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NCCN Guidelines Panel: Myeloid Growth Factors

On behalf of Oncology Analytics, Inc., I respectfully request the NCCN® Myeloid Growth Factors Panel to review the below submission for the re-classification of the febrile neutropenia risk of 5-fluorouracil, oxaliplatin, leucovorin (FOLFOX) in the NCCN Guidelines for myeloid growth factors.

Specific Changes:

We respectfully request in the NCCN® Guidelines for Myeloid Growth Factors on page MGA-A (2 of 4), specifying FOLFOX as FOLFOX4 listed under “intermediate risk (10%-20%) febrile neutropenia” considering FOLFOX6 and variations of FOLFOX6 have a low risk (<10%) febrile neutropenia.

FDA:

The FDA-approved prescribing information for ELOXATIN (oxaliplatin) states the following: “The incidence of febrile neutropenia in the previously treated patients was 1% in the 5-fluorouracil/leucovorin arm and 6% (less than 1% of cycles) in the ELOXATIN (oxaliplatin) and 5-fluorouracil/leucovorin combination arm...in adjuvant patients the incidence of either febrile neutropenia (0.7%) or documented infection with concomitant grade 3/4 neutropenia (1.1%) was 1.8% in the ELOXATIN and 5-fluorouracil/leucovorin arm.”¹

Rationale:

The NCCN Myeloid Growth Factor Guidelines currently lists FOLFOX as a chemotherapy regimen with an intermediate risk for febrile neutropenia. Please note, only FOLFOX4 has an intermediate risk for febrile neutropenia. In a study evaluating the efficacy of adjuvant treatment with FOLFOX6 in colorectal cancer, the incidence of Grade 3/4 febrile neutropenia was 1.8 %.² Another study evaluating the use of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer, resulted in a febrile neutropenia risk of 1.2% and 1.6% respectively.³ In the published clinical trial showing the effect of FOLFOX6 with or without cetuximab in patients with resected stage III colon cancer, the incidence of febrile neutropenia was 2.4% and 1.2% respectively.⁴ The median febrile neutropenia rate reported in clinical trials evaluating FOLFOX6 for the treatment of colorectal cancer is 1.2%.²⁻⁴

Categorizing FOLFOX6 as a chemotherapy regimen with an intermediate risk of febrile neutropenia implies the use of granulocyte colony-stimulating growth factors (G-CSFs) may be necessary as primary prophylaxis. The Infectious Diseases Society of America (IDSA) Fever and Neutropenia Guidelines state that prophylactic use of granulocyte colony-stimulating growth factors (including pegfilgrastim), should be considered in patients with an anticipated high ($\geq 20\%$) risk of febrile neutropenia. This guideline states that if the risk of febrile neutropenia is low (<10%), the benefit of using growth factors such as pegfilgrastim is low and generally not recommended.⁵ In addition, the FDA package insert for pegfilgrastim states, “Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.”⁶ Based on the method of administration of FOLFOX6, pegfilgrastim must be administered within 10 days of the next cycle of chemotherapy. Based on the pharmacokinetics of

pegfilgrastim, some patients will receive chemotherapy while the bone marrow is hyper-stimulated. This may cause short term, and potentially, long term harm to the bone marrow.

Also, the use of G-CSF for the management of patients receiving chemotherapy associated with a low risk of febrile neutropenia exposes the patient to unnecessary adverse effects and an unnecessary financial burden.

To date, no new data has been published reporting febrile neutropenia rates for FOLFOX6 or variations of the FOLFOX6 regimen that would classify it as anything other than low risk of febrile neutropenia. To align with recommendations from evidence-based guidelines such as IDSA and published clinical trial studies, we respectfully request the NCCN Myeloid Growth Factors Panel to revise the classification of FOLFOX6 chemotherapy regimen to low risk febrile neutropenia.

Literature support:

1. Eloxatin [package insert]. Sanofi-Aventis, LLC. Bridgewater, NJ. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021759s012lbl.pdf
2. André T, Boni C, et. al.; Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350(23):2343-51.
3. Allegra CJ, Yothers G, et al. Initial safety report of NSABP C-08: A randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer. J Clin Oncol. 2009;27(20):3385-90.
4. Alberts SR, Sargent DJ, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA. 2012;307(13):1383-93.
5. Freifeld AG, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. CID. 2011;52(4): e56-e93.
6. Neulasta [package insert]. Amgen, Inc. Thousand Oaks, CA. Available at: https://www.pi.amgen.com/~media/amgen/repositorysites/pi-amgen-com/neulasta/neulasta_pi_hcp_english.ashx

Thank you for your time and consideration of our request. Please do not hesitate to contact me should the panel have any questions.

Sincerely,



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