clinical recommendations

Erythropoietins in cancer patients: ESMO Recommendations for use

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Definition of anemia

Anemia in cancer is defined as decrease of hemoglobin (Hb) level below normal lower limit either disease or therapy related. Mild anemia is defined as a Hb ≥10 g/dl and ≤11.9 g/dl, moderate anemia as a Hb of ≤8.0 and ≤9.9 g/dl and severe anemia as a Hb of ≤8.0 g/dl.

Incidence and prevalence of anemia in cancer patients

Cancer anemia is present in 40% of neoplastic patients. Anemia is mild in 30%, moderate in 9% and severe in 1% of patients. Overall incidence of anemia during chemo- or radiotherapy is 54% (mild 39%, moderate 14%, severe 1%). The incidence is highest in lung (71%) and gynaecological cancers (65%) and increases with the number of chemotherapy cycles. High grade of anemia has a negative impact on the performance status and is a major though not the only cause of fatigue, one of the most prevalent and important symptoms of cancer (Table 1).

Indication for the use of erythropoietins in anemic patients with solid cancers

The aim of treating anemia in cancer patients receiving chemotherapy is to reduce the need for red blood cell transfusions. Erythropoietins have not been shown to improve the outcomes of chemotherapy treatment (i.e. better tumor shrinkage, delayed tumor growth or longer survival) [I, A]. Furthermore, data on their effect on health-related quality of life outcomes should be interpreted with caution. Considering the risk of using erythropoietins when hemoglobin levels are >12 g/dl (see cancer therapy outcome and safety and tolerability sections) erythropoietins should only be used in cancer patients with chemotherapy-associated anemia and a Hb concentration of 9–11 g/dl [I, A].

Table 1. Incidence of anemia in patients with malignancies

<table>
<thead>
<tr>
<th>Grade</th>
<th>Anemia of chronic disease (%)</th>
<th>During chemotherapy (%)</th>
<th>Platinum-containing regimen (%)</th>
<th>Myelodysplastic syndromes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/moderate</td>
<td>30/8.7</td>
<td>8–97</td>
<td>10–73</td>
<td>46</td>
</tr>
<tr>
<td>Severe</td>
<td>1.3</td>
<td>0–40</td>
<td>5–42</td>
<td>54</td>
</tr>
</tbody>
</table>

Myelodysplastic syndromes

Erythropoietin + best supportive care ± granulocyte colony-stimulating factors (G-CSF) increases response rates over best supportive care alone [II, B]. Response rates for unselected patients are low (10% for erythropoietin and 35% for erythropoietin + G-CSF). Patients with low-risk myelodysplasia (i.e. refractory anemia, refractory anemia with ringed sideroblasts) and erythropoietin levels <500 U/l may obtain the greatest benefit. Optimal duration of treatment is uncertain, the gain in quality of life is controversial and the costs are very high.

Cancer therapy outcome

Several randomized trials, some published in peer-reviewed journals and some available in ODAC briefing documents posted on the US Food and Drug Administration web site have demonstrated decreased survival times or poorer locoregional control or progression-free survival in cancer patients receiving erythropoietins [I, A]. All but one of these studies, carried out in cancer patients treated or not with chemotherapy or radiotherapy, had a target Hb level >12 g/dl. Therefore, attempts to increase Hb above 12 g/dl may be harmful and should be restricted to clinical trials. Furthermore, erythropoietins should not be recommended to treat anemia of cancer, among patients with either solid or non-myeloid hematological malignancies who are not receiving concurrent chemotherapy or radiotherapy [I, A]. Reasons for these results...
are unclear. Retrospective data demonstrated increased epoietin receptors in head and neck cancer patients with a negative impact of epoietins on treatment outcome. Debate continues on the validity of these assays to measure epoietin receptors. Prospective studies are ongoing.

**comparison between erythropoietic agents**

Epoetin α and darbepoetin α yield a similar efficacy in increasing Hb, in the reduction of transfusion frequency and tolerability [I, A]. No clinically relevant differences between the drugs are known by now. Data concerning comparison with epoetin β are currently not available.

**prediction of response and duration of therapy**

There are no baseline predictive factors of response to erythropoietins that can be routinely used in clinical practice. In hematological malignancies a low serum erythropoietin level is a possible predictive factor for response. Significant increase of Hb (>1 g/dl) after 4 weeks of therapy is the only predictive parameter [II, B]. When erythropoietins are indicated, use the lowest dose possible to gradually increase the Hb concentration to avoid the need for transfusion; increase dose if no reduction in transfusion requirements or rise in Hb ≥1 g/dl after 4–6 weeks; decrease dose by 25% when Hb approaches 12 g/dl or Hb increases by >1 g/dl in any 2-week period; withhold the dose of the erythropoietins if Hb exceeds 12 g/dl; restart dose when Hb <11 g/dl at 25% below previous dose [II, B].

**iron supplementation**

In erythropoietin-treated anaemic patients with iron deficiency parenteral iron substitution leads to greater Hb increment in comparison with oral or no iron substitution [II, B].

**safety and tolerability**

Several trials in cancer patients with and without concurrent chemotherapy have found an increased risk of thromboembolic events [I, A]. Specific risk factors for thromboembolism have not been defined. Caution in the use of these agents is required in patients with previous history of thromboses, surgery and prolonged periods of immobilization or limited activity. There is no evidence for the association of erythropoietin-therapy and development of pure red cell aplasia in cancer patients [II, B].

**pharmacoeconomic considerations**

Use of epoietins and darbepoetin alfa profoundly increases health care costs [I, A].

**note**

Levels of evidence [I–IV] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the authors and the ESMO faculty.

**literature**


