

# Oncologists Cautioned About Use of ESAs

By Caroline Helwick

Oncologists have been experiencing “withdrawal symptoms” since the US Food and Drug Administration (FDA) issued a “black box” warning for erythropoiesis-stimulating agents (ESAs), which were associated with adverse outcomes in recent clinical trials. At the recent American Society of Clinical Oncology annual meeting, experts urged caution in prescribing ESAs. Clinicians should understand the mechanism of action of ESAs and prescribe them only for symptomatic patients, several speakers said.

ESAs have been shown to reduce the need for blood transfusions in patients with anemia who are undergoing chemotherapy for nonmyeloid malignancies, but adverse outcomes have been associated with rapid increases in hemoglobin levels and attainment of high-target hemoglobin, said Fadlo Raja Khuri, MD, of Emory University, Atlanta.

ESAs should be prescribed according to strict evidence-based criteria on a case-by-case basis, he said, noting that although these agents were approved to relieve chemotherapy-related fatigue, they have not been proved to improve quality of life (QOL). Early trials suggested they might, but the methodology for QOL issues was still evolving, he said. Moreover, early trials were not powered to measure trends in survival, nor were these included as primary end points. Evidence for worsened survival began to emerge in 2003.

A Cochran meta-analysis of 57 randomized controlled trials using either epoetin alfa (Epogen, Procrit) or darbepoetin alfa (Aransep), totaling 9353 patients, found a lower risk of transfusion, increased relative risk of thromboembolic events, and a possible decrement in survival.

## Regulatory Action

In March, the FDA Oncologic Drugs Advisory Committee voted 13 to 1 that there is benefit to using ESAs for chemotherapy-induced anemia, but that caution was necessary. The FDA issued a safety advisory and added a “black box” warning to the labeling.

The warning reiterated that ESAs shortened overall survival and/or time to progression when dosed to a target hemoglobin of  $\geq 12$  g/dL for patients with breast, head and neck, lymphoid, and cervical cancers. This does not exclude the potential risk at lower hemoglobin levels; therefore, the drugs should be dosed as low

as possible to avoid red blood cell transfusions. The FDA advised that ESAs should only be used to treat anemia and should be discontinued after chemotherapy is completed.

## Emerging Evidence

Dr Khuri noted that no ESA is indicated for active malignant disease without concurrent chemotherapy or radiotherapy; the American Society of Cytopathology practice guidelines call for treatment when hemoglobin is  $\leq 10$  g/dL.

Studies are underway to elucidate the mechanisms underlying the recent trial conclusions. Evidence is emerging that tumor cells may use the erythropoietin system for growth and increased survival in certain tumor types, said Dr Khuri.

Anthony Blau, MD, of the University of Washington, Seattle, reported retrospective findings from the ENHANCE (Erythropoetin in Head and Neck Cancer) study, which was the first phase 3 study suggesting ESAs have an adverse effect on survival. The study included 351 patients with head and neck cancer undergoing surgical resection and/or radiotherapy, with or without erythropoietin alfa or placebo. Investigators examined tumor samples from 136 patients for messenger ribonucleic acid (mRNA) levels in the erythropoietin receptor and other signaling molecules, and were blinded as to patient outcome.

For the population as a whole, erythropoietin mRNA levels had no association with outcome; however, among patients who had radiation alone, without surgical resection, the level of the receptor was important.

“Patients with levels of the erythropoietin receptor mRNA above the median had a significantly poorer outcome if they were randomized to erythropoietin rather than placebo,” Dr Blau reported. “We did not see this in patients whose tumor had below-median levels.” They hope to confirm these preliminary findings in tumors from other phase 3 trials. “We may eventually have a predictive test for susceptibility for tumor progression with ESA treatment,” he added.

Julie Gralow, MD, also of the University of Washington, commented, “These preliminary findings... may mean that we can use ESAs in a targeted way to offer benefit when we think they will be safe.” ■