leukin; ***Fr.:*** Proleukin; ***Ger.:*** Proleukin; ***Gr.:*** Proleukin; ***Hong Kong:*** Proleukin; ***Hung.:*** Proleukin; ***Irl.:*** Proleukin; ***Israel:*** Proleukin; ***Ital.:*** Proleukin; ***Jpn:*** Celeuk; Imunace; ***Mex.:*** Proleukin; ***Neth.:*** Proleukin; ***NZ:*** Proleukin; ***Pol.:*** Proleukin; ***Port.:*** Proleukin; ***Rus.:*** Proleukin (Пролейкин); Roncoleukin (Ронколейкин); ***S.Afr.:*** Chiron IL-2; ***Singapore:*** Proleukin†; ***Spain:*** Proleukin; ***Switz.:*** Proleukin; ***Turk.:*** Proleukin; ***UK:*** Proleukin; ***USA:*** Proleukin.

Ipilimumab *(USAN, rINN)*

Ipilimumabum; MDX-010; MDX-CTA-4. Immunoglobulin G1, anti-(human CTLA-4 (antigen)) (human γ1-chain), disulfide with human κ-chain, dimer.

Ипилимумаб

CAS — 477202-00-9.

Profile

Ipilimumab is an antibody to the cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4), which is a cell surface receptor involved in the downregulation of T-cell activation. Ipilimumab is under investigation for the treatment of melanoma and various solid tumours. Adverse effects include enterocolitis, hypophysitis, dermatitis, arthritis, uveitis, hepatitis, nephritis, and aseptic meningitis.

◊ References.

1. Beck KE, *et al.* Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 2006; **24:** 2283–9.
2. Weber J. Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events. *Oncologist* 2007; **12:** 864–72.

Iratumumab *(USAN, rINN)*

Iratumumabum; MDX-060. Immunoglobulin G1, anti-(tumor necrosis factor ligand superfamily member 8 (CD30 ligand)) (human monoclonal MDX-060 heavy chain), disulfide with human monoclonal MDX-060 light chain, dimer.

Иратумумаб

CAS — 640735-09-7.

Profile

Iratumumab is an anti-CD30 monoclonal antibody that is under investigation for the treatment of Hodgkin's disease. Reported adverse effects include a rise in liver transaminases, and acute respiratory distress syndrome.

Irinotecan Hydrochloride

(BANM, USAN, rINNM)

Camptothecin 11 (irinotecan); CPT-11 (irinotecan); DQ-2805; Hidrocloruro de irinotecán; Irinotécan, Chlorhydrate d'; Irinotecani Hydrochloridum; Irinotekaanihydrokloridi; Irinotekan Hidroklorür; Irinotekanhydroklorid; U-101440E. (+)-7-Ethyl-10-hydroxycamptothecine 10-[1,4′-bipiperidine]-1′-carboxylate hydrochloride trihydrate; (*S*)-4,11-Diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3′,4′:6′,7′]indolizino[1,2-*b*]quinolin-9-yl [1,4′-dipiperidine]-1′-carboxylate hydrochloride trihydrate.

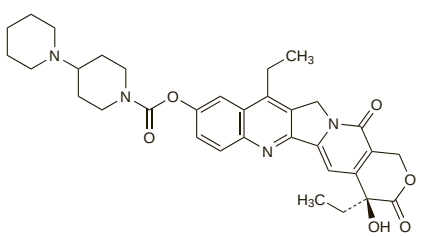
Иринотекана Гидрохлорид

$C_{33}H_{38}N_4O_6,HCl,3H_2O$ = 677.2.

CAS — 97682-44-5 (irinotecan); 136572-09-3 (irinotecan hydrochloride trihydrate).

ATC — L01XX19.

ATC Vet — QL01XX19.



(irinotecan)

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641. Neutropenia and diarrhoea may be dose-limiting in patients given irinotecan. The nadir of the white cell count usually occurs about 8 days after a dose, with recovery by about day 22. Anaemia also occurs and, less commonly, thrombocytopenia. Gastrointestinal disturbances are common: acute diarrhoea, occurring within 24 hours of a dose, may be part of a cholinergic syndrome which can also include sweating, hypersalivation, abdominal cramps, lachrymation, and miosis. These symptoms can be controlled with atropine. However a more severe, prolonged diarrhoea may occur, beginning more than 24 hours after a dose, and can be life-threatening; prompt management with high-dose loperamide and fluid replacement is required (see Effects on the Gastrointestinal Tract, below), and irinotecan treatment should be interrupted and any further doses reduced. Other adverse effects include nausea and vomiting, weakness, alopecia, and skin reactions. Hypertension has occurred rarely during or after infusion. There are rare reports of hypersensitivity reactions, interstitial pneumonia, pneumonitis, intestinal perforation, pancreatitis, muscular contraction or cramps, and paraesthesia.

Irinotecan should not be given to patients with inflammatory bowel disease. The risk of diarrhoea may be increased in the elderly and in patients who have had radiotherapy to the abdomen or pelvis. Radiotherapy also increases the risk of myelosuppression. Blood counts should be monitored weekly and liver function tests should be regularly performed.

Severe toxicity resulting in an increased number of deaths has been reported when irinotecan was given with fluorouracil and folinic acid (see under Interactions, below).

Effects on the gastrointestinal tract. *Acute* diarrhoea occurring as part of a cholinergic syndrome with irinotecan is rarely severe. The syndrome is usually treated or prevented with atropine, but pretreatment with hyoscine butylbromide has also been tried.[1,2] In contrast, *delayed* diarrhoea can be dose-limiting or even fatal in some patients. Standard treatment involves fluid and electrolyte replacement and a high-dose loperamide regimen consisting of 4 mg loperamide immediately after the first loose stool, then 2 mg every 2 hours until 12 hours after the last liquid stool. During the night, the patient may take 4 mg every 4 hours. The high-dose therapy should not be given for more than 48 hours and should never be given prophylactically. Specific recommendations[3] state that if the diarrhoea persists for more than 24 hours despite loperamide therapy, patients should also take an oral fluoroquinolone for 7 days. If the diarrhoea persists for more than 48 hours, patients should be hospitalised for parenteral hydration. Other treatments have been tried, including acetorphan, activated charcoal, budesonide, glutamine, and octreotide.[2,4-9] A regimen of thalidomide with irinotecan has been reported to have a striking lack of gastrointestinal adverse effects such as diarrhoea and nausea.[2,10] However, a pharmacokinetic study found no decrease in gastrointestinal toxicity when these 2 drugs were given together, see Thalidomide, under Interactions, below.

Diarrhoea may be caused by direct intestinal damage due to SN-38, the active metabolite of irinotecan; reduction of intestinal SN-38 concentrations using the poorly absorbed aminoglycoside neomycin as prophylaxis was reported to ameliorate diarrhoea in 6 of 7 patients experiencing this adverse effect.[11]

1. Zampa G, Magnolfi E. Premedication for irinotecan. *J Clin Oncol* 2000; **18:** 237.
2. Yang X, *et al.* Novel agents that potentially inhibit irinotecan-induced diarrhea. *Curr Med Chem* 2005; **12:** 1343–58.
3. Rothenberg ML, *et al.* Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 2001; **19:** 3801–7.
4. Saliba F, *et al.* Pathophysiology and therapy of irinotecan-induced delayed-onset diarrhea in patients with advanced colorectal cancer: a prospective assessment. *J Clin Oncol* 1998; **16:** 2745–51.
5. Lenfers BHM, *et al.* Substantial activity of budesonide in patients with irinotecan (CPT-11) and 5-fluorouracil induced diarrhea and failure of loperamide treatment. *Ann Oncol* 1999; **10:** 1251–3.
6. Savarese D, *et al.* Glutamine for irinotecan diarrhea. *J Clin Oncol* 2000; **18:** 450–1.
7. Ychou M, *et al.* Randomized comparison of prophylactic antidiarrheal treatment versus no prophylactic antidiarrheal treatment in patients receiving CPT-11 (irinotecan) for advanced 5-FU-resistant colorectal cancer: an open-label multicenter phase II study. *Am J Clin Oncol* 2000; **23:** 143–8.
8. Pro B, *et al.* Therapeutic response to octreotide in patients with refractory CPT-11 induced diarrhea. *Invest New Drugs* 2001; **19:** 341–3.
9. Michael M, *et al.* Phase II study of activated charcoal to prevent irinotecan-induced diarrhea. *J Clin Oncol* 2004; **22:** 4410–17.
10. Govindarajan R, *et al.* Effect of thalidomide on gastrointestinal toxic effects of irinotecan. *Lancet* 2000; **356:** 566–7.
11. Kehrer DFS, *et al.* Modulation of irinotecan-induced diarrhea by cotreatment with neomycin in cancer patients. *Clin Cancer Res* 2001; **7:** 1136–41.

Genetic factors. Irinotecan is hydrolysed to SN-38, an active metabolite, which is inactivated by glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes.[1] Genetic variation in the UGT family may affect irinotecan pharmacodynamics. Although UGT1A1*28 polymorphism appears to be only one of several identified causes of altered SN-38 pharmacokinetics,[1,2] it has been strongly associated with the development of severe neutropenia, and genotyping has been proposed as a method of identifying patients at risk of severe toxicity from irinotecan.[3,4] However, genotyping does not predict for all toxicities, and a significant association between the UGT1A1*28 homozygous genotype and diarrhoea has not been proven. Furthermore, a normal UGT1A1 genotype does not ensure lack of toxicity, although the risk is less; the possibility of underdosing in those with the normal genotype may need to be considered.[5] Despite these limitations, it has been suggested that every patient receiving irinotecan for the first time be tested for UGT1A1 genotype.[5]

Licensed product information in the USA states that reduced initial doses should be considered for patients known to be homozygous for the UGT1A1*28 allele; while heterozygous patients may also be at risk, results of studies have been variable and such patients may tolerate normal initial doses of irinotecan. However, the most appropriate dose reduction in the homozygous population is not known. Some have suggested an initial 20% dose reduction, with escalation to full dosage in subsequent courses in the event of little or no toxicity.[5] A prospective study[6] found that the UGT1A1*28 genotype (homozygous or heterozygous) was significantly associated with haematological toxicity, but only during the first cycle of irinotecan-containing chemotherapy. This called into question the need for a dose reduction in irinotecan for patients with this genotype, particularly since homozygous patients showed a trend to improve clinical response. A study in paediatric patients[7] found that, for low-dose, protracted schedules of irinotecan (doses ranged from 15 to 75 mg/m^2 daily, given either intravenously or orally, for 5 days, for 2 consecutive weeks), UGT1A1 genotyping was not a useful prognostic indicator of severe toxicity.

1. Paoluzzi L, *et al.* Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38. *J Clin Pharmacol* 2004; **44:** 854–60.
2. Ramchandani RP, *et al.* The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity. *J Clin Pharmacol* 2007; **47:** 78–86.
3. Innocenti F, *et al.* Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004; **22:** 1382–8.
4. Hahn KK, *et al.* Pharmacogenetics and irinotecan therapy. *Am J Health-Syst Pharm* 2006; **63:** 2211–17.
5. O'Dwyer PJ, Catalano RB. Uridine diphosphate glucuronosyltransferase (UGT) 1A1 and irinotecan: practical pharmacogenomics arrives in cancer therapy. *J Clin Oncol* 2006; **24:** 4534–8.
6. Toffoli G, *et al.* The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 2006; **24:** 3061–8.
7. Stewart CF, *et al.* UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. *J Clin Oncol* 2007; **25:** 2594–2600.

Interactions

Irinotecan is partly metabolised by cytochrome P450 CYP3A isoenzymes. Inducers of this system such as carbamazepine, phenobarbital, or phenytoin reduce exposure to irinotecan and its active metabolite SN-38; use with St John's Wort is contra-indicated. Conversely, inhibitors of this system such as ketoconazole increase exposure to irinotecan and SN-38; use with ketoconazole is contra-indicated.

Antidepressants. In a small, crossover study[1] of cancer patients, use of *St John's wort* during irinotecan therapy was found to decrease plasma concentrations of SN-38, the active metabolite of irinotecan. Myelosuppression was also reduced with this combination. The interaction is thought to be due to the induction of the cytochrome P450 isoenzyme CYP3A4 by St John's wort.

1. Mathijssen RHJ, *et al.* Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 2002; **94:** 1247–9.

Antineoplastics. Although previously reported to be effective, and not associated with excessive toxicity,[1] a regimen of irinotecan with bolus *fluorouracil* and folinic acid was found to be associated with an excess of early deaths in 2 further studies, which were consequently terminated.[2] Deaths were associated with a variety of events including dehydration (due to diarrhoea, nausea, and vomiting), neutropenia, and sepsis. It has been suggested that use of irinotecan with fluorouracil by continuous infusion might be better tolerated,[3,4] and a small study[5] found that the sequence may be important. Irinotecan followed by an infusion of fluorouracil over 48 hours, was associated with less dose-limiting toxicity, and higher maximum tolerated doses, than fluorouracil infusion followed by irinotecan.

Sorafenib may increase systemic exposure to irinotecan.

1. Saltz LB, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; **343:** 905–14.
2. Sargent DJ, *et al.* Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 2001; **345:** 144–5.