ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

The Safety of Erythropoiesis-Stimulating Agents in Cancer Patients

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H&O What options are available for treating anemia related to cancer treatment?

BL When I was at McGill in the 1990s, the only available treatment was blood transfusion. Oncologists were afraid to prescribe blood transfusions in many patients because of the potential risks, including immunologic complications, exposure to infectious agents, transfusion-related acute lung injury, iron overload, and nonimmunogenic hemolytic reactions. Moreover, this was the time when the possibility of transmission of HIV infection was at its height. As a result, a lot of our cancer patients had their hemoglobin level drop to 7, 8, and 9 g/dL, and they were utterly exhausted.

Erythropoiesis-stimulating agents (ESAs) came into widespread use after they became available in the late 1990s, especially in the metastatic cancer setting.

H&O What does the literature say about the safety and effectiveness of ESAs?

BL The usefulness of ESAs in improving quality of life has been shown in multiple studies around the world. Furthermore, some studies—most notably the one by Littlewood and associates that came out in the *Journal of Clinical Oncology* in 2001—found an improvement in overall survival as well. The hypothesis was that the agent made chemotherapy work more effectively by making tumors more responsive, and the preclinical data supported this idea.

We organized the BEST (Breast Cancer Erythropoietin Survival Trial) study, which was published in the *Journal of Clinical Oncology* in 2005. There was also the study by Henke and colleagues in patients receiving radiotherapy only, which was published in the *Lancet* in 2003. We were very optimistic about what we were going to find. What we were not expecting to see was a decrease in overall survival with epoetin alfa in our trial, and a decrease in locoregional progression-free survival with epoetin beta in the Henke trial.

One of the mistakes we made in these original trials was targeting too high a level of hemoglobin. When Tonelli and associates published their meta-analysis of 52 trials in 2009, they found a statistically significant increase in all-cause mortality of 1.15 (95% confidence interval [CI], 1.03-1.29). If the analysis is restricted to the trials in which the hemoglobin is targeted within the normal range, however, the odds ratio gets much closer to 1. For example, when Bohlius and colleagues conducted their 2009 meta-analysis in the *Lancet*, they did a separate meta-analysis that excluded the results of the BEST study. They found that the hazard ratio for mortality during the active study period dropped from 1.10 to 1.03, although neither of these values was statistically significant.

We recently completed a new meta-analysis of 9 studies on ESA use in patients with breast cancer receiving chemotherapy. Although our results fell just short of statistical significance, the odds ratio for overall mortality was 1.17 (95% CI, 0.99-1.39). These results will appear in abstract form at the American Society of Clinical Oncology (ASCO) 2013 Breast Cancer Symposium in San Francisco.

Even when the odds ratio or hazard ratio is not statistically significant, the results of the meta-analyses trend toward harm rather than benefit from erythropoietin. In my opinion, the overall impact of erythropoietin on overall survival is either neutral or slightly worse, not better.

H&O What are some of the other concerns about ESAs?

BL There is this whole concept that the erythropoietin compounds themselves make tumors grow, and I find zero evidence of this at current, pharmacologically recommended doses, as reviewed in our 2012 article in the *British Journal of Cancer*. I think you would need to go up a log order in terms of dose before you had any potential stimulation of tumors.

Even in the BEST trial, in which we targeted a hemoglobin level in the range of 13 to 14 g/dL, we did not see any effect on tumor progression with ESAs. As far as I am concerned, ESAs do not have any adverse effect in regard to tumor progression.

The other concern with ESAs has been the risk of thrombosis. If you look at the studies by Bohlius and colleagues that were published in the *Cochrane Database of Systematic Reviews* and the *Journal of the National Cancer Institute* in 2006, along with the meta-analyses by Tonelli and associates and Glaspy and colleagues, the risk ratios and odds ratios were consistently between 1.48 and 1.69—and statistically significant. There is no question that ESAs increased the number of thromboembolic events across all the studies. These are extremely potent drugs.

Thus, the original vision that we had of ESAs improving survival for cancer patients is gone. They seem to have a somewhat adverse effect on overall mortality, and I ascribe that to an increased risk of thromboembolic events. I do not believe that ESAs have any effect on tumor progression.

H&O What do you think of the guidelines that are available regarding ESA use?

BL The guidelines—from the National Comprehensive Care Network (NCCN), ASCO/the American Society of Hematology, and the European Organization for Research and Treatment of Cancer—are all reasonable. I absolutely advocate using these drugs according to the guidelines. For the treatment of anemia due to concomitant myelosuppressive chemotherapy in patients with nonmyeloid malignancies without curative intent, the NCCN states that ESA use should be considered when the hemoglobin is 11 g/dL or lower, or 2 g/dL or more below baseline.

There is no point in needlessly allowing patients to cope with fatigue that prevents them from leading quality lives, especially those who have metastatic disease and do not have very long to live. Fatigue is linked to depression. When these patients get their hemoglobin level up to 12 or 13 g/dL, they generally have an improvement in their quality of life.

H&O What other changes have occurred that affect ESA use?

BL The other big change that provoked greater use of ESAs was the move to dose-dense chemotherapy regimens in the early 2000s. These regimens required patient support in the form of granulocyte colony-stimulating factor agents and often ESAs. These regimens have become quite a bit less popular than they used to be, so the need to use ESAs in the adjuvant setting is greatly reduced.

In summary, as I wrote in my recent editorial on the Moebus study in the *Journal of the National Cancer Institute*, ESAs are potent pharmacologic tools that need to be prescribed with care, and we need to consider individual patient differences when we prescribe them, especially in this era of personalized medicine. For example, an ESA is far more likely to produce a thromboembolic event in an 83-year-old woman who is frail and sedentary than in a fairly fit young woman with metastatic breast cancer. The decision to prescribe an ESA must factor in performance status. It should also be noted that only providers enrolled in the ESA APPRISE (Assisting Providers and Cancer Patients With Risk Information for the Safe Use of ESAs) Oncology Program may prescribe ESAs. All providers who prescribe ESAs must following the dosing guidelines described in the package insert.

Suggested Readings

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