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ORIGINAL ARTICLE

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# Phase I and pharmacokinetic study of the novel redox-active agent, motexafin gadolinium, with concurrent radiation therapy in patients with locally advanced pancreatic or biliary cancers

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**Abstract** *Purpose*: To determine the maximum tolerated dose and dose-limiting toxicity (DLT) of the novel anticancer agent, motexafin gadolinium (MGd), administered concurrently with radiation therapy (RT) in patients with locally advanced pancreatic or biliary tumors. The pharmacokinetics of MGd were also evaluated. *Methods*: Cohorts of three to six patients were treated with escalating doses of MGd, administered three times per week for a total of 16 doses concurrent with RT. The dose of RT was fixed at 5,040 cGy, and given in 28 fractions, from Monday to Friday of every week. Plasma MGd concentrations were measured by high performance liquid chromatography. *Results*: Eight patients were treated at dose level 1 (2.9 mg/kg), with one DLT (grade 3 fever). Three patients were treated at dose level 2 (3.6 mg/kg), and two DLTs were noted. One DLT was grade 3 nausea and vomiting (N/V), and the other was grade 3 skin toxicity. The most common toxicity was N/V. There were no objective responses. The median survival was 6 months. The MGd plasma concentration versus time profile in each patient was best fit by a two-compartment, open, linear model. There was minimal accumulation of MGd in plasma with the three-times/week dosing schedule. Simulation

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of the time course of MGd in the peripheral compartment indicated that maximal MGd concentrations of 1–2 μmol/kg occurred between 4 and 6 h after MGd infusion. *Conclusion*: Dose level 1 (2.9 mg/kg of MGd) is the recommended dose for combination with (RT) in phase II studies for locally advanced pancreatic and biliary cancers. Patient tolerance might be improved by modification of the RT schedule and antiemetic prophylaxis.

**Keywords** Phase I study · Motexafin gadolinium · Radiation therapy · Pancreatic cancer

## Introduction

The prognosis of locally advanced, surgically inoperable pancreatic and biliary cancers is dismal, with a median overall survival of less than 1 year [1, 2]. Treatment strategies include chemotherapy, radiation therapy (RT), or a combination of both [1–3]. While RT alone is inferior in the treatment of locally advanced pancreatic cancer, it is not clear if there is an advantage for chemoradiotherapy over chemotherapy alone in terms of overall survival [1–7]. Concurrent chemotherapy with 5-fluorouracil (5-FU) and RT is commonly used in the United States to treat locally advanced pancreatic cancer, based on early randomized studies by the Gastrointestinal Tumor Study Group [1, 2]. Though earlier studies with RT utilized a split course [1, 2], the dose of 5,040 cGy given in 28 fractions (5 days/week) is now commonly used in chemoradiation protocols. The search continues for better radiosensitizers, and a number of agents such as gemcitabine and paclitaxel have been combined with radiation in the treatment of patients with locally advanced pancreatic cancers [3–7]. Despite these recent developments, the median overall survival of patients with locally advanced pancreatic cancers continues to be less than 1 year, with most patients having rapid local and distant progression of tumor. Attempts to improve local control by increasing the dose of chemotherapy in combined modality regimens are limited by local and systemic toxicity [3]. Similarly the outcome for locally advanced biliary tumors is poor. Although concurrent chemoradiotherapy with 5-FU is also commonly used to treat locally advanced, unresectable biliary tumors [8], there is no established standard of care because few clinical trials have been performed specifically for biliary cancer.

Motexafin gadolinium (MGd) is a pentadentate aromatic metallotexaphyrin currently under evaluation in clinical trials as an anticancer agent [9–11]. MGd is a redox-active drug with potent activity, and, in preclinical models, it targets tumor cells and enhances the sensitivity of cells to radiation [9, 10]. Futile redox cycling occurs when MGd oxidizes intracellular reducing metabolites producing reactive oxygen species that are toxic to tumor cells [11]. MGd has the advantage of selective accumulation in tumor cells and, because it contains gadolinium, has the added benefit of being detectable by magnetic resonance imaging (MRI) for anatomic tumor visualization [12].

Therefore, MGd offers several benefits to researchers and clinicians, including in vivo synergy with radiation in xenograft models; hence it is used in clinical studies [13–15]. A phase I/II study in patients with brain metastases was conducted to identify the maximum tolerated dose (MTD) of daily MGd given concurrently with whole brain radiation therapy (WBRT) delivered in ten fractions for a total of 3,000 cGy [13]. The MTD of MGd was 6.3 mg/kg × 10 doses, with reversible dose-limiting liver toxicity. This study was also associated with an impressive radiological response of 72% in brain metastasis. Subsequently, Mehta et al. [16] conducted a phase III study of MGd in patients with brain metastasis. Patients were randomized to receive either 3,000 cGy of WBRT given over ten fractions or the same dose of WBRT with the addition of MGd (5 mg/kg/day for 10 doses). Treatment with MGD improved time to neurologic progression in patients with lung cancer, but did not result in an overall survival benefit. [17]. The administration of MGd did not interfere with WBRT and was well tolerated [16].

Based on the promising preliminary reports of efficacy with MGd and RT [13], we evaluated MGd in patients receiving RT for locally advanced pancreatic or biliary tumors. At the time of study initiation, there were no data available for the administration of MGd over 5–6 weeks with RT, so a phase I dose escalation design was implemented. Because a cumulative MGd dose of 50 mg/kg is well tolerated in patients with brain metastases [13], we chose a starting dose of 2.9 mg/kg × 16 doses (cumulative dose 46.4 mg/kg). Based on the reported 28-h terminal half-life of MGd, we elected to administer the drug three times a week for optimum radiosensitization [18].

## Patients and methods

### Study design

This was a phase I dose escalation study to determine the MTD of MGd when combined with a fixed dose of RT in patients with locally advanced pancreatic or biliary tumors. The primary objective was to evaluate safety and toxicity and define the MTD of 16 doses of MGd administered three times a week concurrent with 28 daily 180-cGy fractions of RT. Secondary objectives included identification of a phase II dose for future studies, evaluation of MGd pharmacokinetics, and documentation of objective radiological responses. The protocol was reviewed and approved by the institutional review boards of all participating institutions.

## Patients and methods

Patients who were 18 years or older were eligible for study if they had a histologically confirmed locally advanced, surgically unresectable pancreatic or biliary tree carcinoma. Metastatic disease was allowed if RT was required for control of the primary tumor. Patients were required to have radiologically measurable disease and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. Acceptable organ function was required and defined as absolute neutrophil count (ANC) $>1{,}500/\mu l$, platelets $>100{,}000/\mu l$, serum creatinine $< 1.6$ mg/dl, total bilirubin $\leq 2.0$ mg/dl, and both serum aspartate aminotransferase (AST) and alanine amino transferase (ALT) $\leq 1.5 \times$ the upper limit of normal. Women of childbearing potential were required to have a negative pregnancy test prior to study entry and required to use an effective means of contraception. A written, informed consent was obtained from each patient prior to participation in the study.

Patients were excluded from the study in case of prior radiation to the site of the tumor, pregnancy, lactation, or a major surgical procedure within 3 weeks from entry onto the study. Other exclusion criteria included chemotherapy within 4 weeks before study entry, clinical evidence of ascites, and a history of glucose-6-phosphate dehydrogenase deficiency or porphyria.

## Drug administration

MGd (NSC 695238) was supplied by the Pharmaceutical Resources Branch of the National Cancer Institute (Rockville, MD, USA) in 20-ml vials, containing 2.3 mg/ml of MGd dissolved in mannitol. The required amount of the drug was administered IV over 15 min, after which the infusion line was flushed with a 10% mannitol solution, and patients were hydrated with 500 ml of 5% dextrose in water given IV over 2 h. Patients were requested to increase oral intake of fluids before and after MGd therapy. Prophylactic antiemetics were not given routinely, but were allowed in patients who developed nausea or vomiting (N/V). MGd was given three times a week (Monday, Wednesday and Friday) for a total of 16 doses, with the first dose being scheduled on the first day of RT. MGd was administered, 2–5 h prior to RT.

## Dose escalation and dose-limiting toxicity (DLT)

A standard dose-escalation design with three-patient cohorts was utilized. No intra-patient dose escalation was allowed. Patients within a cohort were observed for DLT until the end of RT, and accrual was paused during this period. Accrual stopped as soon as two patients had DLTs at a dose level, and the MTD (the dose recommended for future phase II studies) was defined to be the next lower dose level. Initially, three patients were accrued to the lowest dose level. If none of these had DLT, three patients would be accrued to the next dose level, but if one had DLT, three additional patients would be accrued at the same level. If one of these six patients had DLT, three patients would be accrued to the next dose level. Dose escalation proceeded in like manner until the MTD was defined. After the MTD was defined, additional patients would be treated at the MTD so that toxicity data would be available for a total of 6–12 patients at the MTD.

DLT was defined as any drug-related $\geq$ grade 3 non-hematologic toxicity, grade 4 vomiting despite antiemetic use, grade 4 thrombocytopenia, grade 4 neutropenia or neutropenia accompanied by infection or fever. NCI-common toxicity criteria (CTC version 1.0) were used for toxicity grading.

## Radiation therapy

The radiation target dose was 5,040 cGy in 28 fractions to the primary tumor and its draining lymph nodes. A radiation boost of 900 cGy was given in five fractions in selected patients if exposure of normal tissue to radiation was limited. RT began on day 1, concurrently with MGd, and continued for 5 days/week. Target volume for head of the pancreatic cancers included the primary tumor with a 2-cm margin, the regional lymph nodes (pancreaticoduodenal, porta hepatic, celiac axis, and suprapancreatic lymph nodes) and the duodenal loop. Target volume for pancreatic body and tail cancers included the primary tumor with a 2-cm margin and the suprapancreatic and splenic hilar lymph nodes. Target volume for biliary tree tumors included the primary tumor with a 2-cm margin and the draining lymph nodes including porta hepatic, pancreaticoduodenal and celiac axis lymph nodes.

## Dose modifications

Patients were required to meet pre-study eligibility criteria prior to starting each week of therapy. If abnormal laboratory values were seen, or $\geq$ grade 2 toxicity attributable to MGd was present, administration of MGd was delayed for a maximum of 2 weeks. RT was continued during this period. RT was held in the case of $\geq$ grade 3 N/V or hospitalization for any toxicity. If MGd or RT was delayed $>2$ weeks, patients were taken off study. Dose modifications were not specified for MGd; if patients did not meet the above criteria, protocol therapy was discontinued.

## Study requirements and assessments

A history and physical examination were done pre-study, and physical examinations were repeated weekly. A complete blood count, evaluation of chemistries and

urinalysis were done pre-study and weekly during treatment. Response was assessed based upon computerized tomograms of the abdomen done pre-study and 4 weeks after RT was completed. World Health Organization (WHO) response criteria were used for the assessment of tumor response [19].

### Pharmacokinetics

Full pharmacokinetic studies were performed on three patients treated with 2.9 mg/kg and on one patient treated with 3.6 mg/kg of MGd. In those 4 patients, intensive pharmacokinetic sampling was performed on days 1 and 17 (MGd doses 1 and 8) of study. Blood samples were collected in heparinized tubes before MGd administration, at the end of the 15-min infusion, and at 5, 10, 15, and 60 min, and at 2, 4, 6, 8 and 24 h after completion of the infusion. Blood samples were also obtained before administration of all other doses (maximum of 15 samples) delivered during the course of the study. In two patients treated with 3.6 mg/kg of MGd, blood was sampled only before and during the first 24 h after their first dose of MGd. Blood samples were centrifuged at 4°C and approximately 1,000×*g*, and the resulting plasma was stored in polypropylene cryotubes at −70°C until assayed for MGd.

Urinary excretion of MGd was assessed in two patients who were treated with 2.9 mg/kg of MGd. In these patients, urine was collected from 0–6 and 6–24 h after the infusion on day 1 of therapy. The volume of each collection was measured, and an aliquot of each collection was stored at −70°C until analysis of MGd.

Concentrations of MGd in plasma and urine samples were quantitated with an HPLC assay that had been developed and validated in our laboratory [20].

All pharmacokinetic modeling was done with the ADAPT II computer program [21]. Two- and three-compartment, open, linear models were fit, with weighted least squares estimation, to the plasma MGd concentration versus time data. Model discrimination was based on Akaike's information criterion (AIC) [22]. In an effort to estimate the time course of MGd in tissues, patient-specific pharmacokinetic parameters and individual patient plasma concentration versus time data were used to simulate the concentration versus time profile of MGd in the peripheral compartment of each patient.

**Table 1** Patient characteristics

| | |
|---|---|
| Total | 12 |
| Evaluable | 11 |
| Male/Female | 6/6 |
| Median age | 59 years |
| Range | 46–72 years |
| Primary tumor | |
| Pancreatic | 11 |
| Biliary | 1 |
| Local-regional disease | 10 |
| Metastatic disease | 2 |
| Performance status | |
| ECOG 0 | 6 |
| ECOG 1 | 6 |

## Results

### Patient characteristics

Between September 1998 and July 2001, 12 chemo naive patients were enrolled in two dose levels (Table 1). Due to rapid development of jaundice, secondary to biliary stent blockage, one patient at dose level 1 was deemed inevaluable and was removed from the study after receiving his first dose of MGd.

Because there was one DLT among the first three patients treated at dose level 1 (2.9 mg/kg of MGd), this cohort was expanded to six patients without further evidence of a DLT. Three patients were then entered at dose level 2 (3.6 mg/kg). Due to the occurrence of DLT in two patients treated with 3.6 mg/kg, further enrollment to that cohort ceased. Subsequently, the 2.9 mg/kg dose cohort was expanded to eight evaluable patients and determined to be the phase II recommended dose (Table 2).

### Toxicity

A total of eight evaluable patients were treated with 2.9 mg/kg of MGd. At this dose level, five of the planned 128 MGd doses were omitted. Four patients received the full course of therapy without any modifications. One patient required a 3-day delay in administration of the last two doses of MGd because of nausea and dehydration. In two patients, treatment delays were due to cutaneous reactions consisting of pruritus and rash that occurred with MGd administration (Table 3). One patient developed a DLT that consisted of grade 3 fever associated with chills and rigors; the patient required hospitalization and was treated with IV antibiotics. A definite source of infection was not identified; after resolution of fever, this patient completed therapy without further incident, and subsequent doses of MGd were reduced for safety reasons by 20% to 2.3 mg/kg. (Patient #3, Table 3). At dose level 2 (3.6 mg/kg), three patients were treated and two experienced DLTs. One patient had protracted grade 3 N/V that required hospitalization and IV hydration. Toxcity was resolved and the patient was removed from study. Another patient developed a grade 3 skin reaction consisting of intense pruritus and burning, which required narcotics for relief. The third patient suffered nausea, vomiting and elevated alkaline phosphatase but did not meet criteria for a DLT. Dose delays occurred in all three patients treated with 3.6 mg/kg of MGd; 17 of the planned 48 doses at this dose level had to be omitted. Following MGd administration, nursing and medical

**Table 2** Drug-related toxicity

| Toxicity | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|
| Gastrointestinal | | | |
| Nausea | 6 | 5 | 1 |
| Vomiting | 5 | 5 | 0 |
| Diarrhea | 4 | 3 | 0 |
| Abdominal pain | 4 | 0 | 0 |
| Laboratory | | | |
| AP | 0 | 0 | 1 |
| AST/ALT | 2 | 0 | 0 |
| Platelets | 1 | 0 | 0 |
| Skin | | | |
| Pruritus/burning | 4 | 0 | 1 |
| Rash | 4 | 1 | 0 |
| Blisters | 1 | 0 | 0 |
| Discoloration | 4 | 0 | 0 |
| Other | | | |
| Fever | 0 | 1 | 1 |
| Anorexia/weight loss | 7 | 2 | 0 |
| Fatigue | 5 | 1 | 0 |

Selected toxicities; worst grade per patient for all cycles *AP* alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

staff noted that there was a slight greenish hue in the skin of most patients, and their urine was green. A cutaneous reaction was observed in three patients. Patients described this as a whole-body pricking, burning, or itching sensation, associated with a erythematous generalized rash that occurred within minutes of MGd administration (Table 3, depicted as C). This reaction occurred late in the treatment schedule, occurring after the tenth dose in two patients and after the fourteenth dose of MGd in one patient. Each of these patients was re-challenged with MGd, and the intensity of the reaction and symptoms increased with subsequent MGd administration despite premedication with diphenhydramine, H2-blockers and/or dexamethasone. This syndrome was reversible in 1–2 h, and was grade 1 or 2 in severity except in one patient, who required narcotics for intense pruritus (grade 3). No specific neurologic abnormalities were noted in association with these symptoms.

Liver enzyme elevations were uncommon, with reversible elevations seen in three patients with one episode of grade 3 toxicity (Patient #10); however, as this patient had elevated alkaline phosphatase levels at baseline, this was not considered a DLT. Hematological toxicities were rare, with only one grade 1 thrombocytopenia noted at the 3.6 mg/kg dose level. Although there were interruptions in MGd treatment, 9 of the 11 evaluable patients, who were entered onto the study, completed their RT according to schedule.

## Pharmacokinetic results

In each of the three patients studied after an MGd dose of 2.9 mg/kg, the plasma MGd concentration versus time data were similar after doses 1 and 8 (Fig. 1A–C). On day 1, peak plasma MGd concentrations in these three patients were 19.14, 37.08, and 34.85 μM, and MGd was still detectable in plasma at 24 and 48 h after MGd administration (Fig. 1A–C). After the eighth dose of MGd, peak plasma MGd concentrations in these three patients were 28.66, 34.7, and 31.23 μM (Fig. 1A–C). In each patient, trough MGd concentrations remained between 0.8 and 2 μM. Although pre-treatment plasma MGd concentrations tended to increase between Monday and Friday of each week during treatment, the interval between Friday and Monday doses was such that the three-times/week dosing schedule did not result in progressive MGd accumulation in plasma (Fig. 2A–C). On day 1, peak plasma MGd concentrations in the three patients treated with 3.6 mg/kg were 8.83, 23.87, and 8.80 μM (Fig. 3). Only one of these three patients had pharmacokinetic sampling performed after more than the first dose of MGd (Fig. 4). After doses 1 and 8, plasma MGd concentration versus time profiles in this patient were similar to the three patients treated with

**Table 3** MGd: dose administration schedule

| | Pt# | MGd dose schedule (16 doses over 5 1/2 weeks) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| 2.9 mg/kg | 1 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | 2 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | 3[a] | + | + | + | + | + | + | + | + | + | + | + | +[a] | + | + | + | + |
| | 4 | + | + | + | + | + | + | + | + | + | + | + | + | + | C | – | C |
| | 5 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | 7 | + | + | + | + | + | + | + | + | + | C | C | – | – | C | – | – |
| | 11 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| | 12 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 3.6 mg/kg | 8[a] | + | + | + | + | + | +[a] | – | – | – | + | + | – | – | – | – | – |
| | 9[a] | + | + | + | + | + | + | + | + | + | – | – | + | + | C | – | C[a] |
| | 10 | + | + | + | – | – | – | + | + | + | – | – | – | + | + | + | + |

Pt# 6 was inevaluable and not included in analysis
+ Dose administered, – dose omitted, *C* cutaneous reaction, *MGd* motexafin gadolinium
[a]Patients (Pt) with DLT and time of occurrence

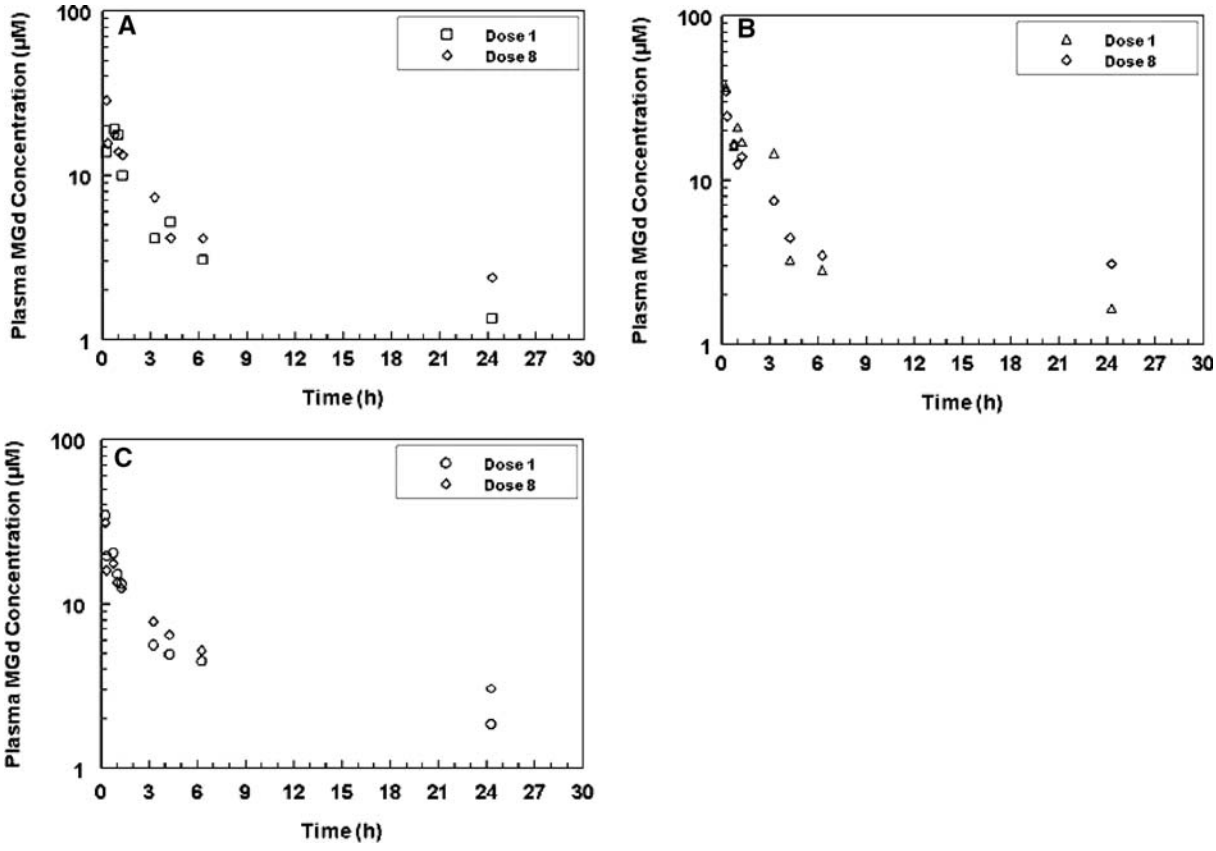


**Fig. 1** Plasma MGd concentration versus time data from three patients during the first 24 h after their first and eighth doses of MGd at 2.9 mg/kg. Data from individual patients are shown in panels **A**, **B**, and **C**

2.9 mg/kg of MGd (Fig. 4). Trough MGd plasma concentrations in this patient ranged between 0.056 and 0.27 μM and, as with patients treated with 2.9 mg/kg, did not indicate progressive accumulation of MGd in plasma.

Based on AUC, the two-compartment, open, linear model provided the most suitable fit to each patient's plasma MGd concentration versus time data. Moreover, this model was able to fit the plasma MGd trough concentrations in addition to the more intensive pharmacokinetic data obtained after doses 1 and 8. (Fig. 2A–C). Table. 4, 5 displays the patient-specific pharmacokinetic parameters resulting from fitting the two-compartment, open, linear model to the plasma MGd concentration versus time data from patients treated with 2.9 mg/kg of MGd. As indicated, there was good agreement with patient-specific pharmacokinetic parameters estimated when the two-compartment, open, linear model was fit to plasma concentration versus time data from the first 48 h after the first dose of MGd or to all of the plasma concentration versus time data obtained after multiple doses of MGd. Patient-specific pharmacokinetic parameters resulting from fitting the two-compartment, open, linear model to the plasma MGd concentration versus time data from patients treated with 3.6 mg/kg (Table. 4, 5) were consistent with those estimated for patients treated with 2.9 mg/kg. The combination of patient-specific pharmacokinetic parameters and individual patient plasma MGd concentration versus time data allowed the estimation of tissue MGd concentration versus time profiles in each patient (Fig. 5). In each patient, MGd concentrations in the peripheral compartment were estimated as increasing during the first 4–6 h after MGd administration and then decreasing slowly over the subsequent 18–20 h. Peak MGd concentrations in the peripheral compartment of the patients treated with 2.9 mg/kg were estimated at 1.2–1.6 μmol/kg after the first dose of MGd and at 1.6–2.0 μmol/kg after the eighth dose (Fig. 5).

Analysis of urine samples obtained from two patients between 0–6 and 6–24 h after administration of 2.9 mg/kg of MGd showed that less than 1% of the administered dose was excreted in the urine during the first day after MGd treatment. The 0–6 h samples contained between 0.28 and 0.46% of the dose, and the 6–24 h samples contained between 0.24 and 0.37% of the dose.

## Antitumor response and survival

Ten of eleven evaluable patients underwent radiological evaluation following the completion of therapy. None of these patients had disease progression at local sites, but six patients developed new or worsening liver metastases. The median survival of patients was 6 months.

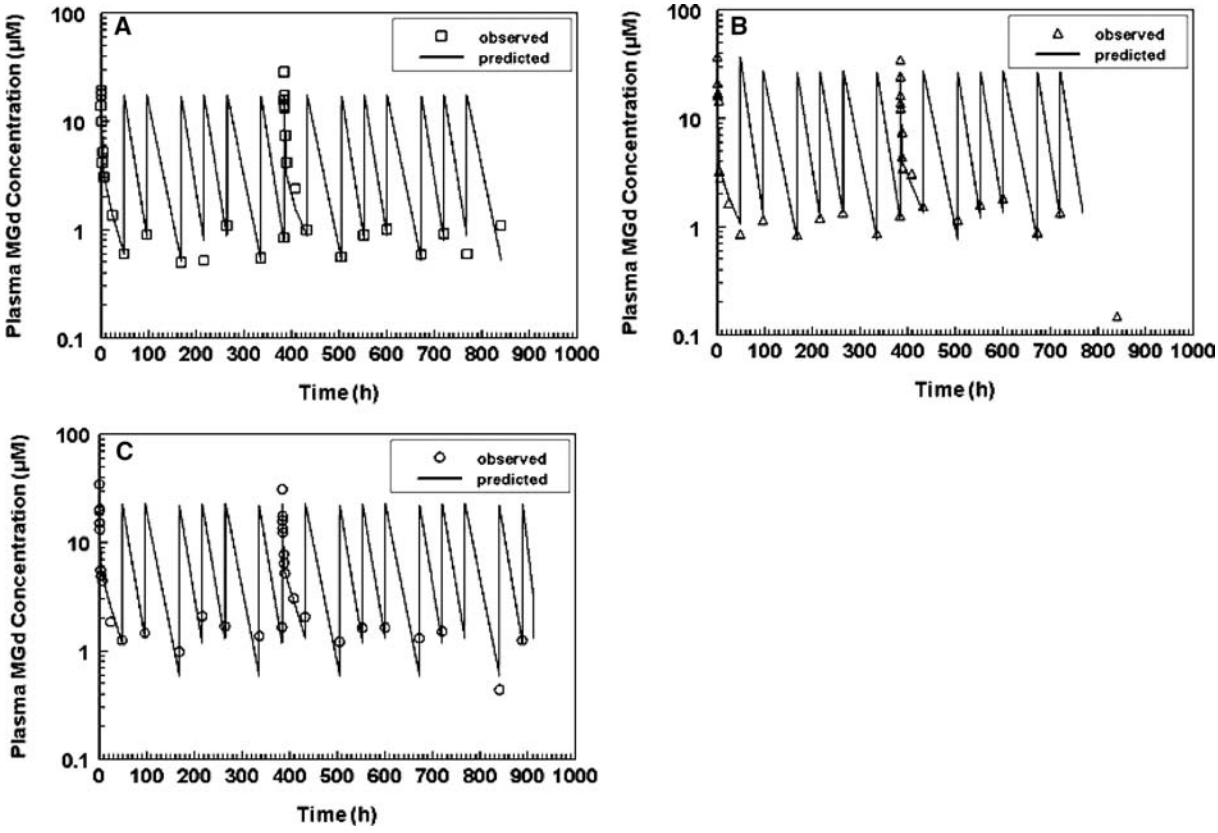


**Fig. 2** Plasma MGd concentration versus time data from three patients receiving MGd at 2.9 mg/kg. Data from individual patients are shown in panels **A**, **B**, and **C**. *Symbols* represent actual data and the *line* represents the fit of a two-compartment, open, linear model to the data

## Discussion

The recommended phase II dose of MGd from our study is 2.9 mg/kg given three times a week for 16 doses and combined with 5,040 cGy of RT given as 28 daily fractions of 180 cGy each. The cumulative dose of MGd is thus 46.4 mg/kg, which is comparable to the 50 mg/kg cumulative dose (5 mg/kg × 10 doses) utilized in the studies of MGd and RT in patients with brain metastasis [16].

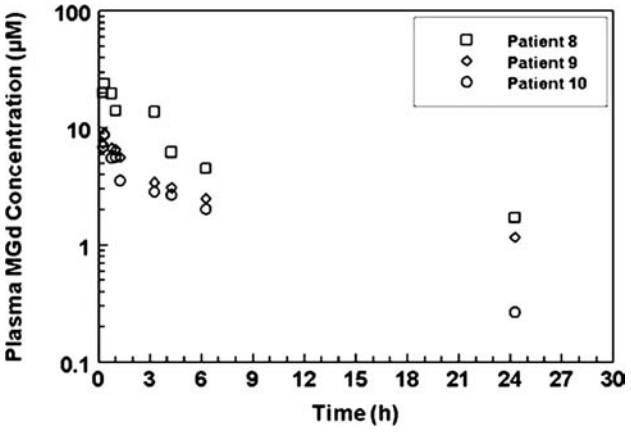


**Fig. 3** Plasma MGd concentration versus time data from three patients during the first 24 h after their first dose of MGd at 3.6 mg/kg

The toxicities seen in our study differ qualitatively from those observed in the studies of patients with brain metastases, where concurrent administration of MGd and RT were well tolerated. However, it should be noted that in our study, a higher dose of RT (5,040 cGy) was given over 5–6 weeks to abdominal organs, which typically causes gastrointestinal toxicity. There were three DLTs noted in this study. One patient at dose level 1 required hospitalization for fever and possible sepsis. The relationship of the toxicity to MGd or RT is unclear as there was no neutropenia and no infectious organism was identified. However, a drug-related fever secondary to MGd is a possibility. Dose level 2 was considered excessively toxic due to dose-limiting skin reactions, and N/V. Therefore dose level 1, 2.9 mg/kg, is the recommend phase II dose.

The grade 2, or higher, N/V that occurred in six (55%) patients on this study is probably due to the concurrent abdominal irradiation. In the future studies of MGd and RT in intra-abdominal malignancies, consideration should be given to omitting lymph node radiation, reducing the radiation field around tumors or utilizing intensity modulated radiation therapy (IMRT) [4–7].

The cutaneous reactions that occurred within minutes of MGd administration in our study have not been

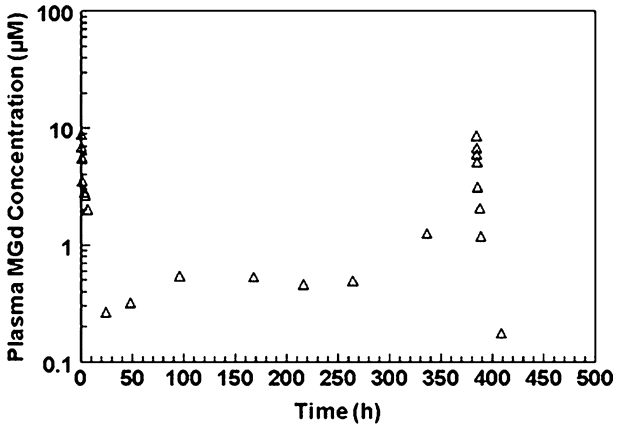


**Fig. 4** Plasma MGd concentration versus time data from one patient receiving MGd at 3.6 mg/kg

described previously and may reflect the repeated and protracted administration of MGd, leading to skin accumulation, which might cause skin sensitization. In other clinical trials employing a short course of MGd, cutaneous toxicities have been described, but consisted mostly of rash, pruritus and blisters, attributable to the porphyrin-based structure of MGd [13–16].

The pharmacokinetic data generated by this study might prove useful in designing future studies with MGd and RT. The terminal plasma half-lives estimated for the six patients in whom MGd pharmacokinetic studies were done are very consistent with the reported 28-h value used to design this study [18]. The pharmacokinetic parameters estimated for patients in the two cohorts studied are comparable, although we cannot explain why the maximum plasma concentrations of MGd in two patients treated with 3.6 mg/kg were so much lower than those of the three patients treated with 2.9 mg/kg. The availability of data after multiple doses of MGd to the individual patients demonstrates the intra-patient consistency of MGd pharmacokinetics. Specifically, there was no evidence for induction or reduction of MGd clearance during the repetitious three-times/week dosing schedule used in this study. Although the peripheral compartment in a two-compartment model does not specifically represent tissue, it can allow an estimation of the concentrations of MGd achieved in tissues and the time course of those concentrations. The 1–2 μmol/kg concentrations of MGd estimated as being in the peripheral compartment are compatible with the concentrations of MGd that are known to enhance RT in vitro and in pre-clinical in vivo models [18]. Furthermore, the estimation of peak peripheral compartment MGd concentrations occurring at 4–6 h after MGd administration might provide some guidance as to the appropriate time after MGd treatment to deliver RT. A population PK study in patients with brain tumors has been done using a three-compartment model to evaluate clinical variables in MGd clearance, and may also prove useful for MGd dosing in subsequent studies [23].

Response and survival data should be interpreted with caution given the small number of patients. Furthermore, our patients had unfavorable prognostics including liver metastases in two patients and relatively bulky pancreatic tumors in the rest.

MGd enhances the activity of several drugs in vivo and combination therapy with docetaxel and doxorubicin are being evaluated in ongoing studies [24–27]. In addition, single agent clinical trials in multiple myeloma and related disorders have been initiated based on the results of preclinical studies [28].

In summary, the administration of MGd on a thrice-weekly protracted schedule at the dose of 2.9 mg/kg

**Table 4** Pharmacokinetic parameters resulting from fit of a two-compartment model to plasma MGd concentration versus time data after the first dose of MGd

| Patient | Dose | Ke ($h^{-1}$) | V (l $kg^{-1}$) | Kcp ($h^{-1}$) | Kpc ($h^{-1}$) | $t_{1/2\beta}$ (h) | Cl (l $h^{-1}$ $kg^{-1}$) |
|---|---|---|---|---|---|---|---|
| 1 | 2.9 | 0.1541 | 0.1398 | 0.3444 | 0.1392 | 19.5 | 0.0215 |
| 4 | 2.9 | 0.2068 | 0.0774 | 0.4658 | 0.0853 | 28.84 | 0.0160 |
| 5 | 2.9 | 0.1467 | 0.0928 | 0.5072 | 0.1452 | 25.11 | 0.0136 |
| 8 | 3.6 | 0.1519 | 0.275 | 1.212 | 0.624 | 6.3 | 0.042 |
| 9 | 3.6 | 0.1491 | 0.280 | 1.255 | 0.545 | 16.3 | 0.042 |
| 10 | 3.6 | 0.2591 | 0.0967 | 1.294 | 0.448 | 11.6 | 0.025 |

**Table 5** Pharmacokinetic parameters resulting from fit of a two-compartment model to all of the plasma MGd concentration versus time data from each patient

| Patient | Dose | Ke ($h^{-1}$) | V (l $kg^{-1}$) | Kcp ($h^{-1}$) | Kpc ($h^{-1}$) | $t_{1/2\beta}$ (h) | Cl (l $h^{-1}$ $kg^{-1}$) |
|---|---|---|---|---|---|---|---|
| 1 | 2.9 | 0.1533 | 0.1305 | 0.2816 | 0.0752 | 29.22 | 0.0215 |
| 4 | 2.9 | 0.1807 | 0.0805 | 0.6029 | 0.1219 | 27.7 | 0.0146 |
| 5 | 2.9 | 0.1322 | 0.0974 | 0.6042 | 0.2409 | 20.54 | 0.0129 |

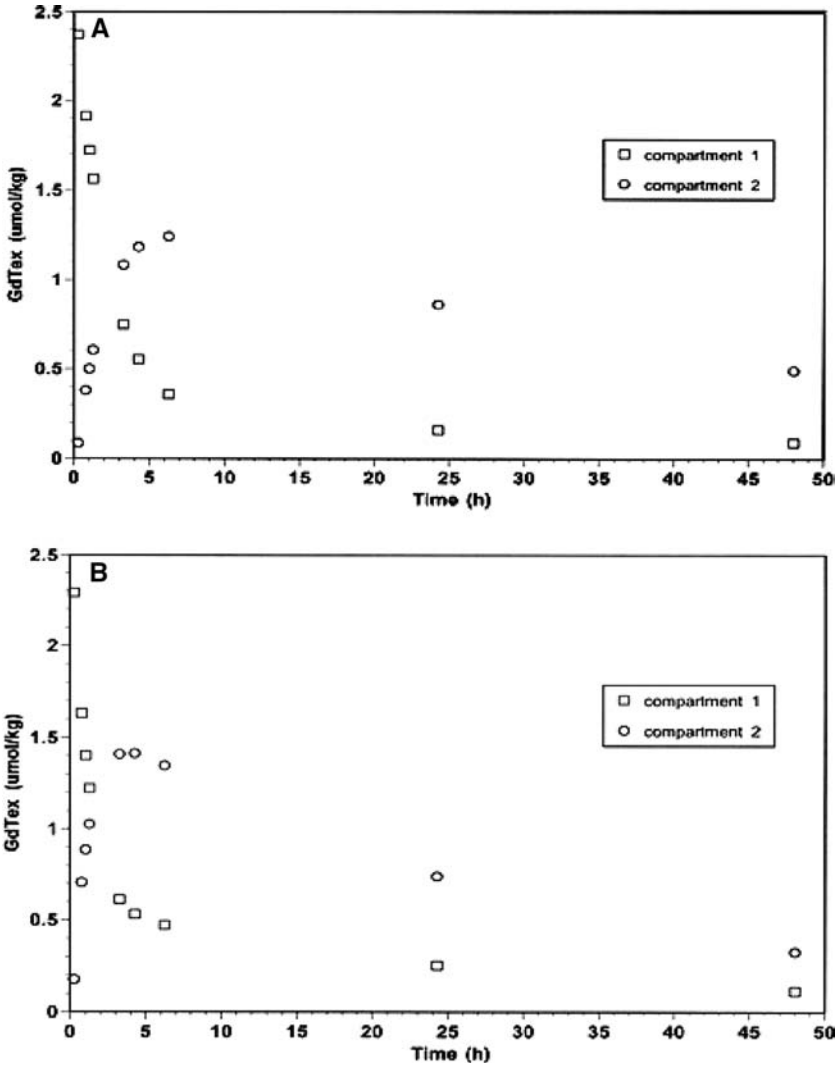


**Fig. 5** Simulated concentrations of MGd in the peripheral compartment of patients treated with 2.9 mg/kg. **A** Displays simulated concentrations after dose 1 and **B** displays simulated concentrations after dose 8

concurrent with standard dose RT in locally advanced biliary or pancreatic cancers is feasible. The incidence of nausea, vomiting and skin reactions remains problematic. In particular, if skin reactions occur, further administration of MGd may need to be discontinued. Future studies with MGd should consider less intensive schedules of MGd administration, such as twice weekly, and reduced field RT or IMRT.

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