Management of the Anemia of Malignancy

Dr. Kevin Imrie
Updated May 2008

Updates:

- Recommendations aligned with updated ASH/ASCO guidelines
- Risks of erythropoietic agents summarized

Introduction

Anemia is a common complication of cancer, occurring in 60-75% of patients with lymphoproliferative disorders [1]. Anemia is a major contributor to fatigue and negatively impacts quality of life. Over the past decade, new therapeutic options have become available to treat this complication. The use of these agents is increasingly being guided by systematic reviews and practice guidelines. The Odette Cancer Centre Hematology Site Group endorses the ASH/ASCO 2008 updated guideline recommendations. For clarity, we have changed the values for hemoglobin to SI units throughout this document.

Investigation

The anemia that is observed in patients with cancer is commonly multifactorial and may be due to:

- Blood loss
- Iron or vitamin deficiency
- Hemolysis
- Bone marrow infiltration
- Chemotherapy
- Anemia of chronic disease

It is important to exclude potentially reversible causes of anemia such as bleeding, iron deficiency or hemolysis before considering therapy with erythropoietin. Investigations should be guided by the clinical circumstance and may include:

- Blood film
- Reticulocyte count
- Serum ferritin
- Serum creatinine
- Serum LDH
- Direct antiglobulin test
- Bone marrow biopsy

The recommendations regarding investigation for such patients from the ASH/ASCO guidelines are as follows [2]:

- As in any medical situation, it is essential to consider other correctable causes of anemia before initiating therapy with stimulants of erythropoiesis. Therefore it is advisable to conduct an appropriate history and physical and consider relevant diagnostic testing aimed at identifying causes of anemia aside from chemotherapy or underlying hematopoietic malignancy. At a minimum, one should take a thorough drug exposure history, carefully review the peripheral blood smear (and in some cases the bone marrow), consider iron, folate, and B12 deficiency where indicated, and assess for occult blood loss and renal insufficiency. Direct antiglobulin test may be appropriate for patients with chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, and for those with a history of autoimmune disease; endogenous erythropoietin levels may predict response in patients with myelodysplasia.
Transfusion

Transfusion is an effective means of increasing hemoglobin and is the preferred means of treating anemia in cases where rapid correction is needed.

Guidelines for transfusion include:

- Signs of inadequate tissue oxygen delivery (tachycardia, dyspnea, syncope, pre-syncope, or ischemic chest pain) and a hemoglobin of less than 100 g/L
- Or a hemoglobin of less than 70 g/L (occasional patients may tolerate lower levels before requiring a transfusion)

Transfusions should be administered one unit at a time during daytime hours in the nonurgent, nonbleeding, inpatient setting. In the outpatient setting, transfusions should be administered at intervals that maintain the hemoglobin above the level where an individual patient develops symptomatic anemia. There is no need to administer routine premedication (Acetaminophen or Benadryl) unless the patient develops recurrent febrile or urticarial reactions. If patients are at risk of congestive heart failure, order transfusions over 3-4 hours. All patients should be evaluated pretransfusion to determine if preemptive diuretics are required to prevent transfusion-associated circulatory overload. All transfusion reactions (including minor reactions) must be reported to the Transfusion Service for reporting to the Public Health Agency of Canada and Canadian Blood Services. Informed consent must be obtained prior to the administration of any blood product. See Appendix C for more details on transfusions.

Erythropoietic agents

Hematologic growth factors are an alternative to transfusion for selected patients. Two agents are clinically available: Erythropoietin alpha (Eprex®) and darbepoetin (Aranesp®). Both of these agents have been studied in randomized trials and are the subject of systematic reviews and practice guidelines. Practice guidelines relating to the use of these agents include:

- CCO-PEBC EBS 6-12 [3]: Treatment of Anemia with Erythropoietic Agents in Patients with Non-Myeloid Hematologic Malignancies
- CCO-PEBC EBS 12-1 [4]: The Role of Erythropoietin in the Management of Cancer Patients with Non-hematologic Malignancies Receiving Chemotherapy
- ASH/ASCO 2002 guideline [5]: Use of Epoetin in Patients with Cancer
- ASH/ASCO 2008 revised guideline [2]: Use of Epoetin and Darbepoetin In Patients with Cancer

Benefits of Erythropoietic Agents

Published studies consistently demonstrate increased hemoglobin levels in the majority of patients treated with either erythropoietin alpha or darbepoetin (CCO EBS 6-12). The majority of trials report a reduction in the proportion of patients transfused of 15-24% with a number needed to treat to prevent a transfusion ranging from 4-6. It remains unclear whether this results in an improvement in quality of life. Some (but not all) trials report a quality of life benefit, but this analysis was poorly done in most studies and published guidelines do not recommend that these agents be used for the purpose of improving quality of life. The use of these agents is not associated with a survival improvement.

Risks of erythropoietic agents: While both erythropoietin alpha and darbepoetin are generally well tolerated and have been considered to have a favorable safety profile, concerning toxicities have recently been reported.
Thromboembolic risk: It is now recognized that these agents are associated with an increased risk of thromboembolic disease, particularly venous thromboembolism. In a Cochrane meta-analysis of 35 trials published in 2006 [6], the relative risk of thromboembolic events was 1.67 (95% CI 1.35-2.06). The number needed to harm (NNH) for a low risk population with a baseline 2% risk would be 75, but would be 7.5 in a high risk group with a 20% baseline risk. A second recent systemic review confirms this increased risk (RR 1.57 [95% CI 1.31-1.87]) [7].

The recommendation on this topic from the ASH/ASCO 2007 guideline is as follows:

- Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbopoietin is prescribed. Randomized clinical trials and systematic reviews of available randomized trials demonstrate an increased risk of thromboembolism in patients receiving epoetin or darbopoietin. Specific risk factors for thromboembolism have not been defined in these trials; therefore physicians should use caution and clinical judgment when considering the use of these agents. Established general risk factors for thrombotic events including previous history of thromboses, surgery, and prolonged periods of immobilization or limited activity. Multiple myeloma patients who are being treated with thalidomide or lenalidomide and doxorubicin or corticosteroids are at increased risk. There are no data regarding concomitant use of anticoagulants or aspirin to modulate this risk.

Decreased survival or increased cancer recurrence: Over the past 5 years, increasing data have suggested that the use of erythropoietic agents is associated with increased risk of cancer recurrence and decreased survival. Five randomized trials report inferior survival and two additional trials report inferior locoregional control or progression-free survival. Decreased survival has been reported for both solid tumors and hematologic malignancies. The results of these trials are provided in detail in the ASH/ASCO guideline. It should be noted that the Hb target for these trials was typically higher than current practice (Hb > 120 g/L), and it is unclear whether these finding apply to current more conservative use of these agents. Until evidence of safety with newer dosing strategies emerges, these agents should be used with caution and patients must be informed of the potential risks.

Dosing and Administration

The ASH/ASCO guidelines make the following recommendations regarding administration:

Threshold for Initiation

- The use of Epoetin or darbopoietin is recommended as a treatment option for patients with chemotherapy-induced anemia and a Hb concentration that is approaching, or has fallen to 100 g/L to increase Hb and decrease transfusions. Red blood cell transfusion are also an option depending on the severity of the anemia or clinical circumstances
- For patients with declining Hb levels but less severe anemia (those with Hb concentration < 120 g/L but have never fallen near 100 g/L), the decision of whether to use epoetin or darbopoietin immediately or wait until the Hb levels fall closer to 100 g/L should be determined by the clinical circumstances (including but not limited to elderly individuals with limited cardiopulmonary reserve, those with underlying coronary disease or symptomatic angina, or substantially reduced exercise capacity, energy, or ability to carry out activities of daily living). RBC transfusion is also an option where warranted by clinical conditions.

Recommendation 6: Discontinuing Therapy for No Response

Continuing epoetin or darbopoietin treatment beyond 6–8 wk in the absence of response (e.g. < 10–20 g/L rise in Hb or no diminution of transfusion requirements), assuming appropriate dose increase has been attempted in non-responders as per the FDA-approved label, does not appear to be beneficial and ESA therapy should be discontinued. Patients who do not respond should be investigated for underlying tumor progression, iron deficiency, or other etiologies for anemia.
**Recommendation 7: Hb Target**

Hb can be raised to (or near) a concentration of 120 g/L, at which time the dosage of epoetin or darbepoetin should be titrated to maintain that level. Dose and dose modification recommendations recorded in the package insert as of March 2007 and approved by the FDA can be found in Table 6 (and Table 6A, based on the November 8, 2007, FDA labeling announcement). Dose reductions are also recommended when Hb rise exceeds 10 g/L in any 2-week period or when the Hb exceeds 110 g/L. Risk of venous thromboembolism should also be considered when determining dose reduction schedules.

**Recommendation 8: Iron Monitoring and Supplementation**

Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for epoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to epoetin. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring.

**Recommendation 9: Anemia in Patients not Receiving Concurrent Chemotherapy**

There is evidence that supports the use of epoetin or darbepoetin in patients with anemia associated with low-risk myelodysplasia. There are no published high-quality studies to support its exclusive use in anemic myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia patients in the absence of concurrent chemotherapy. Analyses of primary data from Study 20010103 [8] submitted to the FDA in March of 2007 support a stronger recommendation against the use of ESAs to treat anemia associated with malignancy, or the anemia of cancer, among patients with either solid or non-myeloid hematological malignancies who are not receiving concurrent chemotherapy. This recommendation is consistent with the black-box warning that was added to the prescribing information for both epoetin alfa and darbepoetin in March of 2007, as follows: "Use of ESAs increased the risk of death when administered to a target Hb of 120 g/L in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated in this population."

**Recommendation 10: Treatment of anemia in patients with non-myeloid hematological malignancies who are receiving concurrent chemotherapy**

Physicians caring for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in Hb is not observed following chemotherapy, treatment with epoetin or darbepoetin for myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined above. Particular caution should be exercised in the use of epoetin or darbepoetin concomitant with chemotherapeutic agents and diseases where risk of thromboembolic complications is increased (see page 3, Decreased Survival or Increased Cancer Recurrence). Blood transfusion is also a therapeutic option.

**Cost Considerations**

In the doses commonly used, there are significant differences in cost between erythropoietin and darbepoetin. The costs for a 12-week course of therapy for each agent and dosing schedule can be found on page 5.
Approximate patient cost for 12 weeks of treatment (dosing based on the recommendations from the Ministry of Health Committee to Evaluate Drugs):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approx. Cost per Dose</th>
<th>Dosing Regimen</th>
<th>Approx. Cost for 12 weeks</th>
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<tbody>
<tr>
<td>Erythropoietin (Eprex® 40,000 IU)</td>
<td>$442</td>
<td>40,000 IU weekly</td>
<td>$5,304</td>
</tr>
<tr>
<td>Darbepoetin Alfa (Aranesp® 150 µg)</td>
<td>$442</td>
<td>150 µg weekly</td>
<td>$5,304</td>
</tr>
<tr>
<td>Darbepoetin Alfa (Aranesp® 200 µg)</td>
<td>$590</td>
<td>200 µg every 2 weeks</td>
<td>$3,540</td>
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<tr>
<td>Darbepoetin Alfa (Aranesp® 300 µg)</td>
<td>$910</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darbepoetin Alfa (Aranesp®) 500 µg</td>
<td>$1,518</td>
<td>500 µg every 3 weeks x 3 doses, then 300 µg every 3 weeks</td>
<td>$5,464</td>
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References