rHuEPO and Treatment Outcomes: the Clinical Experience

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Key Words. Anemia · Cancer · Epoetin alfa · Hemoglobin · Outcomes · Quality of life · rHuEPO · Survival · Tumor hypoxia

ABSTRACT

Increasingly, anemia is being recognized as a negative prognostic and predictive factor for patients undergoing chemotherapy, radiation therapy, or a combination of these treatment modalities. The results of clinical studies have shown correlations between anemia and shorter survival times in patients with a wide variety of solid tumors and hematologic malignancies, including lung, ovarian, breast, and head/neck cancers, non-Hodgkin’s lymphoma, Hodgkin’s disease, Waldenström’s macroglobulinemia, and chronic lymphocytic leukemia. Also, anemia has been shown to predict treatment response in patients with ovarian, cervical, and urothelial cancers, mantle cell lymphoma, and chronic lymphocytic leukemia, as well as refractory/relapsed acute myelogenous leukemia. Based on the presumed causal relationship between anemia and poor patient outcome, several studies have examined the influence of epoetin alfa (a recombinant human erythropoietin) on outcomes in anemic patients undergoing cancer treatment. The results of these studies have been encouraging, with indications of greater locoregional tumor control and higher response rates in epoetin alfa-treated patients. Additionally, epoetin alfa therapy, by correcting anemia, has been shown to improve a patient’s energy level, ability to perform daily activities, and overall quality of life (QOL). Such effects not only enhance a patient’s general well-being, but may also increase their tolerance of, and willingness to undergo, full courses of their cancer therapy in a timely manner. These findings support the use of epoetin alfa to achieve gains in QOL and cancer treatment outcomes in anemic cancer patients and suggest that additional studies be conducted to further investigate the potential benefits of this agent in regard to improved outcomes. The Oncologist 2004;9(suppl 5):55-69

INTRODUCTION

Because of recent advances in treatment, more cancer patients are living longer. Thus, although the main goal of cancer treatment—disease cure—remains unchanged, greater attention is now being focused on treatment goals...
relevant to improved survivorship, including prolongation of life, symptom palliation, and improvement or preservation of quality of life (QOL) during and after cancer therapy.

Where cure is not achievable, the outcomes of cancer therapy are typically measured in terms of overall survival, disease-free survival, progression-free survival, response rate, and QOL. These outcomes are influenced by various baseline characteristics related to the patient (e.g., age, sex, performance score) and the malignancy (e.g., histologic subtype, disease stage), as well as by disease-targeted and supportive therapy. Often, it is possible to identify baseline characteristics as having prognostic or predictive significance. Prognostic factors are variables that independently influence outcome, whereas predictive factors are those that independently affect response to treatment. Because prognostic factors suggest the future course of the disease, they can be helpful in developing treatment strategies. Patients considered high risk on the basis of these factors may, thus, be targeted for more aggressive or experimental regimens, whereas lower-risk patients may be considered for less aggressive therapy, thereby avoiding severe or serious side effects.

One factor known to cause a wide range of symptoms and impairments in cancer patients is anemia, a complication of both the disease and its treatment. The symptoms of anemia, particularly fatigue, can adversely affect a patient’s QOL and may even diminish the patient’s tolerance of, and willingness to undergo, cancer treatment. However, emerging evidence over the past decade has suggested that anemia may additionally be related to poor clinical outcomes, including survival. Results of a meta-analysis performed by Caro et al. [1] indicated an overall estimated 65% greater relative risk of death in anemic cancer patients, compared with nonanemic patients. One possible explanation for this effect may be that anemia plays a role in the development of tumor hypoxia. Studies have shown that tumor hypoxia contributes to a number of processes that culminate in resistance to sparsely ionizing radiation and oxygen-dependent chemotherapeutic agents, and that improving the oxygenation of hypoxic tumor tissue may improve tumor responsiveness to these treatment modalities [2]. Because of the apparent interconnections among anemia, hypoxia, tumor responsiveness to therapy, and outcomes, clinical studies have been conducted to assess the importance of hemoglobin (Hb) level as a prognostic and predictive factor, as well as the impact of increasing Hb levels on patient outcomes. The findings of a representative group of these studies are summarized here. Collectively, the results of these studies suggest that Hb level may, in fact, influence outcome, which could have important implications for the development of management strategies for cancer patients.

**HEMOGLOBIN AS A PROGNOSTIC AND PREDICTIVE FACTOR IN CANCER**

The importance of Hb level as a prognostic and predictive factor for outcome has been examined both in patients with solid tumors and in those with hematologic malignancies. The findings of those studies are generally consistent across the two tumor classes, with nearly all univariate and multivariate analyses demonstrating a low Hb level to be a negative prognostic or predictive indicator of overall survival and other measures of outcome following cancer therapy. The results of many of these studies have been extensively reviewed by Harrison et al. [3] and, more recently, by Van Belle and Cocquyt [4].

In a series of 17 studies of solid tumors conducted between 1991 and 2003, a low Hb level was found to be prognostic for overall survival in patients with lung, ovarian, renal, pancreatic, and head/neck cancers, and predictive for treatment failure in patients with cervical cancer and for treatment response in patients with ovarian and urothelial cancer (Table 1). In another series, which comprised 10 studies of hematologic malignancies conducted between 1998 and 2000, low Hb level proved prognostic for overall survival in patients with non-Hodgkin’s lymphoma, follicular lymphoma, mantle cell lymphoma, Hodgkin’s disease, and chronic lymphocytic leukemia, and predictive for response in mantle cell lymphoma and chronic lymphocytic leukemia (Table 2). In the majority of these studies, the patients had been treated with chemotherapy, although chemoradiotherapy or radiation therapy had been administered in a small proportion of the studies. The Hb level associated with poor outcome varied among the studies, ranging from 10.5-12.0 g/dl.

Henke et al. [5] demonstrated that Hb level affects the prognosis of patients with early breast cancer treated with radiotherapy. Patients with early breast cancer (T1, 2 N0-2 M0 [TNM (tumor/node/metastasis) staging]) had breast-conserving surgery followed by adjuvant radiotherapy (n = 96) or a modified radical mastectomy (n = 194). No prognostic significance of Hb level was noted for patients treated with radical mastectomy; however, Hb level correlated significantly with disease-free survival in patients who were treated with breast-conserving surgery and adjuvant radiotherapy (relative risk: 0.67 per g/dl; p = 0.007). These results suggest that reduced radiosensitivity due to diminished tumor oxygenation in patients with lower Hb levels may be the underlying cause of the lower survival in those patients. Muenstedt [6] retrospectively examined the prognostic influence of Hb level prior to chemotherapy in 250 ovarian cancer patients treated between 1985 and 1998. All patients were scheduled to receive at least six courses of chemotherapy; none had been given recombinant human
erythropoietin (rHuEPO, epoetin alfa). Results of univariate Kaplan-Meier analyses identified Hb levels before and during chemotherapy as significant (range: \( p < 0.001 \) to \( p < 0.003 \)) prognostic factors for overall survival. Hb level also correlated with the scheduled completion of chemotherapy, overall therapeutic success, tumor stage, age at diagnosis, and residual tumor size (all \( p < 0.005 \)). These findings were considered by the investigator to support the use of rHuEPO and other measures (e.g., transfusion) to maintain adequate Hb levels and thereby potentially improve patient prognosis.

In another recent study, Sevelda et al. [7] evaluated the influence of anemia on local relapse-free survival in 424 premenopausal patients with Stage I or II primary breast cancer and hormone-responsive tumors who were undergoing adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy. The study was a prospective, randomized, phase III trial; however, the influence of anemia was determined by retrospective analysis of the prospectively collected data. Anemia developed in 77 of the 424 patients (18.2%) during CMF therapy. After a median follow-up period of 5 years, 8.9% of the patients without anemia had experienced a local relapse, compared with 19.6% of those with anemia (\( p = 0.0006 \), log-rank test). Multivariate analysis of established prognostic factors showed that only anemia, age, and axillary lymph node status were independent significant prognostic factors for local relapse-free survival.

A small study reported in early 2003 by Morganti et al. [8] evaluated the impact of pretreatment Hb level on outcome in patients with locally advanced pancreatic carcinoma...
treated with chemoradiation. Thirty patients undergoing con-
comitant chemoradiation and external beam radiotherapy
were divided into two groups based on the pretreatment
median Hb level (11.5 g/dl; range: 9.6-15.0 g/dl). The
median metastasis-free survival time was 5.1 months for
patients with pretreatment Hb levels ≤11.5 g/dl and was 10.7
months for patients with pretreatment Hb levels >11.5 g/dl
\( (p = 0.010) \). The median actuarial disease-free survival times
were 5.1 months and 10.2 months for patients with pretreat-
ment Hb levels ≤11.5 g/dl and >11.5 g/dl, respectively
\( (p = 0.026) \); median actual overall survival times were 7.5
months and 10.3 months for patients with pretreatment Hb
levels ≤11.5 g/dl and >11.5 g/dl, respectively \( (p = 0.039) \).
Multivariate analysis showed Hb concentration at diagnosis
to be the only factor positively correlated with metastasis-
free survival \( (p = 0.026) \), disease-free survival \( (p = 0.032) \),
and overall survival \( (p = 0.048) \).

Harrison et al. [3], in their 2002 publication, reviewed
the prognostic significance of pretreatment anemia in 12
studies of patients with cervical or head/neck cancer who
underwent radiation therapy between 1995 and 1999. As in
the previous series, the results were generally highly consist-
ent across the studies, with most univariate and multivariate
analyses demonstrating that low pretreatment Hb level is a
significant prognostic indicator of disease control and sur-
vival following curative-intent radiation therapy. The Hb
values associated with poor outcome in those studies
ranged from <14.5 g/dl for males and <13.0 g/dl for females
to <10.0 g/dl. Importantly, Harrison et al. noted findings
in about half the studies suggested that the Hb threshold in
the radiation oncology setting should be within the range of
12-14 g/dl. This recommendation is consistent with that of
Grogan et al. [9], who stressed the importance of correcting
anemia and maintaining Hb level above 12 g/dl to maximize
the efficacy of radiation therapy (see below). Additionally,
Harrison et al. indicated that low intratreatment Hb level,
although not as extensively studied as low pretreatment Hb
level, also appeared to adversely affect radiation therapy
outcomes in patients with cervical or head/neck cancer.

**INCREASED HB AND TREATMENT OUTCOME**

Based on the theorized causal relationship between ane-
mia/low Hb level and poorer outcome, several recent stud-
ies have evaluated the impact of increasing Hb level on
patient outcomes following radiation therapy, chemother-
apy, or radiochemotherapy. In those studies, Hb levels were
increased either by blood transfusion [9, 10] or by the
administration of epoetin alfa [11-15] or epoetin beta [16].

Grogan et al. demonstrated the importance of Hb level
and blood transfusion during radiation therapy with respect
to survival in patients with cervical cancer [9, 10]. In that
study, data on Hb levels, blood transfusions, and outcomes
were collected retrospectively for patients who received radi-
ation therapy during 1989, 1990, and 1992 in seven Canadian

<table>
<thead>
<tr>
<th>Table 2. Effect of low Hb level on outcomes of patients with hematologic tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
</tr>
<tr>
<td>Moullet et al. 1998 [60]</td>
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<tr>
<td>Federico et al. 2000 [61]</td>
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<tr>
<td>Callea et al. 1998 [62]</td>
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<tr>
<td>Samaha et al. 1998 [63]</td>
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<tr>
<td>Hasenclever et al. 1998 [64]</td>
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<tr>
<td>Landman-Parker et al. 2000 [65]</td>
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<tr>
<td>Liao et al. 1998 [66]</td>
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<tr>
<td>Keating et al. 2000 [67]</td>
</tr>
<tr>
<td>Kern et al. 2000 [68]</td>
</tr>
</tbody>
</table>

Abbreviations: multi = multivariate analysis; OS = overall survival; PFS = progression-free survival; Tx = treatment; uni = univariate analysis.
ences were also seen among these patient groups for rates of

Figures 1, the 5-year survival rate for patients who had low

patients with high baseline Hb levels that decreased during

patients with high baseline Hb levels that remained high

Patients with high baseline Hb levels that were corrected with blood trans-

Patients with high baseline Hb levels that dropped during therapy (H-L) had a similar

Patients with low baseline Hb levels that were corrected with blood trans-

Patients with low baseline Hb levels that remained high (H-H). Patients with high

Patients with low baseline Hb levels that remained low (L-L). The difference among groups was significant

Patients with low baseline Hb levels that decreased during

Patients with high baseline Hb levels that remained high (H-H) was 74%, with the worst survival rate shown for

Patients with high baseline Hb levels that decreased during treatment (H-L). The 5-year survival rate for

Overall survival favoring epoetin alfa over placebo (p = 0.13, log-rank test) (Fig. 2), and Cox regression analysis showed an estimated hazards ratio of 1.309 (p = 0.052) favoring epoetin alfa. The investigators concluded that although the study was neither designed nor powered for survival as an end point, the results suggested a possible survival benefit with epoetin alfa. However, they urged caution in interpreting this finding because of the statistical limitations regarding the survival analysis, as well as the fact that variables capable of influencing survival, such as disease stage, bone marrow involvement, and disease progression, were neither controlled for nor stratified in the study nor documented during the follow-up period.
Glaser et al. [12] retrospectively assessed the influence of Hb level and epoetin alfa administration on therapeutic response, locoregional tumor control, and overall survival in 191 patients who received neoadjuvant chemoradiotherapy and surgery for squamous cell carcinoma of the oral cavity and oropharynx. The patients were divided into four groups according to whether their pretreatment Hb levels were <14.5 g/dl or ≥14.5 g/dl and whether or not they had received epoetin alfa during their cancer treatment. Results of the multivariate analysis indicate that the use of epoetin alfa and pretreatment Hb level were independent prognostic factors for response to radiochemotherapy and locoregional tumor control ($p < 0.01$). Patients with pretreatment Hb levels ≥14.5 g/dl had significantly ($p \leq 0.001$ to $p < 0.05$) higher complete response, 2-year locoregional control, and 2-year survival rates than patients with Hb levels <14.5 g/dl who had not received epoetin alfa. Moreover, the response, locoregional control, and survival rates of epoetin alfa-treated patients with pretreatment Hb levels <14.5 g/dl were significantly ($p \leq 0.001$) higher than those of patients with pretreatment Hb levels <14.5 g/dl not given epoetin alfa and were equivalent to those of patients with pretreatment Hb levels ≥14.5 g/dl ($p \geq 0.30$) (Table 3; Fig. 3). These findings confirmed those of other studies suggesting that low Hb level is a negative prognostic factor for response to cancer therapy and demonstrated that the negative influence of low Hb level can be eliminated by epoetin alfa administration during neoadjuvant chemoradiotherapy.

Pangalis et al. [15] evaluated the efficacy of rHuEPO in ameliorating anemia in 25 patients with Rai Stage III B-chronic lymphocytic leukemia (B-CLL). Additionally, the investigators explored the possibility that correcting anemia in these patients could delay initiation of cytotoxic cancer therapy and eventually provide a survival benefit. In B-CLL patients, an Hb level <10 g/dl (National Cancer Institute criteria) is considered an indicator for initiation of chemotherapy. Thus, the investigators theorized that correcting the patients’ anemia might affect treatment decisions. Administration

Table 3. Complete response, 2-year actuarial locoregional tumor control, and 2-year actuarial overall survival rates by pretreatment Hb level and epoetin alfa therapy in head/neck cancer patients who received neoadjuvant chemotherapy and surgery

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group 1 Pre-Tx Hb ≥14.5 g/dl</th>
<th>Group 2 Pre-Tx Hb &lt;14.5 g/dl</th>
<th>Group 3 Pre-Tx Hb &lt;14.5 g/dl</th>
<th>Group 4 Pre-Tx Hb ≥14.5 g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>28/43 (65%)</td>
<td>15/87 (17%)</td>
<td>35/57 (61%)</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>2-year locoregional control</td>
<td>38/43 (88%)</td>
<td>63/87 (72%)</td>
<td>54/57 (95%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>2-year survival</td>
<td>35/43 (81%)</td>
<td>52/87 (60%)</td>
<td>50/57 (88%)</td>
<td>2/4 (50%)</td>
</tr>
</tbody>
</table>

Abbreviation: Tx = treatment.

*p ≤ 0.001 versus group 2.

*p ≤ 0.05 versus group 2 [12].
of rHuEPO resulted in a complete response (rise in hematocrit to level >38%) in 18 of the 25 patients and a partial response (rise in hematocrit of >6% from pretreatment to a level <38%) in two patients (Fig. 4). After 3 months of rHuEPO therapy, it was possible to downstage the disease in 19 patients, and treatment with chemotherapy was avoided or postponed in the majority of them. An effect on survival was not determined, as the median survival had not been reached at the time of study report. The investigators noted that further clinical trials were needed to determine whether rHuEPO therapy had induced a true biologic effect on the disease and whether any induced effect would translate into a survival benefit.

Antonadou et al. [11], at the meeting of the European Cancer Conference in 2001, reported the results of a randomized, phase III study that evaluated the efficacy and safety of rHuEPO in 385 patients with pelvic malignancies who were undergoing radiation therapy with or without rHuEPO. Efficacy end points included weekly increase in Hb level during radiation therapy, local tumor control, disease-free survival, and overall survival. The mean weekly increases in Hb level were 0.54 g/dl in patients treated with rHuEPO and 0.17 g/dl in those not treated with rHuEPO (control group) (Table 4). Patients in the rHuEPO-treated group, compared with the control group, had a significantly higher rate of 4-year disease-free survival (85.3% versus 67.2%; \( p = 0.0008 \)). No information was provided on overall survival. The remaining study, discussed by Blohmer et al. [14] at the 2002 meeting of the American Society of Clinical Oncology, was a prospective, randomized, open-label, multicenter trial that investigated transfusion frequency, QOL, toxicity, disease-free survival, and overall survival in 256 high-risk cervical cancer patients receiving ifosfamide (Ifex®; Bristol-Myers Squibb; Princeton, NJ), carboplatin (Paraplatin®; Bristol-Myers Squibb), and radiation therapy with or without epoetin alfa. As in numerous other studies, the number of transfusions was significantly lower in epoetin alfa-treated patients than in control patients (\( p = 0.02 \)). Also, epoetin alfa support during radiochemotherapy was associated with a significantly lower rate of recurrence (11% versus 22%; \( p = 0.04 \)) (Table 5) and an apparent increase in relapse-free survival time.

Since the conference, new studies have continued to add to our knowledge of epoetin, especially its effect on survival. Those studies are discussed separately as postmeeting notes at the end of this report.

### Table 4. Impact of epoetin alfa therapy on Hb level and survival in patients with pelvic malignancies receiving radiotherapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Radiation therapy + epoetin alfa</th>
<th>Radiation therapy – epoetin alfa (control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraradiation Hb (g/dl)</td>
<td>12.9 ± 2.6</td>
<td>10.6 ± 2.5</td>
</tr>
<tr>
<td>Weekly Hb increase (g/dl)</td>
<td>0.54</td>
<td>0.17</td>
</tr>
<tr>
<td>4-year disease-free survival</td>
<td>85.3%*</td>
<td>67.2%</td>
</tr>
</tbody>
</table>

Abbreviation: Hb = hemoglobin.

*\( p = 0.0008 \) versus control [11].
INCREASED HB LEVEL AND QOL

With the higher cure rates and longer durations of survival now being achieved in cancer patients, maintenance or improvement in patients’ QOL is increasingly being perceived as an important and worthwhile goal of cancer management. A growing body of evidence suggests that anemia is strongly related, possibly in a causative manner, to diminished QOL in cancer patients. The symptoms of anemia, such as dyspnea, weakness, tachycardia, impaired cognitive function, depression, and most especially fatigue, can lead to a substantial reduction in functional ability and a decline in general health, thereby contributing to the patient’s feelings of diminished QOL. Recent studies have demonstrated that even mild and moderate anemia (generally characterized as Hb levels of 10-12 g/dl and 8-10 g/dl, respectively) are associated with fatigue and diminished QOL [18-22]. These findings were highlighted by Cleeland et al. [21, 22], who demonstrated a direct relationship between epoetin alfa-induced Hb increases and improvements in QOL in anemic cancer patients. Analyses of data from two open-label, community-based studies of epoetin alfa [23, 24] (see below) that enrolled 4,712 anemic cancer patients showed that the greatest improvement in the patients’ QOL occurred when the Hb level was increased from 11 g/dl to 12 g/dl (range: 11-13 g/dl) [21, 22]. However, given the concerns raised by the prospective randomized trial, this therapeutic approach cannot be considered outside an appropriate clinical trial.

Epoetin alfa has been shown in both double-blind, placebo-controlled and open-label, single-arm studies to increase Hb levels and thereby produce significant improvements in QOL [13, 23-27]. In 1990, the potential advantage of epoetin alfa with respect to QOL was suggested by the findings of Ludwig et al. [25], who administered epoetin alfa to a small group of patients with multiple-myeloma-associated anemia. Not only were the clinical symptoms of anemia ameliorated in those patients who responded to epoetin alfa, but most reported a heightened sense of well-being as well as an increased tolerance of physical exertion, which was reflected by a marked change in performance status as assessed by World Health Organization criteria. A subsequent series of three placebo-controlled studies demonstrated a relationship between epoetin alfa-induced hematopoietic improvement and improvement in QOL as measured using the Linear Analog Scale Assessment (LASA, also referred to as the Cancer Linear Analog Scale or CLAS) [26]. The LASA, which measures the QOL parameters of Energy Level, Ability to Do Daily Activities, and Overall QOL, is a validated, cancer-specific instrument now commonly used to assess therapy-related QOL changes in anemic cancer patients. The populations of anemic cancer patients in the respective studies were: patients not receiving chemotherapy or radiation therapy; patients receiving non-cisplatin-containing chemotherapy; and patients receiving chemotherapy containing cisplatin (Platinol®; Bristol-Myers Squibb). In the study with patients who did not receive cancer therapy, hematocrit level increased by 2.8% from baseline to last value in epoetin alfa-treated patients but decreased by 0.1% in placebo-treated patients. In the non-cisplatin study, hematocrit increased by 6.9% in epoetin alfa-treated patients and by 1.2% in placebo-treated patients. The respective values in the cisplatin study were 6.0% and 1.3% (p < 0.004 for each study). Moreover, the QOL parameters Energy Level, Ability to Do Daily Activities, and Overall QOL were improved to a significantly greater extent in patients responding to epoetin alfa than in patients given placebo (p < 0.05 for each parameter).

The impact of increasing Hb level on QOL was demonstrated in three large, community-based, nonrandomized, open-label studies. A collective total of 7,724 patients were enrolled, 7,283 of whom were assessable. In those studies, epoetin alfa was administered to anemic patients with non-myeloid malignancies undergoing standard chemotherapy. Two of the studies, one conducted by Glaspy et al. [23] and the other by Demetri et al. [24], used three-times weekly dosing, whereas the third study, conducted by Gabrilove et al. [27], used once weekly dosing. QOL measures included the LASA [23, 24, 27], the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale [24], and the FACT-An Anemia subscale [24, 27]. Results of the QOL analyses as assessed by the LASA are summarized in Table 6 [23, 24, 27, 28]. As shown, the scores for the Energy Level, Ability to Do Daily Activities, and Overall QOL items were significantly (p < 0.001) improved from baseline in each study. Importantly, significant (p < 0.001) increases in Hb levels were also observed in all studies. Multivariate linear

<table>
<thead>
<tr>
<th>Status</th>
<th>Radiochemotherapy + epoetin alfa (n = 79)</th>
<th>Radiochemotherapy (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>9 (11%)</td>
<td>18 (23%)</td>
</tr>
<tr>
<td>No recurrence</td>
<td>70 (89%)</td>
<td>62 (78%)</td>
</tr>
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</table>

*p = 0.04, log-rank test [14].
regression analysis of the data for the Demetri et al. study indicated that both an Hb level increase and tumor response independently predicted QOL improvement. In all three studies, an increase in Hb level was found to correlate significantly with an improvement in QOL (Gabrilove et al.: \( r = 0.27; p < 0.001 \); Demetri et al.: \( r = 0.235; p < 0.001 \); Hudis, Van Belle, Chang et al.: \( r = 0.173; p < 0.001 \)). In the Demetri et al. study, assessments of changes in the FACT-An scale and the FACT-An Anemia subscale scores also showed significant (\( p < 0.001 \)) improvements from baseline, with patients who achieved mean increases in Hb level \( \geq 2 \text{ g/dl} \) having the greatest increase in QOL as measured by these scales. Similarly, an assessment of changes in the FACT-An Anemia subscale score in the Gabrilove et al. study demonstrated a significant (\( p < 0.001 \)) improvement from baseline. As in the Demetri et al. study, patients with Hb level increases \( \geq 2 \text{ g/dl} \) had the greatest improvements in QOL.

In a separate analysis, the impact of epoetin alfa therapy on QOL was retrospectively assessed in a subgroup of 1,500 breast cancer patients who had participated in the three community-based studies [29]. The effects of epoetin alfa in that subgroup were of considerable interest, as anemia occurs commonly in breast cancer patients and can cause a variety of symptoms, particularly fatigue, that compromise patients’ QOL. Surveys conducted by the Fatigue Coalition found that 76% of cancer patients receiving chemotherapy with or without radiation experienced fatigue at least monthly, and that more than 90% of the patients who experienced fatigue felt that it prevented them from leading a normal life [30, 31].

Results of the subgroup analysis demonstrated that epoetin alfa effectively corrected anemia and significantly (range: \( p = 0.0001 \) to \( p < 0.001 \)) improved scores for all three LASA items evaluated. For Overall QOL, the change in score from baseline represented an increase of about 25% in each of the three studies. Importantly, findings in the breast cancer subgroup mirrored those for the full study population [23, 24, 27] and demonstrated the effectiveness of epoetin alfa in that subgroup, irrespective of the dosing regimen used, that is, once weekly or three-times weekly.

The findings of the three community-based studies were consistent with those of the Littlewood et al. [13] multinational, double-blind, placebo-controlled study of epoetin alfa mentioned earlier. In the Littlewood et al. study, QOL was assessed by means of the LASA, FACT-General (G) Total scale, FACT-An Fatigue subscale, and Medical Outcomes Study Short Form-36 (SF-36) Physical Component Summary and Mental Component Summary (primary measures), as well as by the FACT-An Anemia subscale (a secondary measure). The FACT-G Total scale, the FACT-An Fatigue subscale, and the three LASA scales are cancer-specific tools and have demonstrated sensitivities to Hb level; thus, these scales and subscales were designated as primary measures of the QOL effects of epoetin alfa. The two SF-36 scales, although also designated as primary measures, are not cancer specific, and were included as generic QOL instruments. Results of univariate analyses demonstrated significant differences favoring epoetin alfa over placebo for all five cancer-specific primary QOL scales (range: \( p = 0.0007 \) to \( p = 0.0048 \)) and for the FACT-An Anemia subscale (\( p = 0.0007 \)) (Fig. 5 and Fig. 6).

Epoetin alfa was also favored over placebo for the SF-36 items, although the differences did not reach statistical significance. Consistent with the community-based studies, examination of the relationship between change in Hb level and change in QOL by correlation analysis revealed a strong and statistically significant (range: \( p = 0.0002 \) to \( p = 0.0325 \)) correlation between these changes for all seven primary variables evaluated. Similarly, additional examination of the QOL data by multiple linear regression analysis, which controlled for disease progression and other possibly confounding variables, showed a significant advantage for epoetin alfa for the five primary cancer-specific QOL scales (range: \( p < 0.01 \) to \( p < 0.04 \)), but not for the SF-36 scales (Fig. 5 and Fig. 6) [32]. Additionally, for the cancer-specific scales, significant correlations were demonstrated between baseline Hb level and QOL (\( r \) range: 0.14-0.26; all \( p < 0.05 \)) and between change in Hb level and change in QOL (\( r \) range: 0.26-0.34; all \( p < 0.01 \)). Overall, the results

### Table 6. QOL outcomes in community-based studies of epoetin alfa

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>( n = 1,498 )</td>
<td>( n = 1,759 )</td>
<td>( n = 2,258 )</td>
</tr>
<tr>
<td>Energy level</td>
<td>15.0* (38%)</td>
<td>11.5* (29%)</td>
<td>11.9* (30%)</td>
</tr>
<tr>
<td>Ability to do daily activities</td>
<td>13.9* (32%)</td>
<td>11.2* (28%)</td>
<td>10.8* (27%)</td>
</tr>
<tr>
<td>Overall QOL</td>
<td>11.0* (24%)</td>
<td>9.8* (21%)</td>
<td>9.3* (20%)</td>
</tr>
</tbody>
</table>

*Abbreviation: QOL = quality of life.

\( p < 0.001 \) versus baseline [23, 24, 27, 28].

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Garson G et al. 1997 [23]; Demetri et al. 1998 [24]; Gabrilove et al. [27].
of these analyses provided convincing evidence that increasing the Hb level by administering epoetin alfa can significantly improve patient QOL.

Shasha et al. [33] extended the QOL findings to include epoetin alfa-treated patients undergoing radiation therapy. Those investigators performed an incremental (marginal) analysis that examined the relationship between Hb level and QOL and sought to identify the change in Hb level associated with the greatest change in QOL. The analysis was based on data obtained from a prospective, community-based study of once weekly epoetin alfa in 442 eligible anemic (Hb level ≤11 g/dl) patients with solid tumors who received curative-intent concurrent or sequential chemoradiotherapy [34]. Preliminary analysis, based on 376 patients, showed a significant increase in the mean Hb level (from 9.9 g/dl at baseline to 11.7 g/dl; \( p < 0.05 \)), as well as significant (\( p < 0.05 \)) increases in LASA Energy Level, Ability to Do Daily Activities, and Overall QOL scores. The marginal analysis showed a significant correlation between a higher Hb level and higher energy, activity, and overall QOL scores (coefficients: 0.33, 0.32, and 0.29, respectively; \( p < 0.05 \) for each value).

As in the earlier studies by Cleeland et al. [21, 22], greater increases in LASA scores were found to occur when the Hb level increased from 11 g/dl to 12 g/dl. These findings provided evidence of the importance of early (i.e., Hb ≤12 g/dl) and aggressive treatment of anemia in patients undergoing chemoradiotherapy, with the goal of improving posttreatment outcomes and patient well-being.

Two additional studies, reported in 2003, have examined the clinical relevance of the observed effects of epoetin alfa on QOL. Experience with scales and other measures of QOL remains limited. Thus, the conduct of these studies was motivated largely by the perceived need to aid clinicians in...
interpreting the numerical changes in QOL parameters reported in clinical trials and thereby help them better manage anemia and its sequelae in patients undergoing chemotherapy.

In the first of these studies, Patrick et al. [36] derived population normative data to aid clinicians in interpreting clinical trial results based on the FACT-An questionnaire. Those investigators conducted an internet survey using the FACT-An tool to measure QOL in randomly selected individuals (n = 1,400) who represented a demographically balanced sample of the U.S. population. Comparison of the normative data from that survey with the data obtained in the Littlewood et al. [13] study showed that the differences in QOL scores between the epoetin alfa- and placebo-treated patients. Differences between the treatment groups equal to or greater than the MID were considered clinically meaningful. As shown in Table 7, large, positive MIDs were found for all QOL scales, indicating that the differences in QOL scores between the epoetin alfa and placebo groups were clinically important.

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**Further Profiling of Epoetin Alfa and Hb Levels**

In addition to its impact on patient outcomes and QOL, other aspects of epoetin alfa therapy, such as dosage refinements aimed at improving therapeutic response, use in specific diagnostic categories of cancer, and outcomes unrelated to the hematopoietic effects of this agent are currently under evaluation. Hudis et al. [38], in a prospective pilot study, evaluated the efficacy of epoetin alfa at a dose of 60,000 IU once weekly followed by a maintenance dose of 120,000 IU every 3 weeks. Study participants were 20 anemic cancer patients with nonmyeloid malignancies who were undergoing chemotherapy. The initial dose (60,000 IU once weekly) was administered for 8 weeks. If, after week 8, Hb level increases by ≥2 g/dl above baseline, epoetin alfa maintenance therapy was administered for up to 24 weeks. The dosage was decreased by 20,000 IU if the Hb level increased to >15 g/dl or rose by >1.3 g/dl during any 2-week interval. Results of an interim analysis (mean treatment duration: 19.5 weeks) showed mean Hb changes from baseline of 1.0 g/dl by week 4, 2.7 g/dl by week 8, and 2.9 g/dl by the last measurement. In all, 13 patients received maintenance therapy. Thus, an

<table>
<thead>
<tr>
<th>QOL Scale</th>
<th>Stable</th>
<th>Improved</th>
<th>MID</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-G Total</td>
<td>-0.15</td>
<td>2.39</td>
<td>2.54</td>
</tr>
<tr>
<td>FACT-An Fatigue subscale</td>
<td>-0.69</td>
<td>3.55</td>
<td>4.24</td>
</tr>
<tr>
<td>LASA: Energy Level</td>
<td>-0.96</td>
<td>8.65</td>
<td>9.61</td>
</tr>
<tr>
<td>LASA: Daily Activities</td>
<td>-0.45</td>
<td>8.29</td>
<td>8.74</td>
</tr>
<tr>
<td>LASA: Overall QOL</td>
<td>-3.37</td>
<td>6.44</td>
<td>9.81</td>
</tr>
</tbody>
</table>

Abbreviations: FACT-An = functional assessment of cancer therapy-anemia; FACT-G = functional assessment of cancer therapy-general; Hb = hemoglobin; LASA = linear analog scale assessment; MID = minimally important difference; QOL = quality of life [33].
epoetin alfa starting dose of 60,000 IU once weekly was effective at inducing an Hb increase of ≥2 g/dl between week 4 and week 8 of treatment, and this increase was maintained for the duration of the study, either with continued once weekly administration of 60,000 IU or administration of a three-times weekly maintenance dose of 120,000 IU.

In another dosing study, McKenzie et al. [40] retrospectively investigated the efficacy of epoetin alfa at increasing Hb levels when administered less than once weekly in a community-based setting. The study included 1,238 patients with a variety of malignancies, the most prevalent of which were breast cancer (22.1%) and lung cancer (18.7%). Response to epoetin alfa was defined as an Hb change from baseline of ≥1 g/dl without transfusion at week 4 or either an Hb change from baseline of ≥2 g/dl or an Hb level of ≥12 g/dl at weeks 8, 12, or 16 from the start of epoetin alfa therapy without transfusion within the previous 30 days. Among patients who received a starting dose of 40,000 IU, a mean dose of approximately 40,000 IU was administered in 95% or more of the subsequent visits, either once weekly (50.3% of patients), biweekly (32.4% of patients), or once every 3 weeks or more (17.3% of patients). Univariate analysis showed no significant differences in response rates among the three dosing groups at either week 4 or week 16. These findings suggest that, for selected patients, administration of epoetin alfa less frequently than once weekly (e.g., 40,000 IU biweekly or less often) is as effective as once weekly dosing at improving Hb levels. The investigators concluded that these findings supported the conduct of multivariate research to further examine the effect of extended epoetin alfa dosing schedules on Hb response and additional clinical trials to determine the effect of such schedules on patient outcomes.

Cancer patients, particularly those with breast cancer, often experience impaired cognition related to their chemotherapy, and this adverse effect may last for years after the end of therapy, impairing both the patient’s functional capacity and QOL. Studies by Brines et al. [41] and Cerami et al. [42] have demonstrated that epoetin alfa crosses the blood-brain barrier and exerts a neuroprotective effect on the central nervous system. This was evidenced by their findings in animal models that this agent reduced neural injury from ischemic stroke and blunt-force trauma, reduced the severity of experimental encephalomyelitis, and ameliorated the latency, severity, and mortality of kainate-induced seizures [41, 42]. These, and other encouraging findings [43], have led to trials of epoetin alfa aimed at improving cognitive function in patients undergoing chemotherapy. Data were presented by O’Shaughnessy et al. [44] at the 2002 San Antonio Breast Cancer Symposium (San Antonio, TX) suggesting that administration of epoetin alfa may have beneficial effects on cognitive function and QOL during and after chemotherapy. A larger, controlled trial to explore the potential benefits of epoetin alfa on cognitive function in chemotherapy patients has been initiated and is currently enrolling patients.

**POSTMEETING NOTES**

Recent studies have evaluated patient outcomes when patients are treated to higher target Hb levels. It has been hypothesized that any beneficial effects of anemia treatment might be magnified with treatment to higher Hb levels. Three recent reports of double-blind trials were not available at the time of the workshop and are presented here for completeness. Two reports suggest an adverse impact on patient survival with rHuEPO when patients are treated to higher Hb levels, while the third reconfirms the good safety profile with no adverse impact on survival when epoetin alfa is used as indicated.

A randomized, multicenter, double-blind, placebo-controlled trial of epoetin alfa as an adjunct to chemotherapy in metastatic breast cancer patients without anemia was conducted in Europe, Canada, South Africa, and Australia to evaluate the effects of epoetin alfa on survival and was terminated early because of the observed higher mortality in the treatment group [45]. In that trial, patients with metastatic breast cancer, initially normal Hb levels (>13 g/dl), and receiving first-line chemotherapy were treated for up to 12 months with epoetin alfa to maintain their Hb levels in the normal range (>12 g/dl to <14 g/dl). The data showed a 12-month survival rate of 76% in the placebo group, versus 70% in the epoetin alfa group (p = 0.017) [45]. This difference was due primarily to a high mortality rate in the epoetin alfa group in the first 4 months of the study; subsequent follow-up beyond the treatment period showed convergence of the survival curves at 19 months.

The early deaths were primarily due to higher incidences of disease progression and thrombotic vascular events in the epoetin alfa group than in the placebo group. Since these results are in contrast to the numerous other studies in anemic cancer patients suggesting a survival benefit with epoetin alfa, extensive efforts were made to explain the unexpected findings, although no definitive conclusions could be made. Perhaps most importantly, the study was not designed to take into account an imbalance in risk factors between treatment groups other than the presence of metastases beyond bone involvement. A retrospective chart review of available data by independent investigators suggested that patients randomized to epoetin alfa were more likely to have adverse factors, such as advanced age, lower performance status, and greater extent of disease at study entry, and more risk factors for thrombotic vascular events [45]. Further, the study design did not assess or document important prognostic factors for...
survival, including definition of disease site, initial prognosis and specific assessment of tumor response at predefined intervals, and the type, duration, and dose of chemotherapy. Since the study was not adequately designed to account for these confounding variables, one cannot draw any definitive conclusions other than to use epoetin alfa only as it is indicated, that is, in cancer patients who become anemic during chemotherapy treatment.

In the second study, 351 anemic (Hb <12.0 g/dl, women; Hb <13.0 g/dl, men) patients receiving radiotherapy for treatment of head and neck cancer were randomized to receive epoetin beta at doses of 300 IU/kg three times weekly (n = 180) or placebo (n = 171) [16]. Patients were treated to achieve Hb levels higher than 14.0 g/dl in women and 15.0 g/dl in men. The primary end point was locoregional progression-free survival, which was found to be poorer in patients who received epoetin beta than in those who received placebo (adjusted relative risk: 1.62; 95% confidence interval: 1.22-2.14; p = 0.0008).

A very recently reported study demonstrated no adverse survival impact in women with high-risk breast cancer who received high-dose chemotherapy with or without epoetin alfa and in women who received conventional dose chemotherapy [46]. In that multicenter study (n = 1,284), women were randomized to receive a high-dose chemotherapy regimen of three cycles each of epirubicin (Ellence®; Pharmacia and Upjohn; Portage, MI; 150 mg/m²), paclitaxel (Taxol®; Bristol-Myers Squibb; 225 mg/m²), and cyclophosphamide (2,500 mg/m²) at 2-week intervals with G-CSF support (5 µg/kg/s.c. days 3-10) and further randomized to receive either epoetin alfa (150 IU/kg/s.c. three-times weekly) or no epoetin alfa. The comparison arm was conventional chemotherapy of four cycles of epirubicin/cyclophosphamide (90/600 mg/m²) followed by four cycles of paclitaxel (175 mg/m²) at 3-week intervals. Disease-free survival was significantly (p = 0.046) longer in patients who received the dose-dense chemotherapy regimen. Importantly, there was no difference in relapse-free survival between patients who received high-dose chemotherapy with epoetin alfa and those who received this treatment without epoetin alfa. The results of these trials are important in expanding our knowledge on the effects of rHuEPO and underscore the importance of continued study.

SUMMARY

The past decade has been characterized by a growing awareness of the role of anemia with respect to impairment of cancer patients’ physical well-being and QOL. However, appreciation of the significance of anemia in the oncology setting has recently been expanded by the results of clinical studies suggesting that anemia is also an important negative prognostic and predictive factor for several measures of patient outcome, including survival, in patients with a variety of solid tumors and hematologic malignancies. The results of other clinical studies have suggested that maintaining Hb levels in anemic cancer patients by means of epoetin alfa therapy may improve treatment outcomes, including overall survival, disease-free survival, and locoregional control, and additionally may improve patients’ QOL. These results must be tempered by the data from two randomized trials suggesting that maintaining normal Hb levels with erythropoietin during therapy could be associated with worse outcomes. Data from several studies have also shown that dosing schedules of epoetin alfa may be adjusted to maximize patient convenience. Clearly, addressing the problem of anemia is vital to the successful management of cancer patients with this complication, and additional rigorously designed and adequately powered trials are needed to determine the full potential of epoetin alfa with respect to improving survival and other treatment outcomes in anemic cancer patients.

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