Abstract
Erythropoiesis-stimulating agents are indicated for the treatment of chemotherapy-induced anemia in cancer patients. Controlled clinical studies have shown that epoetin alfa consistently and significantly increases levels of hemoglobin (Hb), decreases the need for RBC transfusion, and improves the quality of life that is of such importance in cancer patients with a limited life expectancy. The rise achieved in Hb level correlates with an improvement in quality of life. Studies have also demonstrated that earlier initiation of epoetin therapy (i.e., starting treatment at an Hb level of 10–11 g/dl rather than waiting for Hb to fall to <10 g/dl) is associated with a faster achievement of an optimal Hb level, a lower transfusion requirement, and a maintained quality of life. The Oncologist 2008;13(suppl 3): 27–32

Introduction
Anemia in cancer patients is associated with symptoms of fatigue, depression, and impaired cognitive function (Fig. 1) [1, 2]. Fatigue can be one of the most common and distressing symptoms of cancer, occurring more frequently than pain-related cancer symptoms [3]. The consequences include social isolation, inability to work and pursue activities of daily living, and reduced sexual activity. There is also a concern that a low level of hemoglobin (Hb) has been identified as an indicator of poor prognosis [4, 5]. Correction of anemia is important because of the high correlation between Hb level and quality of life (QoL) [6, 7]. Despite these reasons for intervention, until recently, many cancer patients who suffered from anemia did not have this condition well managed. Data from the European Cancer Anaemia Survey (ECAS) published in 2003 suggest that 60% of cancer patients who experienced anemia were given no treatment [8]. Epoetin was given to 18% (median Hb level at initiation, 9.9 g/dl), 15% had a transfusion (median Hb at initiation, 8.6 g/dl), and 7% were given only iron (Hb at initiation, 11.2 g/dl) [8]. The data from the ECAS also showed that a low Hb level correlated with a poor performance status [8].

RBC Transfusion
Of the two principal treatment strategies for chemotherapy-associated anemia, the one based on blood products seems to be characterized by repeat rescue transfusions, each triggered by the patient falling below an individual but relatively low threshold, probably defined by the presence of symptoms (Fig. 2) [9]. Despite these repeated transfusions, it is relatively unlikely that a patient will achieve an Hb level that is optimal for good QoL and tumor oxygenation that can give anticancer therapy the best prospects of success [10]. In contrast, an approach based on the use of erythropoiesis-stimulating agents (ESAs) can be seen as seeking to maintain an Hb concentration that is relatively stable, consistently above the level at which patients become symptomatic, and compatible with good QoL and optimization of the potential benefits of cancer chemotherapy and/or radiation (Fig. 2) [9].

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In many patients who are managed by transfusion, multiple administrations of blood products are needed simply to maintain an Hb level sufficient to minimize the signs and symptoms of anemia. Such repeated transfusion requires repeated hospitalization. It carries the risk for potential infection, volume overload, acute and delayed reactions, immunosuppression, alloimmunization, and iron overload [11]. There has also been the suggestion that this approach is associated with adverse cancer-related outcomes. Moreover, at a logistic level, it places considerable burden on the donor blood supply and transfusion services. A retrospective review of studies of ESAs given for cancer-induced anemia (which together involved >2,000 patients) showed that the Hb level at the time of transfusion was <8 g/dl in 36% of cases, 8–10 g/dl in 54% of cases, and >10 g/dl in 10% of cases (Fig. 3). In 35% of cases the reason given for transfusion was that the patient had fallen below an Hb trigger level; but in 46% of cases the reason was therapeutic, and in a further 4% it was medically indicated. In only just >1% was the reason prophylactic.

ESAs
The development of ESAs has led to far closer scrutiny of the prevalence and consequences of anemia in cancer patients. It has become clear that >80% of patients administered chemotherapy develop anemia (grade 1–4) at some stage during treatment, and around one third have grade 3–4 anemia [8]. Signs and symptoms of anemia decrease QoL and general health [12]. In the absence of ESAs, the majority of chemotherapy patients require transfusion, and the use of an ESA can approximately halve the transfusion requirement [13]. Large and systematic reviews of the broader trial literature have shown similar reductions in the number of patients transfused [14, 15]. Thus, ESAs substantially reduce the need for transfusions.

A meta-analysis of data from 15 randomized controlled trials of epoetin showed a consistently high rate of hemoglobin response, with an overall risk ratio of 3.42 (95% confidence interval [CI], 3.03–3.06) relative to control (Table 1) [13, 15–30]. The likelihood of Hb response is at least as large when the starting Hb level is 10–12 g/dl as it is when baseline Hb is <10 g/dl. Meta-analysis has also made clear that patients who have epoetin started only when their Hb level falls to <10 g/dl are significantly more likely to require transfusion than patients in whom epoetin is begun at the higher Hb level of 10–11 g/dl (Fig. 4A) [31]. Compared with patients in whom epoetin was initiated early, the risk ratio for needing a transfusion between baseline and the end of

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**Symptoms**
- Fatigue
- Impaired cognitive function
- Depression

**HROQOL**
- Unable to work
- Social isolation
- Unable to complete daily activities
- Reduced sexual activity

**Signs**
- Unfavorable prognostic factor for clinical outcome

**Lab values**
- Low Hb levels
- Low skin temperature
- Increased pulse pressure, systolic ejection murmur

**Figure 1.** Key components of anemia [1–6].
Abbreviations: Hb, hemoglobin; HRQOL, health-related quality of life.

**Figure 2.** Rescue by transfusion versus an improvement/maintenance strategy with ESAs: A conceptual model [9].
Abbreviations: ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.

**Figure 3.** Transfusions in ESA CIA studies: Retrospective chart review of ESA studies (n = 2,286) [9]. Recommendation to transfuse: Hb <8 g/dl or signs or symptoms of anemia.
Abbreviations: CIA, chemotherapy-induced anemia; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.
study was 2.29 for patients starting epoetin at the lower Hb level (95% CI, 1.54–3.42) (Fig. 4B) [31].

While baseline Hb was the most significant factor predicting the need for transfusion during treatment with an ESA, the number of subsequent transfusions was best predicted by the fact that patients had required a transfusion before the start of ESA therapy [31, 32]. Patients pretransfused were approximately twice as likely as those not pretransfused to require subsequent transfusion. Early intervention has also been associated with a lower risk for transfusion and for a fall in Hb to <10 g/dl, and with a significantly longer time to first transfusion [13].

Table 1. Meta-analysis showing proven hematologic response data with epoetin compared with control from 15 randomized clinical trials [13, 15–30].

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hb &lt;10 g/dl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biogentsa 2003</td>
<td>63/133</td>
<td>271/139</td>
<td>6.50</td>
<td>3.29 (2.31–5.88)</td>
</tr>
<tr>
<td>Case 1993</td>
<td>46/79</td>
<td>10/74</td>
<td>3.89</td>
<td>4.31 (2.39–7.90)</td>
</tr>
<tr>
<td>Casazza 1995 c</td>
<td>19/31</td>
<td>5/15</td>
<td>0.81</td>
<td>9.19 (1.36–63.34)</td>
</tr>
<tr>
<td>Casazza 1995d</td>
<td>19/26</td>
<td>1/14</td>
<td>0.49</td>
<td>8.62 (1.27–58.34)</td>
</tr>
<tr>
<td>Heney 1994</td>
<td>31/54</td>
<td>4/11</td>
<td>1.54</td>
<td>7.39 (2.15–19.69)</td>
</tr>
<tr>
<td>Littlewood 2001</td>
<td>172/344</td>
<td>22/110</td>
<td>11.26</td>
<td>3.86 (2.51–5.41)</td>
</tr>
<tr>
<td>Oberhoff 1998</td>
<td>30/114</td>
<td>7/104</td>
<td>2.70</td>
<td>4.95 (2.51–10.68)</td>
</tr>
<tr>
<td>Osterborg 1998a</td>
<td>21/47</td>
<td>4/24</td>
<td>1.99</td>
<td>2.68 (1.04–6.80)</td>
</tr>
<tr>
<td>Osterborg 1998b</td>
<td>23/46</td>
<td>4/25</td>
<td>1.98</td>
<td>2.94 (1.16–7.71)</td>
</tr>
<tr>
<td>Osterborg 2002</td>
<td>114/70</td>
<td>48/173</td>
<td>17.17</td>
<td>3.92 (1.93–7.93)</td>
</tr>
<tr>
<td>Walter 2004</td>
<td>120/165</td>
<td>52/164</td>
<td>19.64</td>
<td>2.29 (1.00–2.93)</td>
</tr>
<tr>
<td>Rose 1994</td>
<td>67/142</td>
<td>13/29</td>
<td>8.25</td>
<td>2.07 (1.69–4.85)</td>
</tr>
<tr>
<td><strong>Hb 10 to 12 g/dl</strong></td>
<td></td>
<td></td>
<td>78.28</td>
<td>3.24 (2.03–5.73)</td>
</tr>
<tr>
<td>Total events: 768 (treatment), 189 (control)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; RR, risk ratio.


Figure 4. Epoetin alfa reduces the relative risk for subsequent transfusion (Hb level of initiating ESA) [31]. (A): Patients initiating therapy at a baseline Hb <10 g/dl had an RR of 2.65 (95% CI, 1.54–4.56) of receiving subsequent transfusions compared with patients initiating therapy earlier (Hb 10–11 g/dl), after day 28 of therapy. (B): Patients initiating therapy at a baseline Hb <10 g/dl had an RR of 2.29 (95% CI, 1.54–3.42) of receiving subsequent transfusions compared with patients initiating therapy earlier (Hb 10–11 g/dl), from baseline to the end of the study.

Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; RR, risk ratio.

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There has been some suggestion that the type of ESA may also affect the transfusion requirement [33]. A randomized, open-label trial compared Hb response to once weekly epoetin alfa (Procrit®; Ortho Biotech Products, L.P., Raritan, NJ) with Hb response to darbepoetin alfa (Aranesp®; Amgen Inc., Thousand Oaks, CA) administered every 2 weeks in anemic patients receiving chemotherapy for their cancer [33]. In that study, a post hoc analysis showed that the overall number of units of transfusions from baseline to the end of the study was significantly lower for the epoetin alfa group (81) than for the darbepoetin alfa group (156) ($p = .0587$) [33]. There was a lower percentage of patients transfused from baseline to the study end and by weeks of ESA therapy. The transfusion requirement by 4-weekly period on therapy showed a consistent difference: over the first 4 weeks on treatment, a transfusion was required by 8.6% of patients in the epoetin group and by 11.3% of patients given darbepoetin; in weeks 13–16, the corresponding figures were 4.8% and 7.4%, respectively (Table 2) [33].

Among the studies in which epoetin alfa was given weekly, a meta-analysis of six trials involving 4,296 patients with a variety of different tumors showed a clear trend toward a lower transfusion requirement with time on treatment [34]. Epoetin alfa resulted in a lower number of transfusions. The proportion of patients receiving a transfusion was 12.2% in the first month, which then fell to 8.9%, 5.7%, and 4.9% in the three succeeding months, respectively [34].

A study by Littlewood and colleagues [22], showed that epoetin alfa rapidly corrected Hb levels (Fig. 5A). This increase in Hb was associated with improvements in QoL (Fig. 5B). In this key study, the increase in score from baseline to last assessment was 8.1 for the energy component of the Cancer Linear Analog Scale (CLAS), 7.5 for the daily activities component of the scale, and 4.8 for overall QoL [22]. In contrast to the increase seen in patients treated with epoetin, those in the latter group experienced reductions of 5–6 points in overall QoL and in the energy and daily activity components of the CLAS over the period of study. At the end of assessment, epoetin alfa resulted in a significantly higher Hb level ($p < .001$) and significantly lower transfusions needs ($p = .0057$) compared with placebo [22]. Adverse events between the two groups were comparable [2].

**Conclusion**

QoL is an important factor for the cancer patient. Fatigue is among the most common cancer-related symptoms and is often associated with a low Hb level. Furthermore,
approximately 80% of patients receiving chemotherapy experience anemia at some stage of their treatment. Low Hb levels are associated with a poor QoL, an essential point for maintenance therapy. The main factors predictive of the need for transfusion are the number of pre-transfusions and a low baseline Hb level. Clinical studies have demonstrated that epoetin alfa increases Hb levels, decreases transfusion needs, and improves QoL measures, and have shown a correlation between Hb level and QoL improvement. Studies have also illustrated that the earlier epoetin alfa therapy is started, the faster the optimal Hb level is achieved, fewer transfusions are required, and QoL is maintained.

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