

NCCN Guideline Recommendation

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NCCN Guideline Panel: Colon/Rectal/Anal Cancer

I respectfully request the NCCN Panel for Rectal Cancer review the enclosed data for inclusion in the initial diagnostic evaluation of patients preparing to receive treatment with a fluoropyrimidine.

Specific Changes: Revise the guidelines to recommend pre-screening of patients using a “functional” test that measures the dihydrouracil/uracil ratio to identify individuals with impaired dihydropyrimidine dehydrogenase (DPD) activity for whom the fluoropyrimidine dosage should be reduced to avoid severe toxic reactions; treatments should also rely upon pharmacokinetic follow-up to indicate more precisely recommended dosage levels.

FDA Clearance: *not applicable*

Rationale: Pre-screening of patients for impaired DPD activity (due to genetic and non-genetic factors) will improve patient care, treatment efficacy, and significantly reduce grade 3 and 4 toxic reactions and fatalities that occur much more frequently than common treatment practices acknowledge (instances of severe toxicity range from 10-40%).

The following articles are submitted to support this proposed change: These studies show that severe reactions are far from rare (estimated 500-1000 fatalities/year in the US) and demonstrate that pre-treatment screening and dose management of fluoropyrimidine can effectively reduce the incidence of severe toxic and fatal reactions.

Zhu, Andrew; Puchalski, Thomas; et al. Dihydropyrimidine Dehydrogenase and Thymidylate Synthase Polymorphisms and Their Association with 5-Fluorouracil/Leucovorin Chemotherapy in Colorectal Cancer, *Clinical Colorectal Cancer*, 2004 (Vol 3, No. 4): 225-234. This paper indicates that toxicity is not a rare condition: 15-20% suffer grade 3, 3-10% grade 4 toxic reactions to 5-FU treatment; between 500-1000 US patients die annually due to 5-FU toxicity.

Caudle, KE; Diasio, RB; et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing, *Clinical Pharmacology & Therapeutics*, (29 August 2013), doi:10.1038/clpt.2013.172. This study reports 10-40% of patients with 5-FU suffer severe and sometimes life threatening toxic reactions and recommends starting dosage at 50%, in order to minimize toxicities, followed by an assessment of the patient's tolerance before increasing dose levels.

Ciccolini, Joseph; Mercier, Cedric; et al. Routine Dihydropyrimidine Dehydrogenase Testing for Anticipating 5-Fluorouracil-Related Severe Toxicities: Hype or Hope?, *Clinical Colorectal Cancer*, 2010 (Vol 9, No. 4): 224-228. This study indicates non-genetic factors may lower DPD levels and put patients at risk; it reports that functional techniques (uracil/dihydrouracil plasma tests and uracil breath tests) are available to identify patients who have a limited ability to metabolize 5-FU; and it asserts that pre-screening and dose tailoring systematically improved clinical outcomes of 5-FU patients.

Piper, Margaret; Aronson, Naomi; et al. Pharmacogenetic Testing to Predict Serious Toxicity From 5-Fluorouracil (5-FU) for Patients Administered 5-FU-Based Chemotherapy for Cancer, *Technology Evaluation Center, Assessment Program* Vol 24, No. 13, Aug 2010. This study reports 30% of patients receiving this treatment regimen suffer severe toxic reactions; genetic testing has poor predictive value.

Saif, M. Wasif, et al. Pharmacokinetically Guided Dose Adjustment of 5-Fluorouracil: A Rational Approach to Improving Therapeutic Outcomes, *Journal National Cancer Institute*, 2009, 101: 1543-1552. The authors offer that dose management may lead to substantial costs savings and better patient outcomes.

Gamelin, Erick, et al. Individual Fluorouracil Dose Adjustment Based on Pharmacokinetic Follow-up Compared With Conventional Dosage: Results of a Multi-Center Randomized Trial of Patients With Metastatic Colorectal Cancer, *Journal of Clinical Oncology*, 2008, 26: 2099-2105. This study found that plasma-level measurements of 5-FU is the optimal means of minimizing toxicity while ensuring the proper dose intensity; it also offered that this practice can be easily integrated into clinical practice.