

Commentary

Talking to ODAC and meeting a stone wall

David H. Henry, MD, FACP | Pennsylvania Hospital, Philadelphia, PA

The large ballroom in the Gaithersburg, Maryland, Holiday Inn was already half full just a few minutes after 7 o'clock in the morning, nearly an hour before the meeting was to begin. Fourteen members of ODAC—the Oncologic Drugs Advisory Committee—were seated on the dais with a few officials from the US Food and Drug Administration (FDA) interspersed among them. As 1 of 20 “public speakers” chosen at random, I was seated in a special section near the front. At 8 o'clock sharp, the meeting was called to order to address the business at hand: evaluating, once again, safety concerns about erythropoiesis-stimulating agents (ESAs) in chemotherapy-induced anemia (CIA).

Curiously, in this trial-like atmosphere, the “defense” went first, before hearing what the “prosecution” had to say. Representatives from Amgen and Johnson & Johnson gave an hour-and-a-half-long presentation addressing in great detail the two recent off-label studies in breast cancer and cervical cancer that induced ODAC to convene on this day, March 13, 2008. In both studies, higher doses of ESAs were used to raise hemoglobin levels above 12 g/dL. Both studies showed an excess number of deaths, although the numbers were not statistically meaningful.

Several times, the company presentations underscored the major points in all ESA studies in CIA that show the negative patient outcomes in the categories of thrombovascular events (TVEs) and survival. The patients who do the worst are those who get the increasing doses of ESA, but fail to re-

spond, and go on to receive transfusions. This is where the safety signal seems to be, and it highlights once again that clinicians should stop using ESAs when, after 8 or so weeks, it's clear the agents are not working in an individual patient. The companies capitulated on the starting hemoglobin levels for CIA, suggesting that 10 g/dL was a reasonable starting threshold. This is what is now required by Medicare, despite the new American Society of Hematology and American Society of Clinical Oncology guidelines recommending that clinicians should always begin administering ESAs at 10 g/dL, but should also consider starting them sooner if the hemoglobin level is rapidly falling toward 10 g/dL. The panel briefly discussed the data addressing the starting hemoglobin value that triggers ESA administration. But they could not reach a consensus—despite ample data that show it's better to prevent a transfusion by starting ESAs sooner rather than later when the hemoglobin level is falling.

And in this corner...

The FDA presentation was next. For an hour and a half, agency officials reviewed the issues somewhat superficially, compared with the pharma talks. A major point of the FDA presentation, allegedly trumping the companies' explanation of the data, was that higher “targeted” hemoglobin levels do not necessarily equal “achieved” hemoglobin levels. Amgen's Anemia of Cancer 103 study targeted hemoglobin values over 12 g/dL, but the average hemoglobin value achieved was 10.6 g/dL. However, FDA's presentation missed an important point—namely, that 10.6 g/dL was an average hemoglobin val-

ue achieved in those patients. The patients who actually did reach the higher hemoglobin values had fewer transfusions and lower ESA dosing and did very well from TVE and survival standpoints. In contrast, those patients with continued ESA dosing who did not respond, whose hemoglobin levels fell, and who needed transfusions, had the greater adverse safety outcomes of TVE and death.

An animated discussion of the pharma and FDA presentations followed from all the ODAC members. Unfortunately, it became clear that about two-thirds of the panel were novices in their understanding of CIA and ESA use and data. Admittedly, the studies and data that have built up over 15 years to the culmination of this ODAC meeting followed a long and tortuous course. But it was disappointing to see how uninformed some of the committee members were. A pause for lunch broke the tension, and we reconvened an hour later to begin the public session.

Twenty public speakers were chosen randomly from the community at large to make any comment they wished in three minutes or less. Most were in support of ESAs in CIA. During my allotted time, I tried to persuade the panel that independent meta-analyses of all the data from the past decade and a half had not shown a legitimate or worrisome safety signal or death, except for the well-known TVE signal of a 1.5 relative risk.

However, perhaps the most arresting presentations during the hour-long public session came from two lay people. The first was a patient, a woman obviously undergoing chemotherapy who had no hair. Speaking clearly and

continued on **page 213**

For your patients

The Oncologic Drugs Advisory Committee has recommended that the US Food and Drug Administration develop a consent form for patients receiving chemotherapy who are prescribed erythropoiesis-stimulating agents (ESAs). Until a formal document becomes available, Linda D. Bosserman, MD, and David H. Henry, MD, co-editors of *Community Oncology*, have compiled the following evidence-based informed consent sheet. You can offer this to your patients to help educate them about these drugs so they can make informed choices. Download this information at www.CommunityOncology.net/journal/0504.html.

What you need to know about anemia caused by chemotherapy and the medications called ESAs used to treat it

To deliver oxygen to the tissues and maintain health, the body makes red blood cells. When the level of red blood cells drops, a condition called anemia can develop. In some cases, chemotherapy can reduce the level of red blood cells and lead to anemia.

People who are anemic can experience extreme fatigue, shortness of breath, and dizziness. They may have difficulty concentrating or performing daily activities.

The production of red blood cells is directed by a hormone called erythropoietin (er-rith-ro-POY-ee-tin). A form of this hormone is now available in the medications Aranesp (darbepoetin) and Procrit (epoetin) as an injection to help you make red blood cells. These drugs are referred to as erythropoiesis-stimulating agents (ESAs) because they encourage the production of red blood cells. ESAs are virtually identical to the natural hormone erythropoietin.

Reasons to use ESAs

Aranesp and Procrit help prevent and treat anemia. Left untreated, anemia can become severe, which may lead to the need for a blood transfusion.

Severe anemia can also affect heart and lung function, especially in someone who already has heart or lung disease. And anemia can in-

terfere with your cancer treatment, causing a delay or even an interruption in your chemotherapy.

How ESAs work

ESAs work in your bone marrow to stimulate the production of more red blood cells. However, they don't work right away and may take several weeks to correct anemia. In one out of every three patients, ESAs don't work at all. Your doctor will monitor whether these medications are helping you and will adjust the dose as needed or discontinue their use.

When to begin using ESAs

Doctors determine the need for ESAs according to a patient's hemoglobin level. Hemoglobin is a protein in the red blood cells that contains iron and transports oxygen around the body. Normal hemoglobin levels are 12 g/dL (grams per deciliter of blood) and higher.

Scientific studies confirm the effectiveness and safety of ESAs if used under strict monitoring. The ESAs Aranesp and Procrit have been extensively studied regarding when to start them in anemia caused by chemotherapy. The best evidence suggests that doctors consider starting ESAs if hemoglobin levels fall below 12 g/dL when symptoms of anemia

may appear. If hemoglobin levels fall below 10 g/dL, symptoms will almost certainly appear.

Many healthcare plans have decided the hemoglobin level at which they will pay for ESAs. So your doctor may have to check with your insurance company to determine whether you are covered for this treatment. Some private insurers will only pay for the medication if hemoglobin levels fall below 10 g/dL or 11 g/dL and will continue coverage until the hemoglobin level rises to 11 g/dL or 12 g/dL.

Medicare will not pay for ESAs until the hemoglobin level drops below 10 g/dL and will not pay once it rises above 10 g/dL.

When to stop using ESAs

If hemoglobin levels reach 12 g/dL or above, ESAs should be stopped.

If hemoglobin levels do not rise after 8 weeks of ESA injections, the drugs also should be stopped.

Note: Your doctor may prescribe ESAs if you become anemic during your chemotherapy treatment. When you complete chemotherapy, you may still need to use ESAs for up to 12 weeks after the last chemotherapy treatment or until your hemoglobin reaches the target level of 12 g/dL or the limit set by your health plan.

How you will be monitored

Your doctor will:

- Test your iron levels and other factors that might contribute to anemia.
- Measure your hemoglobin levels before each dose of ESA or every 2 weeks if you are on a weekly dose.
- Reevaluate your dose after 4–6 weeks; if the hemoglobin level has not risen, you will receive increased doses according to standard guidelines.
- Decrease your ESA dose if you are on weekly medication and you experience a rise of 1 g/dL in the first 1–2 weeks.
- Check your iron levels at least every 3 months if you are on longer term ESAs.

The side effects and risks

Two in every 100 people taking ESAs experience common side effects such as headache, diarrhea, shortness of breath, swelling in the arms and legs, fever, cough, or infections.

Cancer patients receiving chemotherapy are at risk for blood clots in the legs and lungs. ESAs are known to increase this risk. Your doctor will discuss whether this particular risk applies to you.

Some studies have suggested that ESAs might in some way stimulate cancer cells in people with breast cancer or

head and neck cancer. But there is considerable scientific research that questions this theory. Ongoing studies are being conducted to resolve this issue; in the meantime, each patient should discuss this issue with his or her doctor.

In March 2008, the US Food and Drug Administration (FDA) met with a special panel known as ODAC (Oncologic Drugs Advisory Committee). ODAC's task was to study the potential risks of ESAs. In patients treated with ESAs in order to reach hemoglobin levels higher than the standard goal of 12 g/dL, there was a small but significant increase in the death rate. Because of this finding, ODAC recommended that patients with curable cancers and possibly those with breast and head and neck cancers not use ESAs. The FDA will review ODAC's recommendations as well as those of experts in ESA science before advising doctors.

Many scientists do not agree with these restrictions recommended by ODAC. Research shows that the greatest risk of death from ESAs is for those patients treated to reach hemoglobin levels over 12 g/dL and for those who continue to take ESAs but do not respond to the medication after 8 weeks. Many other studies have shown the safety and effectiveness of ESAs when used at the recommended

dosing and hemoglobin target levels.

What happens if ESAs are not used and anemia develops?

Patients who choose to tolerate anemia symptoms (from fatigue and dizziness to heart and lung problems) may require transfusions. In addition to the risks of severe anemia, there are risks to transfusions as well. They can cause less severe symptoms such as rash, fevers, hives, and shortness of breath. But more importantly, doctors are always concerned about infections in the blood supply that we cannot detect and that could be passed on. In general the blood supply is very safe. Infections such as HIV and hepatitis transmitted through transfusions are extremely uncommon today.

For some anemic patients undergoing chemotherapy who refuse transfusions, chemotherapy may need to be delayed from one to several weeks until the hemoglobin level returns to normal. Your doctor can advise you of other risks or benefits of using ESAs during your chemotherapy treatments.

All medical treatments present risks and benefits that you should carefully weigh with your nurses and doctors to make the best medical decision for your health.

Talking to ODAC continued from page 211

eloquently, she described her metastatic colorectal cancer that was diagnosed one month after her child was born some 20 months ago. The woman had outlived her projected 6-month survival by many months, and she pressed her point that her considerable anemia and fatigue were successfully addressed by ESAs, which allowed her more time to care for her child, enjoy her family, and avoid transfusion.

The other lay person was the wife of a man who did not survive his lung cancer. Emotionally, she recounted his final horrible days battling his disease as an outpatient and finally

as an inpatient, during which time he was also given ESAs. The drugs had no impact on his survival, she said, but were nevertheless "forced upon him" at the end by caregivers, including several nurses who told her the hospital made a lot of money on a particular drug and used one drug over the other because it helped the bottom line.

For me, these two presentations underscored how important ESAs can be when they work and how our healthcare system sometimes breaks down at the individual level. The interactions between patients and providers can be harsh and painful for

patients and their families.

For naught?

Sadly, I think much of the professional and lay presentations were lost on most of the ODAC panel. We held our breath as the first question went up for a vote; the panel was asked whether or not the labeled indication for ESA and CIA should simply be removed. They voted no. The next question—should the FDA restrict ESA use in CIA to small cell lung cancer—was asked because of the one study where there was no negative survival outcome in this disease. Again, fortunately, they voted

no, but it was a mixed vote and pre-saged more votes to come.

Next came a philosophical debate that questioned whether curable patients should be exposed to ESAs. The thinking here is that, because of the potential harm of ESAs, only incurable patients should take the medications. What a message this sends—that we place a greater value on the safety of and outcome for the curable as opposed to the incurable patient. People with “terminal” cancer sometimes live years. They deserve the same consideration as our curable patients.

Instead of trying to understand the issues in the large body of data presented, the ODAC panel simply voted to restrict ESA use to incurable patients. Even worse, the panel also voted

to restrict ESAs in patients with metastatic breast cancer and head and neck cancer. Their deliberations were based on two hyped off-label studies, one of which was poorly conducted; the other—although well meaning and well written—was executed poorly, through no fault of the lead author.

ODAC recommended that the FDA initiate a consent process for ESAs, a somewhat cumbersome but certainly reasonable way to ensure that the risks and benefits of ESAs are discussed with every patient. Lastly, no special pharmacy restriction process was recommended.

At the end of the day

So, where were we as the meeting and long day concluded? Lost was the

attempt to question the information and truly define the safety signals. Also, lost were those two patient-related public speaker comments that highlighted so poignantly the best and worst of good medical practice in our healthcare system.

The majority of clinicians prescribe ESAs responsibly, using them on label to avoid transfusions and improve patient quality of life, stopping their use after a reasonable period of time if they are not working. But the good news and outcomes documented in so many ESA studies during the past 15 years was lost on the ODAC panel. And now, the pending FDA decision on these ODAC recommendations threatens to take this good news away from a significant number of patients.

View from Community Oncology Alliance

Let oncologists make the medical decisions

Ted Okon, Executive Director

From the public policy perspective, the most disturbing aspect of the controversy over erythropoiesis-stimulating agents (ESAs) has been the imbalance between labeling approved by the US Food and Drug Administration (FDA) and the National Coverage Determination (NCD), which was implemented by the Centers for Medicare & Medicaid Services (CMS). I say this because the payment agency (CMS) in effect created its own ESA labeling as a part of the NCD, which significantly differed from the approved labeling by the regulatory agency (FDA).

There has been a great deal of debate about this, but facts speak the loudest: Medicare's NCD does not allow an oncologist to administer an ESA to a patient with a hemoglobin level of 10.2 g/dL, for instance, whereas the FDA-approved labeling does. In approving and

revising ESA labeling, the FDA has allowed physicians to exercise their clinical judgment within the guidelines of the labeling. On the other hand, Medicare has greatly restricted the ability of oncologists to exercise their clinical judgment, especially when dealing with the individualized needs and condition of each cancer patient.

Don't tie their hands

Given the recommendations of the Oncologic Drugs Advisory Committee (ODAC), it's expected that the FDA will soon make further revisions to ESA labeling. In considering these recommendations, it is imperative that the FDA not tie the hands of oncologists. Clinicians must be allowed to continue using their experience and expertise to customize treatment for each patient, safely and effectively. As one of the ODAC members commented with great insight, it's impossible to create a

theoretical cancer patient; each one is an individual, with different medical needs. With the FDA revisions to ESA labeling, undoubtedly the issue of FDA-labeling versus Medicare's NCD will arise. Presumably, Medicare will change its NCD if the FDA adopts ODAC's recommendations restricting ESA use. However, will Medicare's NCD be totally consistent with FDA-approved labeling, or will there still be discrepancies? It should be acknowledged that serving on a committee like ODAC is a difficult and sometimes thankless task. We should commend the members for their service. But if ODAC is truly meant to advise the FDA, then more of the members should be community oncologists well versed in clinical research and patient care. More than 80% of the nation's cancer patients are treated by community oncologists, assisted by mid-level practitioners and oncology nurses. ODAC should reflect this reality.