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Review

Patient Blood Management: An Internist's Perspective

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Patient blood management (PBM) is an evidence-based, patient-focused approach to optimize the management of patient and blood transfusion. While PBM is relatively well established in perioperative care, it is not as well established in the medical field. Since anemia in medical patients is heterogeneous and complex in its pathogenesis, the evidence for the threshold of hemoglobin for red blood cell (RBC) transfusion and the use of erythropoiesis-stimulating agents (ESAs) is not strong. While anemia seems to be an adverse risk factor for mortality, it is uncertain if rapid correction of anemia through RBC transfusion can reverse the negative impact of anemia on clinical outcomes. The introduction of ESA is a breakthrough in reducing RBC transfusion and managing anemic patients with renal disease and cancer. Despite promising results from early trials, the United States Food and Drug Administration issued a black box warning for ESAs in 2007 because of concerns about higher mortality, serious cardiovascular and thromboembolic events, and tumor progression. Therefore, the individualized approach to each patient with anemia is recommended in various medical conditions such as acute coronary syndrome, heart failure, chronic kidney disease, and malignancies.

Key words: Transfusion; Iron; Erythropoietin; Chemotherapy-induced anemia; Anemia of renal disease

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INTRODUCTION

Patient blood management (PBM) is a patient-specific, evidence-based and systematic approach to optimize the management of patient and blood transfusion for quality and effective patient care. It aims at improving patient outcomes through the rational and safe use of blood products and minimizing unnecessary exposure to it [1]. The concept of PBM is not only "blood conservation" but also "blood management" which includes the preventive approaches to maintain and optimize hemoglobin (Hb) level and hemostasis [2]. The goal of PBM is not merely to avoid or withhold transfusions, but to timely apply evidence-based medical and surgical concepts designed to manage anemia, optimize hemostasis, and minimize blood loss to improve patient outcomes by relying on a patient's own blood rather than on donor blood [2,3].

The concept of PBM is well established in surgical patients, demonstrating significant reductions in blood usage, yet with improved patient outcomes and reduced cost [4]. However, 52%–65% of recipients of allogeneic blood transfusion are medical patients with hematologic and non-hematologic malignancies, acute gastrointestinal bleed, renal failure, and other chronic disorders, etc [5]. In contrast to surgical patients, PBM is less developed in medical patients, in particular with hematologic/oncologic diseases, by whom a significant percentage of the blood is consumed [3,5].

This review will discuss how to integrate the concept of PBM into medical conditions including acute coronary syndrome (ACS), heart failure, chronic kidney disease (CKD), chemotherapy-induced anemia (CIA), and hematologic malignancies, in the aspect of red blood cell (RBC).

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THE EPIDEMIOLOGY OF BLOOD TRANSFUSION IN MEDICAL PATIENTS

The Korean national data on red cell transfusion from the Health Insurance Review & Assessment Service (HIRA) reported the statistics of RBC units transfused from 2006 to 2010. While the total number of RBC units transfused increased from 1,460,799 units in 2006 to 1,841,695 units in 2010, the proportion of elderly patients (≥65 year of age) increased from 41.4% to 48.8%, and more than 80% of the total RBC units were transfused at tertiary and general hospitals. Patients with malignant and hematological disorders received the total RBC transfusion of about 35%. The diseases of the digestive system and circulatory system comprised the RBC transfusion of 11% each. The patients with genitourinary diseases were about 5–6% of the total patients who received RBC transfusion during the given time period. However, because patients in this report were categorized according to disease classification of the International Statistical Classification of Diseases code, re-categorizing them into medical and surgical groups would not be accurate [6].

The EASTR Study from the United Kingdom (UK) based on National Blood Service (NBS) data showed the patients with digestive and hematologic diseases comprised 19% and 13% of RBC recipients [7]. Patients with renal disorders were 8% of the cohort. A similar trend was observed in the cohort of North England [8]. Data of the United States (US) based on National Blood Collection and Utilization Survey Report of 2011 showed the patients in hematology/oncology was proportioned 15% of total RBC transfusion [9]. Besides RBC, the platelet transfusion was involved more frequently ranging from 27% to 34% in hematology/oncology service from both UK and US data [7,9].

THE INTEGRATION OF THE CONCEPT OF PATIENT BLOOD MANAGEMENT INTO MEDICAL PATIENTS

The concept of 3 pillars of PBM includes to optimize erythropoiesis, minimize blood loss and bleeding, and harness and optimize physiological reserve of anemia [10]. One of the simplest and the most important ways to optimize erythropoiesis is to identify iron or nutrient deficiency and correct them because iron or nutrient deficiency-associated anemia is frequent and relatively easy to correct. Approximate one-third of anemia cases in older adults are attributed to nutrients including iron [11]. The prevalence of iron deficiency anemia (IDA) among patients with solid tumors is even higher ranging 30–60% [12].

Conditions associated with the release of pro-inflammatory cytokines, such as rheumatoid arthritis, infection, and tissue injury, cause anemia of inflammation or anemia of chronic disease (ACD). With chronic inflammation, the primary disease will determine the severity and characteristics of anemia [13]. In patients with ACD, the availability of iron is affected by hepcidin. Increased hepcidin levels block the ferroportin-mediated release of iron from enterocytes and macrophages. In this condition, absolute iron deficiency can occur since hepcidin-mediated blockade interferes the utilization of nutritional or orally administered iron in the long term. In the short term, functional iron deficiency (FID), a condition under which iron cannot be effectively mobilized from the reticuloendothelial system (RES), is caused by hepcidin-mediated blockade. Although serum ferritin generally reflects the status of iron stores, normal or elevated ferritin levels do not necessarily indicate sufficient iron stores since it can also be elevated as an acute phase reactant in a wide range of inflammatory conditions including liver cell damage. On the other hand, transferrin saturation (TSAT) and the Hb content of reticulocytes better reflect the availability of iron. Therefore, serum ferritin levels <100 ng/mL probably indicate insufficient iron stores in patients with cancer or chronic inflammatory disorders in routine clinical practice, and the combination of low TSAT (<20%) and normal or even elevated serum ferritin may indicate FID. However, the definition is different among the guidelines [12]. FID is common in patients with end-stage renal disease (ESRD), inflammatory disease, chronic heart failure (CHF), and cancer [14].

Since anemia could be presented secondary to a certain medical condition itself, it is hard to optimize erythropoiesis in some circumstances. For instance, hematologic disorders such as acute leukemia, myelodysplastic syndrome, or aplastic anemia manifest severe anemia as a result of bone marrow failure. In this circumstance, the restoration of erythropoiesis could only be possible through the treatment of primary diseases. The maintenance of oxygenation and the correction of a bleeding tendency to prevent tissue hypoxia and events of major bleeding would be the internists' main interest for the sake of best supportive care. In the case of CKD, anemia is due to primary deficiency of erythropoietin production by the diseased kidney and a reduction in red cell survival [13].

However, there is some controversy as to whether anemia is an independent risk factor for adverse outcome and also whether the correction of anemia will reverse the outcomes in various medical conditions [14]. Therefore, it would be worth reviewing if it is possible to reduce allogeneic blood transfusion without compromising clinical outcomes. Therefore, following discussion will focus on the prognostic impact of anemia, the optimization of blood transfusion, and the use of pharmaceutical agents to promote blood production.

PROGNOSTIC IMPLICATION OF ANEMIA

1. Acute coronary syndrome and heart failure

Several hypotheses may account for how anemia influences on cardiovascular-related mortality. First, anemia augments the imbalance between myocardial oxygen supply and demand by decreasing oxygen-carrying capacity and increasing myocardial oxygen consumption to increase cardiac output. Second, experimental data suggest that ACS patients with anemia may have an impaired capacity for vascular healing [15]. In humans, anemia has consistently been associated with adverse cardiovascular outcomes in the general population. Many prospective cohort studies provided consistent evidence for mortality or adverse cardiovascular outcomes [16]. Data from the cohort study including 3,921 patients showed that anemia defined by World Health Organization (WHO) increased all-cause mortality and death caused by progressive heart failure in patients diagnosed with acute myocardial infarction (AMI) [16], whereas in a study by Valeur and colleagues anemia was an independent risk factor for mortality in ACS patients with heart failure only [17]. Recently, a large database of over 422,855 ACS patients from England and Wales showed the prevalence of anemia in ACS cohort of 28% and anemia as an independent risk factor for mortality [18].

In the case of heart failure, anemia increased risks of all-cause mortality by 21–47% with more than 1 year of follow-up [16]. Lower Hb concentrations were consistently associated with increased mortality without an obvious increase in specific cardiovascular events [14]. In addition, a prospective, observational study showed that reduced Hb was associated with a poorer quality of life in patients with heart failure [19].

2. Cancer

Causes of anemia in patients with cancer are multifactorial and can be a direct result of cancer invasion, its treatment (radiation or chemotherapy), and/or CKD [20]. The cancer itself can cause or exacerbate anemia in a number of ways [21]. Anemia from a direct invasion of cancer is due to malignancy invading normal tissues causing blood loss, marrow infiltration inhibiting erythropoiesis, and/or inflammation leading to FID. Myelosuppressive chemotherapy either alone or in combination with radiation commonly causes anemia, which is referred to as CIA. Renal injury can occur from tumor invasion, chemotherapy, and/or age-related decline among cancer patients [20].

Anemia adversely impacts on tumor behavior. The transcription factor, hypoxia-inducible factor (HIF)-1α, responds to hypoxia. Head and neck cancer patients with an increase in tumor HIF-1α survived shorter than patients with non-hypoxic tumor (P=0.008) [22]. A similar result was shown in patients with cervical cancer, for whom a higher mortality rate with hypoxic tumors was seen than with non-hypoxic tumors (P=0.0039) [23,24].

The prevalence of anemia among patients with cancer at initial presentation ranges from 30 to 90% from a systematic review of the literature, depending on the type of cancer, the definition of anemia (<9 g/dL vs. <11 g/dL), disease stage, and whether patients have been treated. In this review, patients with anemia had poorer survival and local tumor control than non-anemic counterparts. Quality of life (QoL) appeared to be positively correlated with the Hb level [25]. The European Cancer Anaemia Survey showed that the prevalence of anemia (Hb <12 g/dL) in patients with different cancer types was 39% at enrolment and 67% becoming anemic at least once during the 6-month survey period. Low Hb levels correlated significantly with poor performance status in this survey [26]. Although the number of good-quality studies are small, overall results of these studies suggest that anemia or low Hb is associated with decreased survival or poor QoL [14].

3. Chronic kidney disease

A systematic review including 5 randomized-controlled trials and 13 observational studies concluded that studies consistently showed an association between reduced Hb and increased mortality [27]. Eight prospective cohort studies showed a significant relationship between different Hb concentrations and all-cause or cardiovascular mortality [14]. However, the nature of the relationship between Hb level and mortality in CKD patients remains unclear due to the heterogeneity of patient populations and insufficient power [27]. A trial that enrolled 416 patients with renal anemia (pre-dialysis, hemodialysis, and peritoneal dialysis patients) showed a trend, but not a statistically significant difference, in 52-week survival favoring the greater target Hb group [28]. Although survivals did not differ, the QoL improved in the dialysis patients when Hb was normalized. Of note, this trial enrolled hemodialysis patients without a recent history of CHF or ACS [28]. A trial which included 1,233 hemodialysis patients with CHF or ischemic heart disease did not show survival improvement at a target Hb level of 14 g/dL compared with a target of 10 g/dL [29]. The trial by Foley and colleagues showed improved QoL in the higher Hb group (Hb 10 g/dL vs. 13.5 g/dL) in hemodialysis patients with asymptomatic cardiomyopathy [30]. From the observational studies, there was a consistent trend of decreasing mortality with Hb levels increasing to 10 g/dL but no further significant effect of increasing the Hb level above 11 g/dL. A similar trend was shown in studies using 11 to 12 g/dL as a reference Hb

level. Therefore, the relationship may be affected by the preexisting conditions and the evidence is insufficient for generalization of risks and benefits of normalization of Hb level [27].

STRATEGY OF RED BLOOD CELL TRANSFUSION IN MEDICAL POPULATION

RBC transfusion is one of the mainstays of therapy in the management of anemic patients to improve oxygen delivery to the tissues and the myocardium and to reduce compensatory work by heart to increase cardiac output [31]. Even though it has generally been accepted that anemia is associated with worse outcomes in various medical conditions, rapid correction of anemia by RBC transfusion does not necessarily lead to improved clinical outcomes such as mortality and QoL. Carson et al. reviewed 31 randomized controlled trials involving 12,587 participants to compare restrictive transfusion strategy (Hb 7 g/dL to 8 g/dL to trigger RBC transfusion) to liberal transfusion strategy (Hb 9 g/dL to 10 g/dL to trigger RBC transfusion). The restrictive strategy did not differ from the liberal strategy in the risk of 30-day mortality or any of the other outcomes such as cardiac events, MI, stroke, and thromboembolism (TE). On the other hands, liberal transfusion did not affect the risk of infection. While there was no significant difference in clinical outcomes and adverse events between restrictive and liberal transfusions, restrictive transfusion reduced the risk of receiving RBC transfusion by 43% across clinical specialties. This review provided good evidence that RBC transfusion could be avoided in most patients by adopting restrictive transfusion policies, with the benefit of reducing the risk of transfusion and without compromising clinical outcomes. However, this review mainly included surgical, critical care, and pediatric populations rather than adult medical populations, i.e., of the total of 12,587 patients, there were only 154 patients with MI and 149 patients with hematologic malignancies [32]. Therefore, a blanket application of the restrictive strategy to all medical populations is not fully supported by available data, and further studies will be necessary.

1. Acute coronary syndrome

Given insufficient data from medical patients, especially those with MI, the threshold of RBC transfusion to optimize oxygen delivery and reduce workload to maintain cardiac output remains controversial in clinical practice.

A prospective, parallel-group randomized, pilot trial examined two thresholds (hematocrit (Hct) <30% vs. Hct <24%) for RBC transfusion in 45 patients with MI. The restrictive strategy was associated with a 36% relative decrease in the number of units transfused per patient compared to a 46% decrease in the other group of patients receiving any transfusion. Although the trial was not powered to detect differences in clinical outcomes due to a small number of patients, patients with liberal strategy showed significantly higher adverse outcomes, largely related to heart failure [33]. However, a recent trial did not favor the restrictive transfusion strategy. A randomized controlled trial including 110 patients with ACS and stable angina undergoing a cardiac catheterization showed somewhat different result from the previous pilot trial. Patients with the restrictive strategy of the lower threshold (Hb <8 g/dL) showed higher all-cause mortality, cardiac mortality, and cardiac events than with the liberal strategy of the higher threshold (Hb <10 g/dL). Of note, left ventricular ejection fraction at baseline tended to be lower in patients who were randomized to the restrictive strategy [34].

Other than small prospective parallel randomized trials, a few retrospective observational cohort studies, yet with large samples, seem to provide a clue for the optimal threshold for ACS patients. These studies, albeit retrospective in nature, consistently demonstrated that RBC transfusion at a higher Hb or Hct level is associated with a higher risk of mortality [35-37]. A large retrospective study of 78,974 elderly patients with MI showed RBC transfusion at lower Hct (<33%) was associated with lower 30-day mortality while RBC transfusion at Hct >36% adversely influenced on 30-day mortality [37]. The other large cohort study with the enrollment of 39,922 patients with ACS, transfusion was associated with a decreased risk of cardiovascular death when the baseline Hb was <12 g/dL (adjusted odds ratio [OR] 0.42, 95% CI 0.20–0.89) but not when Hb was ≥12 g/dL (adjusted OR 1.42, 95% CI 0.94–2.17) [36]. Data of 44,242 patients with non-ST-segment elevation ACS (NSTE ACS) in 400 hospitals in the United States showed that in patients with a nadir Hct ≤24%, transfusion seemed to lower mortality (Hct ≤24% adjusted OR 0.68, 95% CI 0.45–1.02). In the median range (Hct 24–27%), transfusion did not impact on mortality (adjusted OR 1.01, 95% CI 0.79–1.30). Although rare, those transfused with nadir Hct ≥27% had higher mortality (Hct of 27% to 30% adjusted OR 1.18, 95% CI 0.92–1.50 and Hct ≥30% adjusted OR 3.47, 95% CI 2.30–5.23) [35].

Two meta-analyses assessed the association between blood transfusion and clinical outcomes among patients with MI, in which more than 200,000 patients were included each [38,39]. While Chatterjee and colleagues found that transfusion adversely affected all-cause mortality and infarction [38], Garfinkle and colleagues showed that transfusion had beneficial or neutral effects on mortality below 8 g/dL and harmful or neutral effects above 11 g/dL [39].

Given the lack of high-quality data from randomized trials, the American Association of Blood Banks (AABB) chose not to recom-

mend for or against a liberal or restrictive transfusion threshold in patients with ACS [40,41]. Patient blood management guideline by the National Blood Authority recommends that RBC transfusion not be advisable in ACS patients with a Hb concentration >10 g/dL. In patients with ACS and a Hb of <8 g/dL, RBC transfusion may be associated with reduced mortality and is likely to be appropriate from the National Blood Authority's guideline. For patients with ACS and a Hb 8 g/dL–10 g/dL, any decision to transfuse should be made with caution and based on careful consideration of the risks and benefits [14].

2. Cancer

The impact of transfusion on treatment outcomes or mortality in patients with cancer remains controversial [42]. Most studies were retrospective analyses and evaluated the impact of RBC transfusions on the treatment outcome in patients with locoregional cancer. A favorable influence on locoregional recurrence or survival were observed after RBC transfusions in patients with head and neck cancer and cervical cancer who received surgery, radiotherapy, or chemoradiotherapy [23]. For example, in a study of 56 patients with unresectable esophageal cancer receiving chemoradiotherapy, blood transfusion was associated with an increase in overall survival (OS) (Hazard ratio [HR], 0.26) [43]. A retrospective analysis of 605 patients with cervical cancer treated with radiotherapy showed that patients whose average weekly nadir Hb level during radiotherapy maintained ≥12 g/dL had a significant reduction in both pelvic and distant recurrence. Data suggested that blood transfusion reduced the negative prognostic implication of low Hb [44]. However, a large retrospective cohort study including 504,208 hospitalizations of cancer patients raised a concern of RBC transfusion. Among 504,208 patients, 70,542 patients received at least 1 RBC transfusion. The study reported that the incidence of venous TE (VTE) and arterial TE (ATE) of the transfused patients were 7.2% and 5.2% which were significantly greater than rates of 3.8% and 3.1% of those without RBC transfusion, respectively. RBC transfusion was also associated with an increased risk of in-hospital mortality (OR 1.34). However, the increased TE events and mortality may reflect a bias of more severe anemia and/or more advanced cancer in patients who require transfusions [45]. Therefore, National Comprehensive Cancer Network (NCCN) recommends that a decision to give RBC transfusion should not be made on the basis of whether the Hb level of the patient has reached a certain threshold [42].

There would be a question as to whether the guidelines for patients with solid tumor could be applied to the patients with hematologic malignancies or undergoing hematopoietic stem cell transplantation (HSCT). Two randomized controlled trials of RBC transfusion for patients with hematologic malignancies were conducted to evaluate the threshold for RBC transfusion [46,47]. Given the experimental evidence in animal model suggesting the bleeding time to be inversely correlated with the Hct, Webert et al. evaluated whether or not the higher target of Hb level (12 g/dL compared to 8 g/dL) could decrease the risk of bleeding in thrombocytopenic patients [47,48]. The study enrolled 29 patients in control group (2 units of RBC transfusion for Hb <8 g/dL) and 31 patients in experimental group (2 units of RBC transfusion for Hb <12 g/dL) who received induction/reinduction for acute leukemia or HLA-matched myeloablative allogeneic HSCT. The proportion of patients with clinically significant bleeding was 75.9% and 71% for the control and experimental groups, respectively, while the experimental group received more RBC transfusions (transfusion/patient-day) than the control group (0.233 vs. 0.151, P=0.003) [47]. A randomized (2:1) study of 89 patients with acute leukemia was conducted to compare restrictive Hb trigger (7 g/dL) to higher Hb trigger (8 g/dL). While the restrictive trigger group was transfused on average 8 units/patient, the higher trigger group received 11.7 units/patient (P=0.0003). There was no significant difference in bleeding episodes or neutropenic fever between the two groups [46]. However, clinical experience has shown that the leukemia and HSCT patient population requires multiple transfusions over the treatment course. Therefore, further studies are warranted to evaluate if it would be possible to reduce transfusions safely in this clinical setting. The recommendations for RBC transfusion in medical patients are summarized in Table 1.

OPTIMIZATION OF HB USING ERYTHROPOIETIN AND INTRAVENOUS IRON THERAPY

Erythropoietin (EPO) is a cytokine produced by the kidney and regulates differentiation and proliferation of erythroid progenitor cells in the bone marrow [49,50]. Erythropoiesis-stimulating agents (ESAs) are genetically engineered form of erythropoietin that are used in the treatment of anemia [51]. However, hematologic response to ESAs is limited (30–75% of treated patients). Concern has also been raised about the increased risk of TE events associated with ESAs, especially in patients with cancer [4,12]. Therefore, neither the routine use of ESAs nor normalization of Hb or Hct is recommended in medical population.

Iron therapy may be used as a primary treatment for anemic or non-anemic iron deficiency, or to enhance the response to ESAs. When administered with ESAs, iron therapy prevents both absolute iron deficiency and FID [14]. Since further details on ESAs and iron

Table 1. Summary of recommendations for red blood cell transfusion in medical patients

Medical conditions	Recommendations
General [42]*	RBC transfusion should not be dictated by a Hb level alone, but should also be based on assessment of the patient's clinical status. Hb <7 g/dL, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where another specific therapy is available. Hb >10 g/dL, RBC transfusion is likely to be unnecessary and is usually inappropriate.
Acute coronary syndrome	AABB chose not to recommend for or against a liberal or restrictive transfusion threshold [40,41] National Blood Authority's guideline recommends that RBC transfusion not be advisable with Hb >10 g/dL. For ACS patients with Hb <8 g/dL, RBC transfusion is likely to be appropriate to reduce mortality. For patients with ACS and an Hb 8 g/dL–10 g/dL, any decision to transfuse should be made with caution [14]
Cancer	NCCN recommends that RBC transfusion should not be made on the basis of whether the Hb levels of the patients with solid tumors have reached a certain threshold [42].

ACS, acute coronary syndrome; AABB, the American Association of Blood Banks; NCCN, National Comprehensive Cancer Network. *Recommendation is from National Blood Authority of Australia. Direct evidence is not available.

therapy are discussed in this issue in the article by Lee and Yuh, the published guidelines in oncology and nephrology fields where ESAs have been approved for clinical use will be only briefly discussed in this review.

1. Cancer

Use of ESAs has consistently been shown to reduce transfusions and increase the Hb level in patients with anemia that arises during or shortly after myelotoxic chemotherapy [52]. The practice guidelines are available from the American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO) last updated in 2010, from the European Organisation for Research and Treatment of Cancer (EORTC) last updated in 2006, and from National Comprehensive Cancer Network (NCCN) [42,52,53].

In an early clinical trial, ESA epoetin alpha clearly increased Hb levels in cancer patients who were receiving non-platinum chemotherapy compared to placebo [54]. An early Cochrane meta-analysis demonstrated that cancer patients treated with ESA had a lower Relative Risk (RR) of receiving a blood transfusion than untreated patients (RR=0.67, 95% CI=0.62 to 0.73). In particular, ESA-treated patients with baseline Hb levels lower than 10 g/dL were more likely to have a hematologic response than untreated patients (RR=3.60, 95% CI=3.07 to 4.23) [55]. However, the U.S. Food and Drug Administration (the U.S. FDA) issued a black box warning in 2007 for the rHuEPO, i.e., warnings of greater mortality, serious cardiovascular and TE events, and tumor progression, based on 4 clinical trials. Among those receiving anti-cancer treatments, a higher mortality rate was observed in patients receiving rHuEPO than in control patients (Erythropoietin to treat head and neck cancer patients with anaemia [ENHANCE study] and Epoetin alfa versus best standard of care in anemic patients with metastatic breast cancer [BEST study]), and in anemic cancer patients not receiving chemotherapy (EPO-CAN-20 non-small cell lung cancer [NSCLC] study and Amgen 103 study) [23]. A meta-analysis showed that there was a higher risk for TE events in patients receiving ESA than in the control group [56]. A recent meta-analysis of survival outcomes from 53 randomized controlled trials showed that ESAs increased on-study mortality (combined hazard ratio [HR] 1.17; 95% CI, 1.06–1.30) and worsened overall survival (combined HR 1.06; 95% CI, 1.00–1.12). Thirty-eight trials enrolled 10,441 patients receiving chemotherapy. The combined HR for on-study mortality was 1.10 (95% CI, 0.98–1.24) and 1.04 (95% CI, 0.97–1.11) for overall survival [57]. Therefore, decision-making to use ESAs for anemic patients with cancer should be individualized. The practice guidelines on the use of ESAs from ASH/ASCO and NCCN are summarized in Table 2.

Iron studies, including serum iron, total iron binding capacity (TIBC), and serum ferritin, should be performed prior to ESA treatment to rule out absolute iron deficiency (ID), which may respond to oral or IV iron monotherapy without ESA. Treatment for iron deficiency is guided by iron status, defined as absolute ID, FID, possible FID, or no ID in NCCN guidelines. For absolute ID (TSAT <20% and ferritin <30 ng/mL), either IV or oral iron products alone (without ESAs) are recommended although IV iron is preferred. If cancer patients have FID (ferritin between 30 ng/mL and 500 ng/mL and TSAT <50%), IV iron supplements with ESAs should be considered. However, IV iron monotherapy without ESAs also can reduce the number of RBC transfusions. Possible FID is defined by a TSAT level <50% and a ferritin level >500 but ≤800 ng/mL. There are insuf-

Table 2. Summary of recommendations for initiating erythropoietin-stimulating agents in patients with cancer from practice guidelines

ASH/ASCO 2010 Guideline [52]	
General	Appropriate history, physical exam, and diagnostic test should be conducted to identify alternative causes of anemia aside from chemotherapy or an underlying hematologic malignancy
CIA: Threshold for initiating ESA therapy	The use of epoetin or darbepoetin is recommended as a treatment option for patients with CIA and Hb <10 g/dL.
Risk of TE	Clinicians should carefully weigh the risk of TE in patients for whom epoetin or darbepoetin is prescribed. Specific risk factors for TE have not been defined in clinical trials. Established, general risk factors for events of TE include the history of thromboses, surgery, and prolonged periods of immobilization or limited activity.
Hb target	Hb can be increased to the lowest concentration needed to avoid transfusions, which may vary by patient and condition.
Anemia in patients not receiving concurrent chemotherapy	ESAs is not recommended in the treatment of anemia associated with malignancy in patients who are not receiving concurrent Myelosuppressive chemotherapy. Use of ESAs in patients with lower risk of myelodysplastic syndrome to avoid transfusion is an exception.
NCCN guideline v1.2018 [42]	
General: hemoglobin ≤11 g/dL or ≥2 g/dL below baseline	Evaluate anemia for possible causes: bleeding, hemolysis, nutritional defect, inherited, renal dysfunction, radiation-induced myelosuppression, hormone dysfunction, etc.
Special category in considering ESA use	Cancer and chronic kidney disease (moderate to severe) Patients undergoing palliative treatment Patients with anemia on myelosuppressive therapy ▷ There is not enough evidence to support ESA use in patients receiving myelosuppressive chemotherapy with curative intent Patients who refuse blood transfusion

ASH, American Society of Hematology; ASCO, American Society of Clinical Oncology; CIA, chemotherapy-induced anemia; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; TE, thromboembolism.

ficient data to support the routine use of IV iron in this setting [42].

2. Chronic kidney disease

Although anemia in patients with CKD is multifactorial in origin, it is primarily associated with relative EPO production deficiency as the glomerular filtration rate (GFR) declines [58]. The introduction of rHuEPO into clinical practice in the 1980s was a major breakthrough in the treatment of the anemia of renal disease. In the early years, rHuEPO was considered beneficial for long-term dialysis patients who were transfusion-dependent. Then, the use of rHuEPO was extended to non-dialysis patients with CKD, and Hb targets increased progressively. Numerous observational studies demonstrated an inverse association between Hb concentration up into the normal range and cardiovascular events, TE events, and death [59]. A new Cochrane Review by Palmer and colleagues evaluated the evidence for pros and cons of using ESAs for anemic adults with CKD from 56 eligible studies involving 15,596 patients [60]. Epoetin alfa (OR 0.18), epoetin beta (OR 0.09), darbepoetin alfa (OR 0.17), and methoxy polyethylene glycol-epoetin beta (OR 0.15) prevented blood transfusions compared to placebo. However, a study examining the risks and benefits of normalizing the Hct in hemodialysis patients with cardiac disease raised concern of the increase in mortality and MI among normal-Hct group (HR 1.3, 95% CI 0.9–1.9) [29]. A trial enrolling CKD patients with diabetes compared achieving Hb level 13 g/dL versus 9 g/dL using ESA. Although there was no difference in death or cardiovascular events in both groups, stroke occurred more often in the Hb 13 g/dL group (HR 1.92, 95% CI 1.38–2.68) [61]. Therefore, when initiating and maintaining ESA therapy, the potential benefits of reducing blood transfusion and anemia-related symptoms should be balanced against the risk of harm in individual patients such as a history of stroke or malignancy [59]. The evidence now suggests that Hb target levels between 10 and 11.5 g/dL should be the aim for patients with CKD, and certainly not levels >13 g/dL [62,63]. The U.S. FDA has emphasized an increased risk for patients with a target Hb >11 g/dL. An appropriate target Hb for ESA therapy has not been defined in patients with CKD, but caution is recommended in patients with a Hb >10 g/dL [14,59].

In patients with CKD, correction of iron deficiency with oral or

IV iron supplementation can improve anemia to some degree. Iron supplementation is widely used in CKD patients to treat iron deficiency, to prevent its development in patients receiving ESA therapy, to raise Hb levels in the presence or absence of ESA therapy, and to reduce ESA doses [59]. A systematic review with a meta-analysis of intravenous (IV) versus oral iron supplementation in patients with CKD (stages III to V) was performed. Thirteen trials were included in this meta-analysis. Compared with oral iron, IV iron significantly increased the Hb level in dialysis patients (weighted mean difference, 0.83 g/dL, 95% CI 0.09–1.57). For patients with CKD either on dialysis or not, there was a small but significant difference in the Hb level favoring the IV iron group (weighted mean difference, 0.31 g/dL, 95% CI, 0.09–0.53). There was no difference in adverse events between those receiving IV and oral iron supplements [64]. A randomized controlled trial comparing IV iron sucrose to oral ferrous sulfate in non-dialysis patients with CKD stages 3 to 5 showed IV iron therapy to be more effective in increasing Hb ≥1 g/dL from baseline than oral iron therapy (44.3% vs. 28.0%, P=0.0344). No serious adverse drug events were seen in patients receiving IV iron sucrose as 200 mg IV over 2 to 5 minutes, although drug-related hypotension occurred in two females (weighing less than 65 kg) after 500 mg were given intravenously over 4 hours. Use of ESA was associated with a higher proportion of patients achieving the primary endpoint (an increase in Hb ≥1 g/dL) in both the IV iron group (EAS use vs. non-use: 53.1% vs 38.3%) and the oral iron group (32.2% vs. 25.5%) [65].

However, the assessment of iron status is difficult. The diagnostic utility of serum ferritin and TSAT test is limited in estimating body iron stores. Even the examination of bone marrow iron stores does not predict erythropoietic responsiveness to iron supplements in patients with CKD with a high degree of accuracy. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group recommended iron supplements if TSAT is ≤30% and ferritin is ≤500 ng/mL when an increase in Hb concentration without starting ESA is desired or a decrease in ESA dose is desired although the evidence to support a recommendation for specific TSAT and ferritin level is limited. Intravenous iron supplements are preferred, but a 1-3 months trial of oral iron therapy can be an alternative in non-dialysis patients with CKD [59].

CONCLUSION

Although PBM is not as well established in medical patients compared with surgical patients, there have been efforts to reduce blood transfusions and to improve clinical outcomes in anemic patients with medical diseases. With the introduction of ESAs, needs for RBC transfusions have been decreased, especially in patients with CKD and/or malignancies. However, significant concerns about adverse effects with ESAs exist. The first step to manage anemia in medical patients is to assess the iron and nutritional status, which can be corrected with supplements. Because of heterogeneity in patient populations and the complexity of pathogenesis of anemia in medical patients such as CKD and cancer, the evidence levels of practice guidelines for the use of ESAs and transfusions are not strong, and an individualized approach for each patient is essential. Further studies would be warranted to establish an appropriate target of Hb and increase Hb safely and cost-effectively, in order to improve survival outcomes and reduce the medical cost.

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