Effects of erythropoiesis-stimulating agents on fatigue- and anaemia-related symptoms in cancer patients: systematic review and meta-analyses of published and unpublished data

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Background: Erythropoiesis-stimulating agents (ESAs) reduce the need for red blood cell transfusions; however, they increase the risk of thromboembolic events and mortality. The impact of ESAs on quality of life (QoL) is controversial and led to different recommendations of medical societies and authorities in the USA and Europe. We aimed to critically evaluate and quantify the effects of ESAs on QoL in cancer patients.

Methods: We included data from randomised controlled trials (RCTs) on the effects of ESAs on QoL in cancer patients. Randomised controlled trials were identified by searching electronic data bases and other sources up to January 2011. To reduce publication and outcome reporting biases, we included unreported results from clinical study reports. We conducted meta-analyses on fatigue- and anaemia-related symptoms measured with the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) and FACT-Anaemia (FACT-An) subscales (primary outcomes) or other validated instruments.

Results: We identified 58 eligible RCTs. Clinical study reports were available for 27% (4 out of 15) of the investigator-initiated trials and 95% (41 out of 43) of the industry-initiated trials. We excluded 21 RTCs as we could not use their QoL data for meta-analyses, either because of incomplete reporting (17 RCTs) or because of premature closure of the trial (4 RCTs). We included 37 RCTs with 10581 patients; 21 RCTs were placebo controlled. Chemotherapy was given in 27 of the 37 RCTs. The median baseline haemoglobin (Hb) level was 10.1 g dl–1; in 8 studies ESAs were stopped at Hb levels below 13 g dl –1 and in 27 above 13 g dl –1. For FACT-F, the mean difference (MD) was 2.41 (95% confidence interval (95% CI) 1.39–3.43; P < 0.0001; 23 studies, n = 6108) in all cancer patients and 2.81 (95% CI 1.73–3.90; P < 0.0001; 19 RCTs, n = 4697) in patients receiving chemotherapy, which was below the threshold (≥3) for a clinically important difference (CID). Erythropoiesis-stimulating agents had a positive effect on anaemia-related symptoms (MD 4.09; 95% CI 2.37–5.80; P = 0.001; 14 studies, n = 2765) in all cancer patients and 4.50 (95% CI 2.55–6.45; P < 0.0001; 11 RCTs, n = 2436) in patients receiving chemotherapy, which was above the threshold (≥4) for a CID. Of note, this effect persisted when we restricted the analysis to placebo-controlled RCTs in patients receiving chemotherapy. There was some evidence that the MDs for FACT-F were above the threshold for a CID in RCTs including cancer patients receiving chemotherapy with Hb levels below 12 g dl–1 at baseline and in RCTs stopping ESAs at Hb levels above 13 g dl–1. However, these findings for FACT-F were not confirmed when we restricted the analysis to placebo-controlled RCTs in patients receiving chemotherapy.

Conclusions: In cancer patients, particularly those receiving chemotherapy, we found that ESAs provide a small but clinically important improvement in anaemia-related symptoms (FACT-An). For fatigue-related symptoms (FACT-F), the overall effect did not reach the threshold for a CID.

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Received 1 April 2013; revised 27 February 2014; accepted 10 March 2014; published online 17 April 2014

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www.bjcancer.com | DOI:10.1038/bjc.2014.171

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Erythropoiesis-stimulating agents (ESAs) reduce the need for red blood cell transfusions (Bohlius et al, 2006b; Ludwig et al, 2009; Tonelli et al, 2009) and may improve quality of life (QoL); however, they increase the risk of thromboembolic events and death. A large meta-analysis based on individual patient data (IPD) from 53 randomised controlled trials (RCTs) demonstrated a statistically significant, 17% higher risk of mortality during the active study phase in cancer patients who received ESAs compared with controls (Bohlius et al, 2009a,b). An increased risk of mortality was also reported in each of the more recent systematic reviews and meta-analyses, which were not funded by the pharmaceutical industry (Bennett et al, 2008; Tonelli et al, 2009; Tonia et al, 2012; Grant et al, 2013) but in none of the systematic reviews and meta-analyses sponsored by the pharmaceutical industry (Aapro et al, 2008b; Glasy et al, 2010). Several meta-analyses have shown that ESAs increase the risk of thromboembolic events in cancer patients (Bohlius et al, 2006a,b; Seidenfeld et al, 2006; Aapro et al, 2008b, 2009; Bennett et al, 2008; Ludwig et al, 2009; Tonelli et al, 2009); the effects of ESAs on tumour progression remain uncertain (Aapro et al, 2012).

The impact of ESAs on QoL is controversial. Positive findings from observational studies (Glasy et al, 1997; Demetri et al, 1998; Gabrilove et al, 2001; Quirt et al, 2001; Cella et al, 2003) and clinical trials (Littlewood et al, 2001; Fallowfield et al, 2002; Chang et al, 2005; Wilkinson et al, 2006) have not been confirmed in more recent RCTs (Smith et al, 2008; Hoskin et al, 2009; Engert et al, 2010; Fujisaka et al, 2011; Nitz et al, 2011). Previous meta-analyses have demonstrated that ESAs effectively reduce fatigue-related symptoms in cancer patients (Minton et al, 2008, 2010; Tonelli et al, 2009). However, these meta-analyses were restricted to the published literature and may be compromised by publication and outcome reporting biases (Egger and Smith, 1998; Dwan et al, 2011; Redmond et al, 2013). Publication bias refers to the fact that studies with positive results are more likely to be published compared with studies with negative results (Egger and Smith, 1998). Outcome reporting bias refers to the selective reporting of outcomes in a published study, where mainly the most statistically significant results or the ones meeting the authors’ assumptions are reported (Dwan et al, 2011; Redmond et al, 2013). Meta-analyses including only published results may be prone to bias and overestimate treatment effects.

We aimed to critically evaluate and quantify the effects of ESAs on QoL in cancer. We systematically reviewed and meta-analysed RCTs that compared ESAs with controls in cancer patients. Our objectives were to examine the effects of ESAs on patient-rated fatigue- and anaemia-related symptoms and to identify groups of patients who may benefit most from treatment with ESAs. To reduce potential publication bias and outcome reporting biases, we included unpublished and unreported data.

We updated literature searches from our previous meta-analyses on ESAs (Bohlius et al, 2006a,b, 2009a,b) in Medline, Embase, Cochrane Central Register of Controlled Trials and databases of conference proceedings for the years 2008 to January 2011 (for details, see Supplementary Webappendix Table 1). We screened the reference lists of relevant meta-analyses and clinical trials registries (http://clinicaltrials.gov/; http://www.isrctn.org/). Four reviewers (AM, JF, NR and TT) worked in pairs and independently determined study eligibility. Data on study characteristics, study quality and outcomes were extracted by one reviewer (TT) and checked for accuracy by another (JB). Our primary sources of data extraction were the published study documents. We complemented these data with information from study protocols and reports, which we had obtained from ESA manufacturers (Amgen, Thousand Oaks, CA, USA; Johnson & Johnson, New Brunswick, NJ, USA; Hoffmann-La Roche, Basel, Switzerland) and clinical study groups for a previous IPD meta-analysis (Bohlius et al, 2009a,b). For that meta-analysis, we had identified published and unpublished trials through electronic searches of published abstracts and articles, screening of clinical trials registries and Oncologic Drugs Advisory Committee hearing documents, and contacting ESA manufacturers and experts in the field. We had obtained clinical study reports as requested for 98% (48 out of 49) of the trials initiated by the ESAs manufacturers and 36% (5 out of 14) of the trials run by clinical study groups, for details see Bohlius et al (2009a,b). In addition, we searched for QoL results in clinical trials registries (http://clinicaltrials.gov/; http://www.isrctn.org/).

Outcomes. Our primary outcomes were fatigue- and anaemia-related symptoms measured with the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subscale and the FACT-Anaemia (FACT-An) subscale. The FACT-F includes 13 fatigue-related questions (range of scale 0–52). The FACT-An (range of scale 0–80) includes the 13 fatigue-related items plus 7 anaemia-related questions, for example, dizziness, headaches, pain in chest and trouble walking. These instruments are widely used in ESA trials, are highly responsive to change, and have good convergent and discriminant validity (Cella, 1997, 2007; Yellen et al, 1997; Cella et al, 2002b). Secondary outcomes included changes in the cancer-specific FACT-G total score (range 0–108) and the subscales on physical, functional and social/family well-being (range 0–28) and emotional well-being (range 0–24). For sensitivity analyses, we included the fatigue- and anaemia-related subscales from studies that used instruments other than FACT-F and FACT-An, that is, EORTC QLQ-C30 (Aaronson et al, 1993), SF-36 (Ware and Sherbourne, 1992), FACT-An subscale non-fatigue items (Cella, 1997), FACT-An full scale (Cella, 1997) and visual analogue scales (VAS) assessing energy, daily activities and overall health or QoL. For each instrument, we predefined the specific domain that best corresponded to fatigue- and anaemia-related symptoms, physical, functional, social/family, emotional well-being and overall QoL as measured by FACT-F, FACT-An, FACT-G and its subscales. We defined a clinically important difference (CID) as a mean difference (MD) of ≥3 for FACT-F (Cella et al, 2002b) and ≥4 for FACT-An (D Cella, personal communication, March 2010). For standardised effect sizes, an effect size of 0.20–0.50 s.d. units was considered small but clinically important, whereas effect sizes of 0.50–0.80 and >0.80 were considered to be moderate and large differences, respectively (Sloan and Dueck, 2004; Sloan et al, 2006).

Statistical methods. Results from individual studies were expressed either as differences in mean changes from baseline to study end or as effect sizes. Effect sizes were calculated as the differences in mean values at the end of treatment divided by the pooled s.d. (Cohen’s d) (Cohen, 1988). If the required data were not reported, we used approximations (Reichenbach et al, 2007) to calculate differences or s.d. Data were analysed according to the intention-to-treat...
approach, using the last observation carried forward if data were missing. In sensitivity analyses, we analysed the data measured closest to week 12, a time point frequently considered in ESA trials. We used random-effects meta-analyses to combine trials and quantified heterogeneity with the $I^2$ statistic (Higgins et al., 2003).

In stratified analyses, we aimed to identify patient characteristics, treatment strategies and aspects of study design associated with the effect of ESAs on QoL, see Supplementary Webappendix Table 2. Tests of interactions and trends were obtained from univariate random-effects meta-regression models (Thompson and Sharp, 1999). Analyses were conducted in the entire data set, including all RCTs, only in chemotherapy trials and only in placebo-controlled RCTs in patients receiving chemotherapy. We investigated the association between trial size and treatment effects in funnel plots and regression tests (Sterne and Egger, 2001). To adjust for potential publication bias, we used the trim and fill method (sensitivity analysis) (Duval 2005). Results are presented as MDs or standardised MDs (SMDs) with 95% confidence intervals (95% CIs). We estimated treatment response as the proportion of patients achieving a CID (threshold 3 for FACT-F and 4 for FACT-An subscales). To estimate this treatment response, we used the inverse of the absolute difference between placebo-controlled RCTs in patients receiving chemotherapy.

Finally, we included 37 studies with 10,581 patients randomised (Abels, 1993; Case et al., 1993; Henry and Abels, 1994; Thatcher et al., 1999; Littlewood et al., 2001; Huddart et al., 2002; Kotasek et al., 2002, 2003; Osterborg et al., 2002; Vansteenkiste et al., 2002; Boogaerts et al., 2003; Hedenus et al., 2003; Iconomou et al., 2005; Milroy et al., 2003; P-174; Chang et al., 2005; Debus et al., 2005; Mystakidou et al., 2005; O’Shaughnessy et al., 2005; Savonije et al., 2005; Witzig et al., 2005; Wilkinson et al., 2006; Charu et al., 2007; Witzig et al., 2009).

RESULTS

Number of eligible, included and excluded studies. We identified 58 eligible RCTs. Clinical study reports were available for 27% (4 out of 15) of the trials run by clinical study groups and 95% (41 out of 43) of the trials initiated by the ESAs manufacturers. Of the 58 eligible RCTs, we excluded 21 RTCs for the following reasons: QoL data were not reported because of premature closure of the trials (Machtay et al., 2007; Thomas et al., 2008; AGO-OVAR 2.7; CR002305); or data reporting was too incomplete to allow any analysis (Rose et al., 1994; Dammacco et al., 2001; Qurt et al., 2001; Thomas et al., 2002; INT-1; INT-3; Leyland-Jones et al., 2005; Goss et al., 2005; Aapro et al., 2008a; Suzuki et al., 2008; EPO-GER-20; Gupta et al., 2009; Ray-Coquard et al., 2009; Yoshizaki et al., 2010; Untch et al., 2011; CDR0000069148; Moebus et al., 2013) (Figure 1).

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Characteristics of included studies. Characteristics of included studies are shown in Table 1 and Supplementary Webappendix Tables 3–5. Quality of life was the primary end point in 11 (30%) studies, a secondary end point in 25 trials, and was not mentioned as a study end point in one study. Most studies (n = 23) used the FACT-F subscale and/or (n = 14) the FACT-An subscale. Among the studies not reporting FACT-F or FACT-An, three studies reported the total score of the full FACT-An scale (47 items); one study used EORTC QLQ-C30, one SF-36 and five studies used VAS. Twenty-one (57%) studies were placebo controlled, 11 (30%) reported sample size calculations for a QoL end point, 9 (24%) defined a QoL hypothesis, 4 (11%) reported definitions for a clinically important change and 4 (11%) reported percentages of patients completing QoL questionnaires (submission rates). Chemotherapy was given in 27 of the 37 studies included (73%). Radiotherapy or radiochemotherapy was given in two studies and no anticancer treatment was given in six (16%). In one study, <70% of the included patients received chemotherapy (P = 0.134). The analysis of FACT-An included (P = 0.001) the FACT-An subscale. Among 14 studies, patients completing QoL questionnaires (submission rates). Chemotherapy was given in 27 of the 37 studies included (73%). Radiotherapy or radiochemotherapy was given in two studies and no anticancer treatment was given in six (16%). In one study, <70% of the included patients received chemotherapy (P = 0.134). The analysis of FACT-An included (P = 0.001) the FACT-An subscale. Among 14 studies, patients completing QoL questionnaires (submission rates). Chemotherapy was given in 27 of the 37 studies included (73%). Radiotherapy or radiochemotherapy was given in two studies and no anticancer treatment was given in six (16%). In one study, <70% of the included patients received chemotherapy (P = 0.134). The analysis of FACT-An included (P = 0.001) the FACT-An subscale. Among 14 studies, patients completing QoL questionnaires (submission rates). Chemotherapy was given in 27 of the 37 studies included (73%). Radiotherapy or radiochemotherapy was given in two studies and no anticancer treatment was given in six (16%). In one study, <70% of the included patients received chemotherapy (P = 0.134). The analysis of FACT-An included (P = 0.001) the FACT-An subscale. Among 14 studies, patients completing QoL questionnaires (submission rates). Chemotherapy was given in 27 of the 37 studies included (73%). Radiotherapy or radiochemotherapy was given in two studies and no anticancer treatment was given in six (16%). In one study, <70% of the included patients received chemotherapy (P = 0.134). The analysis of FACT-An included (P = 0.001) the FACT-An subscale. Among 14 studies, patients completing QoL questionnaires (submission rates). Chemotherapy was given in 27 of the 37 studies included (73%). Radiotherapy or radiochemotherapy was given in two studies and no anticancer treatment was given in six (16%). In one study, <70% of the included patients received chemotherapy (P = 0.134). The analysis of FACT-An included (P = 0.001) the FACT-An subscale. Among 14 studies, patients completing QoL questionnaires (submission rates). Chemotherapy was given in 27 of the 37 studies included (73%). Radiotherapy or radiochemotherapy was given in two studies and no anticancer treatment was given in six (16%). In one study, <70% of the included patients received chemotherapy (P = 0.134). The analysis of FACT-An included (P = 0.001) the FACT-An subscale. Among 14 studies, patients completing QoL questionnaires (submission rates). Chemotherapy was given in 27 of the 37 studies included (73%). Radiotherapy or radiochemotherapy was given in two studies and no anticancer treatment was given in six (16%). In one study, <70% of the included patients received chemotherapy (P = 0.134). The analysis of FACT-An included (P = 0.001) the FACT-An subscale. Among 14 studies, patients completing QoL questionnaires (submission rates). Chemotherapy was given in 27 of the 37 studies included (73%). Radiotherapy or radiochemotherapy was given in two studies and no anticancer treatment was given in six (16%). In one study, <70% of the included patients received chemotherapy (P = 0.134). The analysis of FACT-An included (P = 0.001) the FACT-An subscale. Among 14 studies, patients completing QoL questionnaires (submission rates). Chemotherapy was given in 27 of the 37 studies included (73%). Radiotherapy or radiochemotherapy was given in two studies and no anticancer treatment was given in six (16%). In one study, <70% of the included patients received chemotherapy (P = 0.134). The analysis of FACT-An included (P = 0.001) the FACT-An subscale. Among 14 studies, patients completing QoL questionnaires (submission rates). Ch...
Percentage of patients achieving a CID and NNT. We estimated the percentage of patients achieving a CID and corresponding NNTs based on hypothetical control groups. With a hypothetical response rate of 20% in the control group, the response rate in patients receiving ESAs is 27% (95% CI 24%–30%) for FACT-F and 29% (95% CI 25%–34%) for FACT-An with corresponding NNTs of 14 (95% CI 10–26) and 10 (95% CI 7–19). With a hypothetical response rate of 40% in the control group, the response rate in patients receiving ESAs is 49% (95% CI 45–52) for FACT-F and 52% (95% CI 47%–57%) for FACT-An with corresponding NNTs of 11 (95% CI 8–19) and 8 (95% CI 5–14).

**Table 1. Characteristics of included randomised controlled trials (Continued)**

| Characteristic                  | N of studies (%) |
|--------------------------------|-----------------|
| **Baseline Hb**                |                 |
| < 10 g dl⁻¹                    | 14 (37.84)      |
| 10–12 g dl⁻¹                   | 17 (45.95)      |
| > 12 g dl⁻¹                    | 6 (16.22)       |
| **Tumour type**                |                 |
| Solid                          | 20 (54.05)      |
| Haematological                 | 5 (13.51)       |
| Solid and haematological       | 12 (32.43)      |
| **Anticancer treatment**       |                 |
| Chemotherapy                   | 27 (72.97)      |
| Radiotherapy                   | 2 (5.41)        |
| No anticancer therapy          | 6 (16.22)       |
| Other/unclear                  | 2 (5.41)        |
| **Duration of ESA treatment**  |                 |
| < 9 Weeks                      | 2 (5.41)        |
| 9–16 Weeks                     | 18 (48.65)      |
| ≥ 17 Weeks                     | 4 (10.81)       |
| Until end of chemotherapy      | 13 (35.14)      |
| **Planned weekly ESA dose**    |                 |
| <40 000 U epo x/a or 30,000 U epo β or 100 µg darbepo | 9 (24.32) |
| = 40 000 U epo x/a or 30,000 U epo β or 100 µg darbepo | 9 (24.32) |
| >40 000 U epo x/a or 30,000 U epo β or 100 µg darbepo | 13 (35.14) |
| Other (e.g., weight based or Hb based) | 6 (16.22) |
| **Frequency of ESA administration** |                |
| TIW                            | 19 (51.35)      |
| QW                             | 11 (29.73)      |
| ≤ Q2W                          | 6 (16.22)       |
| Other                          | 1 (2.70)        |
| **Target Hb**                  |                 |
| ≤ 13 g dl⁻¹                    | 8 (21.62)       |
| > 13–15 g dl⁻¹                 | 27 (72.97)      |
| Not reported                   | 2 (5.41)        |
| **Placebo controlled**         |                 |
| Yes                            | 21 (56.76)      |
| No                             | 16 (43.24)      |
| **Study completed?**           |                 |
| Terminated/halted              | 7 (18.92)       |
| Completed                      | 30 (81.08)      |

**DISCUSSION**

We found that ESAs provide a small but clinically important improvement in anaemia-related symptoms (FACT-An), which was confirmed when the analysis was restricted to placebo-controlled RCTs in patients receiving chemotherapy. For fatigue-related symptoms (FACT-F), the overall effect did not reach the threshold for a CID. For FACT-F, there was some evidence that treatment effects were above the threshold for a CID in RCTs in patients receiving chemotherapy. For fatigue-related symptoms (FACT-An), the overall effect did not reach the threshold for a CID. For FACT-An, there was some evidence that treatment effects were above the threshold for a CID in RCTs in patients receiving chemotherapy. For FACT-F, there was some evidence that treatment effects were above the threshold for a CID in RCTs in patients receiving chemotherapy. For FACT-An, there was some evidence that treatment effects were above the threshold for a CID in RCTs in patients receiving chemotherapy.

We estimated the percentage of patients achieving a CID and NNTs based on hypothetical control groups. With a hypothetical response rate of 20% in the control group, the response rate in patients receiving ESAs is 27% (95% CI 24%–30%) for FACT-F and 29% (95% CI 25%–34%) for FACT-An with corresponding NNTs of 14 (95% CI 10–26) and 10 (95% CI 7–19). With a hypothetical response rate of 40% in the control group, the response rate in patients receiving ESAs is 49% (95% CI 45–52) for FACT-F and 52% (95% CI 47%–57%) for FACT-An with corresponding NNTs of 11 (95% CI 8–19) and 8 (95% CI 5–14).
influence of placebo effects (a potential bias in self-reported measures such as fatigue- and anaemia-related symptoms), we conducted additional analyses restricted to (1) chemotherapy RCTs regardless of blinding and (2) only placebo-controlled chemotherapy RCTs. However, there were only few placebo-controlled RCTs reporting QoL outcomes for patients receiving chemotherapy, which limited our ability to conduct stratified analyses in this setting. For example, both in the overall analyses and in those restricted to chemotherapy studies, FACT-F results were more favourable in studies that chose QoL as primary end point, compared with those that chose QoL as secondary end point. Only one study evaluating FACT-F as primary end point in patients receiving chemotherapy was placebo controlled, and so we cannot gauge the extent to which the effect observed for primary vs secondary end point was confounded by lack of blinding. The design of the included studies did not permit us to estimate the relative benefit of ESAs in Hb responders vs non-responders. This would have required RCTs that identified responders in a run in period and then randomised these responders to either stop or continue ESAs. Finally, decreased QoL in cancer patients is affected by factors other than anaemia. Correction of a single factor, as did the studies included in our meta-analyses, may not have adequately reflected the complex pathophysiological and psychological dimensions of patient-reported QoL.

Several limitations of our study underscore the need for open access to all clinical trials results including study protocols, amendments, reports and IPD as currently discussed at the European Medicines Agency (Eichler et al, 2012). First, the quality...
of reporting QoL data was low. Both in the published articles and the clinical study reports key information such as percentage of patients completing QoL questionnaires was missing or not clearly reported for the majority of studies. Critical review of clinical study documents by the academic community may help to improve the quality of reporting in these reports, which will only be possible with open access to these documents. Second, we identified another 16 trials (Kotaske et al, 2002, 2003; Thomas et al, 2002; Vansteenkiste et al, 2002; Boogaerts et al, 2003; Hedenus et al, 2003; Goss et al, 2005; Mystakidou et al, 2005; Witzig et al, 2005; Wilkinson et al, 2006; Aapro et al, 2008a; Gordon et al, 2008; Krazowski, 2008; Pirker et al, 2008; Strauss et al, 2008; EPO-GER-20, 2009a) measuring FACT-An that did not or only incompletely report their FACT-An results and could therefore not be included in our analyses. Access to IPD may have permitted to include these studies in our analysis and it is possible that including these studies would change the results of our analyses. We unsuccessfully tried to retrieve the IPD and hence evaluated unpublished aggregated QoL data found in clinical study reports. However, for results, which were not reported in these documents, we made no additional attempts to obtain these results from the investigators. We also assessed whether QoL results had been published in clinical trials registries, which was not the case. Finally, our analyses are based on aggregated data and therefore analyses of variables at patient level, such as Hb at baseline and stage of disease, are prone to ecological bias (Berlin et al, 2002). This limitation could be overcome with a meta-analysis based on IPD, but this was not available for the current analyses.

When judging the efficacy of ESAs on fatigue- and anemia-related symptoms, it is important to differentiate clinical from statistical significance. The concept of CIDs has been developed to address this problem (Cella et al, 2002a). However, defining CIDs is not straightforward. Depending on the clinical context and the methods selected, the threshold for CID could be set at different levels. For our primary analyses, we used the definition of Cella et al (2002b), which was developed to combine anchor- and distribution-based methods in populations similar to those we studied. Notably, the CIDs defined for FACT-F and FACT-An refer to changes from baseline to end of treatment. In our analyses, we used this yardstick to measure the differences in mean changes between groups from baseline to treatment, according to current practice in QoL studies (Tonelli et al, 2009; Minton et al, 2010).

Harmful effects of ESAs should be balanced against potential benefits. Previous meta-analyses have consistently shown that ESAs increase the risk of thromboembolic events in cancer patients by approximately factor 1.6 (Bohlius et al, 2006a,b; Seidenfeld et al, 2006; Aapro et al, 2008b, 2009; Bennett et al, 2008; Ludwig et al, 2009; Tonelli et al, 2009). Literature-based and IPD meta-analyses showed increased mortality (Bohlius et al, 2009a,b) or shortened overall survival in patients receiving ESAs (Bennett et al, 2008; Tonelli et al, 2009). Whether ESAs are safe for patients undergoing chemotherapy is a matter of debate. Our meta-analyses, and those of others based on IPD, have shown that ESAs increased short-term mortality in patients receiving chemotherapy by approximately 10% (Bohlius et al, 2009a,b; Ludwig et al, 2009), not reaching conventional levels of statistical significance. Statistically, the estimated mortality increase in chemotherapy trials can be explained by the same underlying effect as that in non-chemotherapy trials (Bohlius et al, 2009a,b). Clinically, the increase in mortality associated with ESAs may be less pronounced, or even absent, in patients receiving chemotherapy than in those undergoing other anticancer treatments. Two recent studies in cancer patients receiving chemotherapy did not find evidence for survival differences in patients receiving ESAs compared with controls (Engert et al, 2010; Moebus et al, 2013). In these studies, cancer patients were receiving chemotherapy with a curative intent and ESAs were stopped at Hb levels of 12 g dl$^{-1}$ (Engert et al, 2010) and 14 g dl$^{-1}$ (Moebus et al, 2013). Nevertheless, current evidence does not allow to conclude that ESAs are safe in patients receiving chemotherapy. Basic science studies have evaluated the presence of erythropoietin (EPO) receptors and its functionality in tumour cells (Arcasoy et al, 2005; Szenajch et al, 2010; Kumar et al, 2012). Interestingly, researchers without funding from ESA manufacturers were more likely to identify EPO receptors on cancer cells, EPO-induced signalling events or EPO-induced harmful changes of cellular function; or to conclude that ESAs had potentially harmful effects on cancer cells as compared with investigators receiving funding or being employed by ESA manufacturers (Bennett et al, 2010). Similarly, of the seven meta-analyses on the effects of ESAs in cancer patients conducted since 2008 none of the meta-analyses with funding from ESA manufacturers identified an increased mortality risk (Aapro et al, 2008b; Glaspy et al, 2010). In contrast, each of the meta-analyses conducted by researchers not receiving funding from ESA manufacturers found an increased risk either for on study mortality or overall survival.

Figure 3. Funnel plots for FACT-F (A) and FACT-An (B). Closed circles = results from published literature, open circles = results from clinical study reports.
Table 2. Stratified analyses for FACT-F in (i) all included RCTs, (ii) RCTs in patients receiving chemotherapy and (iii) placebo-controlled RCTs in patients receiving chemotherapy

| FACT-F | All RCTs | Chemotherapy RCTs | Placebo-controlled chemotherapy RCTs |
|--------|----------|------------------|--------------------------------------|
|        | Studies/ESA/ control | MD (95% CI) | P-value* | Studies/ESA/ control | MD (95% CI) | P-value* | Studies/ESA/ control | MD (95% CI) | P-value* |
| Overall | 23/3389/2719 | 2.41 (1.39 to 3.43) | | 19/2566/2131 | 2.81 (1.73 to 3.90) | | 10/1543/1171 | 1.78 (0.82 to 2.73) |
| Anticancer treatment | 0.218 | NA | NA |
| Chemotherapy | 0.063 | NA | NA |
| Radiotherapy | 0.079 | NA | NA |
| None | 0.042 | 0.362 | 0.153 |
| Anticancer treatment (condensed) | 0.025* | 0.005* | 0.225* |
| Chemotherapy | 0.023* | 0.044* | 0.134** |
| Radiotherapy, none | 0.008 | 0.053 | 0.105 |
| Baseline Hb | 0.054 | 0.083 | NA |
| Disease stage | 0.023* | 0.015* | 0.034** |
| QoL primary end point | 0.027 | 0.091 | 0.724 |
| Source of data | 0.907 | 0.537 | 0.446 |
| Full publication | 0.362 | 0.476 | NA |
| Study industry funded | 0.008 | 0.083 | NA |

Abbreviations: CI = confidence interval; ESA = erythropoiesis-stimulating agents; FACT-F = Functional Assessment of Cancer Therapy-Fatigue subscale; Hb = haemoglobin; MD = mean difference; NA = not applicable; QoL = quality of life; RCT = randomised controlled trial. Frequency: ≤Q2W = every second week or less frequent, QW = once per week, TNW = three times per week, other = frequency changing during the study. Planned weekly ESA dose: high = >40 000 U epoetin α/s or 30 000 U epoetin β or 100 μg darbepoetin, middle = 40 000 U epoetin α/s or 30 000 U epoetin β or 100 μg darbepoetin, low = <40 000 U epoetin α/s or 30 000 U epoetin β or 100 μg darbepoetin, other = weight based or Hb based.

*B-value: refers to test for interaction unless otherwise specified.
*BTest for trend.
*Not used for interaction/trend test.

This observation highlights the importance of conflicts of interest both in the clinical and the basic sciences. In the case of ESAs and mortality in cancer patients, this led to misleading results and conclusions in meta-analyses funded by the pharmaceutical industry. Of note, in our analyses we found no evidence that results from industry-funded studies differed from those not funded by the industry. However, this may be due to a lack of power in a setting were >90% of studies were funded by the industry.
These observations on the harmful effects of ESAs in cancer patients led to different recommendations of medical societies and authorities in the USA and Europe (Information for Health Professions, 2007; Aapro and Link, 2008; Rizzo et al, 2010; Schrijvers et al, 2010). The FDA and the American Societies of Clinical Oncology (ASCO) and Hematology (ASH) recommend the use of ESAs only in anaemic cancer patients receiving chemotherapy (Rizzo et al, 2010) with palliative treatment intent (Information for Health Professions, 2007) up to Hb level 12 g dl⁻¹ (Information for Health Professions, 2007) with the goal of

Table 3. Stratified analyses for FACT-An in (i) all included RCTs, (ii) RCTs in patients receiving chemotherapy and (iii) placebo-controlled RCTs in patients receiving chemotherapy

| FACT-An                            | All RCTs | Chemotherapy RCTs | Placebo-controlled chemotherapy RCTs |
|------------------------------------|----------|------------------|-----------------------------------|
|                                    | Studies/ESA control | MD (95% CI) | P-value  | Studies/ESA control | MD (95% CI) | P-value  | Studies/ESA control | MD (95% CI) | P-value  |
| Overall                            | 14/446/1299 | 4.09 (2.37 to 5.80) | 0.709 | 11/1310/1126 | 4.50 (2.55 to 6.45) | 4.55 (1.29 to 7.80) |
| Anticancer treatment               |          | NA               |       | NA               | NA               | NA               |
| Chemotherapy                       | 11/3130/1126 | 4.50 (2.55 to 6.45) | 0.709 | 11/1310/1126 | 4.50 (2.55 to 6.45) | 4.55 (1.29 to 7.80) |
| Radiotherapy                       | 11/126/133 | 1.60 (-2.24 to 5.44) | -     | NA               | NA               | NA               |
| None                               | 1/14/20  | 3.90 (-4.56 to 8.44) | -     | NA               | NA               | NA               |
| Uncleara                           | 1/16/20  | 0.60 (-9.64 to 8.44) | -     | NA               | NA               | NA               |
| Anticancer treatment (condensed)   |          | 0.458            |       | NA               | NA               | NA               |
| Chemotherapy                       | 11/1310/1126 | 4.50 (2.55 to 6.45) | 0.709 | 11/1310/1126 | 4.50 (2.55 to 6.45) | 4.55 (1.29 to 7.80) |
| Radiotherapy, none                 | 2/140/153 | 1.99 (-1.50 to 5.49) | -     | NA               | NA               | NA               |
| Unclearb                           | 1/16/20  | 0.60 (-9.64 to 8.44) | -     | NA               | NA               | NA               |
| Baseline Hb                        | 0.389    | 0.567            | 0.695 | NA               | NA               | NA               |
| >12 g dl⁻¹                          |          | 4.50 (2.55 to 6.45) | 0.709 |          | 4.50 (2.55 to 6.45) | 0.695 |
| <10 g dl⁻¹                          |          | 3.76 (0.87 to 6.64) | 0.709 |          | 3.76 (0.87 to 6.64) | 0.709 |
| Disease stage                      |          | 0.06a            | 0.064a| 0.277a         |          |       |
| >70% not metastatic/advanced       |          | 2.028/212        | 2.028/212 | 2.028/212 | 2.028/212 | 2.028/212 |
| >70% metastatic/advanced           |          | 2.028/212        | 2.028/212 | 2.028/212 | 2.028/212 | 2.028/212 |
| Other                              |          | 2.028/212        | 2.028/212 | 2.028/212 | 2.028/212 | 2.028/212 |
| Unknown                            |          | 2.028/212        | 2.028/212 | 2.028/212 | 2.028/212 | 2.028/212 |
| Frequency                          |          | 0.992c           | 0.801d | 0.64e         |          |       |
| QW                                 |          | 4.11 (0.96 to 7.25) | 0.709 |          | 4.11 (0.96 to 7.25) | 0.709 |
| TIV                                |          | 4.09 (1.84 to 6.34) | 0.709 |          | 4.09 (1.84 to 6.34) | 0.709 |
| Target Hb                          |          | 0.25             |       | NA               | NA               | NA               |
| >13-15 g dl⁻¹                       |          | 5.12 (2.63 to 6.41) | 0.709 |          | 5.12 (2.63 to 6.41) | 0.709 |
| ≤13 g dl⁻¹                          |          | 1.13 (-1.22 to 3.47) | 0.709 |          | 1.13 (-1.22 to 3.47) | 0.709 |
| Placebo control                    |          | 0.985            |       | NA               | NA               | NA               |
| Qol primary and point              |          | 0.471            |       | NA               | NA               | NA               |
| Yes                                |          | 5/473/248        | 0.471 |          | 5/473/248 | 0.471 |
| No                                 |          | 9/120/935        | 0.471 |          | 9/120/935 | 0.471 |
| Source of data                     |          | 0.229            |       | 0.24             | 0.259           |       |
| Full publication                   |          | 7/568/591        | 0.229 |          | 7/568/591 | 0.229 |
| Clinical study report              |          | 7/688/980        | 0.229 |          | 7/688/980 | 0.229 |
| Study industry funded              |          | 0.864            |       | 0.777           | NA               |       |
| Yes                                |          | 13/403/1236      | 0.864 |          | 13/403/1236 | 0.864 |
| No                                 |          | 1/63/63          | 0.864 |          | 1/63/63 | 0.864 |

Abbreviations: CI = confidence interval; ESA = erythropoiesis-stimulating agents; FACT-An = Functional Assessment of Cancer Therapy-Anaemia subscale; Hb = haemoglobin; MD = mean difference; NA = not applicable; Qol = quality of life; RCT = randomised controlled trial. Frequency: ≤ QCW = every second week or less frequent, QCW = once per week, TIV = three times per week, other = frequency changing during the study. Planned weekly ESA dose: high >40 000 U epoetin a/d or 30 000 U epoetin b or 100 µg darbepeoetin, middle = 40 000 U epoetin a/d or 30 000 U epoetin b or 100 µg darbepeoetin, low = <40 000 U epoetin a/d or 30 000 U epoetin b or 100 µg darbepeoetin, other = weight based or Hb based.  

*a-p-value: refers to test for interaction unless otherwise specified.  
*bNot used for interaction/trend test.  
*cTest for trend.
avoiding red blood cell transfusions (Information for Health Professions, 2007; Rizzo et al, 2010). The FDA and ASCO/ASH explicitly do not recommend the use of ESAs to improve QoL because they consider the evidence inconclusive (Information for Health Professions, 2007; Rizzo et al, 2010). Similarly, in 2007, the FDA removed the claim for ESA-related QoL improvements in patients with chronic kidney disease from the product labels because of a lack of evidence from well-conducted trials. In contrast, the European Organization for Research and Treatment of Cancer (Aapro and Link, 2008) and the European Society of Medical Oncology (Schrijvers et al, 2010) recommend the use of ESAs to improve QoL in cancer patients.

Our overall analyses showed a small yet clinically important improvement for FACT-An, which was confirmed when the analysis was restricted to placebo-controlled RCTs in patients receiving chemotherapy. Of 100 patients treated, approximately 10 to 13 patients will have a clinically important improvement of anaemia-related symptoms, which can be attributed to ESA treatment. However, in patients treated with a curative approach it is unlikely that the observed benefits will outweigh the negative effects of ESAs on short-term mortality and thromboembolic events. Studies in cancer patients receiving chemotherapy with a palliative intent and receiving ESAs in accordance to current guideline recommendations (i.e., starting ESAs at Hb <10 g dl–1 and stopping at 12 g dl–1) and reporting QoL outcomes were not available. In this setting, the impact of ESAs on QoL remains unclear.

CONCLUSION

We found that ESAs provide a small but clinically important improvement in anaemia-related symptoms (FACT-An). For fatigue-related symptoms (FACT-F), the overall effect did not reach the threshold for a CID.

ACKNOWLEDGEMENTS

Annette Mettler (AM) and Nadège Robert (NR) screened references and assessed studies for eligibility. Martin Adam developed the Epidata format for data extraction. We thank Kali Tal for her editorial work. This study was funded by OncoSuisse, grant number OCS-02232-04-2008.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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