The effect of intravenous iron therapy on long-term survival in anaemic colorectal cancer patients: Results from a matched cohort study

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ABSTRACT

Introduction: Intravenous iron therapy has been shown to be advantageous in treating anaemia and reducing the need for blood transfusions. Iron treatment, however, may also be hazardous by supporting cancer growth. Present clinical study explores, for the first time, the effect of preoperative intravenous iron therapy on tumour prognosis in anaemic colorectal cancer patients.
Methods: A retrospective cohort study was performed on consecutive patients who underwent surgery for colorectal cancer between 2010 and 2016 in a single teaching hospital. The primary outcomes were 5-year overall survival (OS) and disease-free survival (DFS). Survival estimates were calculated using the Kaplan-Meier method and patients were matched based on propensity score.
Results: 320 (41.0%) of all eligible patients were anaemic, of whom 102 patients received preoperative intravenous iron treatment (31.9%). After propensity score matching 83 patients were included in both intravenous and non-intravenous iron group. The estimated 1-, 3-, and 5-year OS (91.6%, 73.1%, 64.3%, respectively) and DFS (94.5%, 86.7%, 83.4%, respectively) in the intravenous iron group were comparable with the non-intravenous iron group (p = 0.456 and p = 0.240, respectively). In comparing patients with an event (death or recurrence) and no event in the intravenous iron group, a distinct trend was found for decreased transferrin in the event group (median 2.53 g/L vs 2.83 g/L, p = 0.052).
Conclusion: The present study illustrates that a dose of 1000–2000 mg preoperative intravenous iron therapy does not have a profound effect on long-term overall and disease-free survival in anaemic colorectal cancer patients. Future randomised trials with sufficient power are required to draw definite conclusions on the safety of intravenous iron therapy.

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1. Introduction

Anaemia is a frequent complication in malignancies and is present in up to 30% of all colorectal cancer patients [1,2].

Preoperative anaemia is reported to be an independent prognostic factor for impaired short- and long-term outcome [3–5]. Although a causal relationship has not yet been demonstrated, the reported association has led clinicians to aim for correcting preoperative anaemia with the aim of improving survival of colorectal cancer patients. Treatment options for anaemia include the use of erythropoiesis-stimulating agents (ESAs), blood transfusion and iron therapy. As both blood transfusions and ESAs are, similar to preoperative anemia, independently associated with an increased

risk of cancer recurrence and increased mortality [6—10], the use of iron therapy is gaining more attention [11].

Iron deficiency (ID) is the most common cause of preoperative anaemia in colorectal cancer patients [2,12]. This implicates that optimising preoperative haemoglobin level often can be accomplished by preoperative iron supplementation. While oral iron has been shown to correct anaemia, it is also known to be absorbed slowly, to cause constipation, and to be largely ineffective in patients with anaemia of chronic disease [13]. Therefore, the use of intravenous iron has received more consideration. In this regard, several cohort studies have shown that intravenous iron therapy in colorectal cancer patients indeed optimises preoperative haemoglobin level and reduces the use of red blood cell transfusions [14—16].

The effect of intravenous iron, however, on immediate postoperative complication rate has not been elucidated. Also possible long-term effects in colorectal cancer patients are unknown. These long-term effects are of special interest while laboratory, epidemiological and animal studies have shown iron's role in all aspects of cancer development and cancer growth [17—23]. Corroborating evidence moreover implicates changes in the uptake and management of iron as crucial feature of growth of gastrointestinal cancer cells, and suggests that altered iron metabolism is a key metabolic hallmark of gastrointestinal cancer [24].

Considering this established hazardous role of iron in cancer development and especially cancer growth, the important question arises as to whether intravenous iron therapy is negatively affecting tumour prognosis in colorectal cancer patients, independently of the presence of anaemia and the use of blood transfusions. The present clinical study explores, for the first time, this long-term effect of intravenous iron therapy on tumour prognosis in colorectal cancer patients.

2. Methods

2.1. Patient selection

In this retrospective analysis, all patients undergoing resection for colorectal cancer between 1 January 2010 and 1 July 2016 at the Department of Surgery of Reinier de Graaf, a teaching hospital in the Netherlands, were identified. Consecutive patients diagnosed with anaemia (men Hb < 8.0 mmol/L, 12.9 g/dL; women Hb < 7.5 mmol/L, 12.0 g/dL) were eligible for inclusion. Patients who had surgery in an emergency setting were excluded. In our institution, over the course of the last 5 years, preoperative intravenous iron therapy was administered more frequently in anaemic patients. As treatment of anaemia was mostly depending on the clinical assessment, and on the knowledge of patient blood management of each physician, not all anaemic patiens received intravenous iron therapy. None of the patients awaiting surgery in our center did receive preoperative oral iron therapy or erythropoiese-stimulating agents (ESAs).

2.2. Data collection

All data concerning preoperative blood management and long-term survival, including the use of preoperative iron therapy and blood transfusion, Hb values and iron status (i.e. ferritin, transferrin, transferrin saturation) at diagnosis of colorectal cancer, and overall survival (OS) and disease-free survival (DFS) were manually obtained from medical records. In this respect, the preoperative period was defined as the time from diagnosis to surgery. Administration of intravenous iron therapy was defined by a dose of 1000—2000 mg iron(III)carboxymaltose (Ferinject) or iron(III)isomaltoside (Monofer). None of the patients awaiting surgery in our

center did receive preoperative oral iron therapy or erythropoiese-stimulating agents (ESAs). Clinical and pathological data, including age, gender, ASA-classification, overall comorbidities (i.e. cardiologic, vascular, diabetes, pulmonic, neurologic, thrombotic, urologic, musculoskeletal, infectious, malignancy, endocrine) tumour type, pathological tumour stage and neoadjuvant treatment were collected by the Dutch Surgical Colorectal Audit (DSCA), a disease-specific national audit. This audit collects information on patient, tumour, treatment, and 30-day and in-hospital outcome characteristics of all patients undergoing a resection for primary colorectal carcinoma in the Netherlands. The data set is cross-checked on a yearly basis with data from the Netherlands Cancer Registry [25].

2.3. Statistical analysis

Categorical variables were described as whole numbers and percentages while continuous variables were reported as medians with interquartile (IQR) range. Percentages for each variable were calculated based on available data, excluding missing values. Univariable comparison, comparing patients with preoperative intravenous iron therapy with patients with no intravenous iron therapy, was performed using the Pearson chi-square test for categorical variables and using the Mann-Whitney U test for continuous variables. The primary outcomes of the study were 5-year DFS and OS. DFS was calculated from the date of surgery to the first date of radiological or pathological evidence of recurrence or metastases or the date of last follow-up, as applicable. OS was calculated as the time from the date of surgery to the date of death or date of last available follow-up. Survival estimates were calculated using the Kaplan-Meier method. Patients diagnosed with metastatic disease (i.e. AJCC TNM stage 4) and with non-curative intent treatment were excluded in calculating DFS estimate. In addition, in patients with recurrent disease time to recurrence was compared between the intravenous iron and non-intravenous iron group using the Mann-Whitney U test. In order to correct for the baseline differences between the treatment groups, patients were matched based on propensity score, with a caliper of 0.10. Variables matched for were tumour location, Hb level at diagnosis, treatment approach and resection type (all $p < 0.1$). Finally, in all patients in the intravenous iron group and with a minimum follow up of 2.5 years, iron status was studied as a predictive factor for long-term survival using the Mann-Whitney U test. All analyses were performed using SPSS 22.0 (IBM, New York) and the MatchIt package for R 3.0.3 (https://cran.r-project.org/). All tests were 2-sided and $p < 0.05$ defined statistical significance.

Ethical approval for this study was provided by the Ethical Committee METC Zuidwest Holland. Our institution, a teaching hospital, is making use of opt-out consent. Each included patients had given consent by not declining to give consent.

3. Results

In total, 863 patients underwent surgery for colorectal cancer, of whom 82 patients were excluded because of surgery in an emergency setting. A total of 320 patients (41.0%) were anaemic at diagnosis, of whom 102 patients received preoperative intravenous iron treatment (31.9%). No patient received oral iron or ESAs in the preoperative period. Baseline characteristics are shown in Table 1. Median age at presentation was 74 years (66—80) and the majority of patients was male (54.4%). Most patients were operated laparoscopically (70.9%) and the most frequently performed resection was right colectomy (56.6%), followed by sigmoid resection/low anterior resection/abdominoperineal resection (31.9%), left colectomy (9.7%) and other (i.e. panproctolectomy, subtotal colectomy)