Results of a Phase II Study of Maytansine in Patients With Breast Carcinoma and Melanoma [1,2]

Brief Reports and Preliminary Communications

Fernando Cabanillas,* Gerald P. Bodey, Michael A. Burgess, and Emil J Freireich [3]

SUMMARY

During the phase I study of maytansine at our institution, some activity was observed against breast carcinoma and melanoma. A phase II study was thus initiated to more thoroughly investigate the activity of this drug against these two tumors. In 33 evaluable patients with melanoma, no complete or partial responses were observed. Twenty-one evaluable patients with breast cancer were entered and only one response (partial) was seen. The toxicity was similar to that observed in the phase I study and consisted mainly of diarrhea, paresthesias, phlebitis, and flu-like symptoms. Myelosuppression was infrequent and was short-lived when it occurred.

[Cancer Treat Rep 63:507–509, 1979]

Maytansine is a recently discovered ansa macrolide drug derived from the plant *Maytenus ovatus* (1). It is active against the experimental P388 leukemia and B16 melanoma animal tumors.[4] In a phase I trial using a 3-day schedule conducted at our institute, activity was detected against breast carcinoma and melanoma (2). The dose we recommended for further clinical trials was 0.5 mg/m^2 daily × 3 every 2–3 weeks according to toxicity. The dose-limiting toxic effect of this agent was diarrhea; myelosuppression was mild or nonexistent. Consequently, it was thought that this would be an interesting compound for further clinical trials. We initiated a phase II trial in patients with breast carcinoma and melanoma in June 1977.

MATERIALS AND METHODS

Patients with advanced histologically documented carcinoma of the breast or melanoma who had failed to respond to regimens of higher priority were candidates for this study. Physical examination was performed and measurable lesions were recorded. The following pretreatment studies were performed: cbc, platelet count, urinalysis, SMA-12 profile before every cycle of treatment, bone marrow aspiration and biopsy, and chest roentgenogram. The cbc was repeated at least once a week during therapy. Other tests to evaluate the presence of measurable tumor were obtained as indicated and were repeated after two cycles of therapy in order to evaluate response to treatment.

This study was designed as a randomized comparison of two different schedules: (*a*) 0.5 mg/m^2 in 500 ml of dextrose in water over 30 minutes daily × 3 repeated in 2–3 weeks with subsequent increments of 0.1 mg/m^2 according to toxicity, or (*b*) 0.75 mg/m^2 in 500 ml of dextrose in water over 30 minutes iv weekly with 0.25-mg/m^2 increments every week according to toxicity.

Early during the study, it was found that most patients with normal liver function tests could tolerate a dose of 0.6 mg/m^2 daily × 3 and, thus, the starting dose was increased. In the weekly schedule, the starting dose was increased to 1 mg/m^2. Patients with abnormal liver function tests (SGOT or alkaline phosphatase levels increased to twice the normal levels) received a 50% dose reduction, and if the first course was well-tolerated the following dose was increased to the standard starting dose. The dose of maytansine was modified according to the severity of diarrhea. When this was severe (requiring iv fluids for treatment of dehydration or lasting > 5 days), the dose was reduced by 33%. If ileus developed, the dose was reduced by 50% after

[1]Received Oct 31, 1978; revised Jan 11, 1979; accepted Jan 29, 1979.

[2]Supported in part by contract N01-CM-57042 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

[3]Department of Developmental Therapeutics, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston.

[4]Helman L, Henney J, and Slavik M. Clinical brochure: maytansine. Prepared by the National Cancer Institute, Bethesda, Md, 1976.

Reprint requests to: Fernando Cabanillas, MD, Department of Developmental Therapeutics, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Ave, Houston, Tex 77030.

resolution of the obstruction. Myelosuppression was not used as a criterion for dose modification because it occurred infrequently and was almost always associated with diarrhea.

After several patients were entered in the study, the weekly schedule was discontinued at the request of the National Cancer Institute (not because of excessive toxicity). Thus, fewer patients were entered in the weekly regimen compared to the daily × 3 regimen.

RESULTS

Response of Patients With Melanoma

At the close of this study, 33 evaluable patients with melanoma had been entered in the 3-day schedule and 12 had been entered in the weekly schedule. All patients had visceral disease with or without associated nodal or skin lesions. There were no complete or partial responses. Four patients had a less than partial remission, all except one in soft tissue disease. Three of these minimal responses occurred in subcutaneous melanoma nodes which decreased in size with no evidence of a simultaneous response in visceral sites. The fourth minimal response was in a patient who had malignant ascites and pleural effusion which decreased in size with no evident response in a supraclavicular mass. Five patients were stable for 6 weeks or more and 24 failed to respond at all. Of the four less than partial responses, two occurred in the 3-day schedule and two in the weekly schedule.

Response of Patients With Breast Carcinoma

Twenty-one evaluable patients with breast carcinoma were entered. Eighteen were treated with the 3-day schedule and three with the weekly schedule. With the exception of one patient who had exclusively nodal disease, all others had visceral disease. There were no complete remissions. One patient had a partial remission (bone marrow disease) lasting 4 months and one had a less than partial remission in a supraclavicular node. Both of these patients received the 3-day schedule. Three patients had stable disease for ≥ 6 weeks and 16 failed to respond. These patients were heavily pretreated and in most cases maytansine was the third or fourth drug used.

Myelosuppressive Toxicity

Since more patients with breast carcinoma had a history of prior radiation therapy and prior exposure to myelosuppressive drugs (eg, mitomycin C) with cumulative toxicity (compared to patients with melanoma), the myelosuppressive toxicity of maytansine has been analyzed separately for patients with these two diagnoses. The myelosuppressive toxicity is shown in table 1. Myelosuppression was observed infrequently and was seen less frequently in the group that received the weekly schedule.

Gastrointestinal Toxicity

Gastrointestinal toxicity for patients with both breast carcinoma and melanoma is shown in table 2 according to the schedule of treatment. The total amount of drug in milligrams per square meter that was delivered per month is also shown in table 2. The major and most frequent toxic effect of maytansine was diarrhea, which in some cases was severe enough to require hospitalization. This problem seemed to occur less frequently with the weekly schedule. The total amount of drug delivered per month with the weekly schedule was higher, yet the toxicity was less.

Other Toxic Effects

Aside from myelosuppression and gastrointestinal toxicity, other side effects consisted of paresthesias in six patients, superficial phlebitis in four patients,

TABLE 1.—Myelosuppressive toxicity of maytansine

	3-day schedule	Weekly schedule
Melanoma		
No. of evaluable courses	33	36
No. of patients with myelosuppression*	4	1
Breast carcinoma		
No. of evaluable courses	24	8
No. of patients with myelosuppression*	7	0

*Any drop in the wbc count to < 3000/mm³ or the platelet count to < 100,000/mm³.

TABLE 2.—Gastrointestinal toxicity of 3-day vs weekly schedule compared to total maytansine dose delivered (includes both breast carcinoma and melanoma patients)

	3-day schedule	Weekly schedule
No. of evaluable courses	102	49
No. of patients with—		
Nausea/vomiting	36(35%)	17(35%)
Diarrhea	43(42%)	16(33%)
Ileus	3(3%)	1(2%)
Constipation	6(6%)	1(2%)
Dose delivered per mo (mg/m²)	3.29	4.07

flu-like symptoms in four patients, fever or chills in three patients, skin slough in one patient, and mucositis in one patient. In this study, the development of paresthesias was not related to previous vinca alkaloid administration. None of the patients who experienced this toxicity had been previously exposed to vinca alkaloids.

DISCUSSION

The response rate observed in this phase II study of maytansine has been disappointingly low. Using the schedules outlined above, maytansine cannot be considered an active drug against melanoma or breast carcinoma. However, further trials are justified in other tumors. Furthermore, it is conceivable that the schedule selected for this trial might not be the most adequate. Pharmacology studies are necessary to delineate the pharmacokinetics of this interesting compound so that a rational schedule of administration can be designed. Unfortunately, an assay sensitive enough to measure the minute levels of maytansine is not available.

The weekly schedule of administration allowed more drug to be administered with less toxicity than the 3-day schedule. This, however, did not result in a significant increase in response rate. Should this drug prove to be active against other tumors, the weekly schedule might be preferable if the drug has a sufficiently long half-life.

Because of its virtual lack of myelosuppression and overlapping toxic effects with most of the currently available drugs, this agent should be explored more extensively. Using a single-dose schedule of maytansine, the National Cancer Institute has also found very little myelosuppression (3). This compound possesses significant activity against experimental animal tumors. The type of toxicity observed in this and other studies suggests a potentially important role in combination with myelosuppressive drugs. Further exploration of its activity in other tumors and with several different schedules is necessary.

REFERENCES

1. KUPCHAN SM, KOMODA Y, COURT WA, ET AL. Maytansine, a novel antileukemic ansa macrolide from *Maytenus ovatus*. J Am Chem Soc 94:1354–1356, 1972.
2. CABANILLAS F, RODRIGUEZ V, HALL SW, ET AL. Phase I study of maytansine using a 3-day schedule. Cancer Treat Rep 62:425–428, 1978.
3. CHABNER BA, LEVINE AS, JOHNSON BL, ET AL. Initial clinical trials of maytansine, an antitumor plant alkaloid. Cancer Treat Rep 62:429–433, 1978.