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Update on clinical practice guideline on the use of epoetin and darbepoetin in adult patients with cancer

Chemotherapy-induced anaemia can be treated using erythropoiesis-stimulating agents (ESAs), but these can cause serious side-effects including tumour progression, venous thromboembolism, and shorter survival. Following extensive review of recent literature, the American Society of Clinical Oncology and the American Society of Hematology have updated their guidelines on the use of ESAs. New recommendations include minimising the use of ESA in patients receiving chemotherapy with curative intent.

Keywords: Chemotherapy-induced anaemia, darbepoetin, epoetin, erythropoietin-stimulating agents, haemoglobin, thromboembolism

Cancer patients with chemotherapy-induced anaemia have two treatment options for boosting their haemoglobin (Hb) levels: blood transfusion or the use of erythropoiesis-stimulating agents (ESAs). Both have advantages and disadvantages, so to help physicians navigate their way through treatment decisions, the American Society of Clinical Oncology and the American Society of Hematology have collaborated to update an earlier Clinical Practice Guideline on the use of epoetin and darbepoetin in adult patients with cancer [1].

The original publication of 2002 was updated in 2007 following the availability of more information on risks associated with ESAs. The latest (2010) update gives recommendations for the use of ESAs, and also summarises evidence on their effectiveness at reducing transfusions and increasing Hb and reviews the latest evidence on ESA-associated tumour progression, venous thromboembolism, and/or survival. It involved a literature review with one new individual patient data analysis, four meta-analyses, two systematic reviews, and 13 new reports of randomised controlled trials, including through searching MEDLINE and the Cochrane Collaboration Library.

The 2010 update is available, together with a patient guide and other clinical tools and resources at www.asco.org/guidelines/esa and www.hematology.org/guidelines/esa

Overall, the 2010 guideline confirms that ESA therapy is associated with shorter survival and/or increased risk of tumour progression and recurrence—in addition to the previously highlighted increased risk of thromboembolism. The 2010 guideline recommends that for patients receiving myelotoxic chemotherapy with an Hb level of less than 10 g/dL, physicians should discuss with them the potential risks and benefits of ESAs compared to the potential harms and benefits of transfusion. Transfusion carries a risk of serious infections and immune-mediated adverse events, but offers the benefit of a rapid rise in Hb levels. Patient preference should be taken into account in the final decision on treatment, the updated guideline cautions against using ESA under all other circumstances.

Specific recommendations

I General recommendation

The 2010 update includes the general recommendation that alternative causes of anaemia aside from chemotherapy or other

underlying haemopoietic malignancy be explored before ESA treatment commences. Physicians should also aim to minimize the use of ESA in order to reduce the risk of thromboembolism, 'particularly in patients with malignancy being treated with curative intent.'

The US Food and Drug Administration FDA labelling indicates the use of ESAs in patients receiving chemotherapy for palliative intent, in order to reduce the need for transfusions. FDA does not recommend treatment with ESAs for patients receiving curative chemotherapy because of an increased risk of mortality and thromboembolism. The 2010 update notes, however, that because the evaluation of risks versus benefits has not been done according to subgroups with different chemotherapy intent, i.e. curative versus palliative, clinical judgement is required to determine the goal of treatment for individual patients. The update states, 'Clinicians are urged to exercise caution in considering ESA use in patients with malignancy being treated with curative intent. The Update Committee stresses the importance of including a detailed discussion between healthcare providers and their patients about the potential harms and benefits of ESA therapy.'

The 2010 update gives examples of diseases for which the treatment goal should be curative: testicular cancer, first-line therapy of Hodgkin's disease, and early stage breast, lung, or colon cancer.

The 2010 update also summarizes the evidence showing both a statistically significant increased risk of mortality and thromboembolism, and the reduced need for transfusions, with ESA treatment.

II Special commentary on the comparative effectiveness of epoetin and darbepoetin

Regarding the comparative effectiveness of epoetin and darbepoetin, the position remains unchanged since 2007 that these agents are considered to be equivalent with respect to safety and efficacy.

IIIa Chemotherapy-induced anaemia: threshold for initiating ESA therapy

The 2010 update recommends, in accordance with FDA-approved labelling, the use of epoetin or darbepoetin in patients with chemotherapy-induced anaemia and whose Hb concentration has fallen to below 10 g/dL, in order to decrease the require-

ment for transfusions. The question of threshold, however, 'merits further investigation', as the 2010 Update Committee found evidence insufficient for recommending ESA treatment for patients with Hb concentrations higher than 10 g/dL, or any associated increase in harms associated with doing so.

IIIb Chemotherapy-induced anaemia: initiating when Hb is > 10 g/dL but < 12 g/dL

Clinical judgement is needed to decide when to commence ESA treatment in patients with anaemia whose Hb concentration is between 10 and 12 g/dL, as well as consideration of the risks, benefits, and goals of ESA treatment. The goal of such treatment remains the reduction of transfusions, rather than to improve quality of life, for which the evidence remains insufficient.

IV Thromboembolytic risk

The 2010 update confirms the 2007 guideline that the use of ESAs leads to a statistically significant increased risk for thromboembolism. The 2010 update, therefore, recommends that clinicians should carefully weigh the risk of thromboembolism in patients when prescribing ESAs.

V Starting and modifying doses

The 2010 update recommends following FDA guidelines, for example, starting epoetin at a dose of 150 U/g three times a week or 40,000 U weekly subcutaneously, and increasing or reducing the dose, or discontinuing, according to the outcome in terms of reduction of transfusions and Hb levels achieved.

VI Discontinuing therapy for no response

The 2010 update repeats the recommendations of 2007 that ESA treatment be discontinued in patients who do not respond within six to eight weeks.

VII Hb target

Given the evidence that ESA treatment leads to an increased risk in mortality, which has become more apparent since 2007, the 2010 update recommends that treatment aims to increase Hb to 'the lowest concentration needed to avoid transfusions, which may vary by patient and by condition'. The available data do not identify a specific target Hb concentration for ESA therapy that is free from an increased risk of mortality.

VIII Iron monitoring and supplementation

As in 2007, the 2010 update suggests that patients should be monitored for iron status, including iron levels and iron-binding

capacity, and treated with iron supplements where necessary. There is insufficient evidence to support intravenous iron therapy.

IX Anaemia in patients not receiving concurrent chemotherapy

As for the 2007 guideline, the 2010 update continues to recommend that ESA treatment should be limited to patients undergoing concurrent chemotherapy, and that treatment should be discontinued when patients complete their chemotherapy course.

X Treatment of anaemia in patients with non-myeloid haematologic malignancies who are receiving concurrent chemotherapy

As in 2007, the 2010 update recommends that before considering use of ESAs, physicians should first observe the outcomes of chemotherapy and/or corticosteroids in patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukaemia. Treatment with ESAs should commence only if there is no increase in Hb in these patients.

In its conclusions, the 2010 update calls for additional research to 'clarify the mechanisms of harm and, particularly, the groups of patients or circumstances of clinical use that are least associated with these risks'. The authors add, 'This understanding is paramount to the ability of clinicians to extend the benefit of these drugs while reducing the risks.'

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Editor's comments

These guidelines, is based on a comprehensive literature review, conclude that the particular erythropoiesis-stimulating agents mentioned can be considered equivalent choices.

Julie Clayton, PhD, *GaBi Journal* Editor

Reference

1. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Somerfield MR, Temin S. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *J Oncol Pract*. 2010 Nov;6(6):317-20. doi: 10.1200/JOP.2010.000132

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