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Short communication

Phase II trial with high-dose ifosfamide and mesna given in a 24-h infusion for advanced GI tract cancer

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Summary. In all, 26 patients with advanced GI tract cancer (among whom 23 had liver metastases) were treated in a phase II trial with a 24-h infusion of high-dose ifosfamide and mesna (5 g/m^2). Two PR, 1 CR and 4 NC were evidenced among 23 patients evaluable for response. The toxicity was significant and mainly expressed in the hair, digestive tract, granulocytes and CNS. One patient died from CNS and kidney toxicities. Only patients with good clinical indices, normal serum albumin and creatinine levels and without pelvic involvement seemed to be candidates to benefit from the treatment.

Introduction

Ifosfamide (IFO) (with or without urothelial antidote) has been used for treating digestive cancers, mainly colorectal and pancreatic, since 1971 [1, 2]. A compilation of published series suggests significant antitumor activity of the drug in pancreatic cancer and marginal activity in colorectal cancer (< 10% tumor responses [1–4]). Most of these results were obtained with a fractionated schedule of administration for IFO [1, 2]. We report on the activity and toxicity of IFO in a phase II trial in which the drug was given in a 24-h infusion with its urothelial antidote, mesna, for the treatment of advanced GI tract cancers.

Material and methods

Characteristics of the 26 patients included in the study are summarized in Table 1. Seven patients had received previous chemotherapy, mainly consisting of 5-fluorouracil (5FU) alone or in combination e.g., with methotrexate in the fractionated administration (FAM) regimen, as either adjuvant treatment (two cases had been off treatment for 5 and 7 years), palliative treatment (four cases: two partial responses off treatment at the time of inclusion in the study and two progressions), or adjuvant and palliative treatment (one case had undergone adjuvant chemotherapy 10 years before, and had progressive disease at the time of inclusion in the study after a partial response under 5FUdR intraarterial continuous chemotherapy). After prehydration with 1 dextrose-saline, from 0–24 h the patients received both ifosfamide and mesna at a dose of 5 g/m^2 by continuous infusion in a large volume of fluid (at least 3 l dextrose-saline). Mesna was also given at a dose of 1 g/m^2 as an i.v. bolus at 0 h; 2.5 g/m^2 were also infused from 24 h to 32–36 h in 1 l dextrose-saline. Cycles were repeated every 3 weeks or according to tolerance. Evaluation of tumoral responses and toxicities as well as survival duration was carried out by the usual methodology (UICC-WHO criteria; Kaplan-Meier and log-rank tests).

Results

Due to 3 early deaths (1 toxic, 1 suicide, 1 unknown reason), 23 patients were evaluable for response and 24 for toxicity. There were two partial responses (PR) (in one pancreatic and one colorectal tumor; duration, 3+ and 6 months, respectively), one complete response (CR) (colorectal cancer; duration, 26+ months), and four stabilizations (NC) (two pancreatic and two colorectal tumors)

Table 1. Patient characteristics

Included in the study		26
Evaluable[a]	for toxicity	24
	for response	23
Sex ratio (M/F)		19/7
Median age (range) in years		66 (33–77)
Median Karnofsky index (range)		75 (40–100)
Previous therapy:	Surgery[b]	21
	Chemotherapy[c]	7
	Radiotherapy	2
Primary tumor:	Colorectal	17
	Pancreas	8
	Stomach	1
Target lesions:	Liver	23
	Primary (pancreas)	8
	Lung	5
	Abdominal mass	5
	Bone	2
	Spleen	1
	Inguinal nodes	1
Median number of courses (range)		3 (1–10)

[a] There were 3 early deaths: toxic, 1; suicide, 1; unknown reason, 1
[b] No surgery was done in 3 pancreas and 2 colorectal cancer patients
[c] Adjuvant, 3; palliative, 4; adjuvant and palliative, 1

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Table 2. Patient characteristics and response to chemotherapy

	Progressors and early deaths (19)	Nonprogressors (7)	*P*
Median age (range) in years	65 (39–77)	70 (43–76)	NS
Sex ratio (M/F)	14/5	5/2	NS
Previous chemotherapy (Yes/No)	5/14	2/5	NS
Karnofsky index			
mean ± SD	71.2 ± 17.3	88.6 ± 16.8	0.05
median (range)	70 (40–100)	100 (60–100)	0.05
Stage M1 (Yes/No)	18/1	6/1	NS
Target:			
Primary pancreas	5	3	NS
Liver	18	5	NS
Other	10	4	NS

NS, not significant

Table 3. Toxicity in 24 cases (in %)

Type WHO grade	1	2	3	4	1–4
Alopecia	2	9	7	3	21 (87.5)
Nausea/vomiting	5	8	4	–	17 (70.8)
WBC	4	8	1	4	19 (79.2)
Hemoglobin	8	2	1	1[a]	12[b] (50)
Platelets	–	–	2	–	2 (8.3)
Neutropenic fever	–	–	2	1	3 (12.5)
Urothelial/renal	3	–	1[c]	1[d]	5 (20.8)
CNS	1	–	–	2[d]	3 (12.5)
Constipation/diarrhea	2	–	–	–	2 (8.3)
Nonneutropenic fever	1	–	–	–	1 (4.2)
Cardiac arrhythmia	–	1	–	–	1 (4.2)
Hepatic	1[e]	1[e]	–	–	2 (8.3)

[a] Digestive bleeding (stomach ulcer)
[b] Transfusions required in five cases
[c] Transient oligoanuria
[d] One toxic death
[e] Hepatic metastasis also involved

among the 23 patients evaluable for response. Both patients undergoing remissions of colon carcinoma had received effective prior chemotherapy with 5FU.

The median survival time (MST) of the whole group remained short (3.2 months); the MST of progressors was significantly shorter than that of nonprogressors (MST not attained at 26+ months for CR, PR, and NC patients VS MST of only 2 months for progressors; $P<0.001$). Table 2 shows that the only prognostic determinant differing between progressors and nonprogressors was the Karnofsky index, which was significantly higher in patients who underwent some tumor shrinkage.

Toxicity (Table 3) was significant, mainly obvious in the hair (almost 100% alopecia), digestive tract, and WBCs (five cases of grade 3–4 granulocytopenia with three neutropenic fevers). Two patients developed grade 4 CNS toxicity: both presented with pelvic masses and low Karnofsky indices (40 and 50); moreover, one had low serum albumin levels (30 g%) and the other had upper-limit serum creatinine levels. One of these patients, who did not previously receive oncolytic drugs, died of CNS and kidney toxicities. Other side effects are described in Table 3.

Discussion

In this phase II trial, IFO (with mesna) given as a 24-h infusion to a group of patients with GI tract cancer (mainly as first-line chemotherapy) induced two PRs and one CR among 23 evaluable cases. The results obtained do not appear to be superior to those previously obtained by either 5FU alone [6] or fractionated IFO administration [1]. Due to its significant CNS toxicity, this type of treatment should only be offered to pauci-symptomatic patients with good performance status and normal serum albumin and creatinine levels and without important pelvic involvement [5]. The clinical toxicity and difficulty of administration to hospitalized patients will restrict further development of such approaches.

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