

Erythropoietins in Oncology

TO THE EDITOR: Khuri (June 14 issue)¹ highlights safety concerns regarding the use of erythropoiesis-stimulating agents (ESAs) in patients with cancer. The studies that have given rise to these concerns used significantly higher hemoglobin targets than those used in the community or recommended in widely used guidelines,^{2,3} and thus do not reflect the current standard of care. The only study that did not use an excessively high hemoglobin target has not been published and cannot be accurately reviewed.

In these studies, treatment with ESAs was initiated in patients with hemoglobin levels as high as 14.5 g per deciliter. Many of these patients never would have received ESAs in the community, where the use of ESAs is generally initiated at hemoglobin levels below 10 to 11 g per deciliter.

Treatment with ESAs has been of enormous benefit to patients with cancer who have anemia, improving their quality of life and decreasing the need for blood transfusions.⁴⁻⁶ The safety and efficacy of ESAs, when used in accordance with current guidelines, are well established.

Revising the appropriate standard of care for ESA use in patients with cancer requires evidence of either an inferior outcome with the current standard or a superior outcome with a different approach. Studies that use excessively high hemoglobin targets simply indicate that ESAs should not be used excessively; they do not indicate that the current standard of care is harmful.

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THE AUTHOR REPLIES: Achieving the right balance in the use of ESAs in oncology requires a review of the relevant clinical data made available by the Oncology Drug Advisory Committee of the Food and Drug Administration (FDA).¹ ESAs were initially approved for chemotherapy-related anemia (not anemia of cancer) on the basis of data from six randomized, placebo-controlled, double-blind clinical trials involving 131 patients with cancer and anemia who were receiving concurrent chemotherapy with or without epoetin alfa (Procrit).² Despite the expanded indications for both erythropoietin and darbepoetin, no improvements in quality of life were shown.

Misinterpretation of these data has led to the current state of affairs: according to Amgen Pharmaceuticals, 12 to 16% of ESA use in patients with cancer is initiated at hemoglobin levels above 12 g per deciliter.³ As I mentioned in my Perspective article, randomized trials seeking to elevate hemoglobin levels to normal levels showed incontrovertible evidence of harm, including accelerated cancer progression and increased thrombovascular events. This evidence prompted the FDA's black-box warning prohibiting the initiation of ESA use at hemoglobin levels above 10 g per deciliter.¹ Given these and additional data suggesting that anemia associated with chronic disease is a compensatory physiologic response to the chronic condition, these warnings are justifiable.⁴ Although ESAs are effective in reducing transfusion requirements and mitigating severe anemia in patients with cancer who are undergoing chemotherapy, attempts to expand the in-

dications for their use in oncology have been unsuccessful. Ignoring available data on ESAs is unlikely to benefit patients with cancer.

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Recognizing Iodine Deficiency in Iodine-Replete Environments

TO THE EDITOR: Iodine-deficiency disorders are prevalent in regions with low iodine levels but have generally been eliminated in affluent countries through the widespread use of iodized salt.¹⁻⁴ We report on two women, both lifelong residents of the United States, in whom iodine-deficiency disorders developed.

Patient 1 presented with goiter and symptoms of hypothyroidism. Examination of the neck confirmed a diffusely enlarged thyroid gland (approximately 50 g); hypothyroidism was confirmed biochemically (Table 1). A radioactive iodine study, performed before her referral for endocrine evaluation, was reportedly "consistent with hyperthyroidism." The latter finding, together with a history of avoidance of iodized salt and seafood, raised suspicion of iodine deficiency. Levels of urinary iodine during a 24-hour period, which were measured in a commercial laboratory with the use of inductively coupled plasma

mass spectrometry (Mayo Clinic), were markedly decreased (31 μg per day; reference range, 100 to 460). The patient was advised to use iodized salt and to add seafood to her diet. Thyroxine was not prescribed. At follow-up 2 months later, the goiter had resolved completely, and the thyroid panel had normalized (thyroxine, 6.4 μg per deciliter; thyrotropin, 2.0 μU per milliliter).

Patient 2 presented with an enlarged thyroid gland (approximately 60 g). Thyroid ultrasonography showed a diffusely enlarged gland. The left lobe measured 4.4 cm by 1.6 cm by 1.6 cm, and the right lobe measured 4.7 cm by 1.6 cm by 0.7 cm. The patient had avoided the consumption of salt ever since she had had a stroke, 7 years previously, and she rarely ate seafood. A thyroid panel was normal, but the urinary iodine was reported as "undetectable." The patient was advised to use iodized salt and to add seafood to her diet. Two months later, a repeat urinary iodine level was

Table 1. Clinical and Laboratory Characteristics of the Patients at Presentation.*

Patient No.	Age yr	Sex	Thyrotropin $\mu\text{U}/\text{ml}$	Thyroxine	Thyroid Peroxidase Antibodies $\mu\text{U}/\text{ml}$	Neck Examination	Thyroid Ultrasonography	Uptake of Radioactive Iodine	Urinary Iodine $\mu\text{g}/24\text{ hr}$
1	34	F	52.9	Total, 3.4 $\mu\text{g}/\text{dl}$	<10	Diffuse goiter (approximately 50 g)	NA	Diffusely increased (uptake, 42% in 24 hr)	31
2	38	F	0.74	Free, 1.09 ng/dl	<10	Diffuse goiter (approximately 60 g)	Diffuse goiter: left lobe, 4.4×1.6×1.6 cm; right lobe, 4.7×1.6×0.7 cm	NA	Not detected†

* Reference ranges are as follows: thyrotropin, 0.35 to 5.50 μU per milliliter; total thyroxine, 5 to 12 μg per deciliter; free thyroxine, 0.71 to 1.85 ng per deciliter; and urinary iodine, 100 to 460 μg per 24-hour period. NA denotes not available.

† The excretion of urinary iodine, which was undetectable at presentation in this patient, increased to 149 μg per 24 hours at the 2-month follow-up assessment.