I. MECHANISM OF ACTION

A) A cell-cycle specific agent that blocks topoisomerase II activity.
B) Topoisomerase II is part of the cellular scission/reunion reaction need to uncoil and recoil supercoiled DNA. It intentionally causes breaks in DNA to relieve tension and allow DNA to swivel, rotate, and relax.
C) Topoisomerase II separates 2 linked circles of duplex DNA, a process called decatenation. This allows one duplex to pass through the gap in the other. This is essential at the end of DNA replication for separation of daughter DNA molecules and segregation of newly replicated chromosomes.
D) Topoisomerase II exists in two forms, alpha and beta. Beta dissociates more slowly from DNA. Teniposide, another topoisomerase II inhibitor, is more active against the alpha form. Etoposide is 3-4 times less active against the beta form than the alpha.
E) Etoposide stabilizes the cleavable complex of DNA and topoisomerase. There is an accumulation of cells in S and G2 phases. Single and double strand breaks appear in DNA. Topoisomerase II is unable to complete its passage over supercoiled DNA.
F) Resistance is due to P-glycoprotein, lowered concentrations of topoisomerase II, or over expression of the beta form (etoposide less effective against this form).

II. PHARMACOKINETICS

A) Absorption – About half an oral dose is absorbed, although is highly variable. Saturable absorption is achieved at approximately 200 mg per dose.
B) Distribution – Extensively bound (96%) to proteins in the blood. Etoposide achieves CSF concentrations that are 5% of plasma concentrations.
C) Metabolism – 55% metabolized in the liver. Elevation of bilirubin does not imply impaired clearance of etoposide. See dose modification table for dosing recommendations in hepatic impairment.
D) Elimination – 35–40% eliminated in the urine as unchanged drug. Only 6% eliminated through the biliary tree. See dose modification table for dosing recommendations in renal impairment.

III. DOSAGE AND ADMINISTRATION

A) The conventional IV form is poorly soluble in water. Usually it is administered at a concentration of 0.4 mg/mL but can be made more concentrated as needed and if administered soon after compounding. Etoposide is administered over at least 60 minutes.

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–0.4 mg/mL</td>
<td>72 hr</td>
</tr>
<tr>
<td>0.5–0.6 mg/mL</td>
<td>8 hr</td>
</tr>
<tr>
<td>0.7 – 1 mg/mL</td>
<td>2 hr</td>
</tr>
</tbody>
</table>

B) Oral capsules are available (50 mg capsules). The oral dose is twice the IV dose. Oral etoposide can be taken with food. The capsules should be refrigerated.
C) Etoposide phosphate is a different form of etoposide with better aqueous solubility. Dose is the same as conventional etoposide but can be administered over 5 minutes. Upon administration it is converted immediately by plasma phosphatases to parent etoposide.
IV. TOXICITY
   A) Myelosuppression – 25% of patients, onset in 5–15 days, nadir by day 10 in most cases, and recovery by day 24 – 28.
   B) Emesis – mild – moderate. 15% of patients receiving IV etoposide and 50% of patients receiving oral etoposide. Rarely requires ondansetron.
   C) Alopecia– Dose dependent, but most patients do lose their hair.
   D) Mucositis– Usually only at doses used in BMT such as 60 mg/kg
   E) Hypotension, chest pain, flushing, cyanosis, diaphoresis, fever, urticaria, angioedema, or bronchospasm can occur with IV administration. In some studies up to 5–8% of patients develop these symptoms. This reaction is rate related and possibly due to the vehicle Tween 80. The symptoms usually resolve in 5–30 minutes if the infusion is stopped. Subsequent administration should be done at a slower rate with pretreatment with steroids and an antihistamine. Diluting the drug further may help as well.
   F) Secondary AML/MDS (characteristic cytogenetic 11q23 abnormality).

V. CLINICAL MONITORING
   A) Labs – CBC with differential and platelets, SCr, BUN.
   B) Counsel the patient about alopecia and the hypersensitivity reaction described above. Be ready to intervene if the reaction occurs.
   C) Any conversion from IV to PO is mathematically correct to the nearest 50 mg.
TENIPOSIDE (VM-26)
(VUMON®)

I. MECHANISM OF ACTION

A) Teniposide is a cell-cycle specific agent that blocks topoisomerase II activity during G2 phase.
B) Topoisomerase II is part of the cellular scission/reunion reaction need to uncoil and recoil supercoiled DNA. It intentionally causes breaks in DNA to relieve tension and allow DNA to swivel, rotate, and relax.
C) Topoisomerase II separates 2 linked circles of duplex DNA, a process called decatenation. This allows one duplex to pass through the gap in the other. This is essential at the end of DNA replication for separation of daughter DNA molecules and segregation of newly replicated chromosomes.
D) Topoisomerase II exists in two forms, alpha and beta. Beta dissociates more slowly from DNA. Teniposide is more active against the alpha form.
E) Teniposide stabilizes the cleavable complex of DNA and topoisomerase. There is an accumulation of cells in S and G2 phases. Single and double strand breaks appear in DNA. Topoisomerase II is unable to complete its passage over supercoiled DNA.
F) Resistance is due to P-glycoprotein or lowered concentrations of topoisomerase II.

II. PHARMACOKINETICS

A) Absorption – Not available orally.
B) Distribution – Extensively bound (99%) to proteins in the blood. Teniposide achieves CSF concentrations that are 1% of plasma concentrations.
C) Metabolism – 86% metabolized in the liver.
D) Elimination – 40% eliminated in the urine mostly as metabolites. Only 10% eliminated through the stool.

III. DOSAGE AND ADMINISTRATION

A) Stable after compounding for 6 hours only at room temperature.
B) Administer over at least 45 minutes.
C) Manufactured in glass or polyolefin containers. Avoid PVC containers.

IV. TOXICITY

A) Myelosuppression – 65% of patients, onset in 3–14 days, nadir by day 7.
B) Emesis – mild – moderate: 29% of patients. Rarely requires a 5HT3 antagonist.
C) Alopecia – Rare.
D) Hypotension, chest pain, flushing, cyanosis, diaphoresis, fever, urticaria, angioedema, or bronchospasm can occur with IV administration. In some studies up to 5–8% of patients develop these symptoms. This reaction is rate related and possibly due to the vehicle which contains Cremophor EL, a known cause of this syndrome. The symptoms usually resolve in 5–30 minutes if the infusion is stopped. Subsequent administration should be done at a slower rate with pretreatment with steroids and an antihistamine. Diluting the drug further may help as well.
E) Secondary AML.
F) Dermatological-Chemical phlebitis at site of injection.

V. CLINICAL MONITORING: Labs – CBC with differential and platelets, SCr, BUN.

Last Updated on January 15, 2007