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# Phase I Study of Maytansine Using a 3-Day Schedule [1,2,3]

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## SUMMARY

**Maytansine, a new ansa macrolide antitumor antibiotic, was administered to 60 patients as part of a phase I study. The doses given ranged from 0.01 (starting level) to 0.9 mg/m² for 3 days. The toxic effects encountered consisted principally of nausea, vomiting, diarrhea, and occasionally, stomatitis and alopecia. Superficial phlebitis was also encountered and occurred when the drug was diluted in a volume of < 250 ml. Myelosuppression occurred infrequently; it was almost regularly associated with abnormal liver function tests. Antitumor activity was detected in one patient each with melanoma, breast carcinoma, and head and neck clear cell carcinoma. Further studies are indicated with this compound since it has shown evidence of activity with little or no myelosuppression.**

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Maytansine is a natural compound originally isolated by Kupchan from the stem bark of an East African shrub, *Maytenus ovatus* (1). It belongs to the ansa macrolide class of antibiotics which are currently the subject of intense investigation as possible anticancer agents. Maytansine has shown antitumor activity in the P388 leukemia model and B16 melanoma.[5] No significant activity has been detected against L1210 leukemia, and it is only marginally active against Lewis lung carcinoma.[5] The compound produces stathmokinetic effects at extremely low doses (2,3). One of the interesting aspects of this compound is that it has shown activity in experimental animal tumors at microgram/kilogram dose levels while most antitumor agents are active at the milligram/kilogram dose level. While most drugs lose their antitumor activity after a two- to three-fold reduction below the optimal dose, maytansine has been shown to retain its activity against P388 leukemia over a 50–100-fold dosage reduction.[6]

Toxicology studies in beagle dogs showed the highest nontoxic dose to be 0.15 mg/m²/day × 1 while the lethal dose was 2.4 mg/m²/day × 1. In mice, dogs, and monkeys, the most frequently observed toxic effects were related to the gastrointestinal tract, liver, and hematopoietic systems.[5] Gastrointestinal tract toxicity was one of the most prominent side effects observed and consisted of anorexia, emesis, and bloody diarrhea. The liver was also consistently affected at the higher doses as manifested by elevations of the liver enzymes and fatty changes. A consistent effect was also observed in the bone marrow manifested by hypoplasia which did not appear to be cumulative. Other side effects observed were phlebitis at the injection site and reversible elevations of BUN levels.

We elected to conduct phase I trials of maytansine in patients with advanced malignancies. We report the initial results of our clinical experience with this compound.

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[2]Supported in part by contract N01-CM-43801 from the Division of Cancer Treatment (DCT), National Cancer Institute (NCI), National Institutes of Health, Department of Health, Education, and Welfare.

[3]Maytansine was supplied by the DCT, NCI, Bethesda, Md.

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[5]Helman L, Henney J, and Slavik M. Clinical brochure: maytansine. Prepared by the NCI, Bethesda, Md, 1976.

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[6]Plants yield chemicals active against tumors. Chem Eng News, Feb 28, 1972, pp 58–59.

## MATERIALS AND METHODS

Studies with this compound were initiated in the Department of Developmental Therapeutics, M. D. Anderson Hospital and Tumor Institute, in April 1976. Only patients > 15 years old were entered into this study. All had evidence of metastatic malignancy refractory to standard treatment. A 3-day schedule beginning at a dose of 0.01 mg/m² iv was selected as the starting dose level. Dose escalations proceeded at 50% increments initially and later at 100% when it was realized that the starting dose selected was very low (table 1). A total of 60 patients entered in this study received 108 courses of treatment. The number of courses given as the initial dose at each level and the number of subsequent courses are shown in table 1. The drug was administered initially in 50 ml of dextrose solution and infused over 15 minutes. Later in the study, the drug was diluted in 250–500 ml of fluid and infused over 30 minutes to avoid superficial phlebitis. Courses of treatment were repeated every 2–3 weeks, depending on toxicity.

Pretreatment studies included an SMA-12 profile, cbc, differential, and platelet counts, and a bone marrow aspiration. Other laboratory and radiologic studies were performed when indicated. During treatment, the patients had cbc, differential, and platelet counts taken at least twice a week and an SMA-12 profile prior to every course of treatment. Patients were followed closely for any evidence of toxicity or any other biologic effect; all roentgenographic and laboratory studies were repeated after two courses of treatment to assess response.

A partial remission (PR) was classified as a > 50% reduction in the sum of the product of the diameters of measurable lesions. Any objective response of < 50% reduction in the product of the diameters of a lesion was considered less than a PR. Myelosuppression was defined as any decrease in wbc count to < 3000/mm³ or a decrease in platelet count to < 150,000/mm³ in a patient with no tumor involvement of the bone marrow. For the purpose of correlating drug toxicity to pre-existing liver dysfunction, we have considered liver enzymes to be significantly abnormal when any elevation more than twice the normal value for any single liver enzyme occurred in a patient with known or suspected liver disease. Also, any simultaneous elevation of the three liver enzymes of at least 25% was considered to represent significant liver dysfunction.

Informed consent was obtained from the patients prior to instituting therapy according to institutional policies.

TABLE 1.—No. of courses of maytansine at each dose level

| Dose level (mg/m² × 3 days) | No. of courses given— As 1st dose | Subsequently |
|---|---|---|
| 0.01 | 6 | 2 |
| 0.015 | 3 | 2 |
| 0.025 | 3 | 2 |
| 0.037 | 3 | 4 |
| 0.05 | 5 | 3 |
| 0.075 | 6 | 5 |
| 0.15 | 1 | 5 |
| 0.3 | 1 | 4 |
| 0.4 | 2 | 4 |
| 0.5 | 15 | 8 |
| 0.6 | 0 | 4 |
| 0.7 | 5 | 6 |
| 0.9 | 4 | 5 |
| Total | 54 | 54 |

## RESULTS

### Nonmyelosuppressive Toxicity

Of the 108 courses administered, 102 were evaluable for nonmyelosuppressive toxicity. The earliest evidence of toxicity was seen at doses of 0.15/m² and consisted of superficial phlebitis (table 2). This side effect was eliminated by diluting the drug in larger volumes (250–500 ml) of fluid. Gastrointestinal toxicity was first seen at the dose of 0.4 mg/m² and consisted of vomiting and diarrhea which became progressively more severe at higher dose levels (0.7 and 0.9 mg/m²) leading to severe dehydration within a few hours. Fewer episodes of diarrhea were observed at 0.5 mg/m² than at higher doses, and the severity was also considerably less. Deterioration of liver function tests (bilirubin, SGOT, and alkaline phosphatase) was also observed at doses between 0.6 and 0.9 mg/m² as shown in table 2. These instances of possible hepatic toxicity occurred in three patients whose liver function studies were abnormal before treatment was instituted. In each case, rapid deterioration of liver function occurred during therapy associated with the onset of jaundice. All three patients died with liver dysfunction, although the cause of death was probably directly related to hepatic toxicity in only one. An autopsy performed in one of these patients showed fatty infiltration of the liver and early cirrhosis. Moderate stomatitis and mild alopecia were also observed at doses between 0.6 and 0.9 mg/m² in three patients. No evidence of neurotoxicity was observed with the dose levels used.

TABLE 2.—Maytansine nonmyelosuppressive toxicity in 102 courses

| Dose (mg/m² × 3 days) | No. of evaluable courses/ No. of evaluable patients | % toxicity (courses/patients) | | | |
|---|---|---|---|---|---|
| | | Vomiting | Diarrhea | Hepatotoxicity | Other |
| 0.01–0.1 | 49/45 | 0/0 | 0/0 | 0/0 | 0/0 |
| 0.15–0.5 | 30/22 | 16/15 | 33/21 | 0/0 | 14/9 (phlebitis) |
| 0.6–0.9 | 23/20 | 60/70 | 65/70 | 13/15 | 13/15 (stomatitis) 13/15 (alopecia) |

TABLE 3.—Lowest blood cell counts in all patients as related to dose of maytansine

| Dose (mg/m² × 3 days) | No. of evaluable courses/ No. with myelosuppression | Median (cells × $10^3$/mm³) | |
|---|---|---|---|
| | | Lowest wbcs (range) | Lowest platelets (range) |
| 0.01–0.075 | 40/— | 6.5(3.9–22.0) | 300(132–442) |
| 0.15–0.5 | 28/4 | 5.7(2.8–15.9) | 220(110–456) |
| 0.6–0.9 | 20/5 | 4.9(0.7–16.2) | 204(11–690) |
| Total | 88/9 | | |

## Myelosuppressive Toxicity

A total of 88 courses administered to 60 patients were considered evaluable for myelosuppression. The myelosuppressive toxicity is shown in table 3. In only nine courses administered to five patients was some degree of myelosuppression observed (table 4). Eight of these courses of therapy were administered to patients with significant abnormalities in liver function tests prior to or immediately after therapy (table 4). The most frequently observed liver function abnormality was an elevated alkaline phosphatase. In all patients except one (a patient who died with sepsis), myelosuppression was reversible and usually of brief duration. The median day of the lowest wbc count in the patients who showed myelosuppression was Day 8. The counts usually recovered completely within 1 week.

## Therapeutic Response

Of the 60 patients entered, 42 were evaluable for response. Eighteen patients were inevaluable for response (nine early deaths, three protocol violations, and six patients who did not return for further therapy). Antitumor activity with this compound was related to dosage as shown in table 5. No responses were observed with doses < 0.3 mg/m². Of 19 patients receiving doses > 0.3 mg/m², three had an objective response. The diagnoses of these 19 patients are shown in table 6. The patient with melanoma who responded achieved PR of multiple metastatic lung and skin lesions which has lasted for 5+ months. Another patient achieving PR had breast carcinoma with soft tissue involvement of the chest wall and an axillary mass; her response was of brief duration (1 month). The patient with head and neck clear cell carcinoma had objective evidence of response in multiple skin lesions but the reduction in size was not enough to classify it as a PR.

## DISCUSSION

The results of this study indicate that in patients with normal liver function maytansine has tolerable toxicity and can be given safely at a dose of 0.5 mg/m² daily for 3 days. Side effects at that dose level include nausea, vomiting, diarrhea, and phlebitis. Myelosuppression was not observed as a frequent side effect at the doses used in this study. The few instances of myelosuppression occurred almost exclusively in patients with abnormal liver function tests. This suggests that there is either impaired metabolism or a decrease in biliary excretion of the drug in these patients. Pharmacology studies are in progress to clarify this hypothesis. When myelosuppression took place, it usually occurred early, around Days 7–10, and its duration was usually brief, allowing us to administer the drug every 2 weeks in many instances.

The dose-limiting toxic effect of maytansine in the 3-day schedule administered to our patients was diarrhea which in several cases led to rapid and severe dehydration. The diarrhea usually started on the second or third day of therapy, but it has not been a regular toxic effect even at doses of 0.6–0.9

TABLE 4.—Liver function tests in 9 courses of maytansine associated with myelosuppression*

| Alkaline phosphatase (N = 30–80) | SGOT (N = 7–40) | LDH (N = 100–225) | Bilirubin (N = < 1.0) | Lowest wbcs/mm³ | Lowest platelets/mm³ |
|---|---|---|---|---|---|
| 193 | 78 | > 600 | 1.0 | 2800 | 110,000 |
| 180 | 64 | 296 | 0.6 | 2800 | 118,000 |
| 147 | 62 | 332 | 0.8 | 3100 | 102,000 |
| 231 | 27 | 171 | 0.9 | 1700 | 123,000 |
| 117 | 26 | 146 | 0.6 | 2100 | 251,000 |
| 195 | 40 | 220 | 1.0 | 4000 | 96,000 |
| 176 | 90 | 240 | 1.1 | 1600 | 215,000 |
| 315 | 34 | 200 | 0.9 | 700 | 11,000 |
| 142 | 40 | 230 | 0.9 | 2700 | 300,000 |

*N = normal range.

TABLE 5.—Antitumor activity of maytansine related to dosage

| Dose (mg/m² × 3 days) | No. of evaluable patients/ No. responding |
|---|---|
| 0.01–0.05 | 17/0 |
| 0.075–0.15 | 6/0 |
| 0.3–0.9 | 19/3 |
| Total | 42/3 |

TABLE 6.—Diagnoses and response of patients with advanced cancer treated with maytansine at doses > 0.3 mg/m²*

| Tumor type | No. of patients | Response |
|---|---|---|
| Melanoma | 7 | 1 PR |
| Breast carcinoma | 7 | 1 PR |
| Head and neck clear cell carcinoma | 1 | 1 < PR |
| Lung carcinoma | 2 | 0 |
| Renal cell carcinoma | 1 | 0 |
| Adenocarcinoma, unknown primary | 1 | 0 |
| Total | 19 | |

*Includes only patients who have received at least 2 courses of the drug.

mg/m². However, at the higher doses (0.6–0.9 mg/m²), most of the patients did develop this side effect. The severity of the diarrheal episodes was also more pronounced at high doses.

Since myelosuppressive toxicity from maytansine appears to be more severe in patients with elevated bilirubin or with elevation of liver enzymes more than twice the normal levels, we recommend an initial dosage of 0.25 mg/m²/day for 3 days; this may need to be modified in light of pending results of pharmacology tests. In patients with normal liver function tests, the recommended dose for phase II studies is 0.5 mg/m² for 3 days.

At this dose, maytansine appears to be nonmyelosuppressive in patients with normal liver function. This makes it a very attractive compound to use in combination with other myelosuppressive drugs. Other schedules that will allow delivery of a higher dose with less gastrointestinal toxicity need to be investigated. Further phase II studies are indicated since activity in tumors such as melanoma, breast carcinoma, and head and neck clear cell carcinoma has been observed.

## REFERENCES


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