

# BMJ Open Combination with intravenous iron supplementation or doubling erythropoietin dose for patients with chemotherapy-induced anaemia inadequately responsive to initial erythropoietin treatment alone: study protocol for a randomised controlled trial

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**To cite:** Chen L, Jiang H, Gao W, *et al.* Combination with intravenous iron supplementation or doubling erythropoietin dose for patients with chemotherapy-induced anaemia inadequately responsive to initial erythropoietin treatment alone: study protocol for a randomised controlled trial. *BMJ Open* 2016;**6**:e012231. doi:10.1136/bmjopen-2016-012231

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2016-012231>).

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Received 12 April 2016  
Revised 24 August 2016  
Accepted 12 September 2016



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## ABSTRACT

**Introduction:** Erythropoietin (EPO) is a commonly used option in the treatment of chemotherapy-induced anaemia (CIA). However, ~30–50% of patients fail to achieve an adequate response after initial treatment. Prior studies have demonstrated that intravenous iron might synergistically improve therapeutic response to EPO treatment in this patient population.

**Methods and analysis:** We will perform this multicentre, randomised, open-label, parallel-group, active controlled non-inferiority study to compare the two combination therapies of EPO plus intravenous iron regimen versus doubling the dose of EPO in patients with CIA who have an inadequate response to initial EPO treatment at a routine dose. A total of 603 patients with an increase in haemoglobin (Hb) <1 g/dL will be enrolled and randomised to one of the three study treatment groups at a 1:1:1 ratio *Group 1:* EPO treatment at the original dose plus intravenous iron dextran 200 mg every 3 weeks (Q3W) for 15 weeks; *Group 2:* EPO treatment at the original dose plus intravenous iron dextran 100 mg, twice a week for 5 weeks; *Group 3:* the control group, doubling the EPO dose without preplanned iron supplementation. The primary outcome measure to compare is the Hb response rate at week 15 and the secondary end points involve therapeutic blood transfusions. Time-to-progression, adverse events and quality of life will also be evaluated.

**Ethics and dissemination:** All participants will provide informed consent; the study protocol has been approved by the independent ethics committee of Shanghai East Hospital. This study would clearly demonstrate the potential benefit of combining epoetin treatment with intravenous iron supplementation. Findings will be shared with participating hospitals,

## Strengths and limitations of this study

- An adequately powered randomised controlled trial.
- A specific subpopulation that until now has not seemingly been studied well.
- Focus on Chinese population alone, which might limit extrapolations of study findings.

policymakers and the academic community to promote the clinical management of CIA in China.

**Trial registration number:** NCT02731378.

## INTRODUCTION

Chemotherapy-induced anaemia (CIA) is a significant health problem for patients with cancer undergoing chemotherapy, causing fatigue and reducing quality of life (QoL).<sup>1 2</sup> Up to 75% of patients with cancer undergoing chemotherapy and/or radiotherapy reportedly experience mild-to-moderate anaemia (defined by a haemoglobin level of 9–11 g/dL).<sup>1 3</sup> In clinical trials, erythropoietins (EPOs) have been shown to increase haemoglobin levels and improve anaemia and QoL in patients with cancer.<sup>2 4–7</sup> However, recent meta-analyses have highlighted possible safety issues regarding EPO exposure. Preclinical studies have pointed towards the role of EPO in augmenting tumorigenesis, metastasis, risk of thrombosis and drug resistance in certain tumour types (eg, breast cancer), as it can activate

important antiapoptotic pathways (eg, AKT, ERK, JAK/STAT) targeted by current antineoplastic therapies, thus counteracting their effects.<sup>8–12</sup> Current guidelines in western countries<sup>13–16</sup> and China<sup>17</sup> recommend restricted usage of EPOs and reduction/prevention of blood transfusions in the treatment of CIA. Furthermore, it appears that patients with cancer experience a blunted EPO response to anaemia, in addition to inadequate EPO production.<sup>18</sup> Around 30–50% of patients receiving epoetin  $\alpha$  therapy for CIA do not achieve a clinically meaningful haematological response.<sup>2 5 19 20</sup>

However, the inadequate response to erythropoietic therapy has not been well characterised through rigorous studies and hence remains poorly handled in routine clinical practice. A major cause for not responding to EPO treatment is most likely functional iron deficiency (FID), which is defined as the failure to provide iron to the erythroblasts despite sufficient iron stores.<sup>21–23</sup> Patients with FID require supplementation of usable iron to optimise response to erythropoietic therapy, which might not be accomplished with oral iron.<sup>24</sup> In a recent prospective, open-label trial, patients receiving epoetin  $\alpha$  for CIA who were treated with intravenous iron dextran had a significantly greater Hb response compared with those receiving oral iron.<sup>25</sup> Meanwhile, in patients with CIA and no iron deficiency, intravenous iron supplementation significantly reduced treatment failures to darbepoetin without additional toxicity.<sup>26</sup> However, whether that intravenous iron supplementation increases the risk of disease progression, incidence of thrombosis and heart failure, as well as iron overload, is under careful investigation. Though the association between intravenous iron and serious adverse events (AEs)<sup>27</sup> and mortality<sup>28</sup> remains unclear, Zitt *et al.*<sup>29</sup> found that the use of intravenous iron was associated with a 22% reduction in mortality. Therefore, we designed this multicentre randomised trial to investigate EPOs in combination with intravenous iron with regard to an increase of Hb levels in patients who have inadequate responses to initial treatment with routine doses of EPOs. The optimal strategies for intravenous iron supplementation may warrant further investigation.<sup>30 31</sup> To the best of our knowledge, a cumulative intravenous iron dose of 1000 mg administered in our study is frequently used among prior reports<sup>32 33</sup> in an intensive mode (eg, accomplish total dose in the first 5 weeks) or a uniform one (eg, for a duration of 15 weeks); it should also be acceptable in our clinical practice. However, it seems that there is a lack of specific study to compare these various dosing regimens.<sup>30–34</sup> As a result, we included the two iron arms of equal total dose in our study, which makes it possible to carry out direct pairwise comparisons with the control in a single clinical trial.

## METHODS AND ANALYSIS

### Study design

This is a multicentre, randomised, open-label, parallel-group, active controlled non-inferiority study,

which will be conducted at approximately six study centres in China and will enrol ~603 eligible participants. The study flow chart is summarised in figure 1. Its study objectives are to assess the efficacy, safety and tolerability of two combination therapies of EPO plus intravenous iron regimen compared to doubling the dose of EPO in patients with CIA who are inadequately responsive with initial treatment of routine EPO dose. An additional key objective is to ascertain the potential effects of administering aggressive (100 mg, twice a week for 5 weeks) or sustained (200 mg every 3 weeks for 15 weeks) intravenous iron supplementation in the selected subpopulation. The study consists of a 2-week screening period, a 4-week initial treatment lead-in period with a prerandomisation visit, and a 15-week open-label treatment period (6 visits) and multiple post-treatment follow-up visits of up to 2 years until tumour progression, death or the study period ends.

The study will be initiated in April 2016 and may require a 2-year recruitment period. In the screening, patients who are diagnosed as having CIA (Hb <10 g/dL while undergoing chemotherapy) will be recruited for further eligibility assessment. In the lead-in period, the preliminarily screened patients are to be receiving EPO treatment for a planned 4-week period (routine dose 10 000 IU, three times weekly through subcutaneous injections). Thereafter, the patients with an increase of Hb <1 g/dL would be eligible and randomised to one of the following three groups at a 1:1:1 allocation ratio *Group 1*: EPO treatment at the original dose plus intravenous iron dextran 200 mg every 3 weeks (Q3W) for 15 weeks; *Group 2*: EPO treatment at the original dose plus intravenous iron dextran 100 mg, twice a week for 5 weeks; *Group 3*: the control group, doubling the EPO dose with no preplanned iron supplementation according to the current Chinese guidelines.<sup>17</sup> After the end of the 15-week study treatment period, long-term follow-up through a combination of outpatient on-site visits and telephone visits will be conducted for tumour assessment. It is expected that the intravenous iron added in Group 1 and Group 2 would increase the rate of response to EPO, and reduce the risk of required transfusions.<sup>1 21</sup>

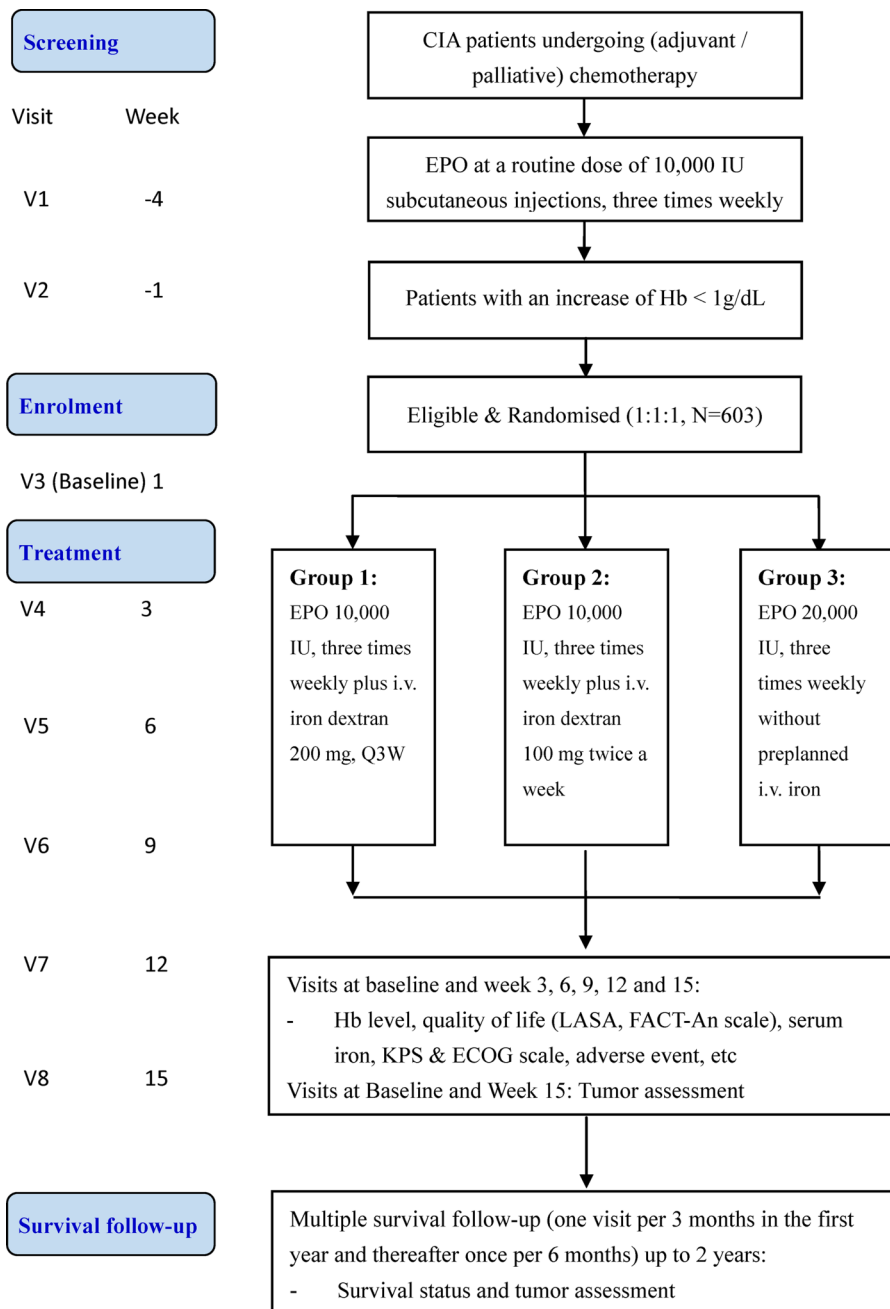
The study has been registered and the registration is ClinicalTrials.gov number, NCT02731378.

### Patients

Patients with cancer undergoing adjuvant or palliative chemotherapy are potential participants for the study. Patients who meet the following inclusion criteria will be considered eligible to recruit:

- ▶ Aged 18 years or older;
- ▶ Had a histologically, cytologically or clinically diagnosed malignant tumour and measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) V.1.1,<sup>35</sup>
- ▶ Undergoing adjuvant or palliative chemotherapy with an expected survival of at least 3 months;

**Figure 1** Study flow chart. CIA, chemotherapy-induced anaemia; ECOG, Eastern Cooperative Oncology Group; EPO, erythropoietin; FACT-An, Functional Assessment of Cancer Therapy-Anaemia; Hb, haemoglobin; IU, International Unit; KPS, Karnofsky Performance Status Scale; LASA, Linear Analogue Self-assessment; Q3W, Every 3 weeks.



- ▶ Inadequately responsive or unresponsive to routine dosages of EPO treatment. Inadequate responders or non-responders are defined as those patients with CIA with an increase of Hb <1 g/dL after 4 weeks of treatment with 10 000 IU of EPO, three times weekly by subcutaneous injection.
- ▶ Eastern Cooperative Oncology Group (ECOG) performance status (PS)  $\leq 2$ ;
- ▶ Are compliant and can understand the research and sign an informed consent form.

Patients with the following conditions will be excluded from the study:

- ▶ History of thromboembolism in the previous 12 months;
- ▶ Family history of haemochromatosis;
- ▶ Anaemia diagnosed with myelodysplastic syndrome or haematological diseases such as Mediterranean anaemia;
- ▶ Received EPO treatment in the prior 3 months;
- ▶ Received erythrocyte suspension transfusion in the prior 2 weeks;
- ▶ Women who are pregnant or lactating;
- ▶ Have a history of hypertension or mental illness.

#### Withdrawal management

Patients with CIA who have any of the following conditions will be allowed (or may be required) to withdraw from the study:

- ▶ Non-compliance in receiving the study drugs as required by study protocol;

- ▶ After enrolment, patients are found to meet major exclusion criteria; or
- ▶ Patients refuse to follow the study process.

### Study early termination

The study might be terminated early if any of the following conditions occur:

- ▶ Unexpected and uncontrolled adverse reactions happen in the course of the trial; or
- ▶ Significant protocol deviations are reported in the course of study conduct, which might substantially affect the treatment efficacy evaluation.

### Recruitment process

Recruitment of study participants will take place at the medical oncology department of all participating sites. Each participant will be assigned a unique identification number during the screening visit. At least one medical oncologist at each site will evaluate each of the screened patients for participation in the study based on inclusion and exclusion criteria.

### Randomisation process

Inadequate responders after 4-week EPO treatment will be randomly assigned to one of three study treatment groups at a 1:1:1 ratio. A stratified block randomisation with randomly varying block size will be performed, stratified according to study site, cisplatin-containing chemotherapy (yes vs no) and iron deficiency status at baseline (absolute vs functional). Random assignment is generated by a statistician from Shanghai Knowlands MedPharm Consulting Co, and implemented via random envelopes assigned to each site. In order to avoid potential selection bias, the sequence is concealed from both clinical staff and patients until assignment. Hence, neither investigators nor participants can influence which group the patients are assigned to.

### Description of the intervention

#### Intervention Group 1

Patients in this group will be administered intravenous iron dextran 200 mg via a 30 min infusion, Q3W, a maximum of five doses during the planned 15-week treatment period, together with a routine dose 10 000 IU of EPO, three times weekly by subcutaneous injections. Previous studies<sup>25 26 36</sup> show that intravenous administration of 100–300 mg of elemental iron every 3 weeks for a total dose of 1000 mg during the correction phase of anaemia will maximise the effectiveness of EPO. The single dose of iron 200 mg Q3W means an average dose of 67 mg per week, which is much lower than that in Group 2 (200 mg per week), since the 3-week administration interval results in a low calculated weekly iron dose in this group. Sensitivity analyses showed that intravenous iron-containing strategies remain cost-effective even with wide variations in the assumptions, particularly for cost savings with regard to EPO.<sup>37</sup> All of the EPO and intravenous iron

supplementations administered in the study are provided by Shenyang 3SBio, but the company will neither participate in data collection, analysis or editing, nor make decisions about any publication strategies.

At baseline prior to the start of treatment and thereafter every 3 weeks in the study treatment period, we will perform the following testing: complete peripheral blood cell count, physical examination, KPS (Karnofsky Performance Status Scale) & ECOG (Eastern Cooperative Oncology Group) scale, QoL, serum iron level (ferritin and transferrin saturation), and liver and kidney function.

#### Intervention Group 2

The EPO treatment for intervention Group 2 is the same as that for intervention Group 1, except for the intravenous iron dextran dosage. Patients here will receive iron dextran 100 mg twice a week through 30 min of intravenous infusion, and the total dose for the possibly consecutive 5-week treatment is 1000 mg (200 mg per week on average). Similar to those in Group 1, peripheral blood cell count will be assessed every week after the start of treatment; QoL and serum iron levels will be evaluated at baseline and at weeks 3, 6, 9, 12 and 15.

#### Intervention Group 3 (controls)

Study patients in the control group will receive double EPO dosage to 20 000 IU, three times a week by subcutaneous injections with a maximum of five doses for the entire study treatment period. Additional study measurements include EPO treatment dose and cumulative EPO costs.<sup>37 38</sup>

### Outcome measures

All of the baseline, in-treatment and follow-up evaluations will be performed by experienced investigators in the study. The primary outcome measure is Hb response rate at week 15. A patient with CIA would be defined as an Hb responder to study treatment if either the Hb concentration of this patient is at least 12 g/dL or there is an increase in Hb levels of more than 2 g/dL compared to baseline level without blood transfusions initiated in the previous 28 days.<sup>36</sup> This definition was also adopted in prior studies of EPOs among patients with CIA.<sup>5 38</sup>

Secondary outcome measures include the proportions of patients requiring therapeutic blood transfusions and the volume of transfused blood. Administration of EPO could significantly reduce the requirement for blood transfusions. In addition, we will also assess QoL of study patients using the Linear Analogue Self-Assessment (LASA) test and the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) test. LASA is a self-assessment tool, with a graduation of 8 mm. It is designed to measure physical status, activities of daily living and overall QoL. FACT-An is a questionnaire which contains 55 tumour-related items, including a



subscale for assessing fatigue-related anaemia. For cost-effectiveness analysis, dose of the study drug (EPO and intravenous iron supplementation) actually prescribed will be collected for each individual patient.

Given the safety concerns regarding EPOs related to survival and tumour progression, we will additionally measure time-to-progression, which is defined as the time interval from randomisation until objective tumour progression. Tumour assessment according to RECIST<sup>35</sup> will be performed at baseline, week 15 and then once per 3 months in the first year and thereafter per 6 months. As in some other trials, AEs related to study treatment will be recorded and collected at each visit. The safety profile of EPO and intravenous iron is evaluated by examining the incidence of AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, VERSION V4.0).<sup>39</sup>

### Sample size calculation

We used R V.3.2.3 (R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2014. <http://www.R-project.org/> (last accessed 10 Dec 2015) to conduct sample size estimation. The primary outcome measure is Hb response rate at week 15. With a sample size of 181 patients per group randomised, the pairwise comparison will be powered at 80% to establish non-inferiority for the primary end point, at a one-sided  $\alpha$  level of 0.025, with a non-inferiority margin of 12%, assuming that the true effects are the same between treatments. Given an expected dropout rate of 10%, a total of 603 patients (201 patients per group) will be required to enrol into the study. Using this 12% non-inferiority margin might keep 75% efficacy of weekly EPO 36 000 IU over placebo among patients with CIA.<sup>40</sup>

### Statistical analysis

The full analysis set according to the intent-to-treat principle will be established as the primary analysis population. Such data as demographics, baseline characteristics, safety and QoL will be summarised according to treatment group. The primary efficacy outcomes will be analysed using the Cochran-Mantel-Haenszel (CMH) test with study site, cisplatin-containing chemotherapy used or not and iron deficiency status at baseline as stratification factors. A logistic regression model will also be used to compare treatment effects by means of OR after adjusting for the aforementioned stratification factors. The TTP as survival data will be described with the use of the Kaplan-Meier curve, and analysed with log-rank test as well as the Cox proportional hazards model if proportional hazard assumptions hold true. Mixed-model repeated measure containing terms for treatment group, time, baseline measurement and time by treatment group interaction will be used to compare QoL data in the study.

The Holm-Bonferroni method<sup>41</sup> will be applied to account for multiple testing of the primary outcomes in the two non-inferiority pairwise comparisons. Therefore,

a p value of  $<0.025$  will be considered to indicate statistical significance for the lower p value, and a p value of  $<0.05$  will be considered to indicate significance for the higher p value. R, V.3.2.3 and SAS software, V.9.2 (SAS Institute, North Carolina, USA) will be used for the statistical analysis.

### Ethics and dissemination

#### Ethical considerations

The independent ethics committee of Shanghai East Hospital approved the study protocol for all the participating centres (Approval No 2016003). The ethics committee agreed that this study will not raise patients' risk or cause extra harm to patients. It also agreed that the study is in accordance with the Declaration of Helsinki and that the study will be conducted without ethics problems. Written informed consent must be signed by patients or patients' proxies in cases of impaired decision-making capacity prior to enrolment.

#### Relevance and dissemination

Our study is to specifically target inadequate responders to erythropoietic therapy at a routine dose alone, a sub-population that until now has not seemingly been studied well. It is expected that this multicentre, adequately powered randomised controlled trial will clearly demonstrate the potential benefit of combining epoetin treatment with intravenous iron supplementation.

First, the intravenous iron supplementation is expected to replace EPO values or reduce the cumulative EPO dose. A cost benefit could be achieved with intravenous iron supplementation added instead of the EPO alone regimen.<sup>42</sup> On the other hand, two regimes of iron supplementation will be compared so as to optimise iron administration for patients with CIA. Overall, as expected, the three treatment regimens will raise haemoglobin levels, reduce the proportion of patients requiring transfusions and improve patients' QoL. Second, collecting TTP information is in response to widespread concern regarding shortened overall survival and/or TTP due to EPOs.<sup>43–49</sup> Such safety issues have been discussed by regulatory authorities in the USA and Europe for several years.<sup>40</sup> In addition, as regards analysis, for the purpose of controlling any possible biases resulting from varied tumour type, chemotherapy agent/regimen, baseline iron level, etc we will use stratified randomisation technique as is appropriate for this study. This had better help set up any statistical modelling for data analysis. Multiplicity issues would also be controlled using the Holm-Bonferroni method.<sup>41</sup>

In summary, intravenous iron supplementation might be considered to be administered concurrently with EPO therapy in patients with CIA. The study findings will be shared with participating hospitals, policymakers and the academic community to promote the clinical management of CIA in China.

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**Acknowledgements** The authors wish to thank Sam Zhong (SZ) for his generous assistance with this study.

**Contributors** YG and LC conceived and designed the study. HJ and SZ supervised the power analyses and wrote the data analyses section. WG and LC bear overall responsibility for the design, ethical conduct and publication of the study. Administrative, technical and material support was provided by FCG and YJM. All authors edited the draft and contributed substantially to the manuscript; they all approved this submission.

**Funding** This study was funded by the National Natural Science Foundation of China (approval number 81573004); the Outstanding Leaders Training Programme of Pudong Health Bureau of Shanghai (PWRI2013-02); the Key Disciplines Group Construction Project of Pudong Health Bureau of Shanghai (PWZxq2014-04); the National Natural Science Foundation of China Youth Science Fund (approval number 81301537); and the Shanghai Young Physicians Training Programme.

**Competing interests** None declared.

**Ethics approval** Independent ethics committee of Shanghai East Hospital.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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**REFERENCES**

- Groopman JE, Itri LM. Chemotherapy-induced anaemia in adults: incidence and treatment. *J Natl Cancer Inst* 1999;91:1616–34.
- Littlewood TJ, Bajetta E, Nortier JW, *et al.* Epoetin Alfa Study Group. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001;19:2865–74.
- Ludwig H, Van Belle S, Barrett-Lee P, *et al.* The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *Eur J Cancer* 2004;40:2293–306.
- Gabrilove JL, Cleeland CS, Livingston RB, *et al.* Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol* 2001;19:2875–82.
- Osterborg A, Brandberg Y, Molostova V, *et al.* Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin beta, in hematologic malignancies. *J Clin Oncol* 2002;20:2486–94.
- Boogaerts M, Coiffier B, Kainz C; Epoetin Beta QOL Working Group. Impact of epoetin beta on quality of life in patients with malignant disease. *Br J Cancer* 2003;88:988–95.
- Mäenpää J, Puistola U, Riska H, *et al.* Impact of epoetin-beta on anaemia and health-related quality of life in cancer patients: a prospective observational study using the generic 15D instrument. *Anticancer Res* 2014;34:2325–9.
- Hedley BD, Chu JE, Ormond DG, *et al.* Recombinant human erythropoietin in combination with chemotherapy increases breast cancer metastasis in preclinical mouse models. *Clin Cancer Res* 2011;17:6151–62.
- Hedley BD, Allan AL, Xenocostas A. The role of erythropoietin and erythropoiesis-stimulating agents in tumor progression. *Clin Cancer Res* 2011;17:6373–80.
- Todaro M, Turdo A, Bartucci M, *et al.* Erythropoietin activates cell survival pathways in breast cancer stem-like cells to protect them from chemotherapy. *Cancer Res* 2013;73:6393–400.
- Zhou B, Damrauer JS, Bailey ST, *et al.* Erythropoietin promotes breast tumorigenesis through tumor-initiating cell self-renewal. *J Clin Invest* 2014;124:553–63.
- Liang K, Qiu S, Lu Y, *et al.* Autocrine/paracrine erythropoietin regulates migration and invasion potential and the stemness of human breast cancer cells. *Cancer Biol Ther* 2014;15:89–98.
- Aapro MS, Link H. September 2007 update on EORTC guidelines and anaemia management with erythropoiesis-stimulating agents. *Oncologist* 2008;13(Suppl 3):33–6.
- Bokemeyer C, Aapro MS, Courdi A, *et al.* EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. *Eur J Cancer* 2007;43:258–70.
- Rodgers GM 3rd, Becker PS, Blinder M, *et al.* Cancer- and chemotherapy-induced anaemia. *J Natl Compr Canc Netw* 2012;10:628–53.
- Rizzo JD, Brouwers M, Hurley P, *et al.* American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood* 2010;116:4045–59.
- Experts Committee on Cancer-Related Anaemia; Chinese Society of Clinical Oncology (CSCO). Clinical practice guidelines on cancer-related anaemia (2012–2013 Edition). *Chin Clin Oncol* 2012;1:18.
- Means RT Jr, Krantz SB. Progress in understanding the pathogenesis of the anaemia of chronic disease. *Blood* 1992;80:1639–47.
- Demetri GD, Kris M, Wade J, *et al.* Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. *J Clin Oncol* 1998;16:3412–25.
- Glaspy J, Bukowski R, Steinberg D, *et al.* Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit Study Group. *J Clin Oncol* 1997;15:1218–34.
- Glaspy J, Cavill I. Role of iron in optimizing responses of anemic cancer patients to erythropoietin. *Oncology (Williston Park, NY)* 1999;13:461–73. discussion 477–8, 483–8.
- Glaspy J, Beguin Y. Anaemia management strategies: optimising treatment using epoetin beta (NeoRecormon). *Oncology* 2005;69:8–16.
- Cavill I, Auerbach M, Bailie GR, *et al.* Iron and the anaemia of chronic disease: a review and strategic recommendations. *Curr Med Res Opin* 2006;22:731–7.
- Pedrazzoli P, Rosti G, Secondino S, *et al.* Iron supplementation and erythropoiesis-stimulatory agents in the treatment of cancer anemia. *Cancer* 2009;115:1169–73.
- Auerbach M, Ballard H, Trout JR, *et al.* Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. *J Clin Oncol* 2004;22:1301–7.
- Pedrazzoli P, Farris A, Del Prete S, *et al.* Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alpha. *J Clin Oncol* 2008;26:1619–25.
- Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. *Kidney Int* 2015;88:905–14.
- Charytan DM, Pai AB, Chan CT, *et al.* Considerations and challenges in defining optimal iron utilization in hemodialysis. *J Am Soc Nephrol* 2015;26:1238–47.
- Zitt E, Sturm G, Kronenberg F, *et al.* Iron supplementation and mortality in incident dialysis patients: an observational study. *PLoS ONE* 2014;9:e114144.
- Kshirsagar AV, Freburger JK, Ellis AR, *et al.* Intravenous iron supplementation practices and short-term risk of cardiovascular events in hemodialysis patients. *PLoS ONE* 2013;8:e78930.
- Petrelli F, Borgonovo K, Cabiddu M, *et al.* Addition of iron to erythropoiesis-stimulating agents in cancer patients: a meta-analysis of randomized trials. *J Cancer Res Clin Oncol* 2012;138:179–87.
- Steensma DP, Sloan JA, Dakhil SR, *et al.* Phase III, randomized study of the effects of parenteral iron, oral iron, or no iron supplementation on the erythropoietic response to darbepoetin alfa for patients with chemotherapy-associated anemia. *J Clin Oncol* 2011;29:97–105.
- Gafter-Gvili A, Rozen-Zvi B, Vidal L, *et al.* Intravenous iron supplementation for the treatment of chemotherapy-induced

- anaemia—systematic review and meta-analysis of randomised controlled trials. *Acta Oncol* 2013;52:18–29.
34. Mhaskar R, Wao H, Miladinovic B, *et al*. The role of iron in the management of chemotherapy-induced anemia in cancer patients receiving erythropoiesis-stimulating agents. *Cochrane Database Syst Rev* 2016;2:CD009624.
  35. Therasse P, Arbuck SG, Eisenhauer EA, *et al*. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
  36. Bastit L, Vandebroek A, Altintas S, *et al*. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alfa administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. *J Clin Oncol* 2008;26:1611–18.
  37. Luporsi E, Mahi L, Morre C, *et al*. Evaluation of cost savings with ferric carboxymaltose in anaemia treatment through its impact on erythropoiesis-stimulating agents and blood transfusion: French healthcare payer perspective. *J Med Econ* 2012;15:225–32.
  38. Pashos CL, Larholt K, Fraser KA, *et al*. Outcomes of erythropoiesis-stimulating agents in cancer patients with chemotherapy-induced anemia. *Support Care Cancer* 2012;20:159–65.
  39. National Cancer Institute (USA). Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. 2010. <http://evs.nci.nih.gov/ftp1/CTCAE/About.html> (last accessed 10 Dec 2015).
  40. Fujisaka Y, Sugiyama T, Saito H, *et al*. Randomised, phase III trial of epoetin- $\beta$  to treat chemotherapy-induced anaemia according to the EU regulation. *Br J Cancer* 2011;105:1267–72.
  41. Aickin M, Gensler H. Adjusting for multiple testing when reporting research results: the Bonferroni vs Holm methods. *Am J Public Health* 1996;86:726–8.
  42. Hedenus M, Näsman P, Liwing J. Economic evaluation in Sweden of epoetin beta with intravenous iron supplementation in anaemic patients with lymphoproliferative malignancies not receiving chemotherapy. *J Clin Pharm Ther* 2008;33:365–74.
  43. Hedenus M, Adriansson M, San Miguel J, *et al*. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. *Br J Haematol* 2003;122:394–403.
  44. Amgen Announces Interim Results of Aranesp? “PREPARE” Study in Breast Cancer Patients. [http://www.immunex.com/media/media\\_pr\\_detail.jsp?year=2007&releaseID=1083091](http://www.immunex.com/media/media_pr_detail.jsp?year=2007&releaseID=1083091) (last accessed 10 Dec 2015).
  45. Smith RE Jr, Aapro MS, Ludwig H, *et al*. Darbepoetin alpha for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Oncol* 2008;26:1040–50.
  46. Henke M, Laszig R, Rube C, *et al*. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 2003;362:1255–60.
  47. Leyland-Jones B, Semiglazov V, Pawlicki M, *et al*. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol* 2005;23:5960–72.
  48. Thomas G, Ali S, Hoebbers FJ, *et al*. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecol Oncol* 2008;108:317–25.
  49. Wright JR, Ung YC, Julian JA, *et al*. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol* 2007;25:1027–32.