The Role of Erythropoietin (EPO) in Selected Hematologic Malignancies and Myelodysplastic Syndromes
QEII Health Sciences Centre/Cancer Care Nova Scotia

Guideline Questions:

➢ Does erythropoietin (EPO) prolong life in patients with hematological malignancies?

➢ Does the magnitude of benefit warrant the use of EPO in patients with hematologic malignancies who are transfusion dependent?

➢ Which patients would benefit from an alternate management strategy of treatment with EPO versus blood transfusions?

➢ What patients would benefit from primary prophylaxis of EPO in cases of transfusion independence?

➢ How long should the intervention occur in situations of primary prophylaxis and treatment with EPO?

Objectives

♦ To make recommendations regarding the use of EPO in patients with hematologic malignancies (ie. Multiple myeloma; Non-Hodgkin’s lymphoma) and myeloproliferative disorders (ie. Myelodysplastic syndrome)

Outcome Measures

♦ To review response, toxicity and quality of life.

Quality of Evidence

♦ Multiple Myeloma

  ▪ Phase I, II, and III studies in multiple myeloma (MM) have been reported. Anemia occurs in 30 – 60% of patients with MM. In some instances, patients were transfusion dependent, transfusion independent, and some were receiving chemotherapy during the study period. Over 10 clinical trials have been conducted with the use of EPO in MM patients, however, sample size was small in most of these trials. Among the larger trials, a randomized study of 84 MM patients (Cazzola et al 1995) with anemia (not requiring transfusion) was conducted. A recent trial by Osterborg et al (1996) included 65 transfusion dependent MM patients. (Level II, III, IV and V evidence).

♦ Non-Hodgkin’s Lymphoma

  ▪ Phase I, II and III studies in low to intermediate grade Non-Hodgkin’s Lymphoma (NHL) have been reported. The incidence of cases where hemoglobin levels are below 100 g/L is approximately 20%. Typically, hemolysis is seen in low grade lymphomas and pure red cell aplasia. Non-randomized trials have been conducted to show a potential benefit of EPO. Some randomized trials have attempted to compare the benefits of EPO over a control group (Level II, III, IV and V evidence).

♦ Myelodysplastic Syndromes

  ▪ Anemia of myelodysplastic syndromes (MDS) can be moderate to severe. Approximately two-thirds of MDS patients will present with anemia and become transfusion dependent. A number of trials have utilized EPO in this setting. A meta-analysis was conducted by Hellstrom-Lindberg et al (1995) looking at the efficacy of EPO across seventeen studies. Other trials have investigated the combination of G-CSF and EPO in these patients, (Level II, III, IV and V evidence).

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Benefit

♦ Multiple Myeloma (MM)

- EPO is an effective and safe drug for treating anemia of MM. Response is in the order of 70%. However, transfused patients with severe anemia and advanced disease seem less likely to respond (ie. 35%). It is unclear how to identify the most responsive group of MM patients, since many trials give conflicting information. A number of factors to predict response include: confirmation of inadequate production of endogenous EPO for the degree of anemia (independent of renal function), evidence of residual normal marrow function, absence of concomitant inflammatory or surgical complications, and low serum levels of circulating cytokines with inhibitory activity on erythropoiesis.

♦ Non-Hodgkin’s Lymphoma (NHL)

- The response rate to EPO is approximately 50 – 60% despite variability of patients, doses and criteria for defining response in these patients. Randomized trials indicate that the use of EPO significantly improves hemoglobin levels and reduces the number of transfusions compared to the control groups. Most reports indicate that EPO is not effective in patients with progressive end-stage diseases. This group of patients often respond to chemotherapy, with improvement in the disease related anemia.

♦ Myelodysplastic Syndromes (MDS)

- Compiled data from 15 separate trials involving patients with MDS, reveal an overall response rate of 20%. The recent meta-analysis indicates that the efficacy of EPO in MDS is low, with a significant response in only 16% of cases. The improvement was observed within 8 weeks in most responders. Patients, who were transfusion independent, had a higher response rate of 40 – 50 %. Patients with the greatest need for transfusion were least likely to respond to treatment. Trials with the combination of EPO and G-CSF are ongoing, to reveal any improvements in response rates. This combination should be reserved for clinical trial investigation.
Adverse Effects

- EPO therapy is well tolerated. Adverse effects include hypertension, headaches, arthralgias, flu-like symptoms and skin reactions (at injection site). Long term safety data is not available. As with other growth factors concerns about disease progression with the use of such an agent has been raised.

Evidence-Based Recommendation

Erythropoietin (EPO) may not directly prolong life in patients with hematologic malignancies. Anemia itself is often the major clinical problem in these patients and may directly cause significant morbidity. Many of these patients are elderly and the low level of hemoglobin may aggravate pre-existing conditions such as congestive heart failure or angina.

Transfusions present a variety of risks including viral infections, allergic reactions and iron overload.

Patients that undergo chronic transfusion therapy for hematologic malignancies risk associated iron overload. Iron excess results from a sustained increase in the amount of iron acquired over the amount lost. Transfusion associated iron overload is usually only diagnosed after a long interval of transfusion therapy. Myocardial disease is the life limiting complication of transfusion associated iron overload. Iron overload also impairs defense mechanisms against infection and tumors.

The majority of trials in hematologic malignancies particularly the randomized trials, indicate a significant benefit with the use of EPO over a placebo or control arm. The degree of benefit in these trials would warrant an alternate management strategy which would include the use of EPO in transfusion dependant patients. As described in the trials with MDS a modest proportion of patients respond to EPO (20%).

The majority of patients who will likely respond are those who are not transfusion dependent. The improvement observed with EPO should be evident within the first 8 weeks in the majority of responders. In most circumstances the continued use of EPO beyond 3 months in non-responders (to prevent or eliminate transfusion dependence) is not warranted. Treatment with EPO may continue in responding patients indefinitely. However in some circumstances reduced weekly doses may be sufficient.

Overall, EPO is a safe, well tolerated and modestly effective agent for the treatment of anemia in patients with a variety of hematologic malignancies.

Patients with MM or low grade NHL, who are transfusion dependent, may benefit from a therapeutic trial with EPO. MDS patients, with declining hemoglobin levels, may have reduced transfusion requirements if EPO is given. Before they become transfusion dependent, it would be a reasonable option to consider EPO therapy for MDS patients.

Many of the trials described did not formally assess quality of life issues. However, the improvements in performance status have been associated with response. Recent observations made in current literature utilizing various validated instruments confirm the statistically significant improvement in quality of life parameters.
Policy Recommendation

♦ Recommend availability of a trial of EPO in transfusion dependent hematologic patients with baseline anemia of \( \leq 90\text{g/L} \) whose transfusion requirements equal or exceed 2 units packed red blood cells (PRBC) monthly.

♦ An initial trial of EPO for 12 weeks with the documentation of dose, hemoglobin and therapeutic outcome (number of transfusions).

♦ Further 12 week cycles are dependent on evidence of satisfactory clinical response of reduced treatment requirement to less than 2 units of PRBC monthly.
**Expected Patient Numbers**

It is estimated based on a dose of 40,000 IU/week of EPO = approximately $535.80 per dose.

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<tr>
<th>Drug</th>
<th>Number of patients</th>
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<td>EPO</td>
<td>6 patients/year will be treated</td>
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**Estimated Cost per Patient**

(minimum 12 weeks-maximum 2 years)

**Range** - $6,500 - $56,000

**Estimate of Drug Cost** – assume 2 patients in each group *(i.e., MM, NHL and MDS) and based on the response rates described in the benefit section.

**Approximate Drug Cost** - $123,000

*Currently, at the QEII Health Sciences Centre, a clinical trial involving the use of a novel erythropoiesis stimulating protein (NESP) is enrolling patients with lymphoproliferative malignancies receiving chemotherapy. This should reduce the patient numbers in the upcoming year.

Current estimates from the Department of Health (DOH) suggest that 40% of the Nova Scotia population is covered by private drug insurance, 40% by public insurance and 20% non-insured. Based on these estimates and realization that not all programs would include this drug on their respective formularies, the approximate drug cost to the QEII Health Sciences Centre would be in the order of $25,000.

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Bibliography