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Notes

Dr. Laderoute has a licensing agreement with Chemicon International, Inc., for the production and sales of the 167H1 and 167H4 monoclonal antibodies to the alpha-fetoprotein receptor/alpha-
fetoprotein binding protein, for which she receives royalties.

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Re: Irinotecan (CPT-11) and Characteristic Mucosal Changes in the Mouse Ileum and Cecum

Ikuno et al. (1) have recently com-
pared the effects of irinotecan (CPT-11) and cisplatin (CDDP) on the intestinal tract of mice. The conclusion was that characteristic microscopic changes in-
duced by CPT-11 consisted of epithelial vacuolation and apoptosis in the ileum and goblet cell hyperplasia in the cecum, while microscopic changes noted in the CDDP-treated mice were characterized by diffuse intestinal mucosal damage (crypt destruction and villous atrophy). The authors went on to suggest that, since different structural changes were observed with CPT-11 and CDDP, different pathogenetic mechanisms were responsible for the clinically observed diarrheas.

The above conclusions have raised some important questions we would like to address. Specifically, although “marked shortening of the (intestinal) villi” (villous atrophy) in CPT-11-
treated mice was mentioned in the text and nicely illustrated in the photomicro-
graphs, it was not reported in the abstract or discussion, did not appear in the legends of the photomicrographs, and was never taken into account to ex-
plain the mechanism of diarrhea. Furthermore, although the photomicro-
graphs demonstrate similar degrees of villous atrophy in CPT-11- and CDDP-
treated mice, this microscopic finding was considered to be the cause of diar-
rhea only in CDDP-treated mice. In a study conducted at our research facility, we similarly observed marked villous atrophy in the small intestine of CPT-
11-treated mice. We believe that villous atrophy following crypt destruction is the primary lesion and the main cause of diarrhea in mice, while vacuolation of epithelial cells lining atrophic intestinal villi can be regarded as a secondary lesion of little specific pathogenetic sig-
nificance. As for the cecal changes, we did not observe goblet cell hyperplasia in our study and, in any case, we do not feel this finding is of primary pathogenetic significance in the study presented in the report.

In conclusion, we think that the intes-
tinal lesions induced by both CPT-11 and CDDP are compatible with the “radiomimetic lesions” expected with antineoplastic compounds, i.e., villous atrophy secondary to crypt damage. Since the lesions induced by both CPT-
11 and CDDP were essentially similar, it was unclear why different mech-
anism of induction of diarrhea were proposed by Ikuno et al.

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Notes

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Response

We appreciate your interest in and comments on our report regarding the mechanisms of irinotecan (CPT-11)-in-
duced diarrhea in mice. As reported, we observed two characteristic changes in the mucosa of the intestine of CPT-11-
treated mice, which probably induced diarrhea by malabsorption and hyper-
secretion of mucin. In reply to your comments, two points should be con-
sidered: 1) usually, diarrhea is caused by malabsorption and/or hypersecretion (J) and 2) different strains of mice and rats appear to have different suscep-
tibilities for CPT-11-induced diarrhea. For example, we have observed CPT-
11-induced diarrhea in Slc:SD, F344/N Slc, and Slc:Wistar/St rats, but not in Slc:Wistar, Crj:CD(SD), F344/DuCrj, and F344/Jcl rats (Oka M, et al.: un-
published results).

As you pointed out, the degree of vil-
loous atrophy in the small intestine of CPT-11-treated mice was similar to that in cisplatin (CDDP)-treated mice, but the distributions were different. The vil-
loous atrophy alone may induce diarrhea in CPT-11-treated mice as well as in CDDP-treated mice. However, the vacuolation of absorptive epithelial cells in the ileum of CPT-11-treated mice was due to apoptosis but not to the destruction of crypt cells and led to malabsorption. In addition, the changes in the colonic mucosa of CPT-11-
treated mice were minimal compared with those in CDDP-treated mice. Thus, malabsorption in CPT-11-treated mice is thought to be caused by villous atrophy following crypt damage and apoptosis of absorptive cells in the small intestine.

Interestingly, we observed goblet cell hyperplasia with excessive production of sulfomucin in the cecum that could be another major cause in CPT-11-in-
duced diarrhea. Since several in vitro studies (2-7) clearly demonstrated dif-
ferentiation-inducing activity of CPT-
11, we believe that similar activity could be induced by a low concentration of CPT-11 in the intestine in vivo. Con-
versely, to our knowledge, there is no evidence that CDDP has differentiation-
inducing activity in vitro or in vivo. As clearly shown in our study (8), the