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Integrated approach for the preoperative correction of anemia for liver resection in patients with colorectal liver metastases

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Abstract

Aim. To study the features of the pathogenesis of anemia in patients with colorectal cancer and metastatic liver damage, as well as to evaluate the effectiveness of etiological correction of anemia in the preoperative period.
Methods. 90 patients with colorectal liver metastases and anemia (hemoglobin content 75–95 g/L), who were observed at the City Clinical Oncological Center of St. Petersburg between 2014 and 2020, were included. The patients were divided into two groups. The first group consisted of prospectively assessed patients with the preoperative correction of anemia by iron supplements (intravenously 7 mg/kg once a week) and recombinant erythropoietin (subcutaneously 150 IU/kg 3 times a week). The second group included retrospectively assessed patients with the correction of anemia only by red blood cell (RBC) transfusion (1–3 doses). The groups were comparable for gender [sex ratio (male/female) was 17:31 and 16:26 for the first and the second groups, respectively; $p > 0.5$], age (63.3±1.4 and 60.2±1.2 years, respectively; $p > 0.1$) and hemoglobin content (87.4±1.0 and 86.7±0.9 g/l, respectively; $p > 0.2$).
Results. In studying the causes of anemia, a decrease in the mean serum endogenous erythropoietin level was revealed in most patients (36.7±1.9 mIU/ml with the required 70 mIU/ml). A decrease in the concentration of serum iron (6.6±0.3 versus 15.1±0.8 μmol/l) and ferritin (15.5±1.9 versus 102.4±8.4 μg/ml) levels were revealed. At the same time, there was no difference in the concentration of pro-inflammatory cytokines in patients with anemia and healthy controls (tumor necrosis factor α, interleukin-1β, interleukin-6; $p > 0.2$), which indicates a low activity of the immune system in response to a tumor, due to conducted chemotherapy. In the preoperative correction of anemia, a positive effect was achieved with both iron supplementation with erythropoietin preparation (the hemoglobin level increased from 87.6±1.0 to 108.1±0.9 g/l; $p < 0.01$) and RBC transfusion (from 86.7±0.9 to 114.6±0.6 g/l; $p < 0.01$).
Conclusion. In patients with colorectal liver metastases, the most common causes of anemia were low levels of erythropoietin and iron deficiency; also for this group of patients, the prescription of erythropoietin and intravenous iron preparations are effective for the preoperative correction of anemia.
Keywords: anemia, colorectal cancer, liver metastases, erythropoietin, iron supplements, erythrocyte transfusion, liver resection.

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Background. The incidence of colorectal cancer (CRC) has increased significantly in the Russian Federation the past year [1]. CRC is the fifth most common cancer, with 5.4% and 5.7% incidence rates for colon cancer and rectal cancer, respectively, and the mortality rates of CRC reach 32.1% and 25.8% for colon cancer and rectal cancer, respectively, during the first year after its diagnosis [2, 3].

Furthermore, 40% of patients diagnosed with CRC have distant metastases, with 50%–60% of patients having distant metastases in the liver. Moreover, approximately 62% of patients who previously underwent radical surgery for the treatment of CRC subsequently die from distant metastases that mainly affect the liver. Additionally, it should be emphasized that there is no single approach to

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the treatment of CRC. Thus, the authors contradict to the following: some studies recommend palliative surgeries (resection of the primary tumor with the remaining distant metastases) for stage IV CRC, while other studies recommend symptomatic surgeries (formation of a colostomy or bypass intestinal anastomosis). However, it is clear that the prognosis of patients diagnosed with CRC remains unfavorable, and their life expectancy ranges from 6 to 12 months [2].

For patients with disseminated forms of cancer, the standard treatment method is systemic antitumor therapy using the currently accepted chemotherapeutic regimens (capecitabine and oxaliplatin [XELOX]; folinic acid, fluorouracil, and oxaliplatin [FOLFOX]; folinic acid, fluorouracil, and irinotecan [FOLFIRI]). Using these chemotherapeutic regimens, a positive therapeutic effect is achieved in 60%–70% of patients, and when bevacizumab is added in these regimens, the response rate of patients with CRC with liver metastases reaches 80%. When extensive liver resections are performed subsequently, the median survival rate of patients increases [4–9].

Extensive liver resections are surgical interventions that are highly traumatic, complex, and usually accompanied by significant blood loss. Despite the effectiveness of anesthesia and blood transfusions and the improvement of patients' condition after undergoing surgical procedures, the immediate results of these surgical interventions are not satisfactorily sufficient [2, 3]. This is primarily due to the development of complications such as liver failure and anemia. Anemia has a negative impact on the course and outcome of the postoperative period [2]. However, at present, both in the domestic and foreign literature data on the mechanisms of anemia development and effective methods of treating anemia in patients with CRC are insufficient. Considering this reason, determining the main pathogenesis of anemia in patients with CRC with liver metastases will allow us to develop an algorithm for its treatment, which in turn will contribute to the effective treatment of patients and will reduce the frequency of postoperative complications and possibly postoperative mortality.

Aim. This study aimed to determine the features of the pathogenesis of anemia in patients with CRC with liver metastases and to evaluate the effectiveness of the pathogenetic treatment of anemia in the preoperative period.

Materials and methods. The results of treatment of 90 patients with CRC metastatic to the liver who visited the Department of Surgery of the City Clinical Oncology Center of Saint Petersburg from 2014 to 2020 were analyzed. This study included patients diagnosed with stage IV CRC with metastatic liver disease.

All patients included in the study were examined according to the standard protocol. Patients underwent a comprehensive examination aimed at verifying the diagnosis. The following laboratory tests were performed:

– Clinical blood analysis, biochemical blood tests (total bilirubin, alanine aminotransferase, aspartate aminotransferase, glucose, creatinine, urea, serum iron, ferritin, serum erythropoietin)

– Research on cancer markers (cancer embryonic antigen and carbohydrate antigen19-9)

– Determination of the level of cytokines including tumor necrosis factor-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6)

– Determination of tumor morphology and primary tumor prevalence and detection of regional or distant metastases (fibrocolonoscopy with histological, immunohistochemical, and molecular genetic studies)

– Computed tomography of the chest and abdominal organs

– Magnetic resonance imaging of the pelvis

Moreover, it should be emphasized that all patients were initially diagnosed with anemia.

The patients were divided into two groups.

The first group (the main group, a prospective study) comprised patients (n = 48) who underwent a treatment for anemia 3 weeks before undergoing a surgical procedure, allowing them to reduce or eliminate the use of donor blood components. They received intravenous iron carboxymaltose (7 mg/kg body weight, 500 mg per injection, 21 and 10 days before a surgery) and recombinant erythropoietin alpha (150 IU/kg subcutaneously 3 times a week for 3 weeks). This group comprised a total of 17 men (35.4%) and 31 women (64.6%), with age ranging from 44 to 80 years (63.3 ± 1.4 years). All patients were diagnosed with anemia (initial hemoglobin level, 77–95 g/l; average hemoglobin level, 87.4 ± 1.0 g/l).

The second group (comparison group, retrospective study) comprised patients (n = 42) who were treated with a replacement therapy as a preoperative preparation in the treatment of anemia. Two days before a surgery, red blood cell suspension was transfused. Donor red blood cell transfusions were indicated in patients with anemia with hemoglobin level less than 90 g/l. With red blood cell transfusions, the patients' hemoglobin level improved to 100 g/l. Only 2 elderly patients (aged over 75 years) underwent red blood cell suspension transfusion at a hemoglobin level of 95 g/l. The dynamics of red blood cell parameters were evaluated the next day after each transfusion. In

case of insufficient hemoglobin replenishment in the blood, repeated donor red blood cell transfusion was performed intraoperatively. The diagnosis and presence of metastatic liver disease in all patients in the second group were similar to the first group. These patients were comparable to the first group by sex (men, 16 [38.1%]; women, 26 [61.9%]; p >0.5) and age (from 41 to 78 years; average, 60.2 ± 1.4 years; p >0.1). Moreover, all patients in the second group were diagnosed with anemia with hemoglobin levels ranging from 75 to 95 g/l (average, 86.7 ± 0.9 g/l), which is similar to the first group of patients (p >0.2).

Both groups of patients were also divided into two subgroups. In the first subgroup, patients with CRC and metastatic liver disease (n = 29) underwent the first stage of resection of the primary colon tumor to prevent complications (acute intestinal obstruction, bleeding), followed by the treatment of systemic chemotherapy (FOLFOX, XELOX, irinotecan and capecitabine [XELIRI], FOLFIRI). Patients (n = 19) in the second subgroup with the same diseases comparable to the first subgroup were first treated with similar systemic chemotherapy (FOLFOX, XELOX, XELIRI, FOLFIRI), followed by a combined surgical treatment including colon resection with simultaneous extensive resection of metastatic liver disease.

For patients in the first group, levels of hemoglobin, hematocrit, serum iron, ferritin, serum erythropoietin, and proinflammatory cytokines in the blood serum, such as tumor necrosis factor-α, IL-1β, and IL-6, were assessed 3 weeks before undergoing a surgery and receiving the pathogenetic therapy [10, 11].

Statistical analysis was performed using the Microsoft Excel 2010 and Statistica 10.0 application programs. Comparison of the studied samples was performed after testing the hypotheses of normality of distribution and the absence of significant differences between the variances in the comparison in groups using the Kolmogorov–Smirnov test. Statistical significance between the mean values was determined using the Student's t-test (taking into account the equality or differences in variances, it was assessed using the Fisher F-test), and in case of differences from the normal distribution of values, nonparametric statistical methods using the Mann–Whitney U test were performed. In addition, the Fisher angular transformation method was used to compare the proportions of the studied patients. P < 0.05 was considered significant. Results for data with a normal distribution and without a normal distribution are presented as the mean and standard error and as the median and quartiles, respectively.

Results and discussion. The first aim of this study was to determine the pathogeneses of anemia in patients with CRC with metastatic liver disease. Thus, in patients in the first group (n = 48) with hemoglobin level of 87.4 ± 1.0 g/l, the average serum erythropoietin level was 36.7 ± 2.1 mlU/ml (from 5.0 to 73.9 mlU/ml), which was 47.6% lower than the normal serum erythropoietin level with a similar degree of anemia, the concentration of which should average 70 mlU/ml [11, 12]. It is important to note that this group of patients received antitumor chemotherapeutic treatment, which could also have a toxic effect on hematopoiesis.

When studying a number of parameters of iron metabolism for patients (n = 29) in the first subgroup (the primary colon tumor was resected with subsequent chemotherapy), no significant deviations from the norm were obtained: the serum iron content ranged from 9.0 to 31.3 mlU/ml (average, 15.1 ± 0.8 mlU/ml), and the ferritin level ranged from 83.6 to 247.6 mcg/l (average, 102.4 ± 8.4 mcg/l).

In the second subgroup (n = 19) of patients (the primary colon tumor was not resected, but patients only received chemotherapy), a significant iron deficiency was detected: the serum iron level ranged from 4.1 to 8.5 mlU/ml (average, 6.6 ± 0.3 mlU/ml; p < 0.05), and the ferritin level ranged from 5.1 to 32.7 mcg/l (average, 15.5 ± 1.9 mcg/l; p < 0.05), which was significantly lower than that in the first group. Similarly, decreased red blood cell indices in the second subgroup were observed (Table 1). The cause of iron deficiency, which was one of the causes of anemia in the second subgroup of patients, was prolonged bleeding from the primary colon tumor, which was confirmed by imaging (fibrocolonoscopy) and laboratory (benzidine test, Gregersen reaction) studies.

It is known that the pathogenesis of anemia in various tumor diseases often plays a negative role in the overexpression of certain proinflammatory cytokines, which have a suppressive effect on hematopoiesis, causing anemia, which was previously demonstrated in a group of patients with malignant diseases of the lymphatic system [10, 11]. In light of this, we studied the concentrations of inflammatory cytokines of patients with metastatic liver disease with anemia and compared these concentrations to those of the control group of healthy donors aged ranging from 24 to 50 years (35.4±1.9 years), which comprised 8 men (42.2%) and 11 women (57.8%).

It was found that the content of tumor necrosis factor-α of the studied patients was 2.6 ± 0.3 PG/ml (from 0.1 to 7.9 PG/ml), while in the comparison group (healthy donors), it was 2.2 ± 0.5 PG/ml (0.8–8.2 PG/ml, p >0.5). The IL-1β level

Table 1. Blood values of patients with metastatic liver disease and anemia

Indicators	First group (n = 48), prospective study		Second group (n = 42), retrospective study	
	The first subgroup (n = 29)	The second subgroup (n = 19)	The first subgroup (n = 24)	The second subgroup (n = 18)
Hemoglobin, GM/DL	87.6±1.3 (79–95)	87.8±1.2 (77–93)	86.1±1.2 (75–91)	86.6±1.5 (76–95)
Red blood cells, $\times 10^{12}$/l	3.0±0.1 (2.6–3.7)	3.2±0.1 (2.7–3.3)	3.0±0.1 (2.5–3.8)	3.1±0.1 (2.7–3.5)
Hematocrit, %	30.7±0.4 (25.1–35.6)	31.7±0.7 (26.7–35.8)	29.4±0.7 (22.8–32.8)	30.9±1.0 (23.4–34.2)
Average red blood cell volume, fL	86.7±1.4 (72.3–99.5)	78.1±2.0* (63.4–89.0)	85.7±2.9 (72.3–102.4)	77.9±0.4* (73.9–78.3)
Average hemoglobin content in red blood cells, pg	27.4±0.3 (24.4–29.9)	24.6±0.4* (21.4–28.1)	29.2±1.0 (22.1–35.1)	24.7±0.5* (21.9–26.1)
Endogenous erythropoietin, mlU/ml	36.8±2.8 (7.2–73.9)	34.7±3.7 (5.0–52.9)	—	—
Serum iron, mcmole/l	15.1±0.8 (9.0–31.3)	6.6±0.3* (4.1–8.5)	—	—
Ferritin, μg/ml	102.4±8.4 (83.6–247.6)	15.5±1.9* (5.1–32.7)	—	—

Note: *Differences are statistically significant ($p < 0.05$) between the first and second subgroups

of the studied patients was 1.8 ± 0.6 PG/ml (0.3–85.2 PG/ml), while it was 1.2 ± 0.5 PG/ml (0.4–75.4 PG/ml) in the comparison group. The IL-6 of the studied patients was 8.7 ± 1.7 PG/ml (0.4–63.8 PG/ml), while it was 9.6 ± 1.7 PG/ml (0.5–27.4 PG/ml, $p > 0.2$) in the comparison group. Comparative analysis showed that there was no statistically significant difference in the concentration of proinflammatory cytokines of patients with CRC with metastatic liver disease and healthy donors. Apparently, these results may indicate a low tumor activity for our patients, which could be due to the already performed chemotherapy (Figure 1).

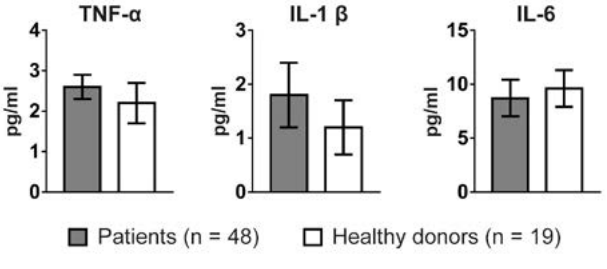

Figure 1. Comparison of proinflammatory cytokine concentrations for patients with metastatic liver disease with anemia and healthy donors (control); TNF, tumor necrosis factor; IL, interleukin

Thus, the study concluded that the following several factors are involved in the pathogenesis of anemia for patients with CRC with liver metastases:

1) Insufficient level of endogenous erythropoietin in the blood

2) Iron deficiency in the body, which we observed in patients who did not undergo tumor resection (resection of the primary colon tumor) of the colon.

Taking into account the results of our study to identify the causal factors of anemia, we used a hemostimulating therapy (recombinant erythropoietin preparations) and intravenous iron preparations for the treatment of patients with CRC with metastatic liver disease in the preoperative period. The combination of these drugs in cancer patients is considered ineffective considering that these patients experienced increased iron deficiency since these drugs increased hemoglobin synthesis during the stimulation of the erythroid germ with recombinant epoetin [10, 13]. This type of therapy is described in the protocols of the Russian Association of Supportive Care in Cancer clinical recommendations for the treatment of cancer patients [13].

The therapy was indicated in patients with anemia with hemoglobin level less than 100 g/l. The hemoglobin level target of this therapy was greater than 110 g/l. The effectiveness of the therapy was evaluated 3 weeks after the start of the therapy, which was 2 days before a surgery. If the effect of the therapy was insufficient or not observed, intraoperative blood transfusion of erythrocyte suspension was performed to increase the hemoglobin level (greater than 100 g/l), making it possible to perform liver resection safely.

It should be emphasized that, previously, patients only underwent donor red blood cell transfusion at 1–3 doses (IU = 2 [1; 2]) in preparation of a surgery. We included these patients in the second group, who were treated with red blood cell transfusions to treat their anemia. These patients were treated for anemia not only to improve their overall health or quality of life but also to preoperatively prepare them for a major surgery (i.e., extensive liver resections), which could result in several complications, including life-threatening blood loss.

The volume of intraoperative blood loss was assessed by weighing patients' napkins. Thus, in the course of the study, the volume of blood loss in our patients during a surgery was usually within 500 ml. For hemihepatectomy, it was 405 ml (312–501 ml), and for extended liver resection, it was 280 ml (156–388 ml). Simultaneously, the volume of blood loss during combined surgeries was higher, but, as a rule, did not exceed to 650 ml. For a colon resection with simultaneous hemihepatectomy, it was 485 ml (320–650 ml), and for a colon resection with simultaneous extended liver resection, it was 430 ml (350–510 ml).

Among the surgical interventions in the first group of patients (using pathogenetic means of treating anemia), 10 (20.8%) patients underwent hemihepatectomies (6 [12.5%] patients underwent right-sided hemihepatectomies, 4 [8.3%] patients underwent left-sided hemihepatectomies), 18 (37.5%) patients underwent extended liver resections, 7 (14.5%) patients underwent colon resections with simultaneous hemihepatectomy (4 [8.3%] patients underwent right-sided resection, and 3 [6.25%] patients underwent left-sided resection), and 13 (27.0%) patients underwent colon resection with simultaneous extended liver resection.

In the comparison group (performing only red blood cell transfusions to treat anemia), surgical interventions performed were similar to those in the main group: 12 (28.5%) patients underwent hemihepatectomies (7 (16.6%) underwent right-sided hemihepatectomy, and 5 (11.9%) patients underwent left-sided hemihepatectomy), 16 (38.0%) patients underwent extended liver resections, 5 (11.9%) patients underwent colon resections with simultaneous hemihepatectomy (3 [7.1%] patients underwent right-sided resection and 2 [4.8%] patients underwent left-sided resection), and 9 (21.4%) patients underwent colon resection with simultaneous extended liver resection.

Taking into account that anemia was detected in both groups of patients, these patients underwent preoperative treatment: the first group of patients received pathogenetic therapy with intravenous iron and erythropoietin administration, and the second group received donor red blood cell transfusion only. Both groups did not differ statistically when comparing their initial values in terms of hemoglobin ($p > 0.2$) and hematocrit ($p > 0.05$) levels.

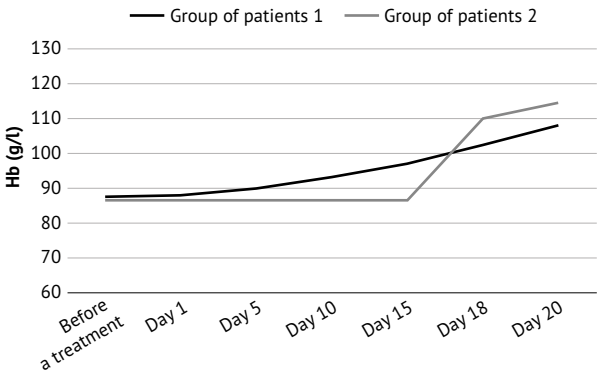

Figure 2. Dynamics of hemoglobin level due to anemia treatment

During the therapeutic treatment of anemia in both groups, there was an increase in red blood counts. Thus, the hemoglobin level in the first group of patients increased from 87.6±1.0 to 108.1 ± 0.9 g/l ($p < 0.01$). In the second group, it increased from 86.7 ± 0.9 to 114.6 ± 0.6 g/l ($p < 0.01$). The hematocrit level in the first group increased from 30.7 ± 0.4 to 38.5 ± 0.3% ($p < 0.01$), and in the second group, it increased from 29.4 ± 0.5 to 39.1 ± 0.3% ($p < 0.01$). Thus, the treatment of anemia with iron and erythropoietin preparations significantly increased the red blood counts of the studied patients and patients who received red blood cell transfusions. However, although the final hemoglobin level was slightly higher after the transfusion of erythrocyte components (108.1 ± 0.9 vs. 114.6 ± 0.6 g/l, $p < 0.02$) in both groups of patients, hemoglobin level reached a safe level for the planned surgical intervention.

The dynamics of hemoglobin indicators are shown in Figure 2. As shown in the graph, for patients in both groups, the initial levels of hemoglobin and its levels immediately before a surgery did not differ significantly. However, it should be noted that in the first group of patients, there was a gradual increase in red blood cell indicators over 3 weeks, in contrast to the second group, where the increase in hemoglobin level was detected within 2–3 days.

The course of the surgical and postoperative periods in both groups was relatively stable. However, when analyzing adverse events, a difference was observed between the two groups. Thus, in the first group of patients, out of the 48 operated patients, complications were observed in 19 (39.6%) patients. Simultaneously, nonsurgical complications were more predominantly observed compared to sur-

Table 2. Nature of postoperative complications of patients with colorectal cancer and metastatic liver disease

Postoperative complications	Major group (n = 48), n (%)	Comparison group (n = 42), n (%)
Abnormal heart rhythm	5 (10.4)	7 (16.7)
Acute cardiovascular failure	4 (8.3)	6 (14.3)
Acute myocardial infarction	0	1 (2.4)
Grade III encephalopathy	2 (4.2)	3 (7.1)
Liver failure	2 (4.2)	3 (7.1)
Failure of anastomotic sutures	2 (4.2)	2 (4.7)
Suppuration of postoperative wound sutures	3 (6.2)	4 (9.5)
Postoperative bleeding	1 (2.1)	1 (2.4)
Total complications	19 (39.6)	27 (64.2)*

Note: *Differences are statistically significant between the first and second groups ($p < 0.01$)

gical complications (Table 2). Furthermore, in the second group of patients (retrospective data), out of the 42 operated patients, complications were observed in 27 (64.2%) patients, which was 1.6 times more common ($p < 0.01$).

As can be observed from Table 2, in the second group of patients, more complications were observed ($p < 0.01$), including one fatal outcome caused by acute heart failure due to acute myocardial infarction. However, there was no significant difference in specific complications according to the results of the study between the two groups ($p > 0.05$).

Thus, in this study, it was shown that with the preoperative treatment of anemia with intravenous iron preparations and recombinant erythropoietin administration in patients with CRC with liver metastases disease, transfusions of erythrocyte-containing blood components for 93.7% of patients were not performed. Previously, when planning and performing similar surgical interventions, all patients with hemoglobin levels less than 100 g/l were transfused with donor red blood cells in the preoperative period.

Conclusion

1. Patients with CRC and metastatic liver disease and anemia experience an inadequate synthesis of endogenous erythropoietin, resulting in iron deficiency, due to bleeding from a primary colon tumor that was not resected.

2. Among the variants for the preoperative treatment of anemia of patients with CRC with liver metastases disease, preference should be given to pathogenetic therapy using recombinant erythropoietin and intravenous iron. This approach avoids erythrocyte suspension transfusions in 93.7% of patients.

3. If the pathogenetic method of treating anemia is ineffective, which was observed only in 6.2% of patients in our study, donor red blood cell transfusions are indicated.

Author contributions. A.E.A. and N.A.R. collected the material, O.E.R. and T.V.G. conducted the study, S.S.B. and N.A.R. analyzed the results, and N.A.R. and M.D.H. supervised the study.

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