Multitargeted Antifolate LY231514 as First-Line Chemotherapy for Patients With Advanced Non–Small-Cell Lung Cancer: A Phase II Study

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Purpose: **To evaluate the efficacy and safety of the multitargeted antifolate LY231514 (MTA) in patients receiving initial chemotherapy for unresectable, advanced non–small-cell lung cancer (NSCLC).**

Patients and Methods: **Patients with measurable, advanced NSCLC who had not received previous chemotherapy for advanced disease were considered for this study. Eligible patients who gave written informed consent initially received MTA 600 mg/m² intravenously (IV) for 10 minutes every 3 weeks. After three patients received treatment at this dose, the dose was reduced to 500 mg/m² IV at the same infusion time and frequency because of toxicity seen in this study and another Canadian MTA trial in colorectal cancer. Patients received up to four cycles after complete or partial remission or six cycles after stable disease was documented.**

Results: **Thirty-three patients were accrued onto the study. All were assessable for toxicity, and 30 patients were assessable for response. All but one patient had an Eastern Cooperative Oncology Group performance status score of 0 or 1, 18 patients (55%) had adenocarcinoma, and nine patients (27%) had squamous cell carcinoma. Twenty-five patients (76%) had stage IV disease, and the remainder had stage IIIB disease at trial entry. Seven patients experienced a confirmed partial response and no complete responses were seen; thus, the overall response rate was 23.3% (95% confidence interval, 9.9% to 42.3%). The median duration of response was 3.1 months (range, 2.3 to 13.5 months) after a median follow-up period of 7.9 months. Four (67%) of six patients with stage IIIB disease and three (12.5%) of 24 with stage IV disease responded to treatment. Four patients (13.3%) experienced febrile neutropenia and 13 (39%) experienced grade 3 or 4 neutropenia, whereas only one patient (3%) developed grade 4 thrombocytopenia. Nonhematologic toxicity was generally mild or moderate, but 39% of patients developed a grade 3 skin rash. Most other toxicities comprised grade 1 or 2 stomatitis, diarrhea, lethargy, and anorexia. Ten patients stopped protocol therapy because of toxicity.**

Conclusion: **MTA seems to have clinically meaningful activity as a single agent against advanced NSCLC. Toxicity is generally mild and tolerable. Further study of this agent in combination with cisplatin and other active drugs is warranted in this disease.**

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THYMIDYLATE SYNTHASE (TS) is the primary target of the fluoropyrimidines fluorouracil (5-FU) and fluorodeoxyuridine, long-established active agents in the treatment of gastrointestinal cancers, breast cancer, and other malignancies.[1,2] Biomodulation of 5-FU by leucovorin,[2] interferon,[3] or methotrexate[4] has resulted in greater inhibition of TS and, consequently, improved response rates[5] and survival,[6] particularly among patients with colorectal cancer. However, the fluorinated pyrimidines, such as 5-FU, are indirect inhibitors of TS, requiring metabolic activation, and are linked to other effects, such as alteration of RNA metabolism.[1] Such non-TS–inhibiting effects may lead to a low therapeutic index due to increased toxicity or loss of efficacy. In addition, inhibition of TS results in an increase in intracellular deoxyuridine monophosphate that can compete with pyrimidine analogs for binding to TS.[8]

Direct and more specific inhibitors of TS have been developed that interact with the folate-binding site of TS.[9-11] These folate analogs have been designed to improve the specificity for TS inhibition; furthermore, deoxyuridine monophosphate would enhance rather than competitively reverse their binding to TS. Multitargeted antifolate LY231514 (MTA) was designed as a folate-based TS inhibitor with a glutamate side chain in this new class of folate antimetabolites.[12,13] Although MTA itself only moderately inhibits TS, polyglutamation of the parent drug and its metabolites readily occurs, and the polyglutamated form of MTA is 100-fold more potent than MTA itself. In addition, other folate-requiring enzymes may act as targets for this drug, including dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, aminoimidazole carboxamide

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ribonucleotide formyltransferase, and C1 tetrahydrofolate synthase.[14,15]

MTA has demonstrated activity in a wide range of tumor types. The drug is highly active against CCRF-CEM human leukemia cells in vitro; the activity is partially reversible with the addition of thymidine.[12-14] The 50% inhibitory concentration in CCRF-CEM cells was 7 ng/mL.[13] It is also cytotoxic in human tumor colony-forming unit assays against human colon, renal, small-cell lung and non–small-cell lung cancers, hepatomas, and carcinoid tumors.[16] MTA can inhibit tumor growth in mice transplanted with human colon xenografts resistant to methotrexate.[17] In beagle dogs treated with a weekly and/or single-dose intravenous (IV) schedule, major toxicities included anorexia, emesis, diarrhea, mucositis, weight loss, neutropenia, lymphopenia, and mild anemia. Plasma concentrations increased linearly with increasing doses, with the terminal half-life occurring at about 2.3 hours.[18] Early studies have suggested that dietary supplementation with folic acid may improve the therapeutic index by reducing toxicity in mice.

A phase I trial of single-agent MTA was recently completed in which patients were treated by 10-minute IV infusion every 3 weeks. Starting at 50 mg/m^2, doses were escalated to 700 mg/m^2, at which point three of six patients developed grade 4 neutropenia and grade 3 or 4 thrombocytopenia. In patients who received 500 to 600 mg/m^2 MTA, serum peak concentrations were 70 to 200 µg/mL, values well above the 50% inhibitory concentration in CCRF-CEM cells (data for peak concentrations provided by J. Walling, personal communication, October 1998). Twenty patients were treated at the 600-mg/m^2 dose level, and 25% of them developed grade 4 neutropenia, 10% developed grade 3 or 4 thrombocytopenia, and 50% developed grade 2 pruritic skin rash. Four partial responses (four [11%] of 37 patients) were seen in patients with pancreatic and colorectal cancer.[19]

With these data, the recommended starting dose for phase II studies using this schedule was 600 mg/m^2. Two phase II studies have been conducted through the National Cancer Institute of Canada Clinical Trials Group, one in colorectal cancer and one in non–small-cell lung cancer (NSCLC). The results of the latter study are reported here.

PATIENTS AND METHODS

Patient Selection

Eligible patients were accrued between September 1995 and February 1997. These patients had histologically or cytologically confirmed inoperable, locally advanced, or metastatic NSCLC with evidence of bidimensionally measurable disease. Prior radiation therapy was permitted if acute side effects had resolved. Previous systemic therapy given for advanced disease was not permitted, but prior adjuvant therapy was allowed if the last dose was given ≥ 12 months earlier. Other eligibility criteria included (1) age ≥ 16 years, (2) Eastern Cooperative Oncology Group performance status of 0 to 2, (3) serum creatinine level within normal limits, (4) good hepatic function (ie, serum bilirubin ≤ 1.5 times the upper normal limit and AST ≤ two times the upper normal limit or ≤ five times the upper normal limit if liver metastases were present), (5) adequate bone marrow function and reserve (absolute granulocyte count > 1.5 × 10^9/L and platelet count ≥ 150 × 10^9/L), (6) absence of clinically detectable third-space fluid collections, (7) absence of clinical evidence of brain metastases, and (8) no concurrent treatment with other experimental drugs, anticancer therapy, or folinic/folic acid supplements.

Drug Administration

MTA was supplied as a lyophilized powder in 100-mg vials and was reconstituted by adding 10 mL of 0.9% sodium chloride. The appropriate dose was then withdrawn, diluted in normal saline, and administered intravenously over 10 minutes every 3 weeks. Retreatment at the initial dose and on schedule was determined by the lack of hematologic (≤ grade 1 on day of treatment and granulocytopenia ≥ 0.5 × 10^9/L and thrombocytopenia ≥ 50 × 10^9/L at nadir) and nonhematologic (grade ≤ 2) toxicity. Patients with grade ≤ 2 nonhematologic toxicity were treated symptomatically without delays, except for cases of grade 2 skin rash, in which case treatment was delayed until rash improved to grade ≤ 1. Patients with severe (grade 3 or 4) nonhematologic toxicity received a 25% dose reduction during subsequent cycles once toxicity had subsided. Those with nadir granulocytopenia less than 0.5 but less than severe thrombocytopenia (≥ 50 × 10^9/L) also received a 25% dose reduction for the next cycle. The use of nonsteroidal anti-inflammatory drugs and salicylates was permitted but not on or around the day of treatment. (This precaution was taken because of previous kinetic data suggesting increased drug levels during coadministration of anti-inflammatory agents.) Supportive-care agents, such as colony-stimulating factors, were permitted but could not be substituted for dose reductions required according to protocol. No dose escalations were permitted.

Measurements of Study End Points

All patients were assessable for toxicity from the time of their first treatment. Patients who had received at least one cycle of MTA and had follow-up measurements performed to assess change in tumor size were assessable for response. Response was assessed on day 1 of each cycle by clinical tumor measurements and documentation of the tumor size of measurable and nonmeasurable disease, using positive radiographic tests. If results were initially negative, tests were repeated only if clinically indicated. All sites with measurable lesions were followed for response. Measurements of undimensional lesions (ie, single largest dimensions) and bidimensional lesions (the products of the largest diameter and its largest perpendicular) were summed at each assessment and the best response on study was recorded.

A complete response required the disappearance of all clinical and radiologic evidence of tumor for at least 4 weeks. A partial response required a ≥ 50% decrease in the sum of the products of the diameters of all measurable lesions, also for at least 4 weeks. Stable disease designated a steady-state of disease, which was a response less than a partial response or progression less than progressive disease, both for at least 6 weeks from the start of therapy. In addition, there could be no new lesions or increases in the size of any nonmeasurable lesions for

complete or partial remissions or for stable disease. Progressive disease indicated an unequivocal increase of at least 25% in the sum of the products of the diameters of all measurable lesions compared with baseline or the appearance of new lesions. Nonmeasurable disease was not considered in the response assessment, except that new lesions would constitute progressive disease; all nonmeasurable lesions had to disappear for a designation of complete response to be made.

Response duration was defined from the time that criteria for response were met until disease progression was objectively documented, with disease progression measured from the time that response was established. Stable disease was measured from the start of therapy until disease progression. All reported responses were verified by independent radiology review.

RESULTS

Thirty-three patients were accrued onto this study. All patients were assessable for toxicity, and 30 patients were assessable for response. The three unassessable patients came off study before the second treatment because of toxicity. One hundred thirty-two cycles were administered; 13 cycles were given to the three patients at the initial 600-mg/m^2 dose (median, six cycles; range, one to six cycles), and 75 cycles were given to patients who started at the 500-mg/m^2 dose (median, four cycles; range, one to eight cycles). Of the 30 patients who started at the 500-mg/m^2 dose, 15 received one cycle at this dose, four received two cycles, and 11 received three or more cycles. Fourteen patients required a dose reduction to 375 mg/m^2 for one or more cycles. Four patients required a further dose reduction to 281 mg/m^2. Characteristics of the 33 patients are listed in Table 1. The majority were male, presented with excellent performance status, and received only radiotherapy as prior treatment. A majority (18 of 33) had adenocarcinoma as a histologic diagnosis, and 26 of 33 patients had more than one site of involvement at study entry. At the time this article was written, the median follow-up was 7.9 months (range, 3.3 to 16.8 months). (For patients who died, the last follow-up date was the date of death.)

Antitumor Activity

Of the 30 patients assessable for response, none had a complete response and seven patients had a confirmed partial response; thus, the overall response rate was 23.3% (95% confidence interval, 9.9% to 42.3%). When all eligible patients are included, the response rate is 21.2%. The median time to progression for all patients was 3.8 months (range, 0.5 to 15.8 months). The median survival time of all patients was 9.2 months (Fig 1), and the 1-year survival rate was 25.3% (95% confidence interval, 9.7% to 40.9%). A higher response was seen among stage IIIB patients (four [67%] of six) compared with those who entered the study with stage IV disease (three [12.5%] of 24).

Table 1. Patient Characteristics

		No. of Patients
Age, years		
Median	63	
Range	42-74	
Sex		
Female		7
Male		26
Performance status*		
0		13
1		19
2		1
Histology		
Adenocarcinoma		18
Squamous		9
Undifferential		6
Prior therapy		
Radiation therapy		11
Sites of disease		
Lung		27
Lymph nodes		24
Liver		8
Bone		7
Adrenal		7
Pleural effusion		5
Subcutaneous		1
Spleen		1
Stage at study entry		
IIIB		8
IV		25
No. of organ sites involved		
1		7
2		11
3		10
≥ 4		5

*Eastern Coopoerative Oncology Group performance status.

Toxicity

After the first three patients were accrued, a decision was made to reduce the starting dose to 500 mg/m^2 based on the combined toxicity of 12 patients entered onto this study and a Canadian study of the same initial dose and schedule in patients with advanced colorectal cancer (Cripps et al, manuscript submitted for publication). Of the first three patients in the present trial, one patient experienced grade 3 dyspnea, mucositis, and high fever with radiographic suspicion of pneumonia. The patient recovered but refused further therapy. The other two patients completed six cycles of therapy at the initial dose. Two of the three patients experienced grade 3 neutropenia, and none experienced higher than grade 2 renal or hepatic toxicity. The hematologic toxicity experienced by the 30 patients who started at the 500-mg/m^2 dose level was similar to that of the other three patients. Hematologic toxicity, as median nadir counts and by worst grade experienced for all patients, is listed in Table 2. Overall, only two patients experienced a grade 4

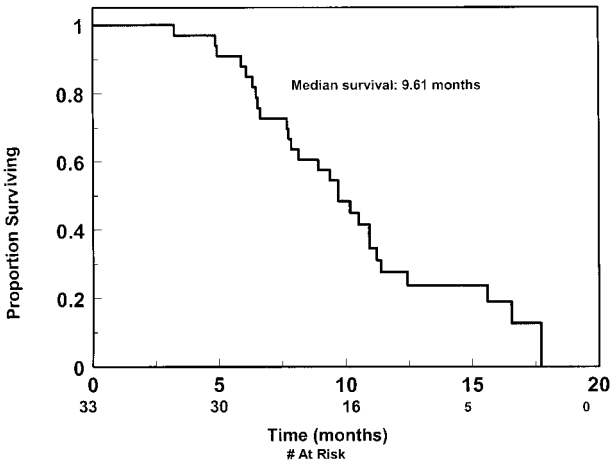

Fig 1. Overall survival of all patients.

adverse event; one experienced a cerebrovascular accident, and the other patient developed a deep vein thrombosis and pulmonary thromboembolus associated with severe shortness of breath. Neither of these events was considered related to the MTA therapy. Other than these cases, the most severe and prevalent nonhematologic toxicities are listed in Table 3. Severe (grade 3) nonhematologic toxicity presented most commonly as a skin rash (39%), lethargy (27%), anorexia (12%), nausea (12%), vomiting (9%), and diarrhea (9%), most of which was attributable to the study drug. The skin rash was generalized in half of affected patients and symptomatic with primarily pruritus in 23 of 26 patients. Subsequent retrospective analysis in this and the colorectal phase II study of the same agent showed that patients who received dexamethasone in their first cycle had a lower frequency and severity of skin rash (without dexamethasone, 93% of cycles with skin rash, 47.5% grade 3; with dexamethasone, 56% of cycles with skin rash, 12% grade 3). Four patients (12% of all patients) on the study developed febrile neutropenia, with one documented severe systemic infection considered related to protocol therapy.

Nonhematologic biochemical changes were mild. Only three patients developed transient grade 3 elevations of their liver function tests (bilirubin and AST), and only one patient developed grade 2 elevation of serum creatinine (Table 4).

Table 3. Nonhematologic Toxicity (n = 33)

Toxicity	Grade (no. of patients) 1	2	3	4	Total No. of Patients	% of Patients	% Drug-Related Only
Skin rash	3	10	13	0	26	79	79
Lethargy	5	15	9	0	29	88	76
Anorexia	8	10	4	0	22	67	58
Diarrhea	9	2	3	0	14	42	33
Nausea	13	9	4	0	26	79	76
Arthralgia	1	4	3	0	8	24	0
Stomatitis	5	4	2	0	11	33	33
Vomiting	8	5	3	0	16	49	46
Tearing	6	3	2	0	11	33	30
Edema	5	5	3	0	13	39	21
Febrile neutropenia			4		4	12	12
Infection	3	3	4	0	10	30	6

DISCUSSION

Initial results from preclinical animal studies and phase I trials suggested clinical activity for MTA primarily against colorectal and pancreatic cancer.[19,20] The level of activity seen in the present study in NSCLC was higher than initially anticipated, and independent reviewers confirmed all responses. This promising level of clinical activity was seen in patients with lung and lymph node involvement as well as in those with visceral and bone involvement, although the proportion of patients who responded was much higher in the group of stage IIIB patients. In another phase II study of MTA in patients with NSCLC by Clarke et al,[21] all patients were initially treated with 600 mg/m^2 MTA. Response rates were comparable to those in this study; among 12 patients assessable for response, the overall response rate was 33% (all partial responses). Toxicity profiles were similar between the two studies; in addition, toxicity seen in the phase I studies was similar to that reported for other drugs in this class.[19,20,22] Neutropenia was the predominant hematologic toxicity, resulting in dose reduction in 12% of patients, but it did not lead to treatment delays; only one patient (3%) experienced dose-reducing (grade 4) thrombocytopenia.

Most symptomatic, nonhematologic toxicity was managed with appropriate supportive care; for ≥ grade 3 toxicity, the next cycle was delayed until symptoms resolved to ≥ grade 1 severity and subsequent doses were reduced by 25%. Nausea and emesis were infrequent and not severe,

Table 2. Hematologic Toxicity (n = 33)

	Nadir (× 10^9/L) Median	Range	Toxicity Grade 0	1	2	3	4
Hemoglobin, g/L	111	73-149	6	14	10	3	0
WBC	2.5	0.4-8.1	6	5	9	11	2
Granulocytes	1.1	0.0-4.0	7	3	10	9	4
Platelets	152	20-278	17	14	1	0	1

Table 4. Biochemical Changes (n = 31)

Test	Toxicity Grade 0	1	2	3	4
Serum creatinine	29	1	1	0	0
Bilirubin	26	0	4	1	0
AST	5	17	7	2	0
Alkaline phosphatase	14	16	1	0	0

and physician discretion was permitted for prophylaxis based on the low emetogenic potential projected from phase I studies. Skin rashes were frequent; 30% of patients had treatment delayed with no subsequent dose reduction, whereas patients with generalized, symptomatic rash (39%) were given a 25% dose reduction. Both groups were treated prophylactically with dexamethasone for 3 days starting the day before each subsequent dose. With this intervention, skin toxicity decreased in subsequent cycles. Later in the study, it was noted that prophylactic dexamethasone given in cycle 1 seemed to have a beneficial effect in reducing the expected frequency and severity of skin rash. Future trials should likely incorporate this premedication at the first dose. Thirty percent of patients came off protocol therapy because of toxicity, most often gastrointestinal. This highlights the considerable interpatient variability of the toxicity experienced. Nonhematologic biochemical alteration of renal and hepatic function was relatively mild and of no clinical consequence. In three patients (9%), grade 3 elevation of bilirubin or AST levels resulted in dose reduction.

The decision to reduce the starting dose from 600 mg/m^2 to 500 mg/m^2 early in this study was based largely on the toxicity seen in a larger cohort of patients in a Canadian phase II study of colorectal cancer that is using the same dose and schedule. The toxicity seen in all other phase II trials of lung, breast, and gastrointestinal tumors at the 600-mg/m^2 dose and schedule has been similar to that seen in our study. Factors that may be associated with the more severe toxicity seen in the Canadian colorectal trial cohort have not yet been identified. The clinical activity in our trial is similar to that seen in the study of Clarke et al,[21] in which all patients started at a dose of 600 mg/m^2. Furthermore, it is interesting that all responding patients were treated at an initial dose of 500 mg/m^2.

MTA clearly has relevant clinical activity in patients with advanced NSCLC and toxicity that is tolerable with conventional dose and schedule adjustments. In addition to its effect on multiple enzymes in the folate-dependent pathways, MTA can synchronize treated cells at the G_1/S interface initially, followed by synchronous entry of treated cells into S phase II 4 hours after initial drug exposure in vitro.[23] A recent study suggests that MTA may enhance the cytotoxic effect of other drugs, such as gemcitabine, when target cancer cells are exposed to MTA 12 to 24 hours earlier.[24] A phase I combination trial of these two agents is in progress. As a result, further studies are planned to test the efficacy of MTA in combination with other agents with proven efficacy against NSCLC, such as the taxanes and platinum compounds. Our group is presently conducting a phase II combination study of MTA and cisplatin in advanced NSCLC. Ultimately, it is hoped that MTA may contribute to an improvement in the survival and quality of life of some patients with this disease.

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