ABSTRACT

BACKGROUND: Prior to 2007, the erythropoiesis-stimulating agents (ESAs) epoetin alfa and darbepoetin alfa were indicated for use in chemotherapy-induced anemia to achieve target hemoglobin (Hb) levels of approximately 12 grams per deciliter (gm per dL), and treatment was to be withheld if Hb exceeded 13 gm per dL. In March 2007, the FDA changed the labeling of the ESAs to add boxed warnings, updated in November 2007, to include the following key points: (a) ESAs should be used only to treat anemia that occurs in patients with cancer while they are undergoing chemotherapy; (b) treatment with ESAs should be stopped when chemotherapy ends; and (c) dosing ESAs to an Hb target of 12 gm per dL or greater has resulted in more rapid tumor progression or shortened overall survival in patients with breast, head and neck, lymphoid, cervical, and non-small cell lung malignancies. In January 2008, the FDA specified that the increased risk of more rapid tumor growth or shortened survival was associated with ESAs when “administered in an attempt to achieve a Hb level of 12 gm per dL or greater, although many patients did not reach that level.” A new black-box warning regarding this association was added to the labels of the ESAs in March 2008, and the FDA mandated further label changes on July 30, 2008, that ESA therapy should not be initiated in patients receiving chemotherapy at Hb levels of 10 gm per dL or higher.

OBJECTIVE: To (a) assess the prevalence and predictors of ESA administrations at Hb levels above 12 gm per dL among patients with a diagnosis of solid or hematologic cancer or myelodysplastic syndrome who began their first regimen of conventional myelosuppressive chemotherapy between 2002 and 2006, and (b) describe patterns of ESA treatment subsequent to the first ESA administration at Hb above 12 gm per dL.

METHODS: Using the Health Insurance Portability and Accountability Act (HIPAA)-compliant Varian Medical Oncology database of de-identified electronic medical records from 17 U.S. outpatient oncology practices, adults (aged 18 years or older) with any cancer diagnosis who began chemotherapy between January 1, 2002, and September 30, 2006, were identified. The Hb value associated with each ESA administration was defined as the closest Hb measurement within 7 days prior to the ESA administration. A first ESAHb > 12 was defined as the first time an ESA, either epoetin or darbepoetin, was given with an associated Hb greater than 12 gm per dL during the first chemotherapy regimen recorded in the database for each patient. Hb levels and ESA administrations after the first ESAHb > 12 were determined. Logistic regression models identified predictors of initial receipt of an ESAHb > 12, and of receiving further ESA treatment during the next 6 weeks (Pearson chi-square = 96.1, P<0.001).

RESULTS: Between January 1, 2002, and September 30, 2006, there were 17,731 patients on chemotherapy, the mean (SD) age was 60 (13.2) years; 58.9% were female; 24.6% had breast cancer, 22.2% had lung cancer, 15.8% had colorectal cancer, 11.8% had hematologic cancer, and 25.6% had other or multiple cancers. Of these, 8,086 (45.6%) received an ESA at any time during the regimen, and 7,606 (42.9%) received an ESA at a known Hb level (i.e., Hb measurement within 7 days prior to ESA administration). During the first recorded chemotherapy regimen, 1,844 patients (10.4% of the chemotherapy cohort, 24.2% of ESA users with a known Hb; n=1,226 epoetin, n=618 darbepoetin) received an ESAHb > 12. Among patients receiving ESA treatment at a known Hb level, significant predictors of receiving an ESAHb > 12 included treatment in a community-based clinic rather than a hospital-affiliated clinic (odds ratio [OR]=2.96, 95% confidence interval [CI]=2.40-3.65), location of practice in the eastern United States (OR for Midwest = 0.67, 95% CI = 0.57-0.78; OR for West = 0.27, 95% CI = 0.22-0.34), hematologic cancer rather than solid tumor (OR=1.44, 95% CI=1.21-1.71), private health insurance (OR for public health insurance =0.80, 95% CI = 0.70-0.93; OR for other/unknown insurance =0.54, 95% CI =0.47-0.62), and year of regimen 2002-2003 (ORs =0.75, 0.74, and 0.71 for 2004, 2005, and 2006, respectively). Following the first ESAHb > 12, 276 (22.5%) of the patients on epoetin and 276 (44.7%) on darbepoetin received no further ESA treatment during the next 6 weeks (Pearson chi-square=96.1, P<0.001).

CONCLUSIONS: This analysis of outpatient oncology practices between 2002 and 2006 revealed that 24% of ESA users with a known Hb level received ESAHb > 12. Dose withholding subsequently occurred in 23%-45% of those patients. A higher proportion of patients on epoetin than darbepoetin continued ESA treatment after the first administration of ESAHb > 12.

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What is already known about this subject

- Prior to 2007, the erythropoiesis-stimulating agents (ESAs) epoetin and darbepoetin were indicated for use in chemotherapy-induced anemia to a hemoglobin (Hb) level of approximately 12 grams per deciliter (gm per dL) and were to be withheld if Hb exceeded 13 gm per dL.
- At least 8 studies have shown that cancer patients with chemotherapy-induced anemia who received ESAs to a target Hb of more than 12 gm per dL have an increased risk of serious cardiovascular and thromboembolic events, mortality, and tumor progression.
- Starting in 2008, FDA label changes restricted initiation of ESAs to Hb below 10 gm per dL and use of the lowest dose of ESA necessary to avoid the need for a blood transfusion; if Hb exceeds a level needed to avoid transfusion, the ESA is to be withheld.
Use of Erythropoiesis-Stimulating Agents Among Chemotherapy Patients With Hemoglobin Exceeding 12 Grams Per Deciliter

What this study adds

- Examination of the treatment patterns of ESA use in outpatient chemotherapy practices during the years 2002-2006 prior to the FDA label changes indicated that less than 11% of chemotherapy patients, representing 24% of ESA users with a known Hb level, received an ESA at Hb exceeding 12 gm per dL (ESA Hb > 12).
- Among patients who were treated with an ESA at any time during the chemotherapy regimen and had a measured Hb level within 7 days prior to the ESA administration, 1,226 of 3,006 epoetin users (40.8%) and 618 of 4,600 darbepoetin users (13.4%) received at least 1 ESA Hb > 12.
- Following the first administration of ESA Hb > 12, ESA treatment was continued in 76.5% (950/1,226) of epoetin-treated patients and 55.3% (342/618) of darbepoetin-treated patients, a treatment pattern that was potentially allowable under 2002 guidelines but would violate 2008 labels and guidelines.
- Among chemotherapy patients treated with ESAs at a known Hb level, predictors of receiving an ESA Hb > 12 between 2002 and 2006 included treatment in a community-based clinic as compared with a hospital-affiliated clinic, practice location in the eastern United States as compared with the West and Midwest, hematologic cancer as compared with solid tumor, private health insurance, and receiving chemotherapy prior to 2004.

Many chemotherapeutic agents used in the treatment of cancer increase the risk of anemia.\(^1\) The development of anemia in cancer patients has been found to predict shorter survival times\(^2\) and may be associated with fatigue that negatively impacts quality of life.\(^3\)\(^,\)\(^4\) Chemotherapy-induced anemia can be treated either by red blood cell transfusions or with erythropoiesis-stimulating agents (ESAs). Epoetin alfa (epoetin) and darbepoetin alfa (darbepoetin) are currently the only ESAs marketed in the United States.

Prior to 2007, both ESAs were indicated for use in chemotherapy-induced anemia to target a hemoglobin (Hb) level of approximately 12 grams per deciliter (gm per dL); treatment was to be withheld if Hb exceeded 13 gm per dL.\(^5\)\(^,\)\(^6\) Studies have demonstrated an increased risk of adverse events and poor disease outcomes when ESAs were used for treatment of anemia in patients with cancer who were not on chemotherapy or when used to target a Hb level exceeding 12 gm per dL.\(^7\)\(^,\)\(^10\) As a result, the U.S. Food and Drug Administration (FDA) mandated label changes for both epoetin and darbepoetin, adding boxed warnings in March 2007 that were updated in November 2007 and again in July 2008. The new labeling in 2008 stated that (a) ESAs are “not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure,” (b) “therapy should not be initiated at hemoglobin levels > 10 g/dL,” and (c) “Withhold Dose if: hemoglobin exceeds a level needed to avoid transfusion.” The ESA product label calls for discontinuation following completion of a chemotherapy course.\(^11\)

Because of findings of shortened survival and decreased time to progression of tumors in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers and increased risk of adverse cardiovascular and thromboembolic events, the ESA labels specify using the lowest dose necessary to avoid red blood cell transfusion and a target Hb range of 10 to 12 gm per dL.\(^12\)\(^,\)\(^13\) The boxed label warnings also emphasize that the use of ESAs to target Hb levels could potentially still be associated with increased risk of poor disease outcomes. Current guidelines from the American Society of Clinical Oncology/American Society of Hematology\(^14\) and the National Comprehensive Cancer Network\(^15\) state that ESA treatment should be discontinued if Hb shows little or no response (i.e., less than 1-2 gm per dL increase in Hb or no reduction in need for transfusion) within 6-8 weeks (see Appendix A).

Because of the stricter limits placed on ESA use under current guidelines and labels, ESA treatment at Hb levels exceeding 12 gm per dL (ESA Hb > 12) is unlikely to occur in the future. Yet, during the years when product labels did not explicitly contraindicate ESA Hb > 12, many patients may have received treatment at higher Hb levels. Treatment patterns before and after patients received an ESA Hb > 12 have not, to our knowledge, been examined.

The present retrospective study was designed to investigate patterns of ESA treatment and Hb levels among patients receiving the first chemotherapy regimen recorded in the database during the years 2002-2006. The goals of the study were to (a) quantify the prevalence and identify the predictors of receiving ESA Hb > 12 and (b) describe patterns of treatment following the first administration of ESA Hb > 12, in patients treated with chemotherapy and diagnosed with solid or hematologic cancer or myelodysplastic syndrome.

Methods

Data Source

The study data were obtained from the Varian Medical Oncology (Palo Alto, CA) database of electronic medical records (EMRs) from outpatient oncology practices. The database includes information on more than 150,000 cancer patients from 17 oncology provider organizations (13 community-based and 4 hospital-affiliated) comprising 71 clinic locations in the United States. At each patient visit to the clinic, the staff entered diagnoses, treatments, and other relevant information into the database. Diagnoses are entered as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, with no limit to the number that can be entered. Treatment data are entered as drug names and include orders or prescriptions for medications, with specifics such as dose and route, as well as duration of supply of oral medications and amount and timing of drugs administered in the clinic. Laboratory results were typically entered into the EMR database.
Use of Erythropoiesis-Stimulating Agents Among Chemotherapy Patients With Hemoglobin Exceeding 12 Grams Per Deciliter

Cohort Definition
Eligible patients were adults (aged 18 years or older) who began their first regimen of conventional myelosuppressive chemotherapy identified in the database between January 1, 2002, and September 30, 2006. All included patients had a diagnosis of solid or hematologic cancer (ICD-9-CM codes 140-165.9, 170-176.9, 179-195.8, 199-208.91) or myelodysplastic syndrome (238.7) prior to or within 7 days after the start of the first chemotherapy regimen. These diseases include all cancer-related diagnoses found in patients administered ESAs in this database; not all diagnoses (e.g., myelodysplastic syndrome) are FDA-approved indications for ESA use. (A list of complete code descriptions is available upon request from the authors.) The first chemotherapy regimen was defined as the earliest treatment plan for each patient in the EMR system (treatment regimen file); records of administration of chemotherapeutic drugs without a specified treatment plan were excluded. Non-myelosuppressive cancer regimens, such as monoclonal antibodies in the absence of cytotoxic chemotherapy, were excluded.

Conventional myelosuppressive chemotherapies were those containing at least 1 cytotoxic chemotherapeutic agent; the most common regimens identified were carboplatin/paclitaxel, cyclophosphamide/doxorubicin, and fluorouracil/leucovorin/oxaliplatin (FOLFOX). The treatment plans include text descriptions of the drugs in the regimen; these text descriptions were standardized and classified according to whether or not they contained at least 1 conventional myelosuppressive agent. Qualifying agents included arsenic trioxide, azacitidine, bleomycin, capcitabine, carboplatin, carmustine, cisplatin, cladribine, cyclophosphamide, cytarabine, darbepoetin, dexamethasone, docetaxel, doxorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gemcitabine, ifosfamide, irinotecan, mechlorethamine, melphalan, methotrexate, mitomycin, mitoxantrone, oxaliplatin, paclitaxel, penicillamine, streptozocin, topotecan, vinblastine, vincristine, and vinorelbine.

Patients with the following characteristics were excluded from the analyses: (a) first systemic cancer regimen was not conventional myelosuppressive chemotherapy (e.g., hormonal therapy or biologic therapy alone), (b) planned cycle length was not specified in the database or was longer than 60 days, or (c) there was a gap of more than 6 months between any 2 antineoplastic drug administrations during the first regimen. One of the 17 oncology provider organizations had a substantial amount of missing data on chemotherapy administrations; thus, patients treated by this provider were also excluded from the study. Follow-up data for each patient were obtained through December 31, 2006.

ESAs Exposure
We identified the dates and doses of all ESA administrations that occurred during each patient’s first chemotherapy regimen and found the closest Hb level measured on or within 7 days prior to the date of ESA administration. Because the analysis focused on treatment of chemotherapy-induced anemia and not anemia of cancer, only ESA administrations that occurred no more than 30 days after the most recent chemotherapy exposure were included. Patients who received at least 1 ESAHb > 12 were identified, and the date of their first ESAHb > 12 was noted. In a descriptive analysis of baseline demographic and clinical characteristics, the group of patients with ESAHb > 12 was compared both with the full population of eligible patients on chemotherapy and with the subset of the full population that received an ESA during chemotherapy with a known Hb level; patients receiving ESAs with no known Hb level were excluded from the ESA group.

We looked for any further use during the chemotherapy regimen of ESAs following the first ESAHb > 12 for each patient. The outcome measure included only ESA administrations that occurred within 30 days after chemotherapy and no more than 42 days apart. The 42-day restriction limited this analysis to ESA administrations that can be considered to fall within a single ESA episode of care. Up to 3 ESA administrations per patient following the first ESAHb > 12 were examined. The closest Hb level within 7 days before each administration was noted.

Analysis
Baseline characteristics were summarized using the information available in the EMR database on or before the start of the first chemotherapy regimen. We constructed a logistic regression model using all patients receiving chemotherapy with at least 1 recorded Hb level to identify factors associated with receiving ESAHb > 12. Variables entered into the model included age, gender, geographic region, year of regimen start, clinic type (community-based or hospital-affiliated), type of health insurance (private, public, or other/unknown), cancer type (solid, hematologic, or multiple), binary indicator for platinum-containing chemotherapy, and lowest Hb level during the first regimen (lowest on or before the first ESAHb > 12 for those with at least 1 ESAHb > 12). Patients lacking an Hb measurement at any time during the first regimen were excluded from the analysis.

A second logistic regression model, also examining receipt of ESAHb > 12, included only patients who received at least 1 ESA with a known Hb level. Because all patients without the outcome included in this model had by design an Hb level less than or equal to 12 gm per dl, this model did not include lowest Hb level as a predictor. A third model, identical to the first with
FIGURE 1  Flow Chart of Patient Selection and Classification

Total patients in chemotherapy treatment regimen file
(N=27,450)

First clinic visit not 1/1/2002-9/30/2006
(N=4,218, 15.4%)

No conventional myelosuppressive chemotherapy with start date
1/1/2002-9/30/2006
(N=910, 3.9%)

Cycle length of first regimen >60 days
(N=340, 1.5%)

<18 years old at start of first regimen
(N=36, 0.2%)

No cancer diagnosis 10 years before to 7 days after regimen start date
(N=2,394, 10.9%)

≥ 180 day gaps during the chemotherapy regimen
(N=191, 1.0%)

Remove patients from site with missing administration data
(N=1,630, 8.4%)

All cancer patients on chemotherapy
(N=17,731)

Patients with no ESA within 30 days after chemotherapy
(N=9,645)

Patients with ESA at unknown Hb
(N=480)

All chemotherapy patients with an ESA at known Hb
(N=7,606)

Patients with no ESA at Hb>12 gm per dL
(N=5,762)

Patients with ESA associated with Hb >12 gm per dL
(N=1,844)

Epoetin
(N=1,226)

Received further epoetin treatment
(N=950)

No further ESA
(N=276)

Darbepoetin
(N=618)

Received further darbepoetin treatment
(N=342)

No further ESA
(N=276)

ESA=erythropoiesis-stimulating agent; gm per dL=grams per deciliter; Hb=hemoglobin.
Results

Of 27,450 patients who had provider-entered data on chemotherapy regimens in the treatment regimen file, we excluded those who started care in the oncology clinic outside of the study period, those lacking conventional chemotherapy or with unusual regimen data (i.e., recorded cycle length over 60 days or a gap in the regimen of at least 180 days), those younger than 18 years of age, those without a qualifying cancer diagnosis, and those who received care from the practice that did not adequately record drug administrations (Figure 1). We identified 17,731 patients who met all inclusion criteria.

Characteristics of all patients included in the cohort, all patients who received an ESA within 7 days of an Hb level measurement (n=7,606, 42.9%), and the group of patients who received an ESA at least 12 hr after the first (n=1,844, 24.2% of ESA patients with known Hb value) are shown in Table 1. In the full cohort, ages ranged from 19-97, with a mean (SD) age of 60 (13.2); 58.9% were female; and 66.7% lived in the southern United States. Most had solid tumor types, with breast (24.6%), lung (22.2%), and colorectal (15.8%) the most common. The cancer types were, for the most part, similar to national distributions reported by Surveillance Epidemiology and End Results (SEER), except that lung cancer was more common and prostate cancer largely under-represented in this database from outpatient oncology clinics.

Of the full chemotherapy cohort of 17,731 patients, 8,086 (45.6%) received an ESA at any time during the regimen. At least 1 ESA associated with a known Hb level was administered to 7,606 patients (42.9%). A total of 1,844 patients (10.4% of the chemotherapy cohort; 24.2% of ESA patients with a known Hb value) received at least 1 ESA at least 12 hr after the first. Of the patients with at least 1 ESA at least 12 hr, the mean (SD) age was 62 (13.3); 63.7% were female; and 79.2% lived in the South. The distribution of tumor types was similar to that of the full cohort. Only 134 (7.3%) of the first ESA administrations were associated with Hb exceeding 13 gm per dL. Among the 7,606 patients treated with an ESA at a known Hb level, 1,226 of 3,006 epoetin users (40.8%) and 618 of 4,600 darbepoetin users (13.4%) received at least 1 ESA at least 12 hr after the first.

The logistic regression model of all chemotherapy patients (Table 2, Equation 1) included 16,207 patients with known Hb levels during the chemotherapy regimen. The model revealed several significant (P<0.05) predictors of receiving at least 1 ESA. These included age 65 or older (odds ratio [OR]=1.21, 95% confidence interval [CI]=1.08-1.35), female gender (OR=1.27, 95% CI=1.14-1.41), residence in the eastern United States (OR for Midwest=0.55, 95% CI=0.47-0.64; OR for West=0.26, 95% CI=0.21-0.32), private health insurance (OR for public health insurance=0.74, 95% CI=0.65-0.84; OR for other/unknown insurance=0.49, 95% CI=0.43-0.56), visiting a community-based rather than hospital-affiliated clinic (OR=4.05, 95% CI=3.31-4.97), having a hematologic cancer rather than a solid tumor (OR=1.54, 95% CI=1.32-1.80), and receiving platinum-containing chemotherapy (OR=1.18, 95% CI=1.05-1.32). The lowest Hb level during the first regimen (prior to the first ESA at least 12 hr) was also associated with receiving at least 1 ESA; patients whose Hb fell below 11 gm per dL at any time during their regimen were most likely to receive ESA, whereas those whose Hb remained above 13 gm per dL at all times were unlikely to receive an ESA (OR=0.17, 95% CI=0.12-0.24).

The model that included only the 7,606 patients who received an ESA with known Hb (Table 2, Equation 2) showed generally similar patterns but weaker effect sizes overall. In this model, there was no apparent effect of age (OR=0.99, 95% CI=0.88-1.11), female gender (OR=1.10, 95% CI=0.98-1.24) or platinum-based chemotherapy (OR=1.00, 95% CI=0.89-1.13). Significant predictors of receiving an ESA at least 12 hr included treatment in a community-based clinic rather than a hospital-affiliated clinic (OR=2.96, 95% CI=2.40-3.65), location of practice in the eastern United States (OR for Midwest=0.67, 95% CI=0.57-0.78; OR for West=0.27, 95% CI=0.22-0.34), hematologic cancer rather than a solid tumor (OR=1.44, 95% CI=1.21-1.71), private health insurance (OR for public health insurance=0.80, 95% CI=0.70-0.93; OR for other/unknown insurance=0.54, 95% CI=0.47-0.62), and year of regimen 2002-2003 (ORs=0.75, 0.74, and 0.71 for 2004, 2005, and 2006, respectively).

Compared with the first model of receiving at least 1 ESA at least 12 hr among all chemotherapy patients, predictors of receiving an ESA at any Hb level during the first regimen (Table 2, Equation 3) were generally similar, with a stronger effect of lowest Hb level and platinum-containing chemotherapy regimen, and a weaker effect of community-based clinic and geographic location in the western United States. Hematologic cancer showed no significant effect in this model (OR=0.93, 95% CI=0.81-1.06). The direction of the effect changed only with the year variables; receipt of any ESA showed a generally increasing pattern over time beginning in 2005.

The examination of the first 3 ESA administrations following the first ESA at least 12 hr showed that the likelihood of continued ESA treatment after the first ESA at least 12 hr was higher for epoetin than for darbepoetin. Following the first ESA at least 12 hr, 276 (22.5%) of the patients on epoetin and 276 (44.7%) of those on darbepoetin received no further ESA treatment in the next 6 weeks (Pearson chi-square=96.1, P<0.001). Of the patients who received additional ESA treatment with a known Hb following the first ESA at least 12 hr, Hb...
levels exceeded 12 gm per dL at the next ESA administration for 437/885 (49.4%) of patients on epoetin and 127/319 (39.8%) of those on darbepoetin (Pearson chi-square = 8.6, \(P = 0.003\)); most of these administrations occurred at Hb ranging from more than 12 gm per dL to 13 gm per dL (37/1437 [84.9%] of epoetin and 106/127 [83.5%] of darbepoetin administrations at Hb exceeding 12 gm per dL). Overall, the 1,844 patients with an ESA_{Hb>12} received a median of 2 additional ESA administrations following the first ESA_{Hb>12}.

The logistic regression model of receiving further ESA treatment after the first ESA_{Hb>12} confirmed the between-drug difference in rates of continued ESA use (Table 3). After adjusting for measured baseline factors, receiving epoetin as the first ESA_{Hb>12} remained a significant predictor of continuing ESA treatment, with an OR of 2.64 (95% CI = 2.04-3.41).

### Discussion
This investigation of treatment patterns in outpatient oncology clinics in the United States revealed that during the years 2002-2006, 10.4% of chemotherapy patients observed, representing 24.2% of ESA users with known Hb levels, received ESAs at Hb levels exceeding 12 gm per dL at some time during their...
first chemotherapy regimen. Many factors were found to predict receiving at least 1 ESA \( \text{Hb} > 12 \). The strongest effects were seen for community-based compared with hospital-affiliated clinics, perhaps because physicians in community-based clinics may be reimbursed directly for each ESA administration, but hospital-based clinics receive pooled reimbursement. Additionally, patients having at least 1 Hb less than 11 gm per dL at some point during chemotherapy were more likely to be treated at higher Hb levels than were patients whose Hb values were consistently greater than or equal to 11 gm per dL.

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<td>0.49</td>
<td>0.43</td>
<td>0.56</td>
<td>0.54</td>
<td>0.47</td>
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</tr>
<tr>
<td>Year of regimen start</td>
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<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>0.76</td>
<td>0.64</td>
<td>0.89</td>
<td>0.75</td>
<td>0.62</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>0.86</td>
<td>0.74</td>
<td>0.99</td>
<td>0.74</td>
<td>0.63</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>0.86</td>
<td>0.73</td>
<td>1.00</td>
<td>0.71</td>
<td>0.60</td>
<td>0.84</td>
</tr>
<tr>
<td>Lowest Hb value( ^e )</td>
<td>&lt;11 gm per dL</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>11-12 gm per dL</td>
<td>0.82</td>
<td>0.73</td>
<td>0.92</td>
<td>0.75</td>
<td>0.62</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>&gt;12-13 gm per dL</td>
<td>0.75</td>
<td>0.64</td>
<td>0.87</td>
<td>0.74</td>
<td>0.63</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>&gt;13 gm per dL</td>
<td>0.17</td>
<td>0.12</td>
<td>0.24</td>
<td>0.17</td>
<td>0.12</td>
<td>0.24</td>
</tr>
<tr>
<td>Platinum-containing regimen</td>
<td>No platinum agents</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Platinum agents</td>
<td>1.18</td>
<td>1.05</td>
<td>1.32</td>
<td>1.00</td>
<td>0.89</td>
<td>1.13</td>
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\( ^a \) C statistic for model=0.73.  
\( ^b \) C statistic for model=0.68.  
\( ^c \) C statistic for model=0.86.  
\( ^d \) East included Northeast and South.  
\( ^e \) Lowest Hb value at any time during the chemotherapy regimen.  
ESA=erythropoiesis-stimulating agent; gm per dL=grams per deciliter; Hb=hemoglobin.
ESA treatment was more likely to continue in patients whose Hb dropped below 12 gm per dL after the first ESA at Hb > 12, but still occurred in 25.9% of patients ((371+106)/1,844) when their Hb was between 12 and 13 gm per dL. These patterns are generally consistent with the prevailing guidelines for most of the study period, under which ESA treatment was initiated when Hb fell below 11 gm per dL, maintained to achieve an Hb of approximately 12 gm per dL, and withheld if Hb exceeded 13 gm per dL.

Continuing ESA treatment after the first administration at high Hb levels occurred in 77% of patients on epoetin and 55% of those on darbepoetin. Patients on epoetin were more likely than those on darbepoetin not only to receive further ESA treatment, but also to have Hb again over 12 gm per dL at the time of the next ESA administration. Epoetin was administered to most patients on a weekly schedule and darbepoetin every 2 weeks. This difference in dosing schedule allows greater opportunity for further administrations of epoetin than darbepoetin during a given time window. To investigate the possibility that the restriction to a window of 30 days after the last chemotherapy administration could have biased the comparison between drugs with respect to further treatment, we conducted a sensitivity analysis using a 60- and a 90-day window after chemotherapy. The results using these 2 different time windows were essentially the same as those using a 30-day period. The 6-week follow-up duration for each patient allowed ample time for any further ESA treatment to appear, regardless of the original dosing schedule.

**Limitations**

To obtain an accurate picture of the treatment patterns occurring in oncology clinics, it is essential to use a database such as this EMR system rather than data from the tightly controlled environment of a clinical trial. Still, there are weaknesses inherent in these real-world data that one would not find in most controlled trials. First, Hb levels were not always measured or, in some cases, may have been measured but not entered into the EMR. Second, anemia-related symptoms may have prompted ESA treatment at these higher Hb levels and may explain some of the continued treatment seen, but information about symptoms was not consistently available in the database.

Third, red blood cell transfusions would also be expected to impact ESA treatment patterns, but again, these are not recorded reliably and, hence, were not examined in the present study. Because transfusions are indicated only at Hb levels well below 12 gm per dL, few if any members of the primary study group in the present analysis are likely to have received any transfusions following the first ESA administration at Hb over 12 gm per dL.

Fourth, while it is possible to identify ESA nonresponders in an EMR system through ESA and data for Hb levels, we did not examine these data, since the focus of the present study was on the use of ESAs at high Hb levels and not on inadequate Hb elevations in response to treatment.

Finally, we included all cancer-related conditions that were associated with actual ESA use rather than restricting to only the indicated uses, since the purpose of the present study was to investigate the actual use of these drugs as supportive care for patients on chemotherapy. For example, we included myelodysplastic syndrome (ICD-9-CM 238.7), a condition that is not

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**Use of Erythropoiesis-Stimulating Agents Among Chemotherapy Patients With Hemoglobin Exceeding 12 Grams Per Deciliter**

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**TABLE 3** Logistic Regression Model of Receiving Further ESA Treatment Following First ESA Associated With Hemoglobin Exceeding 12 Grams per Deciliter (N=1,844)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–64</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>65 and older</td>
<td>0.811</td>
<td>0.645</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.155</td>
<td>0.925</td>
</tr>
<tr>
<td>Clinic Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-affiliated</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Community-based</td>
<td>2.577</td>
<td>1.655</td>
</tr>
<tr>
<td>Geographic Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>East</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>1.208</td>
<td>0.861</td>
</tr>
<tr>
<td>West</td>
<td>0.694</td>
<td>0.444</td>
</tr>
<tr>
<td>Type of Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Hematologic cancer</td>
<td>1.257</td>
<td>0.910</td>
</tr>
<tr>
<td>Multiple primary cancers</td>
<td>1.508</td>
<td>0.876</td>
</tr>
<tr>
<td>Type of Insurance Carrier</td>
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<td>Private carrier</td>
<td>1.000</td>
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</tr>
<tr>
<td>Public health insurance</td>
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<td>0.962</td>
</tr>
<tr>
<td>Other or unknown health insurance</td>
<td>1.162</td>
<td>0.871</td>
</tr>
<tr>
<td>Year of first ESA at Hb&gt;12 gm per dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002–2003</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>0.775</td>
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</tr>
<tr>
<td>2005</td>
<td>0.896</td>
<td>0.619</td>
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<tr>
<td>2006</td>
<td>0.737</td>
<td>0.527</td>
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<tr>
<td>Platinum-containing regimen</td>
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<td></td>
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<tr>
<td>No platinum agents</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Platinum agents</td>
<td>1.067</td>
<td>0.849</td>
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<tr>
<td>Hb at first ESA at Hb&gt;12 gm per dL</td>
<td></td>
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</tr>
<tr>
<td>&gt;13 gm per dL</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>&gt;12–13 gm per dL</td>
<td>1.346</td>
<td>0.909</td>
</tr>
<tr>
<td>ESA at first ESA at Hb&gt;12 gm per dL</td>
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<td></td>
</tr>
<tr>
<td>Darbepoetin alfa</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>2.636</td>
<td>2.036</td>
</tr>
</tbody>
</table>

* c statistic for model=0.66.
* East included Northeast and South.

ESA=erythropoiesis-stimulating agent; gm per dL=grams per deciliter; Hb=hemoglobin.
approved in FDA labeling of ESAs but that, when treated with chemotherapy, has been associated with use of ESAs in oncology practice.

Conclusions
We found that in the 5 years prior to product label changes made in 2007 and 2008, less than 11% of chemotherapy patients, representing 24% of all ESA users with a known Hb level, received an ESA at Hb levels above the 12 gm per dL upper end of the target range that was recommended during the study period. ESA treatment was subsequently withheld in 23% of epoetin users and 45% of darbepoetin users. Among ESA users with a known Hb level, factors predicting receipt of at least 1 ESAHb>12 were treatment in a community-based clinic, eastern region of the United States, private health insurance, and treatment year earlier than 2004. ESA use was more likely to continue following the first ESAHb>12 among patients treated with epoetin than among those treated with darbepoetin. With new product labels, the factors associated with initiation and continuing ESA administrations in chemotherapy-induced anemia as well as use in off-label indications warrant further investigation once sufficient data are available.

References

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DISCLOSURES
The study was conducted under a restricted contract with Amgen, which manufactures epoetin alfa and darbepoetin alfa. Whyte and Nordyke are employed by Amgen, and these 2 coauthors provided guidance and comments as well as contributed to the study concept and design. The principal author (Nordstrom) had final approval authority over the study design, analyses, and data interpretation.

Study concept and design were the work of Nordstrom, Nordyke, and Whyte. The data were extracted, managed, and analyzed by Fraeman and were interpreted primarily by Luo, Nordstrom, and Fraeman. The manuscript was written and revised primarily by Nordstrom.
Use of Erythropoiesis-Stimulating Agents Among Chemotherapy Patients With Hemoglobin Exceeding 12 Grams Per Deciliter

APPENDIX A

Use of Epoetin and Darbepoetin in Patients With Cancer: 2007 American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update and 2008 Guidelines From the National Guideline Clearinghouse

Recommendations for chemotherapy-induced anemia

(Summary from Rizzo et al. [2008]. Available at: www.jco.ascopubs.org/cgi/reprint/26/1/132)

"For patients with chemotherapy-associated anemia, the Committee continues to recommend initiating an erythropoiesis-stimulating agent (ESA) as hemoglobin (Hb) approaches, or falls below 10 gm/dL, to increase Hb and decrease transfusions. ESA treatment continues to be recommended for patients with low-risk myelodysplasia for similar reasons. There is no evidence showing increased survival as a result of ESA treatment. Conclusive evidence is lacking that, absent clinical circumstances necessitating earlier treatment, initiating ESAs at Hb levels greater than 10 gm/dL either spares more patients from transfusion or substantially improves their quality of life. Starting doses and dose modifications based on response or lack thereof should follow the package insert. Continuing ESAs beyond 6 to 8 weeks in the absence of response, assuming appropriate dose increase has been attempted in nonresponders as per US Food and Drug Administration–approved labeling, does not seem to be beneficial, and ESA therapy should be discontinued. The Committee recommends monitoring iron stores and supplementing iron intake for ESA-treated patients. ESAs should be used cautiously with chemotherapy, or in clinical states, associated with elevated risk for thromboembolic complications. The Committee also cautions against ESA use for patients with cancer who are not receiving chemotherapy, since recent trials report increased thromboembolic risks and decreased survival under these circumstances."

This guideline was developed through a collaboration between the American Society of Clinical Oncology and the American Society of Hematology and has been published jointly by invitation and consent in both the Journal of Clinical Oncology and Blood.

From the National Guideline Clearinghouse (January 2008; updated July 31, 2008, and November 8, 2008)


MAJOR RECOMMENDATIONS*

I. General Recommendation

2007 Recommendation

As in any medical situation, it is essential to consider other correctable causes of anemia before initiating therapy with stimulants of erythropoiesis. Therefore, it is advisable to conduct an appropriate history and physical, and to consider relevant diagnostic testing aimed at identifying causes of anemia aside from chemotherapy or underlying hematopoietic malignancy. At a minimum, one should take a thorough drug exposure history, carefully review the peripheral blood smear (and in some cases, the bone marrow), consider iron, folate, and B12 deficiency where indicated, and assess for occult blood loss and renal insufficiency. Coomb’s testing may be appropriate for patients with chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, and for those with a history of autoimmune disease; endogenous erythropoietin levels may predict response in patients with myelodysplasia. Consideration should be given to minimize use of erythropoiesis-stimulating agents (ESAs) in patients with high risk of thromboembolic events, as further discussed in Recommendation IV (below).

II. Special Commentary on the Comparative Effectiveness of Epoetin and Darbepoetin (Note: This Topic Is New to the Guideline)

2007 Update Committee Statement

Based on a comprehensive systematic review comparing outcomes of epoetin and darbepoetin in patients with chemotherapy-induced anemia and on identical cancer-related indications, warnings, and cautions in the relevant U.S. Food and Drug Administration–approved package inserts, the Update Committee considers these agents to be equivalent with respect to effectiveness and safety.

IIIa. Chemotherapy-Induced Anemia: Threshold for Initiating ESA Therapy (Hemoglobin [Hb] Concentration Approaching or < 10 gm/dL)

2007 Recommendation

The use of epoetin or darbepoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a Hb concentration that is approaching, or has fallen below, 10 gm/dL, to increase Hb and decrease transfusions. Red blood cell (RBC) transfusion is also an option depending on the severity of the anemia or clinical circumstances.

IIIb. Chemotherapy-Induced Anemia: Initiation Threshold > 10 gm/dL BUT < 12 gm/dL

2007 Recommendation

For patients with declining Hb levels but less severe anemia (those with Hb concentration > 12 gm/dL, but who have never fallen < 10 gm/dL), the decision of whether to use epoetin or darbepoetin immediately or to wait until the Hb levels fall closer to 10 gm/dL should be determined by clinical circumstances (including but not limited to elderly individuals with limited cardiopulmonary reserve, those with underlying coronary artery disease or symptomatic angina, or substantially reduced exercise capacity, energy, or ability to carry out activities of daily living [ADLs]). RBC transfusion is also an option when warranted by clinical conditions.

IV. Thromboembolic Risk (Note: This Topic Is New to the Guideline)

2007 Recommendation

Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin is prescribed. Randomized clinical trials and systematic reviews of available randomized clinical trials demonstrate an increased risk of thromboembolism in patients receiving epoetin or darbepoetin. Specific risk factors for thromboembolism have not been defined in these trials; therefore, clinicians should use caution and clinical judgment when considering use of these agents. Established, general risk factors for thromboembolic events include previous history of thromboses, surgery, and prolonged periods of immobilization or limited activity. Multiple myeloma patients who are being treated with thalidomide or lenalidomide and dexamethasone or corticosteroids are at increased risk (Bennett et al., 2006). There are no data regarding concomitant use of anticoagulants or aspirin to modulate this risk.
Use of Erythropoiesis-Stimulating Agents Among Chemotherapy Patients With Hemoglobin Exceeding 12 Grams Per Deciliter

APPENDIX A (CONTINUED) Use of Epoetin and Darbepoetin in Patients With Cancer: 2007 American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update and 2008 Guidelines From the National Guideline Clearinghouse

V. Starting and Escalating Doses

2007 Recommendation

The U.S. Food and Drug Administration-approved starting dose of epoetin is 150 U/kg three times per week or 40,000 U weekly subcutaneously. The U.S. Food and Drug Administration–approved starting dose of darbepoetin is 2.25 micrograms/kg weekly or 500 micrograms every 3 weeks subcutaneously. Alternative starting doses or dosing schedules have shown no consistent difference in effectiveness on outcomes including transfusion and Hb response, although they may be considered to improve convenience. Dose escalation should follow U.S. Food and Drug Administration–approved labeling (see table below); no convincing evidence exists to suggest that differences in dose escalation schedules are associated with different effectiveness.

Erythropoiesis-Stimulating Agent (ESA) Dosing

<table>
<thead>
<tr>
<th>Dose and Modifications</th>
<th>Epoetin Alfa</th>
<th>Darbepoetin Alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>150 U/kg SC TIW</td>
<td>40,000 U SC weekly</td>
</tr>
<tr>
<td>Dose increase</td>
<td>Increase dose to 300 U/kg TIW if no reduction in transfusion requirements or rise in Hb after 8 wks</td>
<td>Increase dose to 60,000 U SC weekly if no increase in Hb by &gt;1 gm/dL after 4 wks of therapy, in the absence of a RBC transfusion</td>
</tr>
<tr>
<td>Dose reductions</td>
<td>Decrease dose by 25% when Hb reaches a level needed to avoid transfusion or Hb increases&gt;1 gm/dL in 2 wk</td>
<td>Decrease dose by 40% of previous dose when Hb reaches a level needed to avoid transfusion or Hb increases&gt;1 gm/dL in 2 wk</td>
</tr>
<tr>
<td>Dose withholding</td>
<td>If Hb exceeds 12 gm/dL, withhold dose until Hb approaches a level where transfusions may be required; restart dose at 25% below previous dose</td>
<td>If Hb exceeds 12 gm/dL, withhold dose until Hb approaches a level where transfusions may be required; restart dose at 40% below previous dose</td>
</tr>
</tbody>
</table>

ESA=erythropoiesis-stimulating agent; SC=subcutaneous; TIW=three times per week; Q3W=every 3 weeks; Hb=hemoglobin; wk=week; RBC=red blood cell.

VI. Discontinuing Therapy for No Response

2007 Recommendation

Continuing epoetin or darbepoetin treatment beyond 6 to 8 weeks in the absence of response (e.g., <1-2 gm/dL rise in Hb or no diminution of transfusion requirements), assuming appropriate dose increase has been attempted in nonresponders as per the U.S. Food and Drug Administration–approved label, does not appear to be beneficial, and ESA therapy should be discontinued. Patients who do not respond should be investigated for underlying tumor progression, iron deficiency, or other etiologies for anemia.

VII. Hb Target

2007 Recommendation

Hb can be raised to (or near) a concentration of 12 gm/dL, at which time the dosage of epoetin or darbepoetin should be titrated to maintain that level. Dose and dose modification recommendations recorded in the package insert as of March 2007 and approved by the U.S. Food and Drug Administration (also based on the November 8, 2007, FDA label announcement) can be found in the table above. Dose reductions are also recommended when Hb rise exceeds 1 gm/dL in any 2-week period or when the Hb exceeds 11 gm/dL. Risk of venous thromboembolism should also be considered when determining dose reduction schedules.

VIII. Iron Monitoring and Supplementation

2007 Recommendation

Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated, may be valuable in limiting the need for epoetin or darbepoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to ESA therapy. There is inadequate evidence to specify the timing, periodicity, or testing regimen for such monitoring. There is no change to the recommendation from the 2002 guideline.

IX. Anemia in Patients Not Receiving Concurrent Chemotherapy

2007 Recommendation

There is evidence that supports the use of epoetin or darbepoetin in patients with anemia associated with low-risk myelodysplasia. There are no published high-quality studies to support its exclusive use in anemic myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia patients in the absence of concurrent chemotherapy. Analyses of primary data from Study 20010103 (as yet unpublished) submitted to the U.S. Food and Drug Administration in March 2007 support a stronger recommendation against the use of ESAs to treat anemia associated with malignancy, or the anemia of cancer, among patients with either solid or non-myeloid hematological malignancies who are not receiving concurrent chemotherapy. This recommendation is consistent with the black-box warning that was added to the prescribing information for both epoetin alfa and darbepoetin in March 2007, as follows: "Use of ESAs increased the risk of death when administered to a target Hb of 12 gm/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated in this population."
APPENDIX A (CONTINUED)

Use of Epoetin and Darbepoetin in Patients With Cancer: 2007 American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update and 2008 Guidelines From the National Guideline Clearinghouse

X. Treatment of Anemia in Patients with Nonmyeloid Hematological Malignancies Who Are Receiving Concurrent Chemotherapy

2007 Recommendation

Physicians caring for patients with myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in Hb is not observed following chemotherapy, treatment with epoetin or darbepoetin for myeloma, non-Hodgkin’s lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined previously. Particular caution should be exercised in the use of epoetin or darbepoetin concomitant with chemotherapeutic agents and diseases where risk of thromboembolic complications is increased. (Refer to Recommendation IV.) Blood transfusion is also a therapeutic option. This recommendation is essentially unchanged from the 2002 guideline. Slight modifications to the recommendation appear in italics.

*Differences between the 2002 and 2007 guideline recommendations appear in italicized text.*