Pergamon

European Journal of Cancer Vol. 33, No. 6, pp. 967–969, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(96)00497-2

Short Communication

Hand–foot Syndrome Induced by High-dose, Short-term, Continuous 5-Fluorouracil Infusion

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The aim of this study was to examine in detail the incidence and severity of hand–foot syndrome in advanced colorectal cancer patients receiving 5-fluorouracil (5-FU) and leucovorin (L-LV) chemotherapy. 70 advanced colorectal cancer patients (pts) were given weekly 24 h continuous 5-FU (2600 mg/m^2) infusion plus L-LV (100 mg/m^2 i.v., 50 mg orally). The toxicity, in particular HFS, was analysed, correlated to the main pts characteristics and compared to the other observed side-effects. HFS occurred in 36/70 pts (51%): grade 1 in 16 pts, grade 2 in 16 pts, grade 3 in 3 pts and grade 4 in 1 pt. It occurred after a median number of nine courses. In one case, chemotherapy was interrupted for this toxicity, and in another 5 pts drug reduction and/or treatment delay were undertaken. Changes in the therapeutic programme because of diarrhoea or mucositis were more frequent, even though these toxicities were generally mild in our series of pts. HFS was significantly correlated to previous exposure to chemotherapy ($P = 0.00003$). HFS was a frequent side-effect of high-dose, short-term continuous 5-FU infusion, but the impact on quality of life of pts and on the correct delivery of the planned chemotherapy was limited. © **1997 Elsevier Science Ltd.**

Key words: hand–foot syndrome, 5-fluorouracil, continuous infusion, colorectal cancer

Eur J Cancer, Vol. 33, No. 6, pp. 967–969, 1997

INTRODUCTION

IN ADVANCED colorectal cancer, chemotherapy plays an important role as palliative treatment and, therefore, efforts of current clinical research are directed towards the identification of the regimen with the best therapeutic index.

Modulation of 5-fluorouracil (5-FU) by folinic acid is an advance in terms of response rate; however, stomatitis, leucopenia and diarrhoea are often dose-limiting toxic effects [1, 2]. The rationale for continuous infusion of 5-FU is the short half-life of the drug and the high dose intensity achievable; the response rate is higher and the spectrum of side-effects is modified in comparison to standard regimens [3]. In particular, leucopenia is reduced, whereas hand–foot syndrome emerges as one of the most frequent problems. First described in 1984, this atypical dermatological manifestation of drug toxicity is still rarely investigated and until recently not mentioned in WHO or other commonly used toxicity classifications. The aim of this study was to examine in detail the incidence and severity of hand–foot syndrome in advanced colorectal cancer patients receiving 5-FU and leucovorin chemotherapy.

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Received 27 Jun. 1996; revised 8 Oct. 1996; accepted 27 Nov. 1996.

PATIENTS AND METHODS

From 1993 to 1995, 70 advanced colorectal cancer patients entered a phase II study and were treated weekly on an outpatient basis as follows: leucovorin (L-LV) 100 mg/m^2 by 4 h infusion, followed by 5-fluorouracil (5-FU) 2600 mg/m^2 continuous infusion over 24 h combined with oral L-LV 50 mg every 4 h for 5 doses; 5-FU was delivered by portable infusion pumps. All patients were evaluable for toxicity, 65 for response. They received a median number of 15 courses (range 3–33); the total number of administered cycles was 1039.

Toxicity was reported according to WHO criteria. On the basis of appearance, distribution and symptoms of hand–foot syndrome, this side-effect was graded as follows: grade

Table 1. Overall toxicity (WHO criteria): 70 pts

Grade	Number of patients I–II	III	IV	Total *n* (%)
Diarrhoea	19	18	1	38 (54)
Hand–foot syndrome	32	3	1	36 (51)
Nausea/vomiting	30	3	0	33 (47)
Mucositis	20	3	0	23 (33)
Fatigue	20	3	0	23 (33)
Conjunctivitis	12	1	0	13 (19)
Myelotoxicity	5	1	0	6 (9)
Alopecia	3	0	0	3 (4)

1 = dysesthesia/paresthesia, tingling in the hands and feet; grade 2 = discomfort in holding objects and upon walking, painless swelling or erythema; grade 3 = painful erythema and swelling of palms and soles, periungueal erythema and swelling; grade 4 = desquamation, ulceration, blistering, severe pain.

RESULTS

Toxicity is described in Table 1. Overall, the most frequent toxicities were diarrhoea, hand–foot syndrome and emesis observed in 54%, 51% and 47% of patients, respectively. No patient suffered from cardiotoxicity or neurotoxicity.

Hand–foot syndrome was observed in 36/70 patients (pts): grade 1 in 16 pts, grade 2 in 16 pts, grade 3 in 3 pts and grade 4 in 1 pt. No drug was administered to reverse or to prevent the occurrence of this toxicity. Hand–foot syndrome occurred after a median number of 9 courses (range 4–23), corresponding to a median 5-FU cumulative dosage of 18 500 mg/m^2 (range 10400–62400). The duration of this side-effect was 6–20 days, including the 5–7 days required for the resolution after the discontinuation of chemotherapy. Only 15/36 patients presented hand–foot syndrome alone; in the other cases, it was associated with diarrhoea (58.3%), mucositis (50%), nausea and/or emesis (41.6%) and conjunctivitis (25%).

Table 2. Hand–foot syndrome and patients' characteristics

	All patients ($n = 70$)	Patients with HFS ($n = 36$)	
Median age (years) (range)	63 (35–77)	61 (35–76)	
⩽61 years	32	18	
>61 years	38	18	P = NS
P.S.			
=0	37	23	
⩾1	33	13	$P = 0.053$
Sex			
Male	52	25	
Female	18	11	P = NS
Pretreatment			
No	44	13	
Yes	26	23	$P = 0.00003$
Metastatic site			
Liver	36	20	
Abdomen/pelvis	9	4	
Distant metastasis	25	12	P = NS
Objective response			
CR + PR	23	11	
SD + PD	42	22	P = NS
Not evaluable	5	3	

HFS, hand–food syndrome; P.S., WHO performance status; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3. Treatment-related toxicity data: dose reduction and/or therapy delay

	No./Total* (%)
Diarrhoea	
Dose reduction	4/11 (36%)
Therapy delay	5/15 (33%)
Dose reduction + therapy delay	14/21 (67%)
Hand–foot syndrome (HFS)	
Dose reduction	2/11 (18%)
Therapy delay	2/15 (13%)
Dose reduction + therapy delay	1/21 (5%)
Mucositis	
Dose reduction	5/11 (45%)
Therapy delay	4/15 (27%)
Dose reduction + therapy delay	3/21 (14%)

*Total with dose reduction, therapy delay or both.

In 12 (33%) out of the 36 pts, hand–foot syndrome occurred again at subsequent courses, although dose reduction and/or cycle delay were performed in 4 of these 12 patients. In 2 patients, this side-effect occurred only in the immediately subsequent course, in 5 patients it lasted for 2–4 consecutive courses, whereas in another 5 patients the problem occurred after several other cycles. In only 4/12 patients was there a worsening of this side-effect in subsequent courses.

Analysis of the correlation between occurrence of hand–foot syndrome and characteristics of the patients is presented in Table 2. Correlations were performed using chi-squared test. Analyses demonstrated a higher incidence of hand–foot syndrome in patients with a good performance status (62% (23/37); $P = 0.053$) and in those previously treated (88% (23/26); $P = 0.0003$), whereas no significant differences emerged with regard to age, sex, metastatic site and objective response to chemotherapy. Among the 23 pretreated pts who developed hand–foot syndrome, 19 pts had received first-line treatment with 5-FU alone or with biomodulators.

Overall, in 47 of the total 70 patients, chemotherapy was modified because of side-effects: in 15 pts it was delayed, in 11 patients the drug dose was reduced by 25–50%, in 21 pts both delay and dose reduction were performed. In 4 cases, chemotherapy was interrupted for toxicity: 3 patients suffered from diarrhoea grade 3 (2 cases) or grade 4 (1 case); 1 patient presented a severe hand–foot syndrome (grade 4).

Dose reduction, delay of planned chemotherapy course and both reduction plus delay according to the main observed toxicity are listed in Table 3. Only 5 patients out of the 36 (13.8%) suffering from hand–foot syndrome had their therapeutic programme altered for this toxicity (dose reduction in 2 pts, chemotherapy delay in 2 pts, both reduction and delay in 1 pt).

DISCUSSION

Although a survival benefit with 5-FU plus L-LV has not been confirmed by the meta-analysis of randomised studies,

an improvement in response rate has been demonstrated, and therefore this combination regimen plays an important role in symptom palliation [4]. Moreover, some clinical data support the view that response rate is associated with higher dose intensity of 5-FU [5, 6].

In a recent prospective randomised trial, the two most commonly used schedules of 5-FU plus L-LV (loading schedule daily for 5 days every 4–5 weeks versus weekly schedule for 6 weeks) have been compared: response rate and survival were equivalent, whereas regimens differed for toxicity patterns, with stomatitis being dose limiting in the loading schedule and diarrhoea more common in the weekly schedule [7]. Ardalan and associates [3] demonstrated that high doses of 5-FU and L-LV could be administered by shortly protracted infusion on a weekly basis, without notable toxicity. Significant antitumour activity has been reported even in patients who have failed other schedules of 5-FU.

Dermatitis has been reported during treatment with 5-FU and L-LV in 10–24% of patients [8, 9], but hand–foot syndrome seems to be mainly associated with continuous drug infusion, particularly with protracted infusion, and is the dose-limiting toxicity in the 12 weeks' schedule [10]. Moreover, a strong correlation between this toxicity and high doses of 5-FU has been postulated by some authors, on the basis of the incidence of hand–foot syndrome observed in high-dose, short-term, continuous 5-FU infusion studies [11, 12].

Treatment of hand–foot syndrome with topical or systemic anti-inflammatory agents did not produce any significant results; the role of vitamin B6 in the prevention or reversal of this side-effect deserves further investigation [13].

In our experience, hand–foot syndrome affected 51% of the patients. However, it was generally mild since in only one case was chemotherapy discontinued, and only a limited number of patients received dose reduction and/or treatment delay. Since it may require brief interruption of the infusion, early recognition and eventually dose adjustment are the simple therapeutic measures to undertake. It has been suggested as a skin cumulative effect of 5-FU, since hand–foot syndrome generally appears after a median number of nine courses, but a definite drug cumulative dosage was not identified. Probably, previous exposure to 5-FU-based chemotherapy enhances the probability of developing this particular dermatological toxicity. Although this side-effect appears very frequently, the impact on quality of life of patients and on the correct delivery of the planned therapy is limited [3], particularly in comparison to other 5-FU induced toxicities such as diarrhoea, stomatitis and myelosuppression, which can sometimes be life-threatening with different 5-FU plus L-LV schedules [14, 15].

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