Abstract. Cancer-related anaemia has a major detrimental effect on quality of life (QoL) and adversely affects patient outcome, having a negative impact on local tumour control, disease-free survival and overall survival. The incidence of cancer-related anaemia is particularly high among patients with gynaecological cancers, affecting up to 80% of individuals in this patient group. Anaemia may develop as a consequence of the disease itself; however, the myelosuppressive and nephrotoxic effects of the intensive chemotherapy and/or radiotherapy regimens frequently used in the treatment of gynaecological cancer are major causative factors. Although blood transfusions were traditionally used for the management of anaemia in patients with cancer, associated adverse events and inconvenience of use have meant that they are now reserved for patients with severe anaemia who require rapid improvements in haemoglobin (Hb) levels. As a consequence, epoetins, with their ability to provide stable Hb levels over prolonged periods, are now firmly established in the management of cancer-related anaemia. The efficacy of epoetin beta, a recombinant human erythropoietin, has been investigated in patients with gynaecological malignancies and anaemia in several European trials. These studies confirm that epoetin beta increases Hb levels, reduces transfusion requirements and improves QoL, and support the use of epoetin beta as an integral part of the treatment regimen in patients with ovarian or cervical malignancies receiving radio- and/or chemotherapy.

Anaemia is the most common comorbidity in patients with cancer and its incidence is particularly high among individuals with gynaecological cancers. In the recent European Cancer Anaemia Survey (ECAS), the authors reported that 81% of patients with gynaecological cancers experienced anaemia (defined as a haemoglobin [Hb] level <12 g/dl) at some point during the 6-month survey. In those patients with lung cancer, lymphoma/myeloma or breast cancer, 77, 73 and 62%, respectively, experienced anaemia during the survey (1).

The cause of anaemia in patients with gynaecological cancers is multifactorial. Anaemia may develop as a consequence of the disease itself (as a result of bone marrow necrosis and mechanical haemolysis) or as a result of immune system activation leading to inhibition of erythroid progenitor cell proliferation and suppression of erythropoietin response (2, 3). Chronic blood loss from vaginal bleeding is also an important contributory factor (4). Moreover, anaemia related to the treatment of cancer represents a significant cause of anaemia in this patient group. The chemotherapy used in the treatment of gynaecological cancer is mainly platinum-based, and this has myelosuppressive and nephrotoxic effects, which can exacerbate the development and progression of anaemia. Indeed, the ECAS showed that the frequency of anaemia in patients with gynaecological cancers was substantially greater in those receiving chemotherapy, radiotherapy or concomitant chemoradiotherapy compared with those who received no treatment (1).

0250-7005/2007 $2.00+.40
will result in the irradiation of half the adult functional bone marrow (both femoral necks and heads, both iliac bones and sacrum) (Figure 1).

The burden of anaemia in patients with gynaecological cancers is substantial. The principal symptoms of anaemia in patients with cancer include fatigue, dyspnoea, loss of appetite and cardiovascular effects, all of which severely affect the quality of life (QoL) of patients. A survey of patients with cancer by Vogelzang et al. (6) revealed that 78% of the 419 patients interviewed experienced fatigue, with 32% claiming that fatigue affected their daily routines. In a similar survey by Curt et al. (7) 76% of 379 patients questioned experienced fatigue on a regular basis, with 88% of these patients claiming it had necessitated a change in their daily routine. Although anaemia is not the sole cause of fatigue and poor QoL in patients with cancer, it is a substantial causative factor. Furthermore, there is considerable evidence that anaemia is associated with poor long-term prognosis in patients with cancer; this is discussed in more detail in the next section. The optimal management of anaemia should therefore be considered an essential component of cancer care, not least in patients with gynaecological malignancies receiving aggressive chemotherapeutic and/or radiotherapy.

**Anaemia as a Negative Prognostic Factor**

The presence of anaemia has been shown to adversely affect outcome in patients with cancer and appears to be strongly correlated with reduced survival in this patient group. In a retrospective survey of cancer studies, the presence of anaemia was found to increase the relative risk of death by 19, 75, 47 and 67% in patients with lung carcinoma, head and neck cancer, prostate cancer and lymphoma, respectively (8). The existence of anaemia as a negative prognostic factor has been recognised for some time in patients with cervical cancer, with a number of studies showing that anaemia has a negative impact on local tumour control, disease-free survival and overall survival in this patient group (9-13). Indeed, as long ago as 1965, Evans and Bergsjo (14) showed survival differences between patients with cervical cancer undergoing radiotherapy who had Hb levels ≥11 g/dl compared with those who had Hb <11 g/dl at the time of treatment. The worse outcome for patients with anaemia at the start of treatment persisted for more than a decade of follow-up. A small randomised trial of transfusion support in 132 patients with cervical cancer receiving radiotherapy also showed a significant difference in terms of local relapse rate (LRR) in favour of the transfused group compared with the control group (log-rank adjusted LRR 0.15 versus 0.44; \( p=0.0076 \)) (15). Overall survival was also higher in the transfusion group; however, the difference was not statistically significant (proportion of
patients dying log-rank adjusted for stage and completion of radiotherapy: 0.35 versus 0.49; \( p = 0.2 \).

The impact of Hb levels, both before and during chemotherapy, on survival in patients with ovarian cancer has also been highlighted in a recent study, with the authors reporting a highly significant association between Hb levels of \( \geq 12 \) g/dl before treatment and prolonged overall survival \( (p < 0.001) \) (16). The association between anaemia and poor patient outcome may be attributable to an increase in the proportion of hypoxic regions of the tumour, as a result of the reduced oxygen carrying capacity of the blood. This results in the clonal selection of highly treatment-resistant tumour cells (17). Available data suggest that by treating anaemia and maintaining optimal Hb levels during radio- or chemotherapy, the number of hypoxic, therapy-resistant tumour cells can be reduced, potentially enabling an improvement in tumour control (18, 19).

Current Treatment Options for Anaemia

Anaemia correction has been shown to improve the QoL of patients with cancer. Crawford et al. (20) demonstrated a positive relationship between Hb level and QoL score in anaemic patients with cancer, with the maximum incremental gain in QoL seen at a Hb level of 12 g/dl (range 11-13 g/dl). Correcting anaemia may also have the potential to improve survival. Findings in patients with cervical cancer treated with radiotherapy showed a consistent improvement in survival and tumour control when Hb levels were increased and maintained at \( >11 \) g/dl or \( \geq 12 \) g/dl (21, 22) (Figure 2).

Red blood cell transfusions were traditionally used to manage anaemia in patients with cancer but they do not present a viable option for its long-term correction. Blood transfusions are inconvenient and their effects on Hb levels are short-lived, with repeated transfusions resulting in dramatically fluctuating Hb levels. Therefore, their use tends to be restricted to cases of severe anaemia, where rapid correction of Hb levels is required. Furthermore, serious consequences, including transmission of infection, iron overload and immune or intolerance reactions, may develop following a blood transfusion (23, 24).

Recombinant human erythropoietins have now become established as an effective and convenient treatment for the management of anaemia in patients with malignant disease. Unlike blood transfusions, these agents provide stable Hb levels over an extended period of time. Furthermore, even with the aggressive, multi-modality anticancer treatments used in gynaecological malignancies, epoetins can correct treatment-induced anaemia. One of the earliest studies to show that epoetins were effective in patients with gynaecological cancers receiving aggressive radiotherapy and platinum-based chemotherapy was performed by Dusenbery et al. (25). Later studies also confirmed the feasibility of this approach (26-28).

Epoetin beta (NeoRecormon®), a recombinant human erythropoietin with the same structure and function as the endogenous hormone, has been available in Europe since 1990 and has demonstrated good efficacy in patients with haematological malignancies (29-31) and solid tumours (30, 32-37). The reported benefits of epoetin beta, namely increases in Hb level, reductions in transfusion requirements and improvements in QoL, are in line with the major goals of epoetin therapy outlined in the European Organisation for Research and Treatment of Cancer (EORTC) guidelines (38).

In addition to its clinical and QoL benefits, epoetin may be more cost-effective than relying on transfusion alone to correct anaemia. In a modelling study using cost and effectiveness assumptions taken from a literature review and clinical trials, Cremieux and colleagues reported that the increase in Hb achieved with US $1 spent on standard care (blood transfusion) could be achieved with just US $0.81 spent on epoetin therapy, suggesting that epoetin is approximately 23% more cost-effective than standard care (39). The greater cost-effectiveness of epoetin could be attributed in part to the high costs associated with the collection, storage and delivery of blood.
Benefits of Epoetin Beta in Patients with Gynaecological Malignancies.

Among patients with solid tumours, those with gynaecological malignancies, particularly ovarian and cervical cancer, represent a particularly important target group for epoetin therapy. This is because of the high incidence of clinically significant anaemia, the frequent use of intensive and aggressive treatment regimens and the negative impact of anaemia on disease outcome in this patient group. Two European phase III studies investigated the efficacy of epoetin beta in anaemic patients with gynaecological malignancies who were receiving predominantly platinum-based chemotherapy (27, 34). Moreover, many patients with gynaecological tumours have been included in large-scale studies of mixed tumour types (30, 33, 37). Although of differing design, taken together the results of these studies indicate that epoetin beta is well tolerated and has a beneficial effect in patients with cervical or ovarian cancer in terms of improvements in Hb levels and QoL and reduction in transfusion requirements.

Advanced cervical cancer. One of the most recent studies to evaluate the safety and efficacy of epoetin beta was the Management of Anaemia under Radio-Chemotherapy (MARCH) study (27). This study included 74 patients with baseline Hb levels of 9-13 g/dl who were scheduled to receive radiotherapy and cisplatin for stage IIIB to IVA cervical cancer. Patients were randomised to receive epoetin beta (150 IU/kg three times weekly – with the aim of achieving Hb levels of >13 g/dl during radiotherapy) or standard supportive care for up to 12 weeks. Patients treated with epoetin beta achieved a significant increase from baseline in mean Hb level (1.1 g/dl, p<0.0001) which compared favourably with a decrease of 0.7 g/dl from baseline seen in the control group. The primary end-point of this study aimed to establish a correlation between anaemia correction and response to radiochemotherapy. There were no significant differences in time to progression or death (p=0.99), overall survival (p=0.57) or disease progression (p=0.79) between the two study arms, although these results need to be verified in further studies because of the small sample size.

Preliminary reports from other studies have suggested that epoetin therapy may be associated with improved outcomes in patients with gynaecological cancer. For example, important benefits in terms of survival have been reported with epoetin alfa therapy in a large study conducted by Blohmer et al. (26) in patients with high-risk cervical cancer receiving radiotherapy. Although 5-year follow-up data have yet to be reported, an interim data analysis revealed a significant (p=0.0004) improvement in transfusion requirements following treatment with epoetin alfa 10,000 IU three times weekly (n=113) compared with standard care (transfusion as required; n=116). In addition, there was a significant reduction in the incidence of grade II anaemia (21 versus 47%; p<0.0001) and an improvement in QoL in the epoetin group. The relapse rate was also considerably lower in the epoetin arm than in the control arm (17 versus 25%; p<0.07) (Figure 3) (40).

Similarly, Antonadou et al. (41) examined the effects of epoetin on survival in 385 patients with pelvic malignancies receiving radiotherapy. Hb levels during radiotherapy were higher in patients receiving epoetin 10,000 IU five times weekly than in the control group (mean 12.9 g/dl in the epoetin group and 10.6 g/dl in the control group). There was a significant improvement in local tumour control associated with epoetin treatment: after 4 years of follow-up, the rate of disease-free survival was 85.3% in the epoetin group and 67.2% in the control group (p=0.0008).

Ovarian cancer. Patients with ovarian cancer have made up one of the major patient groups in several large-scale studies of epoetin beta. In addition, epoetin beta has been evaluated in a randomised, controlled study of patients with ovarian cancer (n=122) (34). In this study, a reduction in transfusion need (4.4 versus 39.4% of patients with ≥1 transfusion) and a significantly longer time to first transfusion (p=0.0002) were reported with epoetin beta 150 IU/kg three times weekly (~30,000 IU weekly) compared with control therapy.
in patients with ovarian cancer (n=122) receiving platinum-based chemotherapy (Figure 4). The mean baseline Hb level was ≤12 g/dl in the epoetin beta and control groups; during every cycle of chemotherapy fewer epoetin-treated patients developed anaemia (Hb <10 g/dl) compared with control patients. In a follow-up analysis to this study, there was a trend towards a reduction in tumour progression with epoetin beta (hazard ratio 0.83; 95% confidence intervals [CI] 0.25, 2.74), with no negative effect on survival (42). Interestingly, similar findings were reported in a meta-analysis of nine epoetin beta studies (n=1409) across many different malignancy types (43). The findings of this analysis suggested a lower rate of tumour progression (3.40 versus 3.69 events per patient year) and a reduced death rate (3.13 versus 3.36 deaths per patient year) with epoetin beta versus control therapy and a trend towards a reduced risk of progression among epoetin beta-treated patients (relative risk 0.79; p<0.05).

Epoetin beta has also been shown to have beneficial effects on haematological parameters in a large randomised, controlled study in patients with solid tumours (n=189), the most common of which was ovarian cancer (n=50). The need for blood transfusions was reduced in the epoetin beta-treated group (5000 IU daily) compared with the control group (28 versus 42% of patients); the median Hb level also increased in the epoetin beta-treated patients but remained unchanged in the control group (33). This benefit was apparent within the first 2 weeks of epoetin beta therapy: median Hb increased by 0.15 g/dl in the epoetin group compared with a decrease of 0.34 g/dl in the control group. In another study in patients with solid tumours (35% of whom had ovarian cancer) or lymphoid malignancies, Boogaerts et al. (30) reported a significant (p<0.001) increase in Hb levels with epoetin beta 150 IU/kg three times weekly compared with standard care. In patients with solid tumours, median Hb levels increased by 2.1 g/dl from baseline in the epoetin beta group compared with a smaller increase of 0.9 g/dl in the control group. In addition, there was a significant (p<0.05) and rapid improvement in QoL in the epoetin beta group, as measured by the Functional Assessment of Cancer Therapy-fatigue (FACT-F) subscale (Figure 5), the Short-Form-36 physical component summary score and a visual analogue scale.

In addition, the large NeoPrevent study (n=255) included patients with solid tumours, of which 7.8% had ovarian cancer, receiving platinum-based chemotherapy. Overall, 62.4% of patients treated with epoetin beta 10,000 IU three times weekly achieved a Hb response (>1 g/dl increase) and the overall QoL was significantly improved in patients with a Hb response (p<0.01). Performance status was also maintained among patients responding to epoetin beta but deteriorated significantly in the non-responders (p<0.01) (37).

Findings from prospective research also suggest that epoetin therapy may improve outcome in patients with ovarian cancer. In a small randomised trial, Marinaccio et al. (44) assessed the influence of epoetin alfa therapy on outcome in patients with epithelial ovarian cancer (FIGO stage IC-IV) and mild anaemia (Hb 10.6-11.9 g/dl) at presentation (44). After primary surgery, all patients underwent adjuvant chemotherapy (paclitaxel and carboplatin) and received epoetin 10,000 IU three times weekly or no epoetin (control) for 4-6 weeks. Hb was significantly increased in the epoetin group compared with the control group (p<0.01). The median relapse-free survival was also longer in the epoetin group versus control (26 and 18 months, respectively). Kaplan-Meier 12-month estimates showed a non-significant trend towards increased overall survival in the epoetin group compared with control (65 versus 50%; p=0.12).

*Once-weekly administration.* In common with many other clinical studies of epoetin beta in patients with cancer-related...
anaemia, studies conducted in those with gynaecological cancer have mainly used the traditional three-times-weekly regimen, a strategy that had already proved effective in patients with chronic kidney disease receiving dialysis. However, because three-times weekly administration of epoetin beta may be perceived as inconvenient for both patients and healthcare workers, a more convenient once-weekly regimen has been developed. A once-weekly regimen of epoetin beta 30,000 IU has been shown to be as effective as a three-times-weekly regimen at the same overall weekly dose (i.e. 10,000 IU three times weekly) in patients with haematological malignancies in a randomised, multicentre trial. Both regimens produced high and similar response rates (72 and 75% of patients, respectively) and similar time-adjusted area under the Hb-time curve from weeks 5-16 (31). As a result, the once-weekly dosing schedule has been approved for use in patients with haematological malignancies in Europe for some time (45).

Available data also indicate that this once-weekly schedule is effective in patients with solid tumours receiving platinum-based or non-platinum-based chemotherapy (36, 46). Interim results from the BReast cancer – Anaemia and the Value of Erythropoietin (BRAVE) study involving patients with metastatic breast cancer receiving anthracycline- and/or taxane-based chemotherapy showed a rapid increase in median Hb levels from baseline (mean Hb level 11.5 g/dl) to 13.4 g/dl after 24 weeks of therapy in patients treated with epoetin beta 30,000 IU once weekly compared with no change in the group receiving standard care (36). In a second study, an overall response rate of 60% (Hb increase ≥2 g/dl or achievement of Hb≥12 g/dl) was reported among patients with non-myeloid solid or haematological malignancies (n=691) treated with epoetin beta 30,000 IU once weekly for 16 weeks (46). In this study, mean Hb levels were 10.1 g/dl at baseline and increased by a mean of 2.45 g/dl after 12 weeks of epoetin beta therapy.

Safety. Epoetin beta is generally well tolerated in patients with gynaecological cancers. Adverse events reported to be associated with epoetin beta therapy have included hypertension, headache and thromboembolic events (TEEs) (45). In patients with gynaecological tumours included in a phase III trial (n=122), nine patients experienced adverse events that were possibly related to epoetin therapy: malaise (two patients), dizziness, vomiting, splenomegaly, injection site pain, headache and flu-like symptoms (two patients) (34). In particular, studies to date have shown no evidence of a significant increase in the incidence of TEEs with epoetin beta compared with control therapy. For example, in the recent MARCH study in patients with advanced cervical cancer, epoetin beta was well tolerated and there was no increase in the incidence of TEEs compared with the control group (27). In a meta-analysis of nine randomised controlled studies of epoetin beta in patients with cancer, a higher frequency of TEEs was reported with epoetin beta compared with control therapy (6 versus 4% of patients); however, when the findings were adjusted for the longer observation time in the epoetin beta group (252 versus 181 patient years), the frequency of TEEs was slightly lower with epoetin beta (3.17 versus 3.36 TEEs per patient year) (47). Furthermore, a subsequent independent meta-analysis of randomised controlled trials with epoetin, involving more than 3000 patients with cancer, found no significant difference in the relative risk of TEE complications following epoetin treatment (relative risk versus control therapy 1.58; p=0.99; 95% CI 0.94, 2.66) (48). These findings are promising given the results from an earlier retrospective case-control study (n=147) showing an increased risk of symptomatic venous thrombosis (odds ratio 10.3) among patients with cervical carcinoma who received chemoradiotherapy and epoetin (49).

Although pain at the injection site has been reported with epoetin beta, the results of two studies to specifically investigate this issue suggest that subcutaneous injection of epoetin beta is significantly less painful than subcutaneous injection of either epoetin alfa or darbepoetin alfa (50, 51). Veyes and colleagues used a verbal pain scale (VPS) and visual analogue scale (VAS) to assess local pain resulting from subcutaneous injection of epoetin beta or alfa in patients on haemodialysis (VAS 6-point scale: 0, no pain; 5, severe pain; VAS 11-point scale: 0, no pain; 10, severe pain) (50). The median VPS score was significantly lower with epoetin beta versus epoetin alfa (phosphate buffered) (0 versus 1.5; p≤0.05), as was the VAS score (0.9 versus 2.7; p≤0.001). In a later crossover study conducted by Oudard et al. (51), median VAS and VPS scores indicated that healthy volunteers experienced less pain after injection with epoetin beta compared with darbepoetin alfa (VAS: 1.2 versus 2.9; p<0.05; VPS 1.5 [95% CI: 1.0-2.0] versus 2.5 [95% CI 2.0-2.5]) (51). In addition, significantly fewer patients in the epoetin beta group reported that the injections were moderately-to-very painful (5.4 versus 32.4%; p=0.0005).

Whether epoetins have an effect on the survival of patients with cancer has been the matter of some debate. Henke et al. (52) reported a reduction in locoregional progression-free survival among patients with head and neck cancer treated with epoetin beta; however, differences in prognostic values at baseline and various methodology issues severely limit the interpretation of these results (53, 54). Similarly, Leyland-Jones et al. (55, 56) reported a reduction in 12-month overall survival (p=0.01) with epoetin alfa compared with placebo in patients with metastatic breast cancer. Despite these two studies, there is evidence to suggest that epoetin has a neutral effect on overall survival in patients with gynaecological cancers. As already noted, studies conducted by Blohmer and Antonadou and
Table I. Current guideline recommendations for the initiation of epoetin therapy according to haemoglobin (Hb) level in patients with cancer.

<table>
<thead>
<tr>
<th>Year</th>
<th>Guideline group</th>
<th>Hb level for initiation of epoetin therapy (g/dl)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>European Organisation for Research and Treatment of Cancer</td>
<td>≤9-11</td>
<td>Bokemeyer et al., 2004 (38)</td>
</tr>
<tr>
<td>2003 (revised 2005)</td>
<td>Cancer Care Ontario (Ontario)</td>
<td>≤12 (symptomatic), ≤10 (asymptomatic)</td>
<td>Quirt et al., 2005 (62)</td>
</tr>
<tr>
<td>2002</td>
<td>American Society of Clinical Oncology (ASCO)/American Society of Hematology</td>
<td>≤10 or &lt;12 (in patients with declining Hb levels)</td>
<td>Rizzo et al., 2002 (63)</td>
</tr>
<tr>
<td>2002</td>
<td>Italian gynecological consensus statement</td>
<td>&lt;10.5</td>
<td>Pecorelli, 2002 (64)</td>
</tr>
<tr>
<td>1999</td>
<td>French Standards, Options and Recommendations Guidelines group</td>
<td>12-14</td>
<td>Marchal et al., 2004 (65)</td>
</tr>
</tbody>
</table>

colleagues suggest that epoetin therapy may actually have a beneficial effect on survival (26, 41). Furthermore, in a meta-analysis of pooled data from nine controlled epoetin beta studies, there was no negative association between the risk of mortality and epoetin beta therapy (43). In another more recent meta-analysis of 19 randomised controlled trials of epoetin in cancer patients (n=2805), the authors reported a possible improvement in overall survival with epoetin (adjusted hazard ratio 0.81; 95% CI 0.67-0.99) (48). An update of this analysis found conflicting evidence and concluded that patients should be treated within the target Hb range needed to manage anaemia (≤12 g/dl) (57).

Conclusion

Epoetin beta has proven efficacy and safety across a wide range of solid tumour types, including gynaecological cancers, and is effective at increasing Hb levels and reducing transfusion requirements in patients receiving both platinum-based and non-platinum-based chemotherapy or chemoradiotherapy. The findings of a meta-analysis conducted by Boogaerts and colleagues also suggest that type of chemotherapy (platinum-based or non-platinum based) does not impact on the response to epoetin beta in cancer patients with solid tumours (58). Because of the profound impact of anaemia on QoL, this profile suggests that the use of epoetin beta should be considered as part of the treatment regimen in patients with ovarian or cervical malignancies receiving radio- and/or chemotherapy, when anaemia is common.

There are now several guideline groups that advocate the use of epoetin in cancer treatment-related anaemia (Table I). All emphasise that careful clinical assessment is a key component of anaemia management. This is because epoetin is often prescribed at higher Hb levels in symptomatic patients compared with those who are asymptomatic. Many guidelines also advocate formal screening for other correctable causes of anaemia, such as active bleeding, haemolysis and iron and vitamin deficiency states.

Epoetin beta is well tolerated in patients with solid or haematological malignancies. Importantly, there is evidence that epoetin has a neutral effect on survival in patients with gynaecological tumours and that patients should be treated within the target Hb range needed to manage anaemia (≤12 g/dl) (48). Moreover, recent studies and the results of a meta-analysis suggest that epoetin beta does not increase the risk of TEE-related mortality. Based on these and other published findings, evidence-based guideline groups in Europe and the USA have consistently advocated the correction of anaemia with epoetin therapy during cancer treatment (38, 59-61). The evidence suggests that patients with gynaecological cancer may be a subgroup of cancer patients with the most potential to benefit from epoetin treatment if anaemia develops during cancer treatment.

References


Received October 3, 2006
Accepted November 7, 2006