

From the editor's desk

ESAs: whatever happened to evidence-based medicine?

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With new data, new FDA rulings, and news across the media on rebates—some call them kickbacks—paid to oncologists and other specialists, erythropoiesis-stimulating agents are at the white hot center of a debate in medicine. Are these drugs overprescribed by physicians eager to collect cash from pharma? Or are they quality-of-life-saving medications doled out judiciously and appropriately? In a series of articles found in the next few pages, as well as two Having Your Say opinion pieces beginning on page 367, we sort through the controversy.

As we go to press, the pitched debate on appropriate use of erythropoiesis-stimulating agents (ESAs) rages on. In the following four articles, you will get a sample of a few of the issues in this debate.

But before you go there, I'd like to step back and start at the beginning. After 15 years of both randomized placebo, and active controlled trials, we can draw several simple conclusions: ESAs do decrease blood transfusions, increase hemoglobin levels, and improve quality of life in the majority of patients with chemotherapy-induced anemia (CIA) when the target hemoglobin is no higher than 12 g/dL as per the current label issued by the US Food and Drug Administration (FDA). These data give us many options for ESA use in CIA, but admittedly there are still no clear-cut recommendations on the best dose, schema, target hemoglobin, or CIA patient population to treat.

What about safety, truly the hottest part of this debate? These same 15 years of clinical trials, many of them placebo controlled, gave us very little in the way of a safety signal, venous thromboembolism (VTE) being one notable exception. But then other worries began: Two placebo-controlled trials completed in 2004

raised red flags for overall survival when the ESAs were used in patients with either breast cancer or head and neck cancer. However, these patients were treated with higher ESA doses and to higher target hemoglobin levels than was recommended on the FDA label. The FDA's Oncologic Drugs Advisory Committee convened to review all these data and was satisfied with the safety of ESAs in oncology when used on label. An independent Cochrane meta-analysis published in 2006 also concluded, after reviewing 9,500 patients, that there was still no overall survival safety signal when the body of evidence was viewed as a whole.

This same meta-analysis did reiterate that VTE was a concern, with a hazard ratio of about 1.6 for the ESA-treated patients. But in 2007 several trials again raised concerns about overall survival. They included a Danish head and neck cancer study (not published), an anemia of cancer study (presented but not published), and a non-small cell lung cancer trial terminated prematurely with only about 70 patients (published). With the potential for a negative safety signal once again, the FDA understandably issued a black box warning and ordered another Oncologic Drugs Advisory Committee (ODAC) meeting on May 10th to hear and discuss these data.

The fallout

The day before the ODAC meeting, *The New York Times* weighed in with an article that accused doctors, and the drug companies that supply them, of giving ESAs to patients for profit. For patients, who must surely feel confused by all this, and for clinicians trying to sort through the issues by conducting a scientific debate, the timing could not have been worse.

Several days after the ODAC meeting, Medicare released a proposal to regulate ESAs. If adopted, this broad plan with its sweeping restrictions would largely grind ESA use in CIA to a halt and likely cause a resurgence of blood transfusions in oncology patients. Here's a sampling of some of the restrictions that Medicare is proposing:

- No ESA until hemoglobin level is ≤ 9 g/dL;
- The total duration of ESA therapy should be 12 weeks;
- There should be a ceiling on the total monthly dose;
- No ESA use in myelodysplastic syndrome;
- No ESA use in patients on bevacizumab (Avastin) or cetuximab (Erbix);
- Some vague restraints on patients whose tumors might express erythropoietin receptors (a field just recently clouded by imprecise biochemistry).

Where is the evidence to support these proposals? The truth is, there is none. We know that ESAs work in the majority of patients with CIA. And that we know from carefully designed clinical trials. Shouldn't Medicare be held to the same standard?

Fess up and move on

But let's also make some confessions where all of us are concerned. Do these drugs cost too much? Yes, clearly. Has more than one oncologist profited from the reimbursement on ESAs and should this practice be examined and correct-

ed? Again, yes. Are ESAs safe when used on label in CIA patients? Here the data would suggest the answer is yes, but the recent trials give us pause and suggest that, once again, this issue should receive a fair, balanced review, based on the totality of evidence. Neither *The New York Times* nor the Medicare pronouncements constitute such a review.

We need to thoroughly evaluate the appropriate use of ESAs in oncology based on the entirety of medical evidence, without emotional distractions. Payers, prescribers, the government, and the media should partici-

pate dispassionately in this process so that the end users, our patients, will get the most benefit with the least chance for harm from this important and effective class of drugs.

As one of *Community Oncology's* editors is fond of saying, "Medicine's goal should be T&A: transparency and accountability." So let's do that, and let's get it done quickly. Only in that way can we continue to use ESAs safely and responsibly, as we should use all therapies.

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Adverse Events Alert

The run-up to the ESA controversy and where we go from here

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In recent years, a series of phase III clinical trials have been under way to evaluate administration of epoetin alfa (EPO; Epopgen) and darbepoetin alfa (DARB; Aranesp) in off-label, potentially market-expanding clinical settings. Since 2003, safety concerns with these erythropoiesis-stimulating agents (ESAs) in these settings were noted, based on findings from three trials that had been prematurely terminated.¹ Shortly thereafter, two phase III clinical trials demonstrated increased mortality and tumor progression when cancer patients received EPO versus placebo.^{2,3} The first trial, of patients with head and neck cancer undergoing radiation therapy, sought to raise hemoglobin levels beyond the correction of anemia in an effort to

improve local tumor control and potentially improve survival.^{4,5} The second trial, of women with metastatic breast cancer who were receiving chemotherapy, evaluated EPO use targeted to maintain hemoglobin levels between 12 and 14 g/dL.

The 2004 ODAC meeting

Following publication of these findings, in 2004 the Oncologic Drugs Advisory Committee (ODAC) of the US Food and Drug Administration (FDA) reviewed the safety profiles of EPO and DARB. FDA reviewers reported venous thromboembolism (VTE) rates of 12.1% for EPO versus 3.1% for placebo patients ($P = 0.09$) and 5.0% for DARB versus 3.1% for placebo patients ($P = 0.6$) in phase III registration trials.⁶ The manufacturers reported VTE rates in

phase III industry-sponsored clinical trials: 6.1% versus 3.4% for DARB versus control, $P = 0.02$ (11 Amgen-sponsored clinical trials); 5.8% versus 3.4% for epoetin alfa versus control, $P = 0.06$ (10 Johnson and Johnson-sponsored clinical trials); and 6.1% versus 3.4% for epoetin beta versus controls, $P = 0.05$ (9 Roche sponsored clinical trials).^{2,5-7} However, no increase in death rates among EPO or DARB-treated cancer patients was noted. After this meeting, manufacturers of EPO and DARB revised their package inserts, identifying higher-than-expected VTE rates but not increased mortality rates when cancer patients received these agents.

Note: Parts of this article have been accepted as an abstract and will be presented at the American Society of Clinical Oncology conference in Chicago, IL, June 1-5, 2007.

Additional safety concerns and controversy

Since the 2004 ODAC meeting, additional safety concerns have been identified. For example, although six systematic reviews reported prior to 2004 did not identify *any* safety concerns with EPO or DARB, a 2006 systematic review from the Cochrane Collaboration reported a statistically significant 1.7-fold increased risk of VTE, but not of mortality, when these agents were administered to cancer patients.⁸ In 2007, three phase III trials and a phase II trial all demonstrated adverse effects of erythropoietin treatment on cancer survival.⁹⁻¹² Final results from one of these studies, a controlled trial of EPO versus placebo treatment of anemic patients with non-small cell lung cancer (NSCLC), have been published. Originally designed to test whether erythropoietin improved quality of life, this trial was halted when an interim analysis of 70 patients showed a statistically significant adverse effect of EPO treatment on survival.

Like the 2003 studies, the major cause of accelerated deaths in EPO-treated patients appeared to be cancer progression. The two as yet unpublished phase III trials are the Danish Head and Neck Cancer Group (DAHANCA-10) trial of DARB in patients with head and neck cancer, and the Amgen 103 trial of DARB treatment of patients with advanced cancer, including prostate cancer, breast cancer, and NSCLC.^{9,11} A Roche-sponsored phase II study compared DARB with an investigational erythropoietin derivative, continuous erythropoietin receptor activator, in patients with advanced NSCLC receiving first-line chemotherapy.¹² In response to these studies, a “black box” warning and “Dear Doctor” letter outlining safety concerns with EPO and DARB administration in the oncology setting were issued in March 2007, and a second

meeting of the ODAC was held on May 10, 2007.

The 2007 ODAC meeting

The FDA Briefing Document released by ODAC on May 10, 2007, stated that the safety concerns of EPO use in the on-label setting had not been adequately addressed from 2004–2007. Although an increased risk of VTE is now apparent, whether EPO or DARB is associated with an increased risk of tumor progression or mortality remains unclear. The report urged researchers to continue to weigh the benefits of EPO use against the risks, ie, reduction of blood transfusions versus decreased survival and/or increased tumor progression and VTE. The report also suggested that in order to improve patient safety, the package inserts may need to be modified to restrict the indicated patient population or to limit the dosing and achieve lower target hemoglobin levels.

Implications

The development of recombinant erythropoietin and darbepoetin has had a marked impact on medical practice. Annual cancer-related sales account for \$10 billion, more than any other drug class in the oncology setting.¹³ Among anemic cancer patients who are receiving chemotherapy, EPO and DARB administration reduces transfusion requirements. Despite this benefit, there are increased risks of VTE and, seemingly, death when cancer patients receive these agents in several off-label settings that represent potential expansions of FDA-approved markets. Clinicians should be cognizant of the increased safety hazards when cancer patients receive EPO or DARB for indications other than those specified on the product label.

Acknowledgment: We thank Cara C. Tighe for helpful comments and revisions on earlier drafts of this manuscript and for administrative support.

Fast Facts

EPOETIN ALFA

Anemia occurs commonly among patients with cancer and often results in adverse effects on patients' quality of life.* Endogenous erythropoietin, a glycoprotein that increases the production of red blood cells in the bone marrow, serves as the major regulator of red blood cell production. In 1991, the US Food and Drug Administration approved recombinant epoetin alfa as a treatment for patients with non-myeloid cancers who develop chemotherapy-induced anemia. In 2003, darbepoetin alfa received approval for the same indication.

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A physician's point of view

The FDA spoke: now what?

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Since they were introduced nearly 20 years ago, hematopoietic growth factors have dramatically changed the practice of hematology and oncology. Their use as supportive care agents has reduced neutropenia and infections, maintained chemotherapy relative dose intensities, reduced the need for transfusions, and improved quality of life for countless patients.

Recently, the US Food and Drug Administration (FDA) issued an alert pertaining to the use of erythropoiesis-stimulating agents (ESAs) in anemic and non-anemic patients in various clinical settings.¹ The alert cites research studies that report an excess of serious and potentially life-threatening events associated with these drugs. Of note: the adverse events appear to be a class effect involving both epoetin alfa and darbepoetin alfa.

The FDA's new black-box warning to clinicians states that there is an "increased risk of death when ESAs are administered to a target hemoglobin of greater than 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy." This statement comes mainly from an as yet unpublished clinical trial sponsored by Amgen (20010103) evaluating outcome

in cancer patients with anemia who are not receiving active anticancer therapy. Survival was not a planned endpoint in this study, but was found inferior in darbepoetin-treated patients when the toxicity data were analyzed. ESAs are not indicated in this population. But earlier data² suggested efficacy, and the US Pharmacopoeia (Compendia) had listed "anemia of cancer" as an approved indication, for which reimbursement was granted by Medicare and other payers. However, reimbursement for previous anemia of cancer has now been withdrawn by Medicare and the private payers.

Another recent study, also sponsored by Amgen (20010145) and not yet published, did use survival as a primary endpoint in patients with extensive-stage small cell lung cancer undergoing platinum and etoposide therapy. There was no significant effect of drug therapy on overall survival or on progression-free survival. Few of the patients in this Amgen study had hematologic malignancies and none had myelodysplastic syndrome (MDS).

There are at least two studies of cancer patients in which the use of ESAs to prevent or treat anemia resulted in inferior outcomes when

compared with control groups that did not receive the drugs. These studies^{3,4} were in head and neck cancer patients who were treated with radiation (plus epoetin alfa and/or darbepoetin alfa in the experimental arm); another study was in patients with metastatic breast cancer treated with chemotherapy (plus epoetin beta in the experimental arm).⁵ Hemoglobin targets in these studies were well above the current guideline limit of 12 g/dL. Therefore, both the timing and target ranges used in the study would not be considered appropriate under current guidelines.

Safety first

As practicing hematologists and oncologists who use these agents, our priority is always patient safety, first and foremost. It is our job to use ESAs and all other therapies safely and effectively, protecting against overuse as well as underuse. To do that, it's reasonable and appropriate to follow the current FDA label and the guidelines set up by the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the American Society of Hematology. We can expect new recommendations shortly from the FDA's Oncology Drugs Advisory Committee, which

met on May 10, 2007. They are likely to demand more phase III randomized, placebo-controlled studies from pharma.

In a letter to the FDA sent on April 25, 2007, the American Society of Hematology appropriately recommended phase III trials be initiated to address ESA issues in hematologic malignancies specifically. We anxiously await the full analysis and peer review of all these studies.

Compendia-listed uses for ESAs in cases such as myelodysplasia will be revisited, but for now no additional safety signals have come out

of the studies of ESA therapy for low grade MDS-treated patients. Thus far, reimbursement has followed the Compendia label and guidelines formerly listed by the US Pharmacopoeia. Off-label use of ESAs is clearly inappropriate and for now should be considered possibly unsafe. As always, we need to educate patients about the potential side effects of these therapies.

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A payer's point of view

How one payer has stimulated a change in ESA therapy

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Ideally, the US Food and Drug Administration's (FDA) warning on erythropoiesis-stimulating agents (ESAs) would cause an immediate change in physician prescribing. But experience tells us that, without incentives, changes in therapy occur slowly. So what is the role of a payer in this situation?

Last summer, UnitedHealthcare (UHC) anticipated this issue and implemented a pilot preauthorization program in its Oxford plan. The program required adherence to guidelines for ESA coverage—specifically, guidelines issued by the National Comprehensive Cancer Network and the American Society of Clinical Oncology. Within 6 months, ESA usage decreased by more than 30%.

We also created incentives to accelerate change. Because the Oxford results were so alarming, we began a

national claim policy in April 2007 requiring ESA claims include a hematocrit level. If the hematocrit exceeds 36%, the claim is denied, based on the FDA safety warning.

A claims system isn't a perfect tool for clinical monitoring, but it can be effective, as the Oxford experience proved. UHC processes more than 500,000 ESA claims annually—such volume requires compromises to make the process work smoothly. For example, we don't allow dosage adjustment above the hematocrit of 36% because claims systems can't read "half doses," patients don't have symptoms with a one or two point change in their hematocrit, and the FDA recommends target levels of 30%–33%. We were also aware that many billing systems require programming changes for the hematocrit reporting requirement. But it's simpler to make that change than to revert to

paper claims with attached lab reports.

UHC will continue to use the claim process for safety and quality monitoring. Another UHC pilot study revealed that 12% of patients on trastuzumab (Herceptin) therapy did not have an over-expression of the HER2/*neu* gene. We now prevent that inappropriate therapy by reviewing the HER2/*neu* test as a requirement for coverage beyond the first dose. Unfortunately, 1 year later we still receive initial claims with an underexpressed HER2/*neu* gene.

Ultimately, our goal is to detect and prevent these issues in clinics before patients are treated. ESAs may provide the impetus to begin installing decision support systems in practices.

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Commentary from the administrator's desk

If insurers jump the gun on policy, patients and practices suffer

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As most oncologists know by now, Amgen issued a letter to healthcare professionals in January of this year, alerting them to the results of a study on darbepoetin alfa (Aranesp) in cancer patients with anemia not due to chemotherapy. The drug was found to be ineffective in reducing the need for transfusions in these patients; in addition, trial participants receiving the drug experienced higher mortality. It should be noted that results from the Amgen study have not yet been published in a peer-reviewed journal, and many scientific questions remain.

Not long after the Amgen letter was sent, private payers and the Center for Medicare and Medicaid Services (CMS) embarked on a flurry of policy reviews of coverage and reimbursement, and communications with providers.

CMS coverage decisions often serve as a bellwether for private payer determinations. Medicare has the responsibility to deliberate carefully, not just for the sake of patients the government covers, but for all cancer patients in the country. It's far too easy to formulate reactive policies when there are significant cost savings to be made and to forget that for most patients, these agents provide great value. Better that more time be taken to effect a measured change, if one is needed, than to toss the baby out with the bath water. In this case, that's a

distinct danger, as many practices have already seen.

Frederick M. Schnell, MD, president of the Community Oncology Alliance, expressed these concerns in a letter sent to Steve E. Phurrough, MD, MPA, the director of Medicare's Coverage and Analysis Group. In his April 12, 2007, letter, Dr. Schnell urged the agency to defer any policy decisions on erythropoiesis-stimulating agents (ESAs) until after the US Food and Drug Administration and the medical community thoroughly examined this issue:

Cigna Healthcare has cut by almost one-half, the number of medically necessary diagnoses for red blood cell growth stimulating factors. United Healthcare requires a hemoglobin and hematocrit on ALL patients prior to treatment. Blue Cross/Blue Shield of Tennessee is considering a prior authorization process that will wreak havoc in the treating physician's office and, very significantly, likely delay treatment to the patient who appropriately requires treatment. And, depending on where you live geographically, the indications and approved uses for ESAs may vary widely for Medicare, contractor by contractor.

Treating in good faith

When payment policy jumps the gun and limitations on coverage are enacted swiftly without scientific due process, the impact on practices and patients is significant. We cannot provide

treatment in good faith, in accordance with standards of care and indicated coverage, only to have—often without notice—seemingly arbitrary limitations and reductions imposed such as Cigna's new rules and the disjointed policies of various Medicare contractors.

In the case of UnitedHealthcare, it has used a wide broom to make a sweeping policy: based on established guidelines, it is requiring that all practices expend the additional time and resources to prove on the claim form, rather than in the chart documentation, that the practice is making appropriate decisions and dosage choices. UnitedHealthcare is tarring all physicians with the same brush and adding to the complexity and cost of delivering care across the board.

I believe we need to focus on refining systems that assist the physician, ensuring that he or she has all the tools and lab results needed to determine treatment. I also believe we should continue to use audits and post-audit penalties as the policing mechanism.

Side effects and toxicities are often managed well with supportive care agents such as erythropoietin. Patients cannot afford to pay for suddenly disallowed drugs or do without treatment that helps them endure and complete their fight against cancer.

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