In combination therapy

Severe diarrhoea was observed in 13.1% of patients to follow recommendations for the management of diarrhoea. Of the evaluable cycles, 3.5% have a severe diarrhoea.

Uncounted cases of pseudomembranous colitis have been reported, one of which has been fatal, and in a patient who received irinotecan in combination with 5-FU and leucovorin.

Blood disorders

Neutropenia is a dose-limiting toxic effect. Neutropenia was reversible and not cumulative: the median day to nadir was 8 days whereas the use in monotherapy or combination therapy was not cumulative. RINOWEL contains 100 mg/ml irinotecan, a complex agent with an extensive range of metabolites, some of which may be active, and is not reversible by standard supportive care.

Intravenous administration

Irinotecan is used as a single agent in the management of advanced colorectal cancer. It is also used in combination with other anticancer agents for the treatment of other malignancies, such as non-small cell lung cancer, ovarian cancer, and biliary tract cancer.

Mechanism of Action

Irinotecan is a topoisomerase I inhibitor. It inhibits the activity of topoisomerase I, an enzyme that is responsible for the relaxation of DNA helices during transcription and replication. By inhibiting topoisomerase I, irinotecan prevents the formation of DNA topological defects, which are necessary for the replication and transcription of DNA.

Distribution

Irinotecan is administered intravenously as a 90-minute infusion. After the infusion, irinotecan and its metabolites are distributed throughout the body. Irinotecan is rapidly cleared from the body by renal excretion, with a mean plasma elimination half-life of 3.6 hours.

Elimination

Irinotecan undergoes extensive metabolism by the liver, with about 70% of the administered dose being eliminated as SN-38 and its metabolites through the bile and urine. The main metabolite of irinotecan is SN-38, which is a cytotoxic carboxylic acid that is formed by the metabolic activation of irinotecan.

Stability

Irinotecan is stable in aqueous solutions at neutral pH. In addition, it is stable in the presence of aprotinin, an enzyme that is used to preserve blood samples. Clinical trials have shown that irinotecan is stable at room temperature for up to 6 hours and at 4°C for up to 24 hours.

Precautions

Irinotecan should be administered only by healthcare professionals with experience in cancer chemotherapy. The patient should be monitored closely for clinical signs of toxicity, such as fever, nausea, vomiting, and diarrhea. In case of toxicity, the dose should be reduced or the treatment stopped.

Adverse Reactions

The most common adverse reactions associated with irinotecan therapy are diarrhea, nausea, vomiting, and myelosuppression. Diarrhea is a dose-limiting adverse reaction, and patients should be monitored closely for signs of dehydration. Nausea and vomiting can be managed with antiemetic medication. Myelosuppression, particularly neutropenia, is a significant adverse reaction and can be managed with supportive care.

Pharmacokinetics

Irinotecan is rapidly absorbed following intravenous administration, with a median time to peak plasma concentration of 0.9 hours. The plasma clearance of irinotecan is mainly hepatic, with a mean plasma elimination half-life of 3.6 hours.

Pharmacodynamics

Irinotecan's activity is mediated by the formation of SN-38, which is a potent cytotoxic agent. SN-38 binds to DNA and inhibits DNA synthesis, resulting in cell death.

Irinotecan's pharmacokinetic and pharmacodynamic properties are influenced by a genetic polymorphism in the UGT1A1 gene. Patients with the UGT1A1*7 allele have a reduced capacity to metabolize irinotecan, resulting in higher plasma concentrations of SN-38 and increased toxicity. This polymorphism is associated with a higher risk of severe neutropenia, diarrhea, and other adverse reactions.

Irinotecan exhibits strong potency against colorectal cancer, and it has also demonstrated activity against other solid tumors, including lung cancer, ovarian cancer, and biliary tract cancer. It is an important component of combination therapies for the treatment of advanced colorectal cancer and other malignancies.

This medicinal product can be used in combination with other chemotherapy agents or therapeutic modalities, such as radiation therapy, to enhance the efficacy of treatment and extend survival.

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

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Irinotecan 6 mg/kg/day to rats and rabbits during the period of organogenesis can cause fetal harm when administered to a pregnant woman. Treatment with Irinotecan should be continued until there is an objective response or disease progression. Ambulatory or hospitalized patients who are randomized to receive treatment with Irinotecan and continue to respond should be reevaluated every 3 weeks to determine if the treatment is still necessary. A new cycle of therapy should not begin for 1 to 2 weeks following the last administration of the drug, depending on the patient’s ability to maintain normal performance status and absence of disease progression or unacceptable toxicity. If the dose is reduced because of a lack of efficacy or unacceptable toxicity, subsequent doses of RINOWEL should be reduced accordingly. If the toxic reactions are severe extrapyramidal reactions, at least 1 week prior to starting RINOWEL therapy. Do not administer strong CYP3A4 inhibitors or inducers with RINOWEL with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, ritonavir, saquinavir, telaprevir) or CYP3A4 inducers (e.g., dexamethasone, rifampin) may increase systemic exposure to irinotecan. Inhibitors of CYP3A4 should be avoided if possible. A history of severe adverse reactions to irinotecan has been noted. Patients with irinotecan-hexitol accumulation who may be predisposed to neutralizing effects of irinotecan should be treated with chemotherapy.

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