Use of erythropoietic stimulating agents in the setting of renal disease

David A. Goodkin

Goodkin Biopharma Consulting, LLC, Bellevue, WA, USA; and Arbor Research Collaborative for Health, Ann Arbor, MI, USA

Introduction

As kidneys fail, their capacity to produce erythropoietin (EPO) typically diminishes. This deficiency of EPO is the primary etiology of the progressive anemia of chronic kidney disease (CKD). Hemoglobin concentration decreases in association with the increase in blood urea concentration (Fig. 1) and the decline in creatinine clearance (Fig. 2) of progressive renal failure [1]. The anemic state is exacerbated by a shortened red blood cell lifespan and bone marrow resistance to EPO in the setting of advanced uremia. Bleeding time is prolonged, as well, and gastrointestinal blood loss is not uncommon. In addition, dialytic therapy may consume red cells, due to repeated diagnostic phlebotomy, hemolysis caused by the hemodialysis pump, bleeding associated with hemodialysis needle insertion and removal, recurrent anticoagulation, and incomplete return of blood from the hemodialysis filter and bloodlines at

![Figure 1. Relationship between blood urea concentration and hemoglobin concentration. Four hundred patients with CKD not yet requiring dialysis, 1977–1979. (From [1] with permission.)](image-url)
the end of a treatment. Inflammatory cytokines and nutritional deficiencies may worsen the anemia of CKD.

If one visited a hemodialysis facility in the 1970s or 1980s, on any given day it was usual to see bags of blood suspended at multiple patient stations, with transfusions in progress. Many dialysis patients received 1–3 units of red blood cells per month [2], although some individuals had considerably higher transfusion requirements. Despite recurrent transfusions for approximately 25% of the patients, hematocrit values often oscillated within ranges <25%, causing persistent fatigue, limited capacity for exertion, and numerous other symptoms. In 1989, the first recombinant human erythropoietins (rHuEPO) were approved for commercial use. Most patients undergoing chronic dialysis treatments in developed nations and many patients with earlier stages of CKD now receive erythropoiesis-stimulating agent (ESA) therapy. Consequently, there has been a dramatic reduction in the rate of red blood cell transfusions and hematocrit values are considerably higher. In fact, dialysis professionals of more recent vintage have only seen blood transfusion as an occasionally-needed intervention for dialysis patients and not the common intradialytic process that it was in decades past.

**Benefits of ESA treatment of anemia in patients with CKD**

*Reduction of red blood cell transfusions*

A number of risks are associated with the transfusion of blood. Concern about the potential for transmission of viral infections such as hepatitis B, hepatitis C, and HIV was particularly worrisome for hemodialysis patients with chron-