Epoetin for Cancer Patients: A Boon or a Danger?

New clinical and basic research with erythropoietin, or epoetin, is raising questions about whether the red blood cell growth factor, often given to cancer patients with chemotherapy-associated anemia and fatigue, might actually encourage cancer growth. Two recent trials of epoetin in cancer patients showed that it negatively affected survival, and a growing body of research by Harvard University scientists and others indicates that some cancer cells possess epoetin receptors that respond to exogenous epoetin by accelerating the growth and proliferation of certain cancer cells in vitro. And, as this issue of the Journal went to press, Johnson & Johnson announced that it was stopping a number of trials of its drug Procrit (epoetin alfa) because of a higher-than-expected number of blood clots in cancer patients.

Epoetin is a naturally occurring protein that stimulates the production of red blood cells. The two forms of recombinant human erythropoietin, epoetin alfa and epoetin beta, are given to patients with chemotherapy- and radiation-associated anemia, chronic renal failure, and HIV who are being treated with zidovudine, and also to patients who will undergo surgery. Annual sales of epoetin make it a blockbuster drug: About 300,000 patients in the United States alone take the drug, and sales of one version, Procrit, topped $3 billion in 2002.

In addition to improving the quality of life of anemic cancer patients, there was some initial preliminary evidence that control of anemia could lead to better tumor control and better survival rates. Some thought that epoetin might also improve the efficacy of radiation and chemotherapy by increasing tumor oxygenation. So a number of companies that sell genetically engineered versions of epoetin recently launched clinical trials hoping to demonstrate that the protein has a positive effect on survival.

One study, designed by Johnson & Johnson, was halted early last summer when researchers discovered that metastatic breast cancer patients on chemotherapy taking epoetin alfa (known as Eprex in Canada and Europe and Procrit in the United States) to prevent (rather than treat) anemia had a higher mortality rate than patients on placebo—76% versus 70%, respectively, at 12 months. The findings, which principal investigator Brian Leyland-Jones, M.D., of McGill University in Montreal, called “unexpected,” showed that a number of deaths early in the study were caused by disease progression and an increase in thrombotic and vascular events. In his article in the August issue of Lancet Oncology that described the trial, Leyland-Jones urged that caution be used in interpreting these results because of concerns with the study design.

In a second randomized, double-blind, placebo-controlled trial published in October in the Lancet, 116 of 180 (64%) epoetin-treated patients with head and neck cancer showed tumor progression or died, compared with 92 of 171 (54%) patients taking placebo. All patients in the trial were receiving radiotherapy. These results also surprised lead author and radiologist Michael Henke, M.D., of Germany’s University of Freiburg. Hoffmann-LaRoche (Basel, Switzerland) sponsored the trial of NeoRecormon (epoetin beta), a slightly different molecule than Procrit.

Henke’s trial did not meet the end point of demonstrating that epoetin used in anemic head and neck cancer patients receiving radiotherapy acts as a radiosensitizer, said Hoffmann-LaRoche medical director Andrew Loop, M.D. He also believes that the trial design was problematic, postulating a number of potential confounding factors.

But as a result of these two trials, Henke said he now has second thoughts about giving epoetin to cancer patients who are receiving curative therapy, like those in the trial. “I would still give it to patients on palliative therapy to improve quality of life, however,” he said. Both companies maintain that their drugs are safe when given to anemic cancer patients.

Key to the process of stimulating the production of red blood cells is epoetin’s ability to attach to epoetin receptors on hematopoietic progenitor cells. But a growing body of research indicates that epoetin plays a role in other systems, including the brain and the central nervous system, the gastrointestinal and reproductive systems, and on endothelial cells. And epoetin receptors have now been found on a number of cancer cell types, a fact that concerns some researchers.

Henke found that 80% of the head and neck cancer tumors from patients in the Lancet study have epoetin receptors.
Harvard University researchers Laurie Feldman, Ph.D., and Arthur Sytkowski, M.D., have found epoetin receptors on prostate and ovarian cancer cells, and others have discovered them on breast, renal, and uterine cancer cells, as well as on multiple myeloma cells.

In their laboratory work, the Harvard team discovered that when prostate and ovarian cancer cells are exposed to epoetin, they proliferate. In addition, they found that when transformed but not cancerous prostate cells are given epoetin, they grew more rapidly. The same happened with cultured prostate cancer cells and with normal prostate cells. “The presence of the epoetin receptor could be part of a cancer cell’s malignant transformation,” Sytkowski hypothesized. Whatever it means, one can no longer be cavalier about treating anemic cancer patients with epoetin, they noted.

“One has to be careful about what the presence of receptors mean and do not mean,” said Charles Loprinzi, M.D., professor of oncology at the Mayo Clinic in Rochester, Minn. He noted that, in light of the new trials, he would not treat anemic cancer patients with epoetin until they reach the high—normal range of hemoglobin level, but would stop at a lower level of normal because of a trend in some trials toward more blood clots in patients with higher hemoglobin levels who take epoetin, Loprinzi said.

In very recent work, Feldman and Sytkowski treated ovarian cancer cells with epoetin for 2 months, and afterward, with paclitaxel. They found that the cells became drug-resistant and survived longer than non–epoetin-treated cells. However, the epoetin-treated cells also showed substantially reduced levels of Bcl-2, an anti-apoptotic protein associated with uncontrolled cancer cell growth. “Therefore, the mechanism of drug resistance probably is not mediated by Bcl-2,” Sytkowski said.

The relationship of epoetin to apoptosis and angiogenesis of cancer cells is somewhat murky and complicated and needs clarification, researchers say. In his most recent work, Henke has been examining epoetin’s anti-apoptotic capabilities, and he had found that endogenous epoetin production seems to up-regulate anti-apoptotic pathways. It is also known that the endogenous production of epoetin is normally regulated by the level of tissue oxygenation; hypoxia—usually seen in tumors—and anemia generally increase the production of epoetin, which in turn stimulates erythropoiesis.

Epoetin may also be directly pro-angiogenic, in that it stimulates endothelial cell proliferation and migration, and it may also be indirectly angiogenic in that it is up-regulated by certain factors that up-regulate VEGF, including hypoxia, said Feldman. But it may also be anti-angiogenic, because when epoetin is given to relieve hypoxia, signals that would stimulate VEGF are also down-regulated. The picture is complicated, and requires more study.

Sytkowski and Feldman acknowledge that the association of epoetin with shorter survival times in cancer patients, coupled with the presence of epoetin receptors on certain cancer cells, does not prove a causal relationship. “Still, it is disturbing and warrants a larger study,” Sytkowski said. “Any cancer cell with [an epoetin] receptor deserves another look,” he added.

—Vicki Brower