Effect of Oral Colestimide on the Elimination of High-dose Methotrexate in Patients With Primary Central Nervous System Lymphoma

—Two Case Reports—

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Abstract

Delayed methotrexate (MTX) elimination occurred in two patients with primary central nervous system lymphoma undergoing high-dose MTX treatment. Oral administration of the anion exchange resin colestimide, which binds MTX effectively in vitro, effectively accelerated MTX elimination. Colestimide probably interrupts the enterohepatic circulation, and is a potential oral antidote to MTX toxicity.

Key words: malignant lymphoma, colestimide, methotrexate

Introduction

Methotrexate (MTX), an inhibitor of dihydrofolate reductase, is widely used in the treatment of various malignant tumors. High-dose MTX administration is particularly effective against primary central nervous system (CNS) lymphoma.¹⁾ MTX administered at a dose of 3.5 g/m² penetrates the blood-brain barrier and yields sustained therapeutic cerebrospinal fluid levels lasting longer than 24 hours. However, prolonged exposure to low-level (10⁻⁸ M) concentrations of MTX may cause neurotoxic reactions, mainly myelosuppression, gastrointestinal mucositis, and hepatitis.³⁾ Other types of toxicity depend on the administration regimen: chronic low-dose administration has been associated with cirrhosis, interstitial pneumonitis, and osteoporosis whereas high-dose systemic therapy can result in renal dysfunction, vomiting, and acute desquamative dermatitis. Elimination of MTX from the plasma after intravenous injection passes through three phases: distribution, renal clearance, and enterohepatic circulation.^{11,12,15)} The third phase may be implicated in the reported bone marrow and gastrointestinal toxicity.^{6,7)}

Anion-exchange resins effectively reduce cholesterol levels in patients with hypercholesterolemia. Oral administration of cholestyramine, an insoluble quaternary ammonium anion exchange resin, increases the fecal excretion of bile acids, so blocking enteral reabsorption.⁵⁾ MTX is an anionic drug with a structure containing 2 carboxyl groups and a molecular weight similar to that of bile acids. Therefore, cholestyramine could accelerate MTX elimination in patients experiencing toxicity associated with high-dose MTX therapy by binding MTX in the gut and interrupting the enterohepatic circulation.⁸⁾ Colestimide, a new type of anion-exchange resin, is reported to effectively absorb MTX.¹⁰⁾

We treated two patients with high-dose MTX administration for primary CNS lymphoma which resulted in the delayed elimination of MTX. Oral administration of colestimide effectively accelerated excretion of the MTX.

Case Reports

Case 1: A 32-year-old male was treated under a diagnosis of primary CNS lymphoma with three cycles of high-dose MTX (3.0 g/m²) followed by whole-brain irradiation (30 Gy) in June 2000. At that time, no delayed MTX elimination was observed and complete remission was obtained. However, recur-

Fig. 1 Serum methotrexate (MTX) concentrations throughout the treatment course in Cases 1 (A) and 2 (B). Colestimide was orally administered during the 10th cycle in Case 1 and the 4th and 5th cycles in Case 2.

rence was noted in September 2001, and he received further cycles of high-dose MTX (3.5 g/m^2) consisting of 3-hour infusion administered on the 1st day of the treatment. Urine alkalinization was started with sodium bicarbonate before the start of MTX infusion and citrovorum factor rescue was begun at 24 hours after the beginning of MTX infusion. Serum MTX levels were measured at 24, 48, and 72 hours after the start of MTX infusion. Although the recurrent tumor disappeared after the first treatment, maintenance treatment was continued for 1 year. After the 4th, 8th, and 9th cycles, delayed MTX elimination was noted (Fig. 1A), but he manifested no clinical signs of toxicity other than nausea and appetite loss. There was no bone marrow toxicity and serum creatinine level was within the normal range. Leucovorin rescue was continued until the serum MTX level dropped below $0.1 \mu\text{mol/l}$. Since delayed MTX elimination occurred after the 8th and 9th cycles, oral colestimide (3 g/day) was administered on days 1–3 of the 10th cycle. This

resulted in accelerated MTX excretion and serum MTX level was below $0.1 \mu\text{mol/l}$ at 72 hours after the start of MTX administration (Fig. 1A).

Case 2: A 49-year-old male was treated under a diagnosis of primary CNS lymphoma with a total of five cycles of high-dose MTX (3.5 g/m^2) in December 2001. After the 2nd and 3rd cycles, delayed MTX elimination was noted (Fig. 1B). He experienced nausea and appetite loss and manifested elevation of glutamic oxaloacetic and glutamic pyruvic transaminase, but no bone marrow suppression was noted and serum creatinine level was within the normal range. To accelerate MTX excretion, oral colestimide (3 g/day) was administered on days 1–3 of the 4th and 5th cycles. His serum MTX level was below $0.1 \mu\text{mol/l}$ at 72 and 48 hours after the start of MTX administration, respectively (Fig. 1B).

Discussion

Renal MTX clearance decreases as the serum concentration of MTX increases,¹³⁾ so the drug elimination delay becomes longer with higher administered dose. Since prolonged exposure to low levels of MTX induces neurotoxic reactions,³⁾ the elimination of MTX must be accelerated. MTX levels were higher in the bile than the plasma of patients.⁴⁾ MTX concentration in jejunal aspirate obtained 4 to 5 days after MTX administration was higher than in serum obtained at 24 hours after administration.²⁾ These observations suggest that biliary and possibly enteral secretion and reabsorption contribute to the slow third phase of MTX elimination.

Oral administration of activated charcoal reportedly reduced the serum MTX levels in the second elimination phase.⁹⁾ This may be due to adsorption of biliary excreted MTX which is consequently not reabsorbed enterally. Oral cholestyramine facilitates MTX excretion in the enterohepatic circulation^{8,14)} without affecting the serum MTX level at 24 hours after infusion, which may reflect the renal elimination of the drug⁸⁾ and suggests that cholestyramine may improve the total body clearance of MTX by enhancing extrarenal excretion.

We administered colestimide to our patients because this agent has greater adsorptive capacity than cholestyramine for bile acids and MTX in vitro.¹⁰⁾ Oral colestimide accelerated MTX elimination without producing any side effects, so provides a simple, safe method for the control of serum MTX levels in patients with malignant CNS tumors.

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