Melphalan Hydrochloride for Injection

**DESCRIPTION**

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-phenylalanine mustard, is an alkylating agent of the bischloroethylamine type. As a result, it is leukemogenic in humans. Melphalan for injection produces chromosomal alterations in vitro and in vivo, and, therefore, should be considered potentially mutagenic in humans.

**INDICATIONS AND USAGE**

Melphalan hydrochloride for injection is indicated for the palliative treatment of patients with multiple myeloma and for patients with refractory ovarian carcinoma who have demonstrated prior resistance to this agent. Patients who have demonstrated hypersensitivity to melphalan should not be rechallenged with melphalan.

**CONTRAINDICATIONS**

Melphalan should not be used in patients whose disease has demonstrated prior resistance to this agent. Patients who have demonstrated hypersensitivity to melphalan should not be rechallenged with melphalan.

**WARNINGS**

Melphalan hydrochloride for injection may cause local tissue damage which may extend to involve vital structures. Therefore, the following tests should be performed at the start of therapy and at regular intervals, as indicated:

- Hemoglobin
- Hematocrit
- White blood cell count
- Platelet count

**ADVERSE REACTIONS**

Because of changes in protocol design after week 22, other efficacy parameters such as survival time and response rate could not be accurately compared between the IV and oral arms. However, the dose escape of the IV melphalan arm appears to be related to the extent of its interstrand cross-linking activity. The median time to disease progression was 7.3 months in the IV arm compared to 5.7 months in the oral arm (P<0.04). Response rates at week 22 were 44% and 34%, respectively.

**PHARMACOKINETICS**

Following injection, drug plasma concentrations declined rapidly in a biphasic manner with distribution phase and terminal elimination half-lives of approximately 7 and 75 minutes, respectively. Estimates of average total body clearance varied among studies, but typical values of approximately 7 to 9 mL/min/kg (250 to 325 mL/min/m²) were observed. One study has reported that on repeat dosing of 0.5 mg/kg every 6 weeks, the clearance of melphalan decreased from 8.1 mL/kg after the first course, to 5.5 mL/kg/min after the third course, but did not decrease appreciably after the third course. Mean (±SD) peak plasma melphalan levels were 2.0 ± 0.4 mg/L in patients receiving oral melphalan and 2.1 ± 0.3 mg/L in patients receiving intravenous melphalan. Doses of 10 mg/m² of body surface area were 1.2 x 0.4 and 2.8 x 1.9 mg/day, respectively.

The steady-state volume of distribution of melphalan is 0.5 L/kg. Penetration into cerebrospinal fluid is low. The apparent volume of distribution of melphalan is large and includes the body water and extravascular tissue compartments.

Melphalan is an alkylating agent that is active against selected human neoplastic diseases. It is known chemically as 4-(N-chloroethyl)-N-methyl-L-phenylalanine. The molecular formula is C₁₃H₁₈Cl₂N₂O₂ and the molecular weight is 302.38. The structural formula is: 

**CLINICAL PHARMACOLOGY**

**ELIMINATION**

Melphalan is a liver-specific and the compound was first synthesized in 1952 by Bergel and Stock; the D-isomer, known as medphalan, is less active against certain animal tumors, and the dose needed to produce effects in animals is about 2 to 3 times greater than the L-isomer. Melphalan-l/₂ is known as melphalan or sarcolysin.

**METABOLISM**

Melphalan has a plasma protein binding of about 90% and in the presence of hypoproteinemia may be used. As a result, it is leukemogenic in humans. Melphalan for injection produces chromosomal alterations in vitro and in vivo, and, therefore, should be considered potentially mutagenic in humans.

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**PRECAUTIONS**

General: In all instances where the use of melphalan hydrochloride for injection is considered for chemotherapy, the physician must evaluate the need for and potential benefits of the drug for each individual patient. Melphalan should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy or whose marrow function is otherwise impaired.

Dose reduction should be considered in patients with renal insufficiency receiving IV melphalan. In one trial, increased bone marrow suppression was noted in patients with renal insufficiency (BUN > 30 mg/dL). Experience in patients responsive to the drug who received IV melphalan should decrease the incidence of severe bone marrow suppression in the latter portion of this study.

Adrenal administration of live vaccines to immunocompromised patients should be avoided.

Information for Patients: Patients should be informed that the major acute toxicities of melphalan are neurotoxicity, hypersensitivity, and reactions, gastrointestinal toxicity, and pulmonary toxicity. The major long-term toxicities are related to infertility and secondary malignancies. Patients should be advised to avoid pregnancy and breast feeding for at least 1 year after receiving melphalan. If pregnancy occurs, IV melphalan should not be given to nursing mothers. IV melphalan should not be administered if the patient is receiving concurrent chemotherapy or radiation therapy. The patient should be advised to consult their physicians if they experience skin rash, signs or symptoms of vasculitis, bleeding, fever, persistent cough, nausea, vomiting, amenorrhea, weight loss, or unusual lumps/masses. Women of childbearing potential should be advised to avoid becoming pregnant.

**Laboratory Tests:** Periodic complete blood counts with differentials should be performed during the course of treatment with melphalan. At least 1 determination should be obtained prior to each dose. Patients should be observed closely for早on consequences of bone marrow suppression, which may include severe infections, bleeding, and symptoms (see **WARNINGS**).

**Drug Interactions:** The development of severe renal failure has been reported in patients treated with oral and IV melphalan following standard oral doses of cyclosporine. Cyclosporine may inhibit melphalan kinetics by inducing renal dysfunction and subsequently altering melphalan clearance. IV melphalan should not be given to patients receiving oral or IV cyclosporine. Cisplatin may affect melphalan kinetics by inducing renal dysfunction and subsequently altering melphalan clearance. IV melphalan should not be given to patients receiving oral or IV cisplatin.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Necrotic enterocolitis has been reported to increase in pediatric patients. When nalidixic acid and oral doses of cyclosporine. Cisplatin may affect melphalan kinetics by inducing renal dysfunction and subsequently altering melphalan clearance. IV melphalan should not be given to patients receiving oral or IV cisplatin.

**Hypersensitivity:** Acute hypersensitivity reactions including anaphylaxis, bronchospasm, hypotension, and shock have been rarely reported following an injection for myeloma (see **WARNINGS**). These reactions were characterized by dyspnea, lightheadedness, flushing, bronchospasm, dyspnea, and hypotension. These patients appeared to respond to antianaphylactic and corticosteroid therapy. If a hypersensitivity reaction occurs, IV melphalan therapy should be discontinued. If a hypersensitivity reaction has also been reported with oral melphalan. Carcinoma arrest has also been reported rarely in association with such reactions. Miscellaneous: Other reported adverse reactions include skin hypersensitivity, skin ulceration at injection site, skin necrosis rarely requiring skin grafting, maculopapular rashes, urticaria, alopecia, hemolytic anemia, allergic reaction, gastrointestinal reactions, skin reactions, and jaundice. Nephrotic syndrome has been observed in patients with BUN levels ≥30 mg/dL. A 50% reduction in the IV dose of melphalan is recommended in patients with renal insufficiency (BUN ≥30 mg/dL) (see **WARNINGS**). These reactions were characterized by changes in skin color, cutaneous edema, necrotic ulceration, and skin grafting.

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