Preliminary Results of a Phase I Study With MTA (LY231514) in Combination With Cisplatin in Patients With Solid Tumors

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MTA (multitargeted antifolate, LY231514) is a novel antimetabolite resulting from structure/activity studies of the lometrexol-type antifolates. It has been shown to inhibit various enzymes of folate pathways and has broad antitumor activity in a variety of in vitro and in vivo tumor models. Clinical phase I studies have been performed using different administration schedules, and subsequently the every-21-days schedule has been selected for further development. We report the preliminary findings from a combination phase I study of MTA and cisplatin administered every 21 days. In the first cohort (34 patients), both agents were administered on day 1 with a starting dose of 300 mg/m² MTA and 60 mg/m² cisplatin. In a second cohort (10 patients), MTA (500 or 600 mg/m²) was administered on day 1 followed by cisplatin (75 mg/m²) on day 2. The maximum tolerated doses were reached at 600 mg/m² MTA/100 mg/m² cisplatin (cohort 1) and 600 mg/m² MTA/75 mg/m² cisplatin (cohort 2). In cohort 1, dose-limiting toxicities consisted of reversible myelosuppression with leukopenia and neutropenia. In addition, delayed fatigue also was of clinical significance. Pharmacokinetic analyses indicated that hydration administered before the administration of cisplatin did not influence the major pharmacokinetic parameters of MTA. Eleven objective remissions were observed, including one complete response in a patient with relapsed squamous cell carcinoma of the head and neck and partial responses in four of seven patients with mesothelioma. In contrast, the dose-limiting toxicities in patient cohort 2 consisted of neutropenic sepsis, diarrhea, and skin toxicity with two possibly treatment-related deaths on study. No objective remissions are presently observed in cohort 2. We conclude that the combination of MTA and cisplatin is feasible and clinically active when both agents are administered on day 1 and that it should be pursued for further clinical development.

Semin Oncol 26 (suppl 6):89–93. Copyright © 1999 by W.B. Saunders Company.

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 antimetabolite resulting from structure/activity studies of the lometrexol-type antifolates.[1,2] After cellular uptake, the compound undergoes polyglutamation with production of predominantly triglutamates and pentaglutamates.[3] MTA, as well as its polyglutamates, has been shown to inhibit various enzymes of the folate pathways, including thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide ribonucleotide formyltransferase.[3] The compound arrests CCRF-CEM cells at the G1/S transition and has been shown to induce apoptosis in these cells.[4] 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.[5] The preclinical toxicology studies demonstrated that nutritional folate supplementation decreased toxicity of the compound while enhancing its activity.[5]

Clinical phase I studies have been performed using three different administration schedules (every 21 days, daily ×5 every 3 weeks, weekly ×4 every 6 weeks).[6-8] Based on the toxicity profile, the ability to give repeat doses, and the ease of administration, the 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 appears to be active in the colon, pancreas, and breast cancer. We report here the preliminary results of a phase I combination study of MTA and cisplatin.

PATIENTS AND METHODS

The objectives of the study were to determine the maximum tolerated dose and the dose-limiting toxicity (DLT) of MTA when combined with cisplatin, to recommend a safe and feasible dose and schedule for subsequent phase II studies, and to collect anecdotal information on the antitumor activity of this

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Sponsored by Eli Lilly and Company.

Dr Thödtmann has received honorarium from Eli Lilly and Company. Drs Blatter and Johnson are employees of Eli Lilly and Company. Dr Hanauske is a consultant for Eli Lilly and Company and Ilex Oncology; has received honoraria from Eli Lilly and Company, Yewtree, Nycomed, and Ilex Oncology; has received research support from Eli Lilly and Company, SmithKline Beecham, Asta Medical, Rhône-Poulenc Rorer, and Esai, and is a provider of expert testimony for Rhône-Poulenc Rorer.

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0093-7754/99/2602-0614$10.00/0

combination. In addition, characterization of pharmacokinetic parameters of MTA and cisplatin were planned at higher doses of the combination.

Major eligibility criteria included histologic or cytologic diagnosis of cancer for which no proven therapeutic option was available, World Health Organization performance status ≤2, estimated life expectancy of ≥12 weeks, granulocytes ≥1.5 × 10^9/L, white blood cell count ≥3.0 × 10^9/L, platelets ≥100 × 10^9/L, hemoglobin ≥9.0 g/L, serum bilirubin concentration ≤1.5 mg/dL, alanine transaminase or aspartate transaminase ≤3 times upper normal value (≤5 times normal in case of disease metastatic to the liver), prothrombin time and partial thromboplastin time within normal range, creatinine ≤1.5 mg/dL or calculated creatinine clearance ≥60 mg/min, and written informed consent. Exclusion criteria included diagnosis of hematologic malignancy, platinum therapy within 6 months before study entry, chemotherapy within 3 weeks before study entry (6 weeks in case of nitrosoureas or mitomycin C), clinical evidence for brain metastasis, active heart disease, myocardial infarction within 6 months before study entry, childbearing potential without adequate contraception, pregnancy, breast feeding, active infection, and serum calcium concentration above upper limit.

Two treatment schedules were studied. In cohort 1, patients received MTA as an intravenous infusion over 10 minutes after prehydration with 1 L of normal saline. Thirty minutes after the end of the MTA infusion, cisplatin was administered over 2 hours together with 150 mL of mannitol. Patients were subsequently posthydrated with 2 L of normal saline and glucose and appropriate substitution with potassium chloride, sodium bicarbonate, and magnesium. An antiemetic regimen was administered intravenously before the infusion of MTA and consisted of dexamethasone (8 mg), granisetron (5 mg), and alizapride (50 mg). The starting 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, cisplatin administration, and posthydration on day 2. The hydration schedules and antiemetic regimen were identical in both patient cohorts. The starting doses for patient cohort 2 were MTA 500 mg/m^2 and cisplatin 75 mg/m^2.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria.[9] Dose-limiting toxicities were defined as follows: grade 4 neutropenia lasting longer than 5 days, febrile neutropenia, grade 4 thrombocytopenia, and grade ≥3 nonhematologic toxicity (except for alopecia or inadequately treated nausea or vomiting). The maximum tolerated dose was defined as the dose level at which two or more of six patients developed a DLT. At each dose level, a minimum of three patients were entered. Three additional patients were entered if toxicities one grade below the DLT were observed in at least one of the initial patients. Patients experiencing DLTs were taken off study unless a benefit from the therapy could be demonstrated. In this case, treatment was continued at a lower dose at the discretion of the investigator.

While the determination of tumor response was not a primary objective of this phase I study, tumor measurements were recorded and response status was assigned according to standard World Health Organization criteria.[10]

For pharmacokinetic analyses, blood samples were taken at higher dose levels during the first cycle after the administration of MTA and cisplatin, and urine was collected for up to 48 hours after the end of the MTA infusion. A liquid chromatography mass spectrometry assay was used for determination of MTA concentrations as described earlier.[6]

RESULTS

Forty-four patients were entered into this phase I study. Of these, 34 patients were entered (with 33 evaluable for response) into cohort 1 and 10 patients were entered into cohort 2. Of the patients entered into cohort 1, 29 were men and five were women. The age range was 41 to 72 years and the median performance status was 1 (range, 0 to 2). Sixteen and nine patients had received prior chemotherapy or radiotherapy, respectively. The remaining nine patients were chemotherapy-naive. Doses of MTA and cisplatin were increased stepwise to 600 mg/m^2 MTA and 75 mg/m^2 cisplatin with three to seven patients entered at each dose level. As summarized in Table 1, the most common tumor types were mesothelioma, head and neck cancer, and non-small cell lung cancer.

Table 2 summarizes the hematologic toxicity seen at each dose level. When administered in combination with cisplatin on day 1, the DLT of MTA was myelosuppression, consisting predominantly of leukopenia and neutropenia. Dose-limiting toxicities were not seen exclusively during course one in all patients, but occasionally were delayed until further cycles were administered. However, we have seen no evidence for reproducible cumulative bone marrow toxicity. When the first cycle was used exclusively to define maximum tolerated dose, it was found to be 600 mg/m^2 MTA and 100 mg/m^2 cisplatin. If all cycles were evaluated, the maximum tolerated dose was 600 mg/m^2

Table 1. Tumor Type Distribution

Tumor Type	No. of Patients
Mesothelioma	7
Head and neck	7
Non-small cell lung	5
Colorectal	3
Esophagus	3
Hepatocellular	2
Melanoma	2
Unknown primary	2
Small cell lung	1
Pancreas	1
Osteosarcoma	1

Table 2. Grade 3 and 4 Hematologic Toxicity of MTA and Cisplatin by Dose Level* and National Cancer Institute Common Toxicity Criteria Grades

Dose MTA/ Cisplatin (mg/m^2)	No. of Patients	Leukopenia		Neutropenia		Anemia		Thrombocytopenia	
		3†	4	3	4	3	4	3	4
300/60	6	1	0	2	1	0	0	0	0
300/75	7	3	0	2	2	1	0	3	1
400/75	6	1	0	0	1	1	0	0	0
500/75	3	1	0	1	0	0	1	1	0
600/75	6	4	0	3	2	1	0	0	0
600/100	6	2	3	1	4	1	1	1	1

* Both agents were administered on day 1 of each course.
† National Cancer Institute Common Toxicity Criteria grades.

MTA and 75 mg/m^2 cisplatin. Nonhematologic toxicities are summarized in Table 3. Due to the extensive premedication for the prevention of cisplatin-induced emesis, nausea and vomiting were mostly mild to moderate. While diarrhea was observed occasionally 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, a delayed occurrence of fatigue was notable at high doses of MTA.

Several objective antitumor responses were observed in patient cohort 1 and are listed in Table 4. Clinical antitumor activity of MTA/cisplatin was notable throughout all dose levels. Most importantly, one patient with a relapsed squamous cell carcinoma of the head and neck developed a complete, although short-lasting, response. In addition, four of seven patients with mesothelioma developed a partial remission. Each of these four mesothelioma responses has been confirmed by an independent reviewer with a specialty in radiology. This reviewer verified that three of the four patients had lesions that were bidimensionally measurable and one patient had unidimensionally measurable thickening of the pleura.

A preliminary analysis of pharmacokinetic parameters indicates that the plasma half-life of MTA is approximately 3.2 hours, which corresponds to the published half-life after single-agent therapy.

Because MTA is renally excreted, it may be hypothesized that the prehydration with cisplatin administration might influence the clearance of MTA and modify the pattern of toxicity or anti-

Table 3. Nonhematologic Toxicity of MTA and Cisplatin by Dose Level*

	Dose MTA/Cisplatin (mg/m^2)																	
	300/60 (N = 6)			300/75 (N = 7)			400/75 (N = 6)			500/75 (N = 3)			600/75 (N = 6)			600/100 (N = 6)		
Toxicity Type	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
Nausea	1	0	1	3	1	0	4	1	0	2	0	0	4	1	0	4	1	0
Vomiting	0	1	1	3	0	0	0	0	0	2	0	0	2	1	0	3	1	0
Diarrhea	1	0	0	3	0	0	1	0	0	0	0	0	0	1	0	0	1	0
Mucositis	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Infection	0	0	0	0	0	0	1	0	0	0	1	0	1	1	0	1	0	0
Fatigue	1	0	0	2	2	0	2	1	0	1	0	0	3	0	0	1	3	0
Anorexia	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0

* Both agents were administered on day 1 of each course.

Table 4. Objective Tumor Responses Observed After Treatment With MTA and Cisplatin*

Dose Level (mg/m^2)	Tumor Type	Response	Duration (mo)
300/60	Non–small cell lung	PR	2
300/60	Colorectal	PR	7
400/75	Cancer of unknown primary	PR	7
400/75	Head and neck	PR	4+
600/75	Mesothelioma	PR	8+
600/75	Melanoma	PR	2
600/75	Head and neck	PR	4
600/75	Head and neck	PR	3+
600/75	Mesothelioma	PR	5
600/100	Mesothelioma	PR	3+
600/100	Mesothelioma	PR	2+

Abbreviation: PR, partial response.

*Both agents were administered on day 1 of each treatment course.

tumor activity. To gather data regarding this hypothesis, 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. Six patients were treated on this schedule with 500 mg/m^2 MTA/75 mg/m^2 cisplatin and four patients received 600 mg/m^2 MTA/100 mg/m^2 cisplatin. At the lower of the two dose levels, two patients developed grade 3 and one patient grade 4 leukopenia. One patient experienced grade 3 and two patients grade 4 neutropenia. While no severe anemia or thrombocytopenia was observed, one patient each developed grade 2 and 3 skin toxicity. Another patient developed grade 4 diarrhea followed by severe dehydration and sepsis during the second cycle and died due to these treatment-related complications. At the higher dose level, two patients experienced grade 3 leukopenia. Another patient with recurrent head and neck cancer had a grade 4 mucositis requiring parenteral nutrition. This patient died while on study, most likely due to a catheter-related bacterial sepsis after recovery from a short-lasting grade 4 neutropenia.

COMMENTS

The results of our present study indicate that it is clinically feasible and safe to combine MTA with cisplatin using a 3-week 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 reported, but our results concerning toxicity are in agreement with observations reported from single-agent phase I studies using this compound.[6-8] Rinaldi et al,[8] using the same administration schedule of MTA, reported neutropenia, thrombocytopenia, and fatigue as being the DLTs. In contrast, we have not observed a significant proportion of patients with significant thrombocytopenia. This difference might be due to the fact that Rinaldi et al[8] escalated the dose of MTA to 700 mg/m^2 while in the present study the highest MTA dose was 600 mg/m^2.

Of interest is that, in contrast to other single-agent clinical phase I and phase II studies, we have not observed serious skin toxicity in patient cohort 1. We hypothesize that the use of corticosteroids as part of the antiemetic prophylaxis regimen for cisplatin may have prevented the high incidence of severe skin toxicities as described by others. This conclusion is supported by the observation that administration of corticosteroids 24 hours after the administration of MTA in patient cohort 2 was accompanied by the occurrence of grade 3 skin reactions. After the clinical manifestation of skin toxicity, however, corticosteroids are used effectively for treatment.[11]

The combination of MTA and cisplatin has shown antitumor activity at various dose levels and in different tumor types. Of particular interest is the observation that four of seven patients with mesothelioma treated with this combination had confirmed partial responses. Reported single-agent response rates for cisplatin in this notoriously refractory malignancy are roughly 14%,[12] indicating that mesothelioma is a tumor type worthy of further investigation with this combination. However, this conclusion is based on anecdotal observations and the design of our phase I study does not allow for the estimation of response rates. Further clinical studies of MTA/cisplatin in patients with mesothelioma appear promising.

We conclude from our study that MTA may be safely combined with cisplatin. The day 1/day 2 split-dose schedule is inferior to the administration of both agents on day 1 with regard to toxicity and, possibly, activity. Prehydration regimens as used for cisplatin do not appear to affect pharmacokinetic

variables of MTA, although more mature data will be needed to support this hypothesis. Premedication with a single dose of steroids appears to prevent or ameliorate the occurrence of MTA-mediated skin toxicity. Additional clinical studies are planned to further define the activity of this combination in patients with malignant mesotheliomas, non-small cell lung cancer, and head and neck cancer.

ACKNOWLEDGMENT

The authors thank Dr U. Ohnmacht, M. Kemmerich, and Mieke Akker for their expert help during this phase I study and the preparation of the manuscript.

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