Preoperative blood management in colorectal cancer surgery: the controversial role of iron

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Chapter 8 // **General discussion and future perspectives**

GENERAL DISCUSSION

Anemia is a common finding in cancer patients and is observed in up to 40 percent of the patients diagnosed with colorectal cancer.[1] Whilst preoperative anemia has been established as an independent risk factor for adverse short-term outcome following colorectal cancer surgery,[2] such as an increased number of complications and a longer hospital stay, studies on the association between preoperative anemia and long-term cancer outcome show inconsistent results. It has been hypothesized that anemia impairs long-term prognosis via worsening of tumor hypoxia, which is linked to radiotherapy and chemotherapy resistance.[3-5] In addition, by inducing proteomic and genomic changes, hypoxia may also increase the proliferative and metastatic potential.[3] Due to the inconsistencies demonstrated by various studies, we conducted a systematic review and meta-analysis to assess the long-term prognostic value of preoperative anemia in colorectal cancer patients (chapter 2). In meta-analyses including both colon and rectal cancer patients, preoperative anemia was significantly associated with decreased overall survival (HR 1.56, 95% CI 1.30 to 1.88) and disease-free survival (HR 1.34, 95% CI 1.11 to 1.61). However, when restricted to studies exclusively on colon or rectal cancer patients, analyses demonstrated that preoperative anemia is only significantly associated with decreased long-term overall and disease-free survival in rectal cancer patients, and not in colon cancer patients. Following the results of this meta-analysis, raised awareness about the impact of preoperative anemia on long-term survival is justified, but it remains uncertain whether anemia is an independent risk factor for impaired long-term survival or just a marker of the severity of co-morbid disease.

Causes of anemia in patients with colorectal cancer are often multifactorial. Anemia may be attributed to the underlying disease or to therapy-related factors. At diagnosis, however, anemia most often results from iron deficiency (i.e. absolute or functional). The prevalence of iron deficiency is reported to be approximately 50 percent in colorectal cancer patients.[6] The malignancy itself can lead to this iron deficiency in two major ways. Firstly, cancer cells can produce cytokines that lead to increased hepcidin production by the liver, inducing reduced duodenal iron uptake as well as iron mobilization from the reticulo-endothelial system. These effects lead to a functional iron deficiency, often referred as anemia of chronic disease or anemia of inflammation.[7] In this condition, the amount of stored iron is sufficient, but the bioavailable iron necessary for erythroblast production is deficient. Secondly, chronic blood loss at tumor site can deplete iron stores and cause an absolute iron deficiency anemia. Identification of the type of iron deficiency is of major importance because both types of iron deficiency are recommended to be treated differently.[8, 9] Whereas iron is recommended for patients who develop absolute iron deficiency, it is not recommended for patients who develop functional iron deficiency as a result of disease-related factors (i.e. infection or inflammation).9 Oral iron in these patients namely is ineffective, as hepcidin blocks the duodenal iron uptake and thus the subsequent iron transport to the bone marrow.

Our retrospective study in chapter 3 demonstrated that the prevalence of iron deficiency is approximately 50 percent in all colorectal cancer patients, and 80 percent in anemic colorectal cancer patients. This result is in accordance with the prevalence observed in a previous study.6 In regard of the type of iron deficiency, the vast majority was a combination of absolute and functional iron deficiency (81.0%); only 3.7% and 15.3% was an isolated absolute and isolated functional iron deficiency, respectively. The clinical relevance of iron deficiency in our patient cohort, however, was disputable, as only severe iron deficiency was significantly associated with increased postoperative complication rate in a univariate analysis.

Elaborating on the observed prevalence numbers of (type of) iron deficiency, we decided to perform a national survey to assess the current preoperative blood management strategies in the Netherlands, and to determine whether the recommendations formulated in international oncological guidelines are being followed. The concept of patient blood management (PBM) has been developed to promote 'the appropriate provision and use of blood, its components and derivatives, and strategies to reduce or avoid the need for a blood transfusion.[10] Special focus in PBM has been the early identification and treatment of preoperative anemia, the strongest indicator for perioperative blood transfusion. Moreover, there is an increasing awareness of the need and also a debate on how to integrate patient blood management within routine surgical care, resulting in numerous ongoing trials studying the optimal blood management strategy in all types of surgery, including colorectal cancer surgery.[11-13] Results of our survey among surgeons, gastroenterologists and anesthesiologists, as shown in chapter 4, demonstrated a distinct variability in preoperative blood management practices. Strikingly, this variability was not only seen between, but also within Dutch hospitals, as indicated by the varying responses from surgeons, gastroenterologists and anesthesiologists. In general, poor compliance with the recommendations in international guidelines on the management of anemia in cancer patients was observed. This was for example illustrated by the low number of hospitals in which iron status was measured during screening for colorectal cancer (i.e. less than 40 percent), crucial to identify the type of anemia and to determine the optimal treatment.

As anemia is most frequently iron-deficient in etiology, iron supplementation is regarded as a feasible technique to optimize hemoglobin level and minimize the use of blood transfusion, which itself has been independently associated with worse patient outcome, as demonstrated in multiple randomized trials.[14-18] In this regard, the effect of intravenous iron, in opposition to oral iron, is increasingly being explored. Compared to the side effects present in the majority of people taking oral iron preparations, the side effects with intravenous iron are minor, infrequent and short-lasting.[19] Early intravenous iron preparations were associated with a high rate of serious adverse events, most notably anaphylactic shock. Newer formulations, which bind the elemental iron more tightly resulting in a much slower release, are found to be much safer.[20] With this improved short-term safety of intravenous iron preparations, the efficacy of intravenous iron,

in terms of optimizing hemoglobin level and reducing the need for blood transfusions, received new interest.[11, 12] Although all previous studies consistently demonstrated that intravenous iron, as compared to oral iron or placebo, is more effective in treating preoperative anemia, inconsistent results are observed in reducing the blood transfusion requirement.[12, 18, 21, 22] While none of the previous studies identified characteristics/biomarkers associated with the magnitude of response in raising hemoglobin level, our results demonstrated that intravenous iron therapy is most effective in patients presenting with more severe anemia, and with higher transferrin and lower ferritin levels (chapter 5). Our results failed to demonstrate that the distinct hemoglobin increase after iron infusion leads to a decreased proportion of patients with a postoperative complication and/or blood transfusion. Following our results, we believe future studies on the short-term efficacy of intravenous iron should take the type of anemia/iron deficiency (i.e. absolute or functional iron deficiency) into account when studying the potential blood transfusion reducing effect.

Supported by data on the short-term safety and efficacy, many studies advocate a more prominent role for intravenous iron therapy in preoperative/patient blood management.[20, 23] However, before intravenous iron should be considered as the default therapy to treat a mild to moderate preoperative anemia in cancer patients, well-designed trials are required to evaluate the long-term effects and safety. By introducing intravenous iron as a therapy to reduce the blood transfusion requirement, it is essential to extensively investigate all safety aspects of intravenous iron, including the long-term effects, and to compare these results to those of blood transfusion. These long-term oncological effects of iron therapy are of special interest, as the results of laboratory, epidemiological and animal studies have shown iron's role in all aspects of cancer development and cancer growth.[24-29] Iron is an essential nutrient participating in numerous biological and cellular processes, facilitating normal cell proliferation and growth. Results of experimental studies moreover demonstrated that iron therapy is also able to enhance colorectal tumor growth and might contribute to an increased metastatic potential.[25, 26, 30] In addition, many transport proteins that were originally studied for their roles in normal iron metabolism have now been shown to also contribute to malignant tumor growth. Compared to non-malignant colon cells, iron import proteins, such as DMT1 and TfR1, are upregulated, while ferroportin, the only known iron export protein, is downregulated in colon tumor cells, seemingly subverting the normal homeostatic control into a chronic iron acquisition state enabling enhanced proliferation.[31-33] Hypothetically, as extension of these data, anemia of inflammation could be regarded as a potentially effective defense strategy of the human body to limit the growth of tumor cells.7 In this respect, due to increased hepcidin production, iron is sequestered from tumor cells into the reticuloendothelial system, resulting in a limitation of the availability of iron for the growth of tumor cells. In agreement, the avidity of cancer cells for iron has also led to the question of whether iron chelators could be used as anticancer therapy. Iron chelators, such as desferrioxamine (DFO), were initially designed to prevent iron-mediated toxicity in patient with hemoglo-

binopathy. The potential of iron chelators as anticancer therapy first came to light in studies assessing the anticancer effect of iron chelators in experimental studies,[34-37] and ever since, there is a growing interest in iron chelators as anticancer therapy. To date, promising clinical results are demonstrated in patients with hepatocellular cancer,38 prompting future research to iron chelators as a new iron-directed anticancer therapeutic.

Supported by all abovementioned circumstantial evidence, we hence decided to explore the effect of preoperative intravenous iron therapy on colorectal tumor prognosis in a matched cohort study (chapter 7). Our study failed to demonstrate that preoperative intravenous iron therapy has a profound effect on long-term overall and disease-free survival in anemic colorectal cancer patients. However, it should be stressed that the results were derived from a small-sized retrospective study, and therefore should be interpreted with caution.

To conclude, the high prevalence of iron deficiency and associated anemia in our colorectal cancer patient group often involves a functional hepcidin-mediated iron deficiency. This stresses the particular potential of preoperative intravenous iron therapy to 1) optimize hemoglobin level, namely in patients with more severe anemia and with higher transferrin and lower ferritin levels, and 2) reduce the blood transfusion requirement. In this respect, intravenous iron might benefit the patient by reducing the blood transfusion and anemia-related adverse effects. However, to date, only our small-sized retrospective study has addressed the long-term effects of preoperative intravenous iron therapy in colorectal cancer patients, showing no profound effect. Therefore, new well-designed trials studying the possible long-term effects of intravenous iron are required to answer the question whether the use of intravenous iron as first-line/default therapy to treat a mild to moderate preoperative anemia is a safe strategy for oncological patients.

FUTURE PERSPECTIVES: NEW IRON-DIRECTED DIAGNOSTICS AND THERAPEUTICS

Assessment of the long-term effects of iron therapy is needed to identify the optimal blood management strategy in colorectal cancer patients, and therefore, we believe future research should put more focus on this subject. Proper assessment of such long-term effects can be achieved by different means.

Firstly, the long-term effects can be monitored in an observational cohort study, as demonstrated in this thesis. However, this study design involves significant limitations. In a cohort study, significant differences between an iron-treatment and non-iron treatment group (e.g. hemoglobin levels and administration of blood transfusion) would, despite possible matching, likely introduce selection bias or confounding by indication, and significantly affect outcome. Therefore, to eventually demonstrate a potential causal relationship between iron therapy and long-term survival, randomized controlled trials should be considered. Randomized controlled

trials avoid selection bias and are the gold standard for establishing causal conclusions. However, in studying the effect of iron therapy, we believe that it is of importance to not only look at clinical endpoints, such as long-term overall and disease-free survival, but also, more specific and in line with many in vitro and animal studies, to look at what extent iron might enhance tumor growth, and, importantly, which colorectal tumor phenotypes are 'iron-hungry' for their growth. We strongly believe a more patient and tumor specific approach is required, and therefore, a comprehensive picture of exactly how iron metabolism is altered in malignant cells is needed. This namely will determine how iron therapy, or even iron chelation therapy, might influence the tumor itself. For this purpose, new and feasible methods to assess the iron content in colorectal tumors should be explored and be implemented.

To date, multiple experimental studies have already shown the possibility of quantifying iron and assessing the gene and protein expression levels of iron transporters in colorectal cancer specimens/samples. Evidently, the main disadvantage of these experiments is that surgery or biopsy is required in order to enable direct iron assessment in tumor samples. As a non-invasive alternative, novel diagnostic methods to visualize and quantify iron-rich biochemical compounds are being explored.[39, 40] As an example, a novel magnetic resonance protocol might allow reliable preoperative quantification of iron in colorectal tumors and is presently studied. This novel and non-invasive proton magnetic resonance spectroscopy (H-MRS) should of course first be validated against the actual iron content in tumor samples. If the novel scanning method provides high diagnostic accuracy for the assessment of iron load in colorectal tumors, it is the first demonstration of a non-invasive iron-directed test with the possibility to 1) quantity the iron load in colorectal tumors, 2) assess the effect of iron therapy on iron load in the tumor, and 3) to identify iron-dependent and non-iron dependent colorectal tumors, and 4) to investigate whether different treatments in different phenotypes could change the prognosis.

Apart from studying the effects of iron therapy by H-MRS, assessing the optimal management of anemia in colorectal cancer patients may be even more challenging. For this purpose, the detrimental long-term effects of iron treatment must be compared with those of not only anemia, but also with alternatives to treat anemia like ESAs and more important also blood transfusions. The problem here is that a head-to-head comparison of blood transfusion and iron therapy might be impossible in the clinical setting. The indications for both therapies are namely clearly different. While iron therapy is indicated and used in patients with a mild to moderate anemia, blood transfusions are only administered in case of severe anemia. To still assess the optimal management of anemia, animal experiments could be considered. In a colorectal cancer rodent model, the effect on tumor growth of both anemia, blood transfusion and iron therapy (both oral and intravenous) could be accurately assessed and compared.

The abovementioned animal and H-MRS studies will provide a more detailed understanding of

the oncological effect of iron therapy, enabling the identification of high- and low-risk patients for iron therapy. Based on these studies, the execution of a prospective randomized trial should be considered to test the effect of iron therapy on long-term survival. In such a trial, preoperative anemic patients should be randomized into an iron-treatment and a non-treatment group. In designing a study protocol, multiple important issues should be taken into consideration.

Firstly, in conducting a prospective trial randomizing anemic patients in an iron-treatment and a non-treatment group, it could be held unethical to have a non-treatment group because anemia itself is considered as a major risk factor for impaired disease-free and overall survival in cancer patients. As a first alternative, iron therapy could be considered in all anemic patients, subdivided into patients with iron-dependent and non-iron dependent colorectal tumor phenotypes. Assessment of the iron-dependency of the tumor could be, potentially, done by the novel scanning method and by identification of protein expression levels of iron transporters and iron itself in tumor samples. We hypothesize that iron therapy will show to be especially hazardous in patients with an iron-dependent tumor. As a second alternative, all patients with a non-anemic iron deficiency could be randomized into an iron-treatment and a non-treatment group.

Secondly, the dose-response relationship and the administration route (oral versus intravenous) should be considered. Often, the conditions in experimental studies, demonstrating the tumor-growing effect of iron, do not properly reflect the situation in anemic patients using excessive iron doses in iron-replete animals. In addition and of special interest, colorectal cancer animal models studying the effect of intravenous iron administration have so far not been published. In humans, particularly the effect of intravenous iron is of special interest as intravenous iron is presently more frequently being used as compared to oral iron.

Thirdly, as cancer types are shown to be iron-dependent, one might not only refrain from iron administration, but, apart from the presence of anemia or complete surgical eradication, even add iron chelation. In addition to iron chelation, two other iron-directed therapeutics can be explored. First, antibodies targeted towards the transferrin receptor 1 (TFR1) that effectively deplete intracellular iron are being studied. These antibodies have shown to effectively antagonize the growth of leukemia in mice.[41] Second, hepcidin-targeted treatment approaches, aiming at increasing ferroportin or decreasing local hepcidin levels, are being under investigation. The hepcidin depletion could be realized by neutralizing antibodies or hepciding small interfering RNAs.[42-44]

Additionally to all above, also the study of non-surgical patients should be deliberated. By focusing on only preoperative patients, the legitimate question could arise as to whether surgery and resection of the tumor might neutralize the possible detrimental effect of iron therapy on tumor growth and long-term prognosis. Therefore, future research studying the effect of iron therapy should also consider patients with premalignant colorectal adenomas.

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