaluated according to WHO standard criteria.

RESULTS

The pretreatment characteristics of the 32 patients enrolled in this study are shown in Table 1. Although 8 patients discontinued treatment before the end of the first cycle due to grade 3 nausea/emesis, all were considered evaluable for toxicity and response assessment. According to an intent-to-treat analysis, they were rated as treatment failures. A total of 96 cycles was administered to our patients; the median number of treatment courses was 2 (range 1–6).

Table 1. *Patient characteristics*

Total number of patients	32
Median age (years)	63 (range 38–75)
Sex (male/female)	20/12
WHO performance status	
0	9
1	13
2	10
Location of primary	
Cardia	10
Fundus and body	9
Antrum	10
Gastric stump	3
Histology (Lauren classification)	
Diffuse type	18
Intestinal type	14
Prior gastrectomy	
Yes	20
No	12
Disease presentation	
Locoregional	5
Primary excised, metastatic	12
Primary not excised, metastatic	11
Locoregionally recurrent and metastatic	4

There was no complete remission. Partial tumour responses were seen in 5 of 32 patients (16%; 95% confidence interval 5.3–32.7%) with a median duration of 7.2 months (range 3–10 months). 7 patients (22%) had stable disease for a median duration of 5.5 months (range 3–12 months), all other patients progressed. The median time to progression was 2.8 months (range 0.7–12 months), the median survival was 6 months (range 1–18 + months).

Haematological toxicity was moderate, including grade 3–4 granulocytopenia in 4 patients, grade 3 thrombocytopenia in 2 patients, and grade 3 anaemia in 1 patient. The median leucocyte nadir count was 4300/μl (range 900–16 400/μl), the median granulocyte nadir count was 2740/μl (range 140–11 570/μl) and the median thrombocyte nadir was 258 000/μl (range 18 000–589 000/μl), with a median haemoglobin nadir of 10.7 mg/dl (range 6.4–13.5 mg/dl). Non-haematological side-effects were mainly gastrointestinal. 8 patients (25%) discontinued treatment prematurely because of grade 3 nausea/emesis (6 patients before the completion of the first cycle and 2 patients during the second cycle). In addition, 12 of the remaining patients experienced anorexia and weight loss. 9 patients (28%) developed short-lasting grade 2 diarrhoea; only 1 patient developed grade 3 stomatitis, and 2 patients developed grade 1 and 2 stomatitis. Alopecia, grade 1, 2 or 3, was seen in 5 (16%), 8 (25%) and 7 patients (22%), respectively.

DISCUSSION

The use of palliative chemotherapy in patients with advanced gastric cancer is a common practice, and recent investigations have disclosed a potential benefit in terms of survival and quality of life [8, 9]. Based on data supporting a pharmacokinetic advantage of 'chronic chemotherapeutic treatment', as well as using prolonged oral application of etoposide [4] with ELF, we investigated the feasibility and antitumour efficacy of an entirely oral modification of this regimen.

Our results, however, were disappointing: 5 of 32 (16%) patients responded, 7 had stable disease (22%), the remaining, i.e. almost two-thirds of our patients, progressed during treatment. Furthermore, the regimen was associated with substantial toxicity. Whereas haematological side-effects were modest in our series, 8 patients did not comply with treatment as scheduled, but discontinued treatment due to severe nausea/emesis, in spite of prophylactic intake of 5-HT_3 receptor antagonists. We cannot offer a definite explanation for the surprisingly high rate of gastrointestinal toxicity in our series. In contrast to our data, haematotoxicity was more pronounced and gastrointestinal side-effects were rated only minor to moderate in previous trials in various malignancies using similar doses of oral etoposide, either alone [10, 11] or in combination with i.v. 5-FU and leucovorin [4]. In spite of the pronounced gastrointestinal toxicity of i.v. tegafur [12], the use of an oral formulation in divided doses has also been reported to be well tolerated in patients with advanced colorectal cancer [13].

In conclusion, our data suggest that this oral modification of the ELF regimen cannot be recommended for further investigations in gastric cancer using this particular dose schedule.

1. Boring CC, Squires TS, Tong T, Montgomery S. Cancer statistics. *CA Cancer J Clin* 1994, **44**, 19–36.
2. Wilke H, Preusser P, Fink U, *et al.* New developments in the treatment of gastric carcinoma. *Semin Oncol* 1990, **1**, 61–70.
3. Van Cutsem E, Filez L, Dewyspelaere J, *et al.* Etoposide, leucovorin and 5-fluorouracil in advanced gastric cancer: a phase II study. *Anticancer Res* 1995, **15**, 1079–1080.
4. Taal BG, Teller FG, Bokkel Huinink WW ten, *et al.* Etoposide, leucovorin, 5-fluorouracil (ELF) combination chemotherapy for advanced gastric cancer: experience with two treatment schedules incorporating intravenous or oral etoposide. *Ann Oncol* 1994, **5**, 90–92.
5. Sobrero AF, Aschele C, Bertino JR. Fluorouracil in colorectal cancer—a tale of two drugs: implications for biochemical modulation. *J Clin Oncol* 1997, **15**, 368–381.
6. Anttila MI, Slotaniemi EA, Kairaluoma MI, *et al.* Pharmacokinetics of Ftorafur after intravenous and oral administration. *Cancer Chemother Pharmacol* 1983, **10**, 150–153.
7. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997, **15**, 110–115.
8. Scheithauer W, Kornek GV, Hejna M, *et al.* Palliative chemotherapy versus best supportive care in patients with metastatic gastric cancer: a randomized trial. *Ann Hematol* 1996, **73**(Suppl. II), A-181 (abstract).
9. Glimelius B, Ekström K, Hoffman K, *et al.* Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997, **8**, 163–168
10. Ajani J, Dumas P, Pazdur R, *et al.* Phase II trial of oral etoposide in untreated patients with advanced gastric carcinoma. *Proc Am Soc Clin Oncol* 1993, **12**, 217 (abstract).
11. Medical Research Council Lung Cancer Working Party. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small cell lung cancer: a stopped multicentre randomised trial. *Lancet* 1996, **348**, 563–566
12. Frieman MA, Ignoffo RJ. A review of the United States clinical experience of the fluoropyrimidine, Ftorafur (NSC-148958). *Cancer Treat Rev* 1980, **7**, 205–213.
13. Pazdur R, Lassere Y, Rhodes V, *et al.* Phase II trial of uracil and tegafur plus oral leucovorin: an effective oral regimen in the treatment of metastatic colorectal carcinoma. *J Clin Oncol* 1994, **12**, 2296–2300.