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Ambulatory treatment with 5 days continuous venous infusion of ifosfamide for advanced colorectal cancer: a phase II feasibility study

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Eighteen patients suffering from an advanced colorectal cancer were treated with 5 days continuous venous infusion of ifosfamide and mesna (1 g/m^2, 5/21 days). All had previously received 5-fluorouracil-based chemotherapies. Disposable programmable infusion pumps (Cadd-I, Pharmacia Deltec and Intelliject Multisyringe) allowed ambulatory administration of the treatment. Toxicity was manageable; we had mainly to deplore two cases of grade 3 central nervous system manifestations. Only one minor response (lung lesions) and one no change were evidenced. We conclude that for this type of patient, ifosfamide has very limited antitumor activity. Nevertheless, we demonstrated the safety and feasibility of the proposed ambulatory schedule which could be used in other oncological indications.

Key words: Colorectal cancer, continuous venous infusion, 5-fluorouracil, ifosfamide.

Introduction

Ifosfamide (IFO), like cyclophosphamide, is a prodrug requiring *in vivo* activation by the hepatic cytochrome P450 mixed-function oxidase enzymes to exert cytotoxic activity.[1] Near 100% bioavailability was achieved by oral, intravenous (i.v.) or even subcutaneous administration.[2–4] The area under the curve (AUC) increased in a linear fashion with increasing doses (up to 5 g/m^2) after both oral or i.v. IFO administration. If early studies suggested that IFO pharmacokinetics could be both dose and schedule dependent,[1–5] more recent investigations on IFO elimination[2,6–8] refuted these findings; no evidence of saturation kinetics was demonstrated even after high doses.

IFO has demonstrated an increased therapeutic index in a variety of solid tumors when compared with its parent compound, cyclophosphamide.[9–13] The concomitant use of mesna (MSN) as a urothelial antidote has provided safe clinical administration of IFO.[14–16] Due to its pharmacokinetics and its clinical toxicity profiles, IFO has been classically administered by fractionated daily doses over 5 days.[17,19]

More recently, continuous venous infusion (CVI) schedules for 1–5 days have been developed.[9,12,18,20,21] This type of administration, in combination with the uroprotective agent MSN, allowed an improved therapeutic:toxic ratio, in various studies.[14,16,17,20] Up to now, IFO-CVI has been limited to in-patient use only, because long-term stability data on IFO solution as a single drug or as an admixture with other cytotoxic agents or MSN were not available. More recently, studies on the stability of IFO in aqueous solution alone or with other compounds (as MSN and other antineoplastic drugs) at various temperatures, in daylight or in a dark environment, were performed.[22–24] IFO in solution was proven to remain stable for prolonged periods of time (up to 4 weeks) even when it was tested in admixture with MSN.[22–24] Therefore, the out-patient administration with the use of external devices became an attractive treatment alternative.

5-Fluorouracil (5-FU)-based chemotherapies have remained the therapeutic keystone in advanced colorectal cancer.[25] IFO has achieved limited antitumor activity in colorectal cancers, either in fractionated administration or in 24 h infusion (< 10% responses in a compilation of 130 cases).[26] However, in 17 such patients treated with 24 h CVI of IFO at a dose of 5 g/m^2, we recorded one complete response (bone lesion), one partial response (liver metastases) and two minor responses.[21] Those patients had been treated as in-hospital patients.[21]

We proposed to study the administration of IFO (with MSN) at a similar dosage but in a more

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prolonged protracted infusion for 5 days to out-patients suffering from advanced colorectal cancer.

Material and methods

The trial was conducted in accordance with the principles of the Helsinki declaration and after approval by the local ethical medical committee.

After adequate staging [including general biology with tumor markers, CEA and Ca 19.9, chest X-rays, bone scan and X-ray surveys of suspicious areas, recto-colonoscopy and computed tomodensitometry (CT) of measurable lesions] and informed consent, patients were included in this phase II trial.

All patients were required to have a subcutaneous venous access port system implanted (Port-a-cath, Pharmacia Deltec). The port system was accessed using a 90° angle needle (Huber) attached to a short venous line connected to the pump reservoirs.

Patients received IFO and MSN as a CVI at a daily dose of 1 g/m^2 for 5 days. In order to reduce the volumes of infusion as much as possible, according to recommended drug concentrations, the concentrations were adjusted to a maximum of 40 mg/ml for MSN and of 50 mg/ml for IFO.[22,24]

Two types of disposable infusion pumps were used: the CADD-I Pharmacia Deltec digital programmable pump containing a fluid volume reservoir of 100 ml (12 patients) and the Intelliject multisyringe programmable in-time device equiped with four 30 ml syringes (six patients). With the CADD-I pump, both drugs were administered in admixture while IFO and MSN were solved in separate syringes with the Intelliject material. Both drugs were infused at a constant rate over the 120 h period. Reservoirs or syringes were refilled every other day (CADD-I pump) or daily (Intelliject pump).

Courses were repeated every 3 weeks. Toxicity and efficacy of the treatment were recorded according to WHO and UICC recommendations.[27,28] To be fully evaluable with regard to tumor response, patients had to receive at least two courses of chemotherapy. The Kaplan–Meyer estimate was used to calculate median survival time.[29]

Results

The characteristics of the 18 patients included in the trial are presented in Table 1. All patients had received previous 5-FU-based chemotherapy either for adjuvant and/or advanced disease. All patients had good performance status at the time of inclusion and all had well measurable disease as evidenced by CT evaluations. The main targets were the liver, lungs and loco-regional recurrences.

Table 1. Patients characteristics (n = 18)

Sex ratio M/F	11/7
Age	
median	59
range	44–78
Primary tumor	
colon/rectum	12/6
Previous chemotherapy	
adjuvant	4
advanced	17
Previous radiotherapy	5
ECOG	
0/1	3/8
2	7
Target lesions	
loco-regional	5
lung	9
liver	14
bone	2
lymph node	2
other	1
Number of sites	
median	2
range	1–3

Fifty-one courses were evaluated; patients received a mean of 2.8 (±2.1) courses (range 1–7). The clinical toxicity was tolerable (Table 2). However, two cases of grade 3 central nervous system (CNS) manifestations precluded any additional use of the drugs after one course. No dose reduction was applied in the 15 other cases; IFO (and MSN) doses could be increased to 1.2 g/m^2/day in six cases and to 1.4 g/m^2/day in two cases without any further clinical toxicity.

Table 2. Maximal toxicity per patient (WHO grades) (n = 18)

	Grade 1	Grade 2	Grade 3
Hemoglobin	2	1	2
WBC	2	1	2
Granulocytes	1	2	0
Platelets	0	0	0
Nausea–vomiting	1	2	1
Alopecia	3	1	3
CNS	–	–	2
Urothelial[a]	2	–	–
Diarrhea	1	–	1
Stomatitis	1	1	–
Herpes zoster	1	–	–

[a] Including one microscopic hematuria and one dysuria.

All patients were treated in an ambulatory fashion. No complication related to the Port-a-cath venous access or to the programmable devices was registered.

With regard to tumor evolution, one minor response (lung lesions) and one no change (soft tissue metastase) were recorded. Median survival time of the whole group was 86 days.

Discussion

This phase II trial has demonstrated the feasibility of safe ambulatory CVI adminstration of IFO and MSN with programmable pumps.

The toxicity of the treatment at the doses proposed was acceptable. However, two grade III CNS manifestations were recorded. CNS toxicity has been previously reported with IFO use especially with the 24 h CVI infusion.[13,19,21,30] These events were mainly described in subjects with low albumin levels, impaired creatinine clearance and massive pelvic involvement.[15,19,21,30] One of our patients had massive liver involvement, while the other one had previously received a platinum derivative (oxaliplatinum) and had pathologic abdominal lymph nodes. According to a literature survey, none of those clinical conditions could predict for these neurological toxic effects. Indeed, the risk of such undesirable events would be reduced by protracted infusion of IFO.[13,19,30,31] Moreover, according to most authors, the prolonged CVI of drugs for 5 days or more permits an increase in the daily dose from 1–1.2 to up to 3.5 g/m^2 without any further increase in digestive, hematological or even neurological toxicity.[13] Thus, six of our patients tolerated a daily dose increased to 1.2–1.4 g/m^2 without any further clinical side-effects; it is clear that according to our limited experience, daily IFO and MSN doses may be pushed over 1.4 g/m^2/day.

Contrary to usual recommendation rules, administration of the urothelial protective agent MSN was stopped in this trial at the same time as that of IFO. Usually most authors recommend continuing MSN for 8–12 h after IFO withdrawal.[13–16,19,30] At the doses of drugs we used, prolongation of MSN exposure does not seem to be mandatory as only one case of microscopic hematuria was recorded. As a consequence, patients enjoyed a better compliance due to the shorter ambulatory delivery schedule.

Unfortunately we had to stop the trial prematurely due to the lack of significant antitumor effect. By giving IFO for 5 days CVI, we anticipated to obtain a better therapeutic index than that observed with the previously tested 24 h CVI schedule.[21] Indeed, we hoped not only to reduce clinical toxicity while maintaining the patients in their home environment and providing an improved overall quality of life, but also to augment the chance of attaining tumor responses from the more prolonged exposition of tumor cells known to exhibit poor division activity.[25] The first aim has been achieved as the feasibility and tolerance of the therapeutic program has been evidenced. The lack of significant tumor response could be both related to the poor intrinsic efficacy of IFO against colorectal cancers and also to the selection of poor prognosis patients as they were all previously treated with 5-FU-based chemotherapies and were most often suffering from multiple targets lesions. Furthermore, although steady-state plasma concentrations of IFO are reproducible within the same patient, considerable interpatient variations have been observed.[32] These variations reflect differences between patients in the volume of distribution of IFO, rather than differences in drug clearances.[6,32] Nevertheless, such differences may prevent the achievement of a sufficient drug concentration at the cellular level despite the linear relationship between drug doses and AUC already mentioned.[1–8]

The question to evaluate the antitumor efficacy of IFO at higher dosages in more favorable patients may be asked; however, this information would probably lack any real meaning, since we have now been able to induce reproducibly tumor response rates above 50% with safe ambulatory schedules of chronomodulated combination chemotherapy including 5-FU, folinic acid and platinum derivatives, and this without important clinical side-effects or without distressing alopecia.[33–35]

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