Iron therapy and cancer

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Iron therapy and cancer. Anemia in cancer patients has many etiologies. Iron therapy clearly is indicated in patients whose anemias are associated with iron deficiency. However, a frequent cause of anemia in cancer is the “anemia of chronic disorders,” in which, although functional iron may be low, tissue iron remains normal or high. Administration of iron with erythropoietin to such patients requires careful and frequent evaluation of hematologic and iron values. Inadvertent iron loading can contribute to deterioration of a variety of organ systems, as well as to increased proliferation of neoplastic cells.

“The use of iron pills as a ‘tonic’ or for the treatment of an undiagnosed anemia can never be condoned” [1].

Anemia is a common finding in cancer patients. The condition has no dearth of etiologic factors [2]. Hemoglobin (Hb) synthesis may be impaired by nutritional deficiencies (iron, folic acid, cobalamin). Erythrocyte synthesis may be depressed by bone marrow inadequacy (metastases, pure red cell aplasia, chemotherapy, or radiotherapy) or, in renal failure, by erythropoietin (EPO) deficiency. Erythrocyte quantity may be reduced by bleeding, hemolysis, or hypersplenism. Frequently, the anemia ensues from attempts of the host to raise an inflammatory response to defeat the neoplastic invader. This condition has been termed the “anemia of chronic disorders” (ACD) or, more recently, the “hypoferremia of inflammatory diseases.”

Manifestly, the selection of methods for correction of anemia in cancer patients requires precise knowledge of its cause. For some etiologies, exogenous iron is indicated; for others, feeding or injecting iron would be futile or even counterproductive. Clearly, if the particular anemia is caused or complicated by iron deficiency, therapy should include replenishment of the metal. However, excessive amounts of exogenous iron can enhance proliferation of cancer cells and depress cell-mediated immunity [3]. Accordingly, all patients who are being treated with the metal, irrespective of the cause(s) of their anemias, must have their iron status properly evaluated at appropriate intervals.

ANEMIA OF CHRONIC DISORDERS

This review focuses on the very often encountered cause of anemia in cancer, ACD. The initial observation on ACD was reported 67 years ago by Locke, a clinical pathologist [4]. His hospital laboratory possessed samples of plasma from a great variety of patients with different illnesses. Locke et al found that specimens from persons undergoing inflammatory defense processes are hypoferremic. If patients recovered, normal levels of iron would return. Other research workers subsequently demonstrated that this profound shift in iron metabolism is independent of dietary iron, regulated by cytokines, and is important for host defense.

In addition to its occurrence in neoplastic and infectious diseases, ACD is seen in patients with such other causes of inflammation as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease, as well as in persons who recently have had major trauma or surgery. Examples of chronic disorders in which ACD typically does not occur include diabetes mellitus, hypertension, asthma, ischemic heart disease, and congestive heart failure.

Together with the hypoferremia, features of ACD include lowered values of transferrin iron saturation and transferrin iron-binding capacity, high normal or elevated serum ferritin, and ample marrow deposits. Intestinal assimilation of iron is depressed [5]; nevertheless, serum transferrin iron receptor concentration remains normal [6]. This constellation of traits indicates that plasma iron is being lowered by a reduction in the recycling of iron to plasma from macrophages that have digested Hb from effete erythrocytes, as well as by an elevation of the mucosal block that controls assimilation of dietary iron.

In normal adults, serum ferritin values are 20 to 200 ng/ml; if below 15 ng/ml, iron deficiency is present. During ACD, additional ferritin is formed to aid in the up-regulated sequestration of the metal. Consequently, in ACD, serum ferritin values may increase by as much as

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50 ng/ml [1]. Serum ferritin values of greater than 300 ng/ml in persons with or without ACD indicate that the tissues contain excessive amounts of iron deposits.

Ferritin molecules that appear in serum during inflammation contain less iron than normal [7], presumably because they have recently been synthesized. Moreover, some of the elevated serum ferritin in cancer patients may result from production of the protein by tumor cells [8]. Note also that when ferritin is secreted by intact cells, it is glycosylated; when it leaks from damaged cells, it is nonglycosylated [9].

IRON-WITHHOLDING DEFENSE SYSTEM

The consistently observed shift in iron metabolism in ACD is but one aspect of the extensive iron-withholding defense system [10]. Additional features of the system include the continuous presence of: (a) moderately unsaturated transferrin in plasma, lymphatic fluid, and cerebrospinal fluid; (b) unsaturated (apo) lactoferrin in tears, milk, secretions of respiratory, gastrointestinal, and genital tracts, and in secondary granules of neutrophils; and (c) ferritin in all body cells. Furthermore, when iron withholding is up-regulated, neutrophils discharge apolactoferrin into sites of inflammation. Macrophages scavenge lactoferrin-acquired iron; haptoglobin and hemopexin bind extravasated Hb and hemin, and nitric oxide effects efflux of nonheme iron from tumor and other targeted cells. These and other features of the iron-withholding defense system are essential in suppressing the proliferative action of iron for neoplastic and microbial cell invaders, as well as in preventing the hazardous oxidant action of the metal toward normal cells and tissues.

In the inflammatory response to insult, iron-withholding defense is intensified by increased production of such cytokines as interleukin-1 and interleukin-6, tumor necrosis factor-α (TNF-α), and interferon-γ. Interleukin-1 and interleukin-6 and TNF-α, formed by activated macrophages and other cells, can induce suppression of intestinal iron assimilation, reduction in recycling of iron from macrophages to plasma, and increased synthesis of ferritin to sequester macrophage-retained iron [5, 11]. Interferon-γ, produced by T-lymphocytes, induces macrophages to form nitric oxide, which causes depletion of nonheme iron in tumor and other targeted cells [12]. Inhibitory activities of nitric oxide are reversed by exogenous iron [13].

THERAPEUTIC USE OF EPO AND IRON

A mild to moderate anemia (so-called ACD) frequently accompanies inflammatory illnesses. In chronic conditions, the anemia develops during the first few months and rarely progresses thereafter. Although the anemia usually is normocytic and normochromic, mild microcytosis and hypochromia may occur. Hematocrits range from 20% to 40%. In ACD, the erythrocyte life span can be moderately shortened, but the primary cause of the anemia is the failure of the bone marrow to increase the number of circulating reticulocytes.

Serum EPO levels in patients with ACD, although higher than normal, are lower than in patients with anemia from noninflammatory disorders and are lower than expected for the degree of anemia. However, the marrow responds to exogenous EPO. For example, a set of 10 rheumatoid arthritis patients with ACD were treated for 32 weeks with EPO plus oral iron, and their hematocrits increased from an initial mean of 31% to a final mean of 40.8% [14]. Likewise, in 17 patients with inflammatory bowel disease who had chronic anemia, administration of EPO plus oral iron for 12 weeks resulted in a mean Hb concentration that increased from an initial value of 8.81 ± 0.27 g/dl to a final value of 10.52 ± 0.41 g/dl [15]. In these studies, hematocrits and Hb values remained low in patients who received oral iron without EPO.

In a study of 17 patients with colorectal cancer, EPO was given from 10 days prior to two days after surgery [16]. Favorable response was correlated positively with serum ferritin values (P < 0.001) and with transferrin iron saturation (P = 0.0004). When transferrin iron saturation was 15% or less, hypochromic erythrocytes were formed. The ability of EPO to stimulate production of erythrocytes normal both in size and Hb content is highly dependent on availability of functional iron [17].

In conditions in which the anemia results from both bleeding and ACD, intravenous (i.v.) iron without EPO may be effective. In a recent study, 40 patients with Crohn’s disease (Hb ≤ 10.5 g/dl) were given a total of 3.5 g i.v. iron over 16 weeks [18]. In the first eight weeks, half were given EPO, half placebo. In the second eight-week period, EPO was increased or initiated for the nonresponders in each group. Seventy-five percent of the patients had a substantial response to i.v. iron alone. EPO plus i.v. iron permitted a somewhat more rapid increase in Hb concentration as well as a lesser tendency to develop excessive transferrin iron saturation values as compared with i.v. iron alone. However, the authors noted that i.v. iron alone was more effective than EPO plus oral iron in improving Hb values in Crohn’s disease patients. They recommended that i.v. iron saccharate, in which the cost is only 0.8% that of EPO, be considered first-line therapy in patients with severe anemia.

HAZARDS OF IRON LOADING

Unfortunately, unless the patient’s condition involves bleeding, large amounts of injected iron (either as repeated quantities of 0.2 g/dose of iron as saccharate or repeated transfusions of 0.2 g of iron per unit of whole
blood) cannot be given without serious long-term consequences. In the study mentioned earlier [18], i.v. iron was halted when the transferrin iron saturation value exceeded 50%. In such patients, the value returned to normal within two weeks. However, it was not determined how much of the excess iron had been excreted in bleeding or how much had been deposited in such vulnerable tissues as heart, liver, endocrine glands, or joints. It has long been known that parenteral administration of iron during episodes of inflammation does not restore the normal level of plasma iron; instead, the metal is deposited in the monocyte/macrophage system [19, 20]. As this system becomes saturated with iron, the metal overflows into hazardous tissue sites.

The total amount of iron in a normal adult should not exceed 4 to 5 g. By the time that the quantity of iron in a human has increased to 15 g, sufficient organ deterioration has occurred to require medical assistance [21]. The metal contributes to a considerable panoply of diseases that varies with individual patients. The association of iron loading with initiation and proliferation of neoplasms is well established [3]. Iron is carcinogenic because of its catalytic effect on the formation of hydroxyl radicals, suppression of the activity of host defense cells, and promotion of cancer cell multiplication. In both animal models and in humans, primary neoplasms develop at tissue sites of excessive iron deposition.

During the past four decades, numerous research groups have reported, in prospective studies in animals, that administration of excessive amounts of injected or oral iron increases markedly the risk of adenocarcinomas, colorectal tumors, hepatomas, mammary tumors, mesotheliomas, renal tubular cell carcinomas, and sarcomas [3]. In humans, these types of prospective studies would be unethical. However, in large groups of humans such as 0.5% of whites [22] and 10% of sub-Saharan Africans [23], genetic defects result in assimilation of excessive dietary iron. In the white disease, hereditary hemochromatosis, the elevation in tissue iron is associated with an increase in hepatic carcinoma of as much as 200-fold; excessive frequency of nonhepatic malignancies also is observed [3, 22]. In the African disease, African siderosis, the incidence of hepatic carcinoma likewise is quite high. For example, in one study of persons with elevated tissue iron, an increased cancer risk of 15-fold was observed [23].

Even in persons who lack known genetic defects of oral iron assimilation, an association between elevated body iron values and increased risk of malignancy has been reported. For instance, in a set of 3345 men, 6.9% developed cancers during a 10-year period. The patients had a mean transferrin iron saturation value of 33.1% at least four years prior to diagnosis, whereas the men who remained free of cancer had a mean transferrin iron saturation value of 30.7% ($P = 0.002$) [24]. In a group of 41,276 men and women followed for 14 years, 6% developed cancers. Among persons in the group whose initial transferrin iron saturation value was more than 60%, the relative risk (as compared with those with levels of less than 60%) for all cancers, lung cancer, and colorectal cancer was 1.43, 1.51, and 3.04, respectively [25].

As indicated earlier here, blood transfusions can result in iron loading. A meta-analysis of 60 studies comprising 19,687 patients (1982 to 1994) of perioperative blood transfusions and cancer recurrence found an adverse effect in 28 of the reports with an increased risk of 37% [26]. As a corollary, in a study of 37,795 normal blood donors, the relative risk of developing cancers as compared with nondonors was 0.79 ($P < 0.001$) [27].

Iron loading can occur not only via alimentary and parenteral routes but also by inhalation of the metal contained in tobacco smoke, asbestos, and urban air particulates [3, 28]. Moreover, iron can be released from its normal body compartments by hemolysis or by destruction of nonerythrocytic cells that contain iron deposits. For example, endogenous iron released from dying cells in 40 patients given high doses of cytostatic drugs and total body irradiation (two weeks prior to bone marrow transplantation) resulted in transferrin iron saturation values of 75% to 100% [29].

Patients with ACD who might be considered for therapy with EPO plus iron are those with Hb of less than 10.5 g/dl, hypochromic red blood cells of more than 10%, and serum EPO of less than 200 mU/ml. Sufficient EPO plus iron should be given to maintain transferrin iron saturation values of 25% to 35% and hematocrit values of 30% to 36%. The amount of EPO required to ameliorate anemia in ACD is threefold higher than that needed in patients who have chronic renal failure without ACD [2].

If oral iron is employed, note that in ACD, intestinal assimilation of the metal is dampened. If i.v. iron is used, the intervals at which transferrin iron saturation is monitored should be shortened. Moreover, if cancer patients are being treated with experimental protocols that contain such inhibitors of cancer cell iron metabolism as gallium, iron chelators, or antibodies to transferrin receptors, additional care to avoid iron overload must be exercised.

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