BRIEF COMMUNICATIONS

Recombinant Human Erythropoietins and Cancer Patients: Updated Meta-Analysis of 57 Studies Including 9353 Patients

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This is an updated systematic review of 57 trials and 9353 cancer patients from articles, abstracts, and reports published between January 1, 1985, and April 30, 2005, on the effects of epoetin alfa and beta (i.e., epoetin) and darbepoetin alfa (i.e., darbepoetin). We included randomized controlled trials comparing epoetin or darbepoetin plus red blood cell transfusion with red blood cell transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent antineoplastic therapy. The Cochrane Library, MEDLINE, EMBASE, and conference proceedings were searched. Effect estimates and 95% confidence intervals (CIs) were calculated with fixed-effects models. Treatment with epoetin or darbepoetin statistically significantly reduced the risk for red blood cell transfusions (relative risk [RR] = 0.64, 95% CI = 0.60 to 0.68; 42 trials and 6510 patients) and improved hematologic response (RR = 3.43, 95% CI = 3.07 to 3.84; 22 trials and 4307 patients). Treatment with epoetin or darbepoetin increased the risk of thrombo-embolic events (RR = 1.67, 95% CI = 1.35 to 2.06; 35 trials and 6769 patients). Uncertainties remain as to whether and how epoetin or darbepoetin affects overall survival (hazard ratio = 1.08, 95% CI = 0.99 to 1.18; 42 trials and 8167 patients). Caution is advised when using epoetin or darbepoetin in combination with thrombogenic chemotherapeutic agents or for cancer patients who are at high risk for thrombo-embolic events. [J Natl Cancer Inst 2006;98:708–14]

Clinical studies and subsequent meta-analyses *(1–5)* have found that erythropoietins increase hemoglobin levels and reduce the need for blood transfusions in cancer patients. However, there is conflicting evidence concerning the association between erythropoietins and tumor control or survival *(6–8),* and erythropoietins may even increase risk for thombo-embolic events *(9)*.

We report an updated Cochrane Review on hematologic responses, red blood cell transfusions, thrombo-embolic events, and overall survival in cancer patients receiving epoetin or darbepoetin. Additional outcomes (tumor response, quality of life, hemoglobin change, and other adverse events) will be reported elsewhere *(3)*.

The literature searches covered the period from January 1, 1985, to December 31, 2001, for the first Cochrane Review *(4)* and also included articles from January 1, 2002, to April 30, 2005, for the update. The Cochrane Library, MEDLINE, EMBASE, and conference proceedings were searched. Materials presented at a May 2004 U.S. Food and Drug Administration (FDA) hearing related to overall survival and thrombo-embolic event were also reviewed *(10)* [for details, see *(3)*]. We included randomized controlled trials comparing epoetin or darbepoetin plus red blood cell transfusion with red blood cell transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent antineoplastic therapy to prevent or reduce anemia. Control groups of included studies received identical antineoplastic and supportive treatments. Ongoing and small studies (≤10 patients per study arm) were excluded. Study selection, quality assessment, and data extraction were carried out independently by two reviewers. Additional unreported data were obtained from the investigators for the first review but not for the update, because of time constraints. Effect measures used were relative risks (RRs) for binary data and hazard ratios (HRs) for overall survival. Hazard ratios were calculated with individual patient data or with data from published reports *(11)*. Effect estimates and 95% confidence intervals (CIs) were calculated with fixed-effects models and pooled by use of the Mantel–Haenszel method. Homogeneity tests and tests for subgroup differences were one-sided; all other tests were two-sided. The P value of the homogeneity test and the I^2 statistic were used to assess the extent of heterogeneity across trials in each meta-analysis. Results were recalculated with a random-effects model when statistically significant heterogeneity was present. Potential causes of heterogeneity were explored with subgroup analyses for the following prespecified factors: hemoglobin at baseline, tumor entity, antineoplastic therapy, duration of epoetin or darbepoetin treatment, methodologic quality (allocation concealment, intention-to-treat analysis, double-blinding), and source of data. Exploratory subgroup analyses included epoetin versus darbepoetin, epoetin dosages (<40 000 IU/week or ≥40 000 IU/week), administration in accordance with FDA license indication, stopping epoetin or darbepoetin (hematocrit of ≤40% or >40%, where a hematocrit of 40% = a hemoglobin level of 13.3 g/dL), treatment versus maintenance trials, and final hemoglobin level (≤13.3 g/dL or >13.3 g/dL). The current product labels recommended that the dose be reduced or administration be stopped at a hemoglobin level of 13 g/dL. We identified four studies *(12–14,27)* that stopped drug administration when the hemoglobin level reached a maximun level of 13 g/dL. Three studies

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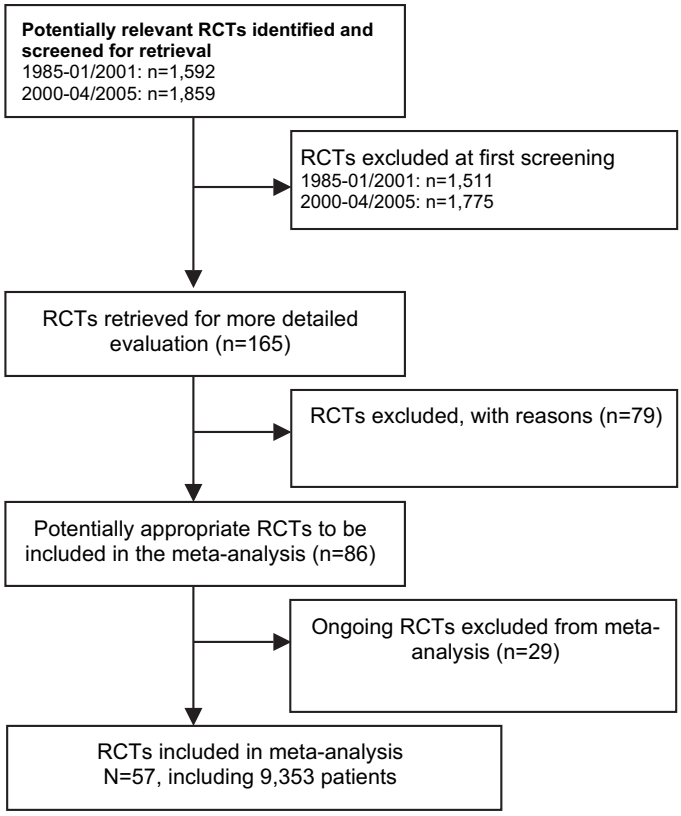

Fig. 1. QUOROM Flow diagram. The process of identifying and evaluating randomized controlled trials (RCTs) for the first review (1985 to December 2001) and the update (January 2002 to April 2005).

(15–17) stopped administration of epoetin at a slightly higher level of hemoglobin (hemoglobin = 13.3 g/dL or hematocrit = 40%) than the currently recommended hemoglobin level of 13 g/dL. We therefore set the cutoff at a hemoglobin level of 13.3g/dL or a hematocrit level of 40%. Using either a hemoglobin level of 13.0 g/dL or 13.3 g/dL as the cutoff did not alter the results substantially. Analyses were performed with the Review Manager program (RevMan version 4.2.7) and the statistical software package R *(18)*.

Literature searches yielded 1592 references for the first Cochrane review and 1859 references for the update. Overall, 165 publications were retrieved for detailed examination, of which 108 trials were excluded, 79 for not meeting selection criteria, and 29 were still ongoing (Fig. 1). A total of 57 randomized controlled trials with 9353 patients were included, of which 27 studies with 3287 participants were analyzed in the first review *(6,12–15,17,19–39)* and another 30 studies with 6066 participants *(7,8, 16,40–66)* were included for the update (Supplemental Table 1, available at: http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol98/issue10).

Meta-analysis found that patients treated with epoetin or darbepoetin had a 36% lower risk of transfusion than control subjects (fixed-effects RR = 0.64, 95% CI = 0.60 to 0.68; random-effects RR = 0.62, 95% CI = 0.57 to 0.69; 42 trials and 6510 patients; test for heterogeneity $P<.001$ and $I^2 = 51.3\%$). In addition, patients receiving epoetin or darbepoetin were more likely to achieve hematologic response, defined as a hemoglobin increase of 2 g/dL (fixed-effects RR = 3.43, 95% CI = 3.07 to 3.84; random-effects RR = 3.52, 95% CI = 2.95 to 4.20; 22 trials and 4307 patients; test for heterogeneity $P = .01$ and $I^2 = 38.5\%$).

On the basis of 6769 patients in 35 trials, thrombo-embolic events (such as transient ischemic attacks, stroke, pulmonary emboli, deep vein thrombosis, and myocardial infarction) were observed in 229 of the 3728 patients treated with epoetin or darbepoetin (median = 4.5%, range = 0%–30%) and in 118 of the 3041 untreated control patients (median = 1.4%, range 0%-22.6%). Thus, the relative risk of a thrombo-embolic event was increased by 67% in the treated group compared with the control group (RR = 1.67, 95% CI = 1.35 to 2.06) (Fig. 2). Heterogeneity was not statistically significant ($P = .82$ and $I^2 = 0\%$). A funnel plot analysis revealed statistically significant asymmetry ($P<.001$), suggesting that negative results (i.e., fewer thrombo-embolic events in the treated group) were underreported. We did not detect statistically significant differences in relative risks for a thrombo-embolic event among various subgroups as defined by prespecified variables. Absolute risk and the number needed to harm vary with the underlying risk of specific cancer populations. With an underlying risk of 1.5%, the number needed to harm is 99.5 (95% CI = 62.9 to 190.5), indicating that for every 100 patients treated with epoetin to darbepoetin, about one additional patient would experience a thrombo-embolic event. With a baseline risk of 20%, the number needed to harm is 7.5 (95% CI = 3.1 to 15.6).

Overall survival was investigated for 8167 patients from 42 studies. The non-statistically significant pooled hazard ratio (HR = 1.08, 95% CI = 0.99 to 1.18) indicates that survival was not improved by treatment with epoetin or darbepoetin and raises the possibility that survival may be decreased among patients treated with epoetin or darbepoetin. Heterogeneity was not statistically significant ($P = .27$ and $I^2 = 11.5\%$) (Fig. 3). Data appeared symmetrical in funnel plot analysis ($P = .35$). Data analysis used individual patient data *(34)*, aggregated time-to-event data [21 studies *(6–8,13,15–17,19,20,23,24, 31,39,42,46,53,54,57,64,65,67)*], or the number of deaths [20 studies *(12,14,22, 27,32,35,37,41,43–45,47,48,51,55,56, 61–63,66)*]. Only seven of the included trials were specifically designed to measure overall or progression-free survival; pooled data from these seven studies with 2188 patients resulted in a pooled hazard ratio of 1.16 (95% CI = 1.01 to 1.33). Another six studies with 1661 patients were stopped prematurely (HR = 1.34, 95% CI = 1.12 to 1.61). No robust statistically significant associations were found for any subgroup explored.

Results of this update confirm earlier findings on hematologic and transfusion outcomes *(3,4)*. Although the first review indicated that treatment with epoetin, compared with no treatment, might be associated with increased survival (adjusted HR = 0.81, 95% CI = 0.67 to 0.99; unadjusted HR = 0.84, 95% CI = 0.69 to 1.02), the updated analysis found no association between treatment and

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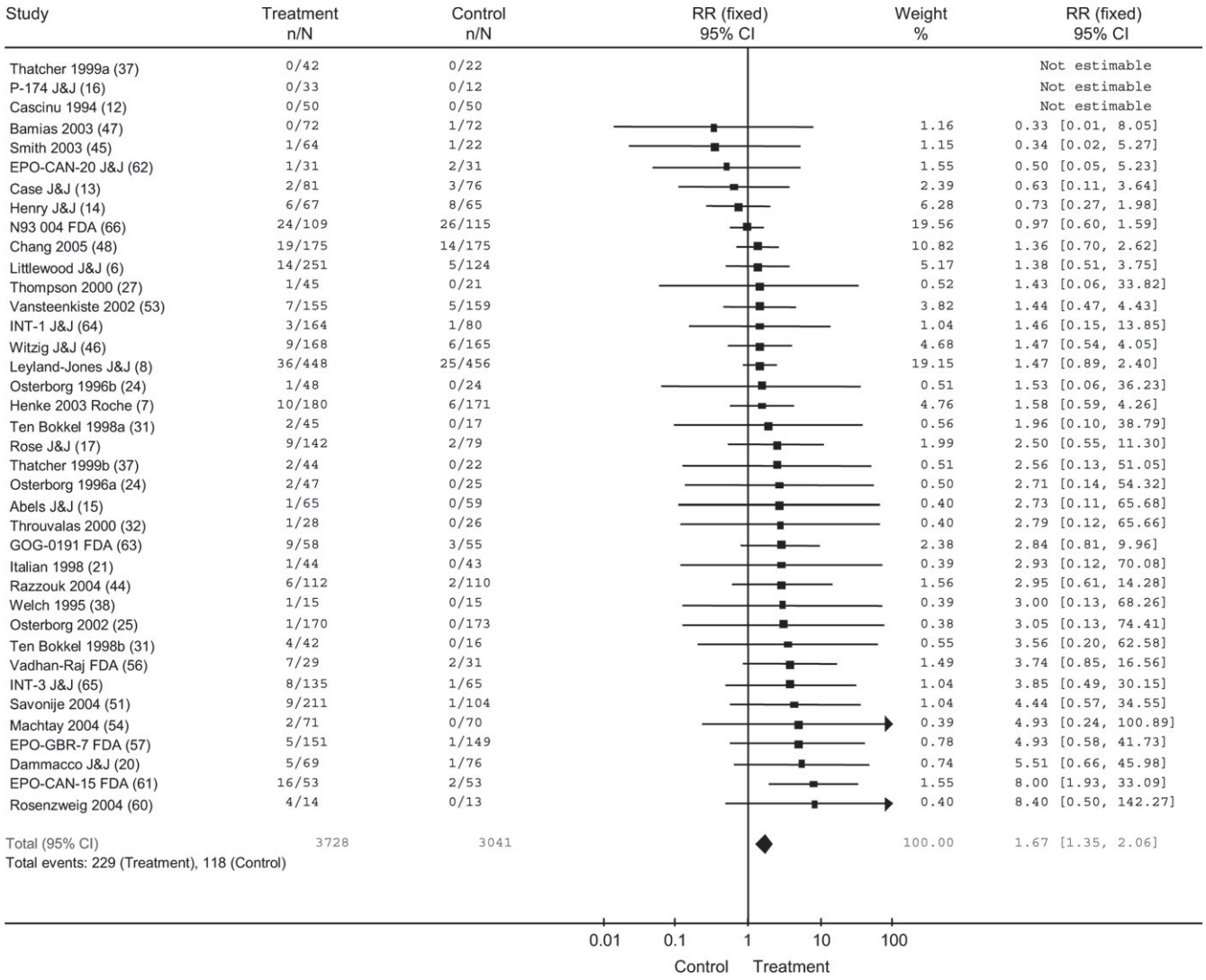

Fig. 2. Meta-analysis of the relative risk (RR) for thrombo-embolic complications in cancer patients receiving epoetin or darbepoetin or standard care. **Solid squares** represent risk estimates for the single studies. The size of the squares is proportional to the sample size and the number of events. **Horizontal lines** denote 95% confidence intervals (CIs). The **diamond** shows the confidence interval for the pooled relative risks. Positive values indicate a relative risk increase for thrombo-embolic complications in patients receiving epoetin or darbepoetin. Test for overall effect: $Z = 4.76$, $P<.001$; test for heterogeneity chi-square = 26.52, degrees of freedom = 34, $P = .82$; $I^2 = 0\%$. J&J refers to data that were taken from the Johnson & Johnson briefing document, Roche refers to the Roche briefing document, and FDA refers to briefing documents prepared by U.S. Food and Drug Administration (FDA) reviewers presented at the FDA Oncology Drugs Advisory Committee hearing on May 4, 2004 *(10)*. Thatcher 1999a *(37)* = patients in treatment arm received 150 IU/kg three times a week; Thatcher 1999b *(37)* = patients in treatment arm received 300 IU/kg three times a week; Ten Bokkel 1998a *(31)* = patients in treatment arm received 150 IU/kg three times a week; Ten Bokkel 1998b *(31)* = patients in treatment arm received 300 IU/kg three times a week; Österborg 1996a *(24)* = patients in treatment arm received 10 000 IU daily; Österborg 1996b *(24)* = patients in treatment arm received 2000 IU daily, and if the level of hemoglobin did not increase after 8 weeks, the dose was increased to 5000 IU and to 10 000 IU daily after 12 weeks.

survival and possibly even that decreased survival might be associated with treatment (HR = 1.08, 95% CI = 0.99 to 1.18). This change in direction for the point estimate reflects results reported by studies published since January 1, 2002, which indicated that treatment, compared with no treatment, was associated with decreased survival (HR = 1.16, 95% CI = 1.04 to 1.29). Compared with the studies in the first review, trials in the updated review tended to enroll patients with higher baseline hemoglobin levels and patients who used higher doses of epoetin or darbepoetin and to target hemoglobin levels that were higher than 13 g/dL to maintain high hemoglobin levels in nonanemic cancer patients.

Although the previous review indicated that epoetin treatment was not statistically significantly associated with an increased risk for thrombo-embolic events (RR = 1.58, 95% CI = 0.94 to 2.66), we found, in the updated review, that this association was strengthened and became statistically significant (RR = 1.67, 95% CI = 1.35 to 2.06). The apparent excess of thrombo-embolic events observed in several trials that enrolled nonanemic patients and/or targeted hemoglobin levels higher than product label recommendations raises concerns that the relationship may be causal *(9)*. In a phase III randomized study of 939 patients with advanced breast cancer undergoing chemotherapy *(8,68)*, treatment with epoetin alfa to maintain hemoglobin levels between 12 and 14 g/dL was associated with higher rates of fatal thrombo-embolic events than placebo [1.3% versus 0.6% for placebo *(68)*]. In a phase III trial with 351 head and neck cancer patients undergoing radiotherapy, the rate of death from cardiac disorder was greater among patients randomly assigned to receive

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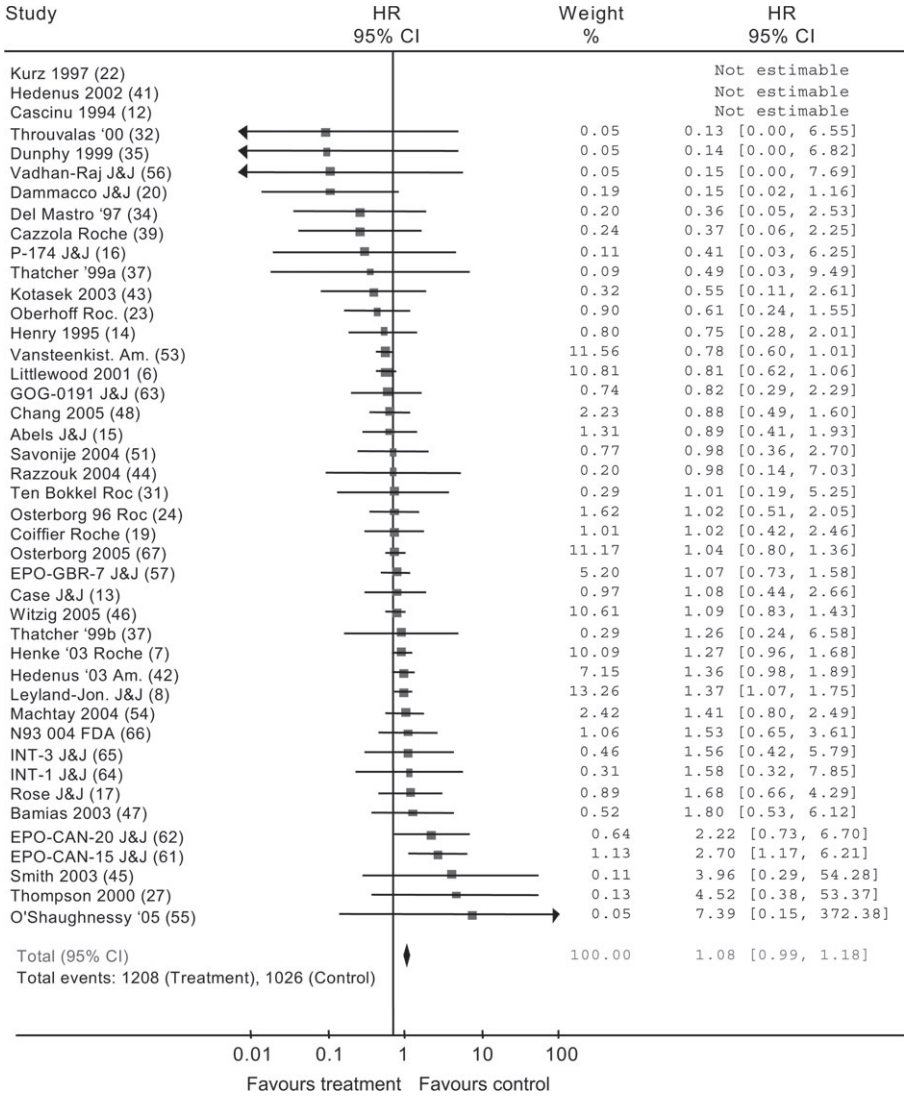

Fig. 3. Meta-analysis of the hazard ratio (HR) for overall survival for cancer patients receiving epoetin or darbepoetin or standard care. **Solid squares** represent risk estimates for the single studies. The size of the squares is proportional to the sample size and the number of events. **Horizontal lines** denote 95% confidence intervals (CIs). The **diamond** shows the confidence interval for the pooled hazard ratio. Positive values indicate a hazard ratio increase for patients receiving epoetin or darbepoetin. Test for overall effect: $Z = 1.63$, $P = .10$; test for heterogeneity chi-square = 44.04, degrees of freedom = 39, $P = .27$; and $I^2 = 11.5\%$. J&J refers to data that were taken from the Johnson & Johnson briefing document, Roche and Roc refer to the Roche briefing document, Am. refers to the Amgen briefing document, and FDA refers to briefing documents prepared by U.S. Food and Drug Administration (FDA) reviewers presented at the FDA Oncology Drugs Advisory Committee hearing on May 4, 2004 *(10)*. Thatcher 1999a *(37)* = patients in treatment arm received 150 IU/kg three times a week; Thatcher 1999b *(37)* = patients in treatment arm received 300 IU/kg three times a week.

epoetin beta to maintain a hemoglobin level between 12 and 14 g/dL for women or between 13 and 15 g/dL for men (5.5% versus 3% for patients who received placebo) *(7)*. The high hemoglobin level at the study's end (i.e., male participants with 15.4 g/dL) might have contributed to the many thrombo-embolic events observed.

A limitation of our study was that, with the available data, we could not detect a statistically significant association between the relative risk for thrombo-embolic events and hemoglobin level at baseline or other factors evaluated, perhaps, in part, because of the lack of standard definitions of venous thrombo-embolism. Events within trials were possibly underreported because no prospective and uniform screening protocol for thrombo-embolic events was included in the clinical trials. Specific individual patient data on hemoglobin levels preceding a thrombo-embolic event would be necessary to clarify a possible association between hemoglobin level and thrombo-embolic events. Although the lack of a statistically significant association in the available data does not exclude a causal relationship, recombinant erythropoietins may be thrombogenic by mechanisms that are independent of hemoglobin levels. A retrospective case-control study in cervical cancer patients with concurrent chemotherapy and radiotherapy and a prospective observational study in ambulatory cancer patients provide some support for this possibility *(69,70)*.

Although more frequent thrombo-embolic events may contribute to reduced survival of patients treated with epoetin or darbepoetin in more recent trials, hypothesized effects on tumor growth may also affect survival. Preclinical studies have reported high levels of erythropoietin receptors in breast cancer cells and other malignant cells *(71–75)*. Consequently, endogenously produced or exogenously administered erythropoietin might stimulate proliferation of cancer cells that express erythropoietin receptors.

Two phase III studies, one in patients with head and neck cancer *(7)* and the other in patients with breast cancer *(8,68),* found that poorer response rates and higher death rates were associated with epoetin treatment than with placebo. Henke et al. *(7)* reported more frequent tumor progression associated with epoetin beta treatment (for locoregional tumor progression, RR = 1.69, 95% CI = 1.16 to 2.47; $P = .007$). In the study reported by Leyland-Jones et al. *(8,68)*, the observed difference in survival (at 12 months, 70% versus 76%; $P = .01$) was partly attributed to increased disease progression in the epoetin beta group (at 4 months, 6% versus 3%). However, other phase III studies *(54,76,77)* in head and neck or breast cancer patients did not observe poorer survival in the epoetin arms, and studies *(78,79)* in pelvic and cervical cancer patients indicated improved tumor control associated with epoetin treatment. The studies reported by Henke et al. and Leyland-Jones et al. had several methodologic limitations, including baseline imbalances *(8)* and protocol violations *(7)*. Thus, despite intensive reanalyses, the exact causes of poorer survival associated with epoetin treatment in these studies remain uncertain.

In view of these uncertainties, treatment with epoetin or darbepoetin to target hemoglobin levels beyond that of anemia (i.e., >12 g/dL) among cancer

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patients is potentially harmful and should be considered only in an experimental setting. Caution is advised when using epoetin or darbepoetin in combination with chemotherapeutic agents that are known to be thrombogenic or for cancer patients who are at high risk for thromboembolic events.

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