INDICATIONS AND USAGE

Mitomycin for injection is not recommended as a single-agent, primary therapy. It has been shown to be useful in the treatment of disseminated adenocarcinoma of the stomach or pancreatic origin, when combination with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed. Mitomycin is not recommended to replace appropriate surgery and/or radiotherapy.

CONTRAINDICATIONS

Mitomycin is contraindicated in patients who have demonstrated a hypersensitive or idiosyncratic reaction to it in the past.

Mitomycin is contraindicated in patients with thrombocytopenia, coagulation disorders, or an increase in bleeding tendency due to other causes.

WARNINGS

Patients being treated with mitomycin must be observed carefully and frequently during and after therapy.

The use of mitomycin results in a high incidence of bone marrow suppression, particularly thrombocytopenia and leukopenia. Therefore, the following studies should be obtained repeatedly during therapy and at least 6 weeks following therapy: platelet count, white blood cell count, differential, and hemoglobin. The occurrence of a platelet count below 100,000/mm³ or a WBC below 4,000/mm³ or a progressive decline in either is an indication to withhold further therapy until blood counts have recovered above these levels.

Patients should be advised of the potential toxicity of this drug, particularly bone marrow suppression. Deaths have been reported due to sepsis and as a result of leukopenia due to the drug.

Patients receiving mitomycin should be observed for evidence of renal toxicity. Mitomycin should not be given to patients with a serum creatinine greater than 1.7 mg percent.

Usage in Pregnancy: Safe use of mitomycin in pregnant women has not been established. Teratological changes have been noted in animal studies. The effect of mitomycin on fertility is unknown.

PRECAUTIONS

Acute shortness of breath and severe bronchospasm have been reported following the administration of vincristine sulfate to patients who had previously or simultaneously received mitomycin. The severity or simultaneity of respiratory embarrassment with mitomycin has not been established, and this acute respiratory distress occurred within minutes to hours after the vincristine sulfate injection. The total number of doses for each drug has varied considerably. Bronchodilators, steroids, and oxygen have been used for symptomatic relief.

A few cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapy and at full doses, concentrations greater than 20 mg/m² per dose. Therefore, caution should be exercised using only enough oxygen to provide adequate arterial saturation since oxygen itself is toxic to the lungs. Careful attention should be paid to fluid balance and overhydration should be avoided.

Other Contraindications include: intravenous administration (not an approved route of administration), in rare cases has required cystectomy.

Nursing Mothers: It is not known if mitomycin is found in human milk. Because many drugs are found in milk, it is recommended that women receiving mitomycin not breast feed because of the potential for serious adverse reactions from mitomycin in nursing infants.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Bone Marrow Toxicity: This is the most common and most serious toxicity, occurring in 60% of 937 patients (64%). Thrombocytopenia and/or leukopenia may occur anytime within 6 weeks after onset of therapy with an average time of 4 weeks. Recovery after cessation of therapy was within 10 weeks. About 25% of the leukopenia of the bone marrow episodes did not recover. Mitomycin produces cumulative myelosuppression.

Integument and Mucous Membrane Toxicity: This has occurred in approximately 4% of patients treated with mitomycin. Cutaneous or injection site at the injection site has been reported and is occasionally severe. Ptosis, blepharoptosis, and cataracts also occur frequently. Flashes are rarely reported. The most important dermatological problem with this drug, however, is the necrotic and consequent sloughing of tissue which results if the drug is extravasated during injection. Extravasation may occur with or without an accompanying stinging or burning sensation and even if there is adequate blood return when the injection needle is aspirated. There have been reports of delayed erythema and/or ulceration occurring either at or distant from the injection site, weeks to months after mitomycin, even when no evidence of extravasation was observed during administration. Skin grafting has been required in some cases.

Renal Toxicity: 2% of 1,281 patients demonstrated a statistically significant rise in creatinine. There appeared to be no correlation between total doses administered or duration of therapy and the degree of total impairment.

Pulmonary Toxicity: This has occurred infrequently but can be severe and may be life-threatening. Dypnea with a nonproductive cough and radiographic evidence of pulmonary infiltrates may be indicative of mitomycin-induced pulmonary toxicity. If other etiologies are eliminated, mitomycin therapy should be discontinued. Studies have been employed as treatment of this toxicity, but the therapeutic value has not been determined. A few cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapeutic agents used at full doses, concentrations greater than 50% in more

b. Mitomycin is a potent inhibitor of DNA synthesis and repair. It has been shown to inhibit the incorporation of thymidine into DNA, thereby blocking the cell cycle at the S phase. This leads to the formation of DNA interstrand cross-links, which result in the inhibition of DNA replication and repair. The accumulation of these cross-links leads to cell death, typically by apoptosis. Mitomycin also inhibits the activity of topoisomerase II, an enzyme that is involved in the relaxation of supercoiled DNA. This inhibition results in the formation of DNA cleavage complexes, which can also lead to cell death. Mitomycin's antitumor activity is thought to be due to its ability to induce DNA damage and inhibit DNA repair, which ultimately leads to cell death.

Mitomycin can be used in combination with other chemotherapeutic agents, such as 5-fluorouracil (5-FU) and cisplatin, to increase its efficacy. The combination of mitomycin and 5-FU has been shown to be effective in the treatment of metastatic colorectal cancer, and the combination of mitomycin and cisplatin has been shown to be effective in the treatment of metastatic lung cancer. The combination of mitomycin and other chemotherapeutic agents can also be used as maintenance therapy after initial treatment with a single agent. For example, mitomycin can be used as maintenance therapy after initial treatment with 5-FU in patients with metastatic colorectal cancer.

Mitomycin can also be used as a radiosensitizer, which enhances the cytotoxic effects of radiation therapy. This is particularly useful in the treatment of patients with brain tumors, where radiation therapy is often used in combination with mitomycin to treat recurrent or refractory disease.

Mitomycin is usually administered intravenously as a bolus injection, typically at a dose of 20 mg/m². The frequency of administration depends on the specific indication and the patient's tolerance. Mitomycin is available as a sterile, lyophilized powder for reconstitution with sterile water. The solution should be freshly prepared and used within 24 hours of reconstitution. Mitomycin should be administered slowly, typically over 2 to 5 minutes, to minimize the risk of extravasation and local toxicity.

Mitomycin is contraindicated in patients with severe bone marrow suppression, particularly thrombocytopenia and leukopenia. Mitomycin is also contraindicated in patients with a serum creatinine greater than 1.7 mg/dL. Mitomycin is not recommended for use in pregnant women, as its effects on fetal development are unknown.

Mitomycin is generally well tolerated, with the most common side effects being myelosuppression, nausea, and vomiting. With proper monitoring and early intervention, most of these side effects can be managed effectively. Mitomycin is associated with a low risk of severe adverse reactions, and any patient treated with mitomycin should be monitored closely for signs of toxicity.

Mitomycin is available in the United States and is approved by the FDA for the treatment of metastatic colorectal cancer, as well as other indications, including the treatment of metastatic lung cancer and brain tumors. Mitomycin is also available in other countries outside of the United States.