Clinical and Laboratory Reevaluation of Dichloromethotrexate

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Summary

Clinical and pharmacologic effects of dichloromethotrexate (DCM) were reevaluated by an intermittent intravenous large dose schedule in patients with advanced malignancies. DCM was tolerated without Leucovorin (calcium folinate) in man, even when the initial immunoassayable DCM level approached $10^{-3}$ M. Hepatic dysfunction occurred more frequently at high doses. Hematologic toxicity was not dose-limiting. Plasma decay of DCM was comparable to that of methotrexate (MTX). Of 50 patients treated, five including two with hepatic metastasis from colon carcinoma, responded with more than 50% regression of tumor.

In vitro comparison of DCM and MTX in Molt 3 cells revealed that DCM was slightly more inhibitory than MTX on an equimolar basis. In the presence of 2.5 g/dl of human serum albumin (HA), however, inhibitory effects of DCM decreased markedly. The decreased biologic effects of DCM compared to those of MTX are due to much higher binding to HA by DCM. This phenomenon appears to explain all of the clinical and pharmacologic characteristics of DCM.

Introduction

Dichloromethotrexate (DCM) given at optimal doses prolonged the survival of mice bearing L1210 leukemia more than fourfold longer than methotrexate (MTX) [8] and inhibited 6C3HED lymphoma more than 11-fold1. By comparison, DCM was about tenfold less toxic than MTX in dogs when given daily parenterally. A recent study showed that renal precipitation of the drug was the dose-limiting toxicity of intravenous (IV) administration of DCM in monkeys which were not hydrated and alkalinized (D. A. Cooney, personal communication).

The initial clinical studies carried out 15 years ago on DCM [7] compared the drug with MTX at both daily oral (PO) and twice weekly intramuscular (IM) schedules in patients with lymphoma. It was shown that there was no difference in antitumor activity at equitoxic doses between the two agents. Five times more DCM than MTX was tolerated in man. A randomized comparison of DCM given twice weekly IM vs three times weekly IM in patients with lung cancer revealed no significant differences.

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1 Dichloromethotrexate, NSC-29630, IND-3168, Annual Report to the Food and Drug Administration, 1976, Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment, NCI

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in antitumor effects, toxicity, or survival time [1]. DCM produced a small number of responses in patients with hepatocellular carcinoma [16].

Clinical pharmacologic studies using DCM-CL\textsuperscript{36} indicated that, in contrast to MTX, as much as half the IV-administered DCM was excreted in the feces; 30\%–40\% of the DCM appeared in the urine within 2 days and the rest was excreted in the stool, starting 2–3 days after the administration of the drug. One-third of the inactivated form of DCM, 7-hydroxy-DCM, was recovered from 24-h urine [4].

Intermittent administration of large doses of MTX followed by Leucovorin (LV) (calcium folinate) was effective in protecting the host and in improving the therapeutic efficacy of the drug in animals [9] and in man [5, 11, 12]. Increase in dihydrofolate reductase and decrease in the transport of MTX have been regarded to be the major mechanisms of resistance [2] and constitute a rationale for using MTX at the large dose. The dose-limiting toxicity of large-dose MTX is nephrotoxicity [3, 11]. Inadequate renal clearance of MTX is accompanied by sustained high levels of plasma MTX and this results in the manifestation of other toxicities such as myelosuppression, stomatitis and other gastrointestinal toxicities, and cutaneous eruption. Protocols have been evolved for the precise sequence of hydration, measurement of creatinine clearance, alkalinization of urine, and MTX blood level determination in order to minimize this complication.

We began clinical and laboratory reevaluation of DCM [6, 15] because (a) DCM is highly active in murine systems, (b) the major excretion route of DCM is through the bile rather than the kidney, which should help avoid nephrotoxicity, and (c) large intermittent IV doses of DCM plus LV have not been studied.

Materials and Methods

DCM was supplied by the National Cancer Institute, Bethesda, Maryland, in a 20-ml vial containing lyophilized DCM 250 mg and sodium hydroxide to adjust the pH to 7.5–8.0.

Clinical Studies

Fifty patients (19 men and 31 women) with advanced malignant neoplasms were included in the study. Their ages ranged from 28 to 77 years with a mean of 51 years. All patients had cancer or leukemia which had been microscopically confirmed and which was not considered amenable to conventional therapy. Table 1 lists the disease categories.

Base-line studies included physical examination, body weight and height, complete blood counts and complete automated chemical profile (SMA 6 and 12), urinalysis, chest X-ray, and measurements of tumor lesions. Bone marrow examinations were carried out in all leukemic patients.

Prior to administration of DCM, all patients were hydrated with 5\% dextrose in water or 5\% dextrose in 0.45\% saline to assure urine output of more than 200 ml/h and alkalinization with sodium bicarbonate PO or IV, and, if necessary, acetazolamide IV, to assure urine pH of more than 7.0. Patients with creatinine clearance of less than 60 ml/min were excluded from the study.