Original Articles

Pharmacokinetic Monitoring of High-dose Methotrexate

Early Recognition of High-Risk Patients

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Summary. The administration of high-dose methotrexate (HDMTX) with leucovorin rescue carries with it a risk of severe toxicity which may be fatal. In the present study, patients with a 24-h serum concentration of < 5 × 10^{-6} M and an elimination half-life (T_{1/2}) of < 3.5 h during the first 24 h after the infusion were considered at low risk for toxicity and received conventional low-dose leucovorin rescue. Patients not meeting these criteria were considered at high risk for toxicity and received an escalated and extended course of leucovorin. The low-risk criteria were met following 109 of 114 HDMTX infusions administered to 30 patients. None of these patients developed toxicity with low-dose leucovorin. The 24-h serum concentration and the T_{1/2} exceeded the low-risk criteria following five HDMTX infusions administered to three patients. In two of these three patients leucovorin was continued until the MTX concentration was < 10^{-8} M (168–265 h) and no toxicity developed. The third high-risk patient discontinued his leucovorin 11 days prior to a MTX serum concentration < 10^{-8} M and developed moderate toxicity. Clinical features present in the three high-risk patients, which were not present in the low-risk group, included a pleural effusion in one patient and gastrointestinal obstruction in the other two patients. The identification of 3/30 high-risk patients in the present study was consistent with a historical control group in which 6/65 patients developed severe toxicity. These data indicate that patients meeting the criteria described herein are at low risk to develop toxicity with conventional leucovorin rescue and that high-risk patients may be identified early enough to reduce or prevent toxicity.

Introduction

High-dose methotrexate (HDMTX) with leucovorin 'rescue' is widely used as adjuvant therapy for osteosarcoma, and in the treatment of non-Hodgkin's lymphoma, head and neck carcinoma, and other solid tumors [3, 23]. However, the administration of HDMTX with leucovorin carries with it the risk of severe toxicity which may be fatal [5, 10, 22]. A nationwide survey conducted prior to 1977 revealed a 6% incidence of mortality attributed to HDMTX [22]. For this reason, efforts have been made to identify factors which predispose to toxicity [5, 10] and to establish guidelines which reduce the risk of morbidity and mortality associated with HDMTX therapy.

Pharmacokinetic monitoring of methotrexate (MTX) has become a standard approach for prospective identification of patients at high risk for toxicity. However, there is no consensus among investigators regarding the exact criteria to be used to identify high-risk patients. Stoller et al. [20] suggest that patients with a 48-h serum concentration > 9 × 10^{-7} M and evidence of delayed clearance beyond 48 h are at high risk for toxicity with conventional rescue. Nirenberg et al. [13] reported that patients with a 24-h serum concentration > 10^{-5} M, a 48-h level > 10^{-6} M, and a 72-h concentration > 10^{-7} M were at high risk for toxicity. However, continued low-dose leucovorin rescue did not prevent clinical toxicity in patients identified at high risk. Tattersall et al. [21] reported that patients with a serum concentration > 5 × 10^{-7} M at 48 h are likely to encounter severe myelosuppression. Isacoff et al. [9] initially reported that patients with serum levels > 5 × 10^{-6} M at 24 h were at increased risk for toxicity. More recently, these investigators have reported [9] that patients with a 24-h level > 10^{-5} M or a 48-h concentration > 5 × 10^{-7} M are at increased risk for toxicity.

To be clinically useful, the criteria for prospectively monitoring HDMTX therapy should identify high-risk...
patients early enough to permit the initiation of a modified leucovorin rescue which would prevent toxicity. Since the effects of MTX may not be readily reversible if adequate leucovorin rescue is delayed for more than 42–48 h [11, 7], identification of high-risk patients at 24–36 h post-infusion would be advantageous. Because the cytotoxic effects of MTX appear to be a function of both concentration and duration of exposure, the rate of elimination of MTX from plasma may also be a useful criterion for identifying high-risk patients. In the present study, patients with a 24-h serum concentration ≤ 5 × 10^{-6} M and an elimination half-life \( t_{1/2} \) ≤ 3.5 h during the first 24 h after the infusion were considered at low risk for toxicity and received conventional low-dose leucovorin rescue. The selection of 5 × 10^{-6} M as the maximum 24-h concentration was based on criteria published prior to the initiation of this study by Isacoff et al. [9]. The selection of 3.5 h as the maximum half-life for decline in serum concentrations was based on a previous study [18] at this institution, which reported a serum half-life of 2–3.5 h in children administered HDMTX. Patients not meeting these criteria were considered at higher risk for toxicity and received an escalated and extended course of leucovorin.

Materials and Methods

From December 1976 to January 1978, 30 patients ranging in age from 15 months to 25 years (median: 14 years) received 114 infusions of HDMTX at St. Jude Children’s Research Hospital. Eighteen patients had osteosarcoma (12 adjuvant therapy), five colorectal carcinoma, four hepatocellular carcinoma, one testicular embryonal carcinoma, one chondrosarcoma, and one fibrosarcoma. All patients had a serum creatinine of < 1.2 mg/dl and a creatinine clearance of ≥ 85 ml/min/1.73 m^2 prior to HDMTX. The dosage of MTX ranged from 725 mg/m^2 to 15,000 mg/m^2. All doses were administered as a constant rate intravenous infusion over six hours. The leucovorin rescue for all patients was begun three hours after the end of the MTX infusion. The dosage of leucovorin was 5% of the total MTX dosage administered in eight equal intravenous doses every three hours, followed by eight oral or intramuscular doses of 12 mg/m^2 every six hours. All patients received intravenous hydration and urinary alkalinization as previously recommended [5]. Patients with MTX serum concentrations > 5 × 10^{-4} M at 24 h following the end of the infusion and/or an elimination \( t_{1/2} \) > 3.5 h were considered at increased risk to develop toxicity and were administered an escalated dose and duration of leucovorin rescue. The escalated dose of leucovorin was calculated to yield serum concentrations of leucovorin one log greater than MTX when MTX concentrations were > 10^{-5} M, based on previously published data describing the concentrations of leucovorin required to rescue given concentrations of MTX [17]. The dose of leucovorin was calculated to yield serum concentrations equimolar to MTX when MTX serum concentrations dropped below 10^{-7} M. Leucovorin dosage calculations were based upon available pharmacokinetic parameters for leucovorin [14], consistent with data reported by Mehta et al. [12].

MTX serum concentrations were measured in duplicate at 0, 6, 12, and 24 h after the end of the infusion by radiimmunoassay (Diagnostic Biochemistry, San Diego, California) and enzyme immunoassay (Syva Co., Palo Alto, California). Samples obtained later than 24 h after the infusion containing < 10^{-7} M MTX were measured by radiimmmunoassay and by a radio-enzymatic ligand binding assay (New England Enzyme, Boston, Massachusetts). The enzyme immunoassay and the radio-enzymatic assays consistently gave results lower than the radiimmmunoassay. Preliminary results of a comparative evaluation in our laboratory of these three assays and analysis by high-pressure liquid chromatography suggest that the radioimmune assay is less specific for the unmetabolized MTX compound. However, results produced by any of the three methods used in the present study produced the same interpretations regarding the low-risk criteria. The (ln) serum concentration versus time data during the first 24 h after the infusion were fitted to a single exponential term by use of a linear least-squares regression computer program. The elimination half-life \( t_{1/2} \) during the first 24 h after the infusion was calculated as

\[
\ln \left( \frac{C_0}{C_t} \right) = -\frac{t}{t_{1/2}}
\]

where \( K = -\text{slope of the least squares regression line of the serum concentration-time data during the 24 h post-infusion period.} \)

Results

Following 109 of 114 HDMTX infusions, the 24-h serum concentration was less than 5 × 10^{-6} M and the elimination half-life was less than 3.5 h. All of these patients received only low-dose leucovorin rescue for 72 h and none developed any evidence of MTX toxicity. The 24-h serum concentration was greater than 5 × 10^{-6} M following five infusions administered to three patients (Fig. 1). The elimination half-life was greater than 3.5 h following all five of these HDMTX infusions. The half-life for the remaining (low-risk) patients ranged from 1.7 h to 3.4 h with a median of 2.8 h. The elimination half-life was independent of MTX dosage or patient age (Fig. 2).

One of the high-risk patients was a 12-year-old boy with metastatic osteosarcoma, who had a left pleural effusion. This patient received 12,000 mg/m^2 of MTX with leucovorin rescue until his MTX serum concentration was < 10^{-8} M (168 h) and developed no MTX toxicity (Fig. 3). The second patient was an 18-year-old boy who had testicular embryonal carcinoma with retroperitoneal and hepatic metastases. This patient had failed prior therapy with cis-platinum and had developed right hydronephrosis and gastrointestinal obstruction secondary to tumor compression. Following his first dose of MTX (5000 mg/m^2) he had elevated serum levels and delayed MTX excretion. Leucovorin was therefore administered until his MTX serum concentration was < 10^{-8} M (265 h) and no MTX toxicity was observed. No subsequent doses of HDMTX were given. The third high risk patient was a 14-year-old boy with adenocarcinoma of the rectosigmoid colon and hepatic metastases. This patient also developed bilateral hydronephrosis and gastrointestinal (distal jejunal) obstruc-