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Synergistic immunotherapy targeting cancer-associated anemia: prospects of a combination strategy

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Abstract

Cancer-associated anemia promotes tumor progression, leads to poor quality of life in patients with cancer, and even obstructs the efficacy of immune checkpoint inhibitors therapy. However, the precise mechanism for cancer-associated anemia remains unknown and the feasible strategy to target cancer-associated anemia synergizing immunotherapy needs to be clarified. Here, we review the possible mechanisms of cancer-induced anemia regarding decreased erythropoiesis and increased erythrocyte destruction, and cancer treatment-induced anemia. Moreover, we summarize the current paradigm for cancer-associated anemia treatment. Finally, we propose some prospective paradigms to slow down cancer-associated anemia and synergistic the efficacy of immunotherapy.

Keywords Cancer-associated anemia, Erythropoiesis, Extramedullary hematopoiesis, Eryptosis, Immune checkpoint inhibitors

Introduction

Anemia is one of the most common complications in patients with cancer, and cancer-associated anemia is indicative of a poor prognosis, irrespective of tumor type. The incidence of anemia in patients with cancer varies according to cancer type, stage, and therapeutic intervention [1, 2]. According to World Health Organization (WHO) criteria and the Common Terminology Criteria for Adverse Events (CTCAE) (v 5.0), cancer-associated anemia is defined as a hemoglobin (Hb) level lower than 120 g/L in women and lower than 130 g/L in men [3]. Anemia in patients with cancer can be classified as cancer-induced anemia, which affects approximately 40% of patients newly diagnosed with cancer and prior to any antineoplastic treatment; and cancer treatment-induced anemia, which affects approximately 40%–70% of patients who are not anemic at diagnosis but develop anemia as a universal side effect of the cancer therapy [2, 4, 5]. The underlying mechanisms of cancer-induced anemia include decreased erythropoiesis and increased erythrocyte destruction, and strategies for treating cancer-induced anemia have been established based on these mechanisms.

Although the anti-cancer efficacy of immune checkpoint inhibitors (ICIs) has allowed immunotherapy to become an established cancer therapy, a long-term clinical response and increased overall survival is only seen in a subset of patients with specific cancer types [6]. In addition to several biomarkers, including programmed cell death ligand-1 (PD-L1) [7], tumor mutational burden (TMB) [8], DNA damage repair [9], and tertiary lymphoid structures [10] used to predict ICIs efficacy,

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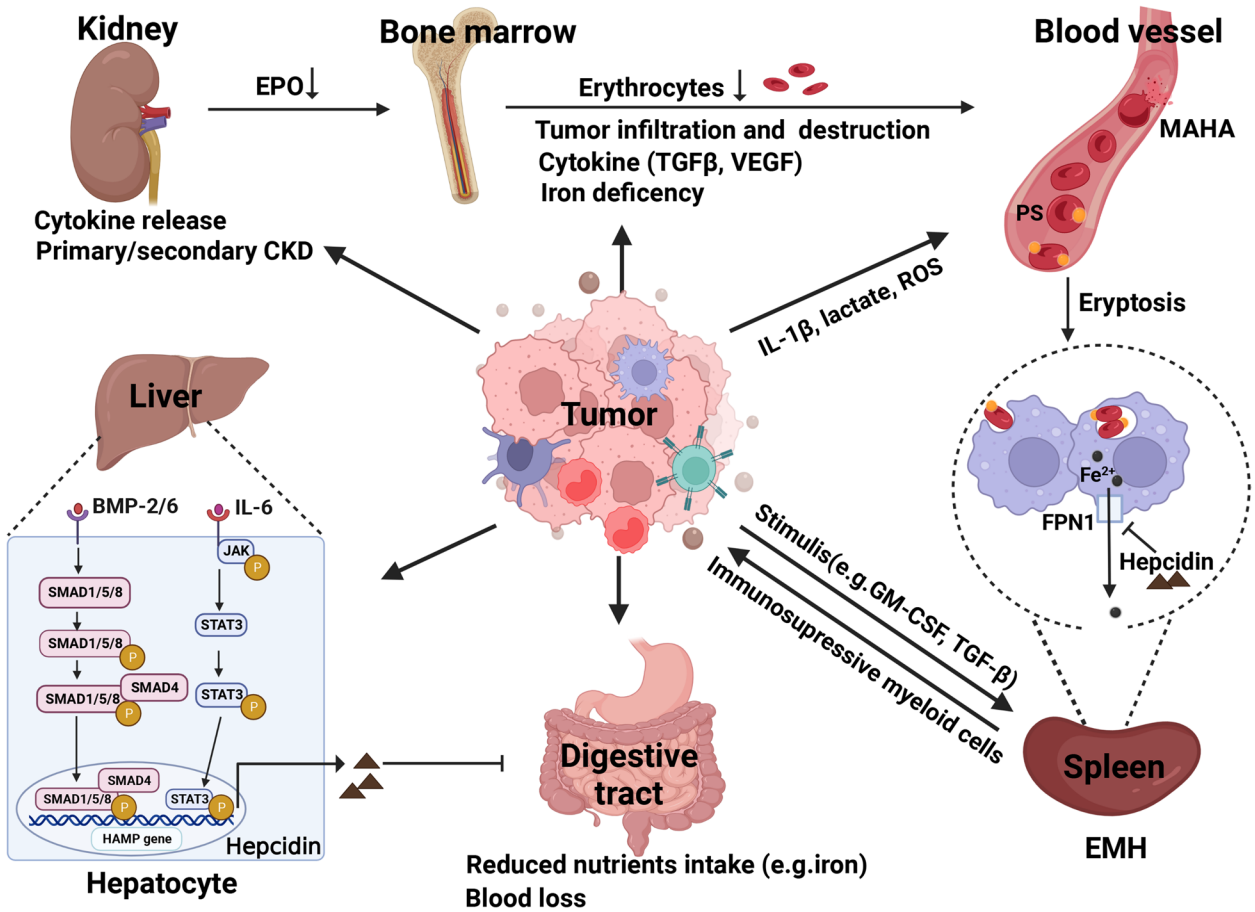

Fig. 1 Mechanisms of cancer-induced anemia. Non-hematopoietic tumors can cause anemia via a range of mechanisms. Tumor-produced cytokines inhibit erythropoiesis directly or indirectly by blunting EPO production and inducing state of iron deficiency. Decreased EPO production is also common in cancer patients with the primary or secondary chronic kidney disease (CKD). Hepcidin, the key regulator of iron metabolism, inhibits iron flux in both gastrointestinal tract and splenic macrophages, and it is upregulated mainly by IL-6/STAT3 and BMP/SMAD pathway. Tumor-released stimulators, including GM-CSF and TGF-β, also trigger extramedullary hematopoiesis (EMH), which causes the defective erythropoiesis and induces immunosuppressive myeloid cells to accelerate tumor progression. Tumor infiltration of bone marrow results in hematopoietic environmental destruction and gastrointestinal tumor progression often accompanied by blood loss. Tumor-released IL-1β, lactate and ROS aggravate the process of eryptosis to promote erythrocytes destruction

cancer-associated anemia has been identified as a risk factor that reduces ICIs efficacy [11, 12]. As approximately 40% of patients with cancer have cancer-induced anemia, elucidating the effect of cancer-induced anemia on ICIs treatment efficacy, and developing strategies to simultaneously treat cancer and anemia is of significant clinical interest. Here we review recent research regarding the mechanism (Fig. 1) and treatment of cancer-induced anemia, and highlight the prospective paradigm of immunotherapy for cancer-induced anemia.

Mechanisms of cancer-induced anemia

Influence of tumor-induced cytokines on erythropoiesis

Normal erythropoiesis is a continuous process occurring in the bone marrow. Early erythroid progenitor cell (EPC)-burst-forming unit-erythroid (BFU-E) are generated in stem- and progenitor cell niches and migrate to erythroblastic islands where the BFU-E differentiate into erythropoietin (EPO)-dependent erythroid progenitors and terminal erythroblasts. Erythroblasts then undergo hemoglobinization, enucleation, and subsequently enter the blood circulation to maintain erythrocyte mass and meet oxygen requirements. The proliferative and differentiative capacity of EPCs is sensitive to stimulatory or inhibitory factors [2], such as transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF).

In normal bone marrow, hematopoietic stem cell (HSC) quiescence and self-renewal is regulated by TGF-β [13]. In vitro, TGF-β plays a paradoxical role in erythropoiesis

by blocking proliferation while accelerating the differentiation of erythroid progenitors [14]. Tumor-secreted TGF-β has been shown to inhibit erythropoiesis via organ-specific mechanisms. In advance-stage cancer, especially hepatocellular carcinoma [15], tumor-secreted TGF-β accelerates the differentiation of megakaryocytes and erythroid progenitors into splenic $CD45^{-}$EPCs [16], which blocks the late stage of erythropoiesis. TGF-β knockout in hepatocellular carcinoma cells and specific-antibody TGF-β neutralization has been shown to reduce the number of splenic $CD45^{-}$EPCs in vivo [16]. Furthermore, a study using Lewis lung carcinoma cells to generate a cancer-induced anemia model found that TGF-β secreted by osteoclasts induces deterioration of the HSC niche in the bone marrow. Treatment with a TGF-β inhibitor therefore improves erythropoiesis and ameliorates cancer-induced anemia [17].

Cancer-induced anemia is also associated with elevated plasma levels of VEGF [18, 19]. VEGF produced by tumor and stromal cells induces neovascularization, vessel remodeling, and expansion of early-stage EPCs in the bone marrow and extramedullary region [20], as well as vascular dilation and bone marrow cell mobilization, which induce HSC depletion through VEGF-VEGFR2 signaling [21]. Bevacizumab, an anti-VEGF antibody, reverses VEGF-induced severe anemia and reduces mortality in tumor-bearing mice [22], indicating that VEGF may be a promising target for cancer-induced anemia treatment.

Impaired systemic iron metabolism

Maturation of erythroid progenitors into erythrocytes is a multi-stage, iron-dependent process. Transferrin, which binds free iron with high affinity, attaches to EPC transferrin receptors. In acidified lysosomes of EPCs, iron is released from transferrin and exported to the cytoplasm by the divalent metal transporter 1 (DMT1). The iron subsequently enters the mitochondria and attaches to protoporphyrin IX during the final step of heme biosynthesis [23]. Cancer-induced anemia is commonly characterized by decreased serum iron concentrations and transferrin saturation despite sufficient iron stores, known as functional iron deficiency anemia (FIDA) [24, 25]. Furthermore, absolute iron deficiency anemia (AIDA) may be triggered by, for example, advanced gastrointestinal cancer, which is accompanied by reduced iron intake, defective iron absorption, and chronic blood loss [24, 26].

Systemic iron metabolism is regulated by hepcidin, which is mainly derived from the liver. Hepcidin is also produced by inflammatory monocytes or macrophages through a toll-like receptor (TLR)-4-dependent pathway in mice or an interleukin (IL)-6-dependent pathway in humans [27]. Increased hepcidin inhibits DMT1 and duodenal cytochrome b, thereby inhibiting intestinal iron absorption [28]. Hepcidin also binds to iron transporters on macrophages and duodenal cells, promoting internalization and degradation of ferroportin (FPN), which inhibits iron output and utilization [29, 30]. The consequent iron retention leads to insufficient plasma iron levels for erythropoiesis, resulting in FIDA [31]. Overexpression of hepcidin and FIDA are often observed in cancer patients [32], and tumor-produced hepcidin has been shown to reduce serum iron levels and cause severe anemia in a mouse model [33]. Several mediators, including IL-6, bone morphogenetic protein (BMP)-2, and growth differentiation factor-15 (GDF-15), regulate hepcidin levels.

IL-6, a proinflammatory cytokine, has been associated with cancer-induced anemia. In patients with renal cell carcinoma, IL-6 levels greater than 10 pg/mL were associated with a marked increase in the risk of anemia [34]. In patients with advanced ovarian cancer, serum IL-6 levels were inversely correlated with Hb levels, and high serum IL-6 levels were attributed to M1 tumor-associated macrophages from the tumor microenvironment [35]. Moreover, cancer treatment with recombinant human IL-6 has been found to induced anemia and hypoferremia [36], and a cancer-induced anemia mouse model has been established by inoculation with IL-6-producing human or mouse tumor cell lines [37]. It has been suggested that high IL-6 plasma levels induce hypoferremia by upregulating hepatic hepcidin expression via signal transducer and activator of transcription 3 (STAT3) activation [38], as well as increasing plasma volume to promote anemia [39]. Treatment with an anti-IL-6 receptor (IL-6R) antibody reversed cancer-induced anemia [37].

In patients with multiple myeloma, BMP-2, rather than IL-6, has been suggested as the major inducer of hepcidin, with BMP-2 levels inversely correlated with Hb levels [40]. Hepcidin is also upregulated by BMP-6/small-mothers-against-decapentaplegic (SMAD) signaling, which is negatively correlated with Hb concentrations in patients with solid tumors [41, 42]. In addition, in patients with gastrointestinal cancer, hepcidin production is downregulated by increased GDF-15, mainly due to chronic blood loss [43]. These studies suggest that hepcidin inhibition may help alleviate cancer-induced anemia.

Reduced EPO production

EPO, a crucial cytokine regulator of erythropoiesis, is produced by kidney interstitial cells and is involved in the regulation of erythroid cell survival, proliferation, and differentiation. EPO binds to the EPO receptor (EPOR), which is expressed in erythroid cell stages from the colony-forming unit-erythroid (CFU-E) to the basophilic

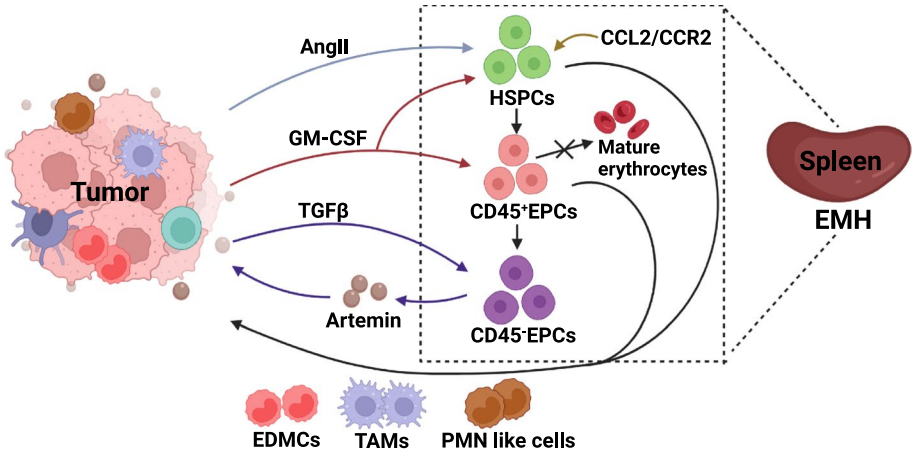

Fig. 2 EMH and erythro-myeloid transdifferentiation during cancer-induced anemia. Tumor-derived stimulators, including AngII, GM-CSF and TGF-β, induce EMH. AngII and CCL2/CCR2 signal lead to the amplification of HSPCs in spleen and erythro-myeloid transdifferentiation as well. AngII triggers the sustained tumor associated macrophages (TAMs), and GM-CSF drives HSPCs into immunosuppressive PMN like cells. EPCs' differentiation is blunted in EMH, $CD45^+$EPCs are incline to convert into EDMCs by the stimulation of GM-CSF, while $CD45^-$EPCs accumulation induced by TGF-β produce artemin. All of which aggravates cancer-induced anemia directly or indirectly by tumor progression

erythroblast, activating the JAK2-STAT1/3/5 [44] and PI3K-AKT-GATA-1 [45] pathways to regulate erythropoiesis. In addition, EPO-induced growth arrest-specific gene 6, released by erythroblasts, improves cell survival and maturation via autocrine or paracrine pathways [46]. However, compared with patients with iron-deficiency anemia, EPO production is reduced in patients with cancer-induced anemia [47, 48]. Mechanistically, EPO-deficiency could be attributed to inflammatory or immune responses involving cytokine release, as well as primary or secondary chronic kidney disease in patients with cancer [2, 49]. Moreover, increased intracellular iron sequestration may promote hypoxia inducible factor-1α (HIF-1α) degradation via prolyl hydroxylation, thereby reducing EPO production in patients with cancer [50]. Thus, EPO deficiency may contribute to anemia in patients with cancer.

Cancer-induced extramedullary hematopoiesis

In advanced cancer, extramedullary hematopoiesis is initiated to maintain erythroid homeostasis [51]. However, extramedullary hematopoiesis may cause deficient or ineffective erythropoiesis, leading to increased numbers of immature erythroid cells and a heightened splenic myeloid response [52] (Fig. 2). Tumor-derived VEGF [53] and platelet-derived growth factor (PDGF)-BB [54] induce extramedullary hematopoiesis, resulting in splenomegaly and tumor progression. Additionally, splenic macrophage-synthesized BMP-4 has been shown to promote splenic erythropoiesis in a 4T1 tumor model [55]. Recently, splenic immature erythroid cells were identified as EPCs ($CD71^+TER119^+$). In patients with cancer, abundant $CD45^+$EPCs are accumulated in the spleen, producing reactive oxygen species (ROS), which inhibits systemic anti-tumor immunity, and $CD45^+$EPCs promote tumor progression through CD8 T-cell immunosuppression [56]. In hepatic cancer, tumor-derived TGF-β contributes to the generation of splenic $CD45^-$EPCs [16], which promote tumor progression via the neurotrophic factor artemin.

Tumor-induced extramedullary hematopoiesis also leads to erythro-myeloid transdifferentiation (Fig. 2). Melanoma-derived IL-3 skews erythroid hematopoiesis towards myeloid lineages, which are characterized by increased myeloid progenitors, specifically CMPs, GMPs, and MEPs, and decreased late-stage splenic erythroblasts [57]. In a mouse model of lung adenocarcinoma, overproduction of angiotensin II (Ang II) induced splenic HSCs and macrophage progenitor amplification, thus providing sustained tumor-associated macrophages during cancer progression [58]. Hepatic cancer-induced CCL2/CCR2 signaling and endogenous granulocyte–macrophage colony-stimulating factor (GM-CSF) have also been shown to drive differentiation of splenic HSCs into immunosuppressive myeloid cells-polymorphonuclear (PMN)-like cells [59]. In breast cancer, 4T1 tumors express granulocyte-CSF (G-CSF) to promote splenic myelopoiesis, causing anemia [60]. Furthermore, tumor-expressed GM-CSF stimulates $CD45^+$EPC differentiation into erythroid differentiated myeloid cells (EDMCs) with an immunosuppressive phenotype, which reduces immune checkpoint therapy efficacy [11]. Tumor-derived growth factors and cytokines may therefore induce EPC accumulation in extramedullary organs, driving erythro-myeloid

transdifferentiation into tumor tissue. And observational study suggested that intratumoral $CD45^{+}CD71^{+}$ erythroid cells suppressed T cells, predicted disease-free survival and overall survival in hepatocellular carcinoma [61]. Thus, further study of erythroid-derived immune cells in tumor tissue may provide new ideas for the outcome of extramedullary hematopoiesis and new targets for tumor therapy.

Increased erythrocyte destruction

Erythrocytes undergo eryptosis, a suicidal cell death characterized by cell shrinkage and cell membrane scrambling resulting in phosphatidylserine (PS) exposure. Binding of the exposed PS to its receptors on red pulp macrophages (RPMs) in the spleen and liver induces rapid clearance of circulating erythrocytes [62]. In tumor-bearing hosts, sustained erythrocyte elimination leads to anemia [63]. Eryptosis plays an important role in accelerating anemia and although numerous mechanisms of eryptosis mediation have been reported for various pathological conditions, the mechanism of cancer-induced eryptosis is not well understood (Fig. 1). Patients with cancer exhibit two to three times greater PS-positive erythrocyte levels than healthy individuals [63, 64], and tumor-induced inflammatory and metabolic remodeling has been shown to increase PS-positive erythrocytes and augment splenic phagocyte activity in tumor-bearing mice [65]. Specifically, IL-1β, propionylcarnitine and valerylcarnitine, as well as TG (54:4) increases PS externalization on erythrocytes, and PS externalization on erythrocytes is induced via the IL-1β/IL-1 receptor 1/caspase 3 pathway. IL-1β and lactate additionally promote the phagocytic activity of splenocytes, which subsequently engulf the erythrocytes [65]. In addition to cytokines and metabolites, increased ROS production may induce eryptosis. Clinical data have shown significantly increased erythrocytic ROS production in patients with lung cancer [63], with the ROS subsequently inducing eryptosis by impairing cytoskeletal proteins [66]. Further studies of the mechanism of tumor-cell induced eryptosis in patients with cancer-induced anemia is, however, required.

Cancer-related microangiopathic hemolytic anemia (MAHA) involves the excessive destruction of erythrocytes and is characterized by the presence of erythrocyte fragments or schistocytes in small blood vessels. It is a serious complication in cancer and is associated with cancer recurrence, metastasis, and a poor prognosis [67]. Cancer can cause MAHA through systemic microvascular metastases, bone marrow metastases, or tumor necrosis. Erythrocyte fragmentation may result from direct contact with tumor emboli or intraluminal fibrin thrombi within blood vessels, and hypersplenism [68–70]. Furthermore, bone metastases may lead to secondary myelofibrosis, inducing direct release of prothrombotic ultra-large von Willenbrand factor multimers and promoting platelet aggregation [71, 72]. Massive tumor necrosis also induces tissue-factor production, which initiates the coagulation cascade and leads to thrombotic microangiopathies [73].

In addition to MAHA, autoimmune hemolytic anemia (AIHA) is a paraneoplastic phenomenon that occurs in most types of solid tumors, including lung, colorectal, renal, and ovarian cancers [74]. Secondary warm-antibody AIHA, the most prominent type of AIHA, develops as a result of tumor- or therapy-induced production of IgG, IgM, or IgA, which bind to the erythrocyte surface and enhance erythrocyte trapping and phagocytosis [73, 75]. It has been suggested that ectopic expression of band 3 protein in sigmoidal colon adenocarcinoma cells is correlated with the development of secondary AIHA, causing anemia by enhancing phagocytosis of autoantibody-bound erythrocytes by macrophages [76].

Table 1 Etiology of cancer treatment-induced anemia

Chemotherapy
Suppression of erythropoiesis in bone marrow
Nephrotoxicity (impaired EPO production)
Increased eryptosis
Hemolysis (AIHA, MAHA)
Gastrointestinal reaction (nutritional deficiency)
Thrombocytopenia (blood loss)
Radiotherapy
Suppression of erythropoiesis in bone marrow
Gastrointestinal reaction (nutritional deficiency)
Targeted therapy
Suppression of erythropoiesis in bone marrow
Impaired iron metabolism
Increased eryptosis
Immunotherapy
ICIs- AIHA
CAR-T- CRS related anemia
Surgery
Blood loss
Nutritional deficiency (resection of stomach/bowel)

The mechanism of cancer treatment-induced anemia

In addition to cancer-induced anemia, cancer treatment-induced anemia is a common adverse event in chemotherapy, radiotherapy, targeted therapy, and immunotherapy (Table 1). Most types of chemotherapeutic agents result in anemia, the incidence and severity of which depends on the type of drug, dose, intensity, and number of cycles [77]. Myelosuppressive agents mainly trigger apoptosis of erythroid precursors via

caspase activation [78]. Platinum-based chemotherapy has a direct toxic effect on erythropoiesis, and exhibits nephrotoxicity, which impairs EPO production [79]. Cisplatin-based agents increase ROS production, which downregulates EPO transcription, leading to reduced EPO synthesis in the kidneys [80]. Furthermore, cytostatic treatment with topotecan and cisplatin has been shown to trigger eryptosis, probably as a result of increased ceramide (a well-known eryptosis stimulator) on the erythrocyte surface [63, 81]. Common chemotherapy drugs, such as gemcitabine, mitomycin, and cisplatin, may also cause MAHA via dose-dependent toxicity or the development of drug-dependent antibodies [82]. Carboplatin and oxaliplatin-based chemotherapy may also induce AIHA [83, 84]. In addition to chemotherapeutic agents, radiotherapy may also lead to anemia by directly damaging the bone marrow or causing myelosuppression, thereby decreasing EPC production. Furthermore, chemoradiotherapy has gastrointestinal adverse events, such as nausea, vomiting, and diarrhea, which may decrease food intake and limit essential nutrients, such as iron and vitamins, for erythropoiesis [1].

Anemia is also observed in patients receiving targeted therapy, with or without combined chemotherapy. Poly ADP-ribose polymerase (PARP) inhibitors, such as olaparib and niraparib, used to treat ovarian and breast cancer, may induce hematotoxicity by increasing replicative stress and decreasing erythroid precursors, as well as impairing iron metabolism [1, 85, 86]. Palbociclib, a cyclin-dependent kinase 4/6 inhibitor used for the treatment of metastatic breast cancer, causes dysplastic anemia by mimicking myelodysplastic syndrome [87]. Sunitinib, a tyrosine kinase inhibitor, is also associated with a high incidence of all-grade (50.4%) and high-grade anemia (6.2%) [88]. Gefitinib, an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), can also induce erythrocyte shrinkage and cell membrane phospholipid scrambling [89], and combination of EGFR-TKI and chemotherapy is associated with an even higher incidence of all-grade anemia [90, 91]. B-cell lymphoma-2 (BCL-2)-inhibitor venetoclax monotherapy for relapsed or refractory multiple myeloma also shows a high incidence of anemia (23%) as a common grade III/IV event [92]. Hormone-related treatment, such as androgen deprivation therapy, also increases the risk of anemia in patients with prostate cancer [93]. Androgens can promote erythropoiesis by directly stimulating the incorporation of iron in EPCs and erythrocytes, and indirectly inhibiting hepcidin production via BMP/SMAD signaling, and upregulating renal EPO [93].

Although autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy has shown an encouraging response in patients with refractory large B-cell lymphoma, it is accompanied by a high incidence of anemia (up to 43%) [94]. CAR T-cell therapy for patients with relapsed or refractory multiple myeloma has also exhibited toxic hematologic effects (approximately 45%) [95]. Furthermore, CAR T cell-induced cytokine release syndrome (CRS), mainly characterized by release of IL-1 and IL-6 from monocytes and macrophages, limits the broad applicability of this treatment [96, 97].

ICIs, such as anti-programmed cell death-1 (PD-1)/PD-L1 and anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), are another form of immunotherapy. Anemia, including all-grade (3.84%) and grade III or higher (0.74%) anemia, is the most common hematologic adverse event of PD-1 and PD-L1 inhibitors in advanced-stage cancer [98]. Moreover, ICIs can induce warm antibody AIHA by augmenting or redirecting immune surveillance [99], and the risk of AIHA is greater with PD-1 or PD-L1 monoclonal therapy than with CTLA-4-inhibitor treatment [100].

Treatment of cancer-associated anemia

The current paradigm

Effective treatment of anemia during antineoplastic treatment could restore oxygenation, enhance therapy response, and reduce tumor invasion and metastasis [101]. Recently, cancer-associated anemia treatment has mainly focused on measures counteracting insufficient erythropoiesis, such as intravenous (IV) iron, erythropoietic stimulating agents (ESAs), and blood transfusion. However, retrospective clinical studies indicate that these treatments are inadequate [3].

For patients with cancer experiencing blood loss and AIDA, IV iron is the recommended therapy [3] as it is better tolerated than oral iron, and ESAs are less effective in treating AIDA and may exacerbate thrombocytosis [102].

The colonic microbiota of patients with colorectal cancer is different between IV iron and oral iron treatment. With IV iron treatment, the on- and off-tumor microbiota increased the abundance of enzymes involved in iron sequestration and anti-inflammatory or oncogenic metabolite production compared with oral iron treatment [103]. Furthermore, IV iron treatment can reduce ferritin expression in colorectal carcinoma and replenish iron stores more effectively than oral iron treatment [104]. In addition to being used as monotherapy, IV iron can reduce the frequency of blood transfusion and combined ESAs with IV iron treatment improves the efficacy of ESAs treatment and reduces the required ESAs dose [3, 105]. When combined with ESAs, IV iron is superior to oral iron for improving Hb level but neither of the iron combinations improve hematopoietic response [106, 107].

There is also no difference in the efficacy and safety between oral lactoferrin and IV iron, combined with recombinant human erythropoietin (rhEPO) therapy, for the treatment of chemotherapy-induced anemia in advanced cancer [108]. However, IV iron therapy has the risk of acute toxicity, including vasodilation, flushing, urticaria, and wheezing [3, 105].

Although treatment of cancer-associated anemia with ESAs increases Hb levels, which may modulate the efficacy of cancer radiotherapy by improving tumor oxygenation and reducing tumor HIF-1α expression [109, 110], and ESAs treatment prior to chemotherapy improves chemotherapeutic outcomes by mediating the prevention of anemia, tumor hypoxia, and increased drug delivery [111], the risks of ESAs have been widely reported. These risks include increased venous thromboembolism events, and tumor progression and recurrence via EPOR activation in tumor cells [112, 113]. In addition, rhEPO can induce angiogenesis by binding to EphB4, an alternative EPO receptor, instead of canonical EPOR [114]. Moreover, EPO inhibits chemotherapy-induced cell death in leukemia cells by increasing Mdm2-dependent p53 degradation and restoring anti-apoptotic Mcl-1 expression [115]. EPO also induces proliferation and protects against vincristine and etoposide in neuroblastoma cells via ERK1/2 and AKT activation [116]. Therefore, despite the efficacy of ESAs in the treatment of anemia, their ability to promote tumor progression limits the applicability of this treatment. Nowadays, ESAs are recommended carefully to patients with non-myeloid hematologic malignancies and iron-refractory anemia requiring frequent blood transfusions, or patients with decreased quality of life after the progressive stage of palliative myelosuppressive antineoplastic therapies. ESAs treatment is not suitable for patients with chemotherapy-associated anemia whose antineoplastic treatment is curative in intent, or for patients with non-chemotherapy-induced anemia, except low-risk myelodysplastic syndromes [3, 107]. Recently, novel distinctive carbon dots have been reported as a potential therapeutic agent for the treatment of cancer-associated anemia. Compared with EPO, carbon dots promote self-renewal of erythroid progenitors to increase Hb level and have no discernible effects on tumor proliferation and metastasis [117]. Thus, novel agents as alternatives for EPO are worth pursuing.

Blood transfusions in cancer patients have transient benefits and are associated with adverse effects, including thrombosis risk, transfusion-related acute lung injury, anaphylactic reactions, congestive heart failure, and iron overload [118]. Furthermore, numerous studies and meta-analyses have suggested that blood transfusions are associated with an increased risk of mortality and recurrence in patients with cancer during the perioperative period [24, 119]. Blood transfusions are therefore only recommended for the treatment of cancer-associated anemia grades II-IV when other therapies have failed [3].

The prospective paradigm

New strategies for the treatment of cancer-associated anemia are required and should, ideally, exhibit a synergistic anti-tumor effect. Combining potential cancer-induced anemia therapeutic targets, such as TGF-β, VEGF signaling, hepcidin, IL-6, CD71, CCL2/CCR2, GM-CSF, and exercise, with ICIs could therefore be an effective therapeutic approach (Fig. 3).

As mentioned previously, TGF-β inhibits erythropoiesis, blocking the maturation of megakaryocyte and erythroid progenitors in hepatocellular carcinoma-bearing hosts [16]. However, in multiple clinical trials, monotherapy with a TGF-β inhibitor showed a limited anti-tumor effect owing to its pleiotropic and dynamically controlled function and freely soluble ligand form [120]. TGF-β neutralization or inhibition does, however, downregulate splenic $CD45^{-}$EPCs [16] and ameliorate cancer-induced anemia [17]. Because of its extensive expression and immunosuppressive function in most cancers, TGF-β has been combined with PD-L1 to develop anti-TGF-β/PD-L1 bispecific antibodies such as M7824 [121], SHR-1701 [122], and YM101 [123]. M7824 (bintrafusp alfa) treatment significantly increases Hb level in mouse models compared with the control, TGF-β trap, and anti-PD-L1 groups [124]. Furthermore, in a phase 1 trial of M7824, only one patient with an advanced solid tumor exhibited anemia (grade III, 5.3%) [121]. A phase 1 trial of SHR-1701 revealed promising anti-tumor activity against advanced solid tumors, and an acceptably low incidence of anemia (any grade, 15%) [125]. However, SHR-1701 treatment of recurrent or metastatic cervical cancer induced a greater anemia incidence (approximately 40%), which may, however, be attributed to prior platinum-based chemotherapy (87.5%) [122]. In addition to this reported phase 1 clinical trial results, other bispecific antibodies targeting TGF-β and PD-L1 are being investigated. Intriguingly, study has been demonstrated that both local tumor radiation and anti-PD-L1 treatment reduced $CD45^{-}$EPCs via a remote effect to reduce artemin [126]. Based on this, combination radiation and ICIs may contribute to relieve cancer-associated anemia. It is noteworthy that both radiotherapy and immunotherapy could induce anemia, suggesting the importance of monitoring Hb level during treatment.

VEGF is a target for anti-angiogenesis and can induce anemia in tumor-bearing hosts. Phase 3 clinical trials of combined regimens of VEGF/VEGFR inhibitors and ICIs have shown significantly greater efficacy of combined therapy than that of VEGF/VEGFR-inhibitor

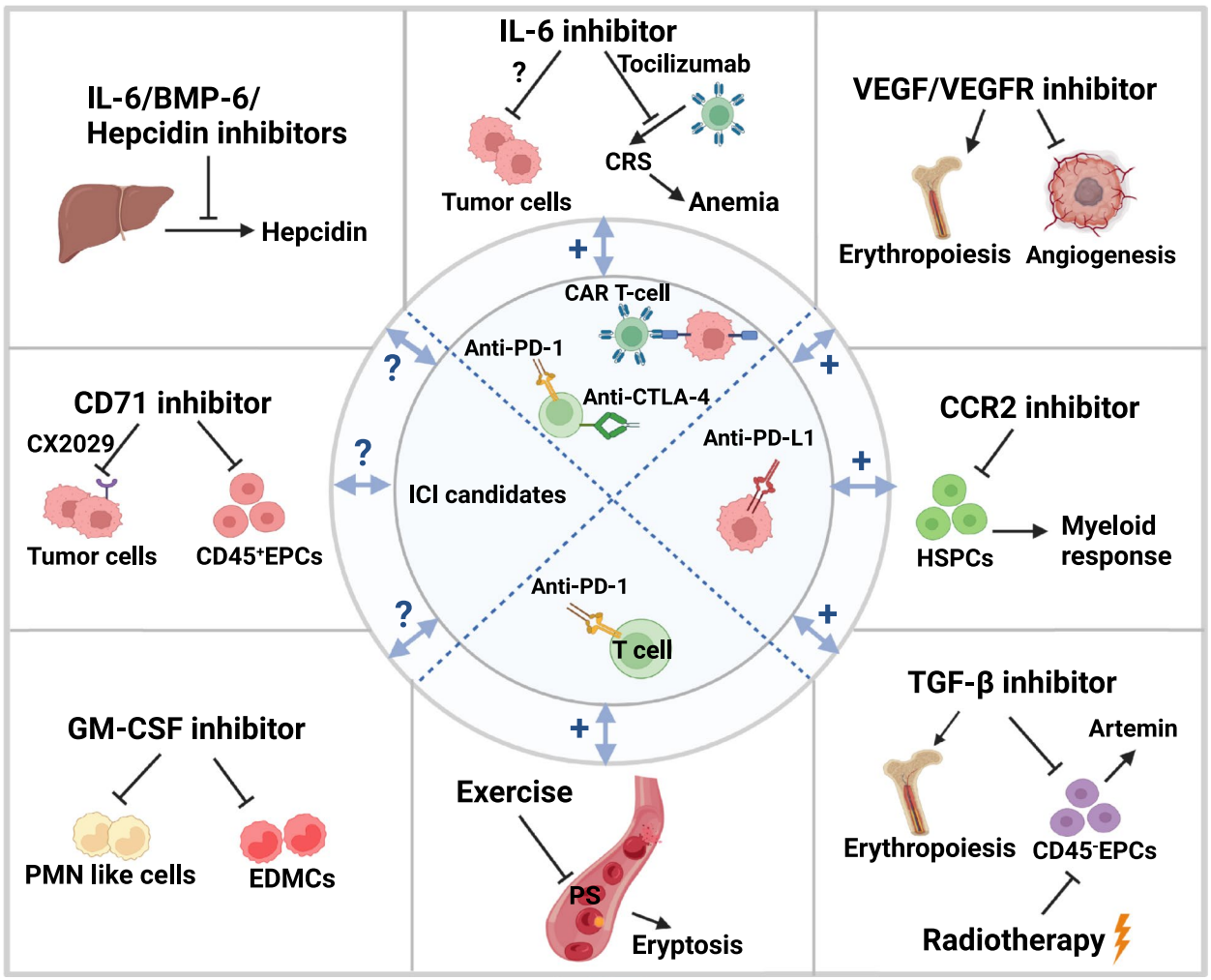

Fig. 3 The prospective therapeutic strategies of cancer-associated anemia for synergistic immunotherapy. Combination the potential targets in cancer-associated anemia with immunotherapy could be the valuable therapeutic approach. Hepcidin inhibition with IL-6/BMP-6/hepcidin inhibitor improves anemia, and BMP-6/hepcidin inhibitors also have the potential to control tumor progression. Similarly, CD71 and CM-CSF inhibitor probably acting on EMH to curtail tumor growth, anemia and enhance immunotherapy efficacy. IL-6 inhibition not only reduces hepcidin production but also relives immunotherapy-related side effect, such as CAR-T induced CRS-related anemia, and synergistically with CAR T-cell therapy, anti-PD-1 and anti-CTLA-4 therapy. VEGF inhibition suppresses tumor angiogenesis and may improve erythropoiesis directly. CCR2 inhibitor relieves myeloid response in EMH. TGF-β inhibitor and radiotherapy decreases the accumulation of splenic $CD45^{-}$EPCs, and TGF-β inhibitor may stimulate erythropoiesis directly. More importantly, VEGF/VEGFR inhibitor, CCR2 inhibitor and TGF-β inhibitor enhances anti-PD-L1 efficiency to alleviate tumor progression. Exercise can decrease eryptosis in tumor and boosts the efficacy of anti-PD-1 therapy

monotherapy. Food and Drug Administration (FDA) has approved the combined atezolizumab and bevacizumab therapy for unresectable hepatocellular carcinoma [127]. In patients with advanced renal cell carcinoma, anemia was exhibited by 21% when treated with combined lenvatinib and pembrolizumab [128]. Combination therapy of biliary tract cancer with regorafenib and avelumab showed 15% anemia [129]. These clinical results suggest that targeting VEGF signaling and PD-L1 could lower the incidence of anemia.

The role of hepcidin in anemia and its upregulation in cancer cells suggests that it is a potential therapeutic target. Combination therapy with ESAs and short hairpin-RNA targeting hepcidin was demonstrated to reduce hepcidin production and alleviate anemia in a mouse model of inflammation-induced anemia [130]. Similarly, NOX-H94, a structured L-oligoribonucleotide targeting hepcidin, increased iron availability for erythropoiesis and inhibited decreased Hb levels in preclinical anemia of a chronic disease model [131]. Furthermore, LY2787106, a hepcidin monoclonal antibody, exhibited tolerance,

safety, and a significant increase in serum iron levels in a phase 1 study of patients with cancer-associated anemia [132]. Lung cancer with high hepcidin expression is associated with decreased infiltration of immune cells and poor prognosis [133]. Colorectal cancer cells ectopically express hepcidin to accumulate iron, thereby promoting nucleotide synthesis and tumor cell proliferation [134]. However, blocking the hepcidin-FPN1 axis may increase iron availability not only for erythroid precursors, but also for cancer cells [135]. Therefore, further studies are needed to evaluate the benefit-risk ratio of hepcidin antagonists in cancer-associated anemia. Neutralizing antibodies of BMP-6 have been widely used to block hepcidin production in preclinical and clinical models of anemia in chronic diseases, such as chronic kidney disease, which also exhibit a potential role in reducing the need for EPO [136, 137]. However, multiple studies have suggested that the absence of or decreased BMP-6 is associated with poor survival and tumor progression in breast and non-small cell lung cancers [138, 139]. Furthermore, in prostate cancer, BMP-6 promotes tumor growth by inducing angiogenesis and castration resistance [140, 141]. Given this paradoxical role of BMP-6 in anemia and cancer, the efficacy of BMP-6 inhibition for the treatment of cancer-associated anemia requires further investigation.

Since IL-6 regulates circulating hepcidin levels under tumor conditions, blocking IL-6 with monoclonal antibodies tocilizumab or siltuximab may be suitable for the management of cancer-associated anemia. Additionally, IL-6 is involved in the survival and progression of tumor cells. IL-6/IL-6R inhibition may be an effective strategy to inhibit tumor progression and metastasis [142–144]. Palladium nanoplate-based IL-6R antagonists have been designed to deliver tocilizumab to the liver for hepcidin suppression, which alleviates cancer-associated anemia and simultaneously inhibits tumor progression, partly due to corrected anemia, in murine models [145]. Higher IL-6 levels and a greater number of T helper 17 (Th17) cells were observed in ICI-induced immune-related enterocolitis, and IL-6 inhibition increased the ICI-induced anti-tumor efficacy [146]. Combined ICIs and IL-6 inhibition may therefore be effective in reducing anemia, limiting immune-related toxicity and enhancing anti-tumor immunity [147]. Moreover, IL-6 is a representative cytokine in CAR-T cell-induced CRS, and the FDA has approved tocilizumab for the treatment of CRS after CAR T-cell therapy [148, 149]. However, another study showed that IL-6R inhibition might promote cholangiocarcinoma progression [150]. This suggests that the anti-tumor efficacy of combined IL-6/IL-6R inhibition and ICIs for cancer-associated anemia may be tumor-dependent.

Tumor-induced extramedullary hematopoiesis produces abundant CD71 (transferrin receptor 1) positive EPCs suggesting that neutralizing CD71 could be an effective strategy to deplete these robust immunosuppressors. Using an anti-CD71 antibody to deplete $CD45^{+}$EPCs in tumor-bearing mice relieved $CD8^{+}$T cell suppression and ameliorated cancer-induced anemia [56]. Furthermore, CD71 has been designed as a probody-drug (CX-2029) for the treatment of advanced solid tumors. Unfortunately, 67% of patients receiving CX-2029 treatment exhibited anemia, which is greater than the incidence of cancer-induced anemia (40%) [151]. Although CX-2029 exhibited high anti-tumor efficacy in patient-derived xenograft mouse models, as well as safety in cynomolgus monkeys [152], this anti-tumor effect seems to directly target tumor cells but not splenic EPCs because of the masked form of CX-2029 in normal cells. Further studies regarding the applicability of combined CX-2029 and ICI therapy are required.

In addition to the depletion of EPCs in extramedullary organs, repression of EPC migration or differentiation could be another potential therapeutic strategy. CCR2 knockout reduces splenic recruitment of circulating HSPCs in hepatoma mice and synergistically enhances anti-PD-L1 efficacy [59]. Moreover, PF-04136309 is a CCR2 inhibitor that targets tumor-associated macrophages, and a phase 1b trial revealed that PF-04136309 in combination with FOLFIRINOX chemotherapy decreases the incidence of grade III anemia (8%) in pancreatic cancer compared with FOLFIRINOX alone [153]. In addition, antibody-mediated GM-CSF neutralization decreases EDMCs in tumors [11]. Although erythroid-myeloid differentiation can be blocked with anti-GM-CSF, the oncolytic virus armed with GM-CSF was approved by the FDA to treat melanoma through the induction of specific anti-tumor immunity [154]. Targeting GM-CSF could therefore reduce the accumulation of immunosuppressive myeloid cells as well as anti-tumor dendritic cells.

Preclinical tumor models have indicated that exercise might ameliorate cancer-associated anemia by reducing circulating blood lactate and IL-1β levels to promote erythrocyte survival [65]. Furthermore, aerobic exercise promotes anti-tumor immunity and reduces tumor growth in pancreatic cancer through the accumulation of tumor-infiltrating $IL15R\alpha^{+}$ CD8 T cells. Additionally, exercise boosts the sensitivity of pancreatic tumors to chemotherapy and anti-PD-1 therapy [155]. Targeting cancer-induced anemia with aerobic exercise may therefore synergistically enhance ICI treatment in patients with cancer.

In addition, effective antineoplastic therapy in patients with cancer could induce regression of the tumor mass to reduce tumor factors for anemia, thereby gaining adequate nutritional support and attenuating cancer-associated anemia.

Conclusion

Anemia is a common occurrence in patients with cancer, with or without antineoplastic therapy, and is associated with significantly decreased quality of life and may have a negative impact on prognosis. Moreover, cancer-associated anemia is a risk factor for ICIs efficacy [11]. Therefore, targeting cancer-associated anemia contributes to synergistic immunotherapy. Some currently available drugs exhibit efficacy in cancer-associated anemia treatments, as well as anti-tumor effects, such as relieving the immunosuppressive tumor microenvironment, anti-angiogenesis, and normalizing metabolism. Combining these multitarget drugs with immunotherapy could achieve a triple-win effect. Moreover, some of these drugs have been approved for cancer treatment, even if they do not ameliorate anemia. Future clinical trials should therefore evaluate these prospective combination strategies for the synergistic treatment of cancer and cancer-induced anemia.

Abbreviations

AIDA	Absolute iron deficiency anemia
AIHA	Autoimmune hemolytic anemia
Ang II	Angiotensin II
BCL-2	B-cell lymphoma-2
BFU-E	Burst-forming unit-erythroid
BMP	Bone morphogenetic protein
CAR	Anti-CD19 chimeric antigen receptor
CFU-E	Colony-forming unit-erythroid
CKD	Chronic kidney disease
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events (CTCAE)
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
DMT1	Divalent metal transporter 1
EDMCs	Erythroid differentiated myeloid cells
EGFR-TKI	Epidermal growth factor receptor-tyrosine kinase inhibitor
EMH	Extramedullary hematopoiesis
EPC	Erythroid progenitor cell
EPO	Erythropoietin
EPOR	EPO receptor
Hb	Hemoglobin
ESAs	Erythropoietic stimulating agents
FDA	Food and Drug Administration
FIDA	Functional iron deficiency anemia
FPN	Ferroportin
GDF-15	Growth differentiation factor-15
GM-CSF	Granulocyte–macrophage colony-stimulating factor
G-CSF	Granulocyte-CSF
HIF-1α	hypoxia inducible factor-1α
HSC	Hematopoietic stem cell
ICIs	Immune checkpoint inhibitors
IL	Interleukin
IL-6R	IL-6 receptor
IV	Intravenous
MAHA	Microangiopathic hemolytic anemia
PARP	Poly ADP-ribose polymerase
PDGF	Platelet-derived growth factor
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PMN	Polymorphonuclear
PS	Phosphatidylserine
rhEPO	Recombinant human erythropoietin
ROS	Reactive oxygen species
RPMs	Red pulp macrophages
SMAD	Small-mothers-against-decapentaplegic
STAT3	Signal transducer and activator of transcription 3
TAMs	Tumor associated macrophages
TGF-β	Transforming growth factor-β
Th17	T helper 17
TLR	Toll-like receptor
TMB	Tumor mutational burden
WHO	World Health Organization
VEGF	Vascular endothelial growth factor

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The concept of this paper was devised by HL, DC and BZ. TY, DC and HL wrote the manuscript, prepared the figures and table. TY, DC and QJ contributed to the discussion. All authors reviewed and approved the final manuscript.

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