Osloda® (Capecitabine)

Category:

Pyrimidine - antimetabolites / Antineoplastic Agent

Pharmacokinetics:

Capecitabine reached peak blood levels in about 1.5 hours (Tmax) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the rate and extent of absorption of capecitabine with mean Cmax decreased by 60%, respectively. The Cmax of 5-FU were also reduced by food by 43% respectively. Food delayed Tmax of both parent and 5-FU by 1.5 hours.

Plasma protein binding of capecitabine and its metabolites is less than 60% and is not concentration-dependent. Capecitabine was primarily bound to human albumin (approximately 35%).

Capecitabine is extensively metabolized enzymatically to 5-FU. The enzyme dihydropyrimidine dehydrogenase hydrogenates 5-FU, the product of capecitabine metabolism, to the much less toxic 5-fluoro-5, 6-dihydro-fluorouracil (FUH_2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureido-propionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine.

Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is recovered in urine. Fecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.

Mechanism of action:

Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by

two different mechanisms. First, FdUMP and the folate cofactor, N^{5-10}-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

Indications:

Colorectal Cancer

- Osloda® is indicated as a single agent for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred.
- Osloda® is indicated as first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred.

Breast Cancer

- Osloda® in combination with docetaxel is indicated for the treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy.
- Osloda® monotherapy is also indicated for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated, eg, patients who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents.

Administration and Dosage:

The recommended dose of Osloda® is 1250 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycles. Osloda® tablets should be swallowed with water within

30 minutes after a meal. In combination with docetaxel, the recommended dose of Osloda® is 1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period, combined with docetaxel at 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks. Pre-medication, according to the docetaxel labeling, should be started prior to docetaxel administration for patients receiving the Osloda® plus docetaxel combination.

Adjuvant treatment in patients with Dukes' C colon cancer is recommended for a total of 6 months, ie, Osloda® 1250 mg/m^2 orally twice daily for 2 weeks followed by a 1-week rest period, given as 3-week cycles for a total of 8 cycles (24 weeks).

Contraindications:

Osolda® is contraindicated in patients with known hypersensitivity to capecitabine or to any of its components. Osolda® is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil. Osolda® is contraindicated in patients with known dihydropyrimidine dehydrogenase (DPD) deficiency. Osolda® is also contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min)

Precautions:

- Cardiotoxicity: The cardiotoxicity observed with Osloda® includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse events may be more common in patients with a prior history of coronary artery disease.
- Dihydropyrimidine Dehydrogenase Deficiency
- Hepatic Insufficiency: Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when Osloda® is administered.
- Hyperbilirubinemia
- Diarrhea: Patients experiencing grade 2 diarrhea (an increase of 4 to 6 stools/day or nocturnal stools) or greater should be instructed to stop taking Osloda® immediately. Standard antidiarrheal treatments (eg, loperamide) are recommended.

- Nausea: Patients experiencing grade 2 nausea (food intake significantly decreased but able to eat intermittently) or greater should be instructed to stop taking Osloda® immediately. Initiation of symptomatic treatment is recommended.
- Vomiting: Patients experiencing grade 2 vomiting (2 to 5 episodes in a 24-hour period) or greater should be instructed to stop taking Osloda® immediately.
- Hand-and-Foot Syndrome: Patients experiencing grade 2 hand-and-foot syndrome (painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patients' activities of daily living) or greater should be instructed to stop taking Osloda® immediately.
- Stomatitis: Patients experiencing grade 2 stomatitis (painful erythema, edema or ulcers of the mouth or tongue, but able to eat) or greater should be instructed to stop taking Osloda® immediately.
- Fever and Neutropenia: Patients who develop a fever of 100.5°F or greater or other evidence of potential infection should be instructed to call their physician.

Pregnancy and breast feeding:

Pregnancy: Category D

Lactation: Because of the potential for serious adverse reactions in nursing infants from capecitabine, it is recommended that nursing be discontinued when receiving Osloda® therapy.

Side effects:

The most common side effects of Osloda® are: hand-and-foot syndrome, diarrhea, nausea, vomiting, sores in the mouth and throat (stomatitis), stomach area pain (abdominal pain), upset stomach, constipation, loss of appetite, and too much water loss from the body (dehydration) (These side effects are more common in patients age 80 and older). Other common side effects are rash; dry, itchy or discolored skin; nail problems; hair loss; tiredness; weakness; dizziness; headache; fever; pain (including chest, back, joint and muscle pain); trouble sleeping; and taste problems.

Drug Interactions:

Antacid: small increase in plasma concentrations of Osloda® and one metabolite (5'-DFCR)**.**

Anticoagulants: Altered coagulation parameters and/or bleeding have been reported in patients taking Osloda® concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon.

CYP2C9 substrates

Phenytoin: The level of phenytoin should be carefully monitored in patients taking Osloda® and phenytoin dose may need to be reduced

Leucovorin: The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by leucovorin.

Packaging:

Osloda® is available as 500 mg F.C tablets in box of 30 tablets.

Storage:

- Store below 30 °C
- Protect from moisture and light
- Keep out of the reach of children