Through the Looking Glass: The Evolution of Erythropoiesis-Stimulating Agent Use

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The perception and reality of the clinical value of erythropoiesis-stimulating agents (ESAs) in cancer supportive care have undergone a dramatic transformation since their initial use in 1990. The perception of ESA value in patients has evolved from panacea to miscreant over a 2-decade period of laboratory research, clinical trial data, and postmarketing experience. Meanwhile, the real clinical benefits of ESAs have changed very little from those described in the joint American Society of Clinical Oncology/American Society of Hematology guidelines originally published in 2002.[1] Even then, the value of initiation of ESAs was clear only in patients with hemoglobin values < 10 g/dL; quality-of-life measures produced inconsistent results.

Patients requiring red blood cell (RBC) transfusions by approximately 20%. The reality of ESA use that came to light following approval was increased mortality rates in certain populations, higher tumor progression and cancer recurrence rates, and more frequent and severe serious adverse effects including thromboembolism, stroke, and cardiovascular events.

Gaps in perception and reality are also evident in the international differences in interpretation and application of risks and benefits of ESA use. In this issue, Bennett et al elegantly describe and chronicle the time- and region-dependent variability in ESA utilization.[2] It is clear that US regulators have taken a more cautious approach to recommendations than their European counterparts. This response may be due in part to the pervasive use of ESAs in the US prior to 2006. There are multiple reasons for the widespread adoption of ESA use in the United States. First, these agents were directly and aggressively marketed to patients; for example, advertisements with sound bites such as “if you’re on chemo and too tired to do the things you used to do” proclaimed that an ESA, specifically Procrit (epoetin alfa), could “help get back the strength you need.”

Increasing ESA Use

The message of an implied but direct relationship between ESA use and the disappearance of weakness associated with cancer/chemotherapy likely resonated with patients. With such a convincing advertising campaign, we suspect no hematologist/medical oncologist escaped from requests to add ESAs to patients’ treatment regimens. While these products were being directly marketed to patients, health-care professionals were also the target of intensive marketing programs, utilizing clinical studies demonstrating lower transfusion requirements for patients receiving ESAs. The combination of positive clinical data and patients directly approaching physicians for ESAs created a situation in which these agents were overprescribed. A third but less frequently discussed contributing factor that increased ESA usage was the financial benefit to the practice. In a time of limited reimbursement for cognitive services, there was great temptation to use a “safe” agent that improved quality of life.

During the period of increasing ESA use in the US, other perceived benefits were investigated. Utilizing ESAs to increase RBC mass with a goal of improving tissue oxygenation and therefore treatment outcomes was hypothesized. The proposed mechanisms of ESA synergy with chemotherapy or radiation were: (1) decreased hypoxia-inducible factors, which, unchecked, led to increased resistance; and (2) increased oxygen delivery to tumor tissue, leading to greater O2 free radical production and DNA damage.
Other applications of ESAs in cancer patients were also investigated, including their use as a neuroprotectant to prevent cognitive decline during and following chemotherapy.[3] Theoretically, activation of Janus-activated kinase 2 (JAK2) via the erythropoietin receptor (EPO-R) would lead to antiapoptotic effects through the upregulation of phosphoinositide 3-kinase (PI3K) and B-cell lymphoma 2 (BCL-2), potentially limiting neuronal cell death. An alternate perception, however, also exists. Increased erythropoietin concentrations in hypoxic conditions have been shown to increase breast cancer cell migration via the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathways, potentially leading to increased metastatic potential.[4] Similarly, PI3K pathway constituents AKT and the mammalian target of rapamycin (mTOR) are upregulated in melanoma cells in response to increasing doses of erythropoietin, suggesting it may promote tumor survival.

Risks Come to Light

The reality of the risk of broader ESA use came to light beginning in 2003, and culminated in a US Food and Drug Administration review of the role of these compounds in oncology in 2007.[5] Large randomized clinical trials testing the use of ever-higher hemoglobin thresholds began reporting inferior disease and mortality outcomes for patients receiving ESAs. Consequently, regulators have steadily increased warning labels regarding their use, and markedly restricted their use in oncology. In addition to negative data for ESA use in cancer, we now have emerging data in other diseases demonstrating inferior outcomes for patients treated to higher hemoglobin values with ESAs vs standard of care, suggesting cancer is not required for adverse vascular events to occur. Pfeffer and colleagues reported a trial of darbepoetin alfa (Aranesp) in patients with diabetes and chronic kidney disease, in which patients were randomized to darbepoetin or placebo with a target hemoglobin level of 13 g/dL, with combined primary endpoints of death or a cardiovascular event.[6] The trial results showed no difference in the primary endpoints between the two study arms, but a statistically significant increase in the number of strokes in patients receiving darbepoetin was observed (101 vs 53; hazard ratio = 4.92, 95% confidence interval [CI] = 1.38–2.68; \( P < .001 \)).

Contrary to earlier studies suggesting a benefit of ESAs in ischemic stroke, a recent phase III trial of 522 patients with a middle cerebral artery territory stroke compared standard-of-care treatment with or without recombinant human erythropoietin (rHuEPO) and reported an increased death rate in patients receiving rHuEPO (16.4% vs 9.0%, odds ratio = 1.98; 95% CI = 1.16–3.38; \( P = .01 \)).[7]

Conclusion

Current data suggest that ESAs still have a reduced role in the care of specific cancer patients with anemia, but they must be utilized judiciously given the serious potential consequences of their use. Unlike the Lewis Carroll fairy tale, in which time runs backward, we cannot reverse previous experience with ESAs. Despite gaps that still exist, the perception vs reality of ESA use has clearly narrowed. It is up to the clinician to exercise care in order to avoid becoming Tweedledee or Tweedledum.

References:


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