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Review Article

Indications for and complications of transfusion and the management of gynecologic malignancies

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HIGHLIGHTS

- We review the incidence and prognosis of anemia in the cancer patient.
- We present indications and risks for red blood cell transfusion.
- We describe peri- and intra-operative management of blood.

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ABSTRACT

Anemia, which is highly prevalent in oncology patients, is one of the most established negative prognostic factors for several gynecologic malignancies. Multiple factors can cause or contribute to the development of anemia in patients with gynecologic cancers; these factors include blood loss (during surgery or directly from the tumor), renal impairment (caused by platinum-based chemotherapy), and marrow dysfunction (from metastases, chemotherapy, and/or radiation therapy). Several peri- and intra-operative strategies can be used to optimize patient management and minimize blood loss related to surgery. Blood transfusions are routinely employed as corrective measures against anemia; however, blood transfusions are one of the most overused healthcare interventions. There are safe and effective evidence-based blood transfusion strategies used in other patient populations that warrant further investigation in the surgical oncology setting. Blood is a valuable healthcare resource, and clinicians can learn to use it more judiciously through knowledge of the potential risks and complications of blood interventions, as well as the ability to properly identify the patients most likely to benefit from such interventions.

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1. Anemia in the cancer patient

1.1. Prevalence and pathogenesis

Secondary to disease progression or as a consequence of treatment, many cancer patients will require blood products at some point during their continuum of care. This need for blood often coincides with the development of symptomatic anemia. According to the World Health Organization, a hemoglobin (Hb) level ≥ 12 g/dL (120 g/L) is considered normal in non-pregnant women. Mild, moderate, and severe anemia are identified at Hb levels of 11.0–11.9, 8.0–10.9, and <8.0 g/dL, respectively [1]. While numerical cutoffs do not reflect patient comorbidities, which contribute significantly to the variation in symptomatology, they are the main parameters used to guide transfusion practice. >-6 million units of red blood cells (RBCs) are transfused in the United States annually, at an estimated cost of $1600–$2400 per transfusion event [2–4]. Oncology patients account for 34% of this blood supply use and cost [5].

Clinicians use low Hb concentration or low hematocrit as the complete blood count parameters to define anemia. Symptoms are dependent upon the degree of anemia and the rate at which it develops. The reduction of Hb concentration to 5 g/dL maintains adequate tissue

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oxygen delivery in healthy resting adults, with symptoms occurring only when the Hb concentration drops below this level. In the postoperative setting, Hb levels of 7.1–8.0 g/dL have a low risk of death, with the mortality rate rising to 34.4% with Hb levels of 4.1–5.0 g/dL [6]. There are several compensatory mechanisms in response to anemia, such as increased heart rate, increased respiratory rate, and a right shift of the oxygen-dissociation curve, all with the goal to maintain adequate oxygen delivery to the tissue. The main symptoms of anemia, such as dyspnea, palpitations and fatigue, are manifestations of these compensatory mechanisms. Functional impairment and a decline in subjective well-being are also highly distressing symptoms that are detrimental to a patient's quality of life and affect their ability to tolerate cancer treatments.

Multiple factors can cause or contribute to anemia in the oncology setting. Patients should undergo a basic work-up to identify possible causes. The work-up should include reticulocyte, creatinine, iron (serum iron, total iron-binding capacity, transferrin saturation, and serum ferritin), B12, and folate measurements [7]. Cancer-related anemia (CRA), which can occur in patients with malignancies, is considered a cytokine-mediated process between tumor cells and the immune system, with an overexpression of certain pro-inflammatory cytokines, specifically interleukin-1 (IL-1) and tumor necrosis factor (TNF). These cytokines have been shown to impair iron utilization, suppress erythroid maturation, and reduce erythropoietin (EPO) production [8]. In CRA, hepcidin, an iron regulatory peptide, is upregulated and inhibits the transport of iron via macrophages in the duodenum, decreasing gastrointestinal absorption and the accessibility of stored iron. CRA is typically a normochromic, normocytic anemia associated with a low reticulocyte count.

The European Cancer Anemia Survey (ECAS), which was conducted across 24 European countries and 748 cancer centers, assessed >13,600 patients for the incidence and prevalence of anemia across various cancer types and stages of treatment. In the study, anemia was defined as an Hb level < 12.0 g/dL. Gynecologic malignancies accounted for 11.6% of all cases. The ECAS found a prevalence of anemia of 39.3% and 67.0% at enrollment and during the survey, respectively. When looking specifically at patients with gynecologic cancers, 48.1% were anemic at enrollment, of which only 42.7% ever received treatment for their anemia [9]. In gynecologic malignancies, the most common factors associated with the development of anemia are blood loss (during surgery or directly from the tumor), renal dysfunction (secondary to platinum-based chemotherapy), and marrow dysfunction (from metastases, chemotherapy, and/or radiation) (Fig. 1).

1.2. Prognosis

In a systematic review assessing anemia as an independent prognostic factor for survival in patients with various cancers, Caro et al. noted reduced median survival times of 20% to 43% across cancer types in anemic patients compared to those without anemia, with an overall adjusted HRR of 1.65 (aHRR, 1.19–1.75) [10]. Findings from a systematic review by Knight et al. showed that nearly all studies reported an association between anemia and decreased survival or increased mortality for multiple cancer types. The authors cautioned that the relationships between anemia and disease progression, treatment response, and overall survival may not be causal, as these findings were based on observational studies [11].

There is abundant evidence establishing anemia as one of the most prevailing prognostic factors in patients with cervical cancer (Table 1) [12–28]. Most published studies exploring this relationship are retrospective and include patients who had undergone some form of radiation therapy. This poses a confounder on prognosis, since anemia may

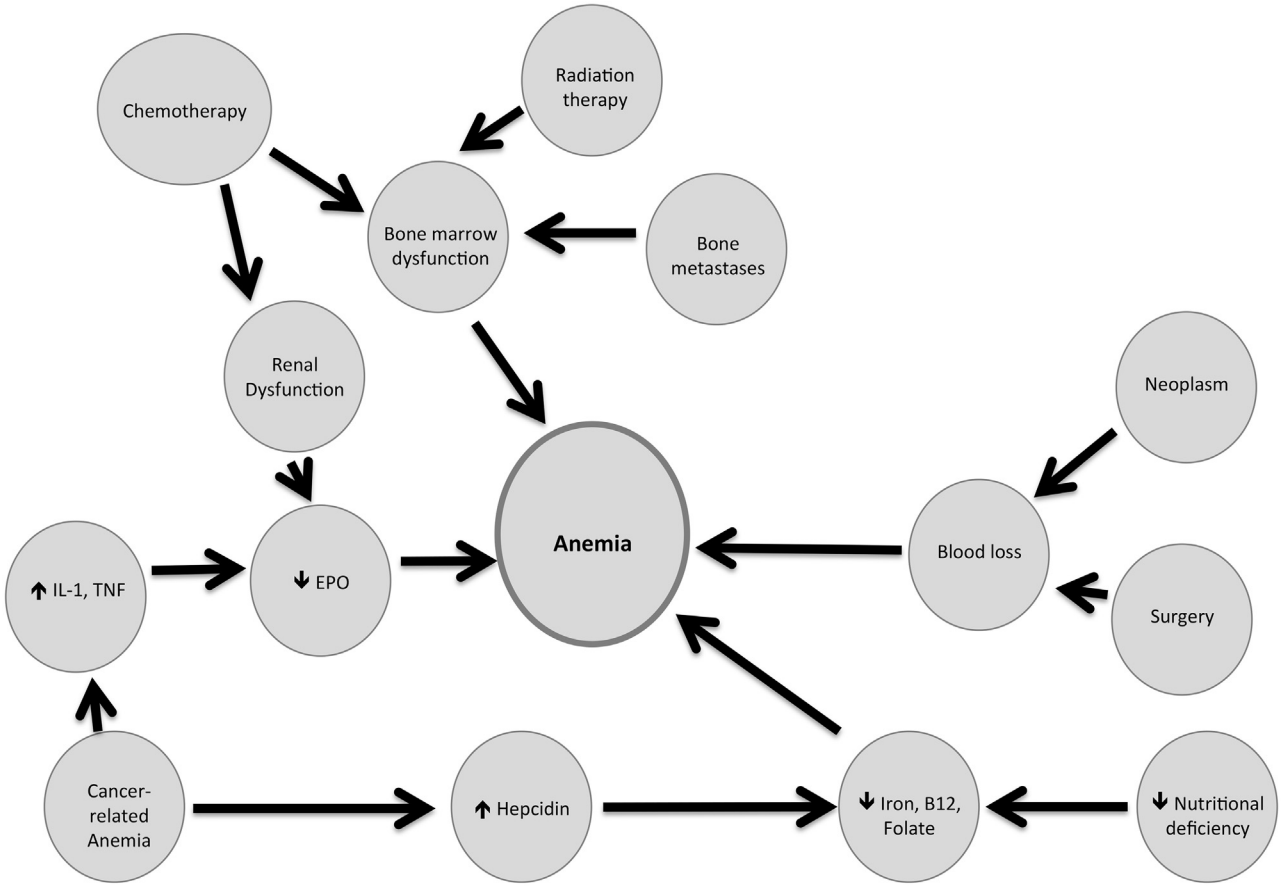

Fig. 1. The multi-factorial pathogenesis of anemia in the cancer patient IL-1 – Interleukin 1; TNF – tumor necrosis factor; EPO – erythropoietin.

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