ANNUAL REPORT

TO THE

FOOD AND DRUG ADMINISTRATION

MAYTANSINE

NSC 153858

IND 11857

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Drug Sponsor:

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Division of Cancer Treatment
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INTRODUCTION

This annual report to the Food and Drug Administration is a summary of the status of clinical trials with Maytansine (NSC 153858, IND 11857). Maytansine, and ansa macrolide antibiotic, was first isolated from alcoholic extracts of the East African shrub Maytenus serrata (formerly known as M. ovatus) and later from the wood and bark of Maytenus buchanii (1,2). Because it was found to have high antitumor activity against P388 lymphocytic leukemia, B16 melanoma and Walker 256 carcinosarcoma, it was developed for clinical trials (2,3). The results of these trials will be summarized and evaluated in this report.

MECHANISM OF ACTION

Maytansine resembles the vinca alkaloids and other tubulin-binding agents in its antitumor activity (4). Histological examination of L1210 cells fixed in alcohol and stained with Giemsa after 24 hours exposure to Maytansine showed 30% mitotic figures compared to 3% mitotic figures in control cells indicating that Maytansine is primarily a mitotic inhibitor (4,5). As a mitotic inhibitor, Maytansine is effective over a wide range of concentrations (6). In HeLa cells, the lowest effective concentration of Maytansine (10.5nm) was 200 times smaller than that for Colcemid (1.37×10^{-7} M), another mitotic inhibitor. In experiments with sea urchin eggs, Maytansine was 100 fold more potent than Vincristine, a vinca alkaloid, in blocking mitosis (7).

Studies with synchronized HeLa cells have shown that (a) cells in mitosis are the most sensitive to Maytansine, (b) cells in G_1 are the most resistant, and (c) cells in S phase are intermediate in their resistance (6). Consequently, it can be concluded that the closer a cell is to mitosis, the more sensitive it is to Maytansine (6).

At the beginning of mitosis, cells usually contain peak concentrations of spindle protein (tubulin). Mitosis is inhibited by depolymerization and inhibition of polymerization of tubulin by oxidation of the sulfhydryl groups in tubulin (8). This maytansine-induced metaphase arrest of dividing cells is the mechanism of action for maytansine's cytotoxicity.

ANTITUMOR ACTIVITY

Kupchan initially reported Maytansine activity in KB cell cultures (human epidermoid carcinoma of the nasopharnyx), sarcoma 180, Lewis lung carcinoma, L1210 leukemia, P388 leukemia, and Walker 256 (i.m.) carcinosarcoma (2,3).

In vitro studies with Maytansine showed L5178Y and P388 leukemias to be inhibited at concentrations in the nanomolar range, with P388 cells being the most sensitive (4). Maytansine was also tested against P388 leukemia cells resistant to Vincristine. It was found that the Vincristine resistant cells were cross resistant to Maytansine (9).

NCI testing revealed significant activity against P388 leukemia, B16 melanocarcinoma, and Lewis lung carcinoma in mice, and marginal activity in the L1210 system. The drug is effective at doses in the mcg/kg/day range (10).

PRECLINICAL TOXICOLOGY

Preclinical toxicity studies were conducted in B6D2F/1 mice, F344 rats, beagle dogs and rhesus monkeys. Histopathologic evaluation of mice revealed lymphoid depletion of spleenic follicles, fatty changes and mild degeneration of hepatocytes (10) while rats showed necrotizing lesions in the gastro-intestinal tract mucosa, thymus, spleen, bone marrow and testes (11). Also reported in rats was the observation of hemorrhagic lesions of the brain, mononuclear infiltration in the meninges and chromatolysis and vacuolation of dorsal and ventral root ganglion cells (11).

Multiple dose and more chronic treatment schedules in the beagle dog and rhesus monkey resulted in pancreatic acinar cell degeneration, enteritis and degeneration of intestinal mucosa, lymphocyte depletion of lymphoid organs, emesis, bloody diarrhea, bone marrow hypoplasia, abnormal BSP retention levels and nephrosis (10). Increased mitotic activity was observed in 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 was dose-related, reversible (except for histopathologic liver lesions) and noncumulative.

Pregnant mice were treated with single injections of Maytansine on days 6, 7 and 8 of gestation and their fetuses examined for malformation on day 17 of gestation (9). 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.

PHASE I STUDIES

Phase I studies (Table I) with Maytansine found the maximum tolerated dose (MTD) to be from 1.8 - 2.1 mg/m^2 every 3 weeks when given as a single dose or 0.6 - 0.9 mg/m^2/d x 3 every three weeks. The M.D. Anderson study established the MTD of Maytansine to be 0.75 - 1.25 mg/m^2 when given as a single dose every week. The dose-limiting toxicity in all studies was determined to be gastrointestinal toxicities consisting primarily of nausea, vomiting and diarrhea (often followed by constipation). These toxicities appeared to be dose-related but not schedule-dependent with toxicity first appearing at doses of 1.2 mg/m^2 and generally becoming severe at doses of 1.8 mg/m^2 and higher.

Maytansine also caused significant central nervous system toxicities consisting of profound weakness, lethargy, dysphoria and insomnia on the single bolus studies but not on the d x 3 study by M.D. Anderson or the d1, 3, 5, study by Mayo. These central nervous system toxicities seemed to be distinct from peripheral nervous system toxicities and were not related to metabolic or electrolytic abnormalities. Dose-limiting Vincristine-like peripheral neuropathies were reported by Sidney Farber after Maytansine treatment on a d x 5 dose schedule. Patients complained of jaw pain and paresthesia as well as severe myalgia. The loss of deep tendon reflexes and marked prolongation of nerve conduction times was also noted. Patients with prior neuropathy either secondary to malignancy or Vincristine treatment demonstrated further neurologic toxicity from Maytansine. Transient paresthesia for 24 hours following drug administration on a single dose schedule, was also reported in four patients on the NCI-MB study.

Transient elevations of serum transaminase, alkaline phosphatase and bilirubin have been reported in all Phase I studies. In patients without initial liver impairment these elevations returned to normal by day 29.

Recommended Phase II doses were:

1. Single dose of 2 mg/m^2 i.v. every 3 weeks
2. Weekly dose of 0.75 mg/m^2 i.v.
3. Course of 3 days: 0.6 mg/m^2/day i.v. for 3 days, every 2, 3, or 4 weeks

In patients with hepatic dysfunction, the weekly dose was recommended to be reduced to 0.6 mg/m^2 and the 3 day schedule to 0.4 mg/m^2/dx3.

PHASE II STUDIES

Phase II studies are listed in Table II. Only single agent trials have been performed. Trials by tumor site are described below. Except for the Mayo W82-989 study in islet cell carcinoma, all studies with Maytansine are now closed.

ISLET CELL

There is one protocol, W82-989, being conducted at the Mayo Clinic for islet cell carcinoma. Two patients have been evaluated in this study. No responses have been seen. This protocol was activated because of a near-complete response seen in a single patient treated with Maytansine at the Mayo Clinic. The patient was assumed to have ductal adenocarcinoma of the pancreas with hepatic metastasis and was entered on GITSG 9376. The patient's response lasted for over three years, during which time the patient was restored from disability to full activity. Although the patient showed progression after voluntarily discontinuing Maytansine therapy, he remains alive at over five years. A pathologic review of the tissue was conducted and the patient was rediagnosed as having a typical islet cell carcinoma.

PANCREATIC

GITSG 9376 and SEG 78 ST 222 have both treated patients with pancreatic cancer on a dx3 schedule. Between the two studies, a total of 46 patients are evaluable for response. Besides the near complete response in the one patient with islet cell carcinoma (see islet cell section), there were no responses

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