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Maytansine

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Introduction

Maytansine is a naturally occurring ansa macrolide with antitumor activity. It possesses metaphase arrest antimitotic properties which are also properties of the vinca alkaloids vincristine and vinblastine. Preclinical rodent tumor testing demonstrated high activity at very low dose levels and antitumor activity over a wide dose range. Phase I clinical testing by the National Cancer Institute (NCI) has now largely been completed and the compound is in Phase II trials.

The purpose of this paper is to review the available information on maytansine, especially with respect to an evaluation of its potential clinical usefulness.

History

Maytansine was first isolated by Kupchan and coworkers (11, 12) in 1971 from alcoholic extracts of the East African shrub *Maytenus serrata* (formerly known as *M. ovatus*) and later from the wood and bark of *Maytenus buchananii*. It was the first ansa macrolide to be isolated from a plant rather than a micro-organism. Previously described ansa macrolides had demonstrated inhibition of bacterial DNA-dependent RNA polymerase (8, 17) and viral RNA-directed DNA polymerase (22), but maytansine was the first compound of this class to show significant antitumor activity (11, 12). It was found to be highly active against the mouse P388 lymphocytic leukemia and to also show activity against the L1210 mouse leukemia, the Lewis lung carcinoma and B-16 melanoma solid tumors (11, 12). Encouraged by its preclinical activity the NCI initiated Phase I clinical testing in 1976.

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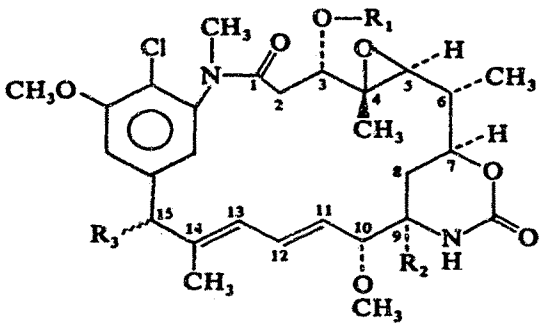
Chemistry

The ansa macrolide class of compounds of which maytansine is a member includes the rifamycins and streptovarcins. The structural formula of maytansine is shown in Figure 1, and consists of an aromatic nucleus to which a macrocyclic aliphatic bridge is attached at two non-adjacent positions. Two homologue compounds are generally isolated with maytansine. These are maytanprine and maytanbutine and differ from maytansine by a methyl group in the first case and two methyl groups in the second case as shown in Figure 1. Both homologues have antitumor activity although to a lesser extent than maytansine in the P388 system (14). Maytansine can be differentiated from its homologues by chromatography in an ethyl acetate system on silica gel, using ultraviolet light to visualize the zones (7).



	R_1	R_2	R_3	
1	$COCH(CH_3)NCOCH_3$ (CH₃ on N)	OH	H	Maytansine
2	$COCH(CH_3)NCOCH_2CH_3$ (CH₃ on N)	OH	H	Maytanprine
3	$COCH(CH_3)NCOCH(CH_3)_2$ (CH₃ on N)	OH	H	Maytanbutine

Figure 1. Structural formula of maytansine and homologues.

The structure activity relationships in the maytansinoid ansa macrolides have recently been reported for a small number of compounds (14). The carbinol amide and ester chain off C-3 appear to be necessary for significant antitumor activity (12, 14).

The extraction of maytansine from plant sources has resulted in low yields of active compound. A search for a microbiological source has recently been reported to be successful (10) and this new source will hopefully relieve the supply problems which have hindered the development of maytansine to date.

Mechanism of action

Maytansine, like the vinca alkaloids vincristine and vinblastine, is a mitotic inhibitor. Treatment of L1210 cells *in vitro* with maytansine resulted in 67% of the cells accumulated in mitosis whereas the untreated control cells demonstrated a mitotic index ranging

between 3.2 and 5.8% (21). Flow microfluorimetry analysis of L1210 cells during exposure to maytansine indicated a shift in the distribution of DNA to a single peak, representing the DNA of cells in G2 & M Phases (23). Experiments with sea urchin eggs and clam eggs suggested that maytansine inhibited mitosis by interfering with the formation of microtubules by inhibiting the polymerization of the microtuble protein, tubulin (19).

The effects of maytansine at 10^{-7} M concentration on DNA, RNA and protein syntheses were examined in murine leukemia cell cultures (21, 22). DNA synthesis was inhibited to the greatest extent. In the P388 cells DNA synthesis was 14% of controls whereas RNA and protein syntheses were 46 and 48% of controls respectively. Unlike other ansa macrolides, maytansine did not inhibit *Escherichia coli* RNA polymerase activity at concentrations as high as 10^{-4} M (22).

As an antimitotic agent maytansine was found to be approximately 100 times more potent than vincristine in sea urchin eggs and 20 times more potent in Chinese Hamster ovary-K cells in tissue culture (20). However both drugs inhibited *in vitro* polymerization of tubulin at about the same concentrations (19). The differences in cellular activity between the two drugs may be explained by differences in uptake. In experiments with rat brain tubulin, maytansine and vincristine were found to bind reversibly and competitively (15). Both drugs were found to share a common binding site although an additional site specific for maytansine seemed to be present (15). The effects of maytansine and vincristine on the flow microfluorimetric characteristics of P388 murine leukemia *in vivo* have been compared. Similar cytokinetic effects were seen after the administration of both drugs although the effects were greater and more persistent with maytansine. Morphologically both drugs produced some degree of multinucleation and endoreduplication and vincristine also produced a population of cells with a DNA content, by fluorescence, equivalent to octaploidy.

Preclinical activity

In vitro P388, L1210 and LY5178 murine leukemic cell suspensions were found to be inhibited by maytansine at doses of 10^{-3} to 10^{-7} μg/ml, with the P388 line being the most sensitive (21). Maytansine was shown to be an active inhibitor of *in vitro* growth of human nasopharyngeal carcinoma cells and the human lymphoblast leukemia line C.E.M. was inhibited by doses as low as 10^{-7} μg/ml (21).

Maytansine has also been shown to be active *in vivo* (21). The P388 lymphocytic leukemia system was inhibited over a 50- to 100-fold dosage range which suggested a high therapeutic index (11). Also maytansine was shown to have significant inhibitory activity against the L1210 mouse leukemia, the Lewis lung carcinoma and B-16 melanocarcinoma solid murine tumor systems (11). The optimal antitumor dose was 25 μg/kg/day for 10 consecutive days intraperitoneally for the P388, L1210 and B-16 tumor systems (21) and 32 μg/kg/day for 9 consecutive days for the Lewis lung carcinoma (9).

Maytansine treatment of mice inoculated with P388 cells intracerebrally resulted in only minimal antitumor activity and suggested that the drug does easily penetrate the blood–brain barrier in the mouse (21). In the P388 *in vivo* system maytansine was most active when given by a 3-hourly dosage schedule on Days 1, 5 and 9 (9). Maytansine was compared with vincristine *in vivo* and in vincristine-sensitive and resistant cell lines (22). Cross resistance was observed but maytansine was active against sensitive strains at a tenfold lower concentration than vincristine.

Preclinical toxicity

Acute toxicity

In the mouse the lethal dose in 10% of the animals treated (LD_{10}) was 1.22 mg/m² for males and 1.29 mg/m² for females when maytansine was given by intraperitoneal injection. Histopathologic evaluation of selected organs from the mice revealed lymphoid depletion of splenic follicles, fatty change and mild granular degeneration of hepatocytes. No other drug related changes were observed (9).

In the rat after a single subcutaneous injection the LD_{10} was of the same magnitude as for the mouse at 1.22 mg/m² (0.4 mg/kg). Histologically, necrotizing lesions were seen in the gastrointestinal tract mucosa, thymus, spleen, bone marrow and testes. Of considerable interest is the reported observation of hemorrhagic lesions of the brain, mononuclear infiltration in the meninges and chromatolysis and vacuolation of dorsal root ganglion cells (18).

In the beagle dog (9) the toxic dose low was 0.3 mg/m² when maytansine was given as a single intravenous dose and 0.75 mg/m² when divided over 5 daily administrations. In the Rhesus monkey the toxic dose low was 0.45 mg/m² when divided over 5 daily intravenous injections (9).

Chronic toxicity

Multiple dose and more chronic treatment schedules in the beagle dog and monkey (9), resulted in pancreatic acinar cell degeneration and nephrosis. Increased mitotic activity was observed in numerous tissues including the pancreas, esophagus, stomach, small and large intestines, adrenal cortex, renal pelvis ureter, urinary bladder, and skin. The results from these studies suggested that toxicity from maytansine was dose related, reversible (except for histopathologic liver lesions) and non cumulative.

Neurotoxicity

The neurotoxic effects of maytansine, vincristine and vinblastine were compared in mice by observing hind limb paralysis following administration of toxic doses (21). Vincristine was found to be neurotoxic causing 80 to 90% of mice to develop hind limb paralysis. In contrast vinblastine was not neurotoxic at the doses given and maytansine produced only mild hind limb paralysis in 10% of the mice receiving daily subcutaneous doses of 1.20 mg/m².

Teratogenicity

Pregnant mice were treated with single injections of maytansine on Days 6, 7 and 8 of gestation and their fetuses examined for malformation of Day 17 of gestation (21). Both embryotoxic and teratogenic effects which appeared to be dose related were demonstrated. They were most marked when maytansine was administered on Day 7 of gestation.

Injection site

When maytansine was given by subcutaneous injection in several animals a local tissue reaction with inflammation and fibrosis was observed (9).

Pharmacokinetics

No satisfactory methodology has thus far been developed for detecting the low concentrations of maytansine present in human blood and tissues following dosage in the clinical range. A quantitative microbiological assay using *Penicillium avellaneum* OC-4376 has been described but the sensitivity of this assay is inadequate (7). The competitive displacement of ^{3}H-vincristine by maytansine on rat brain tubulin (16), has been investigated as a quantitative assay of maytansine, but has yet to be proven effective. Chabner *et al.* (5) using this methodology found that the assay was insufficiently sensitive to measure the low serum levels of maytansine present at clinically tolerated doses.

The development of a radioimmunoassay has been hindered to date by an insufficient supply of maytansine to induce animal antibody production. The future supply of maytansine by a fermentation process (10) rather than by extraction of plants will hopefully allow quantities sufficient for radioimmunoassay development.

Clinical experience

Maximum tolerated dose

The maximum tolerated doses (MTD) generated from the National Cancer Institute Phase I and early Phase II trials are shown in Table 1. There was a good agreement among the dose levels reported from the contributing institutions. The MTD was in the 2 mg/m^2 range when maytansine was given every 3 to 4 weeks either as a single dose or divided over 3 daily doses. When given by weekly injections in the M.D. Anderson Phase II study (3) doses between 0.75 and 1.25 mg/m^2 were the maximum tolerated.

Toxicities

Gastrointestinal. The most common and dose limiting toxicities were gastrointestinal and consisted primarily of nausea, vomiting and diarrhea, often followed by constipation. These toxicities appeared to be dose related.

Table 1. Maximum tolerated doses of maytansine according to schedule

Institution (Reference)	Maximum tolerated dose (mg/m^2)	Schedule	Interval between course (days)	Dose limiting toxicity
Mayo Clinic (6)	2.25	Divided dose Days 1, 3, 5	28	Gastrointestinal Weakness
National Cancer Institute (5)	2.0	Single dose Day 1	21	Gastrointestinal
M.D. Anderson Hospital				
Phase I (4)	1.8–2.1	Divided dose Day 1–3	21	Gastrointestinal
Phase II (3)	1.8	Divided dose Day 1–3	14	Gastrointestinal
Phase II (3)	0.75–1.25	Divided dose Day 1–3	7	Gastrointestinal
Sidney Farber (2)	2.0–2.5	Divided dose Day 1–5	21	Gastrointestinal

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