ANEMIA DRUG MAY IMPAIR TUMOR CONTROL DURING RADIATION

A multicenter European study published in The Lancet (2003;362:1255–1260) suggests that giving some patients erythropoietin during radiotherapy may actually impair tumor control, rather than increase the effectiveness of radiation.

Experts said the results are unlikely to change the current US practice of administering erythropoietin only for the treatment of anemia. But the study raises some important questions about what many consider a potentially promising new application for this widely used drug.

“It’s a very disappointing result,” said Jerome Seidenfeld, PhD, associate director of the Technology Evaluation Center of the Blue Cross and Blue Shield Association, who helped compile guidelines for epoetin use published by the American Society of Clinical Oncology. “The take-home lesson is that it demonstrates why, before new interventions diffuse into clinical practice, it’s very important to test even the most widely believed hypotheses.”

Because radiation is more effective against cells with high oxygen concentrations, many researchers have theorized that raising hemoglobin levels to improve tumor oxygenation would also improve the outcome of radiotherapy. In the new study, however, the opposite happened.

Researchers led by Michael Henke, MD, of the University of Freiburg in Germany found that head and neck cancer patients who were given epoetin-beta during radiotherapy fared worse in terms of tumor control and survival than those given a placebo.

“Despite a reliable rise in hemoglobin concentrations, we saw no benefit for locoregional progression-free survival, locoregional progression, or survival,” Henke wrote.

The study compared 351 patients who began receiving either epoetin-beta or a placebo about two weeks before radiotherapy began, and continued the treatment throughout the course of radiation. Median hemoglobin levels at baseline were close to 12 g/dL, with upper levels exceeding 14 g/dL. Treatment was continued until hemoglobin concentrations exceeded 14 g/dL for women and 15 g/dL in men. Epoetin was given three times weekly at a dosage of 300 IU/kg.

Erythropoietin may reduce benefit of head and neck radiotherapy. Many lung patients believe surgery will cause cancer to spread. Letrozole lowers breast cancer recurrence rate after tamoxifen.
Although more patients who received erythropoietin reached target hemoglobin levels, these patients had worse outcomes in locoregional tumor progression (relative risk 1.69), locoregional progression-free survival (relative risk 1.62), and survival (relative risk 1.39) in intention to treat analyses. The trend was similar when the researchers analyzed patients according to those who did not have violations of radiotherapy protocol or overall study protocol, although those results did not reach statistical significance. The difference in locoregional progression-free survival was limited to patients receiving either postoperative radiation of incompletely resected disease or primary definitive radiotherapy; erythropoietin had no apparent effect on outcomes of patients who received postoperative radiation after complete surgical resection.

The study raises many important questions, however. Might the negative effect on tumor control also apply to patients receiving erythropoietin in conjunction with chemotherapy? Would patients with different types of cancer show similar results? Is the impairment of tumor control related to the drug itself, or to the levels of hemoglobin attained in the study? More research is needed to make those determinations.

“I think one should always interpret a single clinical trial in just that light: It’s a single clinical trial,” said Douglas Rizzo, MD, an associate professor of medicine at the Medical College of Wisconsin and another member of the ASCO epoetin committee.

He noted that some aspects of the trial, particularly the large number of patients whose treatment was not in line with protocol (214 patients were available for the per-protocol analysis), may affect the interpretation of its results. In addition, many patients in this trial had hemoglobin levels higher than what US doctors generally use as a guide to determine who should get erythropoietin.

Rizzo suggested it was premature to generalize the results of this study to patients with other cancer types or those receiving chemotherapy, and mentioned a 1993 ASCO abstract that reported erythropoietin improved one- and two-year relapse-free survival in cervical cancer patients treated with adjuvant chemotherapy and radiotherapy (Blohmer JU, Wurschmidt F, Petry U, et al. Proc Am Soc Clin Oncol. 2003;22:447. Abstract 1798.)

“I don’t know that this should substantially change practice for patients with substantial fatigue and low hemoglobin,” he said. Rizzo added that nevertheless, the study findings might give some doctors pause, particularly if they’re using erythropoietin to augment radiotherapy response, as opposed to strictly for alleviating anemia.

FALSE BELIEFS A THREAT TO LUNG CANCER PATIENTS

Almost 40% of patients with lung disease believe that surgery can make cancer spread by exposing the tumor to air, according a newly published survey. This myth was more common among African Americans than Whites, and researchers suggest it may contribute to lower lung cancer surgery and survival rates for African Americans.

Lead author Mitchell Margolis, MD wrote that “…widespread acceptance of the study belief could undermine the best chance for cure of early-stage lung cancer.” The study is published in the Annals of Internal Medicine (2003; 139:558–563).

Margolis designed the survey because his patients at the Philadelphia Veterans Affairs Medical Center often mentioned the false belief, and several African American patients refused to see a surgeon on that basis. A total of 626 patients with lung cancer or other pulmonary diseases took the survey at clinics around Philadelphia, in Los Angeles, and in Charleston, South Carolina.