Am J Clin Oncol (CCT) 8: 148–150, 1985.

Phase II evaluation of maytansine (NSC 153858) in advanced cancer

A Southeastern Cancer Study Group trial

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MAYTANSINE GIVEN IN A 3-DAY COURSE q3 WEEKS produced only five responses (3%) in 163 evaluable adults with advanced cancer. The dose schedule employed is not recommended for further study.

Maytansine is an ansa macrolide, isolated from the East African shrub Maytenus Ovatus Loes; *in vivo* tumor inhibitory activity was reported in various animal systems such as mouse L1210, P388 leukemia, Lewis lung carcinoma, and B16 melanoma; human phase I studies incidentally demonstrated activity for this drug in breast, head-and-neck, and ovarian cancers, melanoma, leukemia and lymphoma.[6] Encouraged by the spectrum of antitumor activity demonstrated during these trials, we undertook a broad phase II study of maytansine.

Methods

Patients with advanced solid tumors refractory to previous therapy, or untreated but with a poor prognosis, were eligible for study if they: (1) had a definite histologic diagnosis; (2) were considered incurable by existing surgical, radiotherapeutic, or chemotherapeutic approaches; (3) had at least one measurable lesion (bone lesions alone were not acceptable); (4) had a Karnofsky performance status of at least 40%; (5) had recovered from previous myelosuppressive therapy; (6) were 18 years of age or older; (7) gave written informed consent.

Pretreatment studies included: history and physical examination; measurement of tumor indicator lesions; complete blood counts; serum transaminase, bilirubin, alkaline phosphatase, electrolytes, and creatinine; chest roentgenogram and other roentgenograms and scans as appropriate; and electrocardiogram.

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performed q 7 days. Every 21 days and just before each subsequent course of maytansine, the clinical and laboratory assessments were repeated.

Maytansine was diluted in 500 cc of 5% dextrose in water and given by intravenous infusion over 2 hours at a dose of 0.5 mg/m^2/day for 3 consecutive days. In view of possible dose-related hepatic toxicity reported in other studies, patients who had abnormal liver function tests or detectable liver involvement received a half dose initially. Treatment was continued q 3 weeks as long as there was no progression of cancer, and no significant drug toxicity. Escalation of drug dosage, by 20% of the previous dose, was permitted only in patients receiving the lower dose schedule, if no further hepatic deterioration and no significant hematologic toxicity occurred during the previous 3 weeks. Toxicity was rated using standard cooperative group toxicity criteria. An adequate trial required at least two courses of maytansine, and 2 weeks of follow-up after the last course. A complete response required disappearance of all objective evidence of cancer. A decrease of 50% or more in the sum of the products of the diameters of measurable lesions was a partial response.

Results

Of the 194 patients entered into the study, 31 were inevaluable (five were ineligible, nine had major protocol violations, and 17 had inadequate data).

Of the 163 evaluable patients (86%), five (3%) achieved partial responses in the following tumor categories (response duration): 1/22 colorectal (28.1 weeks), 1/25 kidney cancer (92.9+ weeks), 1/8 head and neck (12 weeks), 1/2 myeloma (48.7+ weeks), 1/8 other cancer (3.6 weeks). There were no responses of 26 with lung cancer; 21 with breast cancer; 10 with pancreatic cancer; eight with other GI cancers; three ovarian, two cervix, and two endometrial cancers; two bladder; one testicular and one adrenal carcinomas; five with melanomas; 16 sarcomas; and one mesothelioma. The median age was 55 (range 20–81) and the median performance status was 70 (range 40–100). Forty-eight percent were male. Sixty-two of the evaluable patients began treatment with the low dose; only one of the responders was in prior chemotherapy; of these, one with a colon primary had a partial response.

TABLE 1

Toxicity in 163 Evaluable Cases

	Mild	Moderate	Severe	Life-Threatening
Granulocytes	8	1		
Platelets	11	4	5	1
Cardiovascular	2	1		
Oral	2			
GI	44	17	3	
GU	7		1	
Liver	1			
CNS	8	6	6	

Toxicity

The side effects observed were mostly mild to moderate in severity and clinically tolerable. As the frequency and severity of toxicity were similar on the low dose and high dose, the results were combined (Table 1). Twenty-two patients had falls in hematocrit of uncertain relationship to treatment. Genitourinary effects attributed to the drug included increases in creatinine and/or BUN, and proteinuria in one case. An arrhythmia was reported in one case and nonspecific cardiac abnormalities in two other cases. Neurologic effects attributed to treatment included paresthesias, sensory neuropathy, generalized weakness, hyporeflexia, lethargy, confusion, hallucinations, coma, and seizure; paresthesias and lethargy were the most common neurologic effects. Phlebitis and alopecia were occasionally reported.

Discussion

This study was prompted by the wide spectrum of antitumor activity in phase I studies of maytansine. Unfortunately, we observed no consistent antitumor activity. In this broad phase II trial, several categories did not have adequate numbers of patients and most had had prior chemotherapy; but we did not think further accession was warranted.

Toxicity was mostly mild to moderate and not unexpected, based on previous reports.

Our results and other studies[1–5,7–9] do not suggest a major role for this drug in the treat-

ACKNOWLEDGMENTS

This study was performed by the Southeastern Cancer Study Group and was supported by Public Health Service grants (CA) from the NCI, National Institutes of Health, Department of Health and Human Services. The following institutions participated in the study: University of Alabama in Birmingham (CA03013, CA19657, CA24456); Duke University, Durham, NC (CA03177); Durham V.A. Hospital (CA05634); Emory University, Atlanta, GA (CA03227); University of Miami, FL (CA05641); Washington University, St. Louis, MO (CA03376); University of Puerto Rico, San Juan (CA12223); Rush Medical Center, Chicago, IL (CA12640); Case Western Reserve University, Cleveland, OH (CA15584); University of Tennessee, Memphis (CA17027); St. Louis University, MO (CA17214); University of Kentucky, Lexington (CA20255); University of Cincinnati, OH (CA28138); University of South Florida, Tampa; University of Florida, Gainesville (CA28143); Vanderbilt University, Nashville (CA23909); University of Tennessee, Knoxville (CA13237); University of Louisville, Kentucky (CA16389); and New Jersey College of Medicine.

Maytansine was supplied by the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

References

1. Ahmann, D. L., Frytak, S., Kvols, L. K., et al.: Phase II study of maytansine and chlorozotocin in patients with disseminated malignant melanoma. *Cancer Treat Rep 64: 721–723, 1980.*
2. Borden, E. C., Ash, A., Enterline, H. T., et al.: Phase II evaluation of dibromodulcitol, ICRF-159, and maytansine for sarcomas. *Am J Clin Oncol 5: 417–420, 1982.*
3. Creagan, E. T., Fleming, T. R., Edmonson, J. H., et al.: Phase II evaluation of maytansine in patients with advanced head and neck cancer. *Cancer Treat Rep 63: 2061–62, 1979.*
4. Creech, R. H., Stanley, K., Vogl, S. E., et al.: Phase II study of cisplatin, maytansine, and chlorozotocin in small cell lung carcinoma (EST 2578). *Cancer Treat Rep 66. 1417–1419, 1982.*
5. Eagan, R. T., Creagan, E. T., Ingle, J. N., et al.: Phase II evaluation of maytansine in patients with metastatic lung cancer. *Cancer Treat Rep 62: 1577–1579, 1978.*
6. Issell, B. E., and Crooke, S. T.: Maytansine. *Cancer Treat Rev 5. 199–207, 1978.*
7. Neidhart, J. A., Laufman, L. R., Vaughn, C., et al.: Minimal single-agent activity of maytansine in refractory breast cancer: A Southwest Oncology Group study. *Cancer Treat Rep 64: 675–677, 1980.*
8. O'Connell, M. J., Shani, A., Rubin, J., et al.. Phase II trial of maytansine in patients with advanced colorectal carcinoma. *Cancer Treat Rep 62: 1237–1238, 1978.*
9. Thigpen, J. T., Ehrlich, C. E., Creasman, W. T., et al.: Phase II study of maytansine in the treatment of advanced or recurrent adenocarcinoma of the ovary. *Am J Clin Oncol 6: 273–275, 1983.*