To treat anemia in patients with non-myeloid malignancies receiving concomitant myelosuppressive chemotherapy

Which factors should you consider in determining whether James* is an appropriate candidate to initiate Aranesp® treatment?

Meet James

Would James’s prior myelosuppressive chemotherapy make him an appropriate candidate for Aranesp® treatment?

*Hypothetical patient.

EGFR = epidermal growth factor receptor; ESA = erythropoiesis-stimulating agent; FOLFIRI = leucovorin (folinic acid) + fluorouracil + irinotecan; FOLFOX = leucovorin (folinic acid) + fluorouracil + oxaliplatin; Hb = hemoglobin; VEGF = vascular endothelial growth factor.

Indication

Aranesp® is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Limitations of Use

Aranesp® has not been shown to improve quality of life, fatigue, or patient well-being.

Aranesp® is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
- As a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

Please see Important Safety Information, including Boxed WARNINGS about INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE, on back cover.
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Once Hb begins to fall, it can continue to decline in many patients with cancer receiving myelosuppressive chemotherapy

Based on a retrospective analysis of electronic medical records (EMRs), 35% of patients had a Hb decline from < 10 g/dL to < 9 g/dL at week 3 of chemotherapy

Proportion of episodes of Hb decline from < 10 g/dL to < 9 g/dL in cancer patients receiving chemotherapy

Data are from an aggregated US community oncology clinic electronic medical record (EMR) database of 10,523 patients (representing 10,942 chemotherapy episodes). Patients were at least 18 years of age with non-myeloid malignancies and baseline Hb ≥ 10 g/dL and < 11 g/dL on or after the start of the chemotherapy episode. Patients were treated with a myelosuppressive chemotherapy doublet and could not have received an ESA within 9 weeks before the baseline Hb measurement or at any time during the 18-week study unless Hb was < 9 g/dL. Patients could be in any cycle of their chemotherapy regimen as long as they received at least 2 additional cycles at ≤ 35-day intervals after baseline Hb measurement. Chemotherapy episodes were re-indexed when the Hb level was < 10 g/dL to estimate the proportions of episodes and patients that further declined to hemoglobin < 9 g/dL by 3, 6, and 9 weeks without ESA therapy. The total number of EMR episodes with Hb decline from < 10 g/dL to < 9 g/dL was 5,535.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) list the following possible transfusion triggers:

- Sustained tachycardia
- Tachypnea
- Acute coronary syndrome
- Chest pain
- Dyspnea on exertion
- Lightheadedness
- Syncope
- Severe fatigue, preventing work and usual activity

Important Safety Information

- Aranesp® is contraindicated in patients with:
  - Uncontrolled hypertension
  - Pure red cell aplasia (PRCA) that begins after treatment with Aranesp® or other erythropoietin protein drugs
  - Serious allergic reactions to Aranesp®

Dosing Information

- Initiate Aranesp® in patients on cancer chemotherapy:
  - Only when Hb < 10 g/dL
  - Only when 2 additional months of myelosuppressive noncurative chemotherapy are planned
  - Only with the lowest dose necessary to avoid RBC transfusions

Please see the complete dosing guidelines in the accompanying insert.
Please see additional Important Safety Information, including Boxed WARNINGS, on back cover.
It takes time for hemoglobin to rise\textsuperscript{3,4}

New RBC production requires approximately 26 days\textsuperscript{3-7}

Increased hemoglobin levels are not generally observed until 2-6 weeks after starting treatment with Aranesp\textsuperscript{8,9}

- It takes approximately 26 days for a stem cell to develop into a mature RBC
- Erythropoietin is needed for RBC production
- Once stimulated by erythropoietin, it takes approximately 8 days for CFU-E cells to differentiate into a reticulocyte
- Reticulocytes mature into RBCs, and as the number of RBCs increases, hemoglobin (Hb) levels rise

Aranesp\textsuperscript{®} reduced the need for RBC transfusion vs placebo\textsuperscript{8,9}

Patients requiring RBC transfusions\textsuperscript{8,9}

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Data from a randomized, double-blind, placebo-controlled trial of 314 patients with Hb ≤ 11 g/dL who had lung cancer and were receiving platinum-containing chemotherapy. Patients received once-weekly treatment with either Aranesp\textsuperscript{®} (2.25 mcg/kg) or placebo, administered by subcutaneous injection, for up to 12 weeks. Per the pivotal trial protocol, doses were withheld if Hb exceeded 14 g/dL in women or 15 g/dL in men—the P-value is based on Kaplan-Meier (K-M) proportions.\textsuperscript{8,9}

Based on data from 7 randomized, double-blind, placebo-controlled studies\textsuperscript{8}

- Thrombovascular adverse reactions occurred in 6.1% of 1,203 patients treated with Aranesp\textsuperscript{®} and 4.1% of 909 patients receiving placebo—of which 1.2% (Aranesp\textsuperscript{®}) and 0.6% (placebo) were arterial; 5% (Aranesp\textsuperscript{®}) and 3.5% (placebo) were venous; and 1.7% (Aranesp\textsuperscript{®}) and 1.9% (placebo) were cerebrovascular disorders
- Abdominal pain (13.2% vs 9.4%) and edema (12.8% vs 9.7%) were reported more frequently in patients receiving Aranesp\textsuperscript{®} compared to patients receiving placebo in the same 7 studies
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Important Safety Information, including Boxed WARNINGS, for Aranesp® (darbepoetin alfa)

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

Chronic Kidney Disease:
- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
- No trial has identified a hemoglobin target level, Aranesp® dose, or dosing strategy that does not increase these risks.
- Use the lowest Aranesp® dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Cancer:
- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
- To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions.
- Use ESAs only for anemia from myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

Aranesp® is contraindicated in patients with:
- Uncontrolled hypertension
- Pure red cell aplasia (PRCA) that begins after treatment with Aranesp® or other erythropoietin protein drugs
- Serious allergic reactions to Aranesp®
- In controlled clinical trials of patients with cancer, Aranesp® and other ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.
- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.
- Control hypertension prior to initiating and during treatment with Aranesp®.
- For lack or loss of hemoglobin response to Aranesp®, initiate a search for causative factors. If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA.
- Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with ESAs.
- This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration.
- PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which Aranesp® is not approved).
- If severe anemia and low reticulocyte count develop during treatment with Aranesp®, withhold Aranesp® and evaluate patients for neutralizing antibodies to erythropoietin.
- Permanently discontinue Aranesp® in patients who develop PRCA following treatment with Aranesp® or other erythropoietin protein drugs. Do not switch patients to other ESAs.
- Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur with Aranesp®. Immediately and permanently discontinue Aranesp® if a serious allergic reaction occurs.
- Blistering and skin exfoliation reactions including Erythema multiforme and Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with ESAs (including Aranesp® in the postmarketing setting. Discontinue Aranesp® therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.
- Adverse reactions (> 1%) in Aranesp® clinical studies in cancer patients receiving chemotherapy were abdominal pain, edema, and thrombovascular events.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.


The NCCN Guidelines® are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.