Phase II Study of Maytansine in Patients With Advanced Lymphomas: An Eastern Cooperative Oncology Group Pilot Study[1,2]

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SUMMARY

During phase I trials with maytansine some activity against lymphoma and lymphocytic leukemia was noted. Therefore, a phase II trial of maytansine in patients with advanced lymphomas refractory to conventional chemotherapy was begun. There were three partial responders (10%) among 31 patients entered in the trial. Toxicity was acceptable; gastrointestinal and neurologic side effects were the most common. Little myelotoxicity and no hepatotoxicity were observed. We conclude that maytansine has very limited activity in heavily pretreated patients with Hodgkin's disease and non-Hodgkin's lymphomas.

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Maytansine is a naturally occurring ansa macrolide originally isolated from the stem bark of the East African shrub *Maytenus ovatus* (1). Its mechanism of action is similar to that of the vinca alkaloids. Maytansine produces metaphase arrest by interference with mitotic spindle formation caused by inhibition of tubulin polymerization. Unlike vincristine, however, maytansine binds to tubulin irreversibly and produces an irreversible stathmokinetic effect (2,3).

Early clinical trials with maytansine demonstrated acceptable toxic effects including nausea, vomiting, diarrhea, and abnormalities in hepatic function tests (4,5). Little myelosuppression other than sporadic thrombocytopenia, especially in patients with pre-existing liver disease, was encountered (6). Extravasation of the drug caused phlebitis and local necrosis (5). Dose-related neurotoxicity included both central (lethargy, dysphoria, and drop in performance status) and peripheral (paresthesias, jaw pain, muscle weakness, and loss of deep tendon reflexes) effects. Patients with pre-existing vincristine or carcinomatous neuropathies had greater neurologic toxic effects from maytansine (5).

To date, phase II trials of maytansine have shown little activity against breast cancer (7), melanoma (7), lung cancer (8), and colorectal cancer (9). In September 1977, the Eastern Cooperative Oncology Group initiated a phase II trial of maytansine in patients with advanced lymphomas refractory to conventional chemotherapy.

METHODS

All patients had advanced (stage III or IV) histologically documented Hodgkin's disease or non-Hodgkin's lymphoma and were no longer responsive to conventional chemotherapy. Twenty-nine patients had received prior treatment with vinca alkaloids, and one had received VM-26 as well. Many patients had received prior radiation therapy (table 1). Each patient had at least one site of measurable disease. Criteria for ineligibility included chemo-

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TABLE 1.—Pretreatment characteristics of 31 patients with lymphoma treated with maytansine

Characteristic	No. of patients
Histologic type	
Hodgkin's disease	9
Non-Hodgkin's lymphoma	22
Sex	
Males	21
Females	10
Median age in yrs (range): 56 (19–85)	
Performance status	
0–1	11
2–3	17
4	3
Previous treatment	
Chemotherapy only	7
Chemotherapy and radiotherapy	24
Previous exposure to vinca alkaloids	
Vincristine	18
Vinblastine	1
Vincristine and vinblastine	10
Neither	2
Sites of measurable disease	
Lymph nodes	29
Lung	7
Liver	6
Blood and marrow	5
Skin	5
Spleen	1

therapy within 2 weeks of entry in the study and an expected survival of < 2 months. None of the patients was clinically jaundiced, although several had abnormal liver function tests. Pretreatment characteristics of the 31 patients are summarized in table 1.

Maytansine was administered by iv bolus injection over 3–5 minutes at a dose of 0.5 mg/m² daily for 3 consecutive days, with each treatment cycle repeated at 3-week intervals. Patients with pre-existing liver disease and bilirubin or SGOT greater than twice normal received a 50% dose reduction. No dose adjustment was made for low peripheral blood cell counts resulting from prior therapy or disease involvement. Patients continued to receive therapy until disease progression. Those patients who had no change in measurable disease after three cycles of treatment were also considered to have failed maytansine treatment.

Responses were defined by standard Eastern Cooperative Oncology Group criteria. A partial response was defined as a > 50% reduction in the sum of the products of perpendicular diameters of measurable lesions. Disease progression was defined as the unequivocal appearance of any new lesion or an increase of 25% in the product of the perpendicular diameters of any measurable lesion. Responses were recorded only if the observed improvement persisted for > 1 month. Duration of response was measured from the date treatment was started. All patients were considered evaluable for response, even if they received less than one full course of treatment.

RESULTS

Therapeutic Effects

Thirty-one patients were entered in the study. Six patients died within 4 weeks after starting therapy. In each case death was thought to be due to progressive lymphoma and its complications rather than to maytansine treatment. Nineteen patients had progressive disease while receiving maytansine and three had no improvement. Three patients had partial responses; the response rate was 10%. Details about the three responders are shown in table 2.

For each of the responders, treatment was discontinued after three or four cycles even though responses were continuing. In two cases, the patients refused further maytansine because of toxic effects (paresthesias, diarrhea, nausea, and vomiting). In the patient with nodular mixed lymphoma, maytansine was withheld because of thrombocytopenia (30,000–70,000 cells/mm³). Bone marrow involvement was present, however, and it appears likely that the disease, rather than maytansine, was mainly responsible for the thrombocytopenia. No improvement in platelet count was observed after maytansine was discontinued.

The patient with nodular sclerosing Hodgkin's disease responded in his liver and peripheral nodes after one cycle of maytansine. He refused further treatment after the third cycle but remained in good partial remission with return to a normal activity schedule for a total of 13 months without additional therapy. At that point he relapsed in his peripheral nodes and liver and developed ascites.

Toxic Effects

Twenty-nine of the 31 patients were evaluable for toxic effects. The other two patients died within 4 days after starting therapy. Hematologic toxicity was minimal. No patient had a wbc count of < 2500/mm³, and only two patients had wbc counts of < 4000/mm³. No patient had a platelet count of < 30,000/mm³, and only three patients had platelet counts of < 100,000/mm³. No thrombocytopenic hemorrhage or leukopenic infection occurred.

Gastrointestinal side effects were the most common, usually occurring at the end of the treatment

TABLE 2.—Responders to maytansine

Histologic type*	Stage	Previous vincristine/ vinblastine†	Site of response	Duration (mos)
NM	IVB	−/−	Peripheral nodes	4
DPDL	IVA	+/−	Peripheral nodes	4
Hodgkin's disease (NS)	IVA	+/−	Peripheral nodes, liver	13

*NM = nodular mixed lymphoma; DPDL = diffuse poorly differentiated lymphocytic lymphoma; NS = nodular sclerosis.

†No patients with previous VP–16–213 or VM–26 therapy.

cycle or within a few days after treatment. Nine patients had gastrointestinal side effects (nausea, vomiting, and diarrhea), but in only one patient was the toxic effect considered severe. No patient with normal liver function tests at the start of treatment had evidence of hepatotoxicity while receiving maytansine. Eight patients with pre-existing liver function abnormalities had fluctuations in liver function tests while receiving maytansine, but in no patient could deterioration in liver function be clearly ascribed to maytansine treatment. There was no indication of increased neurologic or hematologic toxicity in those patients with pre-existing liver disease who were treated with 50% doses of maytansine.

DISCUSSION

The response rate of the lymphoma patients treated with maytansine in this study was disappointingly low. All of the patients had far-advanced disease and had undergone extensive previous chemotherapy with or without radiation therapy. In most patients maytansine was the third or fourth chemotherapy regimen employed. Most of the patients, however, were in reasonably good condition, and maytansine could be administered in an outpatient setting in almost all instances. Nevertheless, the 10% response rate offers little encouragement that maytansine, at least at this dose and schedule, will be of significant value in the treatment of Hodgkin's disease or non-Hodgkin's lymphoma. Further trials with this agent in patients with lymphoma are not warranted.

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