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Guidelines and Recommendations for the Management of Anaemia in Patients with Lymphoid Malignancies

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Abstract

Patients with lymphoid malignancies frequently require repetitive and intensive anticancer treatments to induce and maintain disease remission. Anaemia (haemoglobin [Hb] <12 g/dL) is a common and debilitating problem associated with both the malignancy itself and its treatment burden. Anaemia negatively impacts on all aspects of patient quality of life (QOL) and treatment outcomes and survival, particularly in this disease setting.

Widely acknowledged goals of anaemia treatment include Hb correction to ~12 g/dL, reduction in transfusion requirements and optimisation of patient QOL. Since the introduction of recombinant human erythropoietic therapy, transfusion (once the only anaemia treatment option available) is now primarily reserved for non-responders or those with severe or life-threatening anaemia. Data from randomised, double-blind, placebo-controlled studies, and large, non-randomised, open-label, community-based studies, along with almost 15 years of practical experience, support the assertion that epoetin alfa administered at a dosage of 150–300 U/kg three times weekly or 40 000–60 000U once weekly, both of which

are US FDA-approved dose administration schedules, can effectively and safely achieve anaemia treatment goals for the majority of patients with lymphoid malignancies. Data and practical experience collected over the last 5 years on another erythropoietic agent with a slightly longer half-life but lower binding affinity, darbepoetin alfa, show that this agent when administered according to the FDA-approved dose administration schedules (2.25–4.5 μg/kg once weekly or 500μg once every 3 weeks) or according to a commonly-administered dose in clinical practice (3.0–5.0 μg/kg once every 2 weeks) can also effectively and safely correct anaemia, reduce transfusion requirements and improve QOL in many patients with lymphoid malignancies. One comparative head-to-head trial suggested that epoetin alfa might be superior to darbepoetin alfa in anaemic cancer patients receiving chemotherapy with respect to timing and magnitude of Hb correction, although further study is necessary, especially concerning optimal dose administration. Alternative dose administration schedules, such as epoetin alfa 80 000U every 2 weeks from initiation or 80 000U every 3 weeks following initiation with once weekly administration and darbepoetin alfa 4.5 μg/kg every 3 weeks following initiation with once weekly administration, are being actively investigated with the goal of increased flexibility for patients and healthcare providers.

The treatment of anaemia in patients with lymphoid malignancies is an important part of overall disease management, as evidenced by continuous investigation of existing erythropoietic agents and new agents. Although treatment guidelines issued by organisations such as the National Comprehensive Cancer Network (NCCN) and American Society of Hematology (ASH)/American Society of Clinical Oncology (ASCO) suggest intervention with erythropoietic therapy when Hb falls below 10–11 g/dL or based on clinical symptoms, data suggest that anaemia is vastly under-recognised and under-treated. Clearly, an update on the definition, identification and optimal management of anaemia in patients with lymphoid malignancies is warranted.

The lymphoproliferative cancers represent a heterogeneous group of malignancies with differing patterns of behaviour and response to treatment.[1,2] As a result of recent advances in combination chemotherapy treatment approaches, the majority of patients diagnosed with Hodgkin's disease can be treated with curative intent and survival rates have increased dramatically in this disease setting.[2] In contrast, although patients with indolent non-Hodgkin's lymphoma (NHL) have a relatively good prognosis, with median survival as long as 10 years, the disease is usually not curable in advanced clinical stages and survival rates have not improved over the last several decades.[1-3] The aggressive type of NHL has a shorter natural history but a significant number of patients can be cured.[1,2,4]

Lymphoid malignancies are a leading cause of new cancer cases and of cancer deaths.[5] It is estimated that lymphoid malignancies account for 4.6% of cancers (Hodgkin's disease, n = 7350; NHL, n = 56 390) diagnosed in the US and 3.6% (n = 20 610) of cancer deaths.[5] Ten-year survival rates for Hodgkin's disease and NHL are 77% and 42%, respectively.[5] Because of the prolonged disease course associated with many types of lymphoid malignancies, most patients can be expected to undergo several courses of intensive anticancer treatments that can include radiation, cytostatic drug combinations, high-dose chemotherapy with bone marrow or

stem cell support, or monoclonal antibody therapy to induce and maintain clinical and/or molecular remission.[1,3,4,6,7] While indolent NHL is responsive to radiation therapy and chemotherapy, a continuous rate of relapse is usually seen in advanced stages.[1,2] However, patients can often be re-treated with considerable success as long as the disease histology remains low grade.[1,2] Patients who present with or convert to aggressive forms of NHL may have sustained complete remissions with combination chemotherapy regimens or aggressive consolidation with marrow or stem cell support.[1,2]

The treatment burden for patients with lymphoid malignancies is associated with substantial disruption in well-being and quality of life (QOL).[6] One of the most common and debilitating adverse effects associated with lymphoid malignancies and their treatment is anaemia.[6] Anaemia is thought to be a major contributor to the development of fatigue, which negatively impacts on QOL, and to poor treatment outcomes and reduced survival in patients with lymphoid malignancies.[6,8-10] The purpose of this paper is to develop a greater understanding of the scope of anaemia in patients with lymphoid malignancies, and to review evidence and guidelines which provide recommendations for how this troublesome adverse effect can be managed optimally by clinicians.

1. Anaemia in Patients with Lymphoid Malignancies

The National Cancer Institute toxicity criteria classify severity of anaemia by grade based on haemoglobin (Hb) level. Grade 1 (mild) anaemia is defined as Hb of 10.0 g/dL to lower limit of normal (normal range: 12.0–16.0 g/dL for women and 14.0–18.0 g/dL for men); Grade 2 (moderate) anaemia as Hb of 8.0–9.9 g/dL; Grade 3 (severe) anaemia as Hb of 6.5–7.9 g/dL; and Grade 4 (life-threatening) anaemia as Hb <6.5 g/dL.[11] The major National Cancer Institute cooperative groups in the US classify anaemia identically and the WHO defines only mild or grade 1 anaemia differently (Hb <11.0 g/dL).[12] Many retrospective and prospective studies evaluating cancer patients have universally defined being anaemic as having Hb <12 g/dL.[13-15] Notably, high rates of anaemia have been reported in patients with lymphoid malignancies included in these surveys. For example, a large prospective European survey (European Cancer Anaemia Survey) reported that 73% of the over 2000 patients with lymphoma or myeloma who participated in the survey experienced anaemia (Hb <12 g/dL) at some time during the 6-month survey period, irrespective of treatment or disease status.[14] More recently, a prospective chart survey of 273 patients undergoing four cycles of non-platinum chemotherapy conducted in 35 Austrian oncology centres demonstrated anaemia (Hb <12 g/dL) rates of 35% and 22% at baseline and 74% and 55% after cycle 4 of chemotherapy in patients with NHL and Hodgkin's disease, respectively.[15] Other data suggest that pre-treatment anaemia rates are much higher (42–82%) in patients with lymphoid malignancies.[13,16,17] In one of these reports, which included 100 patients with malignant lymphoma, 82% of patients had anaemia at presentation, with 88% of NHL patients experiencing anaemia during cyclophosphamide, epirubicin, vincristine and prednisone (CEOP) chemotherapy and 75% of Hodgkin's patients experiencing anaemia during doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy.[13] With respect to anaemia severity, chemotherapy-induced grade 1–2 and grade 3–4 anaemia rates were 55–63% and 9–79%, respectively, in patients with NHL and from 5–31% and 0–13%, respectively, in patients with Hodgkin's disease, depending on regimen.[12] In addition, data from a retrospective survey suggested that, at the start of cycle 4 of nonplatinum chemotherapy, moderate anaemia (Hb 8.0 to ≤10.5 g/dL) occurred in 35% of patients with NHL and 26% of patients with Hodgkin's disease.[16]

The aetiology of anaemia in patients with lymphoid malignancies is multifactorial and includes neoplastic cell infiltration of the bone marrow, haemolysis, nutritional deficiencies and, most notably, treatment-induced bone marrow suppression.[18] In fact, many of the standard chemotherapy combinations used in treating advanced Hodgkin's disease

and NHL are associated with anaemia.[12] The degree of anaemia can also be related to the severity of the disease itself as evidenced by high pretreatment anaemia rates.[15,17] This type of anaemia is associated with blunted erythropoietin production in response to hypoxia, impaired bone marrow response to erythropoietin and defective iron reutilisation, consequent to the effects of inflammatory cytokines.[18]

Anaemia negatively affects nearly every body system, with associated symptoms including fatigue, exhaustion, dizziness, headache, dyspnoea, palpitations, depression and decreased motivation.[19] As a result, patients with anaemia experience impairments in all aspects of QOL.[18] In fact, in a survey of 300 haematologists and a similar number of patients, fatigue was reported as the most frequent and long-lasting symptom in patients with haematological malignancies, with effects on daily routine, work and social interactions, and physical and emotional well-being.[20] Not surprisingly, anaemia was found to be the leading cause of fatigue in this survey. Importantly, utilising the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) scale, QOL has been shown to correlate directly with degree of anaemia in cancer patients, such that patients with Hb >12 g/dL reported significantly ($p \leq 0.02$) better physical and functional well-being, and fatigue and nonfatigue FACT-An subscale scores versus patients with Hb ≤12 g/dL.[21] Furthermore, lower Hb levels correlated significantly ($p < 0.001$) with poorer WHO performance status scores in the overall population and the over 2000 patients with lymphoma or myeloma who participated in the European Cancer Anaemia Survey.[22]

In addition to its demonstrated effects on QOL, findings from many retrospective and prospective studies have supported the finding that anaemia is a negative predictive factor for treatment outcomes and a negative prognostic factor for survival after multivariate analysis in patients with lymphoid malignancies (table I).[8,23] The biological basis for this negative impact is complex but may involve cellular hypoxia secondary to anaemia.[8] Notably, a recent systematic, quantitative review of 60 papers that reported the survival of cancer patients according to Hb levels or presence of anaemia concluded that the relative risk of death is increased by 65% in anaemic cancer patients overall and 67% in anaemic cancer patients with lymphoma.[24] Importantly, data suggest that post-treatment Hb level is also prognostic for survival in lymphoma patients, implying that anaemia correction prior to and during cancer treatment is of equally high priority for these patients.[10]

2. Goals for the Treatment of Anaemia

With the introduction of newer erythropoietic agents in the last several years, it has become even more critical to clearly define goals and expectations of anaemia treatment so that the efficacy of these agents and the optimal treatment choices can be determined. The National Comprehensive Cancer Network (NCCN), American Society of Hematology (ASH)/American Society of Clinical Oncology (ASCO), and European Organisation for the Research and Treatment of Cancer (EORTC) guide-

Table I. Summary of studies suggesting anaemia is an independent predictive/prognostic factor for treatment outcomes and survival in patients with lymphoid malignancies (reproduced from Van Belle and Cocquyt[8] with permission from Elsevier)

Study (year)	Retrospective or prospective	No. of patients	Outcome, p-value (if available)
Non-Hodgkin's lymphoma			
Moullet et al.[25] (1998)	Retrospective	1077	Overall survival, p = 0.0001 Progression-free survival, p = 0.0048
Samaha et al.[26] (1998)	Retrospective	121	Overall survival, p < 0.05
Hodgkin's disease			
Hasenclever and Diehl[27] (1998)	Retrospective	1618	Freedom from disease progression
Liao et al.[28] (1998)	Retrospective	109	Overall survival
Landman-Parker et al.[29] (2000)	Prospective	202	Event-free survival

lines support that the overall goals of treating anaemia in cancer patients are to correct anaemia to target Hb levels of ~12 g/dL, to minimise transfusion requirements and to resolve clinical symptoms associated with anaemia.[30-32] Importantly, multivariate longitudinal and incremental analyses of data from three large, open-label, community-based studies (conducted independently) with a total of over 3500 anaemic cancer patients receiving chemotherapy or chemoradiation therapy and epoetin alfa three times weekly or once weekly have all consistently demonstrated a direct and significant relationship between incremental Hb increases and linear analogue scale assessment (LASA) improvements with the greatest incremental gain in QOL occurring when Hb level increased from 11 to 12 g/dL (range 11–13 g/dL), which supports this as the optimal target Hb level (figure 1).[33-35] It is important to note that the recommended target Hb level for both men and women should not exceed 12 g/dL (see further discussion in section 4).[32]

Despite the high prevalence and broad impact of anaemia in patients with lymphoid malignancies and the availability of references defining clear goals for the treatment of this condition, treatment rates remain low. Importantly, data suggest that nearly 50% of symptomatic or anaemic patients with haematological malignancies are not receiving anaemia treatment.[14,15,20] Clearly, a review of available anaemia treatment options is warranted.

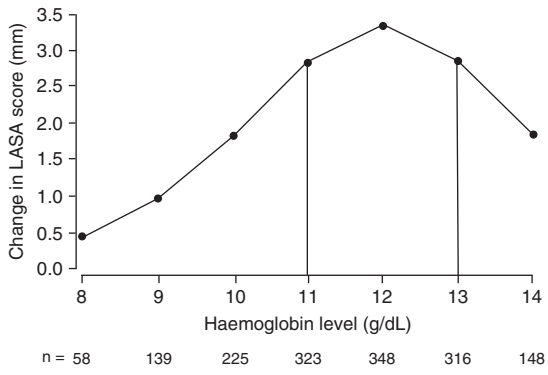

Fig. 1. Incremental changes in linear analogue scale assessment (LASA) overall quality-of-life scores and haemoglobin levels based on a longitudinal analysis of data from a large, community-based study of epoetin alfa 10 000U three times weekly in anaemic cancer patients receiving chemotherapy.[33,36] Reproduced from Crawford et al.,[33] with permission.

3. Anaemia Treatment Options

Consistent with the overall goals of anaemia treatment, key endpoints measured in clinical trials of erythropoietic agents include change in Hb, overall transfusion requirements, QOL improvements, and overall haematopoietic response rate (Hb increase ≥2 g/dL or Hb ≥12 g/dL unrelated to transfusion). Because anaemic cancer patients who achieve Hb increases of ~1 g/dL after 4 weeks of erythropoietic therapy subsequently require significantly fewer transfusions and have higher rates of Hb response, shorter time to Hb response and significantly better QOL improvements, another critical measure of efficacy of erythropoietic agents is early Hb response.[37-39]

3.1 Transfusion

Before the early 1990s and the introduction of recombinant human erythropoietin (rHuEPO), red blood cell transfusion was the only treatment option for anaemia in cancer patients. The safety of routine blood transfusions became questionable in the 1980s leading to conservative usage and leaving no treatment option for patients with mild-to-moderate anaemia.[32] Currently, transfusions are still associated with many risks, albeit small, including infection (e.g. hepatitis viruses), acute haemolytic reactions, delayed haemolytic reactions and transfusion-related acute lung injury.[19,40] Furthermore, transfusion does not represent an appealing choice in the treatment of mild-to-moderate anaemia in cancer patients since it does not result in durable correction of Hb levels that are expected with anaemia correction in current clinical practice.[41] Therefore, reserving transfusion for emergent situations in which the goal is not to restore normal Hb levels but to control severe anaemia in cancer patients is accepted practice.[32]

3.2 Epoetin Alfa

Epoetin alfa is a 165-amino acid glycoprotein with a carbohydrate content of ~40% and a molecu-

lar weight of 30.4 kDa.[42] It has the same molecular structure, weight, carbohydrate and sialic acid content, amino acid sequence and receptor binding affinity as endogenous erythropoietin, and both stimulate erythropoiesis in precisely the same way.[42,43] In cancer patients, epoetin alfa was approved in the US in 1993 for the treatment of chemotherapy-related anaemia, and in Europe in 1994 for the treatment of platinum-based chemotherapy-related anaemia and in 2000 for nonplatinum chemotherapy-related anaemia. Two epoetin alfa administration schedules are approved by the US FDA for anaemic cancer patients receiving chemotherapy: 150–300 U/kg three times weekly subcutaneously and the schedule most commonly used in clinical practice, 40 000–60 000U once weekly.[32,44-46] In anaemic cancer patients, the average half-life of epoetin alfa was similar after both dosage regimens (40 hours with a range of 16–67 hours).[46] Additionally, both administration regimens have been demonstrated to be clinically equivalent.[47-49]

Over the last decade, data from randomised, double-blind, placebo-controlled studies, large open-label, community-based studies, and clinical practice provide support that epoetin alfa, given three times weekly or once weekly, results in statistically significant mean Hb increases of ~1 g/dL after 4 weeks and ~2 g/dL after 8 weeks that are maintained through treatment, as well as significant overall transfusion reductions and QOL improvements in anaemic cancer patients receiving chemotherapy and/or radiotherapy (table II).[30,32,36,41,49-52] In a large, randomised, international, double-blind, placebo-controlled study (n = 375), anaemic cancer patients undergoing nonplatinum chemotherapy who received epoetin alfa 150–300 U/kg three times weekly required significantly (p = 0.006) fewer transfusions versus placebo (25% vs 40%).[41] Similarly, in a randomised, double-blind, placebo-controlled study evaluating epoetin alfa 40 000–60 000U once weekly in anaemic patients with advanced cancer receiving myelosuppressive chemotherapy (n = 344), transfusion requirements

Table II. Summary of key studies evaluating US FDA-approved dose administration schedules of epoetin alfa in anaemic cancer patients (including lymphoma patients) receiving chemotherapy and/or radiotherapy (reproduced from Henry[53,54] with permission)

Study (year)	Mean baseline Hb (g/dL)	Number of patients (epoetin alfa cohort only)	Number of patients with haematological malignancies (epoetin alfa cohort only)	Starting dosage	Study duration (wk)	Mean Hb increase after 4wk (g/dL)	Mean Hb increase at study end (g/dL)	QOL assessment tool
Glaspy et al.[50] (1997)	9.2	2030	467	150 U/kg tiw	16	1.1	1.8	LASA
Demetri et al.[36] (1998)	9.3	2289	515 (NHL: 233; Hodgkin's lymphoma: 46)	10 000U tiw	16	1.0	2.0	LASA, FACT-An
Littlewood et al.[41] (2001)	9.9	251	60 (NHL: 41; Hodgkin's lymphoma: 19)	150 U/kg tiw	28	0.8[a]	2.2	CLAS, FACT-An, SF-36
Gabrilove et al.[49] (2001)	9.5	2964	489 (NHL: 254; Hodgkin's lymphoma: 36)	40 000U qw	16	1.0	1.8	LASA, FACT-An
Shasha et al.[51] (2003)	9.9	442	5 (NHL: 4; Hodgkin's lymphoma: 1)	40 000U qw	16	1.1	1.9	LASA
Witzig et al.[52] (2005)	9.5	166	NR	40 000U qw	16	1.2	2.8	Uniscale (LASA), FACT-An, SDS

a Estimated value based on graph of mean Hb over time.

CLAS = Cancer Linear Analogue Scale, also known as LASA; **FACT-An** = Functional Assessment of Cancer Therapy-Anaemia; **Hb** = haemoglobin; **LASA** = Linear Analogue Scale Assessment; **NHL** = non-Hodgkin's lymphoma; **NR** = not reported; **QOL** = quality of life; **qw** = once weekly; **SDS** = Symptom Distress Scale; **SF-36** = Short Form-36; **tiw** = three times weekly.

were also significantly (p = 0.005) lower in the epoetin alfa arm versus the placebo arm (25% vs 40%).[52] In studies evaluating epoetin alfa three times weekly or once weekly, overall haematopoietic response rates (Hb increase ≥2 g/dL or Hb ≥12 g/dL unrelated to transfusion) were 60–75%.[36,41,49,51,52]

Many of the trials evaluating epoetin alfa three times weekly or once weekly included patients with lymphoid malignancies (table II). In fact, in a *post hoc* analysis of data from the Littlewood et al. trial,[55] patients with haematological malignancies who were treated with epoetin alfa 150 U/kg three times weekly (n = 115) versus placebo (n = 58) achieved mean Hb increases of ~1 g/dL vs −0.1 g/dL after 4 weeks and 2.2 g/dL vs 0.3 g/dL by study end, and a haematopoietic response rate of 75% vs 17% with 25% vs 43% of patients requiring transfusions during the study. Importantly, results in the haematological subgroup were consistent with significant findings in the overall population (figure 2).[55] Furthermore, subanalysis of data from nearly 1500 patients with haematological malignancies treated with epoetin alfa three times weekly or once weekly who participated in three large, community-based studies supported these findings by demonstrating significant (p < 0.001) mean Hb increases of ~1 g/dL after 4 weeks and ~2 g/dL by study end, and significant (p < 0.05) reductions in transfusion requirements from 21–39% at baseline to 6–13% at study end.[36,49,50,56] Importantly, epoetin alfa is safely used and well tolerated in this setting (see further discussion in section 4).

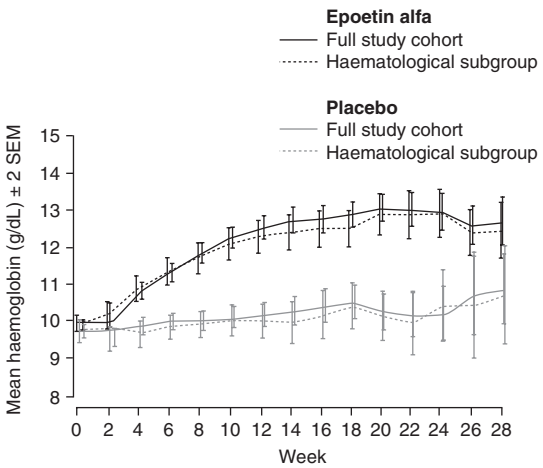

Fig. 2. Comparison of the mean bi-weekly haemoglobin values for the full population and haematological subgroup of patients treated with epoetin alfa 150 U/kg three times weekly or placebo in the trial by Littlewood et al.[41,55] **SEM** = standard error of the mean (reproduced with permission © John Wiley & Sons Limited).

Significant LASA and/or FACT-An QOL improvements that correlate with Hb increases have been documented in nearly all of the trials described in this section evaluating epoetin alfa three times weekly or once weekly for the treatment of anaemic cancer patients receiving chemotherapy or chemoradiation therapy.[36,41,49-51] In fact, a meta-analysis of data from 11 459 anaemic cancer patients in 23 trials found that epoetin alfa significantly (p = 0.05) improved FACT-An, FACT-Fatigue (FACT-F), and LASA QOL scores, with results consistent after adjusting for confounding factors.[57] Significant (p < 0.001) QOL benefits have also been demonstrated in the aforementioned subgroup analyses of patients with haematological malignancies treated with epoetin alfa three times weekly or once weekly in three large, community-based trials (figure 3).[36,49,50,56] Additionally, data in the haematological subgroups demonstrated a significant (p < 0.05), direct and positive relationship between change in Hb and change in QOL.[56] Furthermore, in the Littlewood et al.[55] subgroup analysis, patients with haematological malignancies who were treated with epoetin alfa three times weekly had substantial self-reported QOL improvements as measured by the FACT-F subscale (+4.30) and LASA (+8.96 to +11.57mm) instruments, whereas patients treated with placebo had substantial decreases in FACT-F subscale (−0.16) and LASA (−2.53 to −5.23mm) scores.[55]

Because, theoretically, less frequent dose administration could confer improved flexibility for patients and healthcare providers, alternative doses and schedules of epoetin alfa have been the subject of recent investigations. One of the first such trials was a small 24-week proof-of-concept study that was conducted in 20 anaemic cancer patients receiv-

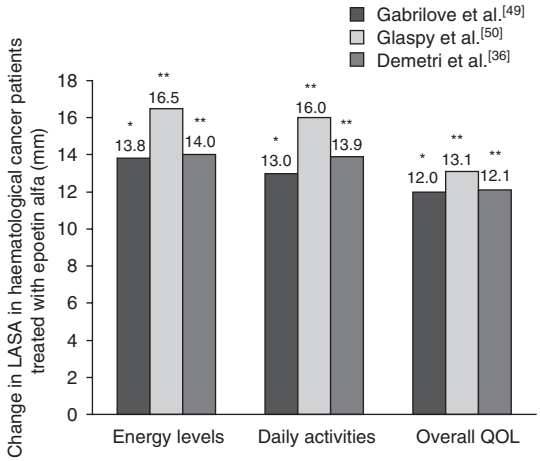

Fig. 3. Mean changes in linear analogue scale assessment (LASA) scores from baseline to last value in nearly 1500 anaemic patients with haematological malignancies who received epoetin alfa 150 U/kg or 10 000U three times weekly or 40 000U once weekly in three large, community-based studies.[36,49,50,56] **QOL** = quality of life; * $p < 0.0001$, ** $p < 0.001$.

ing chemotherapy.[58] Data suggested that a 60 000U once-weekly initial dose of epoetin alfa subcutaneously followed by a 120 000U dose every 3 weeks in patients whose Hb increased ≥2 g/dL from baseline after at least 8 weeks of once-weekly administration resulted in an early mean Hb increase of 1.0 g/dL after 4 weeks, a haematopoietic response rate of 86% after only 8 weeks, and maintenance of mean target Hb with administration every 3 weeks until the end of study. Other more recent data suggest that epoetin alfa 60 000U once weekly initially followed by 60 000U every 2 weeks (n = 129) or 80 000U every 3 weeks (n = 115) may be effective and safely used alternative administration schedule options.[59,60] Most impressive are the results of a large, phase III, randomised, 21-week North Central Cancer Treatment Group trial evaluating 365 anaemic cancer patients who received 3 weeks of initial treatment with epoetin alfa 40 000U once weekly followed by randomisation to continue once-weekly administration or be treated with 120 000U every 3 weeks.[61] On the basis of findings that included no significant difference in transfusion requirements, similar QOL improvements and comparable safety between treatment arms, the authors concluded that epoetin alfa can be administered at a higher dose every 3 weeks after initial administration with 40 000U once weekly.[61] Additionally, recently published data from a randomised, open-label, 12-week study of 310 anaemic cancer patients undergoing chemotherapy suggested that epoetin alfa 80 000U every 2 weeks from initiation provides similar efficacy and safety compared with 40 000U once weekly.[62] Epoetin alfa was safely used and well tolerated in these studies, suggesting that dose administration flexibility is an option with this agent. Further investigations are ongoing.

3.3 Darbepoetin Alfa

Darbepoetin alfa received approval in the US and Europe in 2002 for the treatment of chemotherapy-related anaemia.[63] The FDA-approved dose administration schedules are 2.25–4.5 μg/kg once weekly or 500μg every 3 weeks subcutaneously, however, 3.0–5.0 μg/kg (200–300μg) every 2 weeks is reported to be the dosage most commonly used in clinical practice.[45,63,64] Structural and pharmacokinetic differences between darbepoetin alfa and natural human erythropoietin or epoetin alfa include 5 versus 3 N-linked sugar chains, an increased negative charge due to an increased number of sialic acid residues, 50% vs ~40% carbohydrate content and a 22% increased molecular weight (37.1 kDa vs 30.4 kDa), respectively.[42] Darbepoetin alfa also has a slightly increased half-life (49 hours vs 40 hours after subcutaneous administration) and a decreased binding affinity (1 : 4 ratio) versus epoetin alfa.[42,46,47,65] The clinical implications of these differences have been the subject of study for the last few years.

Clinical trial results with darbepoetin alfa 2.25 μg/kg once weekly and 3.0 μg/kg every 2 weeks have demonstrated significant mean Hb increases of 1.5–1.8 g/dL by end of treatment, with significant reductions in transfusion requirements in anaemic cancer patients receiving chemotherapy (table III).[66-69] To that end, in a double-blind, randomised, controlled phase III study of anaemic lung cancer patients receiving chemotherapy (n = 320), a signifi-

cant ($p < 0.001$) reduction in transfusion requirements was seen in the darbepoetin alfa 2.25 μg/kg once weekly group versus placebo (27% vs 52%).[66] To further study the efficacy of the most commonly used dosage of darbepoetin alfa in US clinical practice (3.0 μg/kg every 2 weeks), a large, randomised, open-label phase II trial was conducted in anaemic cancer patients receiving chemotherapy (SOAR [Successful Outcomes in Anaemia Research]).[67,68] Interim analysis on 1173 patients reported a mean Hb increase of 1.0 g/dL at week 9 and 1.7 g/dL at week 17 ($p < 0.001$).[67,68] Nineteen percent of patients required at least one transfusion from week 5 to the end of study and overall haematopoietic response rate by study end was 84%. QOL results in this study were promising, with a 4.9 increase in mean FACT-F subscale score and an 8.8 increase in mean Energy Numerical Rating Grade (ENRG) score from baseline to week 17.[67,68] The efficacy of the 500μg every 3 weeks dosage was supported by findings from a randomised, double-blind, active-controlled, 16-week trial of darbepoetin alfa administered 500μg every 3 weeks vs 2.25 μg/kg once weekly to 705 anaemic cancer patients undergoing chemotherapy, which reported non-inferiority with respect to transfusion requirements, similar Hb changes and FACT-F improvements, and comparable safety between arms.[70] Generally, early mean Hb increases (~1 g/dL at week 4) were not reported by darbepoetin alfa-treated patients in these trials (table III).

Darbepoetin alfa has not been studied extensively in patients with haematological malignancies, but available data suggest it has comparable efficacy and safety as when administered to populations representing mixed tumour types. For example, results for the 148 patients with haematological malignancies who were treated with darbepoetin alfa in the SOAR trial included an overall mean Hb increase of 1.9 g/dL and mean FACT-F and ENRG score increases of 6.0 and 11.0, respectively, from baseline to end of study (calculated based on available QOL data only rather than standard last-observation carried forward [LOCF] methodology).[67,68,71] Notably, one phase III, randomised, double-blind, placebo-controlled study was conducted specifically in 344 anaemic cancer patients with lymphoproliferative malignancies.[69] Findings in the darbepoetin alfa 2.25 μg/kg once weekly ($n = 174$) vs placebo-treated ($n = 170$) patients included: (i) mean Hb increase of 1.8 g/dL vs 0.19 g/dL ($p < 0.001$); (ii) haematopoietic response rate of 65% vs 24% ($p < 0.001$); (iii) reduction in transfusion requirements (31% vs 48%; $p < 0.001$); and (iv) greater QOL

Table III. Summary of key studies evaluating common dose administration schedules of darbepoetin alfa in anaemic cancer patients (pts) [including lymphoma pts] receiving chemotherapy and/or radiotherapy (reproduced from Henry,[53,54] with permission)

Study (year)	Mean baseline Hb (g/dL)	No. of pts (darbepoetin alfa cohort only)	No. of pts with haematological malignancies (darbepoetin alfa cohort only)	Starting dosage	Study duration (wk)	Mean Hb increase after 4wk (g/dL)	Mean Hb increase at study end (g/dL)	QOL assessment tool
Vansteenkiste et al.[66] (2002)	10.3	156	0	2.25 μg/kg qw	12	NR	NR	FACT-F
Hedenus et al.[69] (2003)	9.5	174	174 (MM: 89; NHL: 44; CLL: 29; Hodgkin's lymphoma: 12)	2.25 μg/kg qw	12	NR	1.8	FACT-F
Vadhan-Raj et al.[67,68] (2003)	10.4	1173	148	3.0 μg/kg q2w	16	0.6[a]	1.7	FACT-F, ENRG
Canon et al.[70] (2006)	9.8	353	85 (NHL: 33; MM: 26; CLL: 13; Hodgkin's lymphoma: 11; other: 2)	500μg q3w	16	0.5[a]	1.0[a]	FACT-F

a Estimated value based on graph of mean Hb over time.

CLL = chronic lymphocytic leukaemia; **ENRG** = Energy Numerical Rating Grade; **FACT-F** = Functional Assessment of Cancer Therapy-Fatigue subscale; **Hb** = haemoglobin; **MM** = multiple myeloma; **NHL** = non-Hodgkin's lymphoma; **NR** = not reported; **QOL** = quality of life; **qw** = once weekly; **q2w** = every 2 weeks; **q3w** = every 3 weeks.

improvements (or less notable QOL decreases) regardless of baseline QOL score (figure 4). Importantly, there was a significant ($p < 0.001$) association between change in Hb and change in FACT-F scores, such that patients achieving an Hb change of ≥2 g/dL, between 0 and 2 g/dL, or <0 g/dL had mean FACT-F score changes of +4.2 points, +2.2 points and −1.7 points, respectively.[69,72] Furthermore, for every 1 g/dL increase in Hb, the estimated mean increase in FACT-F score was 1.39 based on regression analysis.[69,72] Specifically, in lymphoma patients, mean FACT-F score improvement from baseline was 3.4 points for those who were treated with darbepoetin alfa vs 1.8 points for those treated with placebo.[72] Overall, darbepoetin alfa has been safely used and well tolerated in clinical studies to date (see further discussion in section 4).

Alternative dose administration schedules have also been studied with darbepoetin alfa.[73-75] One of the first such trials was a 16-week study conducted with darbepoetin alfa in 242 anaemic patients with nonmyeloid malignancies receiving chemotherapy, evaluating a 325μg fixed or 4.5 μg/kg weight-based once weekly dose followed by a maintenance dose of 325μg or 4.5 μg/kg every 3 weeks after first achievement of Hb ≥12 g/dL.[73] After ~8–9 weeks, a mean Hb level of 12 g/dL was reached in both groups and maintained with the every 3 weeks dosage until the end of study (week 16), and the overall haematopoietic response rates were 84% and 86% for the 4.5 μg/kg and 325μg arms, respectively. The effectiveness of another darbepoetin alfa dose administration regimen under investigation, 300μg every 3 weeks, has been supported in a large (n = 386), phase III, randomised, double-blind, placebo-controlled, 15-week study in patients with chemotherapy-induced anaemia.[75] Importantly, subanalysis of data from an open-label, multicentre study suggests that this fixed every-3-weeks dose administration regimen may also be effective at correcting anaemia in patients with haematological malignancies (n = 216) undergoing chemotherapy.[74] Darbepoetin alfa was well tolerated in these studies and further evaluation of these novel dose administration regimens is ongoing.

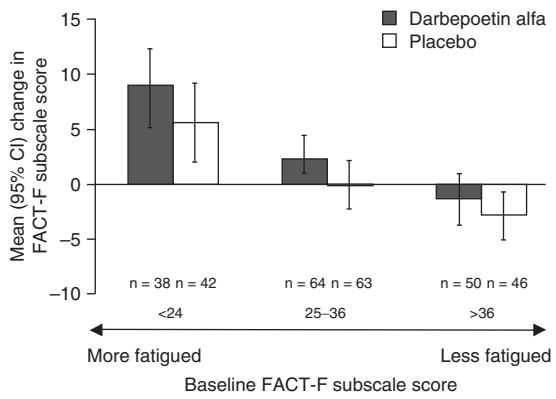

Fig. 4. Mean change (95% CI) in Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subscale score by baseline FACT-F subscale score for haematological cancer patients treated with darbepoetin alfa 2.25 μg/kg once weekly vs placebo in the trial by Hedenus et al.[69] (reproduced with permission).

3.4 Comparative Studies of Epoetin Alfa and Darbepoetin Alfa

Until recently, direct comparisons of epoetin alfa and darbepoetin alfa were not available. However, a recently completed phase III, randomised, head-to-head, multicentre, 16-week trial was specifically designed to compare epoetin alfa 40 000–60 000U once weekly versus darbepoetin alfa 200–300μg every 2 weeks in 358 anaemic (Hb ≤11 g/dL) patients with solid tumours receiving chemotherapy.[76] Agents were dose-escalated according to NCCN anaemia treatment guidelines (after 4 weeks for epoetin alfa and after 6 weeks for darbepoetin alfa). The trial was powered for comparison of haematological and QOL endpoints (both timing and magnitude) and rigorously designed with stratification of patients by platinum vs nonplatinum chemotherapy. Results demonstrated that: (i) the proportion of patients achieving a Hb increase of ≥1 g/dL by week 5 was significantly ($p = 0.008$) higher in epoetin alfa-treated (47%) versus darbepoetin alfa-treated patients (32.5%); (ii) the mean Hb increase from baseline was significantly ($p \leq 0.02$) higher at weeks 5, 9, 13 and end of study in epoetin alfa-treated patients; and (iii) the number of units transfused per patient was significantly ($p = 0.03$)

lower for epoetin alfa-treated patients. The proportion of patients transfused, mean QOL improvements and tolerability profiles were comparable between groups. Another comparative study was a phase III, randomised, noninferiority trial evaluating the same doses and schedules of these agents, but with a different dose escalation protocol (after 4 weeks for both agents) in 1209 anaemic (Hb ≤11 g/dL) cancer patients undergoing chemotherapy.[77] Trial results suggested noninferiority with respect to transfusion endpoints and similar efficacy with respect to Hb, QOL and safety endpoints. Findings from other comparative studies using data abstracted from medical charts at US oncology practices support the comparability of both agents with respect to effects on Hb and transfusion requirements.[45,64] Both agents are effective and may have minor differences with respect to response and efficacy depending on dosage and frequency of administration. Ongoing research, especially with respect to optimal dose administration, may help clinicians draw further conclusions regarding the comparability of agents.

3.5 Epoetin Beta

Epoetin beta 150–300 U/kg three times weekly or 30 000–60 000U once weekly subcutaneously has approval in many countries outside the US for the treatment of chemotherapy-related anaemia in patients with select nonmyeloid haematological malignancies. Several European trials over the last few years have studied the efficacy of epoetin beta in anaemic patients with haematological malignancies, most of whom were receiving concurrent or recent chemotherapy for their disease.[78-82]

One of these trials was a randomised, double-blind, placebo-controlled 16-week trial of epoetin beta 150–300 U/kg in anaemic patients with low-grade NHL (n = 106), chronic lymphocytic leukaemia (CLL; n = 126), or multiple myeloma (MM; n = 117). It demonstrated significantly ($p \leq 0.001$) greater transfusion-free and severe anaemia-free survival in the epoetin beta versus placebo arm.[80] Other benefits were significantly better overall haematopoietic response rates (67% vs 27%, $p < 0.0001$) and FACT-An scores ($p < 0.05$) vs placebo.[80] Approval of the 30 000U once weekly dosage was based on an open-label randomised study which demonstrated that epoetin beta once weekly was at least as effective as epoetin beta 10 000U three times weekly in 241 anaemic patients with low-grade NHL, CLL or MM.[82] This study was the first to evaluate a total weekly epoetin beta dose that is equivalent to the cumulative three-times-weekly dose. However, it is important to note that eligibility criteria for this study included low-grade lymphoproliferative malignancies, baseline Hb between 9 and 11 g/dL, no history of transfusion within 2 months prior to study entry and baseline serum erythropoietin level ≤100 mU/mL. In a population with a broader representation of patient characteristics and haematological malignancies, such as those seen in clinical practice, results cannot be assumed to be reproducible. In fact, research suggests that a higher weekly epoetin dose (e.g. 600 U/kg or 40 000U once weekly) may be necessary to achieve the same results seen with the standard three-times-weekly dose (150 U/kg) in a broad population of anaemic cancer patients.[48]

With respect to use in broader populations, findings from an open-label, prospective, randomised study (n = 262) suggest that epoetin beta 150 U/kg three times weekly versus standard care significantly increases Hb and improves QOL in anaemic patients with solid tumours or lymphoid malignancies, although further study is necessary to confirm these findings.[81] Because this agent is not approved in the US, its use for the treatment of anaemia in patients with lymphoid malignancies undergoing chemotherapy cannot be universally recommended.

3.6 Other Agents Under Investigation

Several new agents and classes of agents are under investigation for the treatment of anaemia in cancer patients. These include (i) continuous erythropoietin receptor activator (CERA), a third-generation molecule with a longer half-life than currently available erythropoietic agents and different receptor binding characteristics; (ii) CNTO 528, an erythropoietin receptor agonist capable of rescuing

erythropoietin-dependent cells from apoptosis *in vitro* and stimulating erythropoiesis *in vivo*; (iii) Hematide™ [1], a synthetic peptide-based erythropoiesis-stimulating agent; and (iv) FG-2216, an orally active, small-molecule inhibitor of hypoxia-inducible factor-prolyl hydroxylase (HIF-PH).[83-86] All of these agents are either in preclinical or early phase I or II investigation, therefore, their use for the treatment of anaemia in cancer patients cannot be recommended outside of clinical trials.

4. Safety of Erythropoietic Agents

4.1 Summary of Safety Data in Anaemic Cancer Patients

Generally, erythropoietic agents are safely used and well tolerated when administered according to prescribing information. Common adverse events occurring in >10–15% of cancer patients receiving chemotherapy during administration of erythropoietic therapy in registration and other placebo-controlled trials included anorexia, asthenia, constipation, cough, diarrhoea, dizziness, dyspnoea, oedema, fatigue, fever, nausea and vomiting.[41,46,52,63,66,87] These generally occurred with similar frequency in placebo-treated patients or were consistent with the underlying disease state.[41,46,52,63,66,87] Hypertension associated with a significant increase in Hb has been noted rarely in patients treated with erythropoietic therapy and mainly in patients with renal disease.[46,63] Nevertheless, it is recommended that blood pressure should be monitored carefully during erythropoietic therapy, particularly in patients with an underlying history of hypertension or cardiovascular disease.[46,63]

Although epoetin-induced antibody-mediated pure red cell aplasia (PRCA) was very rare prior to 1998 (three reported cases), an increase in the number of global cases was observed from 1998 to 2003 in patients treated with erythropoietic agents for the anaemia associated with chronic kidney disease (~200 reported cases).[88-90] The number of global cases of this immunological form of PRCA has declined precipitously since 2003 following increased awareness and adjustment of product-related factors that have the potential to affect immunogenicity.[89,90] Current recommendations suggest discontinuing erythropoietic treatment immediately and not resuming treatment with any erythropoietic agent. Some analyses suggest that immunosuppressive therapy may effectively reconstitute the erythropoietic response in patients with PRCA.[90,91] Fortunately, no cases of PRCA have been reported in anaemic cancer patients undergoing chemotherapy who received erythropoietic therapy, presumably due to a shorter duration of therapy, reduced life expectancy and nonspecific immunosuppression.[88,89]

A numerically higher, but not statistically significant, risk of thrombotic events with erythropoietic therapy (~6% vs ~4% for placebo or control) has always been acknowledged in anaemic cancer patients, based on registration and other placebo-controlled studies.[31,46,63,92] Generally consistent with these findings, a comprehensive meta-analysis of published and unpublished data between 1985 and 2005 on the use of erythropoietic agents in anaemic and non-anaemic cancer patients conducted by Bohlius et al.[93] revealed a 1.67-fold elevated risk of thrombotic events with erythropoietic therapy compared with control (based on 6769 patients in 35 trials) [95% CI 1.35, 2.06].

4.2 Effects on Treatment Outcomes and Survival

Erythropoietin receptors have been found on the surface of some malignant cell lines and tumour biopsy specimens, although the functionality of these receptors is unknown.[94] Results from preclinical studies evaluating the role of erythropoietic therapy in modulating tumour growth rate have been controversial.[94,95] Earlier retrospective analyses of anaemic patients receiving chemoradiotherapy for squamous cell carcinoma of the head and neck and a prospective, randomised, placebo-controlled trial in anaemic patients receiving nonplatinum chemother-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

apy for solid or haematological malignancies that included survival (as a protocol amendment) indicated that treatment with epoetin alfa significantly improved response to treatment, locoregional tumour control and/or survival.[41,96]

Since the earlier findings suggested positive results with respect to potential effects of epoetin alfa on treatment outcomes and survival, several prospective, randomised studies were conducted both within and outside the US. Grote et al.[97] demonstrated similar overall and complete response rates, and median overall survival between groups in a randomised, double-blind, placebo-controlled trial that was conducted in 224 chemotherapy-naïve, nonanaemic patients with small cell lung cancer receiving cisplatin-based combination chemotherapy to investigate whether the concurrent use of epoetin alfa 150 U/kg three times weekly subcutaneously versus placebo stimulated tumour growth. Additionally, based on data from two 16-week randomised, double-blind, placebo-controlled phase III studies of weekly darbepoetin alfa in anaemic patients with lung cancer (n = 314) or lymphoproliferative malignancies (n = 344) who were undergoing chemotherapy, darbepoetin alfa did not seem to influence progression-free survival or overall survival.[98] Another international, randomised, double-blind, placebo-controlled study in 939 women with previously untreated metastatic breast cancer receiving first-line chemotherapy evaluated epoetin alfa 40 000U once weekly with dose titration to maintain Hb levels between 12 and 14 g/dL. The primary endpoint was 12-month survival.[99] At 4 months, the incidences of fatal thrombotic events (1.1% vs 0.2%) and deaths attributed to disease progression (6.0% vs 2.8%) were higher in women receiving epoetin alfa vs placebo, respectively.[99] On the basis of Kaplan-Meier estimates, the proportion of patients surviving at 12 months was significantly lower in the epoetin alfa versus placebo arm (70% vs 76%; p = 0.012), although survival curves converged at 19 months. Finally, in a randomised, double-blind, placebo-controlled study conducted outside the US in 351 patients with head and neck cancer, epoetin beta 300 U/kg was administered three times weekly 10–14 days before and continuing through curative radiotherapy with the aim of achieving a Hb level of 14 g/dL in women and 15 g/dL in men.[100] Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta (adjusted relative risk 1.62; p = 0.0008).

It is important to note that trials suggesting a negative impact of erythropoietic therapy on treatment outcomes and/or survival included patients who were nonanaemic and aimed to achieve target Hb levels well above 12 g/dL. Also, results from the aforementioned meta-analysis conducted by Bohlius et al.[93] determined that there is insufficient information to conclude that use of erythropoietic products has an adverse effect on tumour response (based on 13 trials including 2833 patients) or overall survival (based on 42 trials including 8167 patients). Future clinical trials will investigate these endpoints. Until further information is available, the recommended target Hb level should not exceed 12 g/dL in men or women undergoing chemotherapy for nonmyeloid malignancies.[32]

5. Practice Guidelines for the Management of Anaemia

5.1 Review of Recommendations Based on Practice Guidelines

A debatable, yet important, topic is the timing of intervention with erythropoietic therapy in anaemic cancer patients. Because each patient's normal Hb and symptomatic responses to Hb changes are variable, establishment of a fixed Hb level for intervention can be challenging. Therefore, it is critical to consider symptoms or symptomatic risk (e.g. recent transfusion requirement, history of radiotherapy or prior myelosuppressive therapy, myelosuppressive potential of current therapy, age and baseline Hb level).[32] According to the NCCN guidelines, other causes of anaemia, such as bleeding, haemolysis, nutritional deficiency (especially iron) and hereditary causes, should be ruled out (figure 5).[32] Once the patient has been diagnosed with cancer- or treatment-related anaemia, erythropoietic therapy can be

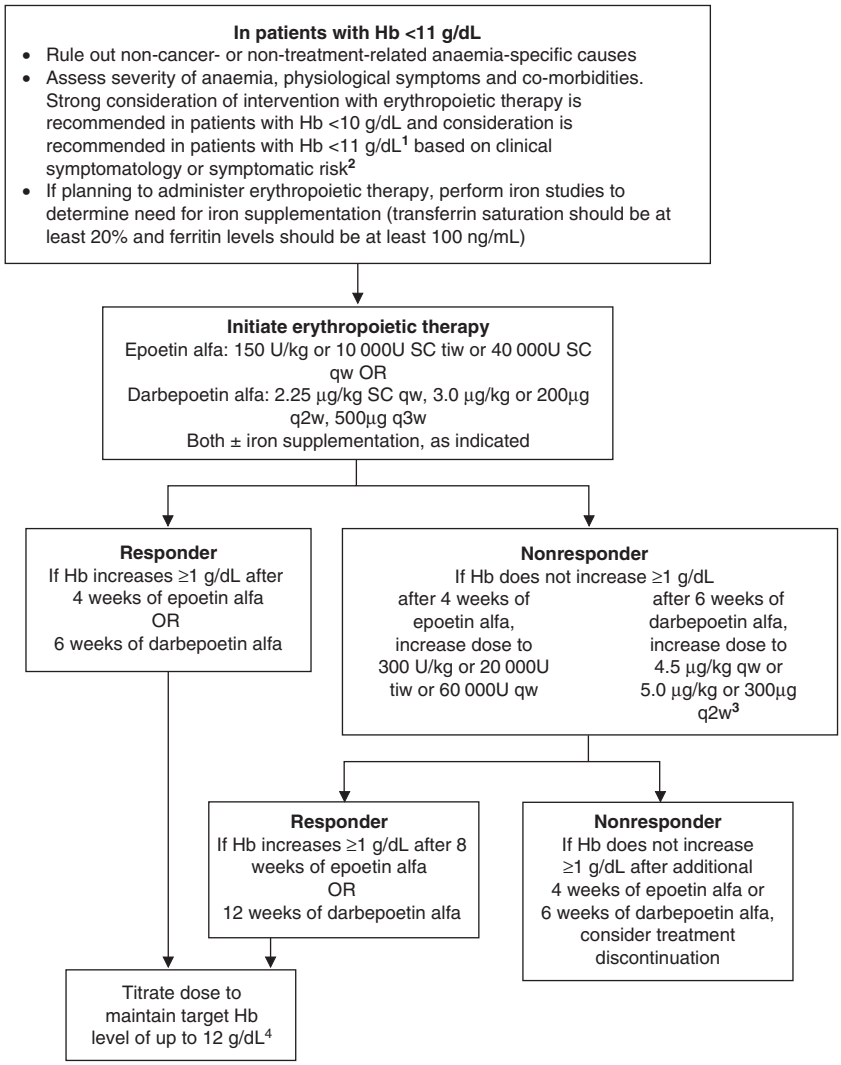

Fig. 5. Schematic diagram illustrating anaemia treatment guidelines for cancer patients receiving chemotherapy according to the National Comprehensive Cancer Network 2006 Guidelines.[32] **1** = American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO) guidelines recommend consideration when haemoglobin (Hb) <12 g/dL in symptomatic patients.[30] **2** = Symptomatic risk defined as history of transfusion in past 6 months, prior myelosuppressive therapy or radiotherapy to >20% of skeleton, myelosuppressive potential of current therapy, and patient age and baseline Hb level. **3** = Dose adjustment not specified for patients receiving initial q3w dose administration. **4** = If Hb exceeds 13 g/dL, epoetin therapy should be withheld and reinitiated at a 25% dose reduction when Hb falls below 12 g/dL, and if epoetin treatment produces a very rapid Hb increase (e.g. an increase of >1 g/dL in any 2-week period) the dose should be reduced by 25% (reproduced from Henry,[53] with permission). **qw** = once weekly; **q2w** = every 2 weeks; **q3w** = every 3 weeks; **SC** = subcutaneous; **tiw** = three times weekly.

administered based on the degree of anaemia and clinical symptomatology (figure 5).[32] In patients with severe anaemia, an immediate transfusion may be necessary.[32] The ASH/ASCO treatment guidelines recommend that erythropoietic therapy be routinely considered when Hb falls below 10 g/dL and

based on clinical symptomatology when Hb falls below 12 g/dL.[30] The NCCN guidelines advise strong consideration of erythropoietic therapy when Hb falls to <10 g/dL and consideration when Hb is in the range of 10–11 g/dL for all patients with symptoms or symptomatic risk (figure 5).[32] The EORTC guidelines recommend intervention at Hb levels of 9–11 g/dL based on anaemia-related symptoms, such as reduced functional capacity.[14,31] Importantly, a randomised, open-label, multicentre trial was conducted to compare the efficacy of epoetin alfa 40 000U once weekly when administered to patients with haematological malignancies (85% NHL) at the start of chemotherapy with Hb levels between 10 and 12 g/dL (n = 135) versus during chemotherapy when Hb levels fell below 9 g/dL (n = 134).[101] Results suggested that early versus late administration of epoetin alfa results in significantly ($p < 0.0001$) higher Hb increases and maintenance at mean target of ~12 g/dL, a significantly ($p < 0.0001$) higher proportion of haematopoietic responders (70% vs 25%), lower transfusion requirements, significantly ($p < 0.05$) better FACT-An and LASA QOL improvements, and significantly ($p < 0.05$) greater reduction in number of days spent in bed and restricted activity days, with trends toward reductions in health resource use.[101]

Once the decision to treat anaemia is established, subsequent considerations include agent selection, initial dose administration, response assessment and dose titration (figure 5). Both the ASH/ASCO and NCCN guidelines recommend that epoetin alfa be administered subcutaneously at 150 U/kg (weight-based) or 10 000U (fixed) three times weekly or 40 000U once weekly for at least 4 weeks.[30,32] If, after 4 weeks, Hb has not increased by at least 1 g/dL, the dose should be increased to 300 U/kg or 20 000U three times weekly or 60 000U once weekly. The ASH/ASCO guidelines concluded that there was not enough evidence to recommend treatment with darbepoetin alfa at the time of review (1999).[30] The 2006 NCCN guidelines recommend that darbepoetin alfa be initiated at 2.25 μg/kg once weekly subcutaneously, 3 μg/kg (weight-based) or 200μg (fixed) every 2 weeks or 500μg every 3 weeks, and initial response assessed at 6 weeks; the dose should be escalated to 4.5 μg/kg once-weekly or 5 μg/kg/ or 300μg (fixed) every 2 weeks in nonresponders (no specification regarding dose adjustment was provided for patients receiving initial every 3 weeks dose administration).[32] Iron supplementation should be provided as necessary with both agents. With both agents, treatment discontinuation should be considered if the patient has still not responded (Hb increase of at least 1 g/dL) 4–6 weeks after dose escalation.[32] In patients who respond to erythropoietic therapy, the dose should be titrated to maintain a target Hb of up to 12 g/dL.[30,32] Erythropoietic therapy should be withheld if Hb exceeds 13 g/dL and reinitiated with a 25% dose reduction when Hb falls to <12 g/dL.[32] If treatment produces a very rapid Hb response (i.e. an increase of >1 g/dL in any 2-week period), the dose should be reduced by 25%, although data to support this recommendation are lacking.

5.2 The Role of Iron Supplementation

Administration of erythropoietic therapy can correct anaemia due to inadequate endogenous erythropoietin production, and can also overcome the suppression of erythroid progenitor cells and impairment of iron mobilisation that is associated with anaemia of chronic disease.[102,103] However, an adequate amount of iron is required to keep pace with the demands of erythropoiesis stimulated by erythropoietic therapy and, therefore, absolute or functional iron deficiency may develop, resulting in treatment nonresponse. Functional iron deficiency (adequate iron stores associated with normal ferritin levels but low transferrin saturation) is presumably a result of the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Functional iron deficiency can also exist before erythropoietic therapy as a result of increased hepcidin levels secondary to inflammatory cytokines such as interleukin-6 associated with the malignancy itself.[104] Before and during erythropoietic therapy, the patient's iron status should be evaluated. Transferrin saturation of at least 20% and ferritin levels of

at least 100 ng/mL should help to maintain adequate iron for erythropoiesis.[32]

A key issue for anaemic cancer patients receiving erythropoietic therapy is the appropriate method for providing iron supplementation. Oral iron is commonly used to treat iron deficiency, but parenteral iron may be necessary for patients who are intolerant or unresponsive to oral therapy. Parenteral administration may also be a more effective way to deliver iron to the anaemic cancer patient receiving chemotherapy, by avoiding the potential problems of poor absorption and defective iron storage and release associated with oral iron supplementation. Parenteral iron preparations include iron dextran, ferric gluconate and iron sucrose.[32] Test doses are required for iron dextran and strongly recommended for patients receiving ferric gluconate or iron sucrose who are sensitive to iron dextran or who have other drug allergies.[32] According to the NCCN practice guidelines, patients receiving these drugs should also receive pretreatment with diphenhydramine and paracetamol (acetaminophen) to minimise adverse events, although clinical data suggest that this is not absolutely necessary.[32,103,105,106] Importantly, recent data support the efficacy of parenteral iron supplementation in anaemic cancer patients receiving erythropoietic therapy, even in patients who are iron-replete.[103,105,107,108] Definitive recommendations regarding parenteral iron supplementation as an alternative to oral iron will probably be made as further data become available.[32]

6. Conclusion

Clearly, cancer- and treatment-related anaemia can have a profound and negative impact on patients with lymphoid malignancies. Goals of treatment in the setting of moderate anaemia (Hb <10 g/dL) are clear and include Hb correction to ~12 g/dL, prevention of transfusions and optimisation of QOL.[30-32] On the basis of available clinical data, published guidelines and practical experience, erythropoietic therapy has revolutionised the management of anaemia in patients with lymphoid malignancies. In the US, universal guidelines recommend either agent in their FDA-approved dose administration schedules: epoetin alfa 150 U/kg three times weekly or 40 000U once weekly or darbepoetin alfa 2.25 μg/kg once weekly or 500μg every 3 weeks. Anaemia management should involve careful consideration of patient and disease characteristics and goals of treatment. Importantly, iron deficiency and supplementation also need to be considered. It has been demonstrated that treatment outcomes, survival and QOL are also compromised for patients with lymphoid malignancies and mild anaemia (Hb 10–12 g/dL);[8,21,22] therefore, it is reasonable to recommend that these patients be treated with the same goals as patients with moderate-to-severe anaemia based on clinical judgment. Importantly, because of a potential risk for increased thrombotic complications, the target Hb should not exceed 12 g/dL in anaemic cancer patients receiving erythropoietic therapy. Ongoing investigations to determine novel alternative dose administration regimens with current erythropoietic agents and the introduction of promising new agents encouragingly suggest that the optimal management of anaemia will continue to evolve.

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