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SHORT COMMUNICATION

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Successful rescue with leucovorin and thymidine in a patient with high-dose methotrexate induced acute renal failure

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Abstract A 54-year-old patient with primary cerebral lymphoma was treated with two 4-weekly cycles of high-dose intravenous cytarabine (12 g/m^2) and methotrexate (3 g/m^2). The administration of the first course proceeded without notable complications. Before the administration of methotrexate in the second cycle blood cell counts and chemistry showed no abnormalities except for slightly increased alkaline phosphatase and γ-glutamyl-transpeptidase levels which was attributed to diphantoin comedication. The patient developed symptoms of acute renal failure 7 h after methotrexate infusion which resulted in a very high serum methotrexate level (39.84 μmol/l) at 20 h after infusion. Rescue therapy was intensified: the leucovorin dosage was increased (1200 mg continuous i.v. infusion every 24 h) and combined with thymidine rescue therapy (8 g/m^2 per day continuous i.v. infusion every 24 h). Urine alkalinization was increased and diphantoin therapy was stopped. Leucovorin eye drops and mouth washes were started 5 days after methotrexate administration to prevent conjunctivitis and mucositis as a result of high methotrexate levels (> 2.4 μmol/l). In spite of the fact that serum methotrexate levels remained persistently higher than 0.1 μmol/l for 12 days, the patient experienced no further short-term systemic toxicity except for anaemia (grade 3 according to NCI Common Toxicity Criteria). After day 12 intensified rescue therapy and the frequency of alkalinization were decreased to standard procedures and stopped on day 19. It is concluded that i.v. administration with high-dose methotrexate can result in unpredictable acute toxicity. In our patient, acute methotrexate toxicity was treated successfully by intensification of classical leucovorin rescue therapy in combination with thymidine infusion. In addition, leucovorin mouth washes and eye drops may have prevented mucositis and conjunctivitis, respectively.

Keywords High-dose methotrexate · Acute renal failure · Toxicity · Leucovorin · Thymidine

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Introduction

High-dose methotrexate (> 1 g/m^2) administered as an intravenous (i.v.) infusion is used to treat a variety of malignancies in single or combination therapy. Methotrexate belongs to the group of antimetabolites. It binds to and inhibits dihydrofolate reductase in the cytoplasm leading to intracellular depletion of reduced folates. Inhibition of thymidylate and de novo purine synthesis occur resulting in decreased RNA and DNA synthesis as a function of both extracellular methotrexate levels and the duration of exposure [3, 19]. The pharmacokinetics of methotrexate vary considerably among patients mainly due to high interindividual variation in renal excretion of methotrexate and its metabolite 7-hydroxymethotrexate (7-OH-methotrexate) [16, 19].

Administration of high-dose methotrexate may result in acute renal failure possibly due to precipitation of methotrexate and/or 7-OH-methotrexate in the renal tubules, especially when the urinary pH is < 7.0. This nephrotoxicity leads to delayed methotrexate elimination, and consequently to toxicities including

myelosuppression, gastrointestinal toxicity, dermatitis, hepatitis and/or mucositis [3, 19]. In order to prevent (lethal) methotrexate toxicity the patient is vigorously hydrated and alkalinized to enhance the solubility and excretion of the drug in the urine. Standard leucovorin therapy has to be initiated within 24 h of methotrexate infusion to rescue the systemic organs. Leucovorin (N_5-formyl-FH_4), the biochemical antidote of methotrexate, replenishes tetrahydrofolate (FH_4).

Serum methotrexate levels above 0.1 μmol/l 48 h after i.v. drug administration are considered to be toxic and require higher doses and/or a sustained period of leucovorin (D,L-diastereomers) rescue therapy due to the short half-life of the L-diastereomers [5, 6, 23]. Alternative rescue therapy may comprise thymidine administration which restores the intracellular thymidylate pool, and can be combined with leucovorin in patients with toxic serum methotrexate levels. It must be administered in high doses by continuous infusion due to its rapid clearance [1, 7, 10, 11]. Rescue therapy may also comprise carboxypeptidase G (CPDG) which decreases extracellular methotrexate concentrations by cleaving it to the inactive metabolites glutamate and 4-deoxy-4-amino-N_{10}-methylpteroic acid. Extrarenal methods, e.g. haemodialysis, haemoperfusion and haemodiafiltration, have also been investigated [4, 8, 12, 13, 14, 15, 17, 20, 21, 22, 24].

In the current report, we describe a patient who developed unpredictable acute renal failure after i.v. administration of high-dose methotrexate despite adequate hydration, prealkalinization of the urine, and standard leucovorin rescue therapy. Despite high serum methotrexate levels over a long period, the patient experienced no further short-term toxicity as a consequence of intensification of intracellular rescue therapy comprising leucovorin in combination with thymidine infusion.

Patient and methods

Case history

A 54-year-old patient with primary cerebral lymphoma was treated with high-dose chemotherapy. Previously the diagnosis had been confirmed by resection of an occipital parenchymal lesion. Chemotherapy consisted of two 4-weekly courses of cytarabine given as a 2-h i.v. infusion every 12 h (2 g/m^2 twice daily, days 1 to 3), and methotrexate as a 1-h i.v. infusion (3 g/m^2, day 21) together with dexamethasone (days 1–15) and leucovorin rescue therapy (first administration 30 mg i.v. then 30 mg orally every 6 h) beginning 24 h after the start of infusion until the serum methotrexate level was below 0.1 μmol/l. Both cycles of methotrexate were preceded by i.v. fluid hydration, and urine alkalinization with sodium bicarbonate tablets (1 g orally every 6 h).

Prior to methotrexate infusion, blood cell counts, serum creatinine, and urea nitrogen levels were within normal limits. Only hepatic enzymes were elevated before both methotrexate infusions. Serum alanine-amino transferase and alkaline phosphatase levels were 45 U/l (upper limit of normal, ULN, 21 U/l) and 130 U/l (ULN 124 U/l), respectively. Before the second infusion, alkaline phosphatase and γ-glutamyl-transpeptidase levels were 149 and 235 U/l (ULN 25 U/l) which was attributed to concomitant diphantoin medication (150 mg orally twice daily). Before and during infusion of methotrexate urinary pH and fluid balance were monitored. After the first administration, the serum methotrexate levels were determined at 24, 48 and 72 h by fluorescence polarization immunoassay. Corresponding values were 0.8, 0.090, and 0.060 μmol/l. Creatinine levels and blood cell counts were monitored during both cycles. The first cycle was complicated by grade 3 (NCI Common Toxicity Criteria) neutropenia (nadir day 11) and grade 4 thrombocytopenia (nadir day 11). Thrombocytopenia was treated with platelet transfusions. On day 15 the patient developed neutropenic fever which was treated with i.v. antibiotics (penicillin 1 MU every 4 h). Furthermore, a mild transient dermatitis was noted 2 days after the first methotrexate infusion.

After the second course of cytarabine the patient developed grade 3 neutropenia (nadir day 10) without fever, grade 2 anaemia (nadirs days 1 and 12; probably due to the first course) and grade 4 thrombocytopenia (nadir day 12) which were treated with red blood cell and platelet transfusions. During the 7 h following the second infusion of methotrexate the patient developed abdominal cramps with fever (38.7°C) and later dyspnoea, coughing and a urinary pH of 6.5. Abdominal radiography and ultrasonography showed no abnormalities, and chest radiography revealed pleural effusion on both sides and signs of interstitial congestion. Treatment with i.v. antibiotics (imipenem 500 mg every 6 h) and diuretics (furosemide 80 mg every 24 h) was started.

The next day (day 1) the serum creatinine level had increased from 87 to 281 μmol/l (Fig. 1). The serum methotrexate concentration was 39.84 μmol/l at 20 h after the start of the infusion. Acute renal failure was diagnosed and treated with increased leucovorin rescue therapy of 1200 mg every 24 h as a continuous i.v. administration. Furthermore, alkalinization was intensified (100 ml sodium bicarbonate 8.4% i.v. every 4 h), and diphantoin comedication was stopped. Serum methotrexate levels were determined daily (Fig. 1). The serum creatinine level was 423 μmol/l (maximum) 3 days after methotrexate administration and a continuous infusion thymidine rescue therapy (8 g/m^2 per 24 h) was started in addition. On day 5 the serum methotrexate levels remained around 2.40 μmol/l. Leucovorin eye drops (0.03%, three drops every 6 h) and leucovorin mouth washes with swallowing (30 mg every 6 h) were started to prevent conjunctivitis and mucositis.

The serum level was 0.150 μmol/l 11 days after methotrexate administration. The leucovorin dosage was then reduced to 600 mg every 24 h, and the thymidine dosage to 5 g/m^2 every 24 h. On day 13 the serum drug level was 0.080 μmol/l, so the leucovorin dosage was further reduced to 300 mg every 24 h and thymidine to 2.5 /m^2 every 4 h, and the alkalinization frequency was decreased (200 ml sodium bicarbonate 8.4% i.v. every 24 h). The patient developed grade 3 anaemia (nadir day 12 after methotrexate infusion; probably due to the first course) which was

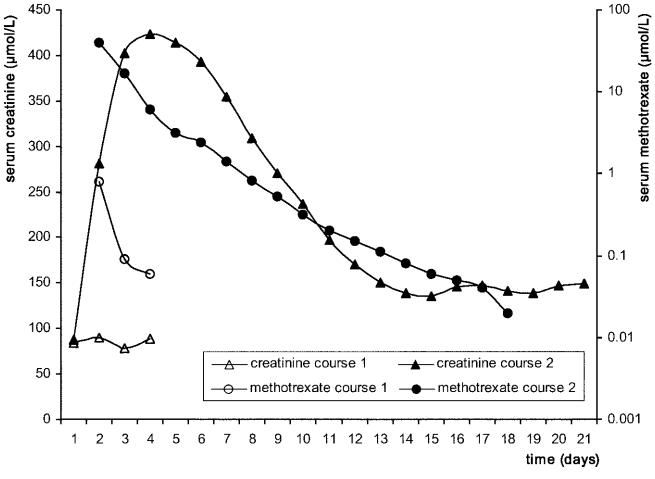

Fig. 1 Serum concentration-time profiles obtained during two 4-week courses of methotrexate

treated with red blood cell transfusion. In comparison with course one, the methotrexate half-life was increased from 13 h (days 0–3) to 32 h (days 0–13).

Serum methotrexate and creatinine concentrations were decreased to < 0.020 μmol/l and 147 μmol/l, respectively, 17 days after methotrexate administration. On day 19 serum hepatic enzyme levels were normal and alkalinization of the urine, and leucovorin and thymidine rescues were stopped. The patient was discharged 21 days after i.v. high-dose methotrexate administration. According to the treatment protocol whole-brain radiation therapy (17×1.8 Gy) was given 1 month after the second course of chemotherapy with a surdosage (8×1.8 Gy). Complete remission of lymphoma was achieved which persisted for 3 years. Unfortunately, the patient suffered from impairment of cognitive functioning which seriously affected quality of life.

Methods

Leucovorin (HPS, Zaandam, The Netherlands) 1.2 g was added with aseptic filtration to 500 ml saline for i.v. infusion. Thymidine (Sigma Chemical Company, St. Louis, Mo.) 15 g was added with aseptic filtration to 1000 ml saline for i.v. infusion. Quality control of both agents was performed by standard laboratory procedures in the laboratory of the hospital pharmacy.

A Medline literature search was performed to find other cases using the following search terms: high-dose methotrexate, toxicity, pharmacokinetics, leucovorin, thymidine, carboxypeptidase G_2, hemodialysis, hemoperfusion, hemodiafiltration, and plasma perfusion.

Results and discussion

Treatment with high-dose methotrexate may result in unpredictable acute toxicity despite hydration, alkalinization of urine, and rescue therapy. Patients who are not sufficiently hydrated and/or have a urinary pH < 7.0 are at increased risk for development of renal dysfunction. Decreased renal excretion may then lead to more severe toxicity. Intensified hydration and alkalinization of urine may decrease the risk of methotrexate toxicity in these patients. Each patient's creatinine clearance, hydration status and urinary pH has to be known prior to drug administration. Furthermore, serum methotrexate levels have to be carefully monitored and standard leucovorin rescue therapy has to be initiated within 24 h of the methotrexate infusion. In patients with serum methotrexate levels exceeding 0.1 μmol/l 48 h after drug administration and/or acute drug-induced toxicity, the rescue therapy needs to be intensified. Leucovorin rescue therapy alone may not prevent acute methotrexate toxicity with serum concentrations exceeding 10 μmol/l [18, 22].

Our literature search yielded a large number of reports on pharmacological research and clinical aspects of methotrexate administration and its rescue therapy [1, 2, 4, 5, 6, 7, 8, 10, 12, 13, 14, 15, 17, 20, 21, 22, 24]. In our patient leucovorin rescue therapy was intensified by continuous i.v. administration in combination with leucovorin mouth washes and eye drops. On day 3 the intracellular rescue was intensified by continuous thymidine infusion since the serum methotrexate concentration persisted at a toxic level (6.0 μmol/l) together with a high serum creatinine level (423 μmol/l). Alternative rescue therapy including CPDG and extrarenal procedures, e.g. haemodialysis, were not used because these methods only lower the extracellular methotrexate concentration. Moreover, extrarenal methods result in transient decreases in extracellular methotrexate concentration which necessitates repeated and/or combined use of haemodialysis, haemoperfusion and haemodiafiltration to efficiently lower methotrexate concentration [8, 9, 13, 17].

In our patient acute renal failure occurred unexpectedly after administration of the second cycle of high-dose methotrexate. This might be attributable to the urinary pH of 6.5 at a certain time which decreases the solubilities of methotrexate and in particular 7-OH-methotrexate and can result in tubular epithelial damage. Interaction of methotrexate with diphantoin and antibiotics may have decreased the plasma protein binding of methotrexate. All these factors may have contributed to higher free methotrexate levels and renal toxicity. Furthermore, the presence of a third compartment (pleural effusion) may have contributed to the long-term high serum methotrexate concentrations due to the retarded distribution in and from the extravascular fluid accumulations [3, 19].

In conclusion, high-dose methotrexate-induced acute severe renal failure was followed by high serum methotrexate levels over a long period of 12 days. Intensification of the intracellular rescue therapy, increased frequency of alkalinization, and cessation of diphantoin therapy was sufficient to prevent further toxicity. Renal clearance improved and serum methotrexate levels decreased to nontoxic levels, and no additional extracellular rescue therapy was needed to prevent further short-term toxicity. It should be noted that the observed loss of cognitive function in our patient may be related to the prolonged high serum methotrexate concentrations in combination with whole-brain radiotherapy. Nevertheless, there is as yet no defined schedule and optimal dosage of rescue therapy in patients with high methotrexate serum concentrations. We would recommend intensification of leucovorin rescue therapy by continuous infusion, eye drops and mouth washes in combination with continuous administration of thymidine to prevent methotrexate toxicity in these patients.

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