An original administration of ifosfamide given once every other week: a clinical and pharmacological study

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Ifosfamide (IFOS) is a bifunctional alkylator with a wide spectrum of activity in solid tumors and has an autoinductive liver metabolism through P450 cytochromes. Autoinduction might permit a better therapeutic index for combination therapy. A phase I trial was investigated with interpatient dose escalation of a single dose of IFOS given every 2 weeks in advanced solid tumor patients. IFOS, its dechloroethylated and active 4-hydroxy metabolites, were measured at cycles 1 and 2 at the end of infusion, 2 and 5 h later, using gas chromatography. IFOS elimination was considered as following monocompartimental model kinetics. The results of 20 patients from January 2004 to June 2006 were included. The median of previous chemotherapies was 2 (0–5). The primary tumor was most often ovarian (5), peritoneal (3), sarcoma (2), melanoma (2) or miscellaneous (8). Ten patients received 2.5 g/m^2 and the other 10 patients received 3 g/m^2. A total of 79 cycles were evaluable for toxicity. The median number of cycles was 4 (1–8). No grade 3–4 toxicity, no alopecia at first dose level and no toxicity-related fatal events were noted. One objective response was noted in a pancreatic cancer patient and one sustained CA125 decline in a heavily pretreated ovarian cancer patient. A slight (7–10%) but reproducible decrease of areas under the curve was detectable at cycle 2, at both dose levels, related to autoinductive metabolism. Intraindividual variations (large SD) were noticed for each pharmacokinetic parameter. A patient-dependent autoinduction of IFOS metabolism was detected rather than a slight nondose-dependent autoinduction. The toxicity profile allows the development of bi-weekly IFOS-based combination therapies. *Anti-Cancer Drugs* 19:295–302

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Introduction

The alkylating agent, oxazaphosphorine ifosfamide (IFOS), has demonstrated clinical activity against a wide range of adult tumors, such as soft tissue sarcomas [1], lung [2,3], breast [4], ovarian [5] and testicular cancers [6]. The acute dose-limiting toxicity is shared with other alkylating agents and is myelosuppression. This acute toxicity at conventional or high-dose IFOS has led to the development of IFOS regimens, usually as a single agent. Other clinical toxicities are alopecia and nausea. The hemorrhagic cystitis is specific to the oxazaphosphorines and is prevented by the concomitant use of the uroprotective agent mesna (2-mercaptoethane-sulfonate sodium). Neurologic and nephrologic toxicities are the limiting toxicities with high doses of IFOS [7]. The metabolism of IFOS requires a minor activation pathway (4-hydroxylation) and a mainly toxification pathway (*N*-dechloroethylation), and there remains uncertainty as to the optimal intravenous schedule [8]. IFOS is a prodrug, metabolized *in vivo* to produce a variety of active and potentially toxic metabolites. The bioactivation is mediated by a cytochrome P450 enzyme (CYP3A4) [9] and results in hydroxylation at the carbon-4 position of the oxazaphosphorine ring (Fig. 1). This 4-hydroxy-ifosfamide (4-OH-IFOS) is unstable and exists in equilibrium with its tautomeric form aldo-ifosfamide (aldo-IFOS). Aldo-IFOS decomposes spontaneously to form the alkylating agent isophosphoramide mustard and acrolein. The active alkylating metabolite of IFOS is isophosphoramide mustard which is able to induce DNA crosslinks. Acrolein is responsible for the urotoxic effects of IFOS. Alternatively, aldo-IFOS can be oxidized by an aldehydedehydrogenase enzyme to carboxy-IFOS (CX), which is an inactive metabolite. Approximately, half of the dose of IFOS undergoes oxydative *N*-dealkylation to produce inactive metabolites: 2-dechloroethyl-IFOS and 3-dechloroethyl-IFOS (2-DCI and 3-DCI, respectively) with renal elimination [10]. Another metabolite, chloro-acetaldehyde, is formed during these reactions and this toxic metabolite is implicated in the neurotoxicity and furthermore in nephrotoxicity. Oxydation of 4-OH-IFOS results in another inactive metabolite which is 4-keto-IFOS (KETO). IFOS is able to increase activity of cytochrome P450 and therefore to induce its own

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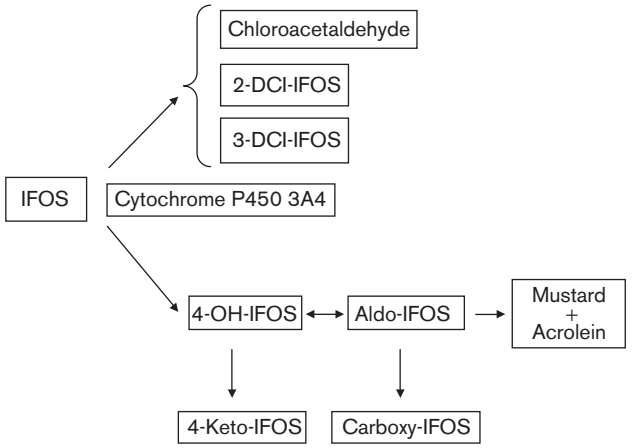
Fig. 1



Metabolism of ifosfamide.

metabolism [11]. This process appears during the 24 h after the first injection provided that the concentrations of the systemic circulation are elevated enough (corresponding at initial dose more than 1.5 g/m^2 administered in 2-h infusion) [12,13]. Optimal conditions of administration of IFOS have not been defined despite the use for nearly three decades. Fractionated infusion for several consecutive days is the standard treatment modality, which is not easily compatible with combination chemotherapy. The number of days and the length of perfusion, however, are not exactly defined. The difficulty in establishing the optimal schedule of administration is the fact of the high complexity of IFOS metabolism [14]. We evaluated a new schedule of administration in an attempt to take advantage of the autoinductive metabolism of IFOS to improve its therapeutic index. A secondary objective was to develop a schedule allowing combination chemotherapy and a dose-dense schedule of IFOS.

Patients

Patient eligibility

The inclusion criteria were those commonly used for phase I clinical trials. Patients with histological or cytological proof of solid tumors refractory to prior therapy or for whom no standard therapy exists were eligible and enrolled in the study. Other eligibility criteria included age $\geq$ 18 years, Eastern Cooperative Oncology Group performance status of 2 or less, life expectancy of more than 2 months, clinically or radiologically assessable disease, effective contraception during the study, adequate renal (clearance of creatinine evaluated by Cockroft formula $\geq$ 50 ml/min), hepatic (serum bilirubin at least $< 1.5\times$ the upper normal limit, hepatic transaminases ≤ 3 times upper normal limit) and hematological functions (absolute neutrophil count $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l). Exclusion criteria were progressive disease under IFOS, concomitant therapy by corticosteroids started less than 2 weeks before initiating IFOS, use of corticosteroid like antiemetic regimen before IFOS perfusion, concomitant therapy being able to modify activity of CYP3A4, prior history of hemorrhagic cystitis, pregnant or lactating women and patients with severe clinically and uncontrolled relevant systemic disease. All patients signed an informed consent before the beginning of treatment or of other procedures related with the schedule.

Treatment plan

IFOS (Baxter Oncology, Halle, Germany) was given as a 2-h infusion in 500 ml 5% dextrose. IFOS was administered at initial dose of 2.5 g/m^2 every 2 weeks. Prophylactic antiemeting used setron (Zophren) 8 mg. Oral mesna, used as uroprotector, was given each day at the beginning, the end of IFOS infusion and 4 h post-IFOS. The initial dose represented 2/3 of total IFOS dose. Pre-hydratation consisted of 1000 ml NaCl 0.04%/dextrose 5%/KCl 4% and was given 30 min before of the beginning of IFOS perfusion and during 3 h. The concomitant administration of prophylactic granulocyte colony-stimulating factor, prophylactic antibiotherapy, antitemporal catatonic treatment and all treatment which changed the activity of cytochrome P450 enzyme (CYP3A4) was not authorized. The treatment was stopped in case of tumor progression or severe toxicity despite dose reduction. In case of lack of induction without severe adverse events in the first patients, we proposed to increase dose of IFOS at 3.0 g/m^2 every 2 weeks.

Patient evaluation, evaluation of toxicity and dose modifications

A complete medical history and physical examination were completed in the 21 days before registration. Before the first cycle (minimum 5 days) and each course, the physical examination was repeated, and hematology and serum chemistry were checked. All toxicities were graded according to the Common Toxicity Criteria. Dose-limiting toxicity (DLT) was defined as any grade 4 neutropenia lasting longer than 7 days, any grade 3/4 neutropenia accompanied by fever ($\geq 38.5^\circ$C) and/or infection, any grade 4 thrombocytopenia or grade 3 thrombocytopenia associated bleeding and any grade 3 or grade 4 nonhematologic toxicity (except alopecia, and nausea and vomiting). At retreatment, minimal values for neutrophils had to be $\geq 1.0 \times 10^9$/l and for platelets $\geq 80 \times 10^9$/l. The treatment was administered if no toxicity grade greater than 1 persisted (except grade 2 anemia and grade 3 alopecia); otherwise, the next course was delayed by 1 week. The dose at the next cycle was reduced to 25% if the patient presented DLT or the cycle was delayed by 1 week. The patient went off-study for toxicity if the treatment was not administrated after 35 days.

Assessment of response

Although assessment of the antitumor activity was not a primary objective of the study, tumor evaluations were performed by computed tomography scan after completion of the courses. Patients were evaluated according to the RECIST criteria.

Pharmacologic studies and analysis

Blood samples were collected at the end of the infusion and 2 and 5 h later. About 1 ml of blood was dropped in special tubes, containing the trapping agent, prepared as previously described. This was used to stabilize the 4-OH-IFOS. Tubes were weighted before sampling and after the blood collection. The difference gave the exact volume withdrawn.

A gas chromatography method with a natrium phosphorus detector was used to calculate the levels of the parent compound and of its metabolites [15]. Calibration curves were obtained by nonweighted least-squares linear regression analysis of each investigated compound/internal standard versus the concentration. Calibration curve equations were used to calculate the concentrations of IFOS, 2-DCI-IFOS, 3-DCI-IFOS and 4-OH-IFOS.

Pharmacokinetic parameters were determined by the Win Nonlin (Pharsight, Mountain View, California, USA) program for the two consecutive courses (C1 and C2). Elimination of the parent compound was considered as a first-order elimination rate after the intravenous infusion. The areas under the curve (AUCs) for IFOS and the metabolites were estimated by the linear trapezoidal rule for the IFOS/metabolites ratios between the beginning and 5 h after the end of the infusion. Extrapolated AUC were used only for the kinetic parameters determination.

Nine patients were included in each series (2.5 and 3.0 g/m^2). Nevertheless, eight of them were evaluable for pharmacokinetic studies.

Objectives of study

The primary objective of this study was to define the proportion of patients associated to induction after IFOS administration every 2 weeks. The secondary objectives were the evaluation of the pharmacokinetics of IFOS and its metabolites after administration every 2 weeks, the toxicity profile of IFOS administered every 2 weeks with doses of 2.5 or 3.0 g/m^2, the possibility to define individual doses of IFOS after the third injection, using the data of autoinduction and, finally, the detection of antitumoral activity.

Results

Patient characteristics

Between January 2003 and July 2006, a total of 20 patients were included in the study. Patient characteristics are presented in Table 1. Ten female and 10 male patients were present, 16 patients had a performance status of 0–1 and four patients had a performance status of 2. The median age of the patients was 61 years (range: 39–78). The most commonly treated tumors were ovarian ($n = 5$), peritoneum ($n = 3$), digestive ($n = 3$), melanoma ($n = 2$) and sarcoma ($n = 2$). Two patients had no prior treatment and the other patients received 2–5 prior chemotherapy regimens. One patient received a prior chemotherapy with IFOS.

Table 1 Patient characteristics

	No.
Total	20
Male/female	10/10
Age and median age	61 (39–78)
Performance status at baseline	
0	0
1	16
2	4
Malignancy type	
Sarcoma	2
Digestive	3
Ovarian	5
Peritoneum	3
Melanoma	2
Renal	1
Lung	1
Other	3
No. of metastatic site	
0	6
1	5
2	7
>3	2
No. of prior chemotherapy regimens	
0	2
1	0
2	10
3	5
4	3
>4	1

Ten patients received IFOS at the dose of 2.5 mg/m^2 and 10 patients at the dose of 3.0 mg/m^2.

A total of 79 valuable cycles of IFOS every 2 weeks was administered. The median number of cycles per patient was four with a range of 1–8. One patient received eight cycles. Two patients went off-study after one course because of progression or fatal evolution.

Adverse events

All patients were evaluable for toxicity. The main adverse events are presented in Table 2.

Hematological toxicity

No thrombocytopenia was noted; grade 2 anemia and grade 2 neutropenia were observed, respectively, in one case.

Nonhematological toxicity

The main toxicities encountered with IFOS every 2 weeks were nonhematological. No drug-related severe

Table 2 Adverse events

	2.5 g/m^2(n=10)	3.0 g/m^2(n=10)
Hematological toxicities		
Neutropenia		
Grade 1–2	1 (5%)	1 (5%)
Grade 3–4	0	0
Thrombocytopenia		
Grade 1–2	0	0
Grade 3–4	0	0
Anemia		
Grade 1–2	1 (5%)	0
Grade 3–4	0	0
Nonhematological toxicities		
Nausea		
Grade 1–2	6 (30%)	4 (20%)
Grade 3–4	0	0
Vomiting		
Grade 1–2	1 (5%)	0
Grade 3–4	0	0
Mucitis		
Grade 1–2	2 (10%)	1 (5%)
Grade 3–4	0	0
Alopecia		
Grade 1–2	0	2 (10%)
Grade 3–4	0	0
Fatigue		
Grade 1–2	3 (15%)	3 (15%)
Grade 3–4	0	0
Diarrhea		
Grade 1–2	0	0
Grade 3–4	0	0

($\geq$ grade 3) event was observed. The main events related were not severe (grade ≤ 2) and included nausea (50%), vomiting (5%), mucositis (15%), alopecia (10%) and fatigue (30%).

No neurologic toxicity was noticed. No cystitis was noted. No difference in toxicity profile was observed between the two doses of IFOS (2.5 vs. 3.0 mg/m^2), except for alopecia. No reduction of IFOS dose was necessary and no cycle was delayed for toxicity reasons.

Antitumoral activity

All patients were evaluable for response. No complete response was observed. Two patients achieved a partial response (after two and four cycles, respectively) at the dose of 3.0 mg/m^2, eight patients had stable disease (five at 2.5 mg/m^2 and three at 3.0 mg/m^2) and nine patients had disease progression at first evaluation. One patient had stable disease after four cycles and showed disease progression after eight cycles. Tables 3 and 4 outlines response rates for the two subsets of patients.

Pharmacokinetics

Two patients (one at 2.5 g/m^2 and one at 3.0 g/m^2) were not evaluable for pharmacokinetics analysis. The second course was not performed because of fatal evolution in one patient and because of evidence of disease progression for the second one. As previously reported, a large interpatient variability was found. Therefore, results were presented using median value with the 25th and 75th quartile for a general observation and individually for the

Table 3 Antitumoral activity

Malignancy types	No.	Partial response	Stable disease	Progressive disease
Sarcoma	2		1	1
Digestive	3	1	1	1
Ovarian	5		1	4
Peritoneum	3	1		2
Melanoma	2			2
Renal	1		1	
Lung	1			1
Other	3		2	1
Total	20 (100%)	2 (10%)	6 (30%)	12 (60%)

Table 4 Antitumoral activity

	2.5 g/m^2	3.0 g/m^2
Complete response	0	0
Partial response	0	2 (20%)
Stable disease	5 (50%)	3 (30%)
Progressive disease	5 (50%)	5 (50%)
Total	10	10

inducting process. IFOS and its metabolites were detectable in samples from all investigated patients during IFOS administration using the quantitative gas chromatography method.

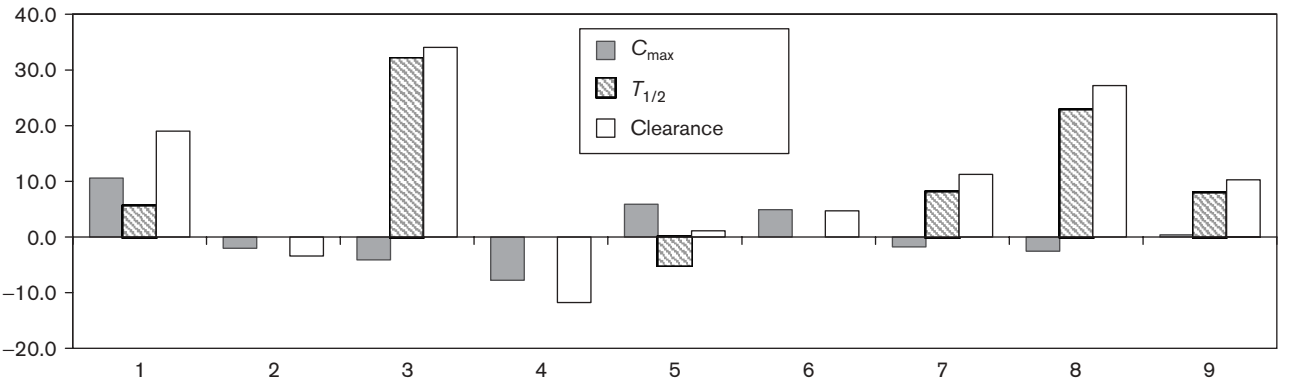
Nine patients received IFOS infusion with dose of 2.5 g/m^2. The concentrations of IFOS at the end of infusion (C_{max}) were similar at C1 and C2: 52.9 versus 53.9 µg/ml, respectively. The decline of the parent compound levels with time following intravenous administration could be described using a mono-exponential function. Calculated in these conditions, a 13.8% decrease of the median half-life (435 vs. 375 min) was observed between C1 and C2. The calculated AUC followed a comparable decrease as observed for the half-life (86.4%). Consequently, an increase of 16.6% was calculated for the total clearance between C1 (55.8 ml/min) and C2 (55.1 ml/min) (Table 5). Nevertheless, these results represent the mean values for the different parameters, and correspond to a general view of the processes. Considering individual variations, we observed a large difference in the reactions to the drug. The percentages of induction are summarized in Fig. 2. We considered as an inductive process, a decrease of the C_{max} and of the half-life and an increase of the clearance. An induction effect (decrease of the concentration) was observed for the C_{max} in four of nine patients and an increase of these levels at the second course for five of nine patients. Identically, the calculated half-life showed a lower value in five of nine patients at the second infusion and a higher value in four of nine patients. The total clearances presented a more homogeneous phenomenon than for the two previous constants with an induction concerning seven of nine patients and an increase only in two of nine patients. An increase of 27.1 and 26.2%, respectively, for 2-DCI-IFOS and 3-DCI-IFOS AUCs were noted between C1 and C2. The calculated ratio metabolites dechloroethylated

Table 5 IFOS (2.5 g/m^2) pharmacokinetics results

	$T_{1/2}$ (min)	C_{max} (μg/ml)	Extrapolated AUC (μg × min/ml)	Clearance (ml/min)
C1/2.5 g/m^2				
Median (25th–75th) quartile	435.0 (408.0–562.5)	52.9 (43.15–67.15)	82 156 (52 083–111 685)	55.8 (45.4–93.5)
C2/2.5 g/m^2				
Median (25th–75th) quartile	375.0 (296.0–520.0)	53.9 (45.7–66.0)	71 022 (38 174–111 742)	65.1 (43.1–132.1)
% (C2/C1)	86.2	101.9	86.4	116.6

AUC, area under the curve; IFOS, ifosfamide.

Fig. 2



Individual variations of induction of ifosfamide (2.5 g/m^2).

Table 6 Metabolites IFOS (2.5 g/m^2) pharmacokinetics results

	AUC IFOS	AUC 2-DCI-IFOS	AUC 3-DCI-IFOS	AUC 4-OH-IFOS	% AUC Metabolites/IFOS	% AUC 4-OH-IFOS/IFOS
C1						
Median (25th–75th) quartile	15 265 (13 060–19 358)	374.0 (223–517)	730.5 (390–1150)	93.1 (55.6–132.9)	6.1 (4.2–10.5)	0.48 (0.34–1.02)
C2						
Median (25th–75th) quartile	15 694 (12 896–18 635)	475.5 (194–691)	922.0 (468–1208)	101.7 (63.7–164.6)	7.4 (5.3–14.3)	0.67 (0.38–1.06)
% (C2/C1)	102.8	127.1	126.2	109.2	121.2	139.5

AUC, area under the curve; DCI-IFOS, dechloroethyl-ifosfamide.

AUC/IFOS AUC was 6.1% for C1 and 7.4% for C2. Therefore, a 21.2% increase of inactive metabolites was observed between the first and the second course. A slight increase of the 4-OH-IFOS AUC (9.2%) was noted between C1 and C2. The calculated ratio 4-OH-IFOS AUC/IFOS AUC was 0.48% for C1 and 0.67% for C2. Therefore, a 39.5% increase of the active metabolite was observed between the two consecutive courses (Table 6).

Nine patients received IFOS infusion with dose of 3.0 g/m^2. The same calculation procedures were applied for the different parameters. A comparable interpatient variability of IFOS metabolism was observed for these nine patients. Taking into account the median values, the concentrations of IFOS at the end of the infusion (C_{max}) for C1 and C2 were comparable, 93.9 and 91.4, respectively, that is, a slight increase (+ 2.7%) between the two courses. Compared with the 2.5 g/m^2 infusion, these second values were higher than our expectations. Nevertheless, a similar decrease of the half-life was observed than previously. The median value for C1 was 333.0 and 310.9 min for C2. The result was a 6.7% decrease between C1 and C2. The extrapolated AUCs were reduced of 3.1% at the second course.

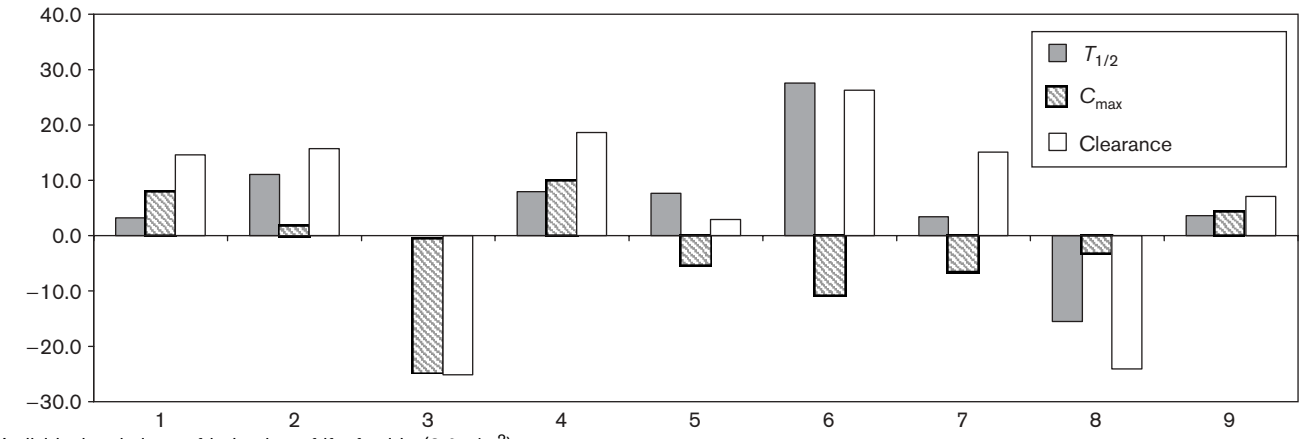
In these conditions the mean values of the total clearances increased by 12.1% from 52.5 ml/min for the first infusion to 58.9 ml/min for the second one (Table 7). Large interindividual variations were also noted in this series. If we considered the percentage of induction, defined as previously, we found different comportment in relation with the induction process. Indeed, six of nine patients showed a decrease of the half-life during the second course and consequently an induction. In contrast, a decrease of the C_{max} was observed only for four of nine patients. Finally, an increase of the total clearances was calculated in seven of nine patients. These results are presented in the Fig. 3. At this dose

Table 7 IFOS (3.0 g/m^2) pharmacokinetics results

	$T_{1/2}$ (min)	C_{max} (μg/ml)	Extrapolated AUC (μg × min/ml)	Clearance (ml/min)
C1/3.0 g/m^2				
Median (25th–75th) quartile	333.0 (290.8–447.6)	93.9 (79.6–98.4)	98 666 (85 683–138 091)	52.5 (42.9–59.4)
C2/3.0 g/m^2				
Median (25th–75th) quartile	310.9 (247.9–423.5)	91.4 (89.7–95.9)	95 681 (69 745–140 047)	58.9 (48.5–77.0)
% (C2/C1)	93.3	97.3	96.9	108.4

AUC, area under the curve; IFOS, ifosfamide.

Fig. 3



Individual variations of induction of ifosfamide (3.0 g/m^2).

Table 8 Metabolites IFOS (3.0 g/m^2) pharmacokinetics results

	AUC IFOS	AUC 2-DCI-IFOS	AUC 3-DCI-IFOS	AUC 4-OH-IFOS	% AUC Metabolites/IFOS	% AUC 4-OH-IFOS/IFOS
C1						
Median (25th–75th) quartile	25 613 (23 707–27 320)	1073 (758–1198)	1187 (1053–1662)	135.5 (109.2–170.6)	8.5 (7.8–10.6)	0.54 (0.40–0.67)
C2						
Median (25th–75th) quartile	24 202 (23 583–27 903)	1001 (655–1184)	1225 (972–1662)	140.9 (118.1–171.9)	8.6 (7.5–11.1)	0.56 (0.45–0.73)
% (C2/C1)	94.5	93.3	111.6	103.9	101.1	103.7

AUC, area under the curve; DCI-IFOS, dechloroethyl-ifosfamide.

there was no significant difference between the two courses C1 and C2, either for the 2-DCI-IFOS or for the 3-DCI-IFOS AUC from the beginning of the infusion to 5 h after the end of this infusion. Indeed, the percentages of variation were 93.3 and 103.2%, respectively. As previously observed for the parent compound, however, the levels are proportionally higher than the expected values after the 2.5 g/m^2 infusion for C1 as C2. The 2-DCI-IFOS AUC was 374 (223–517) in the first series and 1073 (758–1198) in the second one. For 3-DCI-IFOS, the AUCs were 730.5 (390–1150) and 1187 (1053–1662), respectively. Consequently, the AUC ratio: metabolites AUC/IFOS AUC remained stable between the two consecutive courses. A constant level was noted for the AUC of the active metabolite (135.5 vs. 140.9) at the first and the second course. Finally, the AUC ratios between metabolites (active or inactive) and IFOS, in contrast with the first series, remained stable during the two courses. The percentages of variation were calculated as 101.1 and 103.7% (Table 8).

Discussion

We reported a new IFO treatment modality using simple infusion every 2 weeks. Our aim was to improve the therapeutic index favoring the production of active metabolites without increased new toxicity. Interestingly, we observed a different toxicity profile with little alopecia. Fractionated dosage is the major mode of administration of IFOS. An EORTC study compared in randomized phase II trial in advanced soft tissue sarcomas a dose of 5 g/m^2 as a daily infusion of IFOS with a dose of 3 g/m^2 for 3 consecutive days as 4 h infusion of IFOS, every 3 weeks [16]. The response rate was significantly

better in the group with fractionated IFOS 9 g/m^2 during 3 days (17.5 vs. 3%). It was, however, very difficult to discriminate the dose effect (5 vs. 9 g/m^2) and the fraction effect. No trial has directly reported a randomized study comparing a fractionated dose on 2 days or more with an administration during 1 day. Therefore, the fractionated administration is actually the most frequent modality of administration. The rationale of this schedule is the saturable metabolism of IFOS by cytochrome P450. IFOS is not metabolized and so not activated with doses more than 3 g/m^2. Moreover, the production of active metabolites is increased after successive injections by autoinduction of IFOS. The first limit of fractionated injection on several days is the progressive increase of plasmatic concentrations of 2-DCI- and 3-DCI-IFOS and chloroacetaldehyde. These metabolites are responsible for neurologic (encephalopathy) and renal (tubulopathy) toxicities after a few days of treatment. The risk of toxicities is dependent on the increase of production by enzymatic induction and the progressive accumulation of these metabolites (with long half-life of elimination). We think that this fractionated schedule does not increase the therapeutic index of IFOS. Moreover it makes any IFOS-based combination chemotherapy difficult. In this study, we used the autoinductive potential of IFOS. IFOS was administered in a single injection with an initial dose of 2.5 g/m^2 every 2 weeks. After 14 days, we confirmed that the toxic metabolites were eliminated. Indeed, the treatment was well tolerated. We noted no grade 3–4 toxicities, no neurologic and renal toxicities. As a consequence, this schedule seems suitable for the development of IFOS-containing chemotherapy regimens. In our study, there was evidence of antitumoral activity with 50% of patients with stable disease and two objective responses in heavily pretreated patients. This schedule of IFOS is an opportunity to increase the dose-density of IFOS treatments. Indeed, similar approaches using an every-2-weeks schedule using cyclophosphamide in breast cancer patients are promising [17]. After two cycles, we found a slight autoinduction with decrease of half-life, C_{max} and IFOS AUC. The induction was associated with variable pharmacokinetics, individual data as described in several studies [18,19]. A second step was to improve the autoinduction, the choice to increase IFOS dose at 3 g/m^2 with the same schedule. We noted the same toxicities and antitumoral activity. We observed a slight increase of the therapeutic index (20% partial response and 30% stability) with the same profile of autoinduction. For the data presented it is not possible to determine a schedule associated with a strong autoinduction. We confirmed that the activity of cytochrome P450 is associated with large interindividual variations. Furthermore, the metabolism of cytochrome P450 is very complex. Few factors are known to influence and to evaluate this activity. These known factors are inflammation, denutrition and sex. We believe that doses more than 3 g/m^2 are saturable and do not change the induction of the activity of cytochrome P450. Nevertheless, this schedule decreases the time of hospitalization to a half day.

In conclusion, IFOS given at the dose of 2.5 or 3 g/m^2 every 2 weeks as a single injection is very well tolerated, has some evidence of antitumor activity and appears to be associated with slight patient-dependant autoinduction. The first limit of this study is the variability of IFOS metabolism in all patients. We confirm that the autoinduction is not dose-dependant but rather patient-dependant. Perhaps the individual analysis of IFOS metabolism should be studied before chemotherapy based on IFOS injection in solid tumors. Further schedules in phase I studies are ongoing with a short time between two administrations and without modification of doses to increase the activity of cytochrome P450 and the metabolism of IFOS. We proposed to evaluate the feasibility and activity of IFOS in association with other agents using this every 2 weeks schedule.

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