Topic 1. Pharmacogenetics of Irinotecan: Scientific and Clinical Impact of UGT Polymorphism

Camptosar (Irinotecan hydrochloride injection) received accelerated approval on June 14, 1996 for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial flurouracil based therapy. Camptosar was subsequently approved as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic colon or rectal cancer. Camptosar is administered as weekly, or biweekly, or once every 3-week dosage schedules. In two clinical trials, irinotecan treatment in combination with 5-fluorouracil and leucovorin significantly increased the median survival, objective tumor response rates, and time to tumor progression of patients with metastatic carcinoma of the colon or rectum. In two multicenter, randomized trials single-agent irinotecan given once-every-three-week dosage schedule significantly increased survival of patients with metastatic colorectal cancer whose disease has recurred or progressed following prior 5-flurouracil therapy.

The most clinically significant adverse events for patients receiving irinotecan-based therapy were diarrhea, neutropenia, nausea, vomiting and alopecia. Irinotecan can induce both early and late forms of diarrhea and requires dose adjustment based on severity of diarrhea. Sepsis related death following severe neutropenia is reported in irinotecan treated patients. Dose adjustment based on neutrophil count is recommend in the label.

Pharmacokinetic studies of irinotecan have shown large inter-individual variability of SN-38 exposure (AUC). SN-38 is an active metabolite of irinotecan and is responsible for the pharmacological and toxic effect of irinotecan. SN-38 is glucuronidated by Uridine diphosphate-glucuronyl transferase enzymes (UGT), predominantly by UGT1A1 isoenzyme. UGT1A1 is a polymorphic enzyme. The TA repeats (5, 6, 7, or 8) in the TATA box of the UGT1A1 promoter region is inversely correlated with gene transcription efficiency and overall enzyme activity. The presence of seven repeats (TA_7) compared to the normal genotype of six (TA_6) repeats results in the variant allele UGT1A1*28. This allele is associated with reduced gene expression and reduced glucuronidation in human liver microsomes. Approximately 10% of the North American population carry the two deficient alleles (homozygous). In the European population[1], the allele frequencies for TA_6 and TA_7 are 0.613 and 0.387.

A prospective study[2] of 66 patients receiving 350 mg/m^2 every 3 weeks showed homozygous TA_7 genotype patients had a relative risk of 9.3 (95% CI, 2.4 to 36.4) for grade 4 neutropenia. Fifty percent (3 out of 6) of the homozygous TA_7 patients had grade 4 neutropenia compared to 12.5% heterozygous $TA_{6/7}$ patients (3 out of 24). No patients with the normal TA_6 genotype (0 out of 29) had any grade 4 neutropenia. SN-38 exposure directly correlated with the UGT1A1 genotype (mean$\pm$S.D: 542 $\pm$ 195, 458 $\pm$ 380, and 336 $\pm$ 168 ng*h/mL for TA_7 homozygous, $TA_{6/7}$ heterozygous, and normal genotype). UGT1A1*28 genotype is associated with 1.8 to 3.9-fold lower SN-38 glucuronidation compared to patients with normal genotype. Pretreatment total bilirubin levels which is

also glucuronidated by UGT1A1 was significantly higher in patients with grade 4 neutropenia compared to those without grade 4 neutropenia. The prevalence of grade 3 diarrhea was only 5% (N=3) and none of the patients with diarrhea was TA_6 genotype. In another study[3] patients receiving combination regimen of irinotecan and 5-fluorouracil, 5 out of 7 patients (71%) with homozygous TA_7 genotype had grade 3 or 4 neutropenia compared to 10% patients (3 out of 31) with normal alleles. The study did not assess the pharmacokinetics of irinotecan. The occurrence of grade 4 diarrhea was not significantly different in TA_7, $TA_{6/7}$, and $TA_{6/6}$ patients. Irinotecan courses had to be postponed in 70% (5 of 7) TA_7 patients compared to 32% (10 of 31) $TA_{6/6}$ patients.

Marcuello[4] et al. reported 40% (4 of 10) colorectal cancer patients with TA_7 genotype receiving irinotecan based therapy had grade 3 or 4 neutropenia compared to 15% patients with normal alleles (6 or 40). This study also reported 70% (7 of 10) TA_7 patients suffered grade 3 or 4 diarrhea compared to 17% (7 of 40) patients with normal alleles. Doses of irinotecan administered in TA_7 patients were 1398 mg/m^2 compared to TA_6 patients receiving 1725 mg/m^2 dose.

In a Phase 2 study[5], weekly regimen of irinotecan/docetaxel in previously treated non-small cell lung cancer patients (N= 51) did not show any correlation between UGT1A1 genotype and toxicity. The incidences of grade 3 and 4 hematologic toxicity and diarrhea were 10% and 25%, respectively.

A small prospective pilot study[6] of 20 patients and a retrospective analysis[7] of 118 patients also indicated a higher risk for neutropenia for TA_7 homozygous genotype patients.

The Agency appreciates the Clinical Pharmacology Subcommittee's advice on the scientific and clinical perspectives of the information regarding the association between irinotecan toxicity and UGT1A1*28.

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