RAPID PUBLICATION

Clinical and Pharmacokinetic Phase I Study of Multitargeted Antifolate (LY231514) in Combination With Cisplatin

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Purpose: **Multitargeted antifolate (MTA; LY231514) has broad preclinical antitumor activity and inhibits a variety of intracellular enzymes involved in the folate pathways. This study was designed to (1) determine the maximum-tolerated dose (MTD), dose-limiting toxicities (DLT), and pharmacokinetics of MTA combined with cisplatin; (2) determine a recommended dose for phase II studies; and (3) collect anecdotal information on the antitumor activity of MTA combined with cisplatin.**

Patients and Methods: **Patients with solid tumors received MTA intravenously over 10 minutes and cisplatin over 2 hours once every 21 days. In cohort 1, both agents were administered on day 1 starting with MTA 300 mg/m² and cisplatin 60 mg/m². In cohort 2, MTA (500 or 600 mg/m²) was administered on day 1, followed by cisplatin (75 mg/m²) on day 2.**

Results: **In cohort 1, 40 assessable patients received 159 courses of treatment. The MTD was MTA 600 mg/m²/cisplatin 100 mg/m². DLTs were reversible leukopenia/neutropenia and delayed fatigue. Hydration before cisplatin therapy did not influence MTA pharmacokinetics. Eleven objective remissions included one complete response in a patient with relapsed squamous cell head and neck carcinoma, and partial responses in four of ten patients with epithelial pleural mesothelioma. In cohort 2, 11 assessable patients received 23 courses of treatment. The MTD was MTA 600 mg/m² and cisplatin 75 mg/m². DLTs were neutropenic sepsis, diarrhea, and skin toxicity. Two patients died of treatment-related complications during the study. Two patients had objective remissions (one mesothelioma patient, one colon cancer patient).**

Conclusion: **The combination of MTA and cisplatin is clinically active, and administering both agents on day 1 is superior to a split schedule. Further development of this combination for mesothelioma is warranted.**

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MTA (multitargeted antifolate; LY231514; *N*-[4-[2-(2-amino - 3, 4 - dihydro - 4- oxo - 7H - pyrrolo[2, 3-d]pyrimidin-5-yl)ethyl]-benzoyl]-L-glutamic acid) is a novel antifolate that was developed during structure/activity studies of the lometrexol type of compounds.[1,2] After cellular uptake, MTA undergoes polyglutamation and predominantly produces triglutamates and pentaglutamates.[3] Polyglutamation results in prolonged intracellular retention of the active compound and increases potency against the target enzymes, thereby producing more sustained cytotoxic effects.[4] MTA and its polyglutamates have been shown to inhibit various enzymes of the folate pathways, including thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide ribonucleotide formyltransferase.[3] In CCRF-CEM cells, MTA-mediated cytotoxicity was partially, but not completely, reversed by the addition of thymidine. An exogenous supply of hypoxanthine was required to achieve full reversal, suggesting that both purine and thymidine syntheses are the major sites of action of MTA. The compound arrests CCRF-CEM cells at the G1/S transition and has been shown to induce apoptosis in these cells.[5] MTA has broad antitumor activity in a variety of in vitro tumor models and is active against lymphoma, colon, lung, pancreas, and breast cancer xenografts in vivo. In preclinical toxicology studies, nutritional folate supplementation decreased toxicity of the compound while slightly enhancing its activity.[6] Folinic acid has been used successfully as a rescuing agent in Beagle dogs.

Clinical phase I studies have been performed using three different administration schedules (once every 21 days, once daily for 5 days every 3 weeks, and once weekly for 4 weeks every 6 weeks).[7-9] On the basis of the toxicity profile, the once-every-21-days schedule was subsequently selected for further development of MTA in clinical phase II studies. At present, several single-agent phase II studies are in progress or under analysis, and MTA seems to be active in non—small-cell lung, head and neck, breast, colon, pancreatic, cervical, and bladder cancers. The objectives of this study were to determine the maximum-tolerated dose (MTD), toxicities,

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and pharmacokinetic parameters of MTA when it was combined with cisplatin and to derive a dose and schedule recommendation for subsequent clinical phase II studies. In addition, we have collected anecdotal antitumor information about this combination regimen.

PATIENTS AND METHODS

Patient Selection

Before entry onto the study, each patient underwent a complete physical examination, history, and radiologic and laboratory evaluations. Major eligibility criteria included the following: (1) histologic or cytologic diagnosis of cancer for which no proven therapeutic option was available; (2) World Health Organization performance status ≤ 2; (3) estimated life expectancy of ≥ 12 weeks; (4) adequate bone marrow function (granulocyte value $\geq 1.5 \times 10^9$/L, white blood cell count $\geq 3.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, hemoglobin value ≥ 9.0 g/dL); (5) adequate liver function (serum bilirubin concentration ≤ 1.5 mg/dL, alanine transaminase or aspartate transaminase value $\leq$ three times the upper normal value [$\leq$ five times normal in case of known disease metastatic to the liver]); (6) prothrombin time and PT and activated partial thromboplastin time within normal range; (7) normal renal function (creatinine level ≤ 1.5 mg/dL or calculated creatinine clearance rate ≥ 60 mg/min); and (8) provision of written informed consent according to institutional guidelines.

Exclusion criteria included the following: (1) hematologic malignancy; (2) prior therapy (platinum-based therapy within 6 months before entry onto the study, chemotherapy within 3 weeks before entry onto the study [6 weeks in case of nitrosoureas or mitomycin C therapy]); (3) clinical evidence of brain metastasis; (4) active heart disease and/or myocardial infarction within 6 months before entry onto the study; (5) pregnancy, current breast-feeding, and/or childbearing potential without adequate contraception; (6) active infection; and (7) serum calcium concentration above the upper limit of normal.

Treatment Regimen

MTA disodium salt was supplied as lyophilized powder in vials of 100 mg and was dissolved in physiologic saline. The appropriate dose volume was withdrawn and further diluted with physiologic saline to yield a total volume of 100 mL. Cisplatin was provided as solution in vials of 10 and 50 mg. The appropriate volume was withdrawn and further diluted with physiologic saline to yield a total volume of 1,000 mL. Two treatment schedules were studied. In cohort 1, MTA was administered intravenously over 10 minutes after patients were prehydrated with 1,000 mL normal saline. This was followed by a 30-minute wash-out with 150 mL normal saline. Subsequently, cisplatin was administered intravenously over 120 minutes in a volume of 1,000 mL, together with 50 mL mannitol. All patients received posthydration with 2,000 mL normal saline and glucose, and appropriate substitution with potassium chloride, sodium bicarbonate, and magnesium chloride. The antiemetic regimen was administered intravenously before the infusion of MTA and consisted of dexamethasone 8 mg and tropisetron 5 mg. The initial drug doses were MTA 300 mg/m^2 and cisplatin 60 mg/m^2. In cohort 2, patients received MTA without hydration or antiemetic medication on day 1. This was followed by prehydration, antiemetic treatment, cisplatin administration, and posthydration on day 2. The hydration schedules and antiemetic regimens were identical in both patient cohorts. The initial doses for cohort 2 were MTA 500 mg/m^2 and cisplatin 75 mg/m^2. Treatment was repeated every 3 weeks in the absence of tumor progression or serious toxicities. At each dose level, the initial patients were observed for one full treatment course before further patients were entered onto the study. On the basis of preclinical experience, folinic acid rescue was considered in case of grade 4 leukopenia/neutropenia lasting longer than 7 days. All serious adverse events were reported to the study sponsor (Eli Lilly GmbH, Bad Homburg, Germany) and to the local institutional review committees. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria.[10] Dose-limiting toxicities (DLTs) were defined as follows: (1) grade 4 neutropenia lasting more than 5 days; (2) febrile neutropenia; (3) grade 4 thrombocytopenia; and (4) grade 3 or higher nonhematologic toxicity (except for alopecia or inadequately treated nausea or vomiting). The MTD was defined as the dose level at which two or more of six patients developed a DLT. The recommended dose for subsequent clinical phase II studies was defined as the dose that caused moderate and reversible toxicities. Intrapatient dose escalation was not allowed. At each dose level, the minimum number of patients treated was three. Three additional patients were entered onto the dose level if toxicities one grade below the DLT were observed in at least one of the initial patients. Patients who experienced DLTs were taken off the study unless a benefit from the therapy could be demonstrated, in which case treatment was continued at a lower dose at the discretion of the investigator. In cohort 1, dose levels (MTA/cisplatin) in mg/m^2 were 300/60, 300/75, 400/75, 500/75, 600/75, and 600/100. On the basis of the data generated in cohort 1, cohort 2 received the following dose levels: 500/75 and 600/75.

Analytical Method

Blood samples for the analysis of MTA in plasma were collected at higher dose levels (500 and 600 mg/m^2) for pharmacokinetic assessments. Plasma MTA concentrations were analyzed by a liquid chromatography mass spectroscopy/mass spectroscopy method.[11] The plasma assay was specific for LY231514, and was able to detect concentrations with a reliable limit of quantification of 5 ng/mL. Urine was collected for the determination of MTA concentrations up to 48 hours after administration. The urine assay was specific for LY231514, and was able to detect concentrations with a reliable limit of quantification of 50 ng/mL.

Pharmacokinetic parameters for MTA were calculated by noncompartmental methods. Maximum plasma concentration and the corresponding sampling time were identified from the observed data. Concentration-time data were plotted on a semilogarithmic scale and the terminal log-linear phase was identified by visual inspection. Blood samples were obtained up to at least 24 hours after drug administration. The terminal slope (λ_z) was determined by linear regression for the terminal log-linear portion of the concentration-time curve up to 24 hours after administration. A predicted concentration ($\hat{C}$) at the last sampling time at which the assay value was above the limit of quantification was calculated from the regression equation.[11]

Area under the plasma concentration versus time curve ($AUC_{0\text{-}t}$) and area under the first moment curve ($AUMC_{0\text{-}t}$) were calculated by the trapezoidal method and extrapolated to infinite time using the $\hat{C}$ at the last measurable sampling time (T) and λ_z values as:

$$AUC_{0\text{-}\infty} = AUC_{0-t} + \hat{C}/\lambda_Z \quad (1)$$

$$AUMC_{0\text{-}\infty} = AUMC_{0-t} + \hat{C}/\lambda_Z \cdot (T + 1/\lambda_Z) \quad (2)$$

Mean residence time (MRT), plasma clearance (CL_p), fraction of drug excreted unchanged in urine (Fe), renal clearance (CL_r), and volume of distribution at steady state (V_{ss}) were calculated as:

$$MRT = (AUMC_{0\text{-}\infty}/AUC_{0\text{-}\infty}) - (\tau/2) \quad (3)$$

$$CL_p = Dose/AUC_{0\text{-}\infty} \quad (4)$$

$$CL_r = Ae_{0\text{-}24}/AUC_{0\text{-}24} \quad (5)$$

$$Fe = Ae_{0\text{-}24}/Dose \quad (6)$$

$$V_{SS} = CL_p \cdot MRT \quad (7)$$

where τ is the duration of infusion (10 minutes) and $Ae_{0\text{-}24}$ is the total amount of drug excreted in the urine over 24 hours.

Statistical Analysis

Statistical analysis of the dose-independent parameters (CL_p, V_{ss}, and CL_r) was performed to assess the effect of the two treatment regimens on the pharmacokinetics of MTA.

Pharmacokinetic parameters from each treatment were compared by an analysis of variance, using Procedure GLM within SAS (SAS Institute, Cary, NC). Dose and treatment regimen were included in the model as fixed effects.

Efficacy

Assessment of antitumor effects was performed every one to two courses, using standard response criteria.[12] A complete response was defined as the absence of all tumor-related signs for more than 4 weeks. A partial response was defined as a $\geq$ 50% decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions and required confirmation after at least 4 weeks. Also, no new lesion or enlargement of $\geq$ 25% of any existing lesion was allowed. Progressive disease was defined as either occurrence of a new lesion or an increase of $\geq$ 25% in an existing lesion. Stable disease was defined as neither objective response nor progression.

Table 1. Patient Characteristics

	Cohort 1	Cohort 2
No. entered	42	12
No. assessable	40	11
Male/female	35/7	9/3
Age, years		
Median	57	55
Range	42-73	29-73
WHO performance scale		
Median	1	1
Range	0-2	0-2
Prior therapy		
None	16	4
Chemotherapy	24	7
Radiation	12	5
Tumor type		
Mesothelioma	10	3
Head and neck	9	2
Non–small-cell lung	6	1
Colorectal	3	1
Esophagus	2	0
Hepatocellular	2	0
Melanoma	2	1
Stomach	2	0
Cervix	2	0
Unknown primary	1	2
Small-cell lung	1	1
Pancreas	1	0
Sarcoma	1	0
Bladder and non–small-cell lung	0	1

Abbreviation: WHO, World Health Organization.

RESULTS

Table 1 summarizes the patient characteristics. A total of 54 patients were entered onto the study. Of these 54, 42 patients were entered onto cohort 1, and 12 patients were entered onto cohort 2. Two patients in cohort 1 were registered but did not receive therapy. One patient had a rapidly declining performance status, and, on histologic review, another patient was found to have small-cell cancer, which prompted the choice of another method of first-line chemotherapy. One patient with a pleural mesothelioma was not assessable for response because he refused a computerized tomography scan and went off-study after his first cycle. One of the patients entered onto cohort 2 was not treated because he withdrew his consent before his first course of therapy. Of the patients entered onto cohort 1, 35 were male and seven were female. Patients' age range was 42 to 73 years, and their median performance status was 1 (range, 0 to 2). Twenty-four patients had received prior chemotherapy and 12 had received prior radiotherapy. Sixteen patients were chemotherapy-naive. In cohort 2, four patients had had not prior treatment, seven had received prior chemotherapy, and five had received prior radiotherapy. In cohort 1, doses of MTA and cisplatin were increased stepwise to MTA 600 mg/m^2 and cisplatin 100 mg/m^2, with three to seven patients entered at each dose level. The most common tumor types were mesothelioma, head and neck cancer, and non—small-cell lung cancer.

Toxicities

Table 2 summarizes the hematologic toxicities for each dose level. The DLT of MTA when administered in combination with cisplatin on day 1 was myelosuppression, which consisted predominantly of leukopenia and neutropenia. DLTs did not occur after course one in all patients and occasionally were delayed until further cycles were administered. However, there was no evidence for reproducible cumulative bone marrow toxicity. The MTD with this schedule was MTA 600 mg/m^2 and cisplatin 100 mg/m^2 when the first cycle was exclusively evaluated. If all cycles were evaluated, the MTD was MTA 600 mg/m^2 and cisplatin 75 mg/m^2. Nonhematologic toxicities are summarized in Table 3. A total of eight patients developed grade 2 skin toxicity, which consisted of a maculopapular rash predominantly confined to the trunk. Treatment with dexamethasone 8 mg resulted in prompt resolution of the rash without persistent skin changes. No skin biopsies were performed, and the occurrence of this toxicity tended to diminish with

Table 2. Hematologic Toxicity of MTA and Cisplatin, by Patient

MTA/Cisplatin (mg/m²)	No. of Patients	CTC Grade							
		WBC		ANC		Hb		PLT	
		3	4	3	4	3	4	3	4
Day 1									0
300/60	6	1	0	2	1	0	0	0	0
300/75	7	3	0	3	1	1	0	0	0
400/75	6	1	0	0	0	1	1	0	0
500/75	3	1	0	1	0	0	1	0	0
600/75	12	7	0	5	2	6	2	0	0
600/100	6	3	3	1	3	1	1	0	0
Day 1/day 2									
500/75	7	3	1	1	1	1	0	0	0
600/75	4	0	1	0	1	0	1	0	0

Abbreviations: ANC, absolute neutrophil count; Hb, hemoglobin; PLT, platelet.

subsequent cycles. However, the skin toxicity seemed to be more pronounced with the split-schedule administration. Because of the extensive premedication for the prevention of cisplatin-induced emesis, nausea and vomiting were mostly mild to moderate. Although diarrhea was occasionally observed at higher doses, it did not cause clinical complications. Similarly, mild to moderate mucositis was occasionally observed. The treatment-induced myelosuppression was not complicated by higher-grade infections. However, at high doses of MTA, a delayed occurrence of fatigue was notable.

Because MTA is renally excreted, it was hypothesized that hydrating patients before the administration of cisplatin might influence the clearance of MTA and, subsequently, may modify the pattern of toxicity or antitumor activity. To investigate this possibility, a second cohort of patients received MTA on day 1 without prehydration or antiemetic medication, followed by cisplatin on day 2 after antiemetic premedication and hydration. Using this schedule, seven patients were treated with MTA 500 mg/m^2/cisplatin 75 mg/m^2, and four patients received MTA 600 mg/m^2/cisplatin 75 mg/m^2. At MTA 500 mg/m^2/cisplatin 75 mg/m^2, three patients developed grade 3 and one patient grade 4 leukopenia. One patient each had grade 3 and grade 4 neutropenia. No severe anemia or thrombocytopenia was observed. However, two patients developed grade 2 and one patient grade 3 skin toxicity. The character of skin toxicity observed with the split-schedule administration of MTA and cisplatin did not differ from that observed when both compounds were administered on day 1. Another patient developed grade 4 diarrhea followed by severe dehydration and sepsis during his second cycle and died because of these treatment-related complications. At MTA 600 mg/m^2/cisplatin 75 mg/m^2, one patient had grade 4 leukopenia. Another patient with recurrent head and neck cancer had a grade 4 mucositis requiring parenteral nutrition. This patient died while on the study, most likely because of a catheter-related bacterial sepsis that occurred after the patient had recovered from a short-lasting grade 4 neutropenia.

MTA Pharmacokinetics

The pharmacokinetics of MTA were evaluated in four patients who received MTA on day 1 followed by cisplatin on day 1 (cohort 1) and in 11 patients who received MTA on day 1 followed by cisplatin on day 2 (cohort 2). In cohort 1, patients were given an antiemetic regimen and were hydrated before being administered both MTA and cisplatin. In cohort 2, patients were given the antiemetic regimen and were hydrated on day 2 before being administered cisplatin.

For comparison purposes, plasma concentrations were normalized to a dose of 500 mg/m^2. Individual normalized plasma MTA concentration-time profiles for both cohorts are illustrated in Fig 1. Visual inspection of the plots illustrates that the normalized MTA plasma concentrations were similar between the two cohorts. For patients in cohort 2, blood samples were collected up to 96 hours after MTA administration. Residual plasma concentrations were low but quantifiable for up to 96 hours in some patients, suggesting the presence of a prolonged terminal phase. This prolonged terminal phase was not observed in cohort 1 because blood samples were not collected beyond 24 hours.

A summary of mean pharmacokinetic parameters is presented in Table 4. The mean CL_p, V_{ss}, and CL_r values for cohort 1 were consistent with those in cohort 2, irrespective of the administered dose. Results from statistical analysis demonstrated a lack of statistical significance for all three parameters with respect to both dose and treatment regimen. Therefore, the pharmacokinetics of MTA were independent of the timing of cisplatin administration and corresponding hydration treatments.

The relationship between CL_p, CL_r, and renal function as assessed by the calculated creatinine clearance (CL_{cr}) was explored. Plots of individual CL_p and CL_r values as a function of CL_{cr} are illustrated in Fig 2. Visual inspection of the plots shows that there was no relationship between CL_p, CL_r, and CL_{cr}. Results from regression analyses demonstrate that the slopes of both lines were not significantly different from zero ($P = .76$ for CL_p *v* CL_{cr} and $P = .74$ for CL_r *v* CL_{cr}). Therefore, for this treatment combination, MTA elimination did not seem to be related to renal function over the range of creatinine clearance values obtained in this study.

Antitumor Activity

Eleven objective antitumor responses were observed in cohort 1 and are listed in Table 5. Throughout all dose levels, clinical antitumor activity of MTA/cisplatin was notable.

Table 3. Nonhematologic Toxicity of MTA and Cisplatin, by Patient

Toxicity/Grade*	MTA/Cisplatin Dose (mg/m²) 300/60	300/75	400/75	500/75	600/75	600/100
Day 1 schedule						
Anorexia						
2	0	0	0	0	1	0
3	0	0	0	0	1	0
4	0	0	0	0	0	0
Nausea						
2	1	3	5	2	9	4
3	0	1	1	0	2	1
4	0	0	0	0	0	0
Vomiting						
2	0	3	0	2	4	3
3	1	0	0	0	4	1
4	1	0	0	0	0	0
Diarrhea						
2	1	3	1	0	0	0
3	0	0	0	0	1	1
4	0	0	0	0	0	0
Fatigue						
2	1	2	2	1	4	3
3	0	2	1	0	1	2
4	0	0	0	0	0	0
Infection						
2	0	0	1	0	2	0
3	1	0	0	1	1	0
4	0	0	0	0	0	0
Mucositis						
2	0	0	0	0	2	1
3	0	1	0	0	0	0
4	0	0	0	0	0	0
Skin						
2	1	2	2	0	0	3
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Day 1/day 2 schedule						
Anorexia						
2					1	0
3					0	0
4					0	0
Nausea						
2					6	2
3					1	0
4					0	0
Vomiting						
2					4	1
3					1	0
4					0	0
Diarrhea						
2					0	0
3					0	0
4					1	0
Fatigue						
2					3	0
3					0	0
4					0	0
Infection						
2					0	0
3					0	0
4					1	1
Mucositis						
2					1	0
3					0	0
4					0	1
Skin						
2					2	0
3					1	1
4					0	0

NOTE. Two deaths occurred during the study period due to neutropenic sepsis (diarrhea, pneumonia).

*National Cancer Institute common toxicity criteria grade.

Most importantly, one patient with a relapsed squamous cell carcinoma of the head and neck developed a complete, although short-lasting, response. A further two patients with head and neck cancer had partial responses. Four patients with pleural mesothelioma developed partial remissions. These responses have been confirmed by an independent reviewer with a specialty in radiology. The reviewer verified that three of the four patients had lesions that were bidimensionally measurable and one patient had unidimensionally measurable thickening of the pleura. In cohort 2, one patient with an adenocarcinoma of the submandibular gland developed a minimal response after one cycle of treatment, but her disease progressed after the third cycle. Two patients (one mesothelioma patient, one colon cancer patient) had a confirmed partial response. The overall activity of MTA/cisplatin against mesothelioma indicates marked clinical activity in this difficult-to-treat disease.

DISCUSSION

From previous clinical phase I studies, the every-21-days schedule has been chosen for further development of MTA single-agent phase II and combination phase I studies.[7-9] The results of the study presented here indicate that it is clinically feasible and safe to combine MTA with cisplatin using a once-every-21-days administration schedule. When both agents are administered on day 1, the acute DLTs consist of leukopenia and neutropenia. In addition, delayed fatigue may be observed at high doses of MTA. No other phase I combination studies with MTA have yet been completed, but our results are in agreement with observations from single-agent phase I studies with this compound.[7-9] Rinaldi et al, using the same once-every-21-days administration schedule of MTA, reported neutropenia, thrombocytopenia, and fatigue as DLTs. However, we have not observed significant thrombocytopenia in our patients. This difference might be because Rinaldi et al escalated the dose of MTA to 700 mg/m², whereas in the study presented here, the highest MTA dose was 600 mg/m².

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