The modulation of 5-FU with leucovorin (LV) and the potential synergism of 5-FU, etoposide and cisplatin make the combination of these four drugs (FLEP) an appealing one. In a preliminary report in 1989, Preusser and associates obtained a 57% response rate with this scheme in a series of 14 patients [5], so we decided to assess its efficacy.

From May 1989 to December 1992, 46 consecutive, previously untreated patients with unresectable measurable gastric carcinoma were treated with LV 300 mg/m^2, etoposide 100 mg/m^2, 5-FU 500 mg/m^2 and cisplatinum 30 mg/m^2 on days 1, 2 and 3 every 28 days. All courses were administered on an outpatient basis. All the patients were less than 70 years old, had a life expectancy of > 3 months and histologically confirmed gastric cancer. Table 1 shows the patients' characteristics.

A total of 169 cycles were administered to the 46 patients (median 3.6 per patient, range 1–6). 18 out of 46 patients (39%) obtained an objective response (95% confidence interval, 25–54%) and 2 a complete response (4%). The median duration of response was 5 months. The main side-effects were haematological and gastrointestinal; grade 3–4 toxicity was as follows: leucopenia in 9.5% of courses, anaemia in 3%, thrombocytopenia in 3%, nausea/vomiting in 4%, and diarrhoea in 5%. Hospitalisation, due to fever and neutropenia, was required in 5 patients, 3 of whom died of sepsis.

Our results indicate that the FLEP combination shows moderate activity, although with high toxicity. It should be noted that some of our patients' characteristics, such as the high percentage of a bad performance status (ECOG 2–3 in 85%) or distant metastases (87%) are adverse prognostic factors for response and survival [6, 7]. However, our results coincide with those of Preusser and colleagues who, after studying 29 patients, reported a lower response rate of 38% and high toxicity (one toxic death) [8].

The currently available data with the FLEP combination do not permit its recommendations for treatment of gastric carcinoma.

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Escalating Doses of Mitoxantrone With Granulocyte Colony-stimulating Factor (G-CSF) Rescue Plus 5-Fluorouracil and High-dose Levofolinic Acid in Metastatic Breast Cancer

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The combination of mitoxantrone (DHAD) plus levofolinic acid (1-FA) and 5-fluorouracil (5-FU) has been reported to be highly active (47.3% mean overall response rate) in metastatic breast carcinoma (MBC) with an excellent tolerance, as recently reviewed by Hainsworth [1]. In this paper, we report the results of a dose-finding study in which DHAD dosage, in combination with 1-FA/5-FU and granulocyte colony-stimulating factor (G-CSF) rescue, has been progressively increased up to the identification of the dose-limiting toxicity (DTL) and the maximum tolerated dose (MTD) in a series of patients with MBC. Analysis of dose intensity (DI) and objective response is also presented.

Standard eligibility criteria have been described elsewhere [2,3]. Chemotherapy consisted of 1-FA 100 mg/m^2 intravenous (i.v.) bolus and 5-FU 400 mg/m^2 over 15 min on days 1–3, plus DHAD on day 3 starting from 14 mg/m^2 cycle for the first group of 3 patients. DHAD dosage was then escalated by 2 mg/m^2 for subsequent groups of 3 patients until unacceptable toxicity was recorded. G-CSF 5 μg/kg/day was given subcutaneously (s.c.) for 10 days, starting at least 48 h after DHAD administration. WHO criteria were employed for definitions of both objective responses and toxicity. DLT was represented by any of the following side-effects occurring in at least 2 of the 3 patients entered at any given dose level: nadir absolute neutrophil count (ANC) <500/mm^3 for ≥5 days; grade 4 thrombocytopenia for ≥5 days; fever lasting >5 days requiring antibiotics; grade 3–4 extrahaematological toxicity; decrease in left ventricular efection fraction (LVEF) >15% from basal level; toxicity-related delay >8 days. The MTD of DHAD was established as the level below the dose at which DLT was seen.

There were 22 patients with a mean age of 54.4 years (range 36–68), and a mean Karnofsky index of 85 (range 70–100). There were 20 ductal infiltrating (91%), one lobular and one mixed ductal/lobular carcinomas; 12 patients (55%) were premenopausal, and 10 (45%) postmenopausal; basal oestrogen receptor (ER) status was positive in 8 patients (36%), negative

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Table 1. Toxicity pattern (WHO criteria) according to DHAD dosage escalation

DHAD dose (mg/m²)	Patient no.	Haematological						Gastrointestinal			Other
		WBC (grade)	ANC (grade)	Duration (days)	Fever	Ptl (grade)	Hb (grade)	Stomatitis (grade)	Diarrhoea (grade)	Vomit (grade)	
14	01	0	0	—	No	0	0	1	0	0	No
	*02	1	0	—	No	1	0	0	1	1	No
	03	1	1	—	No	0	1	2	0	0	Skin
16	04	1	2	—	No	0	0	0	0	1	Alopecia
	*05	1	2	—	No	0	0	1	0	0	No
	*06	2	3	4	Yes	1	1	1	1	1	No
18	07	2	3	—	No	0	0	0	0	0	No
	*08	3	4	5	No	1	1	2	1	2	Cardiac
	09	3	4	4	No	2	2	0	0	1	Alopecia
20	10	3	3	—	No	0	1	0	0	2	No
	11	2	3	—	No	2	1	0	1	0	Alopecia
	*12	4	4	6	Yes	2	0	2	2	1	Conjunctivitis
22	13	3	3	—	No	0	0	1	0	3	No
	14	3	4	5	No	2	1	0	1	1	Alopecia
	*15	4	4	7	Yes	1	1	3	2	2	TGO/TGP
24	16	3	4	5	No	2	1	0	1	1	Alopecia
	17	4	4	8	Yes	2	2	3	0	3	Alopecia
	18	3	4	5	No	0	1	1	1	2	Proctitis Cardiac
26	19	4	4	10	Yes	3	2	2	0	3	Alopecia
	20	4	4	8	No	1	2	1	0	1	No
	21	4	4	11	Yes	2	1	3	1	3	Alopecia

DHAD, mitoxantrone; WBC, white blood cells; ANC, absolute neutrophil count; Ptl, platelets; Hb, haemoglobins.

in 10 (45%) and unknown in 4 (18%). Pretreatments included surgery in 22 patients (100%), adjuvant radiotherapy in 4 (18%), adjuvant chemotherapy in 22 (100%) (18 CMF and 4 FEC) and adjuvant tamoxifen in 10 (45%). Sites of disease were node 8 (36%), liver 4 (18%), bone 12 (54%), lung 3 (14%), pleura 3 (14%), controlateral breast 1 (5%) and skin 2 (9%). All patients had normal LVEF evaluated by ecocardiography, were at their first metastatic relapse and had measurable and/or evaluable disease according to WHO criteria [4].

One patient was not evaluable because of refusal to continue chemotherapy after day 1 of the first cycle. No chemotherapy-related deaths were observed. The DLT of DHAD was myelosuppression. In fact, at 26 mg/m², all patients experienced grade 4 neutropenia lasting >5 days, 1 patient had grade 3 thrombocytopenia and 2 had grade 2 anaemia. The ANC decreased as the DHAD dosage increased, with a statistically significant linear correlation between the two variables ($r = -0.817$; $P = 0.025$). A similar but stronger relationship was observed between DHAD levels and total white blood cell count (WBC) ($r = -0.936$; $P = 0.002$), and duration of leucopenia ($r = 0.732$; $P = 0.011$), but hospitalisation due to fever and cytopenia was required in only 3 patients. A low statistically significant correlation was also found between DHAD dosage and thrombocytopenia ($r = 0.526$; $P = 0.014$) and anaemia ($r = 0.540$; $P = 0.012$). Although no correlation was seen between DHAD dosage and the occurrence of stomatitis or diarrhoea, vomiting ≥ grade 2 was associated with higher doses of DHAD ($r = 0.620$; $P = 0.003$). Alopecia ≥ grade 2 was recorded in 8 patients (38%) : 5 cases had received more than 20 mg/m² of DHAD. Cardiac toxicity was recorded in 2 patients: the first patient had sinus tachycardia >110 at rest after four cycles, which returned to normal after 4 days, and the second was a 52-year-old female, previously untreated with antracyclines, who developed a 20% fall in LVEF after six cycles for a cumulative DHAD dose of 140 mg/m².

Table 2. Dose intensity according to DHAD dosage esaclation

DHAD dose (mg/m²)	Planned dose intensity (mg/m²/week)	Received dose intensity (mg/m²/week)	Mean no. of cycles	Cumulative dose delivered (mg/m²)
14	4.67	4.60 (98.5%)	5.3	72.7
16	5.33	5.10 (95.8%)	5.0	80.0
18	6.00	5.58 (93.1%)	6.0	92.0
20	6.67	5.65 (84.7%)	5.3	98.0
22	7.33	6.92 (90.3%)	5.0	115.0
24	8.00	7.10 (88.7%)	6.0	135.0
26	8.67	6.58 (75.9%)	4.7	105.0

The MTD of DHAD in combination with 1FA/5-FU was 24 mg/m². However, patients 12 and 15 showed grade 4 neutropenia with fever lasting >5 days at lower dosages. When the toxicity profile was analysed according to the presence of bone metastases as predominant site of disease, it became evident that DHAD could not be safely increased over 22 mg/m² in patients with predominant bone metastatic sites.

Received DI, programmed DI, mean number of cycles and cumulative dose delivered, calculated accordingly to Hryniuk and colleagues [5], are shown in Tables 1 and 2. While at the

14–18-mg/m^2 dose levels, the received DI was higher than 90% of the programmed DI, at higher dosages, the received DI progressively decreased reaching 75.9% for DHAD 26 mg/m^2. Moreover, while at lower DHAD dosages (14–18 mg/m^2), the haematological side-effects were generally recorded after the third cycle, at higher dosages, haematological toxicity was recorded much earlier. In fact, at the dosage of 26 mg/m^2 prolonged grade 4 neutropenia was observed before the third cycles in all patients.

The overall response rate was 62% [95% confidence interval (CI) 41–83%; 13/21 patients], with 3 patients showing a complete response (CR) (14%; 95% CI 6.4–21.6%) with a mean duration of 10.6+ months (9.2+, 10+, 12.6+), and 10 a partial response (PR) (48%; 95% CI 36–59%) with a mean duration of 9.8+ months (4.0+/13.4). Among non-responding patients 4 had no change (NC) (19%) and 4 progressed (19%). CRs were recorded at node, bone and skin metastatic deposits. The median overall survival was not reached after a mean follow-up of 14 months.

In conclusion, the DLT of DHAD in combination with 3-day 1FA and bolus 5-FU is myelotoxicity. The MTD of DHAD is 24 mg/m^2, unless predominant bone metastatic disease is present. These results further demonstrate that G-CSF bone marrow rescue may allow oncologists to safely increase the dosage of DHAD far above the conventional dose even in combination with 1FA/5FU. The 62% overall response rate, with a 14% complete response rate, achieved in this study is comparable to that reported in other trials employing the combination of DHAD with FA and 5-FU both as bolus [1,3] or continuous venous infusion [2]. Whether higher doses of DHAD are associated with an increase in both rate and duration of objective tumour regressions with a survival benefit for metastatic patients cannot be concluded from this paper. This issue can be precisely defined only in prospective studies comparing this combination to standard first-line regimens.

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