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Epidemiological and nonclinical studies investigating effects of iron in carcinogenesis—A critical review☆

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Abstract

The efficacy and tolerability of intravenous (i.v.) iron in managing cancer-related anemia and iron deficiency has been clinically evaluated and reviewed recently. However, long-term data in cancer patients are not available; yet, long-term i.v. iron treatment in hemodialysis patients is not associated with increased cancer risk. This review summarizes epidemiological and nonclinical data on the role of iron in carcinogenesis. In humans, epidemiological data suggest correlations between certain cancers and increased iron exposure or iron overload. Nonclinical models that investigated whether iron can enhance carcinogenesis provide only limited evidence relevant for cancer patients since they were typically based on high iron doses as well as injection routes and iron formulations which are not used in the clinical setting. Nevertheless, in the absence of long-term outcome data from prospectively defined trials in i.v. iron-treated cancer patients, iron supplementation should be limited to periods of concomitant anti-tumor treatment.

Keywords: Iron deficiency; Anemia; Carcinogenesis; Tumor progression; Nonclinical; Intravenous iron; Parenteral iron

1. Introduction

Iron-containing proteins participate in many essential biological processes such as oxygen transport, cellular respiration and redox reactions. However, ferrous iron (Fe^{2+}) can catalyze the production of hydroxyl radicals ($^{\bullet}OH$) [1] which are stronger oxidants than the antimicrobial superoxide radicals ($O_2^{\bullet-}$), and therefore can exert oxidative damage to nearby lipids, carbohydrates, proteins or DNA. Since iron is not actively secreted from the body, systemic iron levels are regulated by the liver-derived peptide hepcidin, whereas cellular iron levels are controlled by iron-regulatory proteins (IRPs) that bind to iron-response elements (IREs) in the messenger RNA of iron-related genes (Fig. 1) [2,3]. These highly conserved mechanisms of iron sequestration also provide protection against infectious diseases by depriving invading pathogens of this essential nutrient [4,5]. However, these mechanisms are also activated by inflammatory processes associated with chronic diseases such as cancer.

Interleukin (IL)-6 and IL-1 are the main inflammatory effectors that increase the expression of hepcidin [2], which in turn deactivates ferroportin, the iron export protein on the surface of enterocytes, hepatocytes and macrophages [6,7]. The reduced absorption and release of iron leads to an imbalance between iron requirements for erythropoiesis in the bone marrow and the iron supply from macrophages. This functional iron deficiency (FID) is believed to be one of the major causes of the anemia of chronic disease (ACD). Conversely, low hepcidin activity results in increased dietary absorption and mobilization of iron from cellular stores, which can result in iron overload.

In cancer patients, anemia is associated with shorter survival time [8], and symptoms of iron deficiency and anemia (e.g. weakness and fatigue) affect patients' quality of life [9,10]. Intravenous (i.v.) iron in conjunction with erythropoiesis-stimulating agents (ESAs) has been shown to improve hemoglobin status and reduce blood transfusion needs in anemic cancer patients [9,11–17]. In contrast, oral iron has very limited efficacy in this patient population, and therefore, treatment guidelines recommend i.v. iron supplementation [18,19].

Although i.v. iron preparations passed genotoxicity testing (e.g. Ames) as part of the development and approval process, an open question remains whether iron supplementation of cancer patients might influence tumor progression. One preliminary study with long-term follow-up showed no effect of i.v. iron on 3-year progression-free survival in anemic patients with lymphoid malignancies [20,21]. However, there are insufficient data from prospectively defined studies to address this question. Several prior reviews have outlined mechanisms how elevated iron levels may influence signaling pathways and tumor progression or, vice versa, how signaling through certain pathways may contribute to altered iron metabolism in cancer patients [1,22–24]. In order to facilitate informed decisions on the clinical use of i.v. iron supplementation, the review presented here evaluates how the designs and results of published epidemiological and nonclinical studies compare to the clinical use of i.v. iron, which is intended to provide sufficient iron availability and normalization of hemoglobin levels in patients with cancer-related iron deficiency or anemia.

2. Clinical data

2.1. Hereditary hemochromatosis

The most common cause of iron overload is hereditary hemochromatosis (HH), a genetic condition with inappropriately low hepcidin levels or activity. This results in accumulation of iron in the liver and other organs and can be diagnosed by transferrin saturation >45% and elevated