Erythropoiesis-Stimulating Agents in Oncology

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Abstract

Patients who have cancer, particularly those undergoing chemotherapy, frequently become anemic. Therapy with erythropoiesis-stimulating agents (ESAs) is associated with an increase in hemoglobin levels, a reduction in transfusion requirements, and, according to many clinical trialists and experienced clinicians, an improvement in functional status, productivity, and quality of life. Several randomized trials of ESAs in patients who have cancer have recently reported inferior outcomes in tumor progression or survival, raising appropriate concerns about the safety of ESAs in oncology. However, 3 important caveats to these reports exist. First, these clinical trials did not reflect the common use of ESAs in oncology practice (i.e., to treat, rather than prevent, anemia in patients undergoing chemotherapy). Second, the trials were seriously flawed and did not meet reasonable standards for cancer progression or survival trials. Third, during the same period, randomized trials were presented or published that showed no negative impact on tumor progression or survival; these trials have approximately the same shortcomings as trials that suggest a safety issue exists. The lack of definitive answers about the safety of ESAs for treating chemotherapy-related anemia has placed physicians, regulators, and most importantly patients in a difficult position that can only be addressed with additional data. This article reviews relevant preclinical and clinical available data to help improve understanding and guide decision making. (JNCCN 2008;6:565–575)

Background

Erythropoiesis-stimulating agents (ESAs) are drugs that mimic the effects of endogenous erythropoietin (EPO), binding to the erythropoietin receptor (EPO-R) on erythroid progenitors in bone marrow and increasing production of mature red blood cells. All agents available worldwide are recombinant forms of human EPO.

Three major preparations have been studied in multiple randomized clinical trials and widely used to treat chemotherapy-induced anemia (CIA): epoetin alfa, epoetin beta, and darbepoetin alfa. Available data show no differences among these agents in terms of safety or efficacy; therefore, this article considers them together as ESAs.

Data from randomized, controlled clinical trials have conclusively established that therapy with ESAs for CIA is associated with a reduced incidence of red cell transfusions. Although many studies have also shown a decrease in fatigue or an increase in functional status, productivity, or quality of life in association with ESA therapy for CIA, incontrovertibly substantiating improvement of a subjective and multifactorial end point has obvious difficulties, and no ESA has regulatory approval for use solely to improve quality of life. Because transfusions are frequently administered to patients with CIA to relieve symptoms of anemia and not simply in response to a particular hemoglobin level, even this end point has a subjective component. It is probably more accurate to state that ESA therapy for CIA has not received regulatory approval to prevent or relieve symptoms that are insufficiently severe to warrant treatment with red cell transfusion.

In 2003, the results of 2 studies were published exploring off-label uses of ESAs in oncology: for tumor oxygenation/anemia prevention during chemotherapy for breast cancer (Breast Cancer Erythropoietin Trial [BEST]) or during radiotherapy for head and neck cancer (Enhance trial). These data raised a concern that ESA therapy might be associated with an increase in tumor progression or a reduction in survival. In May of 2004, the FDA Oncology Drug Advisory Committee (ODAC) met to review safety data on ESA use in patients with cancer (http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2.htm). This forum allowed previously published and

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unpublished data relevant to the appropriate use of ESAs in oncology to be given a detailed public examination. These events also prompted acknowledgement that the available clinical trial data, including those supporting safety and those raising a safety concern, are seriously limited, and speculation as to what mechanisms, if any, might underlie ESAs possible effect on tumor progression or survival.\(^\text{11}\)\(^\text{13}\)

Over the intervening 4 years, 2 additional large trials raising safety issues were reported, both exploring off-label uses of ESAs in oncology practice. One trial randomized anemic patients with active cancer who were not undergoing chemotherapy to receive either ESA or placebo, with the primary end point being reduction in red cell transfusions.\(^\text{14}\)\(^\text{15}\) Patients with various nonmyeloid malignancies were enrolled and not stratified to balance baseline factors predicting survival in the 2 groups. The patients receiving ESAs showed a statistically significant decreased survival.

The second report provides results of an interim analysis of the Preoperative Epirubicin Paclitaxel Aranesp (PREPARE) trial, which have not been published; in this trial, patients with breast cancer undergoing preoperative adjuvant chemotherapy were randomized to begin ESAs or no treatment when hemoglobin level fell below 13 \(\text{g/dL}\).\(^\text{11}\) At the time of this writing, more relapses and deaths have been reported in the group randomized to receive an ESA than the control group, although the differences are not statistically significant.\(^\text{14}\)\(^\text{15}\)

In addition to these trials, a safety issue was raised in 3 other randomized trials reported since 2004. The Danish Head and Neck Cancer Group (DAHANCA) posted\(^\text{16}\) and subsequently presented\(^\text{17}\) the results of a randomized trial (DAHANCA 10) of ESAs given to patients with head and neck cancer during radiotherapy to determine whether an ESA-induced increase in hemoglobin during radiotherapy would improve the efficacy of radiotherapy. This trial apparently did not have the baseline prognostic imbalances and high frequency of protocol violations that occurred in the Erythropoietin in Head and Neck Cancer (ENHANCE) trial. A decreased time to progression without a significant difference in survival was observed in the ESA-treated group, and the investigators concluded that improving the results of radiotherapy is futile.

Another randomized trial, terminated early after 70 patients were enrolled, of ESA versus placebo in a mixed population of patients with lung cancer, some of whom were undergoing chemotherapy, showed an inferior survival outcome in the ESA arm.\(^\text{18}\) This trial had not been previously published, but the results were available and discussed at the May 2004 ODAC meeting. Finally, a randomized trial of ESAs in patients with cervical cancer undergoing chemoradiotherapy (GOG-191), was closed because of an increase in thrombotic complications in the ESA arm.\(^\text{19}\)

Several other randomized trials reported after ODAC 2004 failed to show a negative effect of ESAs on tumor progression or survival. A tumor oxygenation/anemia prevention study in patients with metastatic breast cancer (the Breast Cancer-Anemia and the Value of Erythropoietin [BRAVE] trial), which had a similar design to the BEST trial, showed no significant difference in survival.\(^\text{20}\) Moreover, survival differences favoring the placebo group in the BEST trial are no longer apparent with additional follow-up,\(^\text{15}\) and an additional randomized trial in breast cancer\(^\text{21}\) have not shown a decrease in progression-free or overall survival in the ESA arm.

In contrast to results in the ENHANCE and DAHANCA 10 trials, a third randomized trial of ESAs during radiation for head and neck cancer (RTOG 99-03) did not detect an effect of study drug on either locoregional progression or survival.\(^\text{22}\) Two randomized trials—one published and one only presented—of ESAs for patients with small cell lung cancer undergoing chemotherapy showed similar relapse-free and overall survival in the ESA and control arms.\(^\text{22}\)\(^\text{23}\)

A trial in patients with esophageal carcinoma undergoing chemoradiotherapy showed superior survival among patients receiving ESAs.\(^\text{24}\) ESA therapy was not associated with an observed decrease in relapse-free or overall survival in patients with ovarian cancer undergoing platinum-based chemotherapy.\(^\text{25}\)

The ODAC met in May of 2007\(^\text{23}\)\(^\text{26}\)\(^\text{27}\) and again in March 2008\(^\text{14}\)\(^\text{15}\) to review the accumulating data and reconsider the safety issues. The briefing documents for those meetings provide a detailed exposition of the current data. This article summarizes the salient features of the trials that have raised safety concerns and our current understanding of ESAs and their effects in patients with cancer.
How Might ESAs Alter Cancer Biology, Response to Treatment, or Survival?

A theoretical construct for understanding the potential mechanisms through which ESAs may alter tumor progression or survival outcomes can inform and focus a review of the clinical data. If ESAs affect these end points, they are probably acting through the EPO-R, and speculation has focused on which target tissues express relevant, functional receptors. Three candidate tissues—bone marrow, vascular endothelium, and tumor cells—have been proposed, each associated with specific mechanisms for an effect on tumor progression or survival. A complete understanding of the biology of ESAs and cancer must acknowledge that endogenous EPO would have similar biologic effects as ESAs.

EPO-R on Erythropoietic Cells

The expression of functional EPO-R on hematopoietic cells enhances the survival of committed erythroid progenitors, thereby increasing the production of red blood cells. This may be the only tissue in which the EPO/EPO-R axis is biologically imperative; it is the only site of EPO-R expression required for viability in mice. EPO increases red cell production. Because red cells transport oxygen to tissues, a decrease in red cell mass can cause tissue and/or tumor hypoxia.

The cellular response to hypoxia includes an increase in the expression hypoxia response genes, including vascular endothelial growth factor (VEGF), that enhance angiogenesis and resistance to apoptosis. For malignant tissue, hypoxia has been shown to be associated with a more aggressive phenotype and an increased resistance to the effects of radiation and chemotherapy. Studies have shown that hypoxia is more common in human cancers when anemia is present (hemoglobin < 11–12 g/dL). In anemic animals with tumors, ESA therapy enhances the efficacy of chemotherapy or radiation.

These considerations suggest that anemia adversely impacts the progression of cancer and efficacy of anticancer therapy. This prompted the oxygenation/anemia prevention randomized trials of ESAs in patients undergoing radiation or chemotherapy to determine whether increasing hemoglobin levels would be associated with better tumor outcomes.

Tumor vasculature is very different from the vascular anatomy of normal tissues, with increased tortuosity that may significantly alter the relationship between hemoglobin level and blood rheology. Evidence now shows that the oxygenation of human cancers may increase as hemoglobin concentration rises until a level of 12 to 13 g/dL is reached; thereafter, as hemoglobin concentration continues to rise toward what is considered normal, tumor oxygenation declines, presumably because of a decrease in flow in tortuous tumor blood vessels.

These considerations suggest that the effects, for better or worse, on tumor biology of a given ESA-induced increase in hemoglobin concentration may depend heavily on the baseline hemoglobin. The potential for hemoglobin levels in excess of 13 g/dL to decrease tumor oxygenation is especially interesting, given that several trials suggesting a negative impact of ESAs on tumor outcomes used treatment protocols that achieved these higher levels, including BEST, ENHANCE, and DAHANCA.

EPO-R on Vascular Endothelium

Some evidence shows that functional EPO-R may be present on endothelial cells. When ESAs are administered to healthy volunteers, an increase in circulating e-selectin and blood pressure are observed, suggesting an effect on endothelial cell activation. If functional EPO-Rs are present on endothelium, ESAs may impact either tumor progression through an effect on tumor vasculature and angiogenesis or patient survival through increased thrombosis.

Obviously, any concern about the effects of ESAs on tumor angiogenesis must be balanced against the potential for anemia and tissue hypoxia to increase VEGF expression in and around tumor cells. Thrombosis may be more of a concern; accumulating evidence shows that thrombosis may play a role in the pathophysiology of cancer progression and that anticoagulation, even in the absence of a clinically apparent thrombosis, may improve survival in some malignancies.

EPO-R on Cancer Cells

Over the past several years, studies have reported the presence of immunoreactive EPO-R on human tumor cells from cell lines or tumor samples. Experts have postulated that hypoxic cancer cells may express EPO-R and EPO, leading to improved tumor cell survival or resistance to treatment through an autocrine or paracrine mechanism, which may be enhanced by the administration of ESAs. These studies have largely used polyclonal rabbit antihuman EPO-R antisera that have been shown to lack specificity and to
detect proteins, such as heat shock protein 70, that are unrelated to the EPO/EPO-R axis and are known to correlate with more aggressive tumor phenotypes and decreased survival across a wide spectrum of human cancer.\textsuperscript{71–77} Until immunoreagents specific for human EPO-R are available, the presence of EPO-R protein on human tumor cells cannot be definitively shown.\textsuperscript{74,79} Various nonhematopoietic human tissues contain low levels of EPO-R messenger RNA, and their malignant tissue counterparts do not express higher levels of message, suggesting that EPO-R is not an oncogene.\textsuperscript{80} However, the possibility of functional EPO-R on human cancer cells can never be excluded, especially because EPO-R may be present in sufficient quantity to effect EPO signaling and still be beneath the level of detectability with any currently available technique, even if a specific reagent is developed. Because any detected EPO-R may not be functional and therefore may be irrelevant and because functional EPO-R may be present but undetectable, attempts to show EPO-R expression on human tumor cells will probably not settle this issue.

A more direct approach has been to observe the effects of ESAs on in vitro proliferation of human tumor cell lines, or the in vivo behavior of human tumor xenografts.\textsuperscript{73} In the in vitro work, the only consistent observation of an effect of ESAs is on erythroleukemia lines.\textsuperscript{81} Most reports involving nonmyeloid cancer lines have reported no effect of ESAs, even when functional EPO-R may be present.\textsuperscript{82,83} Few studies have reported an increase in proliferation markers\textsuperscript{84} or a change in drug-sensitivity phenotype.\textsuperscript{85,86} Most in vivo studies have reported either a beneficial effect on tumor biology or response to treatment\textsuperscript{87,88} or no effect, with a few reporting an increase in tumor growth or resistance to treatment.\textsuperscript{89}

If human tumors bear functional EPO-R and are acted on by endogenous EPO produced locally in response to hypoxia, resulting in enhanced proliferation, survival, or resistance to treatment, the impact of ESA therapy is difficult to predict. If patients were anemic and their tumors hypoxic, ESA treatment might decrease (through decreasing local EPO production) or increase (through ESA effect on tumor cell EPO-R) tumor progression and resistance to therapy.\textsuperscript{90} Most in vivo studies suggesting an effect of EPO on tumor progression have removed EPO or blocked its effects, rather than added ESAs. If EPO-R–driven effects on tumor biology can only be shown using this approach, this suggests that endogenous EPO is sufficient to produce all of the effects. This may be relevant to targeting the EPO/EPO-R axis in cancer therapeutics but does not establish a deleterious effect of ESA therapy. Ultimately, even if functional EPO-Rs exist on human tumor cells, the effects of ESAs can only be determined through dedicated, well-designed, and well-executed clinical trials.

The Importance of Understanding Biology

The biology of the interplay among endogenous EPO, ESAs, hemoglobin, tumor oxygenation, and EPO-R, wherever they may be, is important to understand because it provides a framework for understanding the data and designing the safest and most rational approach to anemia in patients with cancer. For example, safety signals have been observed in some trials that have used ESAs to normalize hemoglobin or treat anemia in patients who were not undergoing chemotherapy, but not in trials that have used ESAs to treat CIA, which has been their major use in clinical oncology.

Is this because the biology of CIA is different, or because sufficiently powered and high-quality survival trials have not been performed in CIA? Preclinical evidence shows that tumor cell hypoxia increases resistance to chemotherapy\textsuperscript{10} and that treating anemia with ESAs in an animal model improves the response to chemotherapy.\textsuperscript{45} When used in CIA, are ESAs providing a benefit that is offset by an effect on another complex and emerging area: thrombosis and its role in tumor outcomes?\textsuperscript{25} The implications for rational practice and clinical trial design, moving forward, are clear.

Clinical Data

When concerns arose regarding ESA effect on disease progression or survival in patients with cancer, ESAs were largely being used in clinical oncology practice to treat, and not prevent, anemia in patients undergoing chemotherapy, not radiation therapy. This practice reduced transfusions and their associated risks (Figure 1), inconvenience, cost, and effects on blood supply. Any assessment of risks associated with ESA treatment should be balanced against these known risks. Unfortunately, the ability to predict and improve transfusion risk is imperfect and the necessary clinical trial data are not available to define the risks associated with ESAs when used to treat CIA.
Observational studies across malignancies found that anemic patients have inferior survival outcomes compared with non-anemic patients. However, whether these groups differ only in their hemoglobin levels is unclear; anemic patients may have more advanced and aggressive cancers, associated with bleeding, malnutrition, or an inflammatory cytokine storm. Nevertheless, anemia may be associated with cancer cell hypoxia and thereby with progression and resistance to treatment. With all other things equal, most physicians would prefer that patients not become significantly anemic because of the associated symptom burden, transfusion risk, and theoretical impact on treatment response.

### Studies Showing a Deleterious Effect on Outcomes
A randomized controlled trial that would definitively show the effects of ESAs on survival outcomes or tumor progression would need the following attributes:

1) Minimal exposure to ESA in controls
2) Homogeneous cancer type and treatment
3) Baseline balance in known prognostic factors
4) Sufficient power to reliably detect/exclude meaningful differences
5) Careful adherence to study protocol
6) Adequate follow-up
7) Reproducibility
8) ESA use relevant to current clinical practice

Key characteristics include subjects who have a defined tumor type and undergo a defined treatment for that cancer, and that known prognostic factors are balanced in the ESA and non-ESA arms at study entry. The protocol must also be followed, without a substantial proportion of patients undergoing treatment other than that specified. Unfortunately, no studies that meet the criteria either suggest a negative effect on cancer progression/survival or show safety in terms of these end points, except possibly one study in patients with small cell lung cancer and CIA that established noninferiority in terms of tumor response associated with ESA use.

Table 1 lists the trials that noted a deleterious effect on progression or survival outcomes and their limitations. The strengths and limitations of the older trials were previously well summarized and should be familiar, but the emerging data that have contributed to the debate on the safety of ESAs are summarized here.

#### The Anemia of Cancer Trial: The Anemia of Cancer trial was a randomized, placebo-controlled study designed to show the impact of ESAs on the incidence of red cell transfusion in patients with anemia of cancer (AOC) not undergoing chemotherapy. The trial was stratified for several factors predictive of transfusion risk but not for any predictive of survival. Although thrombotic events were more common in patients treated with ESAs (9.7% vs. 7.7%), differences in detected and reported thromboses did not explain the observed mortality. Baseline imbalances were present in factors predicting survival, all favoring the placebo arm. However, when the survival results were adjusted for these known factors, the survival difference was diminished and no longer statistically significant, but the trend remained.
Interestingly, the survival differences favoring placebo were not observed in women in general or breast or ovarian cancers in particular. A reduced observed survival was associated with ESA use in patients with B-cell malignancies and those who underwent transfusion; rapid hemoglobin rise was not associated with a reduced survival.

These data are not consistent with previously published trials of ESAs in AOC, which were smaller and did not restrict entry to patients with active cancer. However, the benefit of ESAs for patients with AOC should be considered unproven and associated with a risk of diminished survival. It should not be part of routine practice.

ESA treatment for AOC never received regulatory approval, and ESAs have been used primarily to treat CIA. The cause of the observed survival difference is currently unknown. Potential explanations include artifact related to baseline imbalances of prognostic factors, an increase in occult thromboses, and a direct effect of ESAs on tumors or tumor blood vessels, although the latter is difficult to reconcile with previous studies that suggest that effect would be observed in patients with breast cancer and not those with multiple myeloma. Ultimately, this study cannot be interpreted for survival outcomes because it was not designed to address this question.

**PREPARE Trial:** The PREPARE trial was only presented as an interim analysis and in abstract form. Recently, concern developed when an interim analysis of the data showed an imbalance in relapse-free and overall survival favoring patients who were not randomized to receive ESAs that did not achieve statistical significance. In this trial, patients with early breast cancer who were undergoing neoadjuvant chemotherapy were randomized to receive ESA to maintain a hemoglobin level of 12.5 to 13 g/dL during the 24 weeks of treatment. In some instances, patients did not develop anemia and were therefore never potentially eligible for or exposed to ESA therapy. No differences in tumor response were noted in patients receiving ESAs.

Now, with a median follow-up of 3 years, an unplanned interim analysis showed that the survival and progression-free survival rates were lower (86% vs. 90%, hazard ratio, 1.42; and 73% vs. 79%, hazard ratio, 1.33, respectively) in the arm randomized to receive ESA if and when hemoglobin level decreased. These results are concerning, particularly in light of the earlier BEST trial results, but 3 caveats exist.

First, the differences between the ESA and control arms diminish substantially when the analysis is confined to patients who actually became anemic and were therefore treated according to their randomized group. Why being randomized as at risk for needing ESA and then not requiring it would impart a risk for relapse relative to patients randomized for observation who did not become anemic is difficult to explain.

Second, the time course of the mortality observation is different in the 2 studies. In the BEST trial, the only increase in observed mortality occurred early, in the first 4 months of treatment; in the PREPARE trial, the differences occurred more than 2 years after discontinuing the study drug. This discrepancy may at

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**Table 1 Studies in Which ESA Therapy Has Been Associated With Reduced Progression-Free or Overall Survival**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Tumor</th>
<th>Entry HB</th>
<th>Progression-Free Survival?</th>
<th>Overall Survival?</th>
<th>Quality Issues (As Numbered on Page 569)</th>
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</thead>
<tbody>
<tr>
<td>BEST</td>
<td>939</td>
<td>Breast</td>
<td>13 g/dL</td>
<td>Neutral</td>
<td>Reduced</td>
<td>3,5,7,8</td>
</tr>
<tr>
<td>Hedenus</td>
<td>344</td>
<td>B-cell</td>
<td>&lt; 11 g/dL</td>
<td>—</td>
<td>Reduced</td>
<td>2,3,7</td>
</tr>
<tr>
<td>ENHANCE</td>
<td>351</td>
<td>Head &amp; neck</td>
<td>12 g/dL F</td>
<td>Reduced</td>
<td>Reduced</td>
<td>3,5,8</td>
</tr>
<tr>
<td>DAHANCA 10</td>
<td>484</td>
<td>Head &amp; neck</td>
<td>12–13 g/dL</td>
<td>Reduced</td>
<td>Neutral</td>
<td>8</td>
</tr>
<tr>
<td>Wright</td>
<td>70</td>
<td>Lung</td>
<td>&lt; 12 g/dL</td>
<td>—</td>
<td>Reduced</td>
<td>2,3,4,7, +/-8</td>
</tr>
<tr>
<td>Smith</td>
<td>985</td>
<td>Multiple</td>
<td>&lt; 11 g/dL</td>
<td>—</td>
<td>Reduced</td>
<td>2,3,5,7</td>
</tr>
<tr>
<td>PREPARE</td>
<td>735</td>
<td>Breast</td>
<td>13 g/dL</td>
<td>Trend</td>
<td>Trend</td>
<td>7,8</td>
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<tr>
<td>GOG 191</td>
<td>109</td>
<td>Cervical</td>
<td>12 g/dL</td>
<td>Trend</td>
<td>Trend</td>
<td>3,4,7,8</td>
</tr>
</tbody>
</table>

**Abbreviations:** BEST, Breast Cancer Erythropoietin Trial; DAHANCA, Danish Head and Neck Cancer Group; ESA, erythropoiesis-stimulating agents; F, female; GOG, Gynecologic Oncology Group; HB, hemoglobin; M, male.
least be partially explainable by the difference between metastatic and early breast cancer. Finally, the observation has not been reproducible in other randomized trials of ESAs in breast cancer.19,20

What is Known?
Large and important gaps in knowledge exist on the use of ESAs in oncology. Several points are apparent given the state of the data:

- Increasing hemoglobin concentrations to levels of 13 g/dL or more to improve tumor oxygenation and response to treatment has been adequately explored and is a failed experiment (ENHANCE, DAHANCA 10). This should not be done in routine clinical practice, and the wisdom of any further clinical trials addressing this hypothesis is questionable.
- The use of ESAs during radiotherapy for head and neck cancer cannot be regarded as safe and should not be part of routine clinical practice.
- The use of ESAs in patients with cancer is associated with an increase in the incidence of venous thrombosis and thromboembolism.9 Overall, this relative risk is 1.4 to 1.6, with an increase in the incidence of observed thrombosis increasing from approximately 3% to 5% to 6%. This risk is not evenly distributed across all tumor types and treatments; it appears to be more frequent when patients have pelvic malignancies, are undergoing radiotherapy, or are taking other medications, such as hormonal therapy or thalidomide, that increases thrombosis risk. The mechanism underlying this increased risk is not well understood and has not been definitively linked solely to changing hemoglobin levels. The optimal prevention strategy is not known; low-dose warfarin does not reduce the risk.24
- Treatment of AOC with ESAs may be associated with a decrease in survival.12,13 Although the cited trials are seriously flawed and inconclusive, until the safety (and efficacy) of ESAs in this setting are shown, it should not be routine practice.
- No negative survival signals have arisen in trials addressing treatment for CIA, which is the most frequent use of ESAs in oncology.91
- A severe paucity exists of well-designed and executed studies examining the effect of ESAs on survival, particularly regarding their use for treating CIA.

Re-examination of the safety of ESAs for patients with cancer has caused a revision to the guidelines60 and a change in reimbursement, and therefore access for patients. In general, the change restricts use to patients with CIA and initiates treatment at a lower hemoglobin level (< 10 g/dL) than previously used in uniform practice, although not all revised guidelines have specified this lower hemoglobin initiation point.96 This trend will likely continue, and oncology practice will move toward lower hemoglobin initiation and target levels.

What Knowledge is Needed?
Several very important scientific and public health issues remain to be clarified:

- Is therapy with ESAs associated with inferior tumor progression or survival outcomes in patients with cancer?
- If therapy with ESAs is associated with inferior outcomes, what is the mechanism?
- Do ESAs pose a risk to patients with a particular tumor type? As noted, results from available trials do not consistently show a signal in a particular tumor type, and most studies are seriously flawed; this comment applies equally to those suggesting safety and those raising a safety concern. Well-designed (Table 1) and -executed trials are needed in the major tumor types (e.g., breast, lymphoma, non-small cell lung) to determine whether survival is impacted when ESAs are used to treat CIA.
- What are the public health impacts of decreasing hemoglobin initiation points to less than 10 g/dL? This will decrease total exposure to the whole population of patients with CIA, and if ESAs have a deleterious effect in that setting, this may be a good thing. However, no data support a conclusion that starting at lower hemoglobin levels will enhance patient safety.99 Because ESAs can be slow to stop the hemoglobin decline in patients undergoing chemotherapy, initiating at hemoglobin concentrations under 10 g/dL is likely to increase transfusion rates97-99 and the proportion of patients with CIA who receive both ESAs and red cell transfusions. This may not be a good thing. A randomized trial of early (10–11 g/dL) versus late (10 g/dL) initiation with appropriate design and sufficient power for both transfusion and survival end points would be very helpful in designing rational policy.

What Helpful Data Are Coming Soon?
Several randomized trials of ESAs are maturing, and data in breast cancer and B-cell malignancies are
forthcoming and should help, to some extent, clarify the outstanding issues. Although important, results of any additional large randomized trials are years away. Study-level meta-analyses have failed to show an overall significant effect of ESAs on survival, especially when analysis is confined to patients with CIA. Although the meta-analysis approach has shortcomings, including a tendency to dampen even a large effect if it is confined to one subset of patients, it has the advantage of statistical power and ready access to data. Recently, the 3 sponsors of ESAs in oncology have provided the Cochrane group with their patient-level data; this will permit a much more powerful and complete meta-analysis, and results are expected shortly.

Conclusions

Because of the lack of well-designed and -executed randomized trials with survival as an end point, not much more is known about the safety of ESAs in patients with cancer since the previous publication in JNCCN in 2005, particularly for the treatment of CIA. Additional data, some suggesting safety and some suggesting risk, have been reported, but flaws in the trial designs and a lack of clear relevance to the CIA setting severely limit their usefulness. Less ESA therapy will probably be given for the treatment of CIA as the initiation and target hemoglobin concentration decreases. This may not be a sound public health strategy, because no evidence shows that it will reduce any risk to patients, and some even shows that it will increase their exposure to the known risks of red cell transfusions. Additional data are expected, but future trials are still needed to study 1) the overall safety of ESAs in treating CIA in patients with common tumor types, and 2) the public health impacts of decreasing initiation and target hemoglobin levels. Pursuing laboratory work to further elucidate the interplay of oxygenation, hemoglobin level, EPO, EPO-related play in anemic cancer patients receiving epoetin alfa therapy. Cancer 2002;95:888–895.


References


Erythropoiesis-Stimulating Agents


