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Guidelines

EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer

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Abstract

Anaemia is frequently diagnosed in patients with cancer, yet it is difficult to identify a single cause due to its multifactorial aetiology. We conducted a systematic literature review (1996–2003) to produce evidence-based guidelines on the use of erythropoietic proteins in anaemic patients with cancer (see Table 4). Level I evidence exists for a positive impact of erythropoietic proteins on haemoglobin (Hb) levels when administered to patients with chemotherapy-induced anaemia or anaemia of chronic disease, when used to prevent cancer anaemia, in patients undergoing cancer surgery and following allogeneic bone marrow transplantation. The Hb level at which erythropoietic protein therapy should be initiated is difficult to determine as it varied between studies; a large number of Level I studies in patients with chemotherapy-induced anaemia or anaemia of chronic disease enrolled patients with a Hb concentration $\leqslant$105 g/L, but none compared the effect of different baseline Hb levels on the response to treatment. Similarly, several studies defined the target Hb concentration as 120–130 g/L following treatment with erythropoietic proteins, but none specifically addressed the correlation between target Hb level and clinical benefit in a randomised fashion. Level I evidence shows that red blood cell (RBC) transfusion requirements are significantly reduced with erythropoietic protein therapy in patients with chemotherapy-induced anaemia or when used to prevent cancer anaemia (approximately 20% reduction compared with controls). We found indirect Level I and III evidence that patients with chemotherapy-induced anaemia or anaemia of chronic disease initially classified as non-responders to standard doses proceed to respond to treatment following a dose increase (absolute increases in response rate ranged from 8% to 18%). However, none of these studies examined the effect on response rates of a longer treatment period at the lower dose, or performed a randomised comparison of a dose increase versus an unchanged dose. There is Level I evidence to show that quality-of-life (QOL) is significantly improved in patients with chemotherapy-induced anaemia and in those with anaemia of chronic disease, particularly in patients achieving a Hb response to erythropoietic protein therapy. There are insufficient data to determine the effect on survival following treatment with erythropoietic proteins in conjunction with chemotherapy or radiotherapy. There is Level I evidence that dosing of erythropoietic proteins less frequently than three times per week (TIW) is efficacious when used to treat chemotherapy-induced anaemia or prevent cancer anaemia. There is Level III evidence that initial doses of erythropoietic proteins considered to be higher than current standard practice produce higher haematological responses

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in patients with chemotherapy-induced anaemia or anaemia of chronic disease. Level I evidence demonstrates that several baseline patient parameters (e.g., low endogenous erythropoietin [EPO] concentration, age <60 years, Hb concentration $\geqslant$ 90 g/L) impact upon the response to erythropoietic proteins when used to treat chemotherapy-induced anaemia or prevent cancer anaemia. Evidence indicates that endogenous EPO concentration impacts on response in patients with lymphoproliferative malignancies, but is not a valid parameter in patients with solid tumours. There is Level I evidence that fixed doses of erythropoietic proteins can be used at the start of therapy to treat patients with chemotherapy-induced anaemia, but maintenance doses should be titrated individually. There is no evidence that pure red cell aplasia (PRCA) occurs following treatment with erythropoietic proteins in patients with chemotherapy-induced anaemia or when used prophylactically in patients with cancer. There is Level I evidence that the risk of thromboembolic events and hypertension are slightly elevated in patients with chemotherapy-induced anaemia receiving erythropoietic proteins. Level I evidence supports the effectiveness of erythropoietic proteins to prevent anaemia in non-anaemic cancer patients receiving chemotherapy or radiotherapy or in those undergoing cancer surgery. However, these are non-licensed indications and we do not currently recommend the prophylactic use of erythropoietic proteins to prevent anaemia in patients who have normal Hb values at the start of treatment.

Additional trials are warranted, especially on the issues of iron replacement and cost-effectiveness of erythropoietic protein therapy, as well as on tumour response/progression and survival.

Keywords: Erythropoietic proteins; Anaemia; Cancer; Treatment guidelines

1. Introduction

Anaemia is frequently diagnosed in patients with cancer, yet it is difficult to identify a single cause due to its multifactorial aetiology. Treatment-induced anaemia occurs as a result of bone marrow damage; radiotherapy and most cytotoxic chemotherapeutic agents cause some degree of myelosuppression. Blood loss following radical cancer surgery can also trigger anaemia. The most common type of non-treatment-induced anaemia in patients with cancer occurs mainly as a result of the tumour and is referred to as the anaemia of chronic disease [1]. In such cases, activation of inflammatory cytokines is thought to result in inadequate erythropoietin (EPO) production [2,3], impaired iron utilisation and suppressed proliferation of erythroid progenitor cells [4].

Allogeneic red blood cell (RBC) transfusions have been the mainstay of treatment for anaemia, and are still used in severe cases, but they do not provide long-term correction of anaemia. Cloning of the human EPO gene in 1983 [5] heralded the way forward for the treatment of cancer-related anaemia and allowed viable quantities of recombinant human erythropoietin (rHuEPO) to be produced commercially. rHuEPO was initially used for the correction of renal anaemia in 1986 [6] with the first pilot study published in anaemic patients with cancer in 1990 [7]. rHuEPO poses fewer risks to patients than RBC transfusions and provides a more sustained correction of anaemia, as well as being more convenient for patients. The efficacy of rHuEPO in anaemic cancer patients has been confirmed in numerous clinical trials, both in terms of increased haemoglobin (Hb) levels and decreased RBC transfusion requirements, and, more recently, improved quality-of-life (QOL). Some trials have reported a trend for improved survival following rHuEPO therapy [8,9], however, recent randomised trials specifically designed for survival analyses have shown findings in the opposite direction in head and neck cancer patients undergoing radiotherapy [10] and in metastatic breast cancer patients receiving chemotherapy [11].

Clinicians today are faced with an expanding choice of erythropoietic proteins and a wealth of data on appropriate dosing regimens, approved indications and safety. In addition, the cost of erythropoietic protein therapy is significant, and not all patients respond to treatment; thus, guidelines on its use and the accurate selection of patients most likely to respond are vital. Suggested clinical guidelines for the treatment of cancer-related anaemia were first published by an American group in 1998 [1]. The National Comprehensive Cancer Network subsequently produced clinical practice guidelines on cancer and treatment-related anaemia in 2001, with an update published in 2003 [12]. The most comprehensive set of clinical practice guidelines for the use of epoetin in patients with cancer were published jointly in 2002 by the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) [13]. These United States (US) evidence-based guidelines recommend the use of epoetin for patients with chemotherapy-associated anaemia and a Hb concentration $\leqslant$100 g/L, with clinical circumstances determining the use of epoetin for patients with less severe anaemia (Hb concentration 100–120 g/L).

As the management of cancer anaemia continues to move at a rapid pace, and new drug therapies are approved, treatment guidelines must be reviewed and updated regularly. Indeed, since the release of the ASCO/ASH guidelines, a number of important studies have been published and another erythropoietic protein, darbepoetin alfa, with a longer serum half-life than rHuEPO [14,15] has been approved in this field. An independent task force, endorsed by the European Organisation for Research and Treatment of Cancer

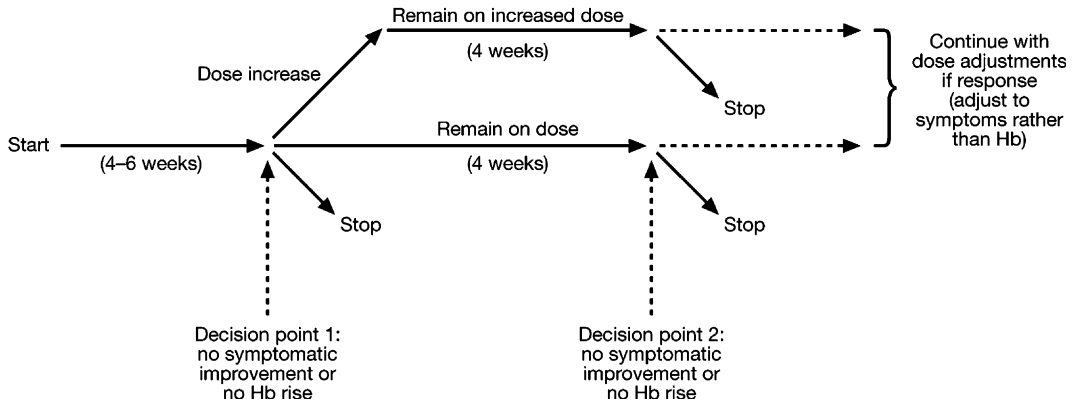

Fig. 1. Suggested dosing algorithm for erythropoietic proteins in patients with cancer. The target haemoglobin (Hb) levels are discussed in Table 4 and are not above 130 g/l.

(EORTC), was therefore established to systematically review the literature and produce up-to-date, evidence-based guidelines for the use of erythropoietic proteins in anaemic patients with cancer in Europe. These guidelines cannot account for inter-individual variation and clinicians should apply their best judgement when deciding on treatment options.

2. Patients and methods

The chosen database was MEDLINE due to its precise indexing and general availability. Electronic searches were conducted using the MEDLINE database for English language records from 1, January 1996 to 1, September 2003. The cut-off date of 1996 was chosen to follow-on from previous EORTC work conducted in this area [16]. Search terms were used to extract records limited to clinical studies with erythropoietic proteins in anaemic patients with cancer or lymphoproliferative malignancies aged $\geqslant 18$ years. An additional search was performed to identify papers relating to bone marrow or stem cell transplantation published between 1, January 1990 and 1, September 2003, as this particular area was not previously investigated. Pre-MEDLINE covers more recent literature not yet entered into the MEDLINE database and thus Pre-MEDLINE was also searched using the criteria defined above.

Abstract books from the following key international meetings were manually searched for relevant material: ASCO 2000, 2001, 2002, 2003; ASH 2000, 2001, 2002; European Cancer Conference (ECCO) 2001; European Society for Medical Oncology (ESMO) 2000, 2001, 2002; European Haematology Association (EHA) 2000, 2001, 2002, 2003; American Association for Cancer Research (AACR) 2000, 2001, 2002, 2003. In addition, Amgen, F. Hoffmann-La Roche Ltd and Ortho-Biotech, manufacturers of erythropoietic proteins, were invited to submit papers accepted for publication (by September 2003), but not yet published. Abstracts and papers published after this cut-off date, but considered to be of great importance, were also included. All papers and abstracts were subject to the same exclusion criteria (see Section 3).

Evidence levels defined by ASCO [17] (Table 1) were applied to the results of the literature search to classify data according to study design. An EORTC task-force reviewed the search findings and agreed the evidence levels for each of the questions described in Table 2, defining the evidence as either supporting or conflicting. This allowed grading recommendations to be made, based on the ASCO definitions, on the use of erythropoietic proteins in anaemic patients with cancer (Table 3). The total number of papers and abstracts addressing each of the therapeutic areas and each of the questions is highlighted in Table 3.

3. Results

A total of 78 published studies (34 using epoetin alfa, 20 unspecified rHuEPO, 16 epoetin beta and 8 darbepoetin alfa) relating to the administration of erythropoietic proteins in anaemic patients with cancer were considered to be relevant from a total of 235 papers identified by the search. An additional 50 relevant abstracts were also identified (33 using epoetin alfa, 10 unspecified rHuEPO, 5 darbepoetin alfa and 2 epoetin beta). Criteria for exclusion included review articles, *in vitro* studies, patients aged <18 years, patients with myelodysplastic syndrome, patients not diagnosed with cancer and papers not published in English.

3.1. Treatment-induced anaemia

3.1.1. Chemotherapy-induced anaemia

In total, 77 studies relating to the use of erythropoietic proteins for the treatment of chemotherapy-induced

Table 1
ASCO levels of evidence and grades of recommendation [17]

Level	Type of evidence
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies or from high-power randomised, controlled clinical trial
II	Evidence obtained from at least one well-designed experimental study or low-power randomised, controlled clinical trial
III	Evidence obtained from well-designed, quasi-experimental studies such as non-randomised, controlled single-group, pre-post, cohort, time or matched case-control series
IV	Evidence obtained from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies
V	Evidence obtained from case reports and clinical examples
Grade	**Type of supporting evidence**
A	There is evidence of type I or consistent findings from multiple studies of type II, III, or IV
B	There is evidence of type II, III, or IV and findings are generally consistent
C	There is evidence of type II, III, or IV, but findings are inconsistent
D	There is little or no systematic empirical evidence

ASCO, American Society of Clinical Oncology.

Table 2
Questions addressed by the guidelines

In anaemic patients with cancer:
1. Is $\leqslant$105 g/L the Hb threshold for initiation of therapy with erythropoietic proteins?
2. Is the target Hb concentration 120–130 g/L?
3. Does treatment with erythropoietic proteins have a positive impact on Hb levels?
4. Does increasing the dose of erythropoietic proteins in non-responders produce a subsequent response?
5. Does treatment with erythropoietic proteins decrease RBC transfusion requirements?
6. Does treatment with erythropoietic proteins lead to QOL improvements?
7. Does treatment with erythropoietic proteins improve survival?
8. Is less frequent dosing of erythropoietic proteins possible (i.e., less than TIW)?
9. Do higher initial doses of erythropoietic proteins produce higher haematological responses (i.e., higher than current standard practice of 30,000–40,000 IU/week)?
10. Do baseline patient parameters impact on response to erythropoietic proteins?
11. Can erythropoietic proteins be used prophylactically to prevent anaemia?
12. Can a fixed, rather than a weight-based, dose of erythropoietic protein be used?
13. Does PRCA occur following treatment with erythropoietic proteins?
14. Are the risks for thromboembolic events and hypertension increased in patients receiving erythropoietic proteins?

Hb, haemoglobin; RBC, red blood cells and QOL, quality of life; TIW, three times per week; PRCA, pure red cell aplasia.

anaemia were identified. Forty-one of these were published papers (17 using epoetin alfa, 11 epoetin beta, 7 darbepoetin alfa and 6 unspecified rHuEPO) and 36 were abstracts (24 using epoetin alfa, 6 unspecified rHuEPO, 4 darbepoetin alfa and 2 epoetin beta).

3.1.1.1. Hb threshold for initiation of therapy. Overall, 50 of the 77 studies, graded as Levels I–V, enrolled patients with a Hb level $\leqslant$105 g/L for the initiation of therapy with erythropoietic proteins. However, none compared the effects of different baseline Hb levels on response to treatment.

3.1.1.2. Target Hb concentration. Twenty of the 77 studies, graded as Levels I–IV, defined the target Hb concentration as 120–130 g/L following treatment with erythropoietic proteins, but none specifically addressed the correlation between target Hb level and clinical benefit. Indirect Level III evidence was provided by one study, in which Hb levels showed a significant positive correlation with improvements in QOL as measured by changes in Functional Assessment of Cancer Therapy-Anemia (FACT-An) total and subscale scores, although the study did not relate these benefits to a specific Hb target [18].

3.1.1.3. Impact of erythropoietic proteins on Hb concentration. Of the 73 studies addressing the impact of erythropoietic proteins on Hb levels, all but two provided supporting evidence for a positive impact in patients with chemotherapy-induced anaemia (Hb response rate: 24–75%). All studies reported significantly higher Hb/haematopoietic response rates in patients receiving erythropoietic proteins than in controls. Seventeen studies and one meta-analysis were graded as Level I, of which seven used epoetin alfa [9,19–24], four epoetin beta [25–

Table 3
Summary of grade recommendations

Question[a]	Chemotherapy-induced anaemia (77)	Radiotherapy-induced anaemia (1)	Anaemia due to surgery (9)	Anaemia of chronic disease (13)	Prevention of chemotherapy- or radiotherapy-induced anaemia (15)	Bone marrow or HSC transplantation (13)
1	D (64)	D[b] (1)	N/A	D (10)	N/A	D (7)
2	D (31)	D[b] (0)	D (2)	D (4)	D (11)	D (4)
3	A (73)	D[b] (1)	A (9)	A (13)	A (14)	A (8)
4	B (10)	D[b] (0)	D (0)	B (2)	D (0)	D (0)
5	A (44)	D[b] (0)	C (8)	C (5)	A (10)	B (13)
6	A (41)	D[b] (1)	D (0)	A (6)	C (5)	D (1)
7	D (5)	D[b] (0)	D (1)	D (2)	D (4)	D (1)
8	A (34)	D[b] (0)	D[b] (1)	B (3)	A[b] (2)	D (0)
9	B (7)	D[b] (0)	D (1)	B (2)	D (1)	D (0)
10	A (18)	D[b] (0)	D (0)	D (1)	A (2)	D (0)
11	B (4)	D[b] (0)	A (9)	D (0)	A (15)	D (0)
12	A (41)	D[b] (1)	D[b] (1)	D (7)	D (4)	D[b] (2)
13	A −ve (12)	D[b] (0)	D (0)	B −ve (3)	A −ve (2)	D (1)
14	A (15)	D[b] (0)	B (3)	B (2)	C (2)	D (1)

A = there is evidence of type I or consistent findings from multiple studies of type II, III, or IV; B = there is evidence of type II, III, or IV and findings are generally consistent; C = there is evidence of type II, III, or IV, but findings are inconsistent; D = there is little or no systematic empirical evidence.

[a] Questions are defined in Table 2.

[b] Abstract evidence only; −ve indicates a negative recommendation; N/A = not applicable; HSC = haematopoietic stem cell. The total number of papers and abstracts addressing each of the therapeutic areas and each of the questions is shown in parentheses.

28], three darbepoetin alfa [8,29,30] and four unspecified rHuEPO [31–34]. Ten studies graded as Level II and 34 studies graded as Level III provided additional supporting evidence. Two studies provided conflicting (i.e., non-supportive) evidence, one at Level II ($n = 30$) [35], and one at Level III ($n = 20$) [36].

3.1.1.4. Dose increases in non-responders. Ten studies described erythropoietic protein dose increases (i.e., above the standard dose of 30,000–40,000 IU/week rHuEPO or 2.25 μg/kg/week darbepoetin alfa) in non-responders, but none examined the effect on response rates of a longer treatment period at the lower dose, or performed a randomised comparison of a dose increase versus an unchanged dose. Indirect evidence that increasing the dose of erythropoietic protein in non-responders produces a subsequent response was provided by one Level I study [26]. Increasing the dose of epoetin beta from 2000 to 5000 or 10,000 IU/day increased the cumulative response rate from 14% to 42% and 60%, respectively (absolute increase of 18%), in patients with multiple myeloma or low-grade non-Hodgkin's lymphoma. Indirect evidence was also provided by eight Level III studies. All studies demonstrated increased response rates in patients initially defined as non-responders receiving a subsequent dose increase.

3.1.1.5. RBC transfusion requirements. Of the 77 studies, 33 provided supporting evidence that erythropoietic proteins decrease RBC transfusion requirements in patients with chemotherapy-induced anaemia (approximately 20% reduction compared with controls). All studies reported statistically significantly lower RBC transfusion requirements in patients receiving erythropoietic proteins compared with controls. Seventeen studies and one meta-analysis were graded as Level I, of which eight used epoetin alfa [9,19–24,37], four epoetin beta [25–28], two darbepoetin alfa [8,30] and four unspecified rHuEPO [31,33,34,38]. Additional supporting evidence was provided by 13 studies at Level II or III. Two studies reported that rHuEPO-treated patients required fewer RBC transfusions than controls, but this difference failed to reach significance, providing conflicting Level I evidence [29,32]. A further eight studies reported the same findings, providing conflicting Level II and III evidence.

3.1.1.6. QOL improvements. Forty-one studies addressed the issue of QOL, with 36 providing supporting evidence that erythropoietic proteins lead to QOL improvements in patients with chemotherapy-induced anaemia. Each of these studies reported statistically significant improvements in QOL, as determined by various QOL measures (FACT-Fatigue [FACT-F], FACT-An, Linear Analog Scale Assessment [LASA], QLQ-C30), in patients receiving erythropoietic proteins compared with controls. Eleven studies were graded as Level I, with six using epoetin alfa [9,19–22,37], two epoetin beta [25,27], two darbepoetin alfa [29,30] and one unspecified rHuEPO [32]. There was also supporting Level II and III evidence. In the majority of these studies, patients who achieved a Hb response experienced

greater improvements in QOL than non-responders. Inconclusive evidence was provided by one Level I study, which reported that QOL data were insufficient for meta-analysis, however, statistically significant effects of epoetin alfa on QOL were noted in studies enrolling patients with Hb concentration $\leqslant$100 g/L [31]. Four studies provided conflicting Level I [8,23,33] or Level II evidence [39], observing no statistically significant difference in QOL between rHuEPO-treated patients and controls.

3.1.1.7. Survival. Four of the 77 studies and one meta-analysis in chemotherapy-induced anaemia addressed the issue of survival, however, none provided statistically significant evidence that survival is improved in patients with chemotherapy-induced anaemia following treatment with erythropoietic proteins [8,9,24,34,40]. A trend towards improved survival with erythropoietic proteins was observed in all of these studies, but no statistically significant effects were reported.

3.1.1.8. Less frequent dosing. Five of the 77 studies provided supporting Level I evidence that erythropoietic proteins can be administered to patients with chemotherapy-induced anaemia less frequently than three times per week (TIW) and result in increased Hb/haematopoietic responses, decreased RBC transfusion requirements or improved QOL compared with untreated controls. Three of these studies used darbepoetin alfa, while one used epoetin beta, and one used unspecified rHuEPO. In most studies, patients received erythropoietic proteins once per week (QW) or once every 2 weeks (Q2W) [8,30,33,41], while in one of the studies patients received darbepoetin alfa once every 3 weeks (Q3W) [29]. An additional five studies provided Level II evidence, while 19 provided Level III evidence.

3.1.1.9. Higher initial doses. Indirect evidence that higher initial doses of erythropoietic proteins (i.e., higher than current standard practice of 30,000–40,000 IU/week rHuEPO or 2.25 μg/kg/week darbepoetin alfa) produce higher haematological responses than standard doses was provided by seven studies graded as Levels I and II. Four of the studies used darbepoetin alfa [29,42–44], two used epoetin beta [39,45] and one used epoetin alfa [46]. In all of these studies, numerically higher response rates than with standard doses were noted, but no statistically significant differences in the response rates between the doses were reported.

3.1.1.10. Predictors of response. Four Level I studies provided evidence that baseline patient parameters impact upon the response to erythropoietic proteins, three using epoetin beta [25–27] and one using darbepoetin alfa [30]. Österborg and colleagues [25] noted that baseline platelet count $\geqslant 100 \times 10^9$ cells/L, Hb concentration $\geqslant$ 90 g/L and a lower pre-study transfusion requirement were the factors most strongly associated with a low risk for failure. Subgroup analyses demonstrated that the likelihood of response to epoetin beta versus placebo was increased in patients with a high (55%) versus low platelet count (21%), and a high (51%) versus low Hb level (26%). Low endogenous EPO concentration (i.e., $\leqslant$100 mIU/mL) was a significant factor for prediction of response in three Level I studies [26,27,30] and a further study by Cazzola and colleagues [41] graded as Level III. The majority of patients enrolled in these studies had haematological malignancies, however, the impact of endogenous EPO levels on response to treatment is less well established in solid tumour patients. In the Cazzola study [41], changes in Hb between weeks 1 and 3, and changes from baseline in serum transferrin receptor levels in weeks 2 and 3, were found to be early indicators of response. Additional supporting evidence was provided by six Level II and III studies. Conflicting evidence regarding a correlation between pre-treatment serum EPO levels and response to erythropoietic proteins was provided by two Level I studies, two Level II studies and one Level III study [18,19,28,39,42].

3.1.1.11. Prophylactic use of erythropoietic proteins. Supporting Level I evidence for the prophylactic use of erythropoietic proteins in non-anaemic patients receiving chemotherapy was provided by one meta-analysis [34] and one study using epoetin alfa [22]. However both were published as abstracts only. Additional supporting Level III evidence was obtained.

3.1.2. Radiotherapy-induced anaemia

One abstract relating to the use of erythropoietic proteins for the treatment of radiotherapy-induced anaemia was identified [47].

Pantellakos and colleagues [47] enrolled patients with a Hb level $\leqslant$105 g/L for the initiation of therapy with erythropoietic proteins, but did not compare the effects of different baseline Hb levels on response to treatment. The study, graded as Level IV, provided supporting evidence that erythropoietic proteins have a positive impact on Hb levels. In addition, significant improvements in QOL following epoetin alfa therapy were reported.

3.1.3. Anaemia due to surgery

Eight published studies were identified relating to the peri-operative use of erythropoietic proteins to prevent the development of anaemia in cancer patients. Of these, five used epoetin alfa, two epoetin beta and one unspecified rHuEPO. One relevant abstract was also identified that examined the use of epoetin alfa to treat anaemic patients following cancer surgery [48].

Two Level III studies provided conflicting evidence that 120–130 g/L is the target Hb concentration, stating

that patients should maintain Hb $\geqslant$ 100 g/L [48] or $\geqslant$ 160 g/L [49]. However, neither of these studies compared the effects of different baseline Hb levels on the response to treatment. All of the studies provided supporting Level I–III evidence that treatment with erythropoietic proteins has a positive impact on Hb levels [48–56].

In terms of preventing RBC transfusion requirements, during and after surgery, four studies gave supporting Level II and III evidence [49–52], while four provided conflicting Level I–III evidence [53–56]. One study provided Level II evidence that treatment with erythropoietic proteins improves survival, with 1-year survival rates significantly higher in patients receiving epoetin alfa than placebo (80.6% versus 59.3%, $P = 0.04$) [50].

Indirect evidence that higher initial doses of erythropoietic proteins produce higher haematological responses was provided by one Level III study, with significantly better outcomes seen in patients receiving epoetin alfa every 4 days at a dose of 100 *versus* 50 IU/kg [52], although both doses are considered to be lower than current standard practice.

Eight studies found Level I–III evidence that erythropoietic proteins can be used prophylactically to prevent anaemia in patients undergoing cancer surgery.

3.2. Anaemia of chronic disease

Thirteen studies relating to the use of erythropoietic proteins in cancer patients with anaemia of chronic disease not receiving anticancer treatment were identified. Seven of these were published papers (three using epoetin alfa, two unspecified rHuEPO, one epoetin beta and one darbepoetin alfa) and six were abstracts (three using epoetin alfa, two unspecified rHuEPO and one darbepoetin alfa).

3.2.1. Hb threshold for initiation of therapy

One study graded as Level I used a Hb threshold of $\leqslant$105 g/L for the initiation of therapy with erythropoietic proteins in patients with anaemia of chronic disease [19]. A further four studies gave supporting Level III evidence. However, none compared the effects of different baseline Hb levels on the patient's response to treatment [57–60]. There was also conflicting Level I–III evidence regarding the threshold level for anaemia treatment [61–63].

3.2.2. Target Hb concentration

One Level III study and another Level IV study used a target Hb concentration of 120–130 g/L, but neither study addressed the correlation between target Hb level and clinical benefit [58,64]. However, two Level III studies obtained conflicting evidence stating 140 g/L as the Hb target [57,60].

3.2.3. Impact of erythropoietic proteins on Hb concentration

A positive impact on Hb levels was observed following erythropoietic protein therapy in all studies (Hb response rate: 43–72%), providing Level I–III supporting evidence.

3.2.4. Dose increases in non-responders

The studies by Quirt and colleagues [57], and Pangalis and colleagues [59], provided indirect Level III evidence that increasing the dose of erythropoietic proteins in non-responders produces a subsequent Hb increase. Of the 39% of patients with Hb increase <10 g/L after 4 weeks of epoetin alfa therapy in the Quirt study, 28% achieved a Hb response after dose-doubling from 150 to 300 IU/kg TIW [57]. Similarly in the Pangalis study, rHuEPO dose-escalation from 150 to 300 IU/kg TIW was performed in 28% of non-responding patients, 29% of whom went on to achieve a complete response [59]. However, neither of these studies examined the effect on response rates of a longer treatment period at the lower dose.

3.2.5. RBC transfusion requirements

Mixed evidence was obtained for a reduction in RBC transfusion requirements following erythropoietic protein therapy. Two studies provided supporting Level III and IV evidence with epoetin alfa [57,65], while one study gave conflicting Level I evidence [19] and two gave conflicting Level III evidence [58,60]. All of these studies displayed a trend towards fewer RBC transfusion requirements with darbepoetin alfa [58], epoetin beta [60], or epoetin alfa therapy [19], but no statistically significant differences were observed.

3.2.6. QOL improvements

Five studies graded as Level I or III provided supporting evidence that QOL is improved following erythropoietic protein therapy in patients not receiving chemotherapy [19,57,58,60,61].

3.2.7. Survival

There was no evidence to support an improvement in survival in patients receiving erythropoietic proteins. Two Level III studies found conflicting evidence. Daneryd and colleagues [61] reported no statistically significant difference in survival between study and control patients. The median survival of responders has not yet been reached in the study by Pangalis and colleagues [59]. However, there is no evidence for a decrease in survival.

3.2.8. Less frequent dosing

Two studies provided supporting Level III evidence that less frequent dosing of erythropoietic proteins is possible [58,66]. The widest dosing interval was in the

randomised, phase II Smith study [58] (graded as Level III), in which patients received open-label darbepoetin alfa subcutaneously (s.c.) at doses of 1.0, 2.25 or 4.5 μg/kg QW, or double-blind at doses of 6.75 μg/kg Q3W or once every 4 weeks (Q4W) or 10.0 μg/kg Q4W ($n = 166$). A higher proportion of patients receiving darbepoetin alfa Q3W or Q4W than placebo achieved a Hb response, haematopoietic response, decrease in RBC transfusion requirements and improvement in QOL.

3.2.9. Higher initial doses

The Smith study found Level III evidence that higher initial doses of erythropoietic proteins produce higher haematological responses; 100% of patients ($n = 30$) receiving 4.5 μg/kg QW darbepoetin alfa achieved a haematopoietic response compared with 70% of patients ($n = 33$) receiving a standard darbepoetin alfa dose of 2.25 μg/kg QW [58]. Johansson and colleagues [60] provided indirect Level III evidence, with significantly better outcomes seen in patients receiving 5000 IU TIW epoetin beta *versus* 1000 IU TIW, although both doses are considered to be lower than current standard practice.

3.2.10. Predictors of response

No supporting evidence was reported to confirm that baseline patient parameters impact on response to erythropoietic proteins. However, one study gave conflicting Level III evidence, reporting no correlation between change in Hb and serum EPO levels at baseline in patients with hormone-refractory prostate cancer receiving epoetin beta [60].

3.2.11. Prophylactic use of erythropoietic proteins

There were no data available on the prophylactic use of erythropoietic proteins in patients with anaemia of chronic disease.

3.3. Prevention of anaemia

3.3.1. Patients receiving chemotherapy

Twelve studies relating to the prophylactic use of erythropoietic proteins in cancer patients receiving chemotherapy were identified, eight were published papers (four using epoetin alfa, one using epoetin beta and three unspecified rHuEPO), and four were abstracts (three using epoetin alfa and one unspecified rHuEPO). An additional study was terminated early, but the results were recently published and are included in this section [11].

Four studies graded as Level I [67–69] and Level II [70] used a target Hb concentration of 120–130 g/L. However, none of the studies addressed the correlation between target Hb level and clinical benefit. All of the studies provided supporting Level I–IV evidence that the prophylactic use of erythropoietic proteins in patients receiving chemotherapy has a positive impact on Hb levels.

Mixed evidence was obtained for the prevention of RBC transfusions with erythropoietic protein therapy in the chemotherapy setting, with supporting Level I and II evidence [67,69,71–74] and conflicting Level II and III evidence [70,75,76]. There was also conflicting Level I and II evidence that prophylactic treatment with erythropoietic proteins maintains QOL compared with placebo in patients receiving chemotherapy [67,70,72,77]. However, one Level I study with epoetin alfa (published as an abstract only) provided supporting evidence [68].

There was no evidence that survival is improved in patients receiving chemotherapy and erythropoietic proteins for the prevention of anaemia. However, conflicting Level I evidence was provided [11,71]. One study, specifically designed for survival analyses and graded as Level I, assessed 12-month survival in patients with metastatic breast cancer receiving chemotherapy and revealed a significantly greater number of patients alive in the placebo group than in the epoetin alfa group (76% *versus* 70%; $P = 0.0117$) [11].

Two Level I studies provided supporting evidence that less frequent dosing of erythropoietic proteins is possible for prophylactic therapy, both utilising QW dosing of epoetin alfa [68,69].

One Level I study gave indirect evidence that higher initial doses of erythropoietic proteins produce higher haematological responses [71]. Dose reductions due to an increase in Hb >20 g/L or a Hb concentration >150 g/L were required more often in the high-dose group (300 IU/kg TIW) than in the low-dose group (150 IU/kg TIW).

Two Level I prevention studies reported that baseline patient parameters impact on response to erythropoietic proteins in patients receiving chemotherapy [68,72]. Ten Bokkel Huinink and colleagues [71] noted that a low baseline serum EPO concentration predicted a lower transfusion need in rHuEPO-treated patients than in controls, while Bamias and colleagues [67] observed greater benefit from epoetin alfa than placebo, in terms of RBC transfusion requirements and prevention of anaemia, in patients with non-lung disease, aged <60 years, receiving taxane treatment, with an observed/predicted ratio $\leqslant 0.9$.

All of the studies found Level I–IV evidence that erythropoietic proteins can be used prophylactically to prevent cancer anaemia in patients receiving chemotherapy.

3.3.2. Patients receiving radiotherapy

Two prevention studies were identified on the use of erythropoietic proteins in cancer patients receiving radiotherapy, one using epoetin alfa [78] and the other epoetin beta [10].

Both studies provided supporting Level I [10] and III [78] evidence that the prophylactic use of erythropoietic proteins has a positive impact on Hb levels and can prevent cancer anaemia in patients receiving radiotherapy.

Neither of the studies provided evidence for an improvement in survival in patients receiving erythropoietic proteins for the prevention of anaemia. However, one study specifically designed for survival analyses gave conflicting Level I evidence. Henke and colleagues [10] investigated whether epoetin beta could improve outcome of curative radiotherapy in patients with head and neck cancer. The authors reported poorer locoregional progression-free survival (adjusted relative risk [RR] 1.62, 95% CI: 1.22–2.14, $P = 0.0008$), locoregional progression (RR 1.69, 95% CI: 1.16–2.47, $P = 0.007$) and survival (RR 1.39, 95% CI: 1.05–1.84, $P = 0.02$) in patients receiving 300 IU/kg TIW epoetin beta compared with placebo.

3.4. Bone marrow or haematopoietic stem cell transplantation

Thirteen studies relating to the use of erythropoietic proteins to support bone marrow or haematopoietic stem cell reconstitution were identified, 11 were published papers (7 using unspecified rHuEPO and 4 using epoetin alfa) and 2 were abstracts (1 using epoetin alfa and one unspecified rHuEPO).

Four studies, graded as Level II and III, initiated erythropoietic protein therapy in patients with a Hb level $\leqslant$105 g/L, however, none compared the effects of different baseline Hb levels on response to treatment [79–82]. Two studies graded as Level II [79,83] used a Hb target of 120–130 g/L, but none specifically addressed the correlation between target Hb level and clinical benefit. Seven studies gave supporting Level I–IV evidence that erythropoietic proteins have a positive impact on Hb levels, while one epoetin alfa study provided conflicting Level II evidence, with a lower mean Hb at the end of the study than at the time of the stem cell transplant [82].

Evidence relating to RBC transfusion requirements was mixed, with supporting evidence for a decreased requirement following erythropoietic protein therapy provided at Level I–III by seven studies [79,80,84–88] and conflicting evidence provided at Levels II and III by four studies [81–83,89]. However, in this setting, many patients were transfusion-dependent at the start of erythropoietin therapy.

One Level III study found supporting evidence that treatment with rHuEPO leads to QOL improvements [87]. No supporting evidence was obtained relating to improved survival following erythropoietic protein therapy. However, one study reported a similar number of epoetin alfa-treated and placebo patients alive at a median follow-up of 433 days, providing conflicting Level II evidence [79].

3.5. Fixed versus weight-based dosing of erythropoietic proteins

Overall, 56 studies graded as Levels I–V administered a fixed dose (ranging from 1000 IU TIW to 60,000 IU QW) of erythropoietic protein to patients with cancer. Sixteen of these studies were graded as Level I [20–22,24,26,28,32,33,37,41,61,67–69,90,91], but only two in patients with chemotherapy-induced anaemia (one with darbepoetin alfa and one with epoetin alfa) compared a fixed dose with a weight-based dose, providing supporting Level I evidence [90,91]. Fixed dosing was also used in seven Level II studies and 23 Level III studies, but none compared this with weight-based dosing.

3.6. PRCA

Among 2299 patients with cancer (1356 receiving darbepoetin alfa, 531 receiving epoetin beta, 310 receiving epoetin alfa and 102 receiving unspecified rHuEPO), enrolled in eight Level I studies [8,19,25,28–30,71,72], one Level II study [42] and eight Level III studies [41,43,44,58,63,89,92,93], no anti-erythropoietic antibodies were detected or pure red cell aplasia (PRCA) cases reported.

3.7. Thromboembolic events

Six Level I studies and a meta-analysis reported the overall incidence of thromboembolic events in cancer patients; a numerically higher risk was noted following erythropoietic protein therapy in each study, but this did not translate into a statistically significant risk [8,9,11,19,26,34,71]. Typical incidences of thromboembolic events in the six studies were 7% for epoetin alfa *versus* 6% placebo [9], 4% epoetin beta *versus* 0% controls [26] and 5% darbepoetin alfa *versus* 3% placebo [8]. Pooled results from 12 randomised, controlled trials of the meta-analysis revealed a 1.55-fold elevated risk of thromboembolic events with rHuEPO therapy compared with controls [34].

3.8. Hypertension

The incidence of hypertension was reported by seven Level I studies in patients with cancer; a numerically higher risk was noted following erythropoietic protein therapy in each study, but this was not statistically significant in any of these studies [8,9,19,23,25,26,84]. Typical incidences of hypertension were 4% for epoetin alfa *versus* 1% placebo [9], 9% epoetin beta *versus* 5% placebo [25] and 6% darbepoetin alfa *versus* 4% placebo [8]. Pooled results of 16 randomised, controlled trials in a meta-analysis revealed a 1.25-fold elevated risk of hypertension with rHuEPO therapy compared with controls ($P = 0.05$) [34].

4. Discussion

The results of this systematic literature review reveal an abundance of data on the use of erythropoietic proteins in cancer patients with chemotherapy-related anaemia, but limited data in the other therapeutic areas examined. Data were particularly sparse for the treatment of radiotherapy-induced anaemia where only one abstract was identified. The quality of the clinical trials varied greatly across the indications, with the majority of well-designed, large, controlled, randomised trials being conducted in patients with chemotherapy-induced anaemia. Furthermore, the quality of the data available on each erythropoietic protein varied, with most studies – including the majority of Level I studies – utilising epoetin alfa.

The evidence obtained was sufficient to make recommendations for patients with chemotherapy-induced anaemia, anaemia due to cancer surgery, anaemia of chronic disease, prevention of chemotherapy- and radiotherapy-induced anaemia and for haematopoietic support following bone marrow or stem cell transplantation, but not for radiotherapy-induced anaemia.

The Hb level at which erythropoietic protein therapy is initiated varies from patient to patient. The studies analysed used different Hb thresholds to initiate erythropoietin therapy. However, a large number of Level I studies in patients with chemotherapy-induced anaemia or anaemia of chronic disease enrolled patients with a Hb concentration $\leqslant$105 g/L; still none compared the effect of different baseline Hb levels on the response to treatment.

In a retrospective analysis of data from 4382 anaemic cancer patients, Crawford and colleagues [94] demonstrated a direct relationship between Hb increases and QOL improvements following epoetin alfa therapy, with maximal QOL benefit observed at a Hb level of 120 g/L (range 110–130 g/L). A number of studies in this search defined the target Hb concentration as 120–130 g/L following treatment with erythropoietic proteins, but none specifically addressed the correlation between target Hb level and clinical outcome, e.g., impact on response to therapy, RBC transfusion requirements, survival or QOL in a randomised setting.

Supporting evidence exists for a positive impact of erythropoietic proteins on Hb levels when administered to patients with chemotherapy-induced anaemia or anaemia of chronic disease, when used to prevent cancer anaemia, in patients undergoing cancer surgery and in patients who have received allogeneic bone marrow transplants.

Several studies describe permitted dose increases in non-responders, but fail to supply subsequent response data. We did, however, find limited evidence that patients with chemotherapy-induced anaemia or anaemia of chronic disease initially classified as non-responders at standard doses proceed to respond to treatment following a dose increase; absolute increases in response rate ranged from 8% to 18% [26,57,59]. However, none of the studies addressed the question in a prospective, randomised fashion and so any conclusions must be regarded as preliminary.

Evidence shows that RBC transfusion requirements are significantly reduced following treatment with erythropoietic proteins in patients with chemotherapy-induced anaemia or when used prophylactically in patients with cancer. This was demonstrated previously in a meta-analysis of 12 controlled clinical trials ($n = 1390$) evaluating the treatment of cancer-related anaemia; administration of epoetin alfa or epoetin beta reduced the proportion of patients requiring RBC transfusion by 38% [31].

We obtained evidence that QOL is significantly improved (according to changes in FACT-F, FACT-An, LASA and QLQ-C30 scores) in patients with chemotherapy-induced anaemia and in those with anaemia of chronic disease following erythropoietic protein therapy.

There is no evidence (at Level I) that treatment with erythropoietic proteins improves survival. Twelve studies ($n = 2741$) and one meta-analysis ($n = 3284$) reported survival data with 11 observing no difference between treatment groups, or a trend towards improved survival in patients receiving erythropoietic proteins. Supporting evidence was provided by one Level II study in patients undergoing surgery for non-metastatic cancer of the gastrointestinal tract ($n = 63$), which reported significantly higher 1-year survival rates in patients receiving peri-operative epoetin alfa than placebo [50]. However, another Level I study ($n = 122$) reported a higher incidence of disease progression in patients with ovarian cancer (stages IIb–IV) treated with platinum-based chemotherapy and receiving prophylactic rHuEPO (13.3% 150 IU/kg TIW, 8.9% 300 IU/kg TIW) than in controls (6.1%), although this was thought to reflect the higher proportion of patients with stage II rather than stage III/IV disease in the control group [71].

Similar findings relating to disease progression were observed in the randomised, double-blind, placebo-controlled study in patients with metastatic breast cancer receiving chemotherapy, which was terminated early due to an observed higher mortality in the epoetin alfa group than the placebo group at 12 months [11]. The increased mortality occurred during the first 4 months of the study and was thought to be partly due to an increased incidence of disease progression in the epoetin alfa group compared with the placebo group (6% *versus* 3%). However, the authors comment that this study suffered from problems in design, conduct and post-trial analysis, which may have complicated the interpretation of the results. Additional data indicating a potential

impairment of disease control with the prophylactic use of erythropoietic proteins were reported by Henke and colleagues [10] in patients with head and neck cancer undergoing radiotherapy. Mean Hb concentrations in the placebo group were 124 g/L (standard deviation [SD] 130) and 129 g/L (SD 190) after 4 and 9 weeks of treatment, respectively, compared with 148 g/L (SD 180) and 154 g/L (SD 170), respectively, in the epoetin beta group. However, compared with the placebo group, patients receiving 300 IU/kg TIW epoetin beta had poorer locoregional progression-free survival (adjusted RR 1.62, $P = 0.0008$), locoregional progression (RR 1.69, $P = 0.007$) and survival (RR 1.39, $P = 0.02$). The authors suggest that this somewhat anomalous effect of epoetin beta might be due to imbalances in particular subgroups at baseline or be related to complex and poorly understood endogenous EPO-activated anti-apoptotic mechanisms. However, it should also be noted that although an intent-to-treat analysis was used, only 69% of patients received radiotherapy according to the protocol, and just 61% of patients were available for per-protocol analyses. Data from the two cited negative survival studies have been the subject of wide discussion [95]. These results and the ensuing discussion have prompted a review of the use of erythropoietic proteins by regulatory authorities. A public hearing was held by the Food and Drug Administration (FDA) of the United States of America (USA), at the May 4, 2004 Oncology Drugs Advisory Committee (ODAC) meeting. Both Amgen and Johnson & Johnson presented data on their USA licensed products, darbepoetin alfa and epoetin alfa. In addition, Roche presented data on epoetin beta, which is not licensed for oncology use in the USA. Full details of FDA questions, question errata, and presentations are available on http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2.htm. The conclusions have been reported by various press agencies and on the "Internet" (http://www.trends-in-medicine.com/May2004/FDAepo054qp.pdf; http://www.fdaadvisorycommittee.com/FDC/AdvisoryCommittee/Committees/Oncologic+Drugs/050404_Aranesp/050404_AranespR.htm), but an official document is lacking. The ODAC continue to support the use of erythropoietic proteins for the treatment of symptomatic anaemic patients with cancer. The committee did not discuss placing any restrictions on the use of these drugs or additional warnings on their labels. The ODAC, like the EORTC taskforce, concluded that there are currently insufficient data available to determine the impact of erythropoietic proteins on tumour growth (including in pre-clinical studies) or survival of cancer patients. The FDA panel agreed that more studies are required to definitively answer these questions.

We found evidence that dosing of erythropoietic proteins less frequently than TIW is possible in patients with chemotherapy-induced anaemia, or when used to prevent cancer anaemia. Studies using darbepoetin alfa with QW, Q2W and Q3W dosing intervals were shown to be efficacious. These less frequent dosing regimens are possible with darbepoetin alfa because of its extended half-life compared with rHuEPO. For epoetin beta, QW dosing is approved for patients with lymphoproliferative malignancies.

There is limited evidence that initial doses of erythropoietic proteins considered to be higher than current standard practice may produce higher haematological responses when used to treat chemotherapy-induced anaemia. However, no adequately powered phase III study has been performed in this area, but preliminary phase II data are available for darbepoetin alfa.

We found evidence from some, but not all, studies that baseline patient parameters including low endogenous EPO concentration (particularly in patients with lymphoid malignancies), age <60 years, Hb concentration $\geqslant 90$ g/L and platelet count $\geqslant 100 \times 10^9$ cells/L impact upon the response to erythropoietic proteins in patients with chemotherapy-induced anaemia. However, the question was not addressed in the same way in all of the studies examined, thus explaining the different evidence provided. In addition, inappropriately low endogenous EPO levels must be interpreted in relation to the degree of anaemia present.

We also found evidence that erythropoietic proteins can be used to prevent anaemia in patients with cancer receiving chemotherapy or radiotherapy and in those undergoing cancer surgery.

There is evidence that fixed doses, rather than weight-based doses, of erythropoietic proteins can be used to treat patients with chemotherapy-induced anaemia, with two studies directly comparing the two. Hesketh and colleagues [91] randomised 241 patients to 325 μg or 4.5 μg/kg darbepoetin alfa QW and obtained similar haematopoietic response rates in both groups (86% fixed dose *versus* 84% weight-based dose). Granetto and colleagues [90] also reported similar Hb response rates in 546 patients randomised to 10,000 IU or 150 IU/kg epoetin alfa TIW (50.5% *versus* 53.0% for the fixed and weight-based groups, respectively). These data suggest that fixed and weight-based doses of erythropoietic proteins are equally efficacious in treating patients with chemotherapy-induced anaemia, and in fact this has already been adopted as common practice for both epoetin alfa and epoetin beta.

There are no reports that PRCA occurs following treatment with erythropoietic proteins in patients with chemotherapy-induced anaemia or when used to prevent cancer anaemia. In February 2002, Casadevall and colleagues [96] reported the development of PRCA, in association with neutralising anti-erythropoietin antibodies, in 13 patients receiving the non-US epoetin alfa preparation (Eprex®) for the anaemia of chronic renal failure. By December 2002, approximately 142 patients

worldwide had been diagnosed with antibody-positive PRCA after receiving Eprex®, and in a minority of cases, following treatment with epoetin beta (NeoRecormon®); to date there have been no cases of antibody-mediated PRCA reported with darbepoetin alfa (Aranesp®) [97]. However, the latest Eprex® data, as published on the Johnson & Johnson website, state that the total number of suspected PRCA cases with Eprex® in the nephrology setting has dropped dramatically from 89 cases in 2002 to 11 cases to date in 2003. Johnson & Johnson suggest that a change in administration practice at the end of 2002 from s.c. to intravenous dosing was responsible for this decreased incidence. However, recent studies have hypothesised that the formulation of Eprex® is the primary cause of the upsurge in PRCA cases associated with this compound [98,99]. All but two reported cases of PRCA to date have occurred in patients with renal failure and not in patients with cancer. These two cases occurred in anaemic patients with myelodysplastic syndrome treated with epoetin alfa and epoetin beta [100].

We found evidence that the risk of thromboembolic events and hypertension is slightly elevated in anaemic cancer patients receiving erythropoietic proteins.

A number of questions still remain concerning the use of erythropoietic proteins in anaemic patients with cancer. Specifically, the issues of iron replacement and cost-effectiveness need addressing; however, they are outside the scope of these guidelines and warrant further investigation in their own rights.

The recommendations of the task-force concerning the use of erythropoietic proteins in anaemia patients with cancer are summarised in Table 4 (See Fig. 1). Well-designed, comparative studies are required to more clearly define the ideal Hb threshold for the initiation of therapy as well as the target Hb. In addition, further randomised studies are needed to address the issue of dose increases in non-responders and the use of higher

Table 4
Recommendations of the task-force, plus grades (see Table 3) and figure 1

Anaemia is a frequent finding in cancer patients and should be carefully assessed. Additional causes of anaemia such as iron deficiency, bleeding, nutritional defects or haemolysis should be corrected prior to erythropoietic protein therapy. The following recommendations are related to adult cancer patients with solid tumours or haematological malignancies:

- In cancer patients receiving chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a Hb level of 90–110 g/L based on anaemia-related symptoms (grade A).
- In patients with cancer-related anaemia not undergoing chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a Hb level of 90–110 g/L based on anaemia-related symptoms (grade B).
- Erythropoietic proteins may be considered in asymptomatic, anaemic patients with a Hb level of 90–110 g/L to prevent a further decline in Hb, according to individual factors (e.g., type/intensity of chemotherapy, baseline Hb) (grade D).
- For anaemic patients who are transfusion-dependent, erythropoietic proteins should be initiated in addition to RBC transfusions (grade D).
- We do not recommend the prophylactic use of erythropoietic proteins to prevent anaemia in patients undergoing chemotherapy and/or radiotherapy who have normal Hb values at the start of treatment (grade B).
- Elderly patients experience the same benefits from treatment with erythropoietic proteins as younger patients (grade B).
- The target Hb concentration should be 120–130 g/L (grade B).
- The two major goals of erythropoietic protein therapy should be to improve QOL and prevent transfusions (grade A).
- The use of erythropoietic proteins with the aim of improving survival or response to treatment is not recommended as there is no evidence to support this (grade A). Further studies are needed.
- Within reasonable limits of body weight, fixed doses of erythropoietic proteins should be used (grade B).
- We recommend the dosing of erythropoietic proteins according to Fig. 1. However, the decision to dose-escalate cannot be generally recommended and must be individualised (grade B). Treatment should be continued as long as Hb levels remain $\leqslant$120–130 g/L and patients show symptomatic improvement. For patients reaching the target Hb, individualised titration of lowest effective maintenance dose should be made repeatedly (grade D).
- Despite the common use of epoetin alfa QW (40,000 IU), there is limited evidence to support this dosing schedule (grade C). The QW application of epoetin beta (30,000 IU) has been shown to be effective in patients with non-myeloid haematological malignancies (grade B). The QW administration of darbepoetin alfa (2.25 μg/kg) can be recommended (grade A). There is currently limited evidence to support the use of darbepoetin alfa in Q2W, Q3W or Q4W dosing intervals (grade C).
- The use of higher initial doses of erythropoietic proteins can currently not be recommended as a standard approach with epoetin alfa (grade D) or epoetin beta (grade D), but limited evidence exists for darbepoetin alfa (grade B). Further studies are needed.
- There are no predictive factors of response to erythropoietic proteins that can be routinely used in clinical practice; a low serum EPO level (in particular in haematological malignancies) is the only verified predictive factor of some importance. Values must be interpreted relative to the degree of anaemia present (grade B).
- For patients undergoing autologous blood stem cell transplants, the effects of erythropoietic proteins have not yet been convincingly shown and they cannot therefore be recommended (grade B).
- For patients undergoing allogeneic blood stem cell transplants, the clinical impact of erythropoietic proteins is limited and they can only be recommended on an individual basis (grade B).
- The fear of PRCA should not lead to erythropoietic proteins being withheld in patients with cancer (grade A).
- When using erythropoietic proteins to treat anaemia in cancer patients, the combined analysis of all study data indicates a slightly increased risk of thromboembolic events. However, this may be related to the target Hb level achieved (grade B).

initial doses of erythropoietic proteins in anaemic patients with cancer. Finally, the issue of tumour response/progression and survival must be carefully studied in order to provide clear guidelines on this issue for the future.

Conflict of interest

Dr. Bokemeyer has served as a consultant on advisory boards, and as a speaker at meetings, for Amgen, Hoffmann-La Roche Ltd and Janssen-Cilag. Dr. Aapro has received research grant support from, and served as a consultant to, Amgen, Hoffmann-La Roche Ltd and Ortho-Biotech. Dr. Osterborg has received research grant support from Amgen and Hoffmann-La Roche Ltd and served as a speaker for Amgen and Hoffman-La Roche. The remaining authors have no conflicts of interest to declare.

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