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Commentary: Do Guidelines Influence Physician Practice Behavior? The Experience With Erythropoiesis-Stimulating Agents

By Marcus Neubauer, MD, Roy A. Beveridge, MD, and Michael Kolodziej, MD

Most oncologists have grown tired of the issue of erythropoiesis-stimulating agents (ESAs). The contentious debate over appropriate use of these agents in chemotherapy-induced anemia, the national coverage decision (NCD) of the Centers for Medicare and Medicaid Services, and finally the US Food and Drug Administration (FDA) label changes have led to dramatic changes in how these agents are used in clinical practice. This journey has not been a pleasant one. Was it necessary? Could adherence to evidence-based guidelines have provided the necessary discipline to ensure appropriate prescribing to optimize outcomes? In this issue of *Journal of Oncology Practice*, Naeim et al¹ report on community physician adherence to published guidelines with respect to ESA use and conclude that 75% of patients were treated according to these guidelines, which antedated the NCD, the revised American Society of Hematology/ASCO guidelines,² and certainly the new FDA label. Although this conclusion seems encouraging, a more rigorous look at the study design and data suggests that community physicians actually did not perform that well.

Naeim et al¹ performed a retrospective review of clinical practices (83 health care providers in 47 sites throughout the United States) willing to undergo an educational intervention program to enhance adherence to anemia and neutropenia

treatment guidelines (the EDUCATE [Educating Clinicians to Achieve Treatment Guideline Effectiveness] program). The report focuses on baseline prescribing characteristics before intervention. The groups selected had to have sufficient patient volume and could not have in place a practice-wide system regulating ESA or colony-stimulating factor use. More than 4,000 providers were initially approached; thus, this was a highly selected group of providers. From these practices, 2,874 patients were deemed eligible for analysis. Baseline clinical features of these patients were representative of patients receiving chemotherapy in the community, with almost 75% having breast, colon, or lung cancer.

Appropriate use of ESAs was adjudicated on the basis of adherence to EDUCATE guidelines, which recommend treatment with ESAs when hemoglobin (Hb) levels are less than 11 g/dL or when Hb levels are from 11 to 12 g/dL but symptoms of anemia or risk factors for symptomatic anemia are present. The study also required a proximate Hb measurement (Hb measured within 14 to 21 days of—but not before—administration of ESA dose). Unfortunately, within the group in which treatment was recommended by guidelines, fewer than half of patients (only 45%) were treated correctly. Among patients treated incorrectly, almost half the time the error was initiation without a proximate

Hb measurement. Closer study of the group with Hb levels of 11 to 12 g/dL, in which clinical factors were important, shows that patients with no symptoms or risk factors still received ESA therapy almost 30% of the time. Thankfully, in the group of patients whose Hb levels were never less than 12 g/dL, only 5% incorrectly received ESAs. These are not results of which to be particularly proud.

Perhaps the most damaging criticism of the study is that the guidelines proposed bear little or no relationship to the guidelines currently considered authoritative. Both the 2002 and 2007 American Society of Hematology/ASCO guidelines on ESAs clearly recommend use of ESAs when Hb levels are 10 g/dL or less and reliance on clinical judgment when levels are from 10 to 12 g/dL. In the 2007 guidelines, appropriate clinical scenarios are more precisely defined. Without question, few of the patients in the current study had Hb levels less than 10 g/dL at initiation, and origin of the trigger of the Hb value of 11 g/dL was not defined. Under the current NCD and FDA label, few or none of the patients treated in this study would be treated today. This question of who formulates guidelines has suddenly become the most critical question in defining the value of guidelines. Self-serving, non-evidence-based, inappropriately influenced, nontransparent guidelines are not worth the paper on which they are written.

This is the messy world in which the ESA debate is occurring. The label and coverage changes that have resulted from this debate should serve as examples of how not to conduct dialogue that determines optimal, evidence-driven patient care. The debate has degenerated into the inappropriate characterization of physicians as profit mongers, sensitive to their wallets but insensitive to best patient outcomes, and of government regulatory agencies as inflexible, out-of-touch bullies only interested in the price tag. There is plenty of blame to go around. The current buy-and-bill reimbursement model, which includes volume-based discounts and rebates, provides perverse incentives to practitioners. Aggressive marketing and direct-to-consumer advertising have created an unhealthy appetite. Pharmacovigilance studies mandated by the FDA have been poorly planned and executed. Dialogue regarding evidence has been neither open nor balanced on either side. And at the end of the day, policies have been adopted that have embittered many. Have we learned from this process so that it will not happen again?

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It is entirely possible, perhaps even plausible, as suggested by the recently published Cochrane meta-analysis,³ that use of ESAs is associated with increased mortality in patients with cancer. But the sad fact is that given what has just transpired, we may well never know the truth about which patients benefit from ESAs and which patients do not; just as important, we may never know why. This is unfair to our patients. Responsible guideline formulation, performed on the basis of a thorough and transparent evidence review process supplemented by appropriate clinical trials that have well-documented and reported outcomes, is something our patients expect and deserve. We believe oncologists can deliver.

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Marcus Neubauer, MD, is a medical oncologist with Kansas City Cancer Center, Overland Park, KS. He is a member of US Oncology's Pharmacy and Therapeutics Executive Committee, and he is Chair of US Oncology's Medical Oncology Pathways Program. Contact him at marcus.neubauer@usoncology.com.

Roy A. Beveridge, MD, is an oncologist with Fairfax Northern Virginia Hematology Oncology and Co-Director of Stem Cell Transplant, Inova Fairfax Hospital, Fairfax, VA, and Medical Director for US Oncology, The Woodlands, TX. Contact him at roy.beveridge@usoncology.com.

Michael Kolodziej, MD, is an oncologist with New York Oncology Hematology, New York, NY. He is Chief of Oncology at St Peter's Hospital, New York, NY, and Medical Director for Oncology Services and Chairman of the Pharmacy and Therapeutics Committee for US Oncology. Contact him at michael.kolodziej@usoncology.com.

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