WARNINGS

Methotrexate should be used only by physicians whose knowledge and experience include the use of antimetabolite therapy.

Because of the possibility of serious toxic reactions (which can be fatal):

- Methotrexate should be used only in life-threatening neoplastic diseases, or in patients with psoriasis or rheumatoid arthritis with severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy.

- Deaths have been reported with the use of methotrexate in the treatment of malignancy, psoriasis, and rheumatoid arthritis.

- Patients should be closely monitored for bone marrow, liver, lung, and kidney toxicities (see PRECAUTIONS).

- Patients should be informed of the risks involved and be under a physician’s care throughout therapy.

The use of methotrexate high-dose regimens recommended for osteosarcoma requires meticulous care (see DOSAGE AND ADMINISTRATION). High-dose regimens for other neoplastic diseases are investigational, and a therapeutic advantage has not been established.

Methotrexate formulations and devices containing preservatives must not be used for intrathecal or high dose methotrexate therapy.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate (see CONTRAINDICATIONS).

2. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity and should receive dose reduction or, in some circumstances, discontinuation of therapy.

3. Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some non-steroidal anti-inflammatory drugs (NSAIDs) (see PRECAUTIONS, Drug Interactions).

4. Methotrexate causes hematopoietic, fibrosis, and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatobiliary disease. Liver biopsy after apparent side effects shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in all patients. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis, but are not always associated with overt clinical disease. Liver biopsy should be considered in patients who report symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it will be effective in remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability, and deformity.

Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3 to 6 months). Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

- In psoriasis, the rate of progression of epithelial cells in the skin is greatly increased in normal skin. This difference in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

- Methotrexate in high doses, followed by leucovorin rescue, is used as a part of the treatment of patients with metastatic osteosarcoma. The oral route is preferred. In vitro methotrexate-induced cell death is greater in malignant tissues than in most normal tissues, but the mechanism of action in rheumatoid arthritis is unknown; it may affect inflammation, fibrosis, and joint destruction. Some reports describe in vitro methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyperproliferative responses. A prospective, 2.5 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of the mechanism of methotrexate’s effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

- In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks. Although methotrexate may reduce symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it will be effective in remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability, and deformity.

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40 mg/m² has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak serum drug concentration.

The terminal half-life has been reported to range from 0.7 to 5.8 hours, dependent on the phase of methotrexate therapy. In patients receiving methotrexate for acute lymphoblastic leukemia who were treated with intermediate-dose methotrexate (50 mg/m²), the terminal half-life has been reported to range from 0.7 to 5.8 hours.

Distribution

After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and the steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight).

Metabolism

Methotrexate undergoes hepatic and intra- cellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. Polyglutamate forms act as inhibitors of thymidylate reductase and dihydrofolate reductase. Polyglutamates may be excreted in the urine, but some may be further metabolized in the liver to form polyglutamates, which may remain in tissue for extended periods. The prolonged retention of methotrexate in tissue has been demonstrated in older individuals.

Excretion

Renal excretion is the primary route of elimination and is dependent on the route of administration of methotrexate. Administration of methotrexate at 80% to 90% of the administered dose is excreted in the urine. In adults, more than 24 hours after the administration of methotrexate, approximately 10% of the total administered dose is excreted in the urine. In infants, the urine concentration of methotrexate is highest at the first 24 hours after the administration of methotrexate.

Nonrenal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal transporters may result in a reduced systemic clearance and increased systemic exposure.

Toxicity

The potential for toxicity from high dose regimens or when methotrexate is used in combination with folinic acid is variable. Patients undergoing treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy should have follow-up laboratory evaluations for signs of toxicity. Following the administration of high dose methotrexate, the terminal half-life is eight to 16 hours.

Methotrexate clearance rates vary widely and are generally at least 50% higher than the clearance rates of healthy young adults. Clearance of methotrexate in healthy young adults is 0.08:1.

Doses of methotrexate up to 7.5 mg/m² may be associated with a small increase in the risk of fibrosis or cirrhosis of the liver. The potential for increased liver toxicity when methotrexate is used in combination with folinic acid is variable.

In patients with a history of cancer, the risk of developing liver toxicity may be increased.

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occurrence of bone marrow suppression, thrombocytopenia, and pneumonitis may increase with age (see boxed WARN-
ing AND PRECAUTIONS). Organ System Toxicity Gastrointestinal System If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, oral rehydration should be started as soon as recovery occurs. Methotrexate should be used with extreme caution in patients with known or suspected peptic ulcer disease or colitis ulcerative.

Hematologic Methotrexate can suppress hematopoiesis and cause anemia, aplastic anemia, hairy cell leukemia, and/or thrombocytopenia. In patients with malignancy and pre-existing hematologic abnormalities, this should be considered with caution, if at all. In controlled clinical trials in rheumatoid arthritis (RA) and psoriatic arthritis (WBC <3000/mm3) in 2 patients, thrombocytopenia (platelets < 100,000/mm3) in 6 patients, and neutropenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be discontinued if there is a significant drop in white blood cell counts. In the treatment of neoplastic diseases, methotrexate should be used with caution in patients with previous severe myelosuppression. Patients with profound granulo- cytopenia and/or thrombocytopenia should be closely monitored and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic Toxidrome The hepatic toxidrome has the potential for acute (transamnestic and/or cirrhotic) hepatitis. Chronic toxic hepatitis is potentially fatal; it generally occurs after prolonged use and is associated with total dose of at least 1.5 grams. In studies in patients, hepatoxicity appeared to be a function of total cumulative dose and serum levels. This effect is usually seen in patients with significant liver disease.

In psoriasis, liver function tests, including serum albumin, should be done monthly and when a rise in aspartate aminotransferase (AST) is noted normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1 pretherapy or six months after therapy. However, (2 mg/m2) of methotrexate doses of 1.5 grams, and 3 after each additional 1 to 1.5 grams of methotrexate. At high dose or abnormal laboratory changes discontinue the drug; mild fibrosis usually suggests a good prognosis and is detectable by biopsy. At risk of fibrosis, and change and low grade portal inflammation are relatively common in patients treated with methotrexate. These findings, usually not a reason to avoid or discontinue methotrexate therapy, do not predict a good outcome.

In rheumatoid arthritis, age at first use of methotrexate and cumulative dose of methotrexate does not appear to be a risk factor for hepatotoxicity, other risk factors, similar to those observed in patients with chronic non-suppurative hepatitis, is seen in doses of 5 mg/m2 in 6 patients who did not fulfill the criteria of chronic viral hepatitis. Liver function tests were not done in 5 patients, and persistent abnormal laboratory tests were not confirmed in 6 patients. Persistent abnormalities in liver function tests and persistence of fibrosis are not associated with the development of cirrhosis in this population. There is a combined reported experience of 21 cases of the development of cirrhosis and 4 cases of death during treatment (after a cumulative dose of at least 1.5 grams). This incidence rate is higher than that of the general population. There are 67% of cases of fibrosis and 0.01% of cases of cirrhosis. Of the cases of fibrosis, 38% of them had chronic hepatitis at baseline, and 62% of them had chronic hepatitis at baseline. Of the cases of cirrhosis, 75% of them had chronic hepatitis at baseline, and 25% of them had chronic hepatitis at baseline.

In rheumatoid arthritis, the incidence of fibrosis is increased in patients treated with methotrexate. In cases of severe toxicity, concomitant treatment and the underlying disease process may contribute to severe changes.

Hematologic findings were not examined in these short-term studies (see Pharmacokinetics).

Neurotoxicity Neuroradiographic abnormalities can be seen on diagnostic imaging studies. Chronic leukoencephalopathy and/or microangiopathic calcifications have been reported rarely.

Central Nervous System: headaches, dizziness, blurred vision, transient blindness, optic neuritis, seizures, and convulsions have been reported. Intrathecal carboxypeptidase G2 treatment to hasten clearance of methotrexate in cases of overdose. There have been reports of death following intrathecal methotrexate.

Eye symptoms include conjunctivitis, serious visual changes of any type, and central retinal vein thrombosis. Newborns exposed to methotrexate in utero may develop blindness. Immediate dermatologic reactions, including alopecia, leukopenia, lymphopenia, and an infiltrate on chest X-ray; inflammation and/or pain in the peripheral joints;

Incidence 1% to 3%: Rash/pruritus/dermatitis, diarrhea, nausea, anemia, mucositis, stomatitis, gingivitis, pharyngitis, stomatitis; Herpes zoster; M. simplex; and dermatitis.

Incidence greater than 10%: Elevated liver function tests (AST, ALT, alkaline phosphatase) greater than 1.5 times the upper limit of normal and bilirubin greater than 1.5 times the upper limit of normal.

Other adverse reactions that have been reported with methotrexate are shown in the table below. There have been reports of death following intrathecal methotrexate.
choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general improvement, maintenance therapy is initiated, as follows: Methotrexate is administered twice weekly for at least one month or intrathecally in the presence of meningeal leukemia. Methotrexate given by the intrathecal route is less toxic and requires a lower dosage concentration than given by the oral route. In an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection, USP is the preferred route of administration because of age and may cause convulsions. Methotrexate given by the intrathecal route is also less toxic and requires a lower dosage concentration than given by the oral route.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should familiarize with the new advances in anti-leukemic therapy.

Meningeal Leukemia

In the treatment of meningeal leukemia, methotrexate must be administered intra-arachnoidally. Preservative free, sterile, methotrexate solution containing a concentration of 5 mg/mL per milliliter is available. In an appropriate sterile, preservative free medium, such as 0.9% Sodium Chloride Injection, USP is the preferred route of administration because of less neurotoxicity.

When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

1. Administration of methotrexate should be delayed until recovery of the following:

- the WBC count is less than 15,000/microliter
- the platelet count is less than 50,000/microliter
- the serum bilirubin is less than 1.2 mg/dL
- the SGPT level is greater than 450 U
- mucositis is less than grade 2

2. Adequate renal function must be documented. Serum creatinine clearance must be greater than 60 mL/min, before initiation of therapy.

3. Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more compared to a prior value, the creatinine clearance must be measured and documented to be less than or equal to 50% of the prior value if the serum creatinine is still within the normal range.

4. Patients must be pretreated with sodium bicarbonate for urinary alkalinization.

5. Leucovorin calcium must be administered by the intravenous route at a dose of 25 mg/m2 daily, or 5 mg/kg/m2 daily, beginning 24 hours after initiation of the methotrexate infusion. For patients with a body surface area of less than 1 m2, the dose of leucovorin calcium must be reduced to a dose of 2 mg/kg daily. Appropriate dosage may be adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

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