5AZ

Mechanism of action

Ifosfamide is a prodrug that requires metabolic activation to compounds that possess cytotoxic activity. Activation occurs by hydroxylation at the 4-carbon position of the alkyl chain (side chain) to form a reactive metabolite—compound acrolein. This active metabolite can then react with DNA, RNA, or proteins to form adducts. The resulting adducts can ultimately lead to cell death. Hydroxylation at the 4-carbon position of the alkyl chain is mediated by hepatic cytochrome P450 enzymes, primarily CYP2B6. This enzyme is inducible by the prodrug ifosfamide, which also increases the metabolic clearance of ifosfamide. Other hepatic cytochrome P450 enzymes that may contribute to ifosfamide activation include CYP2C8, CYP2C9, and CYP3A4. Inhibitors of CYP3A4, such as ketoconazole, may increase the clearance of ifosfamide, while inducers, such as rifampin, may decrease its clearance. Ifosfamide has been shown to induce its own CYP2B6 enzyme activity, potentially leading to increased metabolism and clearance of the drug.

The effective plasma concentration of ifosfamide is unknown. However, the effective concentration of the active metabolite, compound acrolein, is reported to be 0.1 to 0.5 nmol/mL. The active metabolite is primarily excreted in the urine, and the elimination half-life of compound acrolein is approximately 3.5 hours.

Dosage and administration

Ifosfamide is administered as a single intravenous dose, usually over 0.5 hour once daily for 2 days, with or without etoposide. The dosage is based on the patient’s body surface area (BSA) and the desired dose of etoposide. The typical dosage is 1.2 g/m² dose/day for 2 days, with a maximum single dose of 1.8 g/m²/day. Ifosfamide is usually administered on day 1 of a 3-week treatment cycle, followed by a 1-week rest period. The dose is adjusted based on the patient’s renal function, as ifosfamide is primarily cleared renally.

The maximum recommended single intravenous dose of ifosfamide is 1.5 g/m²/day.

Contraindications

Ifosfamide is contraindicated in patients with preexisting severe bone marrow depression, as it may exacerbate this condition.

Warnings

1. Myelosuppression

Ifosfamide-induced bone marrow depression is dose- and schedule-dependent. Myelosuppression can be severe, and the risk of infection and bleeding is increased. Patients should be monitored closely for signs of bone marrow depression, and platelet transfusions may be necessary in severe cases.

2. Nephrotoxicity

Ifosfamide is primarily excreted renally, and the drug is known to cause dose-dependent renal injury. Patients with renal impairment are at increased risk of nephrotoxicity. Ifosfamide should be used with caution in patients with preexisting renal disease, and the dosage should be adjusted accordingly.

3. Allergic reactions

Ifosfamide can cause allergic reactions, including fever, rash, and anaphylaxis. Patients should be monitored for these reactions, and pretreatment with antihistamines or corticosteroids may be necessary.

4. Neurotoxicity

Ifosfamide may cause dose-dependent neurotoxicity, including peripheral neuropathy and optic neuropathy. Patients should be monitored for these symptoms, and the dosage should be adjusted if necessary.

5. Drug interactions

Ifosfamide is metabolized by CYP3A4, and it may interact with other CYP3A4 inhibitors, such as ketoconazole. Patients should be monitored for increased toxicity if these drugs are coadministered.

Precautions

1. Pregnancy

Ifosfamide crosses the placenta and can cause fetal harm. Ifosfamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2. Lactation

Ifosfamide is excreted in breast milk. Women who are breastfeeding should not use ifosfamide, as it may cause harm to the infant.

3. Pediatric use

Ifosfamide is generally not recommended for children, as the drug is toxic to developing cells. However, ifosfamide may be used in children with refractory testicular cancer, with the dosage adjusted based on body surface area.

4. Geriatric use

Ifosfamide may cause dose-dependent myelosuppression and renal injury in elderly patients. The dosage should be adjusted based on renal function.

5. Cautions

Ifosfamide should be used with caution in patients with preexisting liver disease, as the drug may cause hepatic toxicity.

Adverse reactions

Ifosfamide is associated with a number of adverse reactions, including myelosuppression, nephrotoxicity, neurotoxicity, and allergic reactions. These reactions may be dose- and schedule-dependent, and patients should be monitored closely for signs of toxicity.

Patient counseling

1. Specific information

Specific information should be provided to patients, including the following:

- The indication for which the drug is being used
- The dosage and schedule of administration
- The potential for serious adverse events
- The potential for drug interactions
- The need for monitoring for renal and hematologic toxicity
- The need for monitoring for neurotoxicity
- The need for monitoring for allergic reactions
- The need for monitoring for hepatic toxicity

2. Instructions for use

Patients should be instructed to:

- Report any signs of bone marrow depression
- Report any signs of renal injury
- Report any signs of neurotoxicity
- Report any signs of allergic reactions
- Take the drug as prescribed
- Avoid concurrent use of CYP3A4 inhibitors, if possible

3. Burden of disease

Patients should be informed about the potential burden of disease, including the potential for myelosuppression, nephrotoxicity, and neurotoxicity.

References

1. Gehan-Breslow and Mantel-Cox tests


3. Carcinogenesis, Mutagenesis, Impairment of Fertility


5. The risk of bladder and kidney toxicity. Patients should report preexisting cardiac disease.

6. The potential for serious adverse reactions and tumorigenicity. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

7. The potential hazard to a fetus if a patient becomes pregnant during therapy with ifosfamide. Further, men should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

8. The risk of myelosuppression and renal injury. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

9. The potential for neurotoxicity. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

10. The risk of stomatitis and the importance of proper oral hygiene. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

11. The potential for allergic reactions. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

12. The potential for hepatic toxicity. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

13. The risk of bladder and kidney toxicity. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

14. The risk of stomatitis and the importance of proper oral hygiene. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

15. The potential for allergic reactions. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

16. The potential for hepatic toxicity. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

17. The risk of myelosuppression and renal injury. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.

18. The risk of osteonecrosis of the jaw. Patients should be apprised of the potential for serious adverse events and the tumorigenicity of the drug.