Early Clinical Study of an Intermittent Schedule for Maytansine (NSC-153858): *Brief Communication* [1,2]

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ABSTRACT—Maytansine, an ansa macrolide, was evaluated in an early clinical trial in 40 adult patients with various solid tumors. Severe nausea and vomiting, sometimes associated with watery diarrhea and abdominal cramps, and liver function abnormalities, mainly elevation of serum glutamic-oxaloacetic transaminase levels, together constituted what we considered dose-limiting toxicity. Mild hematologic toxicity (mainly thrombocytopenia), neurotoxicity, and possibly cardiac toxicity were also noted. No antitumor effect was seen. An iv dose of 0.750 mg/m² on days 1, 3, and 5 (total dose, 2.25 mg/m²) repeated every 4 weeks is recommended for Phase II trials.—J Natl Cancer Inst 60: 93–96, 1978.

MAYT (NSC-153858) is a naturally occurring ansa macrolide originally isolated from the East African shrub *Maytenus ovatus* (*1*). MAYT belongs to a new class of compounds characterized by the presence of a large macrocyclic lactone ring, frequently N-heterocyclic, and incorporating within it an *m*- or *p*-bridged aromatic moiety.

MAYT possesses stathmokinetic (mitosis-inhibiting) properties including metaphase arrest, an action similar to the vinca alkaloids vincristine and vinblastine (*2*). DNA synthesis is inhibited more than RNA or protein synthesis. DNA-dependent RNA polymerase is also not greatly affected. MAYT is active against a variety of in vivo tumor systems including P388 leukemia, B16 melanoma, and Lewis lung carcinoma as well as against KB, L1210, L51784, and P388 tumors in vitro (*1*).

Drug-related toxicities in dogs and monkeys include enteritis and degeneration of intestinal mucosa, depletion of lymphoid organs, emesis, blood diarrhea, bone marrow hypoplasia, and liver disorder manifested by increased SGOT, serum glutamic–pyruvic transaminase, and bromsulphalein-retention levels. The incidence and severity of toxicities were dose related in dogs and monkeys. Five-day pulses of drug with intermittent 9-day rest periods suggest lack of cumulative toxicity. The reported toxicities were reversible with the exception of some histopathologic liver lesions (*3*). Rarer toxicities included hindlimb paralysis in MAYT-treated mice. Neurotoxicity was not seen in other animals, but, because of the similarity of the drug's action to that of the vinca alkaloids, e.g., its effect on the size of the mitotic spindle believed to be secondary to the inhibition of the polymerization of tubulin (*4*), neurotoxicity was also a possibility. Also, 1 dog and 1 monkey treated with lethal doses showed degenerative myocardial changes of questionable significance according to the authors.

Our early clinical toxicity trial began with a dosage of 0.045 mg MAYT/m² given as 0.015 mg/m² on days 1, 3, and 5 with repeat cycles at 4-week intervals. That starting dose had already been studied at the NCI and represented one-fifth the highest nontoxic dose in the monkey.

MATERIALS AND METHODS

Eligible patients had to have histologic or cytologic evidence of unresectable or metastatic cancer beyond any reasonable hope of cure or significant palliation by more conventional therapy. Patients were excluded from study for any of the following reasons: recent major surgery, radiation therapy or chemotherapy within 4 weeks (8 wk for any nitrosourea), leukopenia (<4,100 cells/mm³), thrombocytopenia (<130,000 cells/mm³), any elevation of the direct-reading serum bilirubin levels, a serum creatinine level greater than 1.5 mg/dl, or an ECOG performance score of 4 (total disability).

Entered into the study were 42 patients. Only 1 was a pediatric patient, a 3-year-old with an advanced neuroblastoma treated at the initial dose level. This patient developed thrombocytopenia with a platelet nadir of 52,000 cells/mm³ on day 18. One adult treated with 1.350 mg MAYT/m² total dose died of tumor-related causes 1 day after her first injection. These 2 patients were not included in the subsequent analysis, which consisted of 40 adult patients with solid tumors. The clinical characteristics of these 40 patients were as follows: median age, 59 years (range, 23–78 yr); 65% males; 65% ECOG performance score of 2 or 3; 92% prior chemotherapy; 42% prior radiation therapy; and the lung (32%) and the colorectum (28%) being the most common primary tumor sites.

Pretreatment (within 72 hr) and retreatment (day 29 and every 4 wk thereafter) tests included a hemoglobin test; WBC count; PLT count and differential test; a 12-test chemistry group including electrolytes, creatinine, bilirubin, alkaline phosphatase, SGOT, calcium, phosphorus, uric acid, and total serum protein; an electrocardiogram; an electromyogram (first patient at each

Abbreviations used: MAYT = maytansine; SGOT = serum glutamic-oxaloacetic transaminase; NCI = National Cancer Institute; ECOG = Eastern Cooperative Oncology Group; WBC = white blood cells; PLT = platelet(s).

[1] Received May 11, 1977; accepted August 23, 1977.

[2] Supported by Public Health Service Phase I contract N01-CM53838 from the Division of Cancer Treatment, National Cancer Institute.

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new dose level); urinalysis; 12-hour urine for total protein; a short iothalamate renal clearance; and a chest X-ray. WBC and PLT counts were also obtained on days 3 and 5 or 6 as well as once per week thereafter for PLT and twice per week for WBC. A repeat chemistry group test was obtained on day 5 or 6, and serum creatinine or blood urea nitrogen and SGOT were measured once per week for 3 weeks.

MAYT was administered by rapid iv infusion over 3–10 minutes into the side arm of a freely floating infusion set-up on days 1, 3, and 5 and repeated every 4 weeks from day 1. MAYT was supplied in 10-ml Flint vials containing a white lyophilized powder consisting of 0.25 mg MAYT and 100 mg mannitol. When reconstituted with 4.9 ml sodium chloride, each milliliter contained 0.05 mg MAYT and 20 mg mannitol. The reconstituted vials were discarded after 8 hours. The initial dose level was 0.015 mg MAYT/m² on days 1, 3, and 5 for an initial total dose of 0.045 mg/m². Subsequent dosage escalations are shown in table 1. A slightly modified

TABLE 1.—*Dosage escalation scheme for MAYT*

Dose on days 1, 3, 5 mg/m²	Total dose per course mg/m²	Multiples of the starting dose
0.015	0.045	1
0.030	0.090	2
0.045	0.135	3
0.090	0.270	6
0.135	0.405	9
	Phase I meeting	
0.300	0.900	20
0.450	1.350	30
0.600	1.800	40
0.750	2.250	50
0.900	2.700	60

Fibonacci escalation scheme (5) was employed initially up to the 0.405 mg/m² total-dose level. At that point, a discussion among the MAYT Phase I investigators and the NCI investigators resulted in a direct escalation to 0.900 mg/m² total dose.

RESULTS

Toxicity was minimal in the 43 treatment courses given to 26 patients at dosage levels up to and including the 1.350 mg/m² total dose level. These 43 treatment courses consisted of 26 initial treatments with MAYT and 17 subsequent or escalation treatments after prior MAYT treatment at the same or a lower dose level. The most common side effects encountered in this group related to the gastrointestinal tract and consisted of mild nausea in 16% (7/43), vomiting in 9% (4/43), and diarrhea in 9%. The next most common toxicity, which did not appear to be dose related, was thrombocytopenia that occurred after 9% of the treatment courses. The PLT nadirs, day of nadir count, and dosage level were as follows: 99,000 on day 29 at 0.090 mg/m², 100,000 on day 13 at 0.270 mg/m², 93,000 on day 17 at 0.900 mg/m², and 90,000 on day 21 at 1.350 mg/m². All PLT counts returned to normal within 4–7 days. Leukopenia, with a WBC nadir of 3,900 on day 14, was noted in only 1 patient. Two patients (5%) developed an increase in SGOT levels on day 5 (at least a 50% increase above pretreatment level), which had returned to normal by day 29 in both patients. Both patients were treated at the 1.350 mg/m² total-dose level (table 2). Two patients also developed neurologic symptoms. One developed an agitated depression and alteration in sleep pattern at 1.350 mg/m² after receiving two prior courses of 0.900 mg/m². One month after his fourth MAYT treatment (at 1.800 mg/m²), he also complained of leg cramps and paresthesia involving the fingers. No further MAYT was given, and all neurologic symptoms had lessened at reexamination 2 months later. This patient was a 78-year-old man with lung cancer. He also developed atrial fibrillation after his first course of 0.900 mg/m². The rate of fibrillation was slowed with digitalization, but the rhythm did not return to normal. No clinical congestive heart failure was apparent. The other patient with neurologic symptoms become "light-headed" after his day-1 treatment at the 1.350 mg/m² total-dose level (i.e., after 0.450 mg MAYT/m²). Blood pressure was not altered. The light-headedness remained stable during the day-3 and day-5 injections and cleared up 1 week later. This patient did not receive further MAYT.

Toxicity became more severe and consistent at total-dose levels of 1.800 mg/m² and higher (table 2). At the 1.800–2.250 mg/m² total-dose levels, 14 treatment courses were given. Ten were initial treatments and four were subsequent or escalation treatments. In this group, nausea, vomiting, and diarrhea occurred in 29% (4/14), 14% (2/14), and 29%, respectively. These symptoms generally began on days 3–5 and persisted for another 24–48 hours. One episode of diarrhea, associated with cramps, was severe but not bloody. It began on day 6 and persisted for 2 days. SGOT elevations were the most frequent toxicity noted, occurring in 43% (6/14). All SGOT levels that had been elevated returned to or toward normal by day 29. The alkaline phosphatase levels became elevated (an increase in 25% or more above base line) in 2 patients on day-5 determinations. One of the 2 patients had extensive liver metastases from a colon cancer that progressed on therapy. Two instances of leukopenia and thrombocytopenia occurred at the 1.800 mg/m² dose level resulting in WBC nadirs of 3,600 and 3,300 on days 15 and 14, respectively, and in PLT nadirs of 126,000 and 121,000 on days 13 and 19, respectively. One patient developed unilateral facial numbness at the 2.25 mg/m² level. This patient had known central nervous system metastases. She had disease progression and did not return for subsequent reevaluation; no further information is available on the facial weakness.

Toxicity was severe in the 4 patients treated at the 2.700 mg/m² total-dose level. All 4 patients received this dose level as their first exposure to MAYT. Severe nausea and vomiting occurred in 3 of the 4 patients beginning on day 3. Two of these patients, who also had abdominal cramps, were eventually hospitalized

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TABLE 2.—*Nature and frequency of toxicities[a] from MAYT based on total dosage of drug (in mg/m²) administered per course*

Dose level mg/m²	No. of initial treatment courses	No. of subsequent escalation courses	Toxic effects[b]							
			Nausea	Vomiting	Diarrhea	↑SGOT[c]	↑Alkaline phosphatase	Neurologic symptoms	↓WBC[d]	↓PLT[e]
0.045	3	0	0	0	0	0	0	0	0	0
0.090	4	1	2	0	0	0	0	0	0	1
0.135	4	2	1	1	0	0	0	0	0	0
0.270	3	3	3	2	0	0	0	0	0	1
0.405	5	1	0	0	0	0	0	0	0	0
0.900	3	7	0	0	2	0	0	1	0	1
1.350	4	3	1	1	2	2	0	1	1	1
1.800	5	3	4	2	3	3	2	0	2	2
2.250	5	1	0	0	1	3	0	1	0	0
2.700	4	0	3	3	0	3	0	0	0	0
Total	40	21	14/61 (23)	9/61 (15)	8/61 (13)	11/61 (18)	2/61 (3)	3/61 (5)	3/61 (5)	6/61 (10)
≤1.350;	26	17	7/43 (16)	4/43 (9)	4/43 (9)	2/43 (5)	0/43	2/43 (5)	1/43 (2)	4/43 (9)
1.8–2.25	10	4	4/14 (29)	2/14 (14)	4/14 (29)	6/14 (43)	2/14 (14)	1/14	2/14 (14)	2/14 (14)
2.7	4	0	3/4 (75)	3/4 (75)	0/4	3/4 75	0/4	0/4	0/4	0/4

[a] Toxicities are included in this table only if noted in >1 patient.
[b] *Numbers in parentheses* indicate percent.
[c] 50% increase above pretreatment level.
[d] A WBC nadir of <4,100 cells/mm³.
[e] A platelet nadir of <130,000 cells/mm³.

because the nausea and vomiting became intractable and led to dehydration. Three of these 4 patients also developed elevations of SGOT above their base line levels, two of which were elevated initially. However, by day 29, the SGOT levels had returned to normal in 1 patient with the normal initial value and to a lower but still elevated level in 1 of the other 2 patients with initially elevated values on whom follow-up data are available.

No objective tumors were noted in the 40 patients treated (table 3). Twenty-eight (70%) patients progressed after one course, 4 (10%) after two courses, 2 (5%) after three courses, and 1 (2.5%) after four courses; 5 (12.5%) currently are stable.

TABLE 3.—*Tumor site or histology in the 40 evaluable patients*

Tumor site or histology	No. of patients
Lung	13
Large cell	6
Adenocarcinoma	3
Squamous cell	3
Small cell	1
Colorectal area	11
Melanoma	3
Adenocarcinoma—unknown primary	3
Stomach	2
Prostate gland	2
Leiomyosarcoma	2
Breast	1
Liver	1
Pancreas	1
Thymoma	1
Total	40

DISCUSSION

The major clinical dose-limiting toxicity from MAYT was severe nausea and vomiting, generally beginning about day 4 or 5 and persisting for 1–5 days. This was sometimes accompanied by stomach cramps and watery diarrhea. These toxicities became most apparent starting at the 1.80 mg/m² dose level. At 2.7 mg/m², 2 of 4 patients had to be hospitalized for intractable nausea, vomiting, and dehydration. The other major toxicity was liver dysfunction as evidenced by increases in SGOT levels and, occasionally, alkaline phosphatase levels. These abnormalities tended to improve or to disappear with time. Most patients received only one course of treatment so that cumulative neurotoxicity as seen with the vinca alkaloids is hard to assess, but the development of paresthesia, leg cramps, agitation, and sleep abnormalities in a patient who received four courses of treatment seems to indicate that neurotoxicity does occur with MAYT. None of the 3 patients who developed apparent neurotoxicity had electromyograms done. Only 1 patient, who was 78 years old, developed a cardiac arrhythmia; it cannot be definitely ascribed to MAYT. Hematologic toxicity was seen infrequently, was mild, and usually presented as a transient throm-

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bocytopenia occurring most frequently between days 14 and 21 post treatment.

No tumor responses were seen. Most treated tumors, colorectal and lung, are relatively drug resistant to single-agent chemotherapy, particularly when the single agent is given after prior chemotherapy. All but 3 patients had received prior chemotherapy.

The recommended starting dosage for Phase II studies is 2.25 mg/m^2 total dose per course. Whether or not transient liver dysfunction, as noted in this study, would progress to permanent hepatic parenchymal damage is unknown at present, since no patient in this current study received sufficient drug over a long enough time to develop persistent liver function abnormalities not associated with liver metastases. There was no clear relationship between the frequency or severity of toxicity and preexisting liver disease in the form of hepatic metastases.

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