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How safe are erythropoiesis-stimulating agents?

THE YEAR 2007 was a rough one for erythropoiesis-stimulating agents (ESAs). Increasing concerns about their safety were raised in important meta-analyses of previously published data, specifically, the possibility that these agents increase the risk of venous thromboembolic phenomena and shorten survival. These trends were seen primarily in studies of cancer patients.¹ Meanwhile, front-page headlines in *The New York Times* were unkind: “Doctors reaping millions for use of anemia drugs.”² However, the signals came earlier than 2007.

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■ THE RISE AND POSSIBLE FALL OF ESAs

1989—These costly drugs are introduced and start their ascent to becoming one of the most widely used drug classes, helped along by direct-to-consumer advertising. (In one ad, Grandpa can run after the grandchildren despite being on chemotherapy because he uses erythropoietin!)

2001—A study declares that the higher the hemoglobin level rises in response to ESAs, the better the quality of life. It also hints that these agents improve survival.³

2002—The American Society of Hematology/American Society of Clinical Oncology Practice Guideline Writing Committee reviews the medical literature, performs a systematic review, and recommends that patients with low-risk myelodysplasia and those on chemotherapy who

become anemic (with a hemoglobin level approaching 10 g/dL) have the option of receiving ESAs to raise their hemoglobin and decrease the need for transfusion.⁴

2003—Henke et al⁵ report that anemic patients with head and neck cancer who underwent radiotherapy and received erythropoietin in a randomized study had poorer survival and progression-free survival.

2005—Leyland-Jones et al,⁶ in another randomized study, report that patients with metastatic breast cancer receiving first-line chemotherapy (most of whom were not anemic) had a higher mortality rate if they received epoetin alfa.

2006—The guideline authors meet again to start the process of writing an update. A meta-analysis shows the thromboembolic risk and survival problems in a more systematic way, covering multiple studies.⁷

2007—The Centers for Medicare and Medicaid Services cuts back the reimbursement for the use of erythropoietin. The US Food and Drug Administration (FDA) publishes a black box warning suggesting that any hemoglobin level greater than 12 g/dL would be detrimental to a patient. The Guideline Writing Committee works on its document with this backdrop of turmoil.

2008—The updated guidelines are published. They recommend continuing to use ESAs for patients with low-risk myelodysplasia, and as an option to raise hemoglobin levels and prevent the need for transfusion in cancer patients undergoing chemotherapy whose hemoglobin level falls to 10 g/dL or less.⁸ The document includes stronger language against the use of ESAs in patients with anemia from cancer who are not undergoing

Preliminary data suggest some tumors have erythropoietin receptors on their surface

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chemotherapy. Meanwhile, some editorialists have suggested that it may be time to abandon ESAs because these drugs may promote more rapid tumor growth or pose a prohibitive risk of thromboembolic disease.^{9,10}

In mid-March 2008, after reviewing the most recent data, an FDA panel calls for new limits on the use of ESAs: cancer patients who are undergoing treatment that could cure their cancer should not receive them, and neither should patients with advanced breast cancer or head and neck cancer. Furthermore, the FDA panel stipulates that when doctors do prescribe these drugs, they should warn patients of the possible dangers and seek their informed consent.

■ WHAT HAPPENS NOW?

Will the FDA take ESAs off the market? That is unlikely. Nephrologists need these drugs to avoid the need for transfusion in dialysis patients (see the accompanying article by Drs. Demirjian and Nurko on the use of ESAs in patients with chronic kidney disease on page 353 of this issue of the *Journal*). Some of the very first signals of harm with raising the hemoglobin too high came from the nephrology field.

Hematologists should still have the option of using ESAs in some settings, particularly in

patients with low-risk myelodysplasia who are becoming more and more anemic and in those who have comorbid conditions in which lower hemoglobin levels are unsafe, particularly if they have coronary artery disease. They also should still be able to use ESAs for selected patients who develop severe chemotherapy-induced anemia and who become so weakened from their anemic state that their life and quality of life are threatened. If ESAs are taken away from the formulary of hematologists and oncologists, these specialists will rely on transfusions to treat their anemic patients, whether the anemia be due to myelodysplasia or to chemotherapy. Some say that the blood supply is so safe that we should not have the same worries about using blood transfusions as we did in the late 1980s. However, we all have seen patients who adamantly do not want transfusions.

Certainly, more events will transpire in the next year with the ESAs. There will probably be more data on erythropoietin receptors on the surface of tumor cells and what happens when pharmacologic doses of erythropoietin interact with these receptors. Patient-specific meta-analyses will probably shed more light on individual patients' risk of thromboembolic disease and early death from the use of these agents.

The ESA story is far from over. ■

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It is unknown what impact ESAs have on the growth of these tumor cells