

BC Cancer Protocol Summary Guidelines for the Use of Erythropoiesis-Stimulating Agents (ESAs) in Patients with Cancer

Protocol Code

SCESA

Tumour Group

Supportive Care

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Drug Acquisition:

- Erythropoiesis-stimulating agents (ESAs) are NOT covered by the BC Cancer Benefit Drug List or Financial Support Drug Program.
- Patients treated with these agents should have prescriptions filled at a community pharmacy and make the necessary arrangements to pay for the drug.
- Some financial assistance may be available through the Spectrum Support Program for Eprex[®] (epoetin) or the Victory Program (darbepoetin) (more details on Patient Assistance Programs at www.bccancer.bc.ca/health-professionals/clinical-resources/systemic-therapy).
- Patients eligible for ESAs under renal/dialysis or other programs should access financial assistance through those programs.

Eligibility:

- ESA use is limited to anemia secondary to concomitant myelosuppressive chemotherapy for palliative purposes.
- Treatment must NOT be started until the patient's hemoglobin is LESS than 100 g/L and there is a minimum of two months of planned chemotherapy.
- Anemia must be related to the myelosuppressive effects of concurrent chemotherapy and NOT be due to the effects of hormonal agents, biological response modifiers or radiotherapy, unless the patient is also receiving concomitant myelosuppressive chemotherapy.
- Anemia must NOT be due to blood loss, hemolysis, iron/folate/B₁₂ deficiency, or due to the malignancy itself.
- The lowest effective dose needed to avoid red blood cell transfusions must be administered.
- ESA therapy must be discontinued at the end of the chemotherapy treatment.
- The benefits of treatment must be weighed against the possible risks for individual patients:
 - a. ESAs may increase the risks of death, serious cardiovascular events, thromboembolic events and stroke.
 - b. ESAs may shorten overall survival and/or increase the risk of tumour progression or recurrence, as shown in clinical trials in patients with breast, head and neck, lymphoid, cervical, non-small cell lung cancers and patients with active malignancies who are not treated with either chemotherapy or radiotherapy.

- Red blood cell transfusions are the preferred treatment for the management of anemia in patients with cancer.

Exclusion:

Absolute

- Anemia secondary to malignancy in the absence of treatment with chemotherapy
- Patients for whom the anticipated outcome of chemotherapy is cure
- Patients who require an immediate correction of severe anemia or emergency red blood cell transfusions
- Patients with uncontrolled hypertension
- Patients who develop pure red cell aplasia (PRCA) following treatment with an ESA
- Patients with known hypersensitivity to the active drug or any of the excipients
- Patients with sensitivity to mammalian cell-derived products
- Patients with sensitivity to albumin (where applicable with albumin formulations)
- Patients who for any reason cannot receive adequate antithrombotic treatment
- Patients who for any reason cannot receive adequate iron supplementation
- Patients with severe coronary, peripheral arterial, carotid, or cerebral vascular disease, including patients with recent myocardial infarction or stroke
- Patients with grossly elevated serum erythropoietin levels (e.g., greater than 200 mU/mL)

Relative

- Past history of thromboembolism, hypercoagulability, or heart disease
- Platelet count below $50 \times 10^9/L$, due to the potential risk of bleeding and development of hematomas
- Liver disease
- Acute infection, including CNS infections
- Brain metastases
- Past history of seizures or convulsions
- Past history of porphyria
- Past history of gout
- Pregnancy, lactation or unreliable contraception

Tests:

- Baseline: CBC, differential, reticulocyte count, serum iron, ferritin, transferrin saturation, blood pressure, serum vitamin B₁₂ and serum folate
- During treatment: weekly CBC, differential, blood pressure

Pre-Therapy Patient Selection:

- Patients must have adequate iron stores at the start of ESA therapy. Serum ferritin levels should be at least 100 ng/mL and transferrin saturation should be at least 20%. Supplemental iron, e.g., oral elemental iron or intravenous iron, is

recommended to increase and maintain transferrin saturation to levels that will adequately support erythropoiesis.

- Adequate antithrombotic prophylaxis, as per current standard of care, is recommended for the prevention of venous thromboembolism.
- The decision to use ESAs should be based on discussions with the patient involving a risk versus benefit assessment. This should take into account the specific clinical context, including the type of cancer and the disease stage, the degree of anemia, life expectancy, the environment in which the patient is being treated and known risks of red blood cell transfusions and ESAs.

Treatment:

- Epoetin alfa 40,000 units subcutaneously once weekly or 150 units/kg subcutaneously three times per week
- Darbepoetin 2.25 mcg/kg subcutaneously once weekly or 500 mcg subcutaneously every three weeks

Response to Therapy

- At least 2 weeks of ESA therapy is required before a meaningful increase in red blood cells could be observed. Response to ESA therapy is predicted with a hemoglobin increase of greater than or equal to 10 g/L from baseline to week 4.

Duration of Therapy and Dose Modifications

1. ESAs should only be given to patients, while they are receiving concomitant myelosuppressive chemotherapy.
2. Target hemoglobin is the lowest level needed to avoid red blood cell transfusions and must NOT exceed 120 g/L.
3. If the patient's hemoglobin increases by more than 10 g/L in a 2 week period or if the hemoglobin reaches a level sufficient to avoid red blood cell transfusions, the dose should be reduced:
 - a. by 25% for epoetin alfa
 - b. by 40% for darbepoetin alfa
4. If the patient's hemoglobin exceeds a level needed to avoid red blood cell transfusions, ESA therapy should be withheld, until the hemoglobin approaches a level where red blood cell transfusions may be required. At that point, ESA therapy may be reinitiated at a dose 25% below the previous epoetin dose and 40% below the previous darbepoetin dose.
5. If the patient's hemoglobin does not rise by 10 g/L after 4 weeks of therapy with epoetin or 6 weeks of therapy with darbepoetin, the dose of ESA may be increased as follows:
 - a. Epoetin alfa may be increased to 60,000 units subcutaneously once weekly or 300 units/kg subcutaneously three times per week for 4 weeks
 - b. Darbepoetin alfa may be increased to 4.5 mcg/kg subcutaneously once weekly for 2 weeks
 - c. Iron supplementation should be considered to improve response to ESA therapy

6. ESA therapy should be discontinued, if there is no further response to the increased dose by week 8. In most circumstances, no therapeutic ESA trial should go beyond 2 months.
7. ESA therapy should be discontinued after the completion of chemotherapy.

Precautions:

- **Thromboembolism:** ESAs may increase the risk of serious thromboembolic events, cardiovascular events, stroke and death. Treatment with ESA should be discontinued in patients at risk or those who are experiencing thromboembolic, cardiovascular, or cerebrovascular events. The lowest dose of ESAs needed to avoid red blood cell transfusions should be used and treatment with ESAs should be discontinued, as soon as chemotherapy is completed.
- **Hypertension:** Patients with uncontrolled hypertension should NOT be treated with ESAs. In patients receiving ESAs, blood pressure should be closely monitored. Particular attention should be paid to the development of unusual headaches or an increase in headaches, as a possible warning signal. If hypertension develops, the dose of ESAs should be decreased or treatment discontinued. The patient's hypertension should be managed in the interim.
- **Seizures:** ESAs should be used with caution in patients who have a history of seizures or those who are predisposed to seizure activity, e.g., CNS infections and brain metastases.
- **Pure Red Cell Aplasia (PRCA):** Any patient who develops a sudden loss of response to ESA therapy, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of the loss of effect, including the presence of neutralizing antibodies to erythropoietin. If PRCA is suspected, ESA therapy must be promptly discontinued and appropriate supportive care measures instituted.
- **Skin Reactions:** Severe and life-threatening skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) have been reported in patients treated with darbepoetin alfa (Aranesp[®]) and epoetin alfa (Eprex[®]). If a severe skin reaction develops, ESA therapy must be discontinued immediately and permanently.²⁷⁻²⁸
- **Survival:** Treatment with ESA has shortened overall survival and/or increased the risk of tumour progression or recurrence in patients with breast, head and neck, lymphoid, cervical, non-small cell lung cancers and patients with active malignancies not treated with either chemotherapy or radiation therapy, when dosed to achieve a target hemoglobin of 120 g/L or greater.

Call Dr. Barb Melosky or Dr. Shirin Abadi @ (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment protocol.

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