NCCN Guideline Recommendation

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NCCN Guideline Panel: Colon/Rectal/Anal Cancer

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

Specific Changes: Revise the guidelines to recommend:

1. A preliminary functional testing for DPD activity, if available.
2. If not: A lower initial dosage, i.e. reduced by 50% with a close monitoring of the tolerance (i.e., neutropenia),
3. Followed by a pharmacokinetic assessment of the patient's clearance rate of 5-FU, and
4. If required, an adjustment of subsequent doses, based on test results, to achieve the targeted therapeutic window for 5-FU.

FDA Clearance: *not applicable*

Rationale: Genetic conditions alone fail to explain the 30% rate of severe toxic reactions (Grades 3-5) and 0.5-3% of fatal outcomes repeatedly associated with the use of fluoropyrimidines. Genetic testing is an unreliable predictor of a patient's risk exposure (see Piper et al., and Ciccolini et al.); pharmacokinetic testing (a.k.a. Test Dose approach), when combined with dose management techniques serve to detect a patient's clearance of 5-FU and identify the dosage required to achieve optimal drug efficacy. A reduced initial dosage followed by an assessment of the patient's clearance of the chemo agent can serve to minimize the risk of severe toxic reaction while achieving improved treatment efficacy (see Caudle et al. and Gamelin et al.).

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; see Zhu et al.), that the rate of severe toxicities is far greater than the genetic DPD deficiency rates should predict (see Piper et al., and Ciccolini et al.) and demonstrate that testing and dose management of fluoropyrimidine can effectively reduce the incidence of severe toxic and fatal reactions thereby improving outcomes and reducing treatment costs.

NCCN Guideline Panel: Colon/Rectal/Anal Cancer, continued

Caudle, KE; Diasio, RB; et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoroupyrimidine 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 or decreasing dose levels (pharmacokinetic guided dose adjustment if available).

Piper, M; Aronson, N; et al. Pharmacogenetic Testing to Predict Serious Toxicity From 5-Fluorouracil (5-FU) for Patients Administered 5-FU-Based Chemotherapy for Cancer, *Blue Cross/Blue Shield 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 pharmacokinetic based, not pharmacogenetic, dose management leads to substantial costs savings (70% reduction) and better patient outcomes.

Zhu, A; Puchalski, T; 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.

Ciccolini, J; Mercier, C; 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.

Gamelin, E, 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.

Sincerely,
Kenneth E. Surprenant