

I am writing on behalf of my fellow physicians at California Cancer Care, a private-practice oncology group serving the Counties of Marin and San Mateo in the San Francisco Bay Area. We appreciate the opportunity to comment on CMS's proposed national coverage policy on erythropoiesis-stimulating agents (ESAs) for non-renal applications (CAG-00383N).

The development and introduction of the ESAs represented a major advance for cancer care in the United States and throughout the world. They have played an important supportive care role in reducing the need for blood transfusions and fighting fatigue, which is a major quality of life issue for our patients. Furthermore, the ESAs have allowed us to provide more effective chemotherapy in full-dose fashion that would not be possible otherwise. Their efficacy in achieving these goals is well documented in the scientific literature.

It is therefore with great disappointment that we read CMS's proposed National Coverage Determination on ESAs ("the NCD"). Overall, we feel that the NCD has little scientific basis, and is in direct conflict with expert opinion delivered during a meeting of the FDA's Oncology Drug Advisory Committee (ODAC). It completely disregards national treatment guidelines set forth by the American Society of Clinical Oncology, the American Society of Hematology, and the National Comprehensive Cancer Network (NCCN). The NCD inappropriately extrapolates data from two sources (namely preclinical laboratory models as well as clinical studies that investigated suprathreshold use of ESAs) in an attempt to force cancer patients and their physicians to accept a substandard of care.

California Cancer Care finds several portions of the proposed NCD to be particularly worrisome:

1. Restriction of coverage to cancer patients with hemoglobin less than 9 g/dl.

It is obvious from our clinical experience that patients on chemotherapy with hemoglobin less than 9 are very fatigued and often require immediate blood transfusion. Forcing a patient to wait to start ESAs until reaching this excessively low threshold runs counter to medical reason. A major objective of ESA use is to *avoid* fatigue, transfusions, and exacerbation of comorbid conditions. ESAs do not improve hemoglobin levels immediately and require weeks to work. The obvious outcome of this restrictive policy would be to diminish the quality of life of our patients, reduce our ability to give them effective chemotherapy, expose them to the risks of transfusions, and place the nation's blood supply at risk. We agree with the expert panel of the NCCN which, on the basis of *scientific* data, advocates use of ESAs in chemotherapy patients with hemoglobin less than 11.

2. Limit of 12 weeks of ESA therapy per patient per year.

This appears to be a completely arbitrary proposal by CMS with no foundation in the medical literature. The majority of our patients require chemotherapy for well in excess of 12 weeks per year. Many curative chemotherapy programs (e.g. for colorectal and breast cancer) far exceed 12 weeks in length. Patients with epo-responsive MDS require treatment throughout the year. Again, this limitation will diminish the quality of life of our patients, reduce our ability to give them effective chemotherapy, expose them to the risks of transfusions, and place the nation's blood supply at risk.

3. Early forced discontinuation of erythropoietin for “non-responders”.

We also object to this provision which again flies in the face of recommendations by the NCCN and other national guidelines. The NCCN clearly states that for patients with hemoglobin rise of less than 1 g/dl in the first 4 weeks, the dose should be *increased* for an additional 4-8 weeks before declaring the drug to be ineffective. In our practice we have witnessed time and time again the effectiveness of a dose increase in stabilizing the hemoglobin level and diminishing the need for transfusions.

4. Elimination of coverage for the anemia of myelodysplastic syndrome (MDS).

This proposal runs counter to years of experience showing improvements in quality of life and decreased transfusion requirements for patients with MDS. There is sufficient, high-level evidence that supports the use of ESAs for the treatment of anemia of MDS to make non-coverage inappropriate. The NCCN guidelines recommend the ESAs as first line therapy for certain subtypes of MDS. The NCD would effectively eliminate an effective, well-tolerated treatment option for many MDS patients. These patients would be forced to undergo repeated blood transfusions unnecessarily, putting themselves and the nation’s blood supply at risk.

5. Elimination of coverage for patients receiving therapy with drugs that target angiogenesis or the epidermal growth factor receptor (EGFR).

The anti-angiogenic drugs like bevacizumab and the EGFR inhibitors (e.g. cetuximab) are often combined with myelosuppressive chemotherapy. Patients often require erythropoietin as with any other chemotherapy regimen. The proposed restriction is based on a bold extrapolation from very preclinical laboratory data that examined suprathreshold doses of ESAs. CMS would be very premature in eliminating coverage for patients on these drugs before specific clinical studies on actual cancer patients are performed.

6. Elimination of coverage for patients whose cancer type is known to express the erythropoietin receptor (EpoR).

This proposal, which arose from studies cited at the ODAC meeting, is based on a misunderstanding of the significance of EpoR on tumor cells. The EpoR does not function as a tumor promoting oncogene, and there is no clinical data to suggest that the use of recombinant erythropoietin has direct tumor-promoting actions in humans. CMS has no scientific basis on which to make this restriction.

7. Perception of red blood cell transfusions as a reasonable and safe alternative to ESAs.

Red blood cell transfusions are not without risk. Risks include major and minor transfusion reactions, rash, fevers, hypotension, transfusion-related acute lung injury, infection, and death. For these reasons, patients do not receive transfusions until absolutely necessary for symptoms or to prevent exacerbation of comorbid disease. Patients requiring transfusions inherently have a lower quality of life and often have delays in receiving their chemotherapy to allow for the transfusion itself. Furthermore, the national blood supply is already stretched to its limit. In our opinion, red blood cell transfusions should only be used in cancer patients on chemotherapy when the ESAs have not been effective. The ESAs are the “safe and reasonable” alternative to transfusion, not the other way around!

California Cancer Care is deeply concerned that CMS's proposal would set a dangerous precedent in which evidence-based standards of high quality care are ignored in setting national policy. Implementation of these provisions has the potential to inflict serious harm to the many cancer patients who rely on ESAs in the course of receiving treatment for their disease. Neither CMS nor local carriers would allow (i.e., reimburse) Medicare providers to treat cancer patients based on such substandard scientific evidence or clinical reasoning. We suspect that this NCD is largely economically-driven, an invalid basis upon which to make clinical decisions. We propose that ESAs be used according to

current nationally-accepted treatment guidelines that have reduced chemotherapy-induced anemia, allowed for optimal cancer treatments, and improved quality of life amongst people living with cancer.

Sincerely yours,

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