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MTA, A Novel Multitargeted Antifolate From Preclinical to Phase I and Beyond

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Overview of Phase I Trials of Multitargeted Antifolate (MTA, LY231514)

David A. Rinaldi

Multitargeted antifolate (MTA, LY231514) is a novel antifolate antimetabolite, with antitumor activity via inhibition of thymidylate synthase, glycinamide formyl transferase, and dihydrofolate reductase. Three dosing schedules have been investigated in the phase I setting: daily ×5 every 21 days, weekly ×4 every 42 days, and once every 21 days. The maximum tolerated doses on these schedules were 4.0 mg/m^2, 30 mg/m^2, and 600 mg/m^2, respectively. The major dose-limiting toxicity seen on all schedules was neutropenia, with a greater degree of reversible liver biochemistry disturbances observed on the daily ×5 schedule. Given that toxicities were manageable and reversible, the antitumor activity exhibited, and the convenience of an every-21-day dosing schedule, this schedule was selected for phase II evaluation.

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MULTITARGETED antifolate (MTA, LY231514) is a novel compound, representative of a new class of folate antimetabolites. Its antitumor effect is via inhibition of the enzymes, thymidylate synthase, glycinamide ribonucleotide formyltransferase, and dihydrofolate reductase. MTA is an excellent substrate for the folylpolyglutamate synthetase, leading to extensive intracellular polyglutamation. This converts the drug from a form that readily effluxes from the cell to a form that is retained intracellularly for a prolonged period, producing a more sustained drug effect. In preclinical models, MTA has demonstrated activity against a wide spectrum of tumor types.[1-4]

Three phase I clinical trials with three different schedules of MTA have now been completed, one in the United Kingdom and two in the United Stats.[5-9] In the three trials, MTA was administered as a 10-minute intravenous infusion in escalating doses to patients with advanced, refractory, solid tumors and relatively normal bone marrow, renal, and hepatic function. Patients requiring chronic aspirin therapy and those with significant effusions were excluded due to the structural similarities of MTA and methotrexate. The maximum tolerated dose (MTD) was defined as that dose level at which 30% of the patient population developed unacceptable toxicity. The recommended dose for phase II clinical trials was defined as the dose that caused moderate reversible toxicity in most patients.

DAILY ×5, REPEATED EVERY 21 DAYS

Thirty-eight patients were treated in this study[4]; the clinical characteristics are listed in Table 1. One hundred sixteen courses of MTA were administered at 10 dose levels, ranging from 0.2 to 5.2 mg/m^2. Myelosuppression and liver biochemistry perturbations were dose limiting on this schedule.

Myelosuppression was not higher than grade 2 in patients treated at doses less than 2.3 mg/m^2. Of the three patients treated with 2.3 mg/m^2, one developed uncomplicated grade 3 neutropenia that was not considered dose limiting. One of the initial three patients treated with 3.0 mg/m^2 experienced grade 3 neutropenia and grade 2 thrombocytopenia; therefore, an additional four patients were treated at this dose level. No further dose-limiting toxicity was seen at this dose level.

Of the five patients initially treated at the 4.0 mg/m^2 dose level, one developed grade 3 hepatotoxicity (bilirubin), which was considered a dose-limiting toxicity, and one developed grade 3 neutropenia. The treatment dose was then escalated to 5.2 mg/m^2, with the first patient at this dose level experiencing no significant toxicity. However, the second patient died despite aggressive medical management after experiencing grade 4 neutropenia, grade 3 thrombocytopenia, and grade 4 gastrointestinal toxicities on day 8 of the first course of treatment. This event resulted in a re-evaluation of the previous dose level and an additional patient was treated with 4.0 mg/m^2. This patient developed uncomplicated, but dose-limit-

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Table 1. Patient Characteristics

	Daily ×5 Every 21 Days	Weekly ×4 Every 42 Days	Every 21 Days
No. of evaluable patients	38	24	37
M/F	19/19	11/13	27/10
Median age, yr (range)	59 (33-73)	59 (20-82)	59 (30-74)
Karnofsky performance status			
100%	7	12	16
90%	0	0	4
80%	26	11	14
60%	5	1	3
No. of prior chemotherapy regimens			
0	9	0	4
1	22	3	8
2	5	12	12
3+	2	9	13
Tumor types			
Colorectal	20	17	25
Pancreas	4	0	3
Melanoma	3	0	0
Other	11	7	9

ing grade 4 neutropenia and grade 3 hepatic transaminase elevations. Because two of six patients at this dose level had experienced dose-limiting toxicity, the MTD was established at 4.0 mg/m^2.

Hepatotoxicity was frequently observed at most dose levels, with grade 3-4 toxicity occurring in at least one patients treated at each dose level ≥2.3 mg/m^2. These abnormalities were observed most frequently during either the first or second course of treatment, did not appear to be progressive, and resolved during continued treatment or on discontinuation of treatment for other reasons.

In patients treated at the 4 mg/m^2 dose level, no patient developed grade 3-4 nonhematologic, nonhepatic toxicity. Grade 1-2 mucositis occurred in two patients, nausea in five patients, vomiting in three patients, and diarrhea in four patients. Prophylactic antiemetics were not routinely used. Table 2 summarizes the course 1 toxicity seen at all dose levels on this dosing schedule.

A patient with pancreatic cancer, treated at the 2.3 mg/m^2 dose level, experienced a fatal gastrointestinal hemorrhage following the second cycle of treatment. Coagulation parameters and platelet count were normal throughout the time on study, although grade 3 elevations of the hepatic transaminases were noted in association with the acute event. Extensive inflammatory changes were seen in the large intestine at postmortem examination, with no focal bleeding source identified. Only microscopic evidence of residual tumor was seen at this point. While the etiology of the event remains unclear, a relationship to MTA administration cannot be excluded.

While no objective tumor responses were noted, antitumor effects were observed in three patients. The first was a patient with metastatic non-small cell lung cancer who was previously treated with platinum. Symptomatic and radiologic improvements, which were observed after six courses of MTA at 3.0 mg/m^2, persisted through the 10th course. A second patient, who had metastatic colon cancer, experienced a reduction on a nonmeasurable hepatic lesion after four courses of treatment with MTA at 4.0 mg/m^2. The third patient, who had pancreatic cancer and was receiving MTA at 2.3 mg/m^2, developed fatal gastrointesti-

Table 2. Daily ×5: Course 1 Toxicity

Dose Level	No. of Patients	Neutropenia					Thrombocytopenia					Transaminases					Hyperbilirubinemia				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
0.2-1.8	22	21	0	1	0	0	18	4	0	0	0	12	7	1	1	0	20	0	1	0	0
2.3	3	1	0	1	1	0	3	0	0	0	0	2	0	0	1	0	2	0	1	0	0
3.0	5	0	1	3	1	0	4	0	1	0	0	1	3	1	0	0	3	1	1	0	0
4.0	6	1	2	1	1	1	4	2	0	0	0	0	2	3	1	0	3	0	2	1	0
5.2	2	0	1	0	0	1	0	1	0	1	0	1	1	0	0	0	1	0	1	0	0

nal bleeding (as described above) 4 weeks after the second course of treatment. This patient's tumor, which had originally been measured at 4 × 4 cm, was not macroscopically detectable at necropsy, although microscopic tumor was found in biopsy specimens taken from the original site of disease. Additionally, eight patients had stable disease. Two patients with metastatic colon cancer, progressing during 5-fluorouracil (5-FU)-based therapy, achieved disease stabilization for 3 and 6 months with MTA.

WEEKLY ×4, REPEATED EVERY 42 DAYS

Twenty-four evaluable patients enrolled in the weekly ×4, repeated every 42 days study.[5] Their characteristics are listed in Table 1. Fifty-eight courses of MTA were administered, with a range of one to seven courses per patient. The dose-limiting toxicity of MTA on this schedule was neutropenia. Nonhematologic toxicities observed included mild fatigue, anorexia, and nausea, with no instances of grade 3 or 4 side effects. There was no evidence of cumulative toxicity.

The dose escalation schema incorporated into this study was based on the modified continual reassessment method (mCRM).[8] The initial dose level was to include at least three patients, with subsequent dose levels of one patient each, and planned expansion of those dose levels when moderate to severe toxicity was observed. The projected phase II dose was to include at least 10 patients.

At the initial dose level of 10 mg/m^2, one of four patients developed grade 4 neutropenia and grade 3 thrombocytopenia, while the remaining three patients tolerated the treatment without significant toxicity. The next patient, who received 20 mg/m^2, also experienced no significant toxicity, so the dose was escalated to 40 mg/m^2. After the first patient developed grade 4 neutropenia, five additional patients were treated at this dose level. Two of these five experienced grade 4 neutropenia, which prompted a de-escalation to 20 mg/m^2. Because none of the three additional patients at this dose level experienced significant toxicity, an intermediate dose level of 30 mg/m^2 was added. Two of the 10 patients treated at this dose level developed grade 4 neutropenia; therefore, this dose level was determined to be the MTD and recommended dose for phase II trials using this schedule.

No major responses were observed; however, minor responses were achieved in two patients with advanced, refractory colon cancer. A patients treated at the 40 mg/m^2 level who had failed 5-FU and folinic acid exhibited a 34% reduction in measurable disease after two cycles, but had progressed by the next computed tomography scan 6 weeks later. A patient with evaluable liver metastases, treated at the 30 mg/m^2 level, exhibited a decline in carcinoembryonic antigen level from 945 ng/mL before the study to 271 ng/mL after three courses of treatment. Of note, this patient had been previously treated with 5-FU and levamisole, 5-FU and folinic acid, and intrahepatic artery 5-FU and interferon.

The inability to deliver scheduled doses due to grade ≥2 myelosuppression at the time of treatment precluded optimal use of the mCRM and also limited dose escalation on this schedule. This toxicity predominantly occurred during week 3 or 4. At the 10 and 20 mg/m^2 levels, 29 of 32 planned doses were delivered and six of eight patients received all doses. At the 40 mg/m^2 levels 18 of the 24 planned doses were delivered, and at the 30 mg/m^2 dose level 30 of the 40 doses were given. Only one patient at each of these dose levels received all four of the scheduled doses during their first course. Table 3 summarizes the course 1 toxicity seen at all dose levels on the treatment schedule.

Table 3. Weekly ×4 Every 42 Days: Course 1 Toxicity

Toxicity	Grade (World Health Organization)				
	0	1	2	3	4
Neutropenia	6	1	7	5	5
Thrombocytopenia	20	0	2	1	1
Anemia	9	8	7	0	0
Nausea/emesis	3	9	2	0	0
Fatigue	13	10	1	0	0
Transaminasemia	20	3	1	0	0
Anorexia	13	11	0	0	0
Mucositis	20	4	0	0	0
Dermatitis	23	1	0	0	0

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