An Update on Twenty Years of Anemia Management with Erythropoiesis-Stimulating Agents in Nephrology and Oncology/Hematology

MATTI AAPRO
Multidisciplinary Oncology Institute, Genolier, Switzerland

Key Words. Anemia • Erythropoiesis-stimulating agents • Erythropoietin • Nephrology • Oncology • Hematology

Disclosures: Matti Aapro: Consultant/advisory role: ESMO, SIOG, ESO, EuroCancer, EORTC, IUCC; Honoraria: Amgen, Johnson & Johnson, Roche, Sanofi-Aventis, Bayer Schering, Merck-Serono, Merck, Helsinn, Novartis, Pfizer, Pierre Fabre; Research funding/contracted research: Amgen, Roche, Sanofi-Aventis, Merck-Serono, Merck, Helsinn, Cephalon, Pierre Fabre.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

Anemia management has long been a priority for nephrologists, yet their experience has been little known to oncologists. This special issue presents, for the first time, nephrologist and oncologist/hematologist experts who discuss together anemia management and erythropoiesis-stimulating agents (ESAs). The papers in this supplement look at where we currently stand on anemia management and discuss how we can improve ESA treatment of patients with renal anemia or chemotherapy-induced anemia (CIA).

In the last 20 years, there have been many changes in the management of anemia. Between 1907 and 1987, RBC transfusion was the only available therapy focused on treating severe anemia (hemoglobin [Hb] <8 g/dl). In the 1980s, recombinant human erythropoietin (rHuEPO) was introduced to eliminate or decrease the need for transfusions. Between 1988 and 1997, the focus of rHuEPO treatment was on the prevention or treatment of severe anemia. During this time, rHuEPO initially received approval for use in renal disease and later for chemotherapy-associated anemia in cancer patients. Between 1998 and 2003, ESA treatment was used to improve patient quality of life (QoL) and the treatment focus also included mild-to-moderate anemia (Hb, 10–12 g/dl). More recently, between 2004 and 2008, oncologists started to learn about the importance of iron and flexible dosing. There are still open questions on ESAs, many of which are discussed in this issue.

The history of the discovery of erythropoietin and introduction of the ESAs into clinical practice was relatively rapid. In the 1980s, the gene for erythropoietin was cloned and recombinant DNA-derived erythropoietin was engineered. By 1986, the first study of erythropoietin in renal anemia was reported, and studies with ESAs in cancer-related anemia were first published in 1990 [1–3]. In 1988 and 1989, ESAs were approved by the European Medicines Agency (EMEA) and the U.S. Food and Drug Administration (FDA), respectively, for the treatment of chronic renal failure anemia. In 1993, the FDA approved ESAs for chemotherapy-related anemia, and in 1994 the EMEA approved ESAs for cisplatin-related anemia. In the early 2000s, ESAs were approved for all chemotherapy-related...
anemia [4]. More recently, questions about the safety of ESAs have arisen as more data and meta-analyses have become available. Bohlius et al.’s [5] meta-analysis of 53 randomized trials (13,933 enrolled patients) found that ESAs led to greater mortality during the active study period (combined hazard ratio [cHR], 1.17; 95% CI, 1.06–1.30) and shorter overall survival (cHR, 1.06; 1.00–1.12). In total, 10,441 patients on chemotherapy were enrolled in 38 trials. The cHR for mortality during the active study period for patients on chemotherapy was a statistically nonsignificant 1.10 (0.98–1.24), and the cHR for overall survival was 1.04 (0.97–1.11) [5]. Tonelli et al.’s [6] review of 52 randomized trials (12,006 patients) showed that all-cause mortality was significantly higher in patients receiving ESAs than in controls receiving placebo or nothing (relative risk, 1.15), so even smaller the risk for thrombosis (relative risk, 1.69) and adverse events (relative risk, 1.16) [6]. Tonelli and colleagues did find that ESAs were associated with a significantly improved QoL and fewer blood transfusions (relative risk, 0.64) [6].

ESAs represent one of the most important developments for dialysis patients in the last 20 years and are among the most significant recombinant DNA-derived human proteins that science has provided. In chronic renal failure, anemia is a result of a decrease in endogenous erythropoietin, and ESAs act as a hormone-replacement therapy. In oncology, the causes of anemia are multifactorial, and ESAs are used as a pharmacological intervention to correct anemia and reduce the need for RBC transfusions by 25%–50% [7].

Several million chronic kidney disease (CKD) patients have benefited from ESAs and >1 million cancer patients have been treated with ESAs. However, following various FDA and EMEA meetings in 2004, 2007, and 2008 to discuss safety concerns with ESAs in oncology and nephrology, the FDA, Committee for Medicinal Products for Human Use, and EMEA introduced ESA label changes. These safety questions, relating to venous thrombotic events (VTEs), including shorter survival in some studies and the debate about erythropoietin receptors, are discussed in detail by Joachim Fandrey and Mario Dicato in this issue [8]. Jerry Spivak, Pere Gascón, and Heinz Ludwig discuss the impact of anemia on survival and QoL and provide some fascinating insights into the role inflammatory cytokines play in anemia [9].

The guidelines in both the oncology/hematology and nephrology settings help us in making decisions in our daily practice [10–15].

QoL data show a significant increase in patient QoL and vitality in CKD and CIA patients, the FDA (contrary to the EMEA) requires more evidence, with additional QoL instruments. Indeed, studies have used different instruments to measure QoL, which makes it difficult to compare QoL across studies. In small studies, where it is not always clear if patients were symptomatic because of their anemia, it is difficult to achieve significant results because only 60%–70% of patients respond, and some patients have progressive disease or treatment-related side effects that obliterate any chance of observing a significant improvement in QoL.

Francesco Locatelli and Pere Gascón discuss differences in the use of ESAs between nephrologists and oncolists/hematologists [24]. ESAs act straightforwardly as hormone-replacement therapy in nephrology patients and the correction rate of anemia is fast. In cancer patients, the anemia is not usually caused by a lack of endogenous erythropoietin production but by many diverse aspects of the disease, such as inflammatory cytokine effects on erythropoiesis and chemotherapy-associated bone marrow toxicity. The rate of anemia correction in cancer patients is normally slower than that for patients with renal disease. In both the nephrology and cancer settings, the use of RBC transfusions is indicated only in the case of an emergency because of the risks associated with transfusions and the general scarcity of blood supplies. Furthermore, nephrology patients may stay on dialysis for a long time (in some cases >20 years), and using RBC transfusions for chronic management of anemia is not a practical option. ESAs create a more stable Hb level than the cycling/zigzag rise and fall in Hb level with repeated transfusions [24, 25]. In both the nephrology and oncology settings, the correction of anemia is accompanied by an improvement in QoL [24]. A rise in Hb up to 12 g/dl [26] is associated with an increase in QoL, but beyond the Hb level of 12 g/dl, the benefits in terms of QoL level off. Some studies even point to a higher incidence of VTEs, which impacts patient outcome [27, 28].

Anatole Besarab, Walter Hörl, and Donald Silverberg discuss iron metabolism, iron deficiency, thrombocytosis, and the cardiorenal anemia syndrome [29]. The use of i.v. iron in nephrology patients is not standard; it depends on each individual patient. Intravenous iron is more effective than oral iron in raising Hb levels in CKD patients. In cancer patients, the chance of reaching the target Hb level is also higher with the use of i.v. iron. Whereas five randomized studies in cancer patients showed a positive impact with the use of i.v. iron (i.e., resulted in a faster time to response with a lower dose of epoetin), the long-term safety data of iron use on cardiac function, tumor response, and possible iron overload are lacking. In cancer patients, it is...
probably prudent to use iron only if the patient has absolute or functional iron deficiency, even if studies show efficacy of i.v. iron in other situations. Functional iron deficiency is defined in oncology with a ferritin cutoff level of 100 ng/ml and in nephrology with a cutoff level of 200 ng/ml, and the transferrin saturation for both groups is \(<20\%\). The role of iron in supporting ESA use in anemia management in nephrology is critical for ESA efficacy in maintaining a consistent Hb level. In oncology, the use of iron to support ESA anemia treatment is still being evaluated. In one of the larger randomized phase III trials comparing an ESA plus i.v. iron with a standard practice arm of an ESA without i.v. iron in patients with nonmyeloid malignancies and chemotherapy-induced anemia, the proportion of patients achieving an Hb level \(\geq\)12 g/dl or an Hb increase \(\geq\)2 g/dl from baseline was significantly higher in the i.v. iron group than in the standard practice group (86\% versus 73\%; \(p = .011\)) [30]. In that study, 28.3\% of patients in the i.v. iron arm (\(n = 199\)) and 29.9\% of patients in the standard practice arm (\(n = 195\)) had a mean baseline transferrin saturation measurement [30]. One percent of patients had a true iron deficiency and 35\% of patients had a functional iron deficiency in the i.v. iron arm (\(n = 200\)), whereas these figures were 1\% and 36\% of patients, respectively, in the standard practice arm (\(n = 196\)) [30]. Fewer RBC transfusions occurred in the i.v. iron group than in the standard practice group (9\% versus 20\%; \(p = .005\)) [30]. Although this study showed that i.v. iron increased the hematopoietic response rates to ESAs in cancer patients, it did not provide information on whether all cancer patients with anemia should receive i.v. iron plus ESA treatment, and it did not clarify which patients might benefit from i.v. iron in addition to ESAs [31]. Further information is thus needed to identify these patients, in order to avoid overtreatment of patients who might not benefit from the additional iron [31].

In this issue, Jerry Spivak and myself provide an update on ESAs in oncology, whilst Francesco Locatelli gives an update in nephrology and Harald Becker discusses biosimilars [32, 33]. Although the more recent meta-analyses show a greater risk for mortality and shorter survival with the use of ESAs, they fail to do so when the drugs are used within guidelines [32]. In some studies, the Hb target level was higher than recommended by the guidelines, and importantly, none of the oncology studies in the latest meta-analysis used ESAs within the current label guidelines. In oncology, a safe goal for the Hb level is around 12 g/dl. This has to be titrated for an individual patient’s needs and particular care has to be taken with regard to plasma volume in nephrology practice and the risk factors for developing VTE in oncology practice (i.e., for both, a high platelet count, bedridden, old age, and a prior history of VTE are important, and in oncology, tumor type, receiving chemotherapy, and first cycle of chemotherapy, etc., are relevant). Interestingly, in a retrospective cohort study that included 504,208 hospitalizations of patients with cancer (of whom 14.0\% received at least one RBC transfusion and 3.0\% received at least one platelet transfusion), 7.2\% developed a VTE and 5.2\% developed arterial thromboembolism, which was significantly greater than the rates for the remaining study population (3.8\% and 3.1\%, respectively; \(p < .001\)) [34]. Both RBC and platelet transfusions were also associated with a greater risk for in-hospital mortality [34].

The value of the Hb goal should not be considered in isolation of the patient as a whole. It was suggested at the meeting of the authors of this supplement that a marker for comorbidities might be helpful to avoid giving too high a dose of epoetin to high VTE risk patients (i.e., patients with cardiovascular disease, bedridden patients, etc.). There were also suggestions that the use of a three times weekly ESA schedule might follow a rhythmic pattern nearer to the physiology of a normal person, although it is a less convenient schedule. In nephrology, the oscillation in Hb levels is important because they might impact the associated high cardiovascular risk of patients with renal failure, and individualized dosing is needed. In oncology practice, Hb cycling is also important and sometimes related to the schedule of chemotherapy. For QoL purposes, it is important to keep a constant Hb level. As the Hb level oscillates through a period of time, more frequent Hb measurement (i.e., twice a month) is prudent to provide more accurate monitoring of the response to ESAs and to allow for prompt action in response to a rise or fall in Hb level (such as ESA dosage adjustments).

In selecting an ESA dose in nephrology and oncology, attention needs to be given to patient characteristics (i.e., weight, nutritional status, plasma volume, comorbidities) to maintain a consistent Hb level. Patients with cardiovascular disease can have a change in plasma volume that will impact the Hb level. It is therefore important to look at the patient as a whole and not just as “an Hb number.”

In oncology patients, suggestions for causes of the potential ESA adverse effects on survival in some settings have included tumor progression resulting from stimulation of tumor cell erythropoietin receptors (EPORs) and a greater risk for VTEs leading to shorter survival. In an experimental model using human breast cancer cells engineered to stably express a constitutively active EPOR-R129C variant, EPOR-R129C expression resulted in increased cellular proliferation and migration of breast cancer cells [35]. In human ovarian cancer cell lines (A2780, CaOV, SKOV, and OVCAR-3), the EPOR was shown to be
functional but none of the four cell lines exhibited a growth response in culture to exogenous erythropoietin [36]. Erythropoietin at pharmacological concentrations can activate signaling cascades in non-small cell lung carcinoma (NSCLC) cell lines [37]. But the increased erythropoietin-induced signaling was not associated with a growth advantage for the NSCLC cells [37].

The problem with EPORs identified on tumor cells using an unspecified antibody is that there is no proof that they are functional, nor that they are not confused with other entities like heat shock protein [8]. There is no evidence of clinical tumor progression when ESAs are used within the approved indication, in cancer patients receiving chemotherapy [8].

We continue to conclude that ESAs are safe and effective in alleviating anemia, diminishing transfusion use and improving QoL in symptomatic anemic patients, when used according to current guidelines.

The authors take full responsibility for the content of this article and thank Rob Stepney, medical writer, and Julie O’Regan, Bingham Mayne and Smith, Edinburgh, supported by an educational grant from Ortho Biotech, a division of Janssen Cilag Europe, for their assistance in preparing a first draft of the manuscript based on an oral presentation at a meeting held on November 20, 2008, in Sitges, Spain, organized by a Scientific Committee of Matti Aapro, Mario Di cato, Pere Gascon, Francesco Locatelli, Jerry Spivak, and Jay Wish.

REFERENCES


8 Fandrey J, Dicato M. Examining the involvement of erythropoiesis-stimulating agents in tumor proliferation (erythropoietin receptors, receptor binding, signal transduction), angiogenesis, and venous thromboembolic events. The Oncologist 2009;14(suppl 1):34–42.


