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Review

EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update

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ABSTRACT

Anaemia is frequently diagnosed in patients with cancer, and may have a detrimental effect on quality of life (QoL). We previously conducted a systematic literature review (1996–2003) to produce evidence-based guidelines on the use of erythropoietic proteins in anaemic patients with cancer.[Bokemeyer C, Aapro MS, Courdi A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. Eur J Cancer 2004;40:2201–2216.] We report here an update to these guidelines, including literature published through to November 2005. The results of this updated systematic literature review have enabled us to refine our guidelines based on the full body of data currently available.

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, and in patients undergoing cancer surgery. The addition of further Level I studies confirms our recommendation that in cancer patients receiving chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a Hb level of 9–11 g/dL based on anaemia-related symptoms rather than a fixed Hb concentration. Early intervention with erythropoietic proteins may be considered in asymptomatic anaemic patients with Hb levels $\leqslant$11.9 g/dL provided that individual factors like intensity and expected duration of chemotherapy are considered. Patients whose Hb level is below 9 g/dL should primarily be evaluated for need of transfusions potentially followed by the application of erythropoietic proteins. We do not recommend the prophylactic use of erythropoietic proteins to prevent anaemia in patients undergoing chemotherapy or radiotherapy who have normal Hb levels at the start of treatment, as the literature has not shown a benefit with this approach. The addition of further supporting studies confirms our recommendation that the target Hb concentration following treatment with erythropoietic proteins should be 12–13 g/dL. Once this level is achieved, maintenance doses should be titrated individually.

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There is Level I evidence that dosing of erythropoietic proteins less frequently than three times per week is efficacious when used to treat chemotherapy-induced anaemia or prevent cancer anaemia, with studies supporting the use of epoetin alfa and epoetin beta weekly and darbepoetin alfa given every week or every 3 weeks. We do not recommend the use of higher than standard initial doses of erythropoietic proteins with the aim of producing higher haematological responses, due to the limited body of evidence available. There is Level I evidence that, within reasonable limits of body weight, fixed doses of erythropoietic proteins can be used to treat patients with chemotherapy-induced anaemia.

This analysis confirms that there are no baseline predictive factors of response to erythropoietic proteins that can be routinely used in clinical practice if functional iron deficiency or vitamin deficiency is ruled out; a low serum erythropoietin (EPO) level (only in haematological malignancies) appears to be the only predictive factor to be verified in Level I studies. Further studies are needed to investigate the value of hepcidin, c-reactive protein, and other measures as predictive factors.

In these updated guidelines, we explored a new question of whether oral or intravenous iron supplementation increases the response rate to erythropoietic proteins. We found no evidence of increased response with the addition of oral iron supplementation, but there is Level II evidence of improved response to erythropoietic proteins with the addition of intravenous iron. However, the doses and schedules for intravenous iron supplementation are not yet well defined, and further studies in this area are warranted.

The two major goals of erythropoietic protein therapy are prevention or elimination of transfusions and improvement of QoL. The total body of evidence shows that red blood cell (RBC) transfusion requirements are reduced following treatment with erythropoietic proteins. This analysis also confirms that QoL is significantly improved in patients with chemotherapy-induced anaemia and in those with anaemia of chronic disease following erythropoietic protein therapy, with more robust evidence now available that QoL was improved in studies investigating early intervention in cases of chemotherapy- or radiotherapy-induced anaemia.

There is only indirect 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. None of the studies addressed the question in a prospective, randomised fashion, and so the Taskforce does not recommend dose escalation as a general approach in all patients who are not responding.

There is still insufficient data to determine the effect on survival following treatment with erythropoietic proteins in conjunction with chemotherapy or radiotherapy. Our analysis of survival endpoints in studies involving patients receiving radio(chemo)therapy found that most studies were inconclusive, with no clear link between the use of erythropoietic proteins and survival. Likewise, we found no clear link between erythropoietic therapy and other endpoints such as local tumour control, time to progression, and progression-free survival.

There is no evidence that pure red cell aplasia occurs in cancer patients following treatment with erythropoietic proteins, and the fear of this condition developing should not lead to erythropoietic proteins being withheld 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.

Additional trials are warranted, especially to define the optimal doses and schedules of intravenous iron supplementation during erythropoietic therapy. While our review did not address cost benefit evaluations in detail, the consensus is that studies taking into account all real determinants of cost and benefit need to be performed prospectively.

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1. Introduction

Anaemia is frequent in cancer patients, especially those receiving chemotherapy or radiotherapy, and is detrimental to the patient's quality of life (QoL). Treatment of anaemia with erythropoietic proteins (EPO) poses fewer risks than red blood cell (RBC) transfusions and provides a more sustained correction of anaemia, and is more convenient for patients.

Erythropoietin therapy is established as an important option for the treatment of patients with anaemia, but questions remain. For example, up to one-third of patients with chemotherapy-associated anaemia do not respond to rHuEPO

(recombinant human erythropoietin), and responses take several weeks to develop. Intravenous, but not oral, iron supplementation improves haemoglobin (Hb) response to rHuEPO in patients with anaemia associated with chronic kidney disease[2,3] and in cancer patients.[4–7] The question of whether treating anaemia with erythropoietins affects survival rates remains contentious, with conflicting study findings.

An independent working party, endorsed by the European Organisation for Research and Treatment of Cancer (EORTC), was 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. The first EORTC guidelines were published in 2004[1] and are herein revised.

2. Patients and methods

Searches used the same databases and search terms as those used in the original (2004) guidelines, limited to clinical studies with erythropoietic proteins in anaemic patients with cancer or lymphoproliferative malignancies aged ⩾18 years. For the 2004 guidelines, electronic searches were conducted using the Pre-MEDLINE and MEDLINE database for English language records from 1 January 1996 to 1 September 2003. The update was performed from 2 September 2003 to 16 November 2005, and included abstracts from the American Society of Haematology (ASH) 2005 annual congress.

For the update search, abstract books were manually searched: American Society of Clinical Oncology (ASCO) 2003–2005; European Cancer Conference (ECCO) 2003, 2005; European Society for Medical Oncology (ESMO) 2004; European Haematology Association (EHA) 2004, 2005; American Association for Cancer Research (AACR) 2004, 2005; ASH 2004, 2005; World Conference on Lung Cancer (WCLC) 2005. In addition, the following manufacturers of erythropoietic proteins, Amgen, F. Hoffmann-La Roche Ltd, and Ortho Biotech, a division of Janssen-Cilag, were invited to submit papers accepted for publication by November 2005. 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[8] (Table 1) were applied to the results of the literature search to classify data according to study design. The EORTC Taskforce reviewed the search findings and agreed the evidence levels for each of the questions described in Table 2. This allowed grading recommendations to be made (Table 3). The Results section below details the studies identified in the update search.

3. Results

In the updated search, a total of 43 published studies (27 using epoetin alfa, six unspecified rHuEPO, seven epoetin beta and 13 darbepoetin alfa) and additional 78 relevant abstracts were identified (33 using epoetin alfa, nine unspecified rHuEPO, 28 darbepoetin alfa and 18 epoetin beta). Overall, 19 studies identified in the update search were classified as Level I (12 full papers and seven abstracts). 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*

Ninety new studies relating to the use of EPO were identified. Twenty-nine were published papers (16 using epoetin alfa, four epoetin beta, 13 darbepoetin alfa and four unspecified rHuEPO) and 61 abstracts (25 using epoetin alfa, eight unspecified rHuEPO, 24 darbepoetin alfa and 13 epoetin beta).

Hb threshold for initiation of therapy. In the updated search, 38 out of 58 studies enrolled patients with Hb between 9 and 11 g/dL, including two Level I studies.[9,10] Twenty studies used alternative thresholds, including one Level I study using a threshold of ⩽12 g/dL.[11]

Target Hb concentration. Fourteen out of 31 studies, graded as Level I–IV, defined the target Hb as 12–13 g/dL, but none specifically addressed the correlation between target Hb level and clinical benefit. Seventeen studies used alternative targets.

Impact of erythropoietic proteins on Hb concentration. Seventy-four studies addressed (all positive) the impact of EPO on Hb.

Table 1 – ASCO levels of evidence and grades of recommendation [8]

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

Table 2 – Questions addressed by the guidelines

In anaemic patients with cancer

1. Is 9–11 g/dL the standard range for initiation of therapy with erythropoietic proteins?
2. Is the target Hb concentration 12–13 g/dL?
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 three times per week)?
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?
15. Does iron supplementation increase the response rate to erythropoietic proteins?
    a) Oral supplementation
    b) Intravenous supplementation

Abbreviations: Hb, haemoglobin; RBC, red blood cell; QoL, quality of life; PRCA, pure red cell aplasia.

Table 3 – Summary of grade recommendations (total publications from original and update searches)

Question[a]	Chemotherapy-induced anaemia (167)	Radiotherapy-induced anaemia (7)	Anaemia due to surgery (11)	Anaemia of chronic disease (24)	Prevention of chemotherapy- or radiotherapy-induced anaemia (26)	Bone marrow or HSC transplantation (13)
1 (initiation at 9–11 g/dL)	A (122)	C (5)	D (1)	A (18)	A (8)	D (7)
2 (target 12–13 g/dL)	C (63)	B –ve (3)	D (3)	C (6)	C (19)	D (4)
3 (treatment increases Hb)	A (147)	B (4)	A (9)	A (22)	A (25)	A (8)
4 (increase dose in non-response)	B (14)	D (0)	D (0)	B (3)	D (1)	D (0)
5 (RBC transfusion)	A (66)	C (3)	C (8)	C (7)	A (14)	B (13)
6 (QoL)	A (77)	D (3)	D (0)	A (9)	C (11)	D (1)
7 (survival)	A –ve (15)	D (2)	D (1)	A –ve (3)	D (6)	D (1)
8 (less frequent dosing)	A (85)	D (0)	D (1)	B (8)	A (6)	D (0)
9 (higher initial doses)	B (12)	D (0)	D (1)	B (2)	D (1)	D (0)
10 (baseline parameters)	A (33)	D (0)	D (0)	C (4)	A (3)	D (0)
11 (prophylaxis)	A (9)	D[b] (1)	A (11)	D (0)	A (16)	D (0)
12 (fixed doses)	A (80)	D (2)	D (1)	B (13)	C (8)	D[b] (2)
13 (PRCA)	A –ve (17)	D (0)	D (0)	B –ve (5)	A –ve (2)	D (1)
14 (TEEs and hypertension)	A (23)	A –ve (1)	B (3)	B (2)	C (4)	D (1)
15 (iron supplementation)	B –ve (5)	D (1)	D (0)	D[b] (1)	D (0)	D (0)
a (oral)	C –ve (2)	D (1)	D (0)	D (0)	D (0)	D (0)
b (intravenous)	B (4)	D (0)	D (0)	D[b] (1)	D (0)	D (0)

The total number of papers and abstracts addressing each of the therapeutic areas and each of the questions is shown in parentheses.
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.
Abbreviations: HSC, haematopoietic stem cell; Hb, haemoglobin; RBC, red blood cell; QoL, quality of life; -ve, negative; TEE, thromboembolic events.
a Questions are defined fully in Table 2.
b Abstract evidence only.

Three published studies[11–13] and one abstract[14] were graded as Level I, all of which used epoetin alfa. Fourteen studies were graded Level II and 53 Level III.

Dose increases in non-responders. There was only Level III and IV support from two published papers[15,16] and two abstracts.[6,17] None performed a randomised comparison of a

dose increase versus an unchanged prolonged dosing. In all studies, an increased response rate (of up to an additional 18%) was observed.

RBC transfusion requirements. All new twenty studies reported statistically significantly lower RBC transfusion requirements (approximately 20% reduction compared with controls). Four studies were graded as Level I, three published papers[11–13] and one abstract,[14] all of which used epoetin alfa; 16 studies were Level II or III. One abstract provided conflicting Level II evidence, in which the median number of transfusions after 4 weeks was 13 with standard care and 7.5 with epoetin alfa ($P = 0.14$).[18]

QoL improvements. Thirty-five studies addressed QoL, with all but one indicating QoL improvements, as determined by various QoL measures (FACT-Fatigue [FACT-F], FACT-An, Linear Analog Scale Assessment [LASA], QLQ-C30). Three published studies were Level I, two using epoetin alfa[11,19] and one unspecified rHuEPO.[4] One Level I published study provided conflicting evidence.[13]

Survival. Ten studies addressed the issue of survival in chemotherapy-induced anaemia, six published[12,13,20–23] and four abstracts.[14,24–26] Only one study suggested some benefit among 42 patients;[26] the other studies showed no significant results.

Less frequent dosing. Fifty-one studies, including five Level I, provided evidence for less than three times per week dosing. Three Level I published studies used epoetin alfa[11,13,27] while two studies used darbepoetin alfa (one published paper[28] and one abstract[29]). A recently published Level II study by Steensma et al.[20] (originally identified as a 2005 abstract in the update search) demonstrated that Q3W dosing of epoetin alfa was as effective as weekly dosing in terms of transfusion requirements and QoL with similar safety profiles. Patients in the QW dosing group, however, achieved a higher mean Hb level at the end of the study compared with the Q3W group (12.0 versus 11.5 g/dL, $P = 0.0006$). An additional 16 studies provided Level II evidence for less frequent dosing regimens (six epoetin alfa, five beta, six darbepoetin, and one rHuEPO), while 25 provided Level III evidence (14 epoetin alfa, two beta, and 12 darbepoetin).

Higher initial doses. Higher than recommended initial doses of erythropoietic proteins increased Hb response in one published study[16] and three abstracts[30–32] graded as Levels II–IV. One abstract provided conflicting Level III evidence.[33]

Predictors of response. One published Level I study using darbepoetin alfa reported that the increase in Hb levels was greater for the group of patients with baseline Hb < 10 g/dL compared with the group of patients with a higher baseline Hb.[10] This contrasts with studies of early intervention to prevent further anaemia (given in Section 3.3.1.), in which patients with higher Hb levels at the start of treatment achieved a greater haematological response.[34,35] Other potential predictors were discussed by nine Level II–IV studies - three published papers[11,15,21] and six abstracts.[36–41] Conflicting evidence was provided by four Level II–III studies - two published papers[13,42] and two abstracts.[43,44]

Prophylactic use of erythropoietic proteins. Level I evidence for the prophylactic use of EPO in non-anaemic patients receiving chemotherapy was provided by one abstract using epoetin alfa,[14] Level II–IV evidence in two published studies[38,45] and two abstracts.[46,47] However, taken together with the data discussed in Section 3.3.2., this approach is not recommended by the Taskforce group.

3.1.2. *Radiotherapy-induced anaemia*

Four papers[48–51] and two abstracts[52,53] relating to the use of erythropoietic proteins for the treatment of radiotherapy-induced anaemia were identified. One study was Level I,[48] one Level II,[52] and four Level III.[50,51,53]

Three showed positive effects of EPO on Hb.[51–53] Reduced need for RBC transfusion[51,52] and improved QoL[49,52] were noted.

An analysis of survival endpoints in patients receiving radio(chemo)therapy was carried out across the evidence base from both this update and that used for the existing guidelines. Of nine studies,[48,51,52,54–59] four used epoetin alfa,[51,56–58] two used epoetin beta,[55,59] one meta-analysis covered studies using both epoetins alfa and beta[48] and two studies did not specify the agent used.[52,54] Of the studies that had overall survival as an endpoint, six were 'neutral', one Level III published study[51] highlighted a trend towards improved overall survival and one Level I published study, Henke et al.,[55] concluded that the use of EPO significantly worsened overall survival. This latter study has used erythropoietic proteins in a prophylactic fashion in mostly non-anaemic patients to achieve higher than recommended Hb levels (after 4 weeks of epoetin therapy, mean [SD] level was 14.8 [1.8] g/dL, with these levels being maintained thereafter). In summary no clear link between the use of erythropoietic agents and survival in patients undergoing radio(chemo)therapy was seen.

3.1.3. *Anaemia due to surgery*

Two new published Level II studies were identified. In one,[60] patients undergoing colorectal surgery had greater mean Hb levels and haematocrit with epoetin alfa plus iron than with iron alone, both before and after surgery, with less transfusion need. Another study[61] compared rHuEPO plus iron with iron alone in women undergoing surgery for gynaecological cancer. Mean Hb levels were significantly higher in the group receiving rHuEPO pre- and post-operatively.

3.2. *Anaemia of chronic disease*

Eleven studies relating to the use of EPO in cancer patients not receiving anticancer treatment were identified (six using epoetin alfa,[35,63–65] two unspecified rHuEPO,[7,66] three epoetin beta[63,67,68] and two darbepoetin alfa.[21,69]

Hb threshold for initiation of therapy. One Level I published study used the range of 9–11 g/dL for the initiation of therapy.[21] A further five studies gave supporting Level II–IV evidence, one published[63] and four abstracts;[7,64,65,69] however, none compared the effects of different baseline Hb levels on response to treatment. There was also conflicting Level I–IV evidence regarding the threshold level for anaemia treatment from two published studies that enrolled patients with Hb levels <12 g/dL.[67,70]

Target Hb concentration. One published Level III study used a target Hb concentration of 12–13 g/dL, but did not address the correlation between target Hb level and clinical benefit.[35] Another Level III abstract presented conflicting evidence.[65]

Impact of erythropoietic proteins on Hb concentration. Was reported positive in nine studies (Hb response rate: 31–90%), providing Level II–IV evidence.[35,62,64,65,67–70]

Dose increases in non-responders. A study in 29 patients[67] provided indirect Level III evidence that increasing the dose of erythropoietic proteins in non-responders produces a subsequent Hb increase. Three patients who did not have a haematopoietic response with epoetin beta at 30,000 IU per week responded to a 50% dose increase.

RBC transfusion requirements. Two abstracts provided evidence for a reduction in RBC transfusion requirements, one Level III study with epoetin beta,[68] and one Level II study with darbepoetin alfa.[69]

QoL improvements. One published study[67] and two abstracts[64,69] graded as Levels II–III provided supporting evidence that QoL is improved following erythropoietic protein therapy in patients not receiving chemotherapy.

Survival. In a Level III abstract, there was no difference in overall survival noted among erythropoietin users as compared with non users.[66]

Less frequent dosing. Two abstracts provided Level II evidence,[62,69] and one published study[67] and two abstracts[64,65] provided supporting Level III evidence that dosing of erythropoietic proteins less than three times per week is possible in anaemia of chronic disease.

Predictors of response. Two Level III studies reported that baseline patient parameters impact on response to erythropoietic proteins, one published study[67] and one abstract.[7] The baseline percentage of hypochromic erythrocytes, week 2 percentage of reticulocytes, week 2 absolute reticulocyte count, week 2 reticulocytes haematocrit, and week 2 reticulocyte Hb were predictors of response to rHuEPO in one study,[7] but another gave conflicting Level II evidence, finding no major differences between patient subgroups.[69]

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 further anaemia or development of anaemia*

3.3.1. *Early intervention (prevention of further anaemia)*

Nine Level II–III studies addressed prevention of more severe anaemia by early erythropoietin treatment in patients whose Hb levels were slightly below 12 g/dL, and Hb levels were improved in all studies, four of which were published papers[35,57,71,72] and five abstracts.[26,47,59,73,74] In a Level III study by Hudis *et al.*[71] patients with breast cancer who had Hb levels between 10 and 14 g/dL received treatment with epoetin alfa (at baseline, 40% of patients had Hb $\leqslant$ 12 g/dL and 60% had Hb > 12 g/dL). Treatment significantly increased Hb levels and improved QoL, and this was true across all subgroups stratified by baseline Hb level (Hb $\geqslant$ 10–$\leqslant$11, Hb > 11–$\leqslant$12, etc). In a Level II study by Straus *et al.*[34] patients received 'early' treatment (Hb levels between 10 and 12 g/dL) or 'late' treatment (Hb level <9 g/dL). A greater proportion of patients in the 'early' treatment group achieved a haematological response (Hb level $\geqslant$12 g/dL or increase by $\geqslant$2 g/dL) compared with the 'late' treatment group (70% versus 25%) and fewer patients in the 'early' group required RBC transfusion (18% versus 26%). Similarly, in a Level III study by Shasha *et al.*[35] 74% of patients receiving radiotherapy and/or chemotherapy with baseline Hb levels $\leqslant$11 g/dL achieved a haematological response with epoetin alfa treatment, with improved QoL also reported. In a Level III study by Reinhardt *et al.*[72] involving patients receiving chemo(radio)therapy with Hb $\leqslant$ 12 g/dL who were experiencing high levels of fatigue, treatment with epoetin alfa increased Hb levels while reducing the severity of fatigue. There was Level III evidence of a survival advantage in patients with ovarian cancer with Hb levels 10.6–11.9 g/dL who were treated with epoetin alfa prior to chemotherapy, with a relapse-free survival time of 26 months compared with 18 for patients not receiving erythropoietin therapy,[26] although conflicting evidence was provided in the Level II study, in which there was a neutral effect on survival.[59] Supporting Levels II and III evidence that less frequent dosing of erythropoietic proteins is possible for early intervention therapy was obtained.[35,72,73,75]

3.3.2. *Prevention in non-anaemic patients*

One published paper[76] and three abstracts[58,75,77] addressed the issue of whether treatment with EPO is effective in preventing anaemia in patients receiving chemo- or radiotherapy who are not yet anaemic. Three showed a positive effect on Hb levels,[75–77] and two showed a reduced need for RBC transfusion.[58,75] Improved QoL was also reported in one study.[58] In the study by Leyland-Jones *et al.*[76] in which epoetin alfa treatment was initiated in breast cancer patients with Hb levels $\leqslant$13 g/dL there was evidence of significantly reduced survival at 12 months (70% in the epoetin alfa group compared with 76% in the placebo group, $P = 0.01$). The study by Vadhan-Raj *et al.*[77] in which patients with a mean baseline Hb level of 13 g/dL received epoetin alfa, was terminated prematurely due to an increased incidence of thromboembolic events (21% with epoetin alfa versus 3% with placebo).

3.4. *Bone marrow or haematopoietic stem cell transplantation*

No new references for this indication were identified in the update searches.

3.5. *Fixed versus weight-based dosing of erythropoietic proteins*

Overall, 51 studies graded as Level I–V administered a fixed dose (ranging from 1000 IU TIW to 60,000 IU QW) of erythropoietic protein to patients with cancer. Two of these studies were graded as Level I,[10,28] but only one in patients with chemotherapy-induced anaemia compared a fixed dose with a weight-based dose, providing supporting Level I evidence.[10]

3.6. *PRCA*

Among 2552 patients (1013 receiving darbepoetin alfa, 133 receiving epoetin beta, and 1220 receiving epoetin alfa) enrolled in one Level I study,[42] three Level II studies,[11,12,78] one Level III study,[66] one Level IV study,[17] and one Level V report,[79] anti-erythropoietic antibodies were detected in two patients

with chemotherapy-induced anaemia[17] and nine patients with chronic kidney disease.[79]

3.7. Thromboembolic events and hypertension

Two Level I studies, one published meta-analysis[80] and one abstract presentation of a meta-analysis,[81] showed evidence for increased risk of thromboembolic events. In a previous COCHRANE meta-analysis by Bohlius *et al.*,[48] a slight increase in the risk of hypertension and thromboembolic events was found to be not statistically significant (based on data from 1656 and 1738 patients, respectively in 12 studies). An updated meta-analysis by Bohlius *et al.*,[80] which analysed data from 6769 patients in 35 trials, concluded that there was evidence that erythropoietin significantly increased the risk of thrombosis or related complications (RR = 1.67; 95% CI 1.35, 2.06).

3.8. Iron supplementation

Seven publications addressed the issue of whether oral or intravenous iron supplementation increased the response rate to erythropoietic proteins; three were published full papers[4,50,82] and four were abstracts[5–7,83] A Level III study by Pawlicki *et al.*[82] of epoetin alfa in 215 patients with chemotherapy-induced anaemia found no additional benefits with oral iron supplementation. Of two Level II studies by Auerbach *et al.*[4] and Henry *et al.*[5] of rHuEPO in chemotherapy induced anaemia, one study demonstrated greater increases in Hb levels, haematopoietic response rates, and QoL improvements in patients receiving intravenous iron supplementation compared with those receiving oral iron or no iron.[4] Intravenous iron supplementation was also beneficial in two Level III studies reported by Katodritou *et al.*[7] and Agrawal *et al.*;[6] in these studies, patients who did not respond to treatment with rHuEPO subsequently showed improved response rates when given intravenous iron. A Level III pilot study by Henke *et al.*[50] also found positive effects of oral iron supplementation in radiotherapy-induced anaemia. In an abstract by Galliano *et al.*,[83] intravenous iron supplementation produced increased Hb levels in 78% of patients who were defined as having functional iron deficiency, although this response rate was not statistically compared with that from a separate group of anaemic patients given epoetin beta alone.

4. Discussion

The results of this updated systematic literature review are broadly similar to those of our previous review. One-hundred and twenty publications were included from our update search, taking the total number of studies considered in these guidelines to 248. Only two studies were found in our update search for treatment of anaemia due to surgery, and none for bone marrow and stem cell transplantation.

In our updated guidelines (detailed in Table 4), we highlight the recommendation that causes of anaemia other than cancer or its treatment should be evaluated first. Iron deficiency, nutritional defects, bleeding, or haemolysis should be corrected prior to erythropoietic protein therapy. Functional iron deficiency should be addressed with intravenous iron (see below).

In the updated search, a total of 38 new studies (including three Level I studies, bringing the total to 122 studies) provided supporting evidence for initiating therapy at a Hb level of 9–11 g/dL in chemotherapy-induced anaemia, while one additional Level III study provided supporting evidence in radiotherapy induced anaemia (total 5 studies) (overall grade A recommendation). Our recommendation that patients with cancer-related anaemia not undergoing chemotherapy and/or radiotherapy should have treatment with erythropoietic proteins initiated at a Hb level of 9–11 g/dL based on anaemia-related symptoms remains a grade B recommendation. We believe that patients whose Hb level is below 9 g/dL should be evaluated for need of transfusions, and that erythropoietic proteins should be added, although the lack of specific studies investigating the need to transfuse these patients results in a grade C recommendation.

Previously, we recommended that erythropoietic proteins may be possibly considered in asymptomatic, anaemic patients with a Hb level of 9–11 g/dL to prevent a further decline in Hb, based on careful evaluation of individual factors (e.g. type, intensity, and remaining duration of chemotherapy, baseline Hb) (grade D). However, early intervention studies have all involved patients whose Hb levels have fallen slightly below 12 g/dL and shown the benefits of using such an approach in terms of haematological response, reducing the need for RBC transfusion, and improving QoL.[26,34, 35,47,57,59,71–74] Therefore, we have updated this recommendation to state that erythropoietic proteins may be considered in asymptomatic, anaemic patients with a Hb level of $\leqslant$11.9 g/dL (based on careful consideration of individual factors and treatment situation in order to prevent more severe anaemia, such as duration and intensity of remaining planned chemotherapy), and upgraded this recommendation to grade B. In contrast to this early intervention approach, 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, and this has been upgraded from grade B to grade A.

The majority of the studies discussed under 3.8. support a grade B recommendation that there is no evidence for increased response with the addition of oral iron supplementation, and a grade B recommendation that there is evidence of improved response with intravenous iron supplementation. However, the doses and schedules for intravenous iron supplementation are not yet well defined. Recently completed and presented studies comprise of the NIFe study and AIM3 study. NIFe is a randomised study of epoetin beta 30,000 IU once weekly alone versus epoetin beta plus intravenous iron, and the group receiving additional iron had quicker and greater Hb responses and a reduced epoetin dose requirement than the group receiving epoetin alone.[84] In the AIM3 study, intravenous iron supplementation with darbepoetin alfa given every 3 weeks improved clinical outcomes compared with oral iron or no iron supplementation.[85] The reader should check for the latest phase III evidence in the literature in this rapidly changing area.

Based on the clinical experience of the Taskforce, elderly patients experience the same benefits from treatment with erythropoietic proteins as younger patients. This was also

Table 4 – Recommendations of the Taskforce, plus grades (see Table 3)

Anaemia is a frequent clinically significant finding in cancer patients and should be carefully assessed.
The following recommendations are offered for anaemia management in adult cancer patients with solid tumours or haematological malignancies:

1. Causes of anaemia other than cancer or its treatment should be evaluated. Iron deficiency, nutritional defects, bleeding, or haemolysis should be corrected prior to erythropoietic protein therapy. Functional iron deficiency should be addressed with intravenous iron (see recommendations 7 and 17).
2. In cancer patients receiving chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a Hb level of 9–11 g/dL based on anaemia-related symptoms (grade A).
3. In patients with cancer-related anaemia not undergoing chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a Hb level of 9–11 g/dL based on anaemia-related symptoms (grade B).
4. Patients whose Hb level is below 9 g/dL should be evaluated for need of transfusions, in addition to erythropoietic proteins (grade C).
5. Erythropoietic proteins may be considered in asymptomatic, anaemic patients with a Hb level of $\leqslant$11.9 g/dL to prevent a further decline in Hb, according to individual factors (e.g. type/intensity of chemotherapy, baseline Hb) and the duration and type of further planned treatment (grade B).
6. 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 A).
7. There is no evidence of increased response to erythropoietic proteins with the addition of oral iron supplementation (grade B). There is evidence of improved response to erythropoietic proteins with intravenous iron supplementation (grade B).
8. Based on the clinical experience of the Taskforce, elderly patients experience the same benefits from treatment with erythropoietic proteins as younger patients (grade D).
9. The target Hb concentration should be 12 to 13 g/dL (grade B).
10. The two major goals of erythropoietic protein therapy are improvement of QoL and prevention of transfusions (grade A).
11. The use of erythropoietic proteins with the aim of improving survival or response to treatment should be evaluated in clinical trials in anaemic patients as there is insufficient evidence to support this use in practice (grade A).
12. Within reasonable limits of body weight, fixed doses of erythropoietic proteins should be used (grade A).
13. We recommend the administration of erythropoietic proteins according to Fig. 1. We do not recommend dose-escalation as a general approach in patients not responding within 4–8 weeks (grade B).
14. Treatment should be continued until the 12–13 g/dL level is reached and patients show symptomatic improvement. For patients reaching the target Hb, individualised treatment with increased intervals of dosing and/or titration of lowest effective maintenance dose should be made repeatedly (grade C).
15. The QW application of epoetin alfa QW (40,000 IU) is common practice (grade B) and registered in many countries. The use of epoetin beta weekly (30,000 IU) is registered for hematological diseases and its use in solid tumours is based on data provided for licensingextension (grade B). The use of darbepoetin alfa given every week or every third week has been shown to be effective in randomised trials (grade A) and registered. There is grade C evidence for the use of darbepoetin alfa given Q2W or Q4W.
16. The use of higher than licensed initial doses of erythropoietic proteins cannot be recommended with epoetin alfa, epoetin beta, or darbepoetin alfa (grade B).
17. There are no predictive factors of response to erythropoietic proteins that can be routinely used in clinical practice if functional iron deficiency or vitamin deficiency is ruled out; 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). Further studies are needed to define the value of hepcidin, c-reactive protein and others.
18. For patients undergoing autologous blood stem cell transplants, the effects of erythropoietic protein support has not yet been convincingly shown and cannot be recommended (grade B).
19. For patients undergoing allogeneic blood stem cell transplants, the clinical impact of erythropoietic proteins is limited and they can only be recommended based on an individual decision (grade B).
20. The fear of PRCA should not lead to erythropoietic proteins being withheld in patients with cancer (grade A).
21. When using erythropoietic proteins to treat anaemia in cancer patients, the combined analysis of all study data indicates an approximately 1.6-fold increased risk of thromboembolic events (grade A).

Abbreviations: Hb, haemoglobin; QoL, quality of life; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; EPO, erythropoietin; PRCA, pure red cell aplasia.

shown in a retrospective subgroup analysis of data from three studies of erythropoietin therapy in chemotherapy-induced anaemia.[86] Compared with younger patients aged <65 years, patients aged 65 years or older had similar increases in Hb levels, reduced need for transfusions, and improvement in QoL. The correction of anaemia may help to offset or delay functional decline in elderly individuals.[87]

A number of studies in the update search defined the target Hb concentration as 12–13 g/dL following treatment with erythropoietic proteins, consistent with our original search, with approximately equal numbers of studies providing supportive and conflicting evidence. Therefore, our recommendation that the target Hb concentration should be 12–13 g/dL remains a grade B.

The two major goals of erythropoietic protein therapy are improvement of QoL and prevention of transfusions (grade A, consistent with our previous guidelines). While RBC transfusion requirements are significantly reduced following treatment with erythropoietic proteins in cancer patients, the average number of units of blood saved is relatively modest in most studies. We confirm that QoL can be significantly improved in anaemic cancer patients following erythropoietic protein therapy.

There is no evidence (at Levels I or II) from our updated search that treatment with erythropoietic proteins improves survival, whereas data from two Level I studies, both of which used a preventive approach (treatment of patients with normal or near normal Hb levels), suggested that epoetin therapy

may (unexpectedly) result in inferior survival. These trials have been intensively discussed and appear not to be confirmed by other recently completed trials or by interim analyses of other, similarly designed ongoing studies. Therefore, our recommendation remains that the use of erythropoietic proteins with the aim of improving survival or response to treatment should be further evaluated in clinical trials in anaemic patients as there is insufficient evidence to conclude upon either a positive or negative impact based on the current literature (grade A).

There is evidence that fixed doses, rather than weight-based doses, of erythropoietic proteins can be used to treat patients with chemotherapy-induced anaemia. Overall, the addition of studies from our update search has approximately doubled the number of studies providing evidence for the use of fixed doses in anaemia associated with chemotherapy and chronic disease. Along with less frequent dosing, fixed dosing provides an improvement in the convenience of erythropoietin therapy. Therefore, we have upgraded our recommendation that, within reasonable limits of body weight, fixed doses of erythropoietic proteins should be used from grade B to grade A.

Six new studies describe permitted dose increases in non-responders, with subsequently improved response rates (resulting in a total of 18 studies across all searches). However, as in our previous review, none of the studies addressed the question in a prospective, randomised fashion and there is no evidence that dose escalation is beneficial compared with continuing erythropoietic proteins for a further period. Therefore, we maintain our grade B recommendation that the decision to dose-escalate in patients not responding within 4–8 weeks cannot be generally recommended and must be individualised, or even not recommended due to the lack of reasonable evidence (we have amended Fig. 1 from the version in our previous guidelines to reflect this). We also maintain that treatment should be continued until the 12–13 g/dl level is reached and patients show symptomatic improvement, and that for patients reaching the target Hb, individualised treatment with increased intervals of dosing and/or titration of lowest effective maintenance dose should be made repeatedly.

We found evidence to confirm that dosing of erythropoietic proteins less frequently than three times per week is possible in patients with chemotherapy-induced anaemia (a total of 83 studies), or when used to prevent cancer anaemia (a total of eight studies). Darbepoetin alfa with Q3W dosing intervals was shown to be effective in two Level I studies,[28,29] leading to a grade A recommendation for this regimen. Less robust evidence for Q2W and every 4 weeks (Q4W) dosing of darbepoetin alfa, however, prompts a grade C recommendation of these regimens. More recent data have recently been published,[88] but this study fell outside the data cut-off point for inclusion in these guidelines. The QW application of epoetin alfa QW (40,000 IU) is now common practice and registered in many countries (which, along with further evidence published for this dose, enabled us to upgrade our recommendation for its use from grade C to grade B). Three level I studies in the update search[11,13,27] demonstrated benefits with this dosing regimen in chemotherapy induced anaemia in terms of increased Hb levels or improved QoL. We maintain our grade B recommendation for the use of epoetin beta weekly (30,000 IU). Seven Level II–IV studies from the update search added to the overall body of evidence for this regimen of epoetin beta, including its use in solid tumours, an extension of the registered indication that is being examined by EMEA.

There is very limited evidence that initial doses of erythropoietic proteins considered to be higher than current standard practice (i.e. higher than current standard practice of 30,000–40,000 IU/week rHuEPO or 2.25 μg/kg/week darbepoetin alfa) may produce higher haematological responses when used to treat chemotherapy-induced anaemia, with only five abstracts reporting Level II–IV studies found in our update search, adding to an already limited body of evidence. We do not, therefore, recommend the use of higher initial doses of epoetin alfa, epoetin beta, or darbepoetin alfa (grade B).

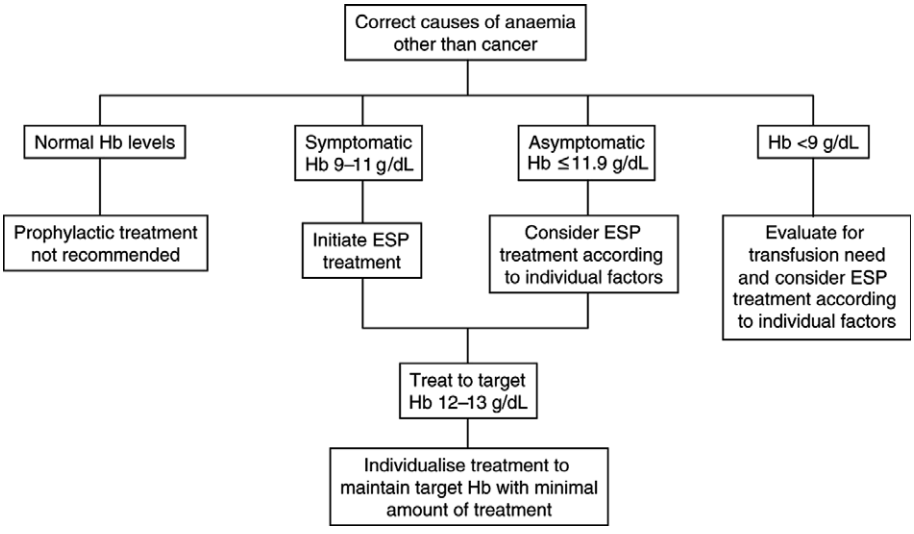

Fig. 1 – Suggested dosing algorithm for erythropoietic proteins in patients with cancer with anaemia due to cancer or its treatment. The target haemoglobin levels are discussed in Table 4 and are not above 13 g/dL. Abbreviation: ESP, erythropoiesis stimulating factor.

Evidence that baseline patient characteristics impact on response to erythropoietic proteins in patients with chemotherapy-induced anaemia was conflicting across studies, as in our previous review. Thus, we maintain our conclusion that there are no baseline predictive factors of response to erythropoietic proteins that can be routinely used in clinical practice if functional iron deficiency or vitamin deficiency is ruled out; a low serum EPO level (in particular in haematological malignancies) appears to be the only verified predictive factor of some importance (as demonstrated in three Level I studies identified in our original guidelines). Further studies are needed to investigate the value of hepcidin, c-reactive protein, and other measures as predictive factors. The iron-regulatory hormone hepcidin is of particular interest as it is believed to be the primary factor in anaemia of chronic disease. Cytokine-mediated induction of hepcidin in inflammatory conditions or infection increases iron uptake and retention by duodenal cells.[89] Likewise, c-reactive protein is also increased in inflammatory conditions, and high levels are associated with reduced Hb levels and resistance to epoetin. Therefore, pre-treatment levels of hepcidin and c-reactive protein may possibly provide important predictive information on the subsequent response to erythropoietic proteins in cancer patients.

As there were no new studies, our previous grade B recommendations remain that for patients undergoing blood stem cell transplants, the effects of erythropoietic proteins has not yet been convincingly shown and cannot be recommended; and that 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.

Out of a total of 4851 patients with cancer receiving erythropoietic proteins included across both searches, anti-erythropoietic antibodies were detected in two patients with chemotherapy-induced anaemia[17] and nine patients with chronic kidney disease[79] and no cases of pure PRCA were reported. The issue of PRCA in erythropoietic protein therapy arose when Casadevall and colleagues[90] reported the development of PRCA, in association with neutralising anti-erythropoietin antibodies, in 13 patients receiving epoetin alfa (EPREX®) for the anaemia of chronic renal failure, and further cases were subsequently reported with EPREX®. The total number of suspected PRCA cases with EPREX® in the nephrology setting has reduced dramatically, possibly due to a change in practice at the end of 2002 from subcutaneous to intravenous administration. However, recent studies have hypothesised that the formulation of EPREX® had been the primary cause of an upsurge in PRCA cases associated with this compound.[91,92] All but two reported cases of PRCA to date have occurred in patients with renal failure and not in patients with cancer.[93] We therefore maintain our original grade A recommendation that the fear of PRCA should not lead to erythropoietic proteins being withheld in patients with cancer. The FDA's interpretation of PRCA as anaemia associated with neutralising antibodies has resulted in a class label change for all three erythropoietic proteins marketed in the USA. If a patient develops a sudden loss of response, accompanied by severe anaemia and low reticulocyte count, an evaluation of causative factors should be undertaken. If anti-erythropoietin antibody-associated anaemia is suspected, erythropoietic proteins should be withheld, and the manufacturers contacted to perform assays for binding and neutralising antibodies. Erythropoietic proteins should be permanently discontinued in patients with antibody-mediated anaemia. Patients should not be switched to other erythropoietic proteins as there is potential for antibodies to cross react.

A meta-analysis of adverse effects with erythropoietin therapy by Bohlius *et al.*,[80] which included data from 35 trials, concluded that there was evidence to conclude that erythropoietin treatment increases the risk of thrombosis or related complications. Therefore, we maintain our previous grade B recommendation that combined analysis of all study data indicates an approximately 1.6-fold increased risk of thromboembolic events. However, this may be related to a variety of factors including the target Hb level achieved and the speed of the Hb increase. Further investigation is required to explore the thromboembolic effects of individual erythropoietins.

We do not comment on the relative efficacies of different erythropoietin formulations due to a lack of consistent findings from comparative studies. For example, two identically designed 16-week open-label studies identified in the update search, which compared weekly epoetin alfa with darbepoetin alfa given every 2 weeks, gave conflicting results. In a study by Waltzman *et al.*,[78] epoetin alfa showed superior efficacy, with a greater proportion of patients achieving an early Hb response, a greater mean increase in Hb levels, and a lower requirement for RBC transfusion with epoetin alfa compared with darbepoetin alfa. In a study reported by Schwartzberg et al.,[42] haemopoietic response was similar in the two groups, being achieved by 69% of patients receiving darbepoetin alfa and 72% of those receiving epoetin alfa. Increase in Hb levels and RBC transfusion requirements were similar in the two treatment groups. Similarly, a recently published study by Glaspy et al.,[88] showed similar benefits with epoetin alfa and darbepoetin alfa in terms of RBC transfusion requirement, increases in Hb levels, and QoL.

Our review also did not address cost considerations because of the absence of sufficient data on this subject. Prospective studies are required that take into account all real determinants of cost and benefits. Actual costs may be difficult to calculate; for example, the cost of a RBC pack is not only made up of the direct cost but also the indirect costs such as the donor's time away from work.

Conflict of interest statement

Carsten Bokemeyer has received presentation honoraria from Johnson and Johnson, F. Hoffmann-La Roche and Amgen; holds research grants from Amgen and serves on advisory boards for F. Hoffmann-La Roche and Amgen. Matti S. Aapro has received grants from, and serves on an advisory board and speaker's bureau for Amgen, F. Hoffmann-La Roche and Sanofi-Aventis. Anders Österborg holds research grants from F. Hoffmann-La Roche and Amgen. Hartmut Link has received grants from, and serves on a speakers bureau for Amgen and F. Hoffman-La Roche.

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