Editorial: Anemia Management with Erythropoiesis-Stimulating Agents: A Risk–Benefit Update

MATTI S. AAPRO

Multidisciplinary Oncology Institute, Genolier, Switzerland

Key Words. Anemia • Erythropoiesis-stimulating agents • Erythropoietin receptors • Risk–benefit

Disclosure: M.A. has received study grants and honoraria for consultancy and/or is on the speakers bureau of Amgen, Johnson and Johnson, Ortho Biotech, Sandoz, and Roche. No other potential conflicts of interest were reported by the author, planners, reviewers, or staff managers of this article.

More than 80% of cancer patients undergoing chemotherapy develop anemia (hemoglobin [Hb] level <12 g/dl), and the need for blood transfusion is frequent [1]. Erythropoiesis-stimulating agents (ESAs) were developed with the aim of reducing transfusion dependence, and meta-analyses of clinical trials confirm that they have been highly successful in achieving this [2, 3].

The systematic review by Bohlius et al. [2] incorporated data from a total of 9,353 cancer patients, with tumors including those of the breast, lung, and gastrointestinal tract, treated in 57 trials. Treatment with epoetin or darbepoetin significantly reduced the need for transfusion (relative risk, 0.64; 95% confidence interval, 0.60–0.68), and the chance of achieving a hematologic response was consistent across tumor types.

These findings were supported by the 2006 analysis of the Agency for Healthcare Research and Quality [3]. Both meta-analyses noted a slightly higher risk for venous thromboembolic events (VTEs) in patients administered epoetin or darbepoetin, and were suggestive that this risk was associated with higher Hb levels.

ESAs have the advantage of avoiding the fluctuations in Hb level associated with RBC transfusions, as well as reducing the risks for disease transmission and the cardiac and hepatic consequences of iron overload (an issue in patients with hematologic malignancies) [4]. Furthermore, under controlled conditions, RBCs can be stored for up to 42 days prior to transfusion, and this is a potential source of problems [5]. Indeed, in retrospective studies, a correlation was found between the duration of RBC storage and the morbidity and mortality rates after transfusion [5–8]. Variations can occur in stored RBCs over time, which may include changes in RBC-dependent vasoregulatory function and S-nitrosohemoglobin (SNO-Hb), and RBC deformability [5]. Changes can occur even soon after blood collection, where SNO levels (and their physiological correlate RBC-dependent vasodilation) become depressed [5]. Thus, changes may occur in stored RBCs that impact the function of the RBCs and can affect clinical outcomes. In the 13 years since recombinant erythropoietin was first approved for the treatment of cisplatin-related anemia, around four million patients have been treated with ESAs; and their quality of life (when symptoms have been anemia related) has been greatly improved as a consequence (Fig. 1) [9–14].

Anemia is one of several factors that contribute to tumor hypoxia, which reduces sensitivity to radiotherapy [15]. However, Hb levels >14 g/dl can actually be associated with reduced tumor oxygenation. This suggests (as discussed in this issue by Peter Vaupel [16]) that Hb levels need to be regulated around a target value of 12 g/dl in cancer patients. This is the level at which the maximum benefits in terms of gains in quality of life have been documented [16]. Jean-Philippe Spano and David Khayat discuss in further detail, in this issue, the risk considerations of blood transfusions versus ESAs and the impact anemia has on the patient’s quality of life [18].
Some recent studies have suggested a link between the use of ESAs in certain clinical settings and reduced survival [19–23]. It is important to realize that this is mainly in nonapproved indications, including in patients who are not anemic or who are not undergoing chemotherapy, sometimes in studies where survival was not a primary endpoint or that were truncated for other reasons. There have also been reports linking the purported presence of erythropoietin receptors on tumor cells to disease progression [24]. The nature of these studies is discussed in detail in this volume in papers by Pere Gascón [25] and Joachim Fandrey [26].

As mentioned above, there has also been concern about the higher risk for VTEs when ESAs are administered, especially to patients who already have relatively high Hb levels. These concerns are considered in a paper by Mario Dicato [27].

A working party of the European Organization for Research and Treatment of Cancer met in September 2007 to update the Organization’s 2006 guidelines on use of ESAs [28]. The changes to the 2006 guidelines are highlighted in this issue.

In conclusion, when ESAs are used within label and the updated guidelines, in cancer patients receiving chemotherapy to correct anemia (only if associated with symptoms) to a target Hb level of about 12 g/dl, they have a favorable benefit–risk ratio, as recently confirmed by the European Medicines Agency [29].

References


