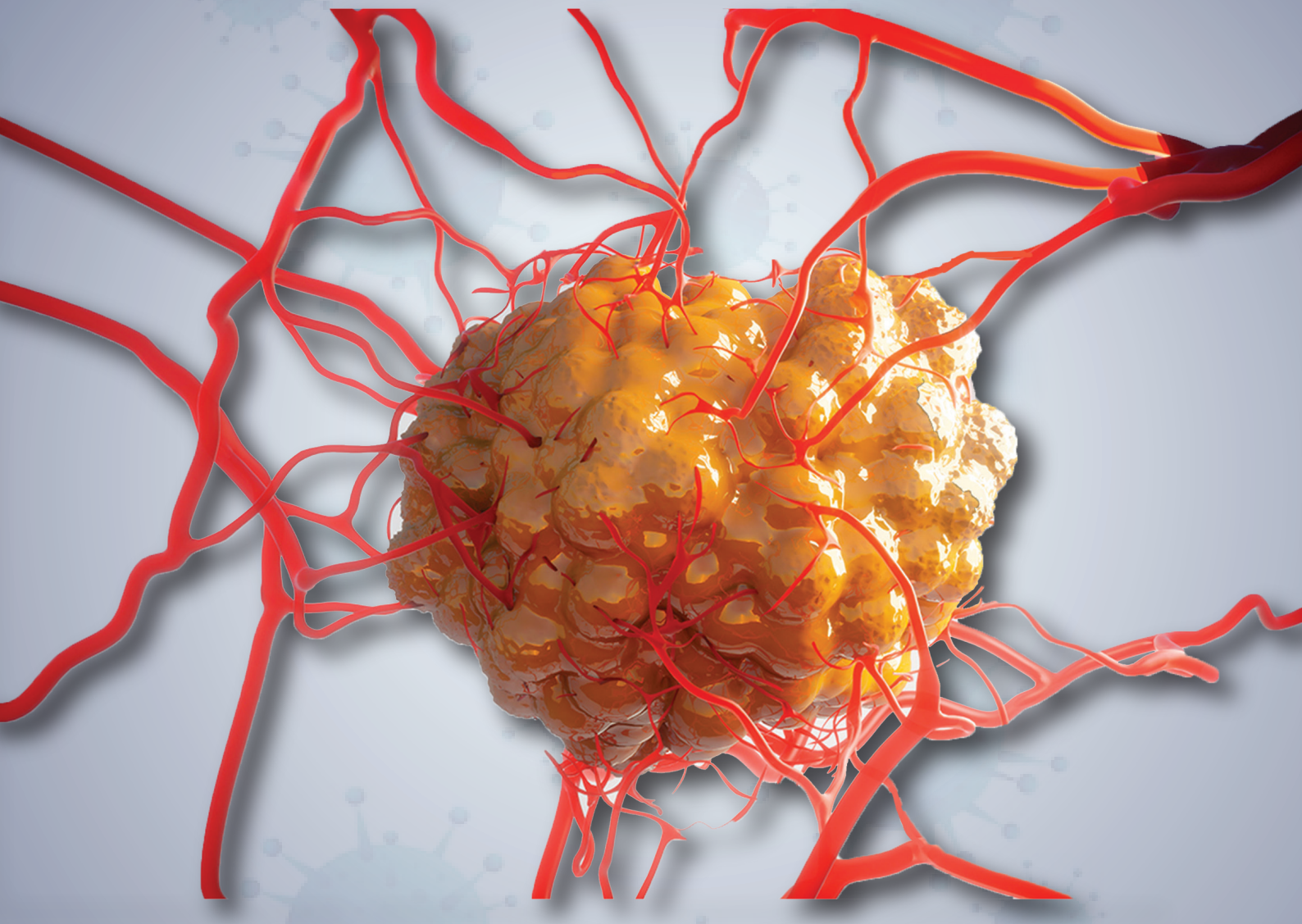
Module in The Area of **Medical Oncology**



Module III

Role of Erythropoiesis-stimulating agents (ESAs) in Medical Oncology.

CONTENT

Introduction

Anemia has a great impact on the quality of life (QoL) of patients suffering from cancer. According to the European Cancer Anemia Survey in 2004, the prevalence of anemia in patients with a solid or hematological malignancy was about 39% .Elevated inflammatory cytokines from cancer cells or toxicity of cancer treatment may be reasons for impaired iron homeostasis and erythropoietic activity. Further causes like chronic bleeding (e.g., occult gastrointestinal bleeding from tumors) or malnutrition can occur simultaneously and should be ruled out during the diagnostic process or treated adequately (e.g., malnutrition).

In some patients with cancer, causes of anemia remain unclear or are inevitable (e.g., myelotoxic chemotherapy). In this scenario, supportive treatment to raise hemoglobin levels and diminish symptoms from anemia, including erythropoiesis-stimulating agents (ESAs), may become necessary.

Use of erythropoiesis-stimulating agents (ESAs) to manage anemia raises hemoglobin (HgB) levels and reduces the need for RBC transfusions, but increases the risk of thromboembolic events. Studies have also reported decreased survival, increased mortality during active study phase, and/or an increased risk of cancer progression or recurrence with the use of ESAs in patients with cancer. The risks of ESAs prompted multiple regulatory actions by the US Food and Drug Administration (FDA) between 2004 and 2009, and in 2010, the FDA approved a Risk Evaluation and Mitigation Strategy for ESA use in patients with cancer. In 2017, the FDA determined that the Risk Evaluation and Mitigation Strategy was no longer necessary: prescribers demonstrated acceptable knowledge of the risks of ESAs and the need to counsel patients about the risks, and utilization data suggested an increase in appropriate prescribing practices.The risks of ESAs remain, however, highlighting the ongoing importance of appropriate use. ESAs are indicated in patients with cancer who are receiving myelosuppressive chemotherapy with noncurative intent and anemia that cannot be adequately managed with transfusional support. *(Bohlius J,et al)*

The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) first published a joint evidence-based clinical practice guideline for the use of ESAs in adults with cancer and anemia in 2002,with updates in 2007 and 2010. Since the 2010 update, additional information has emerged about the safety and efficacy of ESAs in patients with metastatic breast cancer and about the role of iron in conjunction with ESAs. Treatment options have also expanded with the 2018 FDA approval of a biosimilar of epoetin alfa, warranting a guideline update. *(Bohlius J,et al,; Grant MD,et al; Tonia T,et al; Leyland-Jones B,et al; Thomas G,et al; Untch M,et al; Leyland-Jones B,et al; Rizzo JD,et al)*

Recommendations for Use of Esas

Recommendations. (Bohlius J,et al,; Grant MD,et al; Tonia T,et al; Leyland-Jones B,et al; Thomas G,et al; Untch M,et al; Leyland-Jones B,et al; Rizzo JD,et al)

Clinical question 1

To reduce the need for RBC transfusions, should ESAs be offered to patients who have chemotherapy-associated anemia?

- ***Recommendation 1.1.*** Depending on clinical circumstances, ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin (HgB) has declined to < 10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

- ***Recommendation 1.2.*** ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical question 2

To reduce the need for RBC transfusions, should ESAs be offered to anemic patients with cancer who are not receiving concurrent myelosuppressive chemotherapy?

- ***Recommendation 2.1.*** ESAs should not be offered to most patients with nonchemotherapy-associated anemia (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).

- ***Recommendation 2.2.*** ESAs may be offered to patients with lower risk myelodysplastic syndromes and a serum erythropoietin level ≤ 500 IU/L (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Clinical question 3

What special considerations apply to adult patients with nonmyeloid hematologic malignancies who are receiving concurrent myelosuppressive chemotherapy?

- ***Recommendation 3.*** In patients with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia, clinicians should observe the hematologic response to cancer treatment before considering an ESA. Particular caution should be exercised in the use of ESAs concomitant with treatment strategies and diseases where risk of thromboembolic complications is increased (see Recommendations 4 and 6).

In all cases, blood transfusion is a treatment option that should be considered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Clinical question 4

What examinations and diagnostic tests should be performed before making a decision about using an ESA to identify patients who are likely to benefit from an ESA?

• ***Recommendation 4.*** Before offering an ESA, clinicians should conduct an appropriate history, physical examination, and diagnostic tests to identify alternative causes of anemia aside from chemotherapy or an underlying hematopoietic malignancy. Such causes should be appropriately addressed before considering the use of ESAs. Suggested baseline investigations are listed in Table 1 (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Suggested baseline investigations for anemia in patients with cancer receiving chemotherapy

Suggested investigation

Thorough drug exposure history

Review of a peripheral blood smear*

Analyses, where indicated, for iron, total iron-binding capacity, transferrin saturation, ferritin, folate, vitamin B12, or hemoglobinopathy screening

Assessment of reticulocyte count, occult blood loss, and renal Insufficiency

Baseline erythropoietin level

Testing of serum thyroid-stimulating hormone level, where indicated

Investigations may also include direct antiglobulin testing (eg, Coombs test) for patients with chronic lymphocytic leukemia, non-Hodgkin lymphoma, or a history of autoimmune disease

Clinical question 5

Among adult patients who receive an ESA for chemotherapy-associated anemia, do darbepoetin, epoetin beta and alfa originator, and currently available biosimilars of epoetin alfa differ with respect to safety or efficacy?

• ***Recommendation 5.*** The Expert Panel considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to effectiveness and safety (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Clinical question 6

Do ESAs increase the risk of thromboembolism?

• ***Recommendation 6.*** ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Clinical question 7

Among adult patients who will receive an ESA for chemotherapy-associated anemia, what are recommendations for ESA dosing and dose modifications?

• ***Recommendation 7.*** It is recommended that starting and modifying doses of ESAs follow FDA guidelines (see Table 2 for specific dosing information; Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Dose and modifications	**Epoetin alfa**[‡]		**Darbepoetin alfa**	
Initial dose[‡]	150 U/kg SC TIW[‡]	40,000 U SC weekly[§]	2.25 µg/kg SC weekly[‡]	500 µg SC Q3W[§]
Dose increases	Increase dose to 300 U/kg SC TIW if HgB increases by < 1 g/dL and remains below 10 g/dL after 4 weeks of therapy	Increase dose to 60,000 U SC weekly if HgB increases by < 1 g/dL and remains below 10 g/dL after 4 weeks of therapy	Increase dose to 4.5 µg/kg weekly if HgB increases by < 1 g/dL and remains below 10 g/dL after 6 weeks of therapy	N/A
Dose reductions	Decrease dose by 25% when HgB reaches a level needed to avoid transfusion or HgB increases > 1 g/dL in 2 weeks		Decrease dose by 40% when HgB reaches a level needed to avoid transfusion or HgB increases > 1 g/dL in 2 weeks	
Dose withholding	If HgB exceeds a level needed to avoid transfusion, restart dose at 25% below		If HgB exceeds a level needed to avoid transfusion, restart dose at	

Dose and modifications	Epoetin alfa*	Darbepoetin alfa
	previous dose when HgB approaches a level where transfusion may be required	40% below previous dose when HgB approaches a level where transfusion may be required
Discontinue‖	Following completion of chemotherapy course or if no response after 8 weeks of therapy (measured by HgB levels or continuing need for transfusions)	Following completion of chemotherapy course or if no response after 8 weeks of therapy (measured by HgB levels or continuing need for transfusions)

Clinical question 8

• ***Recommendation 8.*** ESAs should be discontinued in patients who do not respond within 6 to 8 weeks. Patients who do not respond to ESA treatment should be reevaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical question 9

Among adult patients with chemotherapy-associated anemia, does iron supplementation concurrent with an ESA reduce transfusion requirements?

• ***Recommendation 9.*** Iron replacement may be used to improve HgB response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels is recommended (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: weak).(Bohlius J,et al)

Erythropoiesis-stimulating agents—benefits and harms in the treatment of anemia in cancer patients

Efficacy and risks

The use of ESA in patients meeting the criteria lowers the number of RBC transfusions by about 35% and 50–70% of patients undergoing treatment with ESA achieve an Hb increment ≥1g/dL. ESAs may be an alternative for patients with anemia-associated symptoms, in whom RBC transfusions should be administered with caution (e.g., patients at risk of volume overload or transfusion reactions in the past). Patients who do not have easy access to transfusion (long distances to appropriate facility) or who refuse transfusion because of personal or religious beliefs (e.g., Jehovah's Witnesses) should be considered for treatment with ESA if indicated.

Whether use of ESAs can significantly improve QoL remains controversial. Although treatment with ESA in patients with chemotherapy-associated anemia improves anemia-related symptoms like dizziness, chest discomfort, and headache, the impact on fatigue-related symptoms was not clinically relevant During treatment with ESA, the risk of thromboembolic complications increases and it is supposedly associated with higher mortality through accelerated tumor growth .The use of ESAs was related to an adverse impact on survival in certain tumor entities (e.g., non-small-cell lung cancer [NSCLC], head and neck cancer receiving radiotherapy, cervical cancer receiving chemoradiotherapy, and metastatic breast cancer receiving chemotherapy), as shown by several controlled trials . High target Hb levels, deaths from thromboembolism, and adverse impact on tumor progression are among the possible explanations for that observation. However, high Hb levels (before or during treatment with ESA) may be a possible explanation for the increased risk of thromboembolic events, as seen in patients with end-stage kidney disease . Based on these trials, several experts and regulatory groups (e.g., European Medicines Agency, US Food and Drug Administration) only recommend the use of ESAs in patients receiving treatment with palliative intention.However, there are still no results from clinical trials or meta-analysis that have compared the use of ESAs in patients undergoing chemotherapy with different treatment goals (cure vs. palliation). A small randomized trial comparing the administration of epoetin beta (Hb target <12g/dl) to placebo in patients with lung and gynecologic cancers showed no difference in the incidence of thromboembolic events between the two groups. Nevertheless, clinicians should carefully reconsider the use of ESA in patients with a high risk of thromboembolism (e.g., immobilization or history of thrombosis).

Overview of Recommendations

Guideline	Year	Key findings/Recommendations for ESA use
Oncology:		
ASCO/ASH	2002	Initiate when Hb < 10 g/dL and in less severe anemia (10–12 g/dL) determined by clinical circumstances. Target no higher than 12 g/dL
NCCN	2002	Target Hb of 12 g/dL
EORTC	2004	Slight elevation in the risk of thromboembolic events and hypertension with ESA use
FDA	2004	Target Hb levels no higher than 12 g/dL
EORTC	2006	Initiate at Hb levels of 9–11 g/dL, target Hb level 12–13 g/dL
FDA	2007	Black box warning to avoid Hb levels greater than 12 g/dL
NCD	2007	Limit ESA use in non-renal disease indications
ASCO/ASH	2007	Initiate when Hb < 10 g/dL, and in less severe anemia (Hb > 10 g/dL and <12 g/dL), use determined by clinical circumstances; cautioned against ESA use in cancer patients not receiving chemotherapy
FDA	2008	Initiate when Hb is ≥10 g/dL. Removed upper limit of 12 g/dL; patients treated with chemotherapy with curative intent excluded from ESA treatment
ASCO/ASH	2010	Lowest dose to achieve an increase in Hb to the lowest level for transfusion avoidance. Recommended ESAs as an option in CIA and Hb < 10 g/dL. Caution advised when used with chemotherapy in diseases associated with increased risk of thromboembolic complications
ESMO	2010	Hb limit of 12 g/dL; ESAs should be carefully reconsidered in patients with a high risk of thromboembolic events, used with caution in liver disease, and not given to patients with ESA hypersensitivity or poorly controlled hypertension
NCCN	2018	Maintain lowest Hb level to avoid transfusion. Avoid increases >1 g/dL in any 2-week period. Removed need to consult REMS
ESMO	2018	Target Hb level of 12 g/dL, initiated at <10 g/dL (symptomatic anemia) or <8 g/dL (asymptomatic anemia). Iron therapy should be given before and/or during ESA therapy in the case of absolute or functional iron deficiency. No clinical evidence for an effect of ESAs on stimulating disease progression or relapse when used within label in cancer patients
Nephrology:		
NKF-DOQI	1997	Target Hb level of 11–12 g/dL
FDA	2007	Black box warning recommending maintenance of Hb levels within the range of 10–12 g/dL for anemic patients with CKD
ERBP	2010	Target Hb level of 11–12 g/dL in CKD patients, do not intentionally exceed 13 g/dL
FDA	2011	Removed target Hb range of 10–12 g/dL; recommended use of the lowest ESA dose to reduce the need for transfusions
KDIGO	2012	For CKD patients with Hb concentration ≥ 10.0 g/dL, ESA therapy should not be initiated. Upper target limit of 11.5 g/dL. Individualization of therapy will be necessary because some patients may have improvements in QoL at Hb concentrations above 11.5 g/dL and will be prepared to accept the risks
NICE	2015	Target Hb range of 10–12 g/dL
Renal Association	2017	Target Hb range of 10–12 g/dL

ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; ERBP, European Renal Best Practice; ESMO, European Society for Medical Oncology; FDA, United States Food and Drug Administration; KDIGO, Kidney Disease Improving Global Outcomes; NCCN, National Comprehensive Cancer Network; NCD, National Coverage Determination; NICE, National Institute for Health and Care Excellence; NKF-DOQI, National Kidney Foundation Dialysis Outcomes Quality Initiative; REMS, Risk Evaluation and Mitigation Strategy.

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