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REVIEW ARTICLE

The significance of perioperative anemia in patients with resectable gastrointestinal tract tumors

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Summary

Cancer-related anemia occurs in more than 50% of patients with malignancies and constitutes a common finding in patients with gastrointestinal tract tumors.

In the present article we present the possible pathogenetic mechanisms as well as the appropriate clinical and laboratory investigations for the anemia, which is associated with gastrointestinal tract malignancies. Moreover, we conducted a MEDLINE database search between 1992-2003, focusing on the currently available methods for perioperative correction and treatment of anemia.

The currently available evidence suggests that perioperative allogenic blood transfusion is associated with increased rates of postoperative infections and constitutes an independent adverse prognostic factor in gastrointestinal malignancies; autologous blood transfusions are of no clinical benefit compared to allogenic transfusions, as autologous blood is not immunologically neutral; and the short-term results of erythropoietin (EPO) use remain controversial, while its long-term results remain unknown.

Correction of anemia in every patient with resectable gastrointestinal malignancy is mandatory, because it improves surgical stress response, wound healing process and quality of life. Although EPO administration constitutes the treatment of choice for patients receiving chemotherapy and/or radiotherapy, the best perioperative method for anemia correction remains unknown and further prospective randomized studies are required. From the surgical point of view, any effort for "bloodless surgery" should be attempted.

Key words: allogenic blood transfusion, autologous blood transfusion, cancer-related anemia, erythropoietin, gastrointestinal tract tumors

Definition

The total amount of circulating erythrocytes represents the final result of a dynamic process between erythroid progenitor cells production in the bone marrow and the daily erythrocytes consumption in the peripheral blood. Any imbalance in the previously mentioned dynamic process caused either by reduced production of stem cells in the bone marrow, or increased red cells peripheral destruction, as well as erythrocytes loss secondary to hemorrhage, results in the reduction of the total mass of circulating erythrocytes, a condition called anemia [1].

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Pathogenesis

Anemia in cancer patients may be related to preexisting hematologic diseases, to paraneoplastic syndromes or may represent a side-effect of radio- or chemotherapy. Cancer-related anemia occurs in more than 50% of patients with malignancies [2].

Several pathogenetic mechanisms have been proposed as predisposing to cancer-induced anaemia: bone marrow infiltration by malignant cells, myelosuppression secondary to chemotherapy or radiotherapy, autoimmune, traumatic or pharmaceutical hemolysis, blood loss, hypersplenism, infection, as well as

iron, folic acid and vitamins nutrient deficiencies [2-7]. However, in a considerable number of cancer patients no cause other than malignancy itself can be implicated. In those cases, the term "anemia of chronic disease" has been used to describe the condition.

Experimental studies at cellular level have shown that activation of immune and/or inflammatory systems leads to cytokines (interleukins-1, 6, 10, interferon-γ, tumor necrosis factor -TNF) release, which then can cause: (1) impaired iron utilization, (2) suppression of erythroid progenitor cells differentiation, (3) inadequate EPO production, and (4) decreased response of the bone marrow to the circulating EPO [2-7].

Symptoms and signs

As the principal function of erythrocytes consists on oxygen delivery to the tissues, symptoms and signs of anemia are related to tissue hypo-perfusion. The classic symptoms of anemia include: pallor, anorexia, tiredness, weakness, dizziness, dyspnea, hypotension, tachycardia and heat intolerance [8,9].

Investigation

Because of the multifactorial etiology of anemia in cancer patients, clinical evaluation and laboratory investigation are considered mandatory, in order to define the particular type and severity of the disease.

A detailed personal and family history should focuses on bleeding disorders, previous blood loss, recent illness, use of medications, alcohol consumption or exposure to toxic agents.

Physical examination may reveal signs of hematological disorder, such as, pallor or jaundice, skin and mucosal lesions, lymphadenopathy, hepatosplenomegaly, neuropathy or microscopic blood loss in the urine or stools.

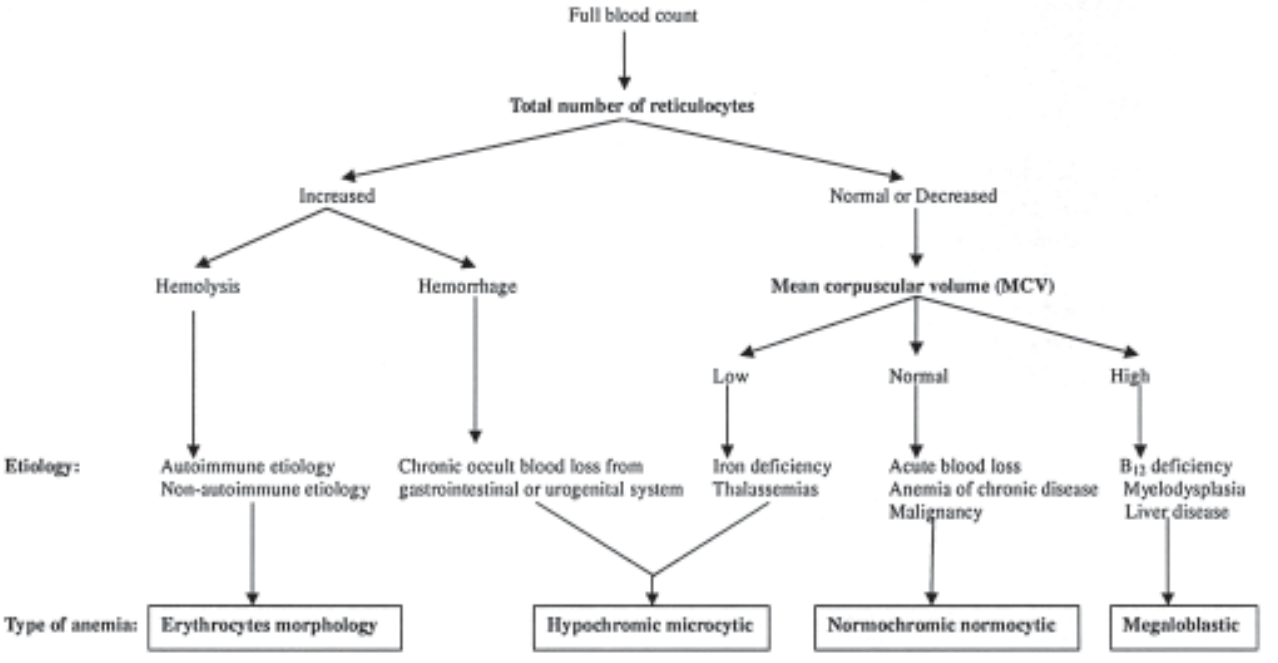
Sophisticated tests, beyond history and clinical examination, are necessary to provide further diagnostic clues regarding the cause of anemia. A diagnostic algorithm, as it is described in Table 1, is crucial to determine the cause and the severity of anemia in cancer patients.

Treatment

Multiple variables must be evaluated by the clinician before he decides to treat anemia. As a general rule, symptomatic anemia requires correction. Absolute indications for correction of the anemia include [10].

- Acute blood loss, more than 15% of total blood volume
- Decrease of arterial blood pressure more than 20%

Table 1. Algorithm for laboratory investigation of anemia



From: Fellin FM, Murphy S. Perioperative evaluation of patients with hematologic disorders. In: Merli GJ, Weith Hh (eds): Medical management of the surgical patient. Saunders, Philadelphia, 1992, p: 85 (with permission) [8].

- Diastolic blood pressure less than 60 mmHg
- Tachycardia, with more than 100 pulses/min
- Angina
- Weakness and fatigue

In every day clinical practice, correction of anemia is usually based on hematocrit (Ht) and hemoglobin (Hb) values. Especially for the surgical patient the maintenance of a baseline Hb level is crucial for tissue oxygenation in order to tolerate the surgical stress and achieve optimal postoperative course and wound healing process. Although there are no strict rules, current expertise suggests that the majority of otherwise healthy patients could tolerate surgical stress having Hb value more than 10 g/dL, whereas in younger patients preoperative Hb values of 6-7 g/dL are sufficient. In case of coexisting conditions, such as, impaired cardiopulmonary function, renal, liver or vascular diseases, the maintenance of Hb level above 10 g/dL is of great significance [10,11].

Allogenic transfusion has been traditionally considered as the therapeutic intervention of choice to correct anemia and to increase Hb value in the perioperative period. Recently, autologous blood donation and EPO therapy have been proposed as effective alternative therapeutic options for correction of cancer-induced anemia.

Allogenic blood transfusion

Perioperative allogenic blood transfusion aims to ameliorate the symptoms of anemia, to improve the quality of life, to provide enough reserves to the patient in order to anticipate surgical stress and to precipitate the rehabilitation of the patient to social life. Regarding the early postoperative outcome, a recent meta-analysis [12] concluded that allogenic blood transfusion is associated with an increased rate of postoperative infections, while the effect of allogenic blood transfusion in cancer patients on the long-term results (overall survival, disease-free survival, recurrence rates) remains a matter of debate. The prognostic role of allogenic blood transfusions in gastrointestinal malignancies was studied in clinical trials during 1992-2003 [13-52] (Table 2). The majority of these studies, especially the prospective randomized trials [25-30], confirmed that allogenic blood transfusion is an independent factor predisposing to poor outcome in gastrointestinal malignancies, affecting the recurrence rate, disease-free survival and overall survival. Although the association between allogenic blood transfusion and poor survival in patients with gastrointestinal cancer has been documented, this relation is not due to promotion of cancer itself [40]. The immunosuppression induced by the allogenic blood transfusion during the early [18] or late [42] postoperative period has been proposed as the most possible pathogenetic mechanism, to explain the adverse relationship between allogenic blood transfusion and prognosis of gastrointestinal malignancies.

Autologous blood transfusion

The adverse relationship between allogenic blood transfusion and cancer prognosis, the increased rates of postoperative bacterial infections [12], the complica-

Table 2. Studies of allogenic blood transfusion (ABT) use in surgery for gastrointestinal tract cancer

References	*Type of study*	*Location of tumor*	*Conclusion*
13-16	4 Retro	Esophageal cancer	Adverse relationship between perisurgical ABT and cancer prognosis
17	1 Retro		No relationship between perisurgical ABT and cancer prognosis
18-21	3 Retro & 1 Pro	Gastric cancer	Adverse relationship between perisurgical ABT and cancer prognosis
22	1 Retro		No relationship between perisurgical ABT and cancer prognosis
23-35	8 Retro, 3 Pro, 2 RCT	Colon & Rectal cancer	Adverse relationship between perisurgical ABT and cancer prognosis
36-39	2 Retro, 2 Pro		No relationship between perisurgical ABT and cancer prognosis
40-42	3 Retro	Periampullary cancer	Adverse relationship between perisurgical ABT and cancer prognosis
43	1 Retro		No relationship between perisurgical ABT and cancer prognosis
44-49	5 Retro, 1 Pro	Hepatocellular carcinoma	Adverse relationship between perisurgical ABT and cancer prognosis
50	1 Pro		No relationship between perisurgical ABT and cancer prognosis
51	1 Retro	Metastatic liver cancer	Adverse relationship between perisurgical ABT and cancer prognosis
52	1 Retro		No relationship between perisurgical ABT and cancer prognosis

Retro: retrospective study; Pro: one-armed prospective study; RCT: randomized clinical trial

tions of transfusions, as well as donors' shortage played pivotal roles in the development of transfusions alternatives. Autologous blood donation reduces the need of allogenic transfusions [53,54] and subsequently, the risk of postoperative infections [53]. Autologous blood may contain cancer cells, which decrease or disappear after 14-day storage. Hence autologous blood donation is safe after 2-week storage [55,56]. Prospective randomized [54,57] as well as retrospective trials [53,58,59] investigated whether prognosis in gastrointestinal cancer is impaired by autologous blood donation as compared to allogenic transfusions (Table 3). Except one retrospective trial [59], no statistically significant advantage of autologous blood donation was documented. This observation substantiates the hypothesis that autologous blood transfusion is not immunologically neutral but carries an intrinsic immunomodulatory potential [60].

Erythropoietin

EPO is a glycoprotein that selectively acts on bone marrow to increase erythropoiesis. The clinical impact of recombinant human EPO in anemia associated with gastrointestinal cancer has been extensively studied in one-armed prospective [61] and prospective randomized [62-66] trials (Table 4). The results of these studies were conflicting, whereas the potential impact of EPO therapy on the natural history of the gastrointestinal cancer remains unknown.

Conclusions

Based on the relevant international literature, the following conclusions can be drawn:

• Correction of anemia in every patient with resectable gastrointestinal malignancy is mandatory, because it improves surgical stress response, wound healing process and quality of life.

• Not only the Hb and Ht values, but also the patient's age and performance status, as well as cardiovascular and pulmonary reserves should be taken into account prior to any attempt of perioperative correction of anemia.

• Perioperative allogenic transfusion has been associated with increased rates of postoperative infections and has been proposed as an independent adverse factor for cancer prognosis in gastrointestinal malignancies. Hence, every effort to minimize the intraoperative blood loss and to limit the needs for transfusions in less than 2 units of blood should be attempted.

• No clinical benefit has been documented in patients treated by autologous blood transfusions compared to allogenic transfusions, as autologous blood is not immunologically neutral.

• For anemic cancer patients receiving chemotherapy and/or radiotherapy, EPO therapy represents the treatment of choice [67]. Meanwhile, because of its high cost for the time being, it is necessary to select only those patients who are most likely to benefit from this therapeutic option [68].

• Perisurgical EPO treatment may be indicated in elective surgical procedures. However, further prospective randomized studies are needed to evaluate the effect of EPO on the early postoperative outcome and its effect on the long-term cancer prognosis [69], to establish an optimal dose for perioperative EPO administration and, finally, to identify the subgroup of patients in which iron replacement therapy (combined with EPO) will be helpful [62,64].

Table 3. Studies of autologous blood transfusion (ABT) use in surgery for gastrointestinal tract cancer

Author	*Reference*	*Type of study*	*Compared groups*	*Location of tumor*	*Conclusion*
Kinishita Y et al	53	Retro	Autologous *vs* Allogenic	Esophageal cancer	ABT was related to a lower incidence of postoperative infections
Heiss MM et al	54	RCT	Autologous *vs* Allogenic	Colon & Rectal cancer	Higher recurrence rate in the ABT group of patients within a 22-month follow-up period
Busch OR et al	57	RCT	Autologous *vs* Allogenic	Colon & Rectal cancer	No difference in cancer prognosis among the two groups of patients, within a 4-year follow-up period
Chan AC et al	58	Retro	Autologous *vs* Allogenic	Metastatic liver cancer	No difference in median survival among the two groups of patients
Motoyama S et al	59	Retro	Autologous *vs* Allogenic	Esophageal cancer	Univariate analysis showed better overall survival in the ABT group of patients

Retro: retrospective study; RCT: randomized clinical trial

Table 4. Studies of erythropoietin (EPO) use in surgery for gastrointestinal tract cancer

Author	*Reference*	*Type of study*	*Compared groups*	*Location of tumor*	*Conclusion*
Levine EA et al	61	Pro		Rectal cancer	EPO reduced the needs for perioperative transfusions
Heiss MM et al	62	RCT	EPO *vs* Placebo	Colon & Rectal cancer	EPO did not reduce the needs for perioperative transfusions
Kettelhack C et al	63	RCT	EPO *vs* Placebo	Right colon cancer	EPO did not reduce the needs for perioperative transfusions
Kosmadakis N et al	64	RCT	EPO *vs* Placebo	GI tract malignancies	■ EPO reduced the needs for perioperative transfusions ■ EPO led to better survival within a 12-month follow-up period
Qvist N et al	65	RCT	EPO *vs* Placebo	Colon & Rectal cancer	■ EPO reduced the needs for perioperative transfusions ■ The Hb concentration remained higher in the EPO-group of patients between 0-7th postoperative day, but this difference disappeared by the 36th postoperative day
Tsuji Y et al	66	RCT	EPO *vs* Placebo	Gastric cancer	■ No statistically significant difference in blood transfusions between the two groups of patients ■ The Hb concentration remained higher in the EPO-group of patients between 0-10th postoperative day

Pro: one-armed prospective study; RCT: randomized clinical trial

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