Cancer Chemother Pharmacol (2001) 48: 467–472
DOI 10.1007/s002800100365

ORIGINAL ARTICLE

**James P. Thomas · Rhoda Arzoomanian · Dona Alberti
Chris Feierabend · Kimberly Binger · Kendra D. Tutsch
Thomas Steele · Rebecca Marnocha · Charlotte Smith
Sheri Smith · John MacDonald · George Wilding
Howard Bailey**

Phase I clinical and pharmacokinetic trial of irofulven

Received: 20 May 2001 / Accepted: 12 July 2001 / Published online: 28 August 2001

Abstract *Purpose*: To evaluate the clinical tolerability of a new schedule of 6-hydroxymethylacylfulvene (irofulven, MGI 114, HMAF, NSC 683863), a semisynthetic sesquiterpene derived from the cytotoxic mushroom metabolite illudin S. Irofulven has been shown to induce DNA damage and apoptosis in vitro and has shown activity in a number of human tumor xenograft models. A number of drug-resistant cell lines including those that express the mdr phenotype, retain sensitivity to irofulven. *Methods*: We conducted a phase I trial of irofulven given as an intravenous infusion (30 min) on a daily ×5 schedule every 28 days. A total of ten patients were enrolled and treated at three dose levels, 6, 8, and 11 mg/m^2 per day. *Results*: Irofulven reached steady-state concentrations during the 30-min infusions with bi-exponential kinetics. Irofulven disappeared rapidly from plasma and was detectable for only 15–30 min after the end of the infusion. The mean half-life was 4.91 min and the mean clearance was 4.57 l/min per m^2. Peak plasma concentrations of irofulven of approximately 300 ng/ml were achieved. Pharmacokinetic parameters did not differ significantly from day 1 to day 5. Irofulven was highly emetogenic. Other prominent toxicities included anorexia and fatigue. One case of delayed-onset metabolic acidosis possibly secondary to irofulven was observed. No other renal or metabolic toxicity was encountered. One patient experienced a late-onset grade 3 extravasation skin injury thought to be secondary to extravasation of irofulven. Minimal marrow suppression was observed. No objective tumor responses were observed. *Conclusions*: The recommended phase II dose on this schedule is 6 mg/m^2.

Keywords Phase I · Irofulven · Illudins

J.P. Thomas · R. Arzoomanian · D. Alberti · C. Feierabend
K. Binger · K.D. Tutsch · T. Steele · R. Marnocha
G. Wilding · H. Bailey (✉)
University of Wisconsin Comprehensive Cancer Center
and Department of Medicine, University of Wisconsin,
Madison, WI 53792, USA

C. Smith · S. Smith · J. MacDonald
MGI PHARMA Inc., Bloomington, MN 55438, USA

Correspondence address: H. Bailey
K4/336 Clinical Science Center, 600 Highland Ave,
Madison, WI 53792, USA
e-mail: hhbailey@facstaff.wisc.edu
Tel.: +1-608-2638600
Fax: +1-608-2638613

Introduction

Irofulven (6-hydroxymethylacylfulvene, MGI 114, HMAF, NSC 683863) is a semisynthetic, acylfulvene analog of illudin S. Illudins are toxic sesquiterpenes found in the mushrooms *Omphalatous illudens* and *Lampteromyces japonicus* [14]. Illudin S has undergone extensive preclinical anticancer testing and multiple interesting observations have been noted. First, while prolonged exposure (48 h) to illudin S results in impressive cytotoxicity (IC_{50} < 10 n*M*) against a wide array of neoplastic and non-neoplastic cell lines, shorter exposure (2 h) results in marked preferential cytotoxicity toward neoplastic cells. Second, highly sensitive tumor cell lines exhibit a rapid, energy-dependent internal transport of illudin S, while less-sensitive tumor cell lines show evidence of a slower, non-energy-requiring incorporation of illudin S [8]. Third, evaluation of illudin-induced DNA damage has revealed a unique pattern of sensitivity in DNA repair-deficient cell lines. Kelner et al. [9] have observed that cell lines deficient in the DNA repair helicases, ERCC2 and ERCC3, are highly sensitive to illudin S and conversely cells with increased ERCC2 are resistant.

The initial preclinical development of illudin S was limited due to toxicity and the lack of an exploitable therapeutic index in animal testing. This led to a structure-activity based synthetic effort to produce chemical derivatives with a greater therapeutic potential. Irofulven is the lead analog developed from this effort [15]. Similarly to illudin S, irofulven exhibits marked cytotoxicity against a wide array of leukemia and solid

tumor cell lines, including tumor cell lines with multidrug-resistant phenotypes [10, 12], e.g. overexpression of gp-170 or gp-180, and elevated glutathione S-transferase pi or glutathione.

The aforementioned lack of cross-resistance with classic DNA-damaging agents such as alkylating agents implies that irofulven's cytotoxic effects differ from those of these other agents. Irofulven has been observed to bind to cellular macromolecules and DNA (as monoadducts only) and to induce apoptosis [7, 16]. Recent work by Woynarowska et al. [17] has further explored the potential etiology of irofulven's cytotoxicity. They observed selective induction of apoptosis in tumor cell lines, despite the fact that the drug-induced growth inhibition paralleled the uptake of irofulven in both tumor cells and normal cells. Normal cells were three- to fourfold more tolerant of the accumulated drug, consistent with the prior observation of selective toxicity of illudin S. Studies of radiolabeled drug in intact tumor and normal cells has revealed that the majority of drug is bound to macromolecules [16]. The authors proposed that irofulven binding to non-DNA targets leads to the pro-apoptotic state observed in tumor cells and that this effect is ultimately responsible for irofulven-induced cytotoxicity. The exact nature of irofulven's preferential cytotoxicity toward tumor cells is as-yet undefined.

Irofulven has been effectively combined with other cytotoxic agents in xenograft models. Britten et al. [3] have observed enhanced antitumor activity of the combination of irofulven and irinotecan as compared to monotherapy in nude mice bearing HT29 xenografts. Kelner et al. [11] have observed a synergistic effect when irofulven is combined with topotecan and administered to nude mice bearing HL60/MRI myeloid leukemia xenografts. Hammond et al. [6] have also noted a synergistic interaction between irofulven and topotecan or paclitaxel in the treatment of nude mice bearing MV522 lung carcinoma xenografts.

The results of preclinical toxicology testing vary between species, with dogs being the most sensitive species. Toxicities include weight loss, anorexia, vomiting, neutropenia, thrombocytopenia, and testicular atrophy. Cardiac lesions consisting of focal or multifocal lymphohistiocytic inflammation with myofibrillar degeneration and necrosis have also been seen in rats, but not dogs. Single- and multiple-dose studies have indicated a steep dose response curve for lethality. Irofulven has been shown preclinically to be a strong vesicant with the potential for producing soft tissue injury if extravasated [13].

The above findings led us to pursue clinical testing of irofulven. Early preclinical testing implied that a daily $\times 5$ administration schedule would result in a greater therapeutic window than single doses [12], and more prolonged infusions might ameliorate some of the toxicity observed in an earlier trial [4]. Therefore, we performed a phase I dose-escalation trial with irofulven given as a 30-min infusion daily for 5 days on a 28-day cycle.

Material and methods

Patient eligibility

The study was approved by the Human Subjects Committee at the University of Wisconsin Hospital, Madison. Patients with microscopic confirmation of malignancy (solid tumor or lymphoma) were eligible for enrollment. Other eligibility requirements included: ECOG performance status of 0–2, life expectancy of >12 weeks, age ≥ 18 years, and ability to provide informed consent. Patients were not allowed to have received chemotherapy and/or radiation therapy in the 4 weeks prior to enrollment and must have recovered completely from any toxicity. Patients who had received more than 300 mg/m^2 of an anthracycline were not eligible. Adequate organ function was required, defined as: WBC $\geq 4000/mm^3$, platelets $\geq 100{,}000$ mm^3, ANC $\geq 1500/mm^3$, serum bilirubin ≤ 2.0 mg/dl, AST no more than twice normal, serum creatinine clearance ≥ 60 ml/min and calcium <11.0 mg/dl. Patients were ineligible if they had known brain metastases, or any serious concomitant systemic disorder incompatible with the study. Patients with arrhythmias requiring medication or with active atrial fibrillation or congestive heart failure were not allowed on study. Pregnant or nursing females were ineligible.

Evaluation during therapy

Patients were monitored with clinical assessment prior to each infusion and with weekly laboratory evaluation for toxicity. Toxicities were graded using the National Cancer Institute Common Toxicity Criterion (NCI CTC, version 1). Evaluation of measurable or evaluable disease was done at least every 8 weeks. Standard solid tumor response criteria for complete and partial response as well as stable and progressive disease were employed.

Study design

Dose levels for irofulven given as a 30-min intravenous (i.v.) infusion daily for 5 days on a 28-day cycle were initially set at 8.0, 11, 14.5, 19, 25 and 33 mg/m^2. A lower dose level (dose level 0) of 6.0 mg/m^2 was subsequently added. The starting dose level of 8.0 mg/m^2 was felt to be safe due to information from an earlier phase I study in which patients had been treated at >10 mg/m^2 as a 5-min infusion administered daily for 5 days [4]. A minimum of three patients were treated and evaluated for at least 4 weeks at each dose level. Dose-limiting toxicity (DLT) was defined as any nonhematologic toxicity of grade 3 or more, or hematologic toxicity of grade 4. If the grade 4 hematologic toxicity was neutropenia or leukopenia and reversal occurred within 5 days, then it was not considered to be dose-limiting. A "best of five" rule for maximum tolerated dose (MTD) determination was employed with the MTD being defined as the dose immediately below that at which a DLT occurred in at least three patients.

Clinical laboratory evaluation

Complete blood counts were done each week and serum chemistries were done every other week while a patient was on study. Due to concerns of renal or metabolic toxicity (hyperkalemia and metabolic acidosis) raised in an earlier phase I study of irofulven [4], multiple renal/metabolic parameters were closely monitored before and during course 1. A 24-h urine collection for creatinine clearance was performed prior to day 1 and was repeated after course 1. Prior to drug administration on days 1, 3, and 5, and also on day 8 of course 1, serum sodium, potassium, chloride, carbon dioxide and creatinine were assessed. At the same time a urine sample was obtained for determination of sodium, potassium, chloride and creatinine. In addition to directly observing renal function via assessment of serum creatinine or 24-h creatinine clearance, the various serum and urine measurements also allowed determination

of the urine anion gap and the transtubular potassium gradient. These parameters allow assessment of specific renal functions, i.e. are indices of ammonium excretion and potassium secretion, under conditions of acidosis or hyperkalemia [2, 5].

Irofulven administration

Irofulven (10 mg) was reconstituted by adding 0.1 ml dehydrated alcohol to each vial followed by 9.9 ml 5% dextrose for a total of 10 ml. The reconstituted drug was further diluted as needed in 5% dextrose to a concentration not less than 0.1 mg/ml. The appropriate dose was calculated based on the individual body surface area at the beginning of each course. Irofulven was administered i.v. over 30 min each day for five consecutive days. Patients did not receive scheduled additional i.v. fluids on days 1–5. The first two patients treated on study did not receive scheduled antiemetics. All further patients received scheduled antiemetics (i.v. 5HT antagonist plus dexamethasone) prior to each administration of irofulven. All treatment was administered at the University of Wisconsin General Clinical Research Center.

Pharmacokinetic sampling and analytical methods

On the 1st and 5th days of course 1, blood samples were drawn predose, 5 min into the infusion, at the end of infusion (time 0), and at 2, 5, 10, 15, 30, 60, 90, 120, and 240 min. On the 2nd through 4th days of dosing, blood samples were drawn predose, 5 min into the infusion and immediately at the end of infusion. Determination of serum irofulven concentrations were performed by Covance CLS, Madison, Wis.

Results

Patients

A total of ten patients (three men, seven women) were entered on this trial and received a total of 16 evaluable courses. Patient characteristics were as follows. The median age was 54 years (range 45–68 years). All had received prior chemotherapy and four had received prior radiotherapy. Eight had a performance status of 1 (ECOG) and two a performance status of 0. Colorectal carcinoma (four patients) and ovarian carcinoma (two patients) comprised the majority of tumor types, with one patient each having endometrial, pancreatic and prostate carcinoma, and uterine leiomyosarcoma.

Toxicity

Table 1 summarizes the observed toxicity pertaining to nausea/vomiting and fatigue/asthenia. Acute nausea/vomiting was the prominent toxicity (70% of patients) and seemed to be dose-related. Grade 2 delayed nausea/vomiting was observed at the 11 mg/m^2 dose level only. Acute nausea/vomiting was reasonably ameliorated by the addition of scheduled antiemetics at dose levels below 11 mg/m^2. Fatigue/asthenia was a prominent symptom in seven of the ten patients and, like nausea/vomiting, appeared to be dose-related. No patient received more than two courses of treatment.

Minimal myelosuppression was observed. Thrombocytopenia was seen in one patient at the 6.0 mg/m^2 level, in four patients at the 8.0 mg/m^2 level and in one patient at the 11.0 mg/m^2 level. All of these occurrences were grade 1 except for grade 3 thrombocytopenia in one patient each at the 8 and 11 mg/m^2 levels. Two patients developed grade 3 anemia while on study and required blood transfusions. No evidence of acute blood loss or hemolysis was observed. One episode of grade 3 leukopenia was observed.

Other observed gastrointestinal toxicities included: grade 1 hiccups during days 1–5 in two patients, grade 1 stomatitis in two patients, grade 1 constipation in one patient, and grade 1 diarrhea in one patient at the 6 mg/m^2 dose level. In addition, one patient at the 6 mg/m^2 level complained of abdominal pain at the tumor site during the infusions of days 1–5. Grade 1 and 2 diarrhea was observed in one patient each at the 8 mg/m^2 and the 11 mg/m^2 dose levels, respectively. One episode of grade 2 transaminase elevation and grade 3 hyperglycemia were each observed and hypothesized to be secondary to concomitant medications (corticosteroids).

Mild facial flushing, which did not require intervention, during the study drug infusions was observed in four patients across all three dose levels. Three patients complained of possible neurologic toxicities (two grade 1 dizziness and one grade 2 mood changes during days 7–14) of uncertain relationship to study drug. At the 8 mg/m^2 dose level one patient had grade 2 headache during days 1–5 possibly related to granisetron.

One patient at the 8.0 mg/m^2 level experienced a presumed extravasation injury (grade 3) with the second course of treatment. During the day-5 infusion of course 2, the patient complained of pain at the peripheral infusion site. The site was without evidence of extravasation and the peripheral i.v. line was free-flowing with good blood return. The presumed extravasation injury became apparent on day 45 and had completely healed with supportive care by day 57.

Table 1 Number of courses with grade of toxicity

Dose (mg/m^2)	No. of patients	No. of courses	No. of courses with toxicity						
			Nausea/vomiting (grade)				Fatigue/asthenia (grade)		
			1	2	3	4	1	2	3
6	3	6	2	0	0	0	1	3	0
8	5	8	3	3	0	1	0	3	0
11	2	2	0	0	0	2	0	0	2

One patient died on study. The patient, with uterine sarcoma, was observed to have a bowel obstruction with evidence of significant progressive disease 5 days after the second cycle of irofulven. The patient died 3 days after an attempted laparotomy of progressive cancer and complications related to the bowel obstruction.

Despite specifically looking for metabolic and renal toxicity in all study patients, only one patient experienced any signs or symptoms of renal or metabolic toxicity. A patient with metastatic colon cancer was treated at 8 mg/m^2 without any signs of renal or metabolic abnormalities during days 1–8. On day 12 the patient started experiencing fevers and chills and was eventually admitted to a local hospital on day 17 with fevers and an erythematous rash. Ciprofloxacin was started for suspected urosepsis. During the hospitalization fevers and rigors continued and the erythematous rash became painful and desquamative, and facial edema was observed. Evaluation for infection was negative throughout the hospitalization. An aminoglycoside was added and the patient received two separate blood transfusions. The patient's serum creatinine then started to increase to a maximum of 2.4 mg/dl on day 20 and had returned to baseline (1.5 mg/dl) by day 26. Mild hyperkalemia (5–5.5 meq/dl), decreased serum bicarbonate (13 meq/dl), and a urinary anion gap (+3) as well as low serum complement levels were noted on day 22. On day 22 corticosteroids were started for suspected interstitial nephritis and on day 23 i.v. bicarbonate was initiated for the metabolic acidosis. The fevers and rash appeared to resolve after starting corticosteroids. Re-evaluation on day 35 revealed no persistent toxicity and the patient declined further treatment on study.

Pharmacokinetics

Pharmacokinetics were consistent with the expected rapid cellular uptake and/or elimination, and marked interpatient variability was also noted. Plasma peak levels were observed to occur during the 30-min infusion with a rapid decrease after completion of the infusion. Irofulven was last detectable in the blood 15–30 min after the end of infusion. Steady-state concentrations were reached secondary to biexponential kinetics. The majority of the area under the concentration × time curve (AUC) occurred during the infusion. Table 2 shows details of various pharmacokinetic parameters of irofulven on days 1 and 5. There were no significant differences (paired *t*-test) between day 1 and day 5 except in the terminal half-life, which was 4.9 ± 2.1 min on day 1 and 7.9 ± 4.0 min on day 5 ($n = 10$, $P = 0.03$). The day-1 pharmacokinetic values of the two patients at the 11 mg/m^2 per day dose level were unexpectedly low and certainly appeared markedly different from the day-5 values.

In addition to the observed interpatient variability (relatively large standard deviations in most parameters), there was some evidence of intrapatient variability. Comparing irofulven concentrations obtained 5 min from the start and at the end of each infusion revealed a two- to threefold variance (data not shown). Mean (±SD) peak plasma concentrations (day 5) in each of the dose groups were (ng/ml) 66.3 ± 30.1, 90.3 ± 33.7 and 122.5 ± 16.3 (269–496 n*M*) at doses of 6, 8 and 11 mg/m^2, respectively. There was no evidence of drug accumulation between daily doses. Clearance was rapid (3.5 l/min per m^2) and did not vary considerably between the first and fifth doses. The less than twofold range of doses tested in this study hampered further pharmacokinetic modeling.

Activity

No objective responses were seen with this administration schedule (30-min infusion daily for 5 days every 28 days).

Discussion

Due to a likely novel mechanism of action and the impressive preclinical antitumor testing, clinical development of irofulven was initiated. The initial phase I trial of irofulven administered as a 5-min infusion daily for 5 days has been reported [4]. The phase I dose-escalation study reported here was begun to determine the toxicity, pharmacokinetic profile and the recommended phase II dose of irofulven when given to humans as a 30-min i.v. infusion daily for 5 days on an every-28-day schedule. It was hoped that a longer infusion would lessen some of the toxicities observed in the 5-min infusion trial such as asthenia and nausea.

It appeared that lengthening the infusion time from 5 to 30 min did not lessen the toxicity of irofulven. Compared to the 5-min infusion trial described by

Table 2 Pharmacokinetics of irofulven during course 1

Dose level (mg/m^2/day)	No. of patients	C_{max} (ng/ml)		AUC (ng/ml·min)		$t_{1/2}$ (min)	CL (l/min/m^2)	
		Day 1	Day 5	Day 1	Day 5	Day 1	Day 1	Day 5
6	3	64 ± 34	66 ± 30	1664 ± 688	1800 ± 923	4.4 ± 2.5	4.1 ± 2.0	4.7 ± 0.8
8	5	105 ± 30	90 ± 33	2792 ± 994	2582 ± 891	5.4 ± 2.3	3.1 ± 0.9	3.5 ± 1.5
11	2	48 ± 23	123 ± 16	1377 ± 601	3403 + 705	4.6 ± 1.0	8.9 ± 3.9	3.3 ± 0.7

Eckhardt et al. [4], the observed toxicities of nausea/vomiting and fatigue/asthenia were equivalent if not worse on this study at comparable doses. While daily scheduled i.v. hydration during days 1–5 was not employed in this study, as was used in the prior study at later dose levels, it is difficult to imagine that this would have accounted for the difference in tolerability of the 11 mg/m^2 per day dose level. A more likely explanation is that the longer infusion time may have changed the pattern of distribution to non-tumor tissues. As mentioned above, illudin S appeared to have a better therapeutic ratio in preclinical testing with shorter exposure times [8].

The predominant and dose-limiting toxicities in this trial were nausea/vomiting and fatigue/asthenia. The 11 mg/m^2 per day dose level was especially difficult in this regard with both patients having good performance status of 0–1 on day 1 with a rapid decrease in performance status to 2–3 by day 5 with gradual recovery to baseline by day 28. The extent of the observed toxicity in these two patients led us not to enroll, per protocol, the third patient at this level. The tolerability of the 8 mg/m^2 per day dose level is uncertain. Even though it did not meet protocol criteria as being intolerable since dose-limiting events occurred in not more than two of five subjects, the occurrence of fatigue/asthenia coupled with moderate nausea limited the patients' willingness to continue with treatment. The 6 mg/m^2 per day dose level appeared quite tolerable despite the fact that in half the courses (three of six) grade 2 fatigue was noted. This was possibly related to the fatigue duration being shorter and the lack of any significant nausea.

It is difficult to comment on whether the fatigue/asthenia would worsen or lessen with repeated courses since no patient received more than two courses of therapy. The nausea and vomiting observed was partially ameliorated by aggressive use of scheduled and as-needed antiemetics (5HT antagonists, corticosteroids, phenothiazines or butyrophenones, and benzodiazepines). Delayed nausea and vomiting was definitely evident at the 11 mg/m^2 per day dose level, but less evident at lower doses. No specific attempts/interventions were undertaken to ameliorate the transient fatigue/asthenia mentioned by the patients. It rapidly developed during days 1–5, especially at the 11 mg/m^2 per day dose level, and tended to be most pronounced on days 5–10.

Based on the then available data from the 5-min infusion study [4], some degree of renal and/or metabolic toxicity, principally hyperkalemia and metabolic acidosis, was expected in our study. Accordingly, multiple specific measurements were assessed to better delineate any renal/metabolic abnormalities which might occur. Possibly related to more stringent renal function criteria or to the longer infusion time, only one case of renal/metabolic toxicity was observed. This one occurrence (8 mg/m^2 per day dose level) did involve a transient decrease in renal function, hyperkalemia and metabolic acidosis similar to the toxicity observed in the earlier study, but the timing of the toxicities relative to drug administration was markedly different. In their study, Eckhardt et al. [4] did observe transient elevations in serum creatinine after day 5, but all occurrences of hyperkalemia and metabolic acidosis occurred by day 5. Given the similar occurrences of hyperkalemic metabolic acidosis with irofulven, there is a strong possibility that our one observation was secondary to irofulven, but multiple other possible etiologies (aminoglycoside, naproxen, blood products) were present as well. No other signs of renal toxicity were observed during the study.

Preclinical evaluation of irofulven suggested that myelosuppression would be a significant toxicity. In the limited number of dose levels evaluated in this study, myelotoxicity was not dose-limiting. Grade 3 thrombocytopenia, occurring after day 21 in two of ten courses at the 8 and 11 mg/m^2 per day dose levels, was the most prominent hematologic toxicity. Very little other hematologic toxicity was observed. Preliminary data indicated that irofulven is likely a vesicant. We did encounter a substantial extravasation skin injury. This extravasation was not apparent during the infusion but became noticeable as erythema a few days later. This presumed extravasation injury resulted in skin necrosis which eventually healed completely without any intervention. Other observed toxicities included facial flushing during the infusions in one patient at each dose level. This was also observed during the 5-min infusion trial [4]. Two patients at the 6 mg/m^2 per day dose level complained of mouth soreness (grade 1 stomatitis) and another patient at that level noted abdominal pain near known metastatic disease during the 30-min infusions.

Pharmacokinetic analysis revealed irofulven to have a short mean half-life of 4.91 min, which is similar to the finding of the prior phase I trial of irofulven [4]. Irofulven could only be detected in patient samples for less than 30 min. This along with the less than twofold range of doses tested in this study limited pharmacokinetic modeling. There was no significant difference in pharmacokinetic parameters between the day-1 and the day-5 data sets other than the aforementioned half-life. The marked difference between the day-1 pharmacokinetic parameters and day-5 values of the two patients treated at the highest dose level is in contrast to the rest of the pharmacokinetic data. The nature of these data in the context of the remaining data raises the possibility of a delivery, processing or technical error, or the difference may have been a result of marked patient variability and limited patient numbers. The mean clearance for irofulven was 4.7 l/min per m^2 which also did not differ significantly between day 1 and day 5. Serum peak concentrations of 269–496 nM are in the range of the IC_{50} values seen for some cancer cell lines.

Our results are similar to the prior published data following administration of irofulven as a 5-min infusion [4]. Our dose range of 6–11 mg/m^2 per day is comparable to the previous doses of 6, 8 and 10.64 mg/m^2 per day. The easiest level to compare is 8 mg/m^2 at which each trial had six patients. As expected with a shorter infusion time, peak concentrations with the 5-min infu-

sion were greater than with 30-min infusion (474 ± 242 vs 105 ± 30 ng/ml). Clearance also appeared to be greater (6.5 ± 3 vs 3.1 ± 1 l/min. Other parameters appear similar including AUC (5-min infusion 2562 ± 1017 vs 2792 ± 994 ng/ml·min) and half-life (4.5 vs 5.4 min). Marked interpatient variability in pharmacokinetics was also observed in the 5-min infusion study.

In examining the two trials from a pharmacokinetic and toxicity standpoint, it is difficult to recommend the prolonged infusion over the shorter infusion for a daily ×5 administration schedule. As mentioned above, the toxicity appeared to be less at comparable doses and there appeared to be no pharmacokinetic advantage with the prolonged infusion since the AUC values were comparable. The only advantage for the prolonged infusion would be the possibility of enhanced cytotoxicity as a result of maintaining the irofulven concentration above a certain threshold concentration.

We did not observe any evidence of a beneficial clinical effect during this study. That coupled with apparent increased toxicity and no obvious pharmacokinetic advantage as compared to the 5-min infusion has resulted in the 5-min infusion schedule advancing into phase II studies. Ongoing phase II studies of irofulven given as a 5-min infusion daily ×5 have shown antitumor activity in patients with refractory ovarian, pancreatic carcinomas, and hormone-refractory prostate carcinoma. In addition, other administration schedules (weekly administration) are being explored in phase I testing [1].

References

1. Alexandre J, Raymond E, Brain E, Ould Kaci M, Smith S, Misset JL (2000) Dose-intensity (DI) based escalation phase I study of MGI 114 (irofulven) exploring 3 different i.v. schedules in advanced solid tumors. Proceeding of the 25th ESMO Congress. Ann Oncol 11 [Suppl 4]:138
2. Batlle DC, Hizon M, Cohen E, Gutterman C, Gupta R (1988) The use of the urine anion gap in the diagnosis of hyperchloremic metabolic acidosis. New Engl J Med 318:594
3. Britten CD, Hilsenbeck SG, Eckhardt SG, Marty J, Mangold G, MacDonald JR, Rowinsky EK, Von Hoff DD, Weitman S (1999) Enhanced antitumor activity of 6-hydroxymethylacylfulvene in combination with irinotecan and 5-fluorouracil in the HT29 human colon tumor xenograft model. Cancer Res 59:1049
4. Eckhardt SG, Baker SD, Britten CD, Hidalgo M, Siu L, Hammond LA, Villalona-Calero MA, Felton S, Drengler R, Kuhn JG, Clark GM, Smith SL, MacDonald JR, Smith C, Moczygemba J, Weitman S, Von Hoff DD, Rowinsky EK (2000) A phase I and pharmacokinetic study of irofulven, a novel mushroom-derived cytotoxin, administered for five consecutive days every four weeks. J Clin Oncol 18:4086
5. Ethier JH, Kamel KS, Magner PO, Lemann JJ, Halperin ML (1990) The transtubular potassium concentration in patients with hypokalemia and hyperkalemia. Am J Kidney Dis 15:309
6. Hammond LA, Hilsenbeck SG, Eckhardt SG, Marty J, Mangold G, MacDonald JR, Rowinsky EK, Von Hoff DD, Weitman S (2000) Enhanced antitumour activity of 6-hydroxy methylacylfulvene in combination with topotecan or paclitaxel in the MV522 lung carcinoma xenograft model. Eur J Cancer 36:2430
7. Herzig MC, Arnett B, MacDonald JR, Woynarowski JM (1999) Drug uptake and cellular targets of hydroxymethylacylfulvene (HMAF). Biochem Pharmacol 58:217
8. Kelner MJ, McMorris TC, Taetle R (1990) Preclinical evaluation of illudins as anticancer agents: basis for selective toxicity. J Natl Cancer Inst 82:1562
9. Kelner MJ, McMorris TC, Est L, Rutherford M, Manda M, Goldstein J, Samson KM, Starr RJ, Taetle R (1994) Characterization of illudin S sensitivity in DNA repair-deficient Chinese hamster cells. Biochem Pharmacol 48:403
10. Kelner MJ, McMorris TC, Est L, Starr RJ, Rutherford M, Manda M, Samson KM, Taetle R (1995) Efficacy of acylfulvene illudin analogues against a metastatic lung carcinoma VM522 xenograft nonresponsive to traditional anticancer agents: retention of activity against various mdr phenotypes and unusual cytotoxicity against ERCC2 and ERCC3 DNA helicase-deficient cells. Cancer Res 55:4936
11. Kelner MJ, McMorris TC, Est L, Samson KM, Trani NA, MacDonald JR (2000) Anti-leukemic action of the novel agent MGI 114 (HMAF) and synergistic action with topotecan. Leukemia 14:136
12. MacDonald JR, Muscoplat CC, Dexter DL, Mangold GL, Chen SF, Kelner MJ, McMorris TC, Von Hoff DD (1997) Preclinical antitumor activity of 6-hydroxymethyl-acylfulvene, a semisynthetic derivative of the mushroom toxin illudin S. Cancer Res 57:279
13. Marshall RF, Arthaud LE, MacDonald JR (2000) Evaluation of antidotes for extravasation injury produced by 6-hydroxy methylacylfulvene (MGI 114), a novel cytotoxic antitumor agent, in an intradermal toxicity model in rats. Cancer Chemother Pharmacol 45:397
14. McMorris TC, Kelner MJ, Chadha RK, Siegel JS, Moon S, Moya MM (1989) Structure and reactivity of illudins. Tetrahedron 45:5433
15. McMorris TC, Kelner MJ, Wang W, Est LA, Manda MA, Taetle R (1992) Structure activity relationship of illudins: analogs with improved therapeutic index. J Org Chem 57:6876
16. Woynarowski JM, Napier C, Koester SK, Chen SF, Troyer D, Chapman W, MacDonald JR (1997) Effects on DNA integrity and apoptosis induction by a novel antitumor sesquiterpene drug, 6-hydroxymethylacylfulvene (HMAF, MGI 114). Biochem Pharmacol 54:1181
17. Woynarowska BA, Woynarowski JM, Herzig MC, Roberts K, Higdon AL, MacDonald JR (2000) Differential cytotoxicity and induction of apoptosis in tumor and normal cells by hydroxymethylacylfulvene (HMAF). Biochem Pharmacol 59:1217