Overview of Phase II Trials of MTA in Solid Tumors

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MTA (LY231514, multitargeted antifolate) represents a new class of folate antimetabolites and inhibits multiple enzymes in the purine and thymidine biosynthetic pathways, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. Based on the results of phase I investigation, the dose and schedule of 600 mg/m^2 administered intravenously every 21 days was selected to carry into the phase II setting. A number of phase II studies are completed or ongoing in a wide range of tumor types, and encouraging results have been observed in colorectal, breast, non-small cell lung, head and neck, bladder, and cervical cancers.

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MTA (LY231514, multitargeted antifolate), is a pyrrolo-pyrimidine analog of folic acid that inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase.[1,2] The antitumor activity of MTA results from the inhibition of these folate-requiring enzymes, which are components of purine and thymidine synthesis. MTA enters the cell via the reduced folate carrier and, once there, rapidly undergoes polyglutamylation. The more extensively polyglutamated species exhibit greater affinity for the target enzymes and greater in vitro activity.[3]

RATIONALE FOR PHASE II DOSE AND SCHEDULE

Three dosing schedules have been investigated in phase I studies. In one study, patients were treated on a once-every-21 days schedule (see Rinaldi, elsewhere in this supplement); in a second study, patients received drug once weekly for 4 weeks every 6 weeks[4] and in a third, patients were treated using a schedule of daily ×5 every 21 days.[5]

Based on the toxicity profile, the ability to give repeat doses, and the ease of administration, the every-21-days schedule was selected for further development of MTA in clinical phase II studies. In the phase I trial investigating this dose, 37 patients were treated at doses ranging from 50 to 700 mg/m^2. Dose escalation proceeded by the Modified Continual Reassessment Method in this study, limiting the number of patients exposed to lower, potentially less-effective doses of drug.[6] Dose-limiting toxicities on this schedule were neutropenia, thrombocytopenia, and fatigue. The maximum tolerated dose on this schedule was determined to be 600 mg/m^2, and of the 20 patients treated at this dose, National Cancer Institute Common Toxicity Criteria grade 4 neutropenia and grade 4 thrombocytopenia occurred in four and one patient, respectively, in the first cycle. National Cancer Institute Common Toxicity Criteria grade 2 toxicities included rash, mucositis, nausea, vomiting, fatigue, anorexia, and elevations of liver transaminases. Patients who experienced rash and were treated in subsequent cycles with 4 mg of dexamethasone twice daily for 3 days starting the day before MTA therapy experienced a decrease in severity or even prevention of the rash. The phase I experience is summarized in Table 1.

Pharmacokinetic calculations based on noncompartmental methods were performed in 20 patients who were treated at the maximum tolerated dose (600 mg/m^2). A mean maximum plasma concentration of 137 μg/mL was attained, with an effective harmonic mean half-life of 3.1 hours (range, 2.2 to 7.2 hours). Mean clearance and steady-state volume of distribution values of 40 mL/min/m^2 (24% coefficient of variance) and 7.0 L/m^2 (20% coefficient of variance) were also calculated. This mean clearance value is similar to that of creatinine clearance in the age range of the patients enrolled (approximately 45 to 55 mL/min/m^2) and the volume of distribution reflects limited distribution outside the blood stream.[7] The clearance was invariant with dose over the entire dose range (0.2 to 700 mg/m^2). The clearance of the drug is primarily renal, with ≥80% of the dose recovered unchanged in the urine during the first 24 hours after dosing. The disposition of MTA does not change after multiple doses and no accu-

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Table 1. Single Agent Phase I Experience

	Daily	Every 3 Weeks	Weekly
Schedule (all doses administered as a 10-min infusion)	Daily ×5, every 21 d	Once every 21 d	Weekly ×4, every 6 wk
No. of patients treated	38	37	24
Dose range (mg/m^2)	0.2-5.2	50-700	10-40
Recommended phase II dose (mg/m^2)	4	600	30
DLT	Neutropenia	Neutropenia, mucositis, fatigue	Myelosuppression, particularly granulocytopenia
Responses	Minor responses in colorectal cancer (1) and NSCLC (1)	Partial responses in pancreas (2) and colorectal (2) cancer	Minor responses in colorectal (2) cancer

Abbreviations: DLT, dose-limiting toxicity; NSCLC, non–small cell lung cancer.

mulation appears to occur with multiple courses. Initial clinical data indicated that an element of cumulative toxicity may have been present (see Rinaldi, this supplement), but so far this has not been borne out in subsequent clinical experience. MTA clearance does appear to decrease with age, although this decrease is most likely related to decreasing renal function.[7]

PHASE II EXPERIENCE

Gastrointestinal Cancers

Clinical activity in metastatic colorectal carcinoma has been demonstrated in two multicenter trials performed in the United States and Canada. Because MTA was initially believed to be primarily a thymidylate synthase inhibitor, early phase II trials were designed to require a 1-year interval from prior treatment with drugs that also inhibit thymidylate synthase. For this reason, prior adjuvant chemotherapy was allowed if completed at least 1 year before study entry. In the Canadian study, the starting dose of 600 mg/m^2 was reduced to 500 mg/m^2 after dose reductions were required in five of the first eight patients. Toxicities leading to these reductions included rash, mucositis, neutropenia, and febrile neutropenia. Responses have been seen at this reduced dose in six patients, for an overall response rate of 20%.[8] In the US colorectal study, objective tumor responses have been seen in six of 39 patients for an overall response rate of 17%.[9] The median times to progressive disease in the two studies were 4.6 months and 3.3 months, and the median survival times have been 16.2 months and 15 months.

Two additional studies were initiated to study the antitumor effects of MTA in colorectal cancer in patients who had received prior therapy. In each of these two trials, 31 patients were evaluated for tumor response. In the first, patients must have been refractory to both 5-fluorouracil and irinotecan, defined as having disease progression on or within 6 months of prior therapy containing 5-fluorouracil and disease progression on or within 6 months of prior irinotecan therapy. In the second, patients must have progressed within 6 months of therapy containing 5-fluorouracil. Although several patients in these studies have maintained stable disease for longer than 4 months, objective tumor responses have not been observed. Median survival times on these studies will be closely monitored as these data mature.

A study in pancreatic cancer is complete; there was one complete and one partial response in 35 evaluable patients, for an overall response rate of 6%. Importantly, the median time to progression to date is 3.9 months with a median survival of 6.5 months, and 13 additional patients have maintained a status of stable disease for longer than 6 months of treatment, suggesting a clinical benefit not immediately apparent from objective tumor measurements.[10]

A study in patients with esophageal cancer was conducted in the United Kingdom and South Africa. Patients had inoperable, locally advanced, recurrent, or metastatic esophageal cancer and had

Table 2. Phase II Activity of MTA in Gastrointestinal Cancers

	Tumor					
	Colorectal	Colorectal	Colorectal	Colorectal	Pancreas	Esophagus
No. of evaluable patients	41	29	31	31	35	20
CR	1	0	0	0	1	—
PR	5	5	0	1	1	—
Overall RR	15	17	0	3	6	—
Median survival, mo (% Cens)	16.2 (54%)	15	—	—	6.5 (34%)	—
Median TTP, mo (% Cens)	4.6 (15%)	3.3	—	—	3.9 (11%)	—

Abbreviations: CR, complete response; PR, partial response; RR, response rate; Cens, censored; TTP, time to progression.
—, Data not available at this time.

not received prior therapy. All patients received a dose of 600 mg/m^2 MTA. This study was designed with two stages, with an early stopping rule in the event of poor antitumor activity, and in fact closed after no objective tumor responses were noted in the first 20 patients. Although this study was not designed to quantify clinical benefit, investigators reported some instances of decreased pain and improved swallowing. The incidence of toxicity in this study was high, with grade 3 and 4 neutropenia experienced by 33% and 23% of patients and grade 3 and 4 thrombocytopenia experienced by 30% and 55% of patients.

Table 2 illustrates the activity of MTA in gastrointestinal cancers.

Breast Cancer

A study of MTA in locally advanced or metastatic breast cancer is complete and involved a heterogenous population, with five of 38 patients having received no prior chemotherapy, 15 of 38 having received prior adjuvant therapy, and 12 of 38 who had received prior therapy in the metastatic setting (additionally, five patients had received therapy both in the adjuvant and the metastatic setting). Of the 36 patients evaluable for response, one complete and 10 partial responses have been documented, for an overall response rate of 31%. Responses have been seen following prior therapy for metastatic disease with a variety of treatments, including epirubicin, ifosfamide, paclitaxel, gemcitabine, and docetaxel. Neutropenia was the major hematologic toxicity observed, with grade 3 seen in 24% of patients and grade 4 seen in 29% of patients.[11]

An additional study of MTA in metastatic breast cancer is ongoing in Europe. Patients participating in this study must have been previously treated with an anthracycline- or anthracenedione-containing regimen and are classified as having failed prior therapy (ie, having disease progression beyond one cycle length of the final dose of this therapy) or as being refractory to prior therapy (ie, having disease progression during or within one cycle length of the final dose of this therapy). While this data set is quite immature at this point, two partial responses have been noted within the group of 12 evaluable patients in the anthracycline-refractory group and two complete responses and four partial responses have been noted within the group of 16 patients in the anthracycline failure group.

Table 3 illustrates the activity of MTA in breast cancer.

Table 3. Phase II Activity of MTA in Breast Cancer

		Ongoing	
	Complete	A (Anthra Refractory)	B (Anthra Failures)
No. of evaluable patients	36	12	16
CR	1	0	2
PR	10	2	4
			—
Overall RR	31	—	

Abbreviations: CR, complete response; PR, partial response; RR, response rate.
—, Data not available at this time.

Non-Small Cell Lung Cancer

A study of MTA in patients with locally advanced or metastatic non-small cell lung cancer was carried out by the National Cancer Institute of Canada Clinical Trials Group. Patients participating in this study had not received prior chemotherapy. The original starting dose of MTA of 600 mg/m^2 was decreased to 500 mg/m^2 after initial patients on this study as well as a study of MTA in colorectal cancer experienced toxicity leading to dose reductions. Of 30 patients evaluable for tumor response, seven partial responses were seen, for an overall response rate of 23% (95% confidence interval, 9.9% to 42.3%). Four of these responses were in patients with stage IIIb disease (of eight patients with stage IIIb disease) and three were in patients with stage IV disease (of 25 patients with stage IV disease). Principal nonhematologic toxicities seen in this study included grade 3 lethargy (21% of patients) and grade 3 skin rash (39% of patients). Subsequent studies have incorporated prophylactic administration of dexamethasone, which has served to ameliorate or prevent this type of rash. Principal hematologic toxicities included grade 3 and 4 neutropenia in 27% and 12% of patients and grade 4 thrombocytopenia in 3% of patients. Grade 3 febrile neutropenia was experienced by 12% of patients.[12]

A similar study of MTA in previously untreated non-small cell lung cancer was carried out jointly between Australia and South Africa. All patients in this study received a starting dose of MTA of 600 mg/m^2. Of the 42 patients evaluable for response, seven partial responses (six in patients with stage IV disease and one in a patient with stage IIIb disease) were noted for an overall response rate of 17%. The median survival to date is 9.8 months, median time to disease progression is 4.5 months, and 42% of patients were alive after 1 year. As these data mature, the time to event intervals are expected to increase. Hematologic toxicity seen on this study included grades 3 and 4 neutropenia in 24% and 8% of patients. Rash was the most common nonhematologic toxicity, experienced by 21% (grade 3) and 11% (grade 4) of patients. Other grade 4 nonhematologic toxicities included vomiting (2% of patients) and diarrhea (4% of patients).[13]

Additionally, a study of MTA in second-line non-small cell lung cancer is currently ongoing in Europe. All patients in this study are receiving a starting dose of 500 mg/m^2. Patients are classified into two groups according to whether prior chemotherapy did (group A) or did not (group B) contain a platinum agent. Of the 27 patients enrolled to date, 15 are currently evaluable for response. Four patients have experienced a partial response, for a preliminary response rate of 27%. No responses have been seen in the group of patients who had received prior platinum therapy, but this is most likely a function of the small sample size, as response to MTA following platinum failure has been noted in other tumor types. Grade 3 or 4 neutropenia occurred in 27% of cycles and grade 3 or 4 thrombocytopenia occurred in 4% of cycles. Grade 3 or 4 infection occurred in 8% of cycles. Skin rash was frequent, although mostly mild, with moderate to severe rash occurring in only 2% of cycles.

Table 4. Phase II Activity of MTA in Non-Small Cell Lung Cancer

	First-Line Canada, Complete	First-Line Australia/ South Africa, Complete	Second-Line, Ongoing	
			A (Prior Treatment Not With Platinum)	B (Prior Treatment With Platinum)
No. of evaluable patients	30	42	10	9
CR	0	0	0	0
PR	7	7	3	0
Overall RR	23	17	—	—
Median survival (% Cens)	9.6 (33%)	9.7 (61%)	—	—
Median TTP (% Cens)	3.8	4.4 (18%)	—	—

Abbreviations: CR, complete response; PR, partial response; RR, response rate; Cens, censored; TTP, time to progression.
—, Data not available at this time.

Table 4 illustrates the activity of MTA in non-small cell lung cancer.

Head and Neck Cancer

A phase II study of MTA in advanced or recurrent squamous cell carcinoma of the head and neck is ongoing in France. Patients may have received chemotherapy in the neoadjuvant or adjuvant setting and the minimum chemotherapy-free interval is 6 months. All patients are receiving a starting dose of 500 mg/m^2, although 17% of 51 total courses have been reduced or delayed. To date, there have been seven responses to MTA in 19 patients treated. Although these data are preliminary, this is an encouraging level of activity. Toxicity that has been observed to date includes grade 3/4 neutropenia in 48% of courses, moderate and severe nausea in 22% of courses, and rash in 13% of courses. Febrile neutropenia has also occurred in 5% of courses. The toxicity seen in this study is possibly related to nutritional status in this patient population. This hypothesis is supported by the work of Niyikiza et al,[14] who have shown that functional folate status is highly correlated to the incidence of hematologic toxicity in patients who receive MTA.

Genitourinary Cancers

A phase II study ongoing in Spain has enrolled 25 patients with advanced transitional cell carcinoma of the urothelium. Six patients received the standard phase II dose of MTA, which was reduced to 500 mg/m^2 in subsequent patients due to unacceptable toxicities. Twenty patients are currently evaluable for response and toxicity. There have been seven partial remissions, for a response rate of 35%. National Cancer Institute Common Toxicity Criteria grade 3 or 4 neutropenia has been seen in 75% of patients, with five patients developing neutropenic fever. Nonhematologic toxicities included grade 3 diarrhea in 10 of patients and grade 4 mucositis in 5% of patients.[15] Although MTA has definitive activity in transitional cell carcinoma, toxicities appear to be severe and results from patients receiving the lower dose are awaited with interest.

A phase II study ongoing in Germany has enrolled 26 patients with renal cell carcinoma. All patients had stage IV disease and had not received prior therapy. Nephrectomized patients were required to have evidence of disease progression before study entry. Of 21 evaluable patients, there have been two durable partial responses, one lasting for 15 months to date and the other lasting 6 months to date, for a response rate of 9%. Disease stabilization has been experienced by 59% of patients. In this study, MTA has been quite well-tolerated, with grades 3 and 4 thrombocytopenia seen in 12% and 8% of patients.

Table 5. Phase II Activity of MTA in Head and Neck, Genitourinary, and Gynecologic Cancers (All Ongoing Studies)

Tumor	Head and Neck	Bladder	Renal Cell	Cervix
No. of evaluable patients	15	20	21	24
CR	1	0	0	0
PR	6	7	2	6
Overall RR	47	29	9	25

Abbreviations: CR, complete response; PR, partial response; RR, response rate.

Gynecologic Cancers

A phase II study of MTA in patients with FIGO stage IIIB or IV cervical cancer is currently ongoing in South Africa. Patients in this study were not permitted to have received prior chemotherapy. Of the 24 patients who are evaluable for response, there have been six confirmed partial responses. Responses have been quite durable, lasting from 4 to 17+ months. Toxicity in patients with cervical cancer has been greater than that experienced in other tumor types. Grade 3 or 4 neutropenia was seen in 63% of patients and grade 3 or 4 thrombocytopenia in 8%. Nearly half of all patients ultimately were discontinued from the study because of decreased creatinine clearance, presumably due to ureteral obstruction, which precluded further dosing. In an attempt to improve the toxicity profile in patients with this tumor, the study protocol has been recently amended to lower the starting dose to 500 mg/m^2 (from 600 mg/m^2).

Table 5 shows the activity of MTA in head and neck, genitourinary, and gynecologic cancers.

CONCLUSION

MTA has shown a broad spectrum of clinical activity in multiple tumor types, including colorectal, breast, non-small cell lung, pancreatic,

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