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ORIGINAL ARTICLE

Phase I clinical and pharmacokinetic study of the glucose-conjugated cytotoxic agent D-19575 (glufosfamide) in patients with solid tumors

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Abstract
Purpose D-19575 (glufosfamide: β-D-glucosylisophosphoramide mustard) is an alkylating agent in which isophosphoramide mustard, the cytotoxic metabolite of ifosfamide, is covalently linked to β-D-glucose. We have performed a phase I study to determine the safety profile, pharmacokinetics, and antitumor activity of D-19575 in Japanese patients with advanced solid tumors
Methods Patients were treated with escalating doses of D-19575 administered by a two-step (fast–slow) intravenous infusion over 6 h every 3 weeks. Thirteen patients received 43 treatment cycles (median 3; range 1–11) at D-19575 doses of 3,200, 4,500, or 6,000 mg/m^2.
Results Hematologic toxicities and other side effects were generally mild. The maximum tolerated dose of D-19575 was 6,000 mg/m^2, at which two patients experienced dose-limiting toxicities (hypophosphatemia, hypokalemia, and metabolic acidosis each of grade 3). Pharmacokinetic analysis revealed a linear relation between the area under the concentration-versus-time curve (AUC) and dose. The AUC values for isophosphoramide mustard were substantially greater than those achieved by bolus administration or continuous infusion of ifosfamide in conventional therapy. One patient with gallbladder cancer previously treated with cisplatin and gemcitabine achieved a partial response lasting for >5 months, and eight patients achieved disease stabilization.
Conclusions Our results show that D-19575 can be safely administered by infusion over 6 h at 4,500 mg/m^2 every 3 weeks. The safety profile and potential antitumor activity of D-19575 show that phase II studies of this drug are warranted.

Keywords Glufosfamide · Isophosphoramide mustard · Glucose transporter · Pharmacokinetics

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Introduction

D-19575 (glufosfamide: β-D-glucosylisophosphoramide mustard) is a new-generation cytotoxic alkylating agent in which isophosphoramide mustard (IPM), the active metabolite of ifosfamide (IFO), is covalently linked to β-D-glucose (Fig. 1). The structure and metabolism of the D-19575 molecule are thought to be associated with two therapeutic advantages: a reduced generation of toxic metabolites compared with IFO, and targeting by the glucose moiety to rapidly proliferating tumor cells [1, 2].

Rapidly proliferating and energy-consuming cancer cells have been shown to overexpress certain glucose transporter proteins [3, 4]. D-19575 has the potential to target tumor

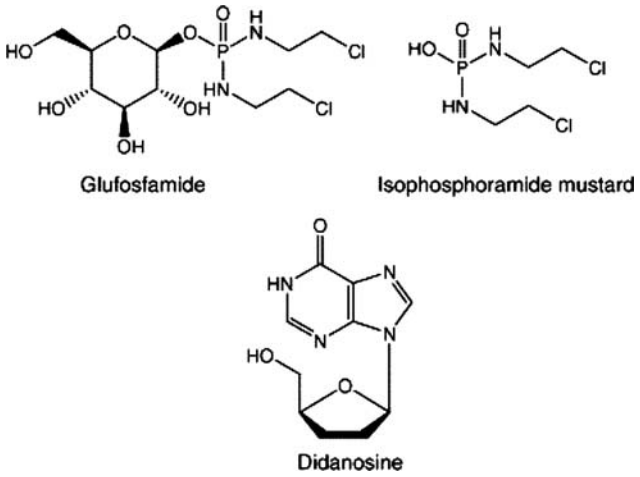

Fig. 1 Structures of D-19575 (glufosfamide), isophosphoramide mustard (the active cytotoxic metabolite of D-19575), and didanosine (internal standard)

cells by serving as a substrate for such glucose transporters in the plasma membrane [5–7]. Together with the increased metabolic rate and glucose consumption of tumor cells, this targeting mechanism may contribute to the relative selectivity of D-19575 for tumor cells.

Another characteristic of D-19575 is that, because of the absence of the oxazophosphorine ring in its structure, it does not release the urothelium irritant acrolein, which has been shown to induce hemorrhagic cystitis in individuals treated with IFO [2]. Moreover, the amount of toxic chloroacetaldehyde generated metabolically after administration of D-19575 is markedly reduced compared with that generated after IFO administration (unpublished data). Although the pathogenesis of IFO-induced nephrotoxicity is poorly understood, the reduced production of chloroacetaldehyde may minimize such toxicity of D-19575. Preclinical pharmacokinetic analysis of D-19575 has revealed that the drug is rapidly cleared by the kidneys and has favorable tissue-distribution and protein-binding profiles [8]. Toxicity studies in rodents have shown that D-19575 is more toxic when administered orally than intravenously, apparently because of a pronounced first-pass effect and increased production of toxic metabolites (data on file; ASTA Medica AG, Germany).

The aims of the present study were to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of D-19575, to otherwise evaluate the safety profile of the drug, and to analyze its pharmacokinetics after administration by biphasic (fast–slow) intravenous infusion over 6 h every 3 weeks in Japanese patients with refractory advanced solid tumors. Furthermore, we performed a pharmacokinetic analysis of IPM generated from D-19575.

Patients and methods

Study objectives

This phase I study aimed to evaluate the safety (including DLTs and MTD) and pharmacokinetic profiles of D-19575 administered by intravenous infusion over 6 h in Japanese individuals with solid tumors who relapsed after adequate or standard chemotherapy or in those with advanced or metastatic solid tumors for whom no effective standard therapy was available. The study was fully supported by Medibic Pharma Co. Ltd (Tokyo, Japan) as a registration-directed clinical trial. D-19575 was synthesized in the Chemical Research Laboratories of ASTA Medica AG (Frankfurt, Germany). ASTA Medica AG's oncology division was acquired by Baxter International in 2001, but Baxter International itself terminated D-19575 development and shortly thereafter licensed their rights to Threshold Pharmaceuticals (Redwood City, CA, USA). In this study, D-19575 was supplied by Medibic Pharma Co. Ltd. Medibic Pharma and Threshold Pharmaceuticals agreed to co-develop D-19575 in Asia on December 2004.

Eligibility

Eligible patients were individuals aged 20–75 years who had solid tumors that were either refractory to conventional treatment or for which no standard treatment was available; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; had adequate hematopoietic reserves [absolute neutrophil count (ANC) of $\geq$1,500/μL, platelet count of $\geq$100,000/μL, hemoglobin concentration of $\geq$9.0 g/dL]; had serum total bilirubin and creatinine concentrations of $\leq$1.5 times the upper limit of institutional normal (ULN); had serum aspartate aminotransferase and alanine aminotransferase activities of $\leq$2.5 times ULN; had not received chemotherapy or radiation therapy within the previous 4 weeks; had no exposure to nitrosoureas or mitomycin within the previous 6 weeks; and had given consent to be hospitalized during the first course of treatment with D-19575. Patients were ineligible if they had symptomatic brain metastasis; other nonmalignant systemic disease; an active, uncontrolled infection; preexisting nephrotoxicity of grade 3 or 4 [National Cancer Institute Common Toxicity Criteria (NCI-CTC)] resulting from previous therapy; or infection with human immunodeficiency virus or hepatitis B or C virus. They were also ineligible if they were pregnant or nursing, or if they required steroid therapy. All patients provided written informed consent before entering the study. The study was approved by the Institutional Review Board at each participating center and conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines.

A medical history was obtained from each patient, and physical examinations and routine laboratory evaluations were performed before treatment initiation and weekly thereafter. Chest and other relevant X-rays were obtained during screening and after alternate cycles of treatment. Adverse events were monitored and recorded throughout the study and were graded according to NCI-CTC, version 3.0. The tumor response was assessed for measurable target lesions according to Response Evaluation Criteria in Solid Tumors (RECIST).

Treatment administration

This open-label, dose-escalation phase I study of D-19575 was based on intravenous infusion of the drug in three cohorts of Japanese subjects with malignant solid tumors. D-19575 was administered intravenously over 6 h in a total volume of 1,000 mL of normal saline at doses of 3,200, 4,500, and 6,000 mg/m^2. One-quarter of the dose was administered during the first 30 min at a rate of 500 mL/h, with the remainder of the dose being administered over the subsequent 330 min at a rate of 136 mL/h. D-19575 was administered on day 1 once every 3 weeks. Antiemetic premedication was not mandatory in the protocol. Granulocyte colony-stimulating factor (G-CSF) was administered for febrile neutropenia, sepsis with neutropenia, or recurrent neutropenia of grade 4.

DLTs and MTD

The starting dose of D-19575 was 3,200 mg/m^2, which was increased to 4,500 and then to 6,000 mg/m^2 in subsequent cohorts of at least three patients. The following adverse events during cycle 1 were defined as DLTs: neutropenia of grade 4 (ANC of <500/μL) for >7 days; febrile neutropenia (fever of >38.0°C with an ANC of <1,000/μL); thrombocytopenia (platelet count of <25,000/μL); nausea or vomiting of grade ≥3 despite maximal antiemetic therapy; and any other nonhematologic toxicity of grade ≥3 considered related to D-19575. If any patient experienced a DLT during the first cycle, three additional patients were treated at the same dose. Patients who experienced a DLT could continue D-19575 therapy at the preceding dose level. Treatment in subsequent courses was reinitiated only after hematologic recovery (ANC of ≥1,500/μL, platelet count of ≥100,000/μL) and resolution of all other toxicities to grade ≤1 or baseline intensity. The MTD was defined as the dose at which two or more patients experienced a DLT in the first cycle. The recommended dose was defined as the dose level immediately below the MTD.

Pharmacokinetic analysis

Pharmacokinetic sampling was performed for the first and second cycles. Blood samples (2.0 mL) for analysis of the plasma concentrations of D-19575 and IPM were collected at 10 time points on the day of drug administration (total volume of 20 mL of blood): immediately before the start of drug infusion and at 0.5, 1, 3, 6 (immediately before the end of infusion), 6.5, 7, 8, 12, and 24 h after the start of infusion. Plasma samples were stored at –70°C until analysis. D-19575 and IPM in plasma samples were measured by high-performance liquid chromatography and tandem mass spectrometry at Covance Bioanalytical Services (Indianapolis, IN, USA).

The plasma concentration-versus-time data for D-19575 and IPM in cycles 1 and 2 were analyzed with a noncompartmental method. The pharmacokinetic parameters of D-19575 and IPM determined included the maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty}$), terminal elimination half-time ($t_{1/2}$), total body clearance (CL_{tot}), and volume of distribution at steady state (V_{ss}). The $AUC_{0-\infty}$ was determined by summing the area from time zero to the time of the last measured concentration (as calculated with the use of a log trapezoidal method) and the extrapolated area. The extrapolated area was determined by dividing the final concentration by the slope (k) of the terminal log linear phase. The absolute value of k was also used to estimate the apparent terminal elimination half-time: $t_{1/2} = \ln(2/k)$. The CL_{tot} was determined by dividing dose by $AUC_{0-\infty}$. The V_{ss} was calculated by multiplying CL_{tot} by the mean residence time, which was determined as the area under the moment curve to infinity divided by $AUC_{0-\infty}$. All pharmacokinetic parameters were calculated with the use of WinNonlin Professional 5.0 software (Pharsight Corporation, Mountain View, CA, USA), and all calculations were performed with the actual times recorded on the case report form and with zero substituted for concentrations below the quantification limit of the assay (5 ng/mL for both D-19575 and IPM). The plasma concentrations of D-19575 and IPM (day 1 of cycles 1 and 2) were listed by subject and summarized by dose (mean, standard deviation, coefficient of variation, minimum, maximum, number of observations). Dose-adjusted $AUC_{0-\infty}$ and C_{max} values were calculated for each subject by dividing $AUC_{0-\infty}$ and C_{max} by dose. Analysis of variance appropriate for a parallel, dose-ascending design was performed on the dose-adjusted parameters to assess dose proportionality. Individual and mean plasma concentrations of D-19575 and IPM versus time after administration of D-19575 were tabulated and presented graphically on both linear and logarithm scales. For the time course graphs,

values below the quantification limit of the assay were set to zero.

Results

Patient characteristics

Thirteen patients (nine men and four women; median age, 62 years) were enrolled in the study between January and August 2007. Patient characteristics are shown in Table 1. Most patients were heavily pretreated, with the median number of prior chemotherapy regimens being three.

Table 1 Patient characteristics

Characteristic	No. of patients (n = 13)
Sex (male/female)	9/4
Age (years)	
Median	62
Range	51–73
ECOG performance status	
0	3
1	10
Tumor type	
Colorectal cancer	7
Non-small cell lung cancer	1
Thymic cancer	1
Thymoma	1
Gallbladder cancer	1
Gastric cancer	1
Uterine corpus-endometrial cancer	1
Previous treatment	
Chemotherapy (no. of regimens)	
1	1
2	4
3	3
4	1
≥5	4
Radiation	3
Surgery	12

DLTs and MTD

Patient distribution by dose level is shown in Table 2. No DLTs occurred in the patient cohorts treated with D-19575 at the doses of 3,200 mg/m^2 (n = 3) or 4,500 mg/m^2 (n = 7). At the dose of 6,000 mg/m^2, however, two of three treated patients experienced DLTs: One patient experienced metabolic acidosis and hypophosphatemia of grade 3, the other patient experienced hypophosphatemia and hypokalemia of grade 3. All DLTs were transient and reversible. The dose of 6,000 mg/m^2 was thus identified as the MTD, and enrollment of patients in the study was stopped. The recommended dose level for phase II evaluation was therefore determined to be 4,500 mg/m^2.

Safety

A total of 43 cycles of treatment was administered to the 13 patients, with a median of three cycles per patient and a range of 1–11 (Table 2). The incidence of hematologic toxicities by dose level is shown in Table 3. Clinically significant effects on ANC or platelet count were rare and only one patient, treated at the dose of 4,500 mg/m^2, experienced neutropenia of grade 4 without infection, which occurred during cycle 2 and was short-lived. Red blood cell transfusion was required in one patient treated at the dose of 4,500 mg/m^2 during cycle 3 because of the development of grade 4 anemia. Other hematologic toxicities were mostly of grade 1 or 2 and were reversible. The predominant nonhematologic toxicities were fatigue, nausea, a high urinary concentration of β_2-microglobulin, hypophosphatemia, hypokalemia, and metabolic acidosis (Table 4). Nonhematologic toxicities were also generally transient and reversible.

Pharmacokinetics

Plasma samples were obtained from all 13 patients during the first and second cycles of treatment. Plots of the mean plasma concentrations of D-19575 and IPM (the active metabolite of D-19575) versus time are shown in Fig. 2a. There was substantial interpatient variability in the pharmacokinetics of D-19575 after intravenous administration

Table 2 Dose-escalation scheme and summary of DLT incidence

Dose (mg/m^2)	No. of patients	No. of cycles	No. of patients with DLT	DLT (grade)
3,200	3	8	0	
4,500	7	28	0	
6,000	3	7	2	Hypophosphatemia (grade 3), hypokalemia (grade 3), metabolic acidosis (grade 3)
Total	13	43	2	

Table 3 No. of patients with hematologic toxicities (all cycles)

Dose (mg/m^2)	No. of patients	Neutropenia				Anemia				Thrombocytopenia			
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
3,200	3	1	0	1	0	1	0	0	0	0	0	0	0
4,500	7	1	0	1	1	2	1	0	1	2	0	1	0
6,000	3	0	1	0	0	0	0	0	0	1	0	0	0
Total	13	2	1	2	1	3	1	0	1	3	0	1	0

Table 4 Number of patients with nonhematologic toxicities (all cycles)

Dose (mg/m^2)	No. of patients	Fatigue/generalized weakness				Hypophosphatemia				Hypokalemia				Metabolic acidosis			
		Grade				Grade				Grade				Grade			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
3,200	3	3	0	0	0	0	1	0	0	0	0	0	0	1	0	1	0
4,500	7	6	2	0	0	0	2	2	0	1	0	1	1	0	0	2	0
6,000	3	2	0	0	0	0	2	2[a]	0	0	0	1[a]	0	0	0	1[a]	0
Total	13	11	2	0	0	0	5	4	0	1	0	2	1	1	0	4	0

[a] DLT

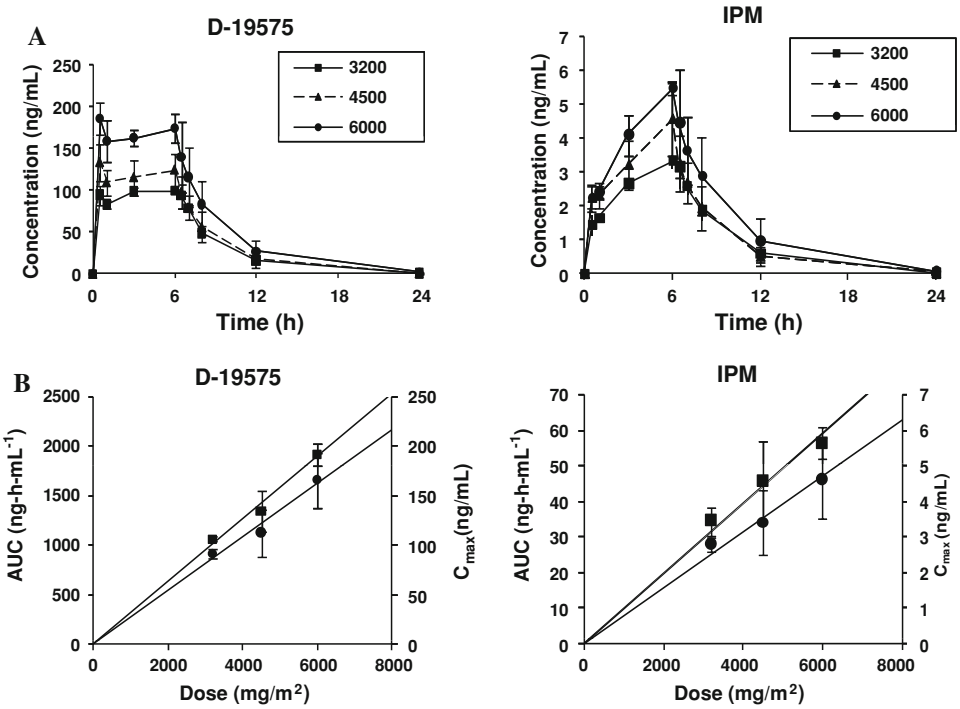

Fig. 2 Time course of the mean plasma concentrations of D-19575 and IPM after a single intravenous infusion of D-19575 (3,200, 4,500, or 6,000 mg/m^2) over 6 h (**a**) and the relations between the $AUC_{0-\infty}$ or C_{max} of D-19575 or IPM and the dose of D-19575 (**b**) for the first cycle of treatment. Data are means ± SD

of single doses of 3,200, 4,500, or 6,000 mg/m^2, but both D-19575 and IPM exhibited linear pharmacokinetics over the dose range studied (Fig. 2b). Pharmacokinetic parameters for D-19575 and IPM are summarized by dose of D-19575 in Tables 5 and 6, respectively. The mean C_{max} values of D-19575 were 107–192 ng/mL and were achieved at 2.46–3.33 h, with the mean $t_{1/2}$ values ranging from 2.30 to 2.53 h. D-19575 exhibited low CL_{tot} values [3.47–4.08 L/(h m^2)] as well as V_{ss} values (8.94–9.76 L/m^2) that were approximately equal to the volume of extracellular fluid. The plasma levels of IPM were smaller than those of D-19575 by a factor of ~25–30. The mean C_{max} values of IPM were 3.46–5.65 ng/mL and were achieved in 6.04–6.59 h, with mean $t_{1/2}$ values being similar to those for D-19575 and ranging between 2.38 and 2.66 h. There was no difference in pharmacokinetic data between cycles 1 and 2 for either D-19575 or IPM (data not shown).

Table 5 Mean pharmacokinetic parameters of D-19575 in plasma after a 6 h intravenous infusion of the indicated doses of D-19575 during cycle 1

Dose (mg/m^2)	No. of patients	$AUC_{0-\infty}$ (ng h/mL)		C_{max} (ng/mL)		$t_{1/2}$ (h)		CL_{tot} [L/(h m^2)]		V_{ss} (L/m^2)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
3,200	3	914	43.6	107	2.65	2.38	0.07	3.47	0.18	8.94	0.74
4,500	7	1,130	239	135	21.0	2.30	0.34	4.08	0.86	9.76	1.37
6,000	3	1,659	276	192	11.0	2.53	0.34	3.65	0.70	9.71	1.43

Table 6 Mean pharmacokinetic parameters of IPM in plasma after a 6 h intravenous infusion of the indicated doses of D-19575 during cycle 1

Dose (mg/m^2)	No. of patients	$AUC_{0-\infty}$ (ng h/mL)		C_{max} (ng/mL)		$t_{1/2}$ (h)	
		Mean	SD	Mean	SD	Mean	SD
3,200	3	28.1	2.04	3.46	0.39	2.38	0.06
4,500	7	34.0	8.84	4.58	1.11	2.47	0.37
6,000	3	46.5	11.2	5.65	0.43	2.66	0.45

Antitumor activity

Among all 13 patients evaluable for response, evidence of antitumor activity was observed in nine individuals, with one partial response and eight subjects showing stabilization of disease (Table 7). A 65-year-old female patient with advanced gallbladder cancer who had been treated with fluorouracil, cisplatin, and gemcitabine achieved a partial response that persisted for >5 months after two cycles of treatment with D-19575 at 4,500 mg/m^2 (Fig. 3). Stable disease was confirmed in four patients with colorectal cancer, one with gastric cancer, one with thymic cancer, one with thymoma, and one with non-small cell lung cancer.

Discussion

D-19575 has been developed as a new-generation cytotoxic alkylating agent whose activity is due in part to the preferential use of glucose by malignant cells [9]. We have now performed a dose-escalation phase I study of D-19575 in patients with solid tumors for evaluation of the safety and pharmacokinetics of this drug. Previous clinical trials with D-19575 were conducted given as short 1 h infusion schedule [10, 11]. However, taking into account the cellular uptake and cleavage of D-19575, a more continuous infusion schedule seemed to be preferable. Indeed, a previous pharmacokinetic analysis found that biphasic (fast–slow) intravenous infusion schedule produced the desired profile of a rapidly achieved and sustained plasma concentration for more than 6 h [12]. Based on the data, we have also employed a two-step, fast/slow 6 h infusion of D-19575 to rapidly achieve steady-state concentrations and expose tumor cells to the study drug over a moderately prolonged time. The MTD was determined to be 6,000 mg/m^2, with the recommended dose for phase II studies being 4,500 mg/m^2. DLTs included hypophosphatemia, hypokalemia, and metabolic acidosis, all of which are presentations of nephrotoxicity. In animals treated with D-19575, nephrotoxicity was evidenced histologically by a focal vacuolization of proximal tubules and a diffuse dilation of distal tubules (data on file; ASTA Medica AG, Germany). A major advantage of D-19575 over IFO is that treatment with D-19575 does not require administration of sodium mercaptoethanesulfonate for protection against urothelial toxicity. Two recent phase II trials performed by the European Organization for Research and Treatment of Cancer (EORTC)—New Drug Development Group [10, 11], demonstrated that active hydration did not show any nephroprotective effect toward D-19575 by reducing the contact time of tubule cells with the drug. On the basis of these results, active hydration was not used routinely in our study. Despite concerns for potential renal dysfunction with D-19575, creatinine clearance did not undergo a substantial decline in any of the treated patients (data not shown).

The initial activation reaction in IFO metabolism that gives rise to antitumor activity is mediated predominantly by the cytochrome P450 enzyme CYP3A4. The oxidation

Table 7 Antitumor activity of D-19575

Response	No of patients (%)
Partial response	1 (8)[a]
Stable disease	8 (62)[b]
Progressive disease	4 (30)
Not evaluable[c]	0 (0)

[a] Dose of 4,500 mg/m^2

[b] Two patients at a dose of 3,200 mg/m^2, four patients at 4,500 mg/m^2, and two patients at 6,000 mg/m^2

[c] Not assessed for response

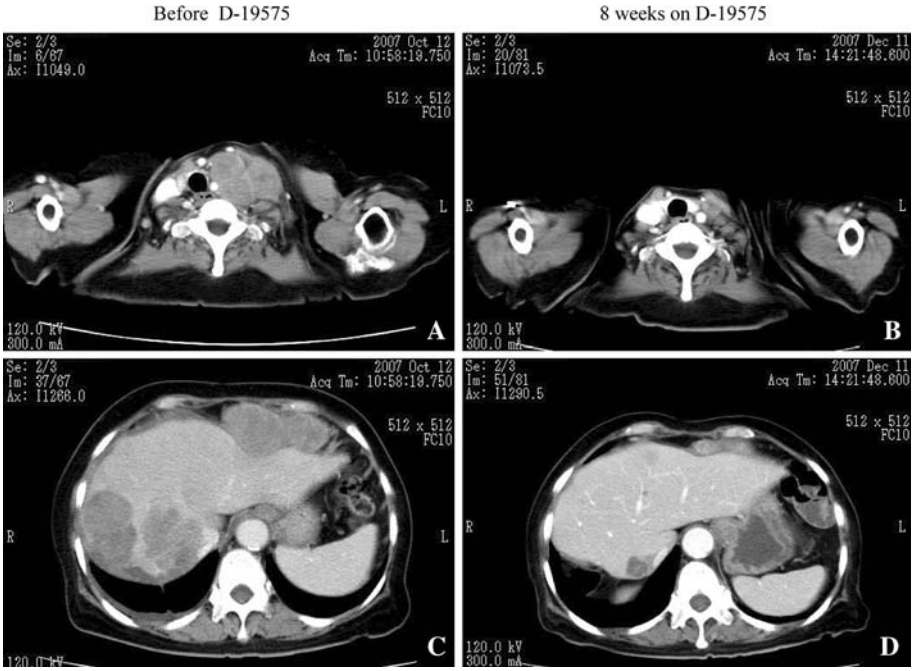

Fig. 3 Representative computed tomography images illustrating response in patient with gallbladder cancer: Tumor shrinkage in cervical lymph node metastasis (**a**, **b**) and multiple liver metastases (**c**, **d**)

of IFO occurs via two major routes: (1) at the cyclic C-4, resulting in the formation of 4-OH-IFO, which is then decomposed to the cytotoxic metabolite IPM [13] and acrolein; and (2) through side-chain dechlorethylation, resulting in the formation of chloroacetaldehyde [14]. We have now shown that the plasma levels of IPM were smaller than those of D-19575 by a factor of ~25–30 in patients treated with D-19575. The $AUC_{0-\infty}$ for IPM increased in a dose-proportional manner within the range of 28.1–46.5 ng h/mL, values that are markedly higher than those achieved for IPM generated from IFO after bolus administration (mean of 11.9 ng h/mL) or continuous infusion (mean of 17.8 ng h/mL) in conventional treatment of soft tissue sarcoma [15]. These pharmacokinetic data suggest that infusion of D-19575 allows the safe achievement of higher concentrations of IPM compared with those achieved with standard IFO therapy. We also obtained no evidence of a relation between pharmacokinetic parameters and the occurrence of renal toxicity in the present study.

The intracellular uptake of D-19575 is mediated by the facilitative glucose transporters GLUT1 to GLUT5, the sodium-dependent glucose transporters SGLT1 and SGLT2, and, possibly, other transporter proteins. Increased rates of glucose transport and glycolysis are characteristic features of malignant transformed cells that result in part from overexpression of glucose transporters [16–19]. Overexpression of GLUT1 to GLUT3 has been detected in a wide range of human cancers, most prominently in those of breast, colon, and liver, with the extent of overexpression generally being inversely correlated with prognosis [20–22]. Its uptake mechanism, coupled with the increased metabolic rate of tumor cells, may contribute the chemotherapeutic activity of D-19575. The level of GLUT1 expression in tumors has been shown to be positively correlated with 2-[^{18}F]fluoro-2-deoxy-D-glucose uptake, semiquantified as standardized uptake value in positron emission tomography [23–26], suggesting that the latter parameter may be a suitable noninvasive biomarker for the sensitivity of cancers to D-19575.

In conclusion, the results of our phase I study suggest that D-19575 can be safely administered at a dose of 4,500 mg/m^2 by infusion over 6 h every 3 weeks to Japanese patients with advanced solid malignancies. They further suggest that this drug may prove clinically effective when administered as a single agent. The AUCs for IPM generated by D-19575 were found to be markedly higher than those achieved by administration of IFO, suggesting that infusion of D-19575 allows the safe achievement of higher concentrations of IPM compared with those generated by administration of IFO according to widespread clinical practice. The safety profile and the potential broad-spectrum efficacy of D-19575 thus warrant additional clinical evaluation of this new alkylating agent.

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