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

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# Overview of Phase II Trials of MTA in Solid Tumors

Peter J. O'Dwyer, Katrina Nelson, and Donald E. Thornton

**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.

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