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Is Nephrology More at Ease Than Oncology with Erythropoiesis-Stimulating Agents? Treatment Guidelines and an Update on Benefits and Risks

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ABSTRACT

Erythropoiesis-stimulating agents (ESAs), which promote RBC production, have been extensively used to reduce transfusion requirements and improve quality of life (QoL) in both cancer patients and those with chronic kidney disease (CKD). However, the likelihood of response and duration of treatment differ in the two settings. In renal anemia, ESAs act straightforwardly as hormone-replacement therapy. The anemia of cancer, however, relates not to a lack of endogenous erythropoietin production but to diverse aspects of the disease (including a relevant inflammatory component) and chemotherapy. Response to ESAs is slower and less certain than in nephrology. In both settings, early studies showed that reversal of severe anemia was accompanied by substantial improvement in QoL. However, again in both settings, subsequent studies indicated that efforts to *normalize* hemoglobin might worsen outcome. In the context of cancer, this concern was reinforced by the suggestion that malignant cells had erythropoietin receptors and that its administration might therefore accelerate tumor growth, and moreover that cancer patients are more susceptible to venous thrombosis. The absence of these concerns for nephrologists, and their greater experience in managing ESAs and patients' iron status, may make them more at ease with ESAs than their counterparts in oncology. However, both groups of specialists have had to deal with reversals in recommended thresholds for intervention and restrictions imposed by regulatory authorities. In both specialties, the broad consensus now emerging is that the optimum balance of benefits and risks lies in using ESAs aimed at a hemoglobin level in the range of 11–12 g/dl, although for CKD patients there is still room for an individualized approach. *The Oncologist* 2009;14(suppl 1):57–62

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Introduction

There was an interval of 4 years between the publication in 1986 of the first studies of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease (CKD) and the first publications describing their use in cancer-related anemia. There was a longer interval between the granting of approval for the indication of renal anemia (in the latter part of the 1980s) and the first approval in oncology, granted in the U.S. and Europe (in 1993 and 1994, respectively) for the treatment of cisplatin-related anemia.

Since their approval, several million patients with CKD have benefited from these agents following clinical trial evidence of a lower requirement for blood transfusion and enhanced quality of life (QoL) [1, 2]. Anemia used to be the major cause of functional impairment in CKD patients, and efforts to combat it frequently led to patients receiving many transfusions per year. The need for such treatment is now rare.

Similarly, more than a million anemic cancer patients have received ESAs following data from controlled studies indicating substantially lower transfusion dependence and improvement in QoL, in general, and symptoms of fatigue in particular [3]. In the case of cancer patients, QoL improvement following a rise in hemoglobin (Hb) is essentially independent of the extent of tumor response [4]. Improvements in QoL are important for nephrology and oncology patients. However, QoL instruments are not always able to adequately discriminate benefits related to ESA therapy from benefits of enhanced clinical care in general. QoL issues are discussed in further detail elsewhere in this supplement by J.L. Spivak et al. [5].

Different Populations, Reasons for ESA Use, and Patterns of Response

In oncology, ESAs represent an element of short-term supportive care whereas in nephrology, they have a longer-term and more fundamental role. For dialysis patients, their introduction has arguably been the most important single advance in treatment over the past decades. Along with achievement of dialysis adequacy, control of anemia is associated with lower patient mortality confirmed at the level of dialysis facilities, with a 17% reduction seen in the standardized mortality ratio since 1985 [6, 7]. That analysis, although referring to standardized mortality, is still partially confounded by other factors (such as the case mix in the dialysis facility, number of comorbidities, dialysis adequacy, type of vascular access, for-profit dialysis center versus academic center, etc.) that influence mortality in end-stage renal disease, considering that it is impossible to fully adjust for all these and unknown confounders.

There are parallels between the benefits and risks of using ESAs in the two settings, in the way that attempts to correct severe anemia evolved into attempts to normalize Hb level, and in the regulatory response to evidence that the latter might adversely affect survival. However, the nephrologist and the oncologist use ESAs in fundamentally different contexts.

Anemia is a severe complication of CKD seen in the majority of stage 3–5 patients and is associated in the dialyzed population with greater mortality [8, 9]. ESAs are given to replace endogenous erythropoietin, which the kidney is failing to produce in adequate quantities in response to anemia, in a situation analogous to that with insulin and diabetes. In the cancer patient, although endogenous erythropoietin production may be suppressed by the tumor, and particularly by the release of inflammatory mediators, anemia is most notable as a side effect of chemotherapy. ESAs are administered not as maintenance therapy but as an aspect of acute patient support. In some cancer patients, levels of endogenous erythropoietin may be relatively high before treatment, although there may still be a rationale for ESAs in an effort to overcome resistance to its effects.

Given these considerations, it is not surprising that the proportion of patients responding to erythropoietin and the rate of correction of anemia are different in the two clinical settings. The great majority of CKD patients respond, and response is rapid, and nephrologists often have to avoid too rapid a correction in order to reduce the risk for complications, including hypertensive crisis and vascular access thrombosis. This is not the case in the anemia of cancer, which is caused by a range of disease- and treatment-related mechanisms. Time to response is slower, the response rate varies in the range of 50%–70%, and the doses of ESA required are much higher.

The presence of supposed erythropoietin receptors on cancer cells, and early in vivo suggestions of enhanced growth of tumor cell lines while on ESA therapy, poses a problem specific to oncology. This contributed substantially to the robust regulatory response following clinical studies of ESAs (largely involving off-label use of the agents) showing poorer outcome. On the other hand, the fact that nephrology patients are likely to receive ESAs for years or decades brings to the forefront issues of long-term safety and efficacy.

Benefits and Risks of ESAs

In cancer patients, anemia is associated with a shorter survival duration. In early clinical trials, there appeared to be a longer survival time in anemic cancer patients receiving ESA treatment [3]. More recent meta-analyses, however, do not support the finding that ESA treatment of anemia improves patient survival in oncology or nephrology practice. In some cases, these results may be attributed to the off-

label use of ESAs. There are also concerns about the higher mortality rates in both specialties when tailoring ESA therapy to achieve higher Hb targets.

Compared with their healthy counterparts, cancer patients (as reported above) are prone to thrombotic events. This is particularly true with certain tumors, such as pancreatic cancer and glioblastoma, but chemotherapy itself—especially during the first cycle—is a major risk factor. Hence, the nature of the risks associated with ESA use are different in the oncology and nephrology settings: in cancer patients, the cardiovascular concern centers on venous thromboembolisms; in nephrology, concern lies more on the arterial side, with myocardial infarction (MI), stroke, and, for hemodialysis patients, clotting of the vascular access, involving both the arterial and venous sides. However, in both indications, there is evidence that efforts to normalize Hb, as opposed to correcting anemia, may have adverse effects.

Published clinical guidelines are available in both nephrology and oncology practice and reflect consensus expert opinion. The European Best Practice Guidelines and the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI™) guidelines recommend treating anemia to a target Hb level of 11–12 g/dl [10–15]. However, in numerous patients, it is difficult to consistently maintain Hb levels within a specified target range over time [12]. These Hb deviations outside a specified target range could be associated with a higher risk for adverse outcomes [12, 16]. A meta-analysis of trials that assigned CKD patients to treatment aimed at achieving either a higher or a lower target Hb determined that all-cause mortality was greater in the high Hb group (relative risk [RR], 1.17; confidence interval [CI], 1.01–1.35) [17]. The largest study contributing to this analysis is that of Besarab et al. [17], published in 1998, in which patients with cardiac disease receiving dialysis and epoetin were randomized to a target hematocrit of either 30% or 42%. Six months following randomization, curves showing the probability of death or MI in the two groups began to show substantial divergence favoring patients randomized to the low hematocrit target, and because of that and for futility the trial was prematurely stopped. However, for the whole population of patients involved in the trial, the adjusted hazard ratio showed a consistent trend toward a lower risk for death or MI as the level of hematocrit actually *achieved* by patients increased [18, 19]. A possible explanation for this paradox is that the excess mortality in the group with the high hematocrit target occurred not only among patients whose CKD or associated comorbidities rendered them incapable of achieving it but also resulted from the too rapid correction of anemia and the large proportion of patients with grafts as vascular access, which, in the case of too rapid anemia correction, particularly in patients with cardiac disease, is associated with thrombotic events and the consequent clinical complications.

The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study showed that patients assigned to the higher Hb target (13.5 g/dl) had a higher rate of cardiovascular events (including death) than those assigned to the 13.5-g/dl target (RR, 1.29; CI, 1.01–1.64) [20]. However, a secondary analysis suggested that it was patients assigned to both targets who did not reach the target and received the largest doses of recombinant human erythropoietin (rHuEPO) that did poorly [21]. Of note, the primary outcome of the CHOIR study was the higher rate of cardiovascular events (and mortality) in patients assigned to the higher Hb target, and caution must be exercised in not overinterpreting the secondary analyses. However, a similar interpretation can be made of data from the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) study [22]. The excess mortality may also lie in the risks related to the patients' need for dialysis and may not be related to the treatment, considering that there were no differences between the high and low Hb groups when patients on dialysis were excluded from the analysis. The explanation may lie in comorbidities preventing a patient from responding to erythropoietin and therefore needing a higher ESA dose, in which case the latter could be a surrogate for (and could also be the cause of) a worse prognosis.

Another point is that differences in patient populations must be taken into account in interpreting these studies. The mortality rate in the lower Hb group in the CHOIR study was greater than that in the higher Hb group in the CREATE study. And the rHuEPO doses were much higher in the CHOIR study than in the CREATE study.

However, targeting an Hb level ≥13 g/dl in the CKD population is associated with greater all-cause mortality, thrombosis of the vascular access of hemodialysis patients, and elevated blood pressure. Any beneficial effect on QoL achieved by raising the Hb level further than the 11–12 g/dl range attained in earlier studies is marginal, and not lasting in the long term, and this is reflected in the current guidelines, discussed below. Furthermore, the health care costs of achieving higher Hb targets in clinical practice should be considered.

In the oncology context, data from two community-based trials of epoetin in cancer patients undergoing chemotherapy suggested a direct relationship between an Hb increase and QoL, with the maximum gain occurring at an Hb level of 12 g/dl [23]. In terms of QoL, reaching this target is, therefore, good. However, controlled studies in which ESAs were administered not with the aim of correcting anemia but to achieve Hb levels within or approaching

Table 1. Summary of international oncology/hematology evidence-based guidelines [29–32]

Recommendation	ASCO/ASH [29]	NCCN [30]	EORTC [31, 32]
Initiate ESA therapy	Hb ≤10 g/dl (clinical decision if Hb >10 g/dl to ≤12 g/dl)	Hb ≤11 g/dl	Hb 9–11 g/dl (clinical decision if Hb ≤11.9 g/dl)
Goal of treatment	Maintain Hb at or near 12 g/dl	Maintain between 10 g/dl and 12 g/dl	Target Hb should be ~12 g/dl

Evidence-based guidelines recommend Hb levels be maintained between 11 g/dl and 12–13 g/dl during erythropoietic therapy.
Abbreviations: ASCO/ASH, American Society of Clinical Oncology/American Society of Hematology; EORTC, European Organization for Research and Treatment of Cancer; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; NCCN, National Comprehensive Cancer Network.

the normal range have shown an adverse effect on disease-free and/or overall survival times [24, 25]. A meta-analysis of 57 studies specifically identified a higher risk for thromboembolic events associated with the use of ESAs in oncology patients [26].

However, there has also been concern that ESAs might lead to tumor progression through erythropoietin receptors on cancer cells [27]. This is discussed in further detail elsewhere in this issue by Fandrey and Dicato [28].

Thresholds for Intervention and Hb Targets

The 2006 NKF-KDOQI™ guidelines recommend an Hb target >11 g/dl and not exceeding 13 g/dl, regardless of comorbidities or dialysis status [11, 12]. The KDOQI 2007 update recommended that, in dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target generally be in the range of 11.0–12.0 g/dl and the Hb target should not be >13.0 g/dl [13]. The position statement developed by the Kidney Disease: Improving Global Outcomes Foundation for anemia in CKD states that current evidence, based on mortality data, is that Hb levels >13 g/dl can be associated with harm [14]. For levels of 11.5–13 g/dl, there is no evidence for harm or benefit compared with higher or lower levels. However, QoL studies (the majority of which are not robust) suggest that a higher Hb level is associated with a superior outcome and functional status. The European Renal Best Practice Work Group recommended maintaining the lower limit of the Hb target and that Hb values of 11–12 g/dl be generally sought in the CKD population, without intentionally exceeding 13 g/dl [15]. Within the U.S., the U.S. Food and Drug Administration (FDA) mandates that Hb levels in renal failure patients not exceed the 10–12 g/dl range.

In the oncology setting, the FDA specifies that ESAs should be used only to treat anemia resulting from myelosuppressive chemotherapy and cautions that shorter survival times and effects on tumor progression cannot be excluded even when ESAs are dosed to a target Hb level <12 g/dl.

Currently, three sets of guidelines relate to the use of ESAs in patients with solid or hematological malignancies (Table 1) [29–32]. The joint guidelines of the American Society of Clinical Oncology/American Society of Hematology suggest starting ESA therapy in patients with chemotherapy-associated anemia if the Hb level "approaches or falls below" 10 g/dl [29]. A clinical decision is to be made if the Hb level is >10 g/dl but ≤12 g/dl. The goal of treatment should be to maintain the Hb level at or near 12 g/dl. The National Comprehensive Cancer Network suggests initiating ESAs when the Hb level is ≤11 g/dl, with the aim of maintaining values of 10–12 g/dl [30]. The European Organization for Research and Treatment of Cancer guidelines recommend starting treatment when the Hb level is 9–11 g/dl, with a clinical decision to be made if the Hb level is in the range of 11–11.9 g/dl [31, 32]. The target should be "around" 12 g/dl.

A problem first seen in hemodialysis patients treated with erythropoietin, but that was later also seen in patients in earlier CKD stages, is that Hb levels typically rise and fall in cycles, each of a few months duration, and with a mean amplitude of 2–3 g/dl [33, 34]. Thus, a patient may have an Hb level approaching 14 g/dl on one measurement but close to 10 g/dl 2 months later. The clinical significance of these excursions—and hence any need for management—is not known, although an association with greater morbidity and mortality has been reported [35].

Is Transfusion an Alternative to ESAs in Either Setting?

We agree that blood transfusion continues to subject patients to an element of risk. Given recent history, the transmission of infection is clearly uppermost in our minds. Although much has been done to reduce this risk by screening blood products for known organisms, there remain three causes for concern. First is the virtual certainty that there are infectious organisms that we do not yet know about. Second is the existence of sources of infection, such as the prions causing spongiform encephalopathy, that we know

about but cannot screen for. Third is the window of infective opportunity (which may extend for several weeks in the case of HIV, human T lymphotropic virus, hepatitis B virus [HBV], and hepatitis C virus [HCV]) offered by the latent period between the acquisition of an infectious organism by a future donor and its detectability in harvested blood. Recent estimates suggest that efforts to reduce the impact of transfusion-transmitted HBV, HCV, and HIV may have achieved their maximum effect, leaving a small but appreciable residual risk for the foreseeable future [36].

Where blood is to be transfused, there is always the risk for error in assigning the correct blood type. The risk for alloimmunization must also be considered, along with volume overload and pulmonary edema (if transfusions do not occur in the context of dialysis), iron overload, and hyperkalemia. A further consideration is that blood is a limited resource. The American Association of Blood Banks regards transfusion as a response to a medical emergency, and not a means of enabling a patient to reach and maintain a specific level of Hb.

There has been little systematic study of the impact of repeat transfusions on outcome in either nephrology or oncology. However, studies in which patients have received either ESAs or placebo suggest that, in both groups, the hazard ratio for death, disease progression, and cardiovascular or thromboembolic events is lower in patients who do not receive transfusions [37]. There have been no randomized head-to-head comparisons between ESAs and transfusions, although a nonrandomized study from Canada suggests a better QoL with the former [2].

In addition to the risks associated with repeat transfusions, it is clear that they are not equivalent to the use of ESAs because they are unable to provide a sustained Hb level. Moreover, CKD patients may have a life-expectancy of decades.

Experience in Managing Iron Status

The use of ESAs has had a longer history in nephrology than in oncology, it relates more fundamentally to the underlying pathology, and (given that erythropoietin receptors on tumor cells are not a relevant consideration) it has not been generally suspected of an adverse effect on disease progression. For these reasons, it would not be surprising if nephrologists felt more at ease with ESAs than their counterparts in oncology, even though judicious use can bring substantial benefit in both clinical settings. A final relevant consideration is that nephrologists have greater experience in managing ESAs and the iron status of their patients. Increasing iron storage and availability has a positive impact on the attainment of Hb targets with erythropoietin, although the risk for hemosiderosis should be considered [38].

Oncology colleagues may as yet feel less comfortable with this element of anemia management. In nephrology, the role of i.v. iron in dialyzed patients, for example, has been established. In oncology, thresholds for initiating iron supplementation are unclear, the relative contributions of oral and i.v. iron have not been compared in well-designed controlled trials, and there is uncertainty about impaired iron absorption and use related to the underlying disease. Nevertheless, there is an important body of evidence suggesting that i.v. iron leads to a higher and faster hematopoietic response [39, 40].

In conclusion, nephrologists probably are more at ease with the use of ESAs than oncologists/hematologists, because ESAs are used as direct hormone-replacement therapy in nephrology, whereas in oncology bone marrow suppression usually needs to be dealt with.

Author Contributions

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