Iron and the Anemia of Chronic Disease: Vindication for the Non-Essential Role of Iron Supplementation

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It is somewhat ironic (no pun intended) that a review whose title, “Iron and the Anemia of Chronic Disease,” suggests content more appropriate to a hematology journal than one devoted to oncology, has been found to have lasting value by practicing oncologists.

The causes of cancer-related anemia are multifarious, but the most common is a nondescript entity, which has been designated the anemia of chronic disease (ACD). ACD is defined as an anemia occurring primarily in three unrelated disease processes: infections, inflammation, and cancer. Abnormal iron metabolism is the hallmark of ACD and was thought to distinguish it from other causes of anemia in cancer patients, as well as in patients with infectious or inflammatory disorders. However, despite our ability to distinguish ACD from other forms of cancer-associated anemia, until recently no therapeutic approach other than blood transfusion existed. Indeed, a little over three decades ago, a prominent oncologist stated, “I have not seen and do not anticipate any remarkable new data in this field. Hematologists, who are interested, have gone into other areas, but medical oncologists have not developed a keen interest. Surgeons need only to know what the deficit is and correct it by transfusion. This is not a pessimistic report but instead a statement of the current status of what is known, has been done, and can be done.”

However, at the time of my 2002 review, the situation had changed radically. The cloning of the erythropoietin gene in 1985 was rapidly followed by the development of its recombinant congener, which was approved for use in anemic renal dialysis patients in 1990, and subsequently for cancer chemotherapy-related anemia in 1993. However, in 2002, barriers to its use for chemotherapy-related anemia were such that only 25% of cancer patients with this indication were receiving the drug. Besides cost, inconvenience of administration was a major issue. However, the introduction of a long-acting erythropoietin changed the debate, which turned to the problem of impaired iron availability—the most seminal ACD abnormality, since an adequate supply of iron is essential for erythropoietin-responsiveness. It was this topic that my review focused on—a timely and important clinical issue now that there was a new erythropoietin formulation that addressed duration of action, the major drawback of existing formulations. About the same time that this new formulation became available, important new information about iron metabolism was discovered; however, the data were published mainly in the basic science literature and thus were not easily accessible to practicing clinicians. Also, because recombinant erythropoietin had moved so rapidly from the laboratory to the clinical setting, there was still a considerable knowledge gap in the medical community at large with respect to the hormone's physiology.
Consequently, I sought to integrate this new information into the working knowledge of practicing oncologists by suggesting a new way to view erythropoiesis and the impact on it of ACD (shown in Table 1 of the review—and also reproduced here), while at the same time addressing erythropoietin physiology and explaining what was new with respect to iron metabolism. To achieve these goals, I used a series of illustrations as an easy means of contrasting normal iron metabolism with that seen in ACD, along with several tables to outline the mechanisms for the perturbation of iron metabolism in ACD.

All of this was, of course, essential background for what I thought were the two most important misconceptions at the time: namely, that lack of available iron was not only the defining ACD defect but also the cause of erythropoietin-unresponsiveness in this syndrome. Both of these notions were incorrect. First, abnormalities of iron metabolism do not define the limits of ACD, since anemic patients with disorders other than infection, inflammation, and cancer have the same metabolic iron abnormalities, while not all anemic patients with these three disorders have ACD. Second, and importantly, not only did many patients with ACD have impaired renal function, but many anemic patients with renal failure had the metabolic iron abnormalities characteristic of ACD. This implied that the common denominator of these disparate disorders was not lack of iron but lack of erythropoietin; the arguments for this were summarized in Table 8 of the review (which is reproduced here).

At that time, this reasoning conflicted with the existing dogma, which was that a common denominator of infection, inflammation, and cancer was inflammatory cytokine production, and that this led to the release of hepcidin, a small molecule that blocks intestinal iron absorption and macrophage iron release and, as a consequence, erythropoietin-responsiveness. As I concluded, “... recombinant erythropoietin therapy can correct the anemia of chronic disease, but it cannot correct the anemia due to iron deficiency. This refutes the concept that lack of available iron is central to the pathogenesis of the syndrome.” A corollary to this conclusion was that in ACD it should not be necessary to give supplemental iron, since body stores were ample and just waiting to be released by recombinant erythropoietin therapy—a conclusion that was also contrary to existing clinical belief.

So, in summary, I think that my review was useful because it integrated a wealth of clinically relevant and applicable basic science and physiologic data about a timely and significant clinical problem. Importantly, this information challenged existing dogma in an evidenced-based fashion and suggested an alternate therapeutic approach.

It is pleasing to look back at that review with the knowledge that continuing research, both basic and clinical, has supplemented and supported the review's contentions. First, the then mysterious “iron stores regulator” mentioned in the review turned out to be hepcidin, and the equally mysterious “erythropoietic and hypoxia regulators” proved to be erythropoietin. Second, it has been definitively shown in vivo that erythropoietin trumps hepcidin with respect to the mobilization of body iron stores. This is not to say that hepcidin does not have an important role in ACD pathogenesis; the tissue iron sequestration it causes results in suppression of erythropoietin gene transcription by accelerating the degradation of hypoxia-inducible factor (HIF)-1α. However, tissue iron sequestration by itself is not sufficient to impair the effectiveness of exogenous recombinant erythropoietin—or
that of endogenous erythropoietin either, when tissue hypoxia is significant. But perhaps most important of all, the contention that iron supplementation, particularly in its intravenous formulation, is essential for the clinical effectiveness of recombinant erythropoietin has been demonstrated in a recent clinical trial in anemic cancer patients receiving chemotherapy to have no basis.[1] This can only be a benefit to patients with ACD, relieving them of the need to take yet another medicine, while at the same time reducing the cost of their medical care.

References:
REFERENCES:


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