

An interview with Samuel Silver, MD, PhD, ASH Executive Committee Councillor; Chair, ASH Subcommittee on Reimbursement; and Professor of Internal Medicine at the University of Michigan in Ann Arbor

New ESA guidelines from ASH-ASCO: the last word?

By Lee S. Schwartzberg, MD | The West Clinic, Memphis, TN

When the Centers for Medicare and Medicaid Services (CMS) issued its policy this past July restricting coverage of erythropoiesis-stimulating agents (ESAs) to treat chemotherapy-related anemia, there was an uproar in the medical and scientific communities. Since then, the agency has gained the support of officials at the US Food and Drug Administration—and the ire of many oncologists. For the past 3 years, the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) have been updating their 2002 practice guidelines on the use of these drugs. On October 23, 2007, they published those guidelines online.*

To learn more about the rationale behind the new guidelines and the ongoing controversy, we spoke with hematologist/oncologist Samuel Silver, MD, PhD, Director of the University of Michigan Cancer Center Network, who serves on the ASH Executive Committee.

Community Oncology: From ASH's perspective, what are the highlights of the new guidelines?

Aside from reviewing all the new literature, the guideline committee was asked to consider two issues. First, darbepoetin alfa was not in the previous guidelines so we needed to explore its toxicities and its efficacy,

compared with standard erythropoietin agents. Epoetin alfa was found to be equivalent to darbepoetin alfa in terms of efficacy and side effects. We have a special commentary on this.

Second, the venous thromboembolism phenomenon has received increased attention since ODAC [Oncologic Drugs Advisory Committee]



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flagged it in 2004. There is now a new section in the guidelines pertaining to this. In part, this section reads as follows: "Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin is prescribed. Randomized clinical trials demonstrate an increased risk of thromboembolism in patients receiving these agents; specific risk factors have not been defined in these trials, and therefore clinicians

should use caution and clinical judgment when considering use of these agents." Specifically, ASH and ASCO are concerned about patients who are post surgery or have a history of thromboses or prolonged immobilization. In addition, myeloma patients on agents such as thalidomide [Thalomid] and lenalidomide [Revlimid] who are at increased risk for thromboembolism are also of concern.

After reviewing the literature, we really didn't change most of the points in the guidelines. As far as initiating ESA therapy, we reviewed early versus late and found that 10 g/dL was still the recommendation; there was no evidence for decreasing the transfusion requirement to 11 g/dL and there was no evidence as far as improving quality of life. The investigators went through all of those studies in great detail and, as they have done before—and I have to agree with this—found that the quality-of-life studies really are problematic in how they have been conducted and published. So we still use 10 g/dL as the initiating number.

As far as the maintenance level, there is no difference between the previous and new guidelines. Where ASH has its *major* differences with the Medicare national coverage determination [NCD], is the maintenance between 10 g/dL and 12 g/dL. We do recommend that when the hemoglobin level exceeds 11 g/dL,

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physicians consider dose reduction. In its black-box warnings, the FDA [US Food and Drug Administration] says that ESAs are not indicated in anemic patients not receiving concurrent chemotherapy. ASH supports this position.

Section 8 of the ASH guidelines is titled ‘Hemoglobin Target’ and the recommendation says to rise to or near a concentration of 12 g/dL. It then references the FDA new package insert from March of this year. But in mid-October, the FDA sent a letter responding to Representatives Pete Stark and Henry Waxman that was a bit surprising to many, as it supported the Medicare NCD on the basis of the March black-box label and other label changes. In that letter, the FDA mentioned that 12 g/dL is not considered a target but the maximally safe level. Do the ASH-ASCO guidelines then differ from that?**

Well, I’m a little perturbed by this and I don’t totally understand the FDA’s response to Stark and Waxman’s letter. Basically, I think the FDA said that the NCD was compatible with FDA labeling. I’d say that it’s compatible with but doesn’t totally encompass the language of FDA labeling. So I’m a little perplexed and I know there are other people on Capitol Hill who are going to be asking the FDA the same questions again. The devil is in the details and I think the use of the words “compatible with” doesn’t really give us the sense of what the FDA labeling is. Of course, we haven’t seen FDA’s response to the recent ODAC meeting. Potentially, the labeling could change after that as well. The guidelines specifically say they will have to look at label changes and see whether they will require another version of the guidelines.

The ASH-ASCO recommendation for 2007 on iron monitoring and

supplementation is not different at all. There is a very nice long summary of the new data on iron supplementation. Why, given these extensive new data, was there no recommendation for either endorsing or at least strongly suggesting IV iron, or information on when to give it and at what parameters?

The actual indication for the use of erythropoietin agents is to avoid transfusion. So as far as I know, there are no current data on whether one gives oral iron or IV iron, or whether in conjunction with erythropoietin agents, oral or IV iron actually changes the transfusion requirement. The hemoglobin levels may go up a little bit higher, maybe a little bit faster. From the point of view of FDA indications, we don’t know the answer to that question.

Let’s talk a little about transfusion. There is a concern among many hematologists and oncologists that the CMS guidelines will increase the number of patients receiving transfusions. Can you talk about ASH’s position on the risk of transfusions and the availability of transfusions, which in some communities is already a difficult issue.

I don’t think we really know whether the number of transfusions will go up. One thing I have said over and over again in meetings with CMS and staffers on Capitol Hill is that if the final NCD is any different than it was before this summer, CMS will need to monitor from a claims database the use of transfusions in this population. It would have to be retrospective and prospective. It’s certainly incumbent upon CMS to measure the effect of its policy. I suspect that transfusions will increase.

There are a number of issues with the use of transfusions: one has to do with the availability of people to administer them. The fact is that 85% of cancer patients are treated in community practices, and outpatient chairs

for transfusions at community hospitals are in short supply. So people will have to be admitted for transfusions, which is certainly a quality-of-life issue. I am not talking about shortness of breath and hemoglobin levels; I am talking about what patients who are undergoing chemotherapy will have to go through in order to support their need for increased hemoglobin.

I am also concerned about something that we didn’t really think about much 15 years ago, although we do now. That is the issue of transfusion-related graft-versus-host disease [GVHD]. These are immunosuppressed patients at higher risk for GVHD, so the blood units have to be irradiated and that puts a further strain on community blood banks that don’t have irradiators. This would cause another delay or would require patients to travel to a hospital in a central area. This is really going to stress the system and I am not even talking about the availability of units of blood.

Absolutely, I totally agree. The CMS guidelines are significantly at odds with the new ASH-ASCO guidelines. So what steps have ASH and ASCO taken?

Well, we’ve taken a lot of trips to Washington! But this message is incredibly important. ASH is not happy about Congress legislating hemoglobin levels. We should be practicing evidence-based medicine. And from the point of view of science, we think that CMS should reopen the national coverage determination. Whether that’s a practical stance or not remains to be seen. It’s worrisome that we are going to have two tiers of patients: those with private insurance and those who are Medicare beneficiaries. Nowhere in the system at the University of Michigan, for example, do we have two tiers of treatment guidelines, depending on insurers. This will change for ESAs if the current NCD stands.

And community oncologists would say that CMS should not

practice medicine and should not create arbitrary values at which therapy can be initiated.

Even if you administer ESAs three times a week, which many of us do not anymore, you'd need to do blood counts on patients 12 times a month, whereas many patients only require counts once every 3 to 4 weeks. The reason we would be getting these counts is not for the medical care of the patient, but purely for reimbursement issues. That's *not* how we should be practicing medicine.

CMS sent a letter asking for additional evidence that would support a change in the national coverage determination. Has ASH responded to that letter and are you aware of any other information? It would seem that your new guideline is very up-to-date.

Each organization has sent a letter, with our guidelines attached, essentially saying, "Here is the guideline, here is where it differs from what you are talking about, take a look at that." I think the questions CMS asked are very interesting. They need to be answered in clinical studies. The National Cancer Institute will meet in mid-December to look at the science of tumor initiation and tumor progression with ESAs. We are thinking about having an NHLBI [National Heart, Lung, and Blood Institute] meeting to look at the thromboembolic phenomenon with ESAs. There are many studies that still need to be done and many questions that need to be answered.

Based on the data that were presented at the ODAC meeting

and the March 2007 changes in the label for both epoetin alfa and darbepoetin alfa, does ASH believe there are any further changes needed in the FDA label?

The major issue that we have been focusing on deals with the maintenance of 10–12 g/dL versus < 10 g/dL. I know that ASCO talks about dosing issues that aren't concordant with FDA labeling. We agree with that, but we have not been pushing it.

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* The guidelines are posted at <http://bloodjournal.hematologylibrary.org/papbyrecent.dtl>

** Representative Stark's letter and the FDA response are posted at www.house.gov/stark/news/110th/letters/20071002-waxman.pdf and www.house.gov/stark/news/110th/letters/20071012-esa.pdf