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Security and Maximal Tolerated Doses of Fluvastatin In Pediatric Cancer Patients

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Background. The role of cholesterol in neoplasic cell growth and its inhibition by drugs has recently been studied. Cholesterol biosynthesis inhibitors have been used as adjuvants in the treatment of cancer and possibly as prophylactic in carcinogenesis.

Objective. The objective of the study was to determine the maximal tolerated doses (MTD) and toxic effects of fluvastatin in pediatric cancer patients.

Methods. This study was carried out in a third level Social Security Hospital in Mexico City. We included pediatric patients from April 1996 to May 1997. They were all terminally cancer patients who did not respond to conventional therapies. Fluvastatin was given p.o. at doses of 2 mg/kg/day for 14 days every 4 weeks in three patients. Subsequent cohorts of three patients each had increments of 2 mg/kg/day of the drug until maximal tolerated doses were found. Toxic effects of the drug were evaluated by physical exploration, laboratory assays and a questionnaire given to each patient.

Results. Twelve patients were included. Diagnosis included 2 osteosarcomas, 8 central nervous system tumors, 1 lung tumor, and 1 Ewing's sarcoma. Ten patients died within 1 to 18 months. Two are alive 22 months after inclusion into the study, both with anaplasic astrocytoma. A total of 27 courses were administered. The MTD was 8 mg/kg/day. Toxic effects were insomnia, nausea, vomiting, abdominal distention and myalgias. Toxicity was dose-dependent. Laboratory assays had no significant changes during treatment.

Conclusions. Fluvastatin can be safely used at doses of 8 mg/kg/day in pediatric patients with cancer. This dose should be used in additional trials. © 1999 IMSS. Published by Elsevier Science Inc.

Key Words: Fluvastatin; Pediatric cancer.

Introduction

Cholesterol is essential for animal life. The integrity of animal cells and cell function depend on cholesterol. In 1992, Buchwald (1) reported the hypothesis in which the inhibition of cholesterol can decrease cancer cell growth. Cholesterol biosynthesis inhibitors (lovastatin, fluvastatin, simvastatin, pravastatin) have been used as adjuvant in the treatment of cancer and possibly as prophylactic in carcinogenesis (1). They inhibit the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (Figure 1) and, therefore, cholesterol synthesis. Some studies in animals have shown that a decrease in serum cholesterol levels diminishes tumoral growth (2). Fluvastatin has a cytostatic effect on the cancer cell by means of two mechanisms: first, it stops the G1 stage and second, it delays the G2 stage during the cell-cycle (3–7). Maltese found that lovastatin suppressed tumor growth in mice and that these tumors had few or no mitotic figures and little or no pronounced cellular degeneration (8).

Cholesterol biosynthesis inhibitors have been studied in *in vitro* and animal models. Buchwald (1) demonstrated a decrease in hepatoma cell cultures with lovastatin. He also reported morphologic changes in the tumoral cells and a loss in adherence capacity (1). In 1991, Jakovisiak and

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