'Blood will have blood'

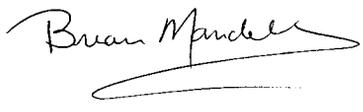
Although Shakespeare was probably not talking about blood replacement strategies when he wrote these words in *Macbeth*, the concept of maintaining a normal hemoglobin level has reasonable face validity. One would think that anemic patients would fare better with more erythrocytes. Compromises have been made over the years to limit the use of blood products, but until relatively recently the compromises were based primarily on concerns over the availability and safety of the blood supply.

Erythropoiesis-stimulating agents (ESAs) changed the landscape, giving us the ability to normalize the hemoglobin level without giving blood products. Patients with renal failure who were making inadequate amounts of endogenous erythropoietin could be given exogenous ESAs. And patients with anemia characterized by resistance to erythropoietin could be given higher doses of an ESA, and the resistance could be overcome. Questions were occasionally raised about the outcomes when boosting the hemoglobin level above 10 g/dL, and seizures and hypertension were reported as complications of therapy, but cost was the major stumbling block to the expanded use of ESAs.

However, as Drs. Sevag Demirjian and Saul Nurko discuss on page 353 in this issue of the *Journal*, striving to fully correct the anemia of chronic kidney disease with the use of ESAs may cause unexpected problems—such as more deaths and cardiovascular events.

Why should more patients with chronic kidney disease die if their hemoglobin levels are normalized? It could be another case of "messing with Mother Nature." Perhaps the decreased erythropoietin production and anemia associated with renal failure are a protective reflex somehow beneficial to patients with decreased renal mass. On the other hand, it seems that the patients who had the most problems with ESAs in randomized trials were actually "resistant" to ESA therapy and were therefore probably given higher ESA doses. More blood may not be the problem, but, rather, too much ESA.

In an editorial in this issue (page 359), Dr. Alan Lichtin discusses additional concerns that have arisen with the use of ESAs when treating the anemia associated with malignancy. One issue relates to the expression of erythropoietin receptors by nonerythroid cells: some tumor cells express erythropoietin receptors, and giving high doses of ESAs might stimulate their growth. Dr. Lichtin concludes by saying the ESA story is far from over, and I believe him.



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