Appendix B:

Independent Analysis of 2005 OPPS Claims by The Moran Company

October 6, 2006

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Memorandum (September 25, 2006)

TO: Chris Topoleski
Christopher Mancill
Amgen

FROM: Rachel Feldman & Kara Suter
The Moran Company

SUBJECT: Comparison of Aranesp to Procrit in Outpatient Hospitals: Volumes and Oncology Utilization for 2005

This memorandum accompanies our comparative analysis of Aranesp and Procrit utilization in the hospital outpatient claims file for 2005 released with the proposed HOPPS 2007 rule.

Findings

A larger proportion of Aranesp claims are oncology related compared to Procrit; almost twice as many Aranesp administrations were on the same date as chemotherapy administration compared to Procrit. The proportional volume is stable from one year (2004) to another (2005) for both years.

For these analyses, we researched the coding history for all relevant codes, and ran frequency distributions in the claims to ensure that we were picking up all relevant volume. The research resulted in some interesting findings and adjustments to our methodology compared to analyses we did in the past. For example, the new chemotherapy administration coding system using CPT®[1] codes was implemented in 2004, and little coding using the old Q-codes remained. We also found additional ICD-9 oncology coding used as an alternative to standard neoplasm coding. These findings increased the volumes shown in identifying oncology claims. We broke out E/M codes into clinic visits, emergency department visits and observation services, for additional clarity.

We included the ESRD codes for both drugs and the unspecified EPO codes to capture all volume, as some coding is present in the outpatient hospital claims despite the elimination of the ESRD bill type from these files. This volume may indicate some medication delivery in outpatient clinic visits for dialysis patients distinct from their dialysis visits. We included all codes, whether or not they are valid for Medicare payment in the outpatient hospital system. We find that invalid or deleted codes still show up in small numbers of claims. In the case of deleted codes, they continue to be paid for some limited time after they are deleted.

[1] Current Procedural Terminology (CPT) is copyright 2005 American Medical Association. All Rights Reserved.

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INTERPRETING MEDICARE OUTPATIENT HOSPITAL CLAIMS DATA

August 2006

The information in this document is intended for use by Amgen staff in interpreting data provided by The Moran Company based upon Medicare outpatient hospital claims files.

Making Comparisons

When looking at the data for both drugs, the easiest way to understand comparisons is to look at the "days" and think of it as "administrations" of the drug.

The Claims Files

The Centers for Medicare and Medicaid Services (CMS) produces two files containing Medicare claims for outpatient services each year. The first file released accompanies the proposed Rule that specifies how rates will be set for the next year. The file released for the proposed year (in this case 2007) contains claims for the prior year (in this case 2005). After interested parties respond to the proposed rule, CMS publishes the final rule in the fall (expected November 2006) and releases another claims file referred to as the "final" file for 2005. The 2004 file used in the accompanying analyses is the final file used with the final Rule setting 2006 rates.

The distinction between files is important because the file released with the proposed rule includes all claims submitted through 12/31 of the year and processed by the time the file is "cut". This means that hospitals that do not submit 4th quarter claims until after January 1st in the new year will not have those claims represented in the rate setting process. Also claims that are still unprocessed for one reason or another will not show up in this file. As a result, we find significant differences in volumes between the two files, most of which are represented by 4th quarter claims. As a result, comparing volume from the 2004 final file to the 2005 proposed file should be viewed as a trend and not an absolute comparison in volume for two years. That comparison cannot be made until the final 2005 claims file is released later in the fall.

Different Approaches to Defining Volume: Claims, days, lines, units

In hospital outpatient claims, services can appear on the claim with more than one date of service. For this reason, we divide claims based on a variable in the file that groups items billed by the same date of service. We cannot see actual dates of service in the claims. We report the number of claims that include "lines" with the drug code of interest. We then subset the data into clusters of items billed for the same date of service. In addition to reporting claims, we report "days". We have used "days" as the variable on which to make comparisons between Aranesp and Procrit, because dose per patient and the unit definitions for drug codes vary.

We also report "lines" with the drug code on the claim, and units associated with the lines. The units are defined by the HCPCS definition of the quantity of the drug for each code. Generally we see one line per day for drugs. However, it is possible in some instances to see more than one line per day, which could represent more than one drug administration per day. The units per

line will generally tell you the average dose of the drug being used. However, we find that hospitals are somewhat inconsistent in the quality of documentation of units in their bills.

Coding Drugs and Identifying Claims for Oncology Patients

Drug codes can change from year to year. EPO drugs include non-ESRD and ESRD specific codes, and codes that are not specific either to a product or to ESRD. Some codes are explicitly covered by Medicare in a setting and some are explicitly not-covered by Medicare in a setting. However, hospital billing is often not up-to-date in ceasing to use a drug code when it is deleted or changes to a new code. Medicare intermediaries are also inconsistent in paying for codes that have been deleted, changed or limited to one setting or another. As a general practice, payments will continue to be made for at least one quarter after a code has been deleted or changed. When quantifying drugs, to get to actual volume, multiply the units by the quantity defined for the unit of a specific drug code. For example, Q0137 is defined as 1mcg, while J0880 is defined as 5mcg.

To determine whether a claim is for an oncology patient, we relied upon diagnosis coding on the claims. Every claim includes a primary diagnosis and a series of other diagnoses. It is not possible to match one diagnosis code to a single line on the claim. Remember a single outpatient hospital claim can have dozens of lines representing a variety of services, drugs and supplies (procedures, drugs, devices, and supplies that are billed to revenue codes with no specific HCPCS code) for several days of service. Therefore, we search all diagnosis code fields that contain an ICD-9 code with 3, 4, or 5 digits. To identify oncology patient claims, we looked for codes in the ranges for neoplasms (except benign neoplasms). Based on an analysis of the actual diagnosis codes on the claims we found that V-codes were used for patients receiving chemotherapy or radiotherapy, and that specific anemia codes were used rather than the underlying diagnosis code for the cause of the anemia.

Table 1: Summary of Arenesp and Procrit Claims: Non-ESRD Use Only[1]

		2005 (proposed)**				
		Claims	**Days**	**Lines**	**Units**	**Units/line**
Aranesp	Oncology Diagnoses[2]		138,114	138,140	30,213,073	219
	Oncology Dx with Chemotherapy Admin.[3] Same day with Aranesp		46,481	46,486	10,466,253	225
	All Diagnoses	212,402	267,278	267,349	45,072,415	169
Procrit*	Oncology Diagnoses[2]		219,854	219,977	9,230,434	42
	Oncology Dx with Chemotherapy Admin.[3] Same day with Procrit		42,653	42,670	1,815,224	43
	All Diagnoses	361,402	550,775	551,050	16,394,572	30

[1] Excludes ESRD codes appearing in outpatient hospital claims

[2] ICD-9: 140-208, 230-239.9, V58.1, V58.0, 285.22

[3] Q0083-Q0085 (technically not paid in 2004, but appear in 1st quarter of data as paid)
96400-96549, 99601-99602

* HCPCS unit definition is 1000 units

** Note: the proposed file is cut based on claims filed, processed and paid by 12/31/2005. Therefore it understates real 2005 volume because claims that were not processed and paid for services delivered in 2005 by 12/31/2005 will not be included.

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Attachment B

Documentation

Prepared for: Amgen, August 2006

Sources: Medicare Hospital Outpatient Prospective Payment Claims Files

Released with 2006 Final Rule (2004 claims) & Proposed 2007 Rule (2005 claims)

Drug codes

Aranesp Codes include: Q0137, C1774, J0880, Q4054
Procrit Codes include: Q0136, Q4055
Other Unspecified Codes include: Q9920-Q9940 and revenue codes without hcpcs codes 0634 and 0635

Oncology Diagnosis Codes

ICD-9: 140-208, 230-239.9, V58.1, V58.0, 285.22

Chemotherapy Administration Codes

Q0083-Q0085 (technically not paid in 2004, but appear in 1st quarter of data as paid)
96400-96549, 99601-99602

E/M Visit codes

99201-99205, 99211-99215=outpatient visit
99281-99285=emergency department visit
99234-99236, 99218-99220=observation care

Disclaimer

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Appendix C:

Analysis of Savings with Aranesp®
Using the Payment Rates Published in the Proposed Rule (CMS-1506-P)

October 6, 2006

ANALYSIS OF SAVINGS WITH ARANESP® USING THE PAYMENT RATES PUBLISHED IN THE PROPOSED RULE (CMS-1506-P)

Aranesp® costs Medicare and beneficiaries the same or less than Procrit®

Aranesp® is less expensive than Procrit® at the payment rates that CMS published in the Proposed Rule. By applying the proposed payment rates for doses based on the aforementioned clinical guidelines and randomized controlled trials, the Medicare program will pay less for Aranesp® than Procrit® and achieve comparable clinical outcomes at both Q2W and Q3W dosing intervals. Table C-1 presents estimated costs under Q2W dosing regimens, while Table C-2 presents cost analysis of Q3W dosing regimens cited above. The estimated costs below are conservative and do not include any potential savings that may result from decreased office visits.

Table C-1: Aranesp® Administered Q2W Costs Less Than or About the Same as Procrit®[1]

Assumptions[2]	**Procrit®**	**Aranesp®**
OPPS Payment per Billing Unit	$370.00 *(ASP + 5 Percent)*	$300.00 *(ASP + 5 Percent)*
Weekly Dose	40,000 IUs *(40,000 IUs QW)*	100 mcg *(200 mcg Q2W)*
Administration Services	CPT® code 90772 (injection SC/IM)	
Injections (APC 0437) per 2 weeks[3]	2 at $25.28	1 at $25.28
Weekly Payment Comparison[4]	***Medicare and Beneficiary Payments are $82.64 Less per Patient, per Week with Aranesp® on Average***	

Based on Q2W dosing referenced in clinical guidelines, the Medicare payment would be, on average, $82.64 less per week, per patient for Aranesp® than Procrit®. Of that total amount, beneficiaries would be responsible for $16.53 less per week in Part B copayments.

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1 This analysis assumes commonly administered doses based on clinical guidelines and randomized controlled trials.

2 This comparison assumes the provision of one administration service on the date that the product is delivered. Because actual services rendered depend on the needs of specific patients, patients may receive an administration service, an outpatient visit, either service, or some other combination of services on a particular date of service.

3 The amount used in this analysis represents the 2007 proposed national average Medicare payment allowable, including the beneficiary copayment, for APC 0437 (CMS-1506-P).

4 Additional cost of using Procrit® calculated at an additional product cost of $70.00 weekly and additional administration costs of $12.64 weekly. Estimated federal Medicare savings are $66.11, and beneficiary savings are $16.53 per week using Aranesp® over Procrit®.

Table C-2: Aranesp® Administered Q3W Costs Less Than or About the Same as Procrit®[5]

Assumptions[6]	Procrit®	Aranesp®
OPPS Payment per Billing Unit	$370.00 *(ASP + 5 Percent)*	$316.20 to $375.00 *(ASP + 5 Percent)*
Weekly Dose	40,000 IUs *(40,000 IUs QW)*	105 to 125 mcg *(Starting dose of between 300 and 500 mcg Q3W)*
Administration Services	CPT® code 90772 (injection SC/IM)	
Injections (APC 0353) per 3 weeks[7]	3 at $25.28	1 at $25.28
Weekly Payment Comparison[8]	***Medicare and Beneficiary Payments are between $11.85 to $70.65 Less per Patient, per Week with Aranesp® on Average***	

As presented in Table C-2, for doses administered Q3W, Medicare would spend between $11.85 and $70.65 less per week on average for Aranesp® than on Procrit®. Of this amount, beneficiaries would save between $2.37 and $14.13 weekly. Please see Appendix D for the economic analysis presented in this section updated for fourth-quarter 2006 ASPs.

Furthermore, the less frequent Q2W and Q3W dosing regimens available with Aranesp® may offer fewer needle sticks and improved convenience for patients and the potential for fewer outpatient visits, thereby reducing the treatment burden on patients, healthcare professionals, and caregivers compared to the weekly anemia treatment available with Procrit®.

Based on the lower costs of Aranesp® administration as outlined in Table C-2, the Medicare program and its beneficiaries would pay an estimated **$18.2 million less for Aranesp® than for Procrit®** in 2007.[9] In light of the clearly demonstrated lower costs of Aranesp®, CMS should finalize the proposed payment rate for the product.

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5 This analysis assumes commonly administered doses based on clinical guidelines and randomized controlled trials.

6 This comparison assumes the provision of one administration service on the date that the product is delivered. Because actual services rendered depend on the needs of specific patients, patients may receive an administration service, an outpatient visit, either service, or some other combination of services on a particular date of service.

7 The amount used in this analysis represents the 2007 proposed national average Medicare payment allowable, including the beneficiary copayment, for APC 0437 (CMS-1506-P).

8 Additional cost of using Procrit® calculated at an additional product cost of - $5.00 to $53.80 weekly and additional administration costs of $16.85 weekly. Estimated federal Medicare savings are $9.48 to $56.52, and beneficiary savings are $2.37 to $14.13 per week using Aranesp® over Procrit®.

9 Estimate based on data from an independent analysis of 2005 OPPS claims conducted by The Moran Company. See Appendix B.

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Appendix D:

Analysis of Savings with Aranesp®
Using More Recent ASP Data

October 6, 2006

ANALYSIS OF SAVINGS WITH ARANESP® USING MORE RECENT AVERAGE SALES PRICE (ASP) DATA

Aranesp® costs Medicare and beneficiaries less than Procrit®

CMS would not only pay less for Aranesp® than for Procrit® at the rates in the Proposed Rule, but also if the ASP-based payment rates for the fourth quarter of 2006 were the base data from which ASP+5 percent were derived. In this appendix, we calculate the savings for Aranesp® compared to Procrit® using fourth quarter 2006 ASP data.[1] Table D-1 presents estimated costs under Q2W dosing regimens, while Table D-2 presents cost analysis of Q3W dosing regimens cited above. The estimated costs below are conservative and do not include any potential savings that may result from decreased office visits.

Table D-1: Aranesp® Administered Q2W Costs Less Than or About the Same as Procrit®[2]

Assumptions[3]	**Procrit®**	**Aranesp®**
OPPS Payment per Billing Unit	$370.95 *(ASP + 5 Percent)*	$296.28 *(ASP + 5 Percent)*
Weekly Dose	40,000 IUs *(40,000 IUs QW)*	100 mcg *(200 mcg Q2W)*
Administration Services	CPT® code 90772 (injection SC/IM)	
Injections (APC 0437) per 2 weeks[4]	2 at $25.28	1 at $25.28
Weekly Payment Comparison[5]	***Medicare and Beneficiary Payments are $87.31 Less per Patient, per Week with Aranesp® on Average***	

Based on Q2W dosing referenced in clinical guidelines, the Medicare payment would be, on average, $87.31 less per week, per patient for Aranesp® than Procrit® as presented in

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1 Amounts based on CMS ASP data increased by an additional 5 percent. This methodology is comparable to that outlined in the Proposed Rule.

2 This analysis assumes commonly administered doses based on clinical guidelines and randomized controlled trials.

3 This comparison assumes the provision of one administration service on the date that the product is delivered. Because actual services rendered depend on the needs of specific patients, patients may receive an administration service, an outpatient visit, either service, or some other combination of services on a particular date of service.

4 The amount used in this analysis represents the 2007 proposed national average Medicare payment allowable, including the beneficiary copayment, for APC 0437 (CMS-1506-P).

5 Additional cost of using Procrit® calculated at an additional product cost of $74.67 weekly and additional administration costs of $12.64 weekly. Estimated federal Medicare savings are $69.85, and beneficiary savings are $17.46 per week using Aranesp® over Procrit®.

Table D-1. Of that total amount, beneficiaries would be responsible for $17.46 less per week in Part B copayments.

Table D-2: Aranesp® Administered Q3W Costs Less Than or About the Same as Procrit®[6]

Assumptions[7]	**Procrit®**	**Aranesp®**
OPPS Payment per Billing Unit	$370.95 *(ASP + 5 Percent)*	$312.28 to $370.35 *(ASP + 5 Percent)*
Weekly Dose	40,000 IUs *(40,000 IUs QW)*	105 to 125 mcg *(Starting dose of between 300 and 500 mcg Q3W)*
Administration Services	CPT® code 90772 (injection SC/IM)	
Injections (APC 0353) per 3 weeks[8]	3 at $25.28	1 at $25.28
Weekly Payment Comparison[9]	***Medicare and Beneficiary Payments are between $17.45 to $75.52 Less per Patient, per Week with Aranesp® on Average***	

As presented in Table D-2, for doses administered Q3W, Medicare would spend between $17.45 and $75.52 less per week on average for Aranesp® than on Procrit®. Of this amount, beneficiaries would save between $3.49 and $15.10 weekly.

Furthermore, the less frequent Q2W and Q3W dosing regimens available with Aranesp® may offer fewer needle sticks and improved convenience for patients and the potential for fewer outpatient visits, thereby reducing the treatment burden on patients, healthcare professionals, and caregivers compared to the weekly anemia treatment available with Procrit®.

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6 This analysis assumes commonly administered doses based on clinical guidelines and randomized controlled trials.

7 This comparison assumes the provision of one administration service on the date that the product is delivered. Because actual services rendered depend on the needs of specific patients, patients may receive an administration service, an outpatient visit, either service, or some other combination of services on a particular date of service.

8 The amount used in this analysis represents the 2007 proposed national average Medicare payment allowable, including the beneficiary copayment, for APC 0437 (CMS-1506-P).

9 Additional cost of using Procrit® calculated at an additional product cost of $0.60 to $58.67 weekly and additional administration costs of $16.85 weekly. Estimated federal Medicare savings are $13.96 to $60.42, and beneficiary savings are $3.49 to $15.10 per week using Aranesp® over Procrit®.

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Appendix E:

Publications

October 6, 2006

USE OF DARBEPOETIN ALFA AND EPOETIN ALFA FOR CANCER-RELATED ANEMIA IN CLINICAL PRACTICE

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BACKGROUND

- Patients with cancer who develop anemia are often treated with erythropoietin-stimulating agents (ESAs)—either darbepoetin alfa (DA) (Aranesp®) or Epoetin alfa (EA) (Procrit®/Epogen®).[1-4]
- Many randomized controlled trials (RCTs) and retrospective chart reviews have compared average weekly dose and clinical outcomes of these ESAs.
  - Dose ratios (EA/DA) from these studies have a wide range
    - 331:1 to 446:1 (between study comparisons for RCTs)[5-8]
    - 352:1 to 475:1 (between study comparisons for effectiveness trials)[9-14]
    - 235:1 to 435:1 (between study comparisons for observational studies)[15-18]
- None of these comparisons have explicitly taken account of the longer serum half-life and duration of clinical benefit of DA compared to EA.
- Failure to account for this difference may bias comparisons of calculated average weekly dosing.

OBJECTIVE

- To compare dosing of DA versus EA in patients with cancer, using methodology that accounts for differences in half-life of these agents in a large, electronic U.S. healthcare claims database.

METHODS

- Claims data were obtained from PharMetrics database, which includes ~70 health plans and over 20 million covered lives annually:
  - Database includes information from inpatient, professional, and outpatient pharmacy claims
- Study subjects were identified based on receipt of ESAs and ≥ 1 encounters with diagnoses (ICD-9-CM) of cancer or receipt of chemotherapy on or before first-noted claim for ESA:
  - Patients with renal disease were excluded
- Information related to ESA dosing for study subjects included billed units (for professional claims), quantity dispensed (pharmacy claims), and dose dispensed (pharmacy claims).
- Claims with "valid" data were defined on basis of:
  - Billed units ≥ 10 and ≤ 80, and reimbursed amount ≥ $50 and ≤ $4000 (professional service claims), or
  - Therapy-days > 0 (pharmacy claims)
- Claims with "questionable" (ie, potentially erroneous) data were defined on basis of billed units < 10 or > 80 and reimbursed amount ≥ $50 and ≤ $4000:
  - Billed units imputed for claims with "questionable" data based on reimbursed amount, assuming paid amount is related linearly to total dose administered.
- All other claims were considered "invalid" and were dropped from analyses.
- Data spanned period 1/1/2005 to 6/30/2005 ("study period").

Defining Episodes of Care (EOCs)

- Episodes of Care (EOCs) were constructed to account for the episodic nature of ESA therapy in cancer and differences in product half-lives based on information on paid claims during the study period[19,20]
- EOC defined as period of time during which patients are assumed to receive benefits of ESA therapy:
  - Includes duration of clinical benefit (DCB) associated with final ESA claim during EOC
- EOCs assumed to begin on date of first-noted claim for ESA therapy, and end on date of last claim for ESA therapy followed by a "clean" period ≥ 42 days:
  - DCB added to last claim in EOC depending on final dose administered:
    - DA: 7 days (≤ 100 mcg), 14 days (101–299 mcg), or 21 days (≥ 300 mcg)
    - EA: 2 days (< 35,000 IU) or 7 days (≥ 35,000 IU)
- Patients could contribute multiple EOCs during the 6-month study period.

Calculation of Weekly ESA Dose and EA/DA Dosing Ratio

- Weekly dose of DA and EA calculated based on:
  - Billed units for professional claims (HCPCS)
  - Therapy-days and dose for pharmacy claims (unique to each NDC)
- Weekly dose calculated using formula:

$$\frac{(\sum \text{Dose}_{\text{in EOC}})}{(\sum \text{Days}_{\text{in EOC}})} \times 7$$

- EA/DA dosing ratio calculated using formula:

$$\frac{\text{Weekly Dose}_{\text{EA}}}{\text{Weekly Dose}_{\text{DA}}}$$

Sensitivity Analyses

- Numerous sensitivity analyses were conducted to assess robustness of methodology, as follows:
  - Analysis 1: Exclude all single-dose EOCs
  - Analysis 2: Change DCB assigned to final claim within EOCs:
    - DA: < 60 mcg, add 2 days; 60–149 mcg, add 7 days; 150–299 mcg, add 14 days; ≥ 300 mcg, add 21 days
    - EA: ≤ 15,000 IU, add 2 days; 15–35,000 IU, add 5 days, > 35,000 IU, add 7 days
  - Analysis 3: Exclude all medical claims for ESA therapy where billed units are < 10 or > 80
  - Analysis 4: Exclude all pharmacy claims for ESA therapy
  - Analysis 5: Exclude all professional claims for ESA therapy where billed units are < 10 or > 80 and exclude all pharmacy claims for ESA therapy
  - Analysis 6: Remove DCB assigned to final claim within EOCs
  - Analysis 7: Exclude all single-dose EOCs and eliminate DCB assigned to ESA final claim within EOCs
  - Analysis 8: Exclude all "questionable" claims and NDC claims, and change DCB as described in analysis 2

Multivariate Analyses

- Analysis of covariance (ANCOVA) was used to examine mean weekly dose, adjusting for differences in patient demographic and clinical characteristics.
- ANCOVA analyses performed for base-case analysis as well as for sensitivity analysis 7 (no single-dose EOCs, no DCB added to last claim in EOC).

RESULTS

Patient Characteristics: Base Case Analyses

- Patients receiving DA:
  - Were younger
  - Were more likely to have breast cancer and less likely to have "other" cancers (ie, other than breast, lung, and non-Hodgkin's lymphoma [NHL])
  - Had higher mean Charlson comorbidity scores.

Table 1. Characteristics of DA and EA EOCs: Base Case Analyses

Parameter	EA	DA	*P*-value
Number of EOCs	683	1,323	
Number of patients	593	1,194	
Mean age, years (SD)	54.8 (10.6)	53.4 (9.6)	0.010
Age category, %			
< 18	0.4	0.3	< 0.001
18–44	13.3	16.7	
45–64	78.4	81.0	
≥ 65	7.9	2.0	
Cancer type, %			
Breast	26.6	33.9	0.011
Lung	12.9	12.3	
NHL	8.8	7.6	
Other	51.7	46.3	
Evidence of metastases, %	30.2	33.5	0.132
Evidence of bleeding, %	6.1	4.8	0.213
Evidence of infection, %	18.3	17.2	0.523
Charlson comorbidity index (SD)	4.1 (3.0)	4.5 (3.1)	0.020
Evidence of radiation, %	15.7	15.9	0.904

EOC Characteristics: Base Case Analyses

- DA EOCs averaged 3.8 administrations over 54.8 days; mean weekly dose was 99 mcg (Table 2)
- EA EOCs averaged 5.6 administrations over 51.3 days; mean weekly dose was 42,634 IU
- EA/DA dose ratio was 431:1.

Table 2. EOC Characteristics: Base Case Analyses

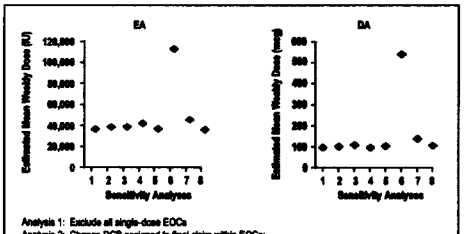
Parameter	EA	DA
Mean weekly dose, (SD)*	42,634 (29,970) IU	99 (52) mcg
Mean dose per administration, (SD)	44,503 (24,310) IU	209 (110) mcg
Median dose per administration	40,000 IU	200 mcg
Number of administrations in an EOC, %		
1	23.7	27.4
2–5	42.3	51.2
≥ 6	34.0	21.4
Mean (SD)	5.6 (5.8)	3.8 (3.2)
Number of days between consecutive administrations in an EOC		
Mean (SD)	11.5 (6.5)	16.8 (6.0)
Median	7	14
Duration of EOC (days), %		
< 30	46.6	40.1
30–59	20.5	25.7
60–89	10.7	14.1
≥ 90	20.2	20.1
Mean (SD)	51.3 (51.3)	54.8 (43.7)
Median	34	42
Evidence of NDC claims, %	7.9	1.0
EA/DA dose ratio	431:1	

*Unadjusted; NDC = National Drug Code

Sensitivity Analyses

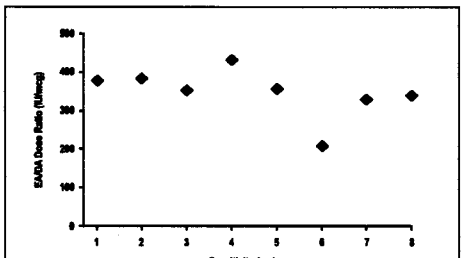
- Elimination of DCB from final ESA claim, but retention of single-dose EOCs, substantially increased estimated mean weekly doses and decreased EA/DA dose ratio:
  - Effect of eliminating DCB more pronounced for DA than EA
    - Estimated weekly dose increased 5-fold for DA (99 to 542 mcg) and 3-fold for EA (42,634 to 113,103 IU) (Figure 1)
    - EA/DA weekly dose ratio reduced from 431 to 209 (Figure 2)
- Effects of varying other assumptions were more modest.

Figure 1. Estimated Weekly Dose of DA and EA: Sensitivity Analyses, Unadjusted Data



Analysis 1: Exclude all single-dose EOCs
Analysis 2: Change DCB assigned to final claim within EOCs:
EA: ≤ 15,000 IU, add 2 days; 15–35,000 IU, add 5 days; > 35,000 IU, add 7 days
DA: < 60 mcg, add 2 days; 60–149 mcg, add 7 days; 150–299 mcg, add 14 days; ≥ 300 mcg, add 21 days
Analysis 3: Exclude all medical claims for ESA therapy where billed units are < 10 or > 80
Analysis 4: Exclude all pharmacy claims for ESA therapy
Analysis 5: Exclude all professional claims for ESA therapy where billed units are < 10 or > 80 and exclude all pharmacy claims for ESA therapy
Analysis 6: Remove DCB assigned to final claim within EOCs
Analysis 7: Exclude all single-dose EOCs and remove DCB assigned to final claim within EOCs
Analysis 8: Exclude all "questionable" claims and NDC claims, and change DCB as described in analysis 2
Dotted line represents estimated mean weekly dose using Base Case Assumptions

Figure 2. EA/DA Dose Ratio: Base Case and Sensitivity Analyses, Unadjusted Data

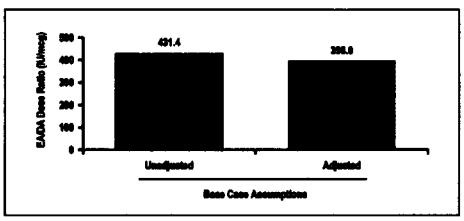


Analysis 1: Exclude all single-dose EOCs
Analysis 2: Change DCB assigned to final claim within EOCs:
EA: ≤ 15,000 IU, add 2 days; 15–35,000 IU, add 5 days; > 35,000 IU, add 7 days
DA: < 60 mcg, add 2 days; 60–149 mcg, add 7 days; 150–299 mcg, add 14 days; ≥ 300 mcg, add 21 days
Analysis 3: Exclude all medical claims for ESA therapy where billed units are < 10 or > 80
Analysis 4: Exclude all pharmacy claims for ESA therapy
Analysis 5: Exclude all professional claims for ESA therapy where billed units are < 10 or > 80 and exclude all pharmacy claims for ESA therapy
Analysis 6: Remove DCB assigned to final claim within EOCs
Analysis 7: Exclude all single-dose EOCs and remove DCB assigned to final claim within EOCs
Analysis 8: Exclude all "questionable" claims and NDC claims, and change DCB as described in analysis 2
Dotted line represents estimated mean weekly dose using Base Case Assumptions

Multivariate Analyses

- After adjusting for potentially confounding differences in patient demographic and clinical characteristics, estimated mean weekly dose of EA decreased, while that of DA increased:
  - Adjusted weekly dose for EA was 39,922 IU and 100 mcg for DA
  - EA/DA dose ratio declined as a result (Figure 3).

Figure 3. EA/DA Dose Ratios (Summary of Results from Different Analyses



LIMITATIONS

- Analyses of administrative claims data may be subject to various forms of bias:
  - confounding by indication
  - data recording and processing errors
- Administrative claims data lack information on patient clinical outcomes of ESA therapy
  - Comparisons of dose using these data must therefore be interpreted with caution
  - These data are best used as supportive rather than conclusive evidence
- Lack of robust information regarding comparative effectiveness.

CONCLUSIONS

- Based on analyses of US healthcare claims data, cancer patients treated with ESAs received a mean weekly dose of 99 mcg of DA or 42,634 IU of EA
  - This results in a dose ratio of 431:1
  - Results are based on an episode of care approach including a duration of clinical benefit
- Average weekly doses are highly sensitive to assumptions concerning the inclusion/exclusion of duration of clinical benefit.
  - All analyses including a duration of clinical benefit resulted in dose ratios greater than or equal to 330:1
- Median time between ESA administrations support the use of product specific duration of clinical benefit in an episode of care.
- Comparisons of DA and EA dosing should account for differences in duration of clinical benefit for these two agents.

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The Oncologist®

Symptom Management and Supportive Care

Darbepoetin Alfa Administered Every Three Weeks Is Effective for the Treatment of Chemotherapy-Induced Anemia

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Key Words. Chemotherapy • Anemia • Darbepoetin alfa • Hemoglobin • Cancer

ABSTRACT

Patients with cancer receiving chemotherapy often have chemotherapy-induced anemia (CIA) and reduced quality of life. Darbepoetin alfa can effectively treat CIA when administered at an extended dosing interval of once every 3 weeks (Q3W). Darbepoetin alfa administered Q3W may allow synchronization of darbepoetin alfa therapy with chemotherapy administered Q3W. This multicenter, open-label, 16-week study evaluated the effectiveness and safety of darbepoetin alfa administered as a fixed dose (300 μg) Q3W in patients with CIA. Eligible patients (≥18 years) were anemic (hemoglobin <11 g/dl), had a nonmyeloid malignancy, and were receiving multicycle chemotherapy. This analysis includes 1,493 patients who received at least one dose of darbepoetin alfa. The effect of baseline hemoglobin (<10 or ≥10 g/dl) on clinical outcomes was evaluated. Patients in the ≥10-g/dl stratum achieved the hemoglobin target range (11–13 g/dl) in less time than patients in the <10-g/dl stratum (3 weeks vs. 9 weeks). More patients in the ≥10-g/dl stratum achieved the hemoglobin target range (87% vs. 66%); however, similar proportions of patients in both strata maintained hemoglobin within the target range (73% vs. 71%). Fewer patients in the ≥10-g/dl stratum received RBC transfusions from week 5 to the end of the study (12% vs. 28%). Over 50% of patients in both strata reported clinically significant improvements (≥3-point increase) in Functional Assessment of Cancer Therapy–Fatigue score. Twenty-eight percent of patients reported serious adverse events; 3% of all patients had a venous or arterial thrombotic event. This study demonstrates that darbepoetin alfa Q3W is well tolerated and effective for treating CIA. *The Oncologist* 2006;11:409–417

INTRODUCTION

Chemotherapy-induced anemia (CIA) is common in patients with cancer [1] and can be treated with the erythropoiesis-stimulating agents darbepoetin alfa and epoetin alfa, which increase hemoglobin levels, reduce the requirement for RBC transfusions, and improve patients' quality of life [2, 3]. Initially, darbepoetin alfa was evaluated using a once per week dosing schedule [3–6]. A broad range of experience has indicated that dosing of darbepoetin alfa at less frequent dosing intervals, such as once every 3 weeks (Q3W), is also effective [7–11]. Darbepoetin alfa can be administered Q3W either synchronously (the same day as

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chemotherapy) or asynchronously with chemotherapy with comparable efficacy and safety [7]. Thus, synchronous administration of darbepoetin alfa Q3W and chemotherapy Q3W potentially offers added convenience to patients and their caregivers.

In a dose-finding, placebo-controlled study of darbepoetin alfa administered Q3W, weight-based doses of 4.5–15.0 μg/kg Q3W effectively produced a lower rate of transfusion and higher percentage of patients with a hemoglobin response (i.e., an increase in hemoglobin of ≥2 g/dl from baseline in the absence of an RBC transfusion in the previous 28 days) [8]. In that trial, the minimally effective dose was 4.5 μg/kg, with some evidence of a better response observed at 6.75 μg/kg; doses above 6.75 μg/kg yielded only small incremental improvements in these endpoints. Fixed dosing of darbepoetin alfa in patients with CIA has been evaluated in clinical trials and appears to result in comparable hemoglobin, transfusion, and safety outcomes [10, 12]. Further, fixed dosing of darbepoetin alfa is common in the clinic as indicated by recent studies of current practice patterns [13, 14].

The objective of this multicenter, open-label, 16-week study was to evaluate the safety and effectiveness of darbepoetin alfa administered at a fixed dose (300 μg) Q3W (roughly equivalent to a weight-based dose of 4.5 μg/kg for an average patient), with a dose increase to 500 μg, if required, in patients with cancer and CIA. We assessed the effectiveness of Q3W darbepoetin alfa in achieving and maintaining hemoglobin concentrations within the range recommended by current evidence-based guidelines (11–13 g/dl) [15–17], lowering the incidence of RBC transfusion, and improving quality of life (assessed using the Functional Assessment of Cancer Therapy–Fatigue [FACT-F] scale). Previous studies have shown that patients treated with erythropoietic agents before their hemoglobin concentration fell below 10 g/dl demonstrate greater clinical improvements than patients whose hemoglobin concentration was allowed to drop below 10 g/dl [18]. Therefore, we also evaluated the effects of baseline hemoglobin concentration (<10 and ≥10 g/dl) on clinical outcomes.

Patients and Methods

Patient Population

The study protocol was approved by the Institutional Review Board (IRB) of each of the participating sites, and all patients provided written, IRB-approved informed consent before initiation of study-related procedures.

Eligible patients were at least 18 years old, had a non-myeloid malignancy for which they were receiving at least eight additional weeks of chemotherapy, and were anemic (hemoglobin <11 g/dl) as a result of cancer and chemotherapy. Patients were excluded if they had inadequate renal and liver function, acute myelogenous leukemia, chronic myelogenous leukemia, a myelodysplastic syndrome, unstable cardiac disease, active bleeding, active systemic or chronic infection, severe active chronic inflammatory disease, any other hematologic disorder associated with anemia, uncontrolled hypertension, iron or other nutritional deficiency, HIV, history of pure red-cell aplasia, or history of positive antibody response to any erythropoietic agent. Patients were also excluded if they had previously enrolled in the study, had planned elective surgery during the study period, had an RBC transfusion within 2 weeks of screening, had erythropoietic therapy within 4 weeks of screening, had drugs or devices not approved by the U.S. Food and Drug Administration for any indication within 30 days of screening, were pregnant or lactating, or had a known hypersensitivity to mammalian cell–derived products.

Study Design

This was a multicenter, 16-week, single-arm, open-label study of darbepoetin alfa administered at a fixed dose of 300 μg Q3W to cancer patients with CIA. Patients received s.c. injections of darbepoetin alfa for ≤13 weeks, with a follow-up visit at week 16 on three weeks after their last dose. At any point during the study, the darbepoetin alfa dose was reduced by 25% if the hemoglobin concentration increased by more than 1 g/dl in a 2-week period. Darbepoetin alfa was withheld if the hemoglobin exceeded 13 g/dl but was reinitiated at a dose approximately 25% below the previous dose if hemoglobin fell to 12 g/dl. If after 6 weeks hemoglobin concentrations remained below 10 g/dl and the increase from baseline was less than 1 g/dl, the darbepoetin alfa dose was increased to 500 μg Q3W. Physician discretion regarding dose increases may have been exercised if the hemoglobin concentration was above 10 g/dl but below the baseline hemoglobin concentration. The dose was not increased if the hemoglobin concentration was within the hemoglobin target range (11–13 g/dl). Hemoglobin concentrations were measured weekly (before dosing with darbepoetin alfa during dosing weeks) and at the end of the study.

Patients answered 13 questions related to the FACT-F scale [19] at baseline, during each clinic visit (every 3 weeks), and at the end of the study.

Efficacy End Points

The objective of the study was to assess the effectiveness of darbepoetin alfa at a dose of 300 μg Q3W in achieving

a hemoglobin concentration ≥11 g/dl and maintaining the hemoglobin concentration in the range of 11–13 g/dl, as recommended by the current evidence-based guidelines [15–17]. The primary endpoints were the percentage of patients who achieved the target hemoglobin concentration (≥11 g/dl in the absence of an RBC transfusion within the preceding 28 days) and the percentage of these patients with a mean hemoglobin concentration of 11–13 g/dl after achieving the target concentration. Secondary endpoints included the percentage of patients who had a hematopoietic response (either a 2-g/dl increase in hemoglobin from baseline or hemoglobin ≥12 g/dl in the absence of aRBC transfusion within the previous 28 days), the percentage of patients that required RBC transfusions, and the change in FACT-F score from baseline.

Safety End Points

Only data on serious adverse events were collected. Serious adverse events and serious treatment-related adverse events that occurred on or after the first dose of darbepoetin alfa and on or before the end of the study were summarized according to the affected body system and by the preferred term within the body system using the Medical Dictionary for Regulatory Activities (MedDRA, version 6.1). Patients were assessed for the presence of antibodies to darbepoetin alfa at the beginning and end of the study.

Statistical Analysis

This analysis included all patients who were correctly consented and who received at least one dose of darbepoetin alfa. Patients were stratified according to their baseline hemoglobin concentration of <10 or ≥10 g/dl. Baseline demographics and clinical characteristics were summarized by number and percentage for categorical variables and mean (standard deviation [SD]) for continuous variables. Hemoglobin-based end points were calculated using two approaches: the last value carried forward (LVCF) approach (missing hemoglobin values or values within 28 days of an RBC transfusion were imputed using the previous value) and an available data approach (not imputation). The number and percentage of patients who achieved the target hemoglobin concentration, who had a hematopoietic response by the end of the study and who received at least one RBC transfusion were calculated (with a 95% confidence interval [CI]). Time to target hemoglobin response was summarized using the Kaplan-Meier (KM) method.

The number and percentage of patients who had a ≥1-g/dl rise in hemoglobin during the first 4 weeks of treatment were also calculated to explore if this end point was a clinically meaningful predictor of response. The sensitivity and specificity of a ≥1-g/dl rise in hemoglobin during the first 4 weeks to the incidence of RBC transfusion and the proportion of patients who achieved the target hemoglobin were determined. Sensitivity was defined as the proportion of patients with a ≥1-g/dl increase in hemoglobin that also had a positive clinical response (either achieved the target hemoglobin or did not receive an RBC transfusion). Specificity was defined as the proportion of patients without a ≥1-g/dl increase in hemoglobin that also had a negative clinical response (either did not achieve the target hemoglobin or did receive an RBC transfusion).

FACT-F scores were calculated using available data from patients who received at least one dose of darbepoetin alfa and who completed both the baseline and one subsequent FACT-F questionnaire.

All statistical analyses were done using SAS version 8.2.

Results

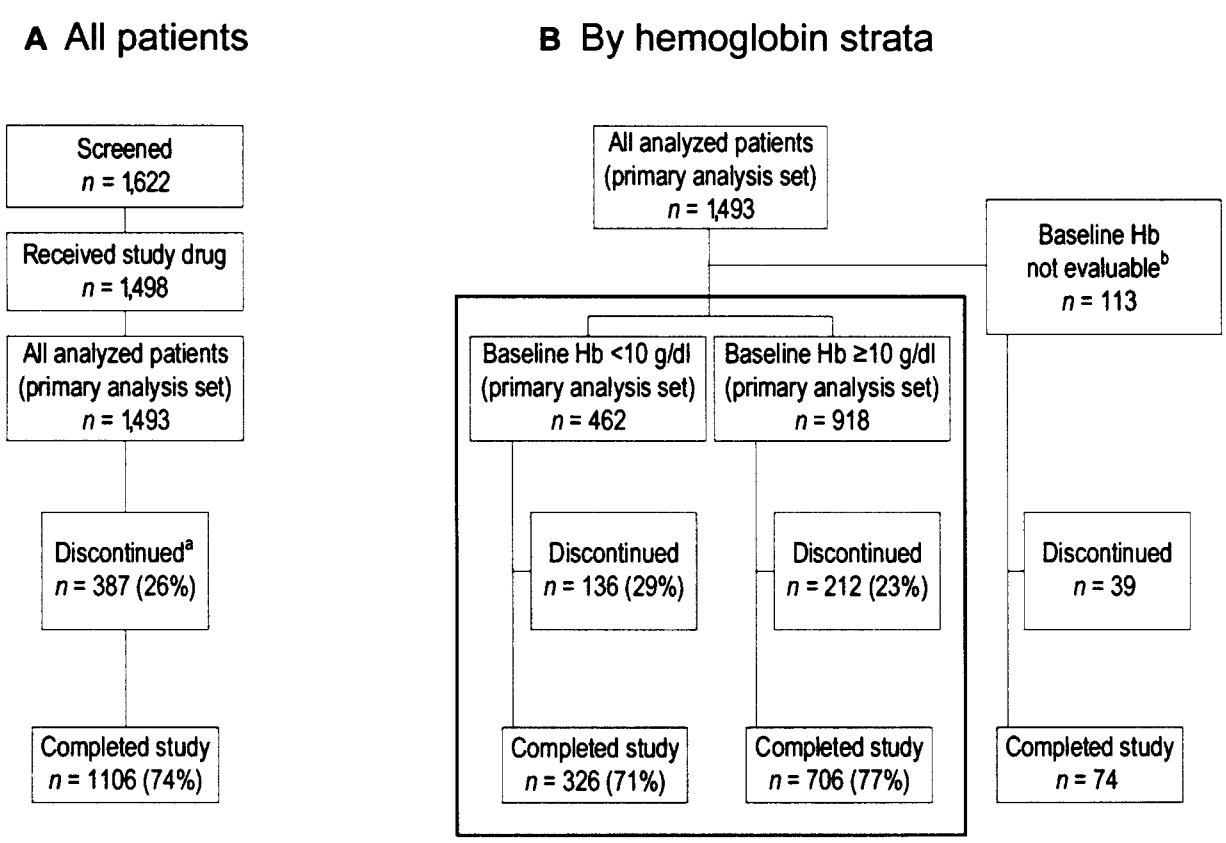
Patient Demographics and Baseline Characteristics

A total of 1,501 patients from 230 sites was enrolled in this study. Of these, 1,493 patients were properly consented, received at least one dose of darbepoetin alfa, and were included in the primary analysis set. Patient disposition is shown in Figure 1. The reasons for discontinuation of darbepoetin therapy were similar for patients in both hemoglobin strata.

The demographic and baseline clinical characteristics of the two baseline hemoglobin strata were similar except that there were 8% more women in the ≥10-g/dl stratum, and 8% more patients had stage IV disease in the <10-g/dl stratum (Table 1). Nearly all (96%) of the patients had received at least one cycle of prior chemotherapy, and 47% had received at least three cycles of prior chemotherapy. Thirty-three percent of patients in both groups received platinum-based chemotherapy during the study. In addition, 10% of the subjects had received prior radiation therapy.

Darbepoetin Alfa Dosing

Darbepoetin alfa use was similar for patients in the two hemoglobin strata (Table 2). When compared with patients in the <10-g/dl stratum, 8% more patients in the ≥10-g/dl stratum had at least one dose of darbepoetin withheld, 4% more had a dose decrease, and 8% less had a dose increase, possibly because of higher baseline hemoglobin values. Eight percent of patients in both strata received at least one extra dose of darbepoetin alfa. Despite the dose adjustments, the average weekly dose administered to the total study population was 105.4 μg.



[a]Reasons for discontinuation: adverse event (2%), death (5%), consent withdrawn (5%), disease progression (3%), administrative decision (4%), lost to follow-up (2%), protocol deviation (1%), and other (4%).
[b]Forty-seven patients had transfusions within 28 days of baseline, and 66 patients had missing baseline hemoglobin values.

Figure 1. Patient disposition. Panel **(A)** describes the disposition of all patients. Panel **(B)** describes the disposition of patients stratified by baseline hemoglobin (Hb) category. One hundred thirteen patients were not included in the analyses stratified by baseline hemoglobin because they either had a missing hemoglobin value on study day 1 or their baseline value was within the 28-day period following an RBC transfusion.

Efficacy End Points

All Patients

In this study of darbepoetin alfa administered at a dose of 300 μg Q3W, 79% of patients achieved the target hemoglobin level by the end of the study (Table 3). The KM estimated median time to achieve the target hemoglobin was 4 weeks, and 73% of patients maintained their hemoglobin levels within the target hemoglobin range after achieving it (Table 3). Eighteen percent of patients required RBC transfusions from week 5 to the end of the study, and the incidence of RBC transfusion was reduced from 12% in month 1 to 3% by month 4. A clinically significant improvement (≥3-point change [20]) in FACT-F score (Table 3) was seen in 55% of patients by the end of the study.

Effect of Baseline Hemoglobin

The mean hemoglobin concentration (using available data) of patients in the ≥10-g/dl stratum was within the target range at week 7 (Fig. 2). In contrast, the mean hemoglobin level of patients with baseline hemoglobin <10 g/dl was lower than 11 g/dl at week 7 (Fig. 2). At week 16, the mean hemoglobin concentration for patients in both strata was within the target range (Fig. 2). Patients in the ≥10-g/dl stratum achieved the target hemoglobin concentration in a median time of 3 weeks (Fig. 3), whereas patients in the <10-g/dl stratum had a median time to target of 9 weeks. The percentage of patients who achieved the target hemoglobin level was approximately 20% greater for patients with baseline hemoglobin ≥10 g/dl (Table 3, Fig. 3). However, once target was achieved, similar percentages of patients in both groups (71% and 73% in the <10-g/dl and ≥10-g/dl

Table 1. Patient demographics and disease characteristics

	Baseline hemoglobin <10 g/dl (n = 462)	Baseline hemoglobin ≥10 g/dl (n = 918)	All patients (n = 1,493)[a]
Women, n (%)	258 (56)	583 (64)	906 (61)
Race, n (%)			
White	360 (78)	721 (79)	1,178 (79)
Black	66 (14)	115 (13)	192 (13)
Hispanic	20 (4)	56 (6)	80 (5)
Other	16 (3)	26 (3)	43 (3)
Age, years, mean (SD)	62.9 (13.0)	62.5 (13.5)	62.6 (31.3)
Geriatric (≥65 years old) age group, n (%)	224 (48)	453 (49)	724 (48)
Primary tumor type, n (%)			
Breast	124 (27)	290 (32)	439 (29)
Gastrointestinal	100 (22)	229 (25)	360 (24)
Hematologic[b]	77 (17)	114 (12)	216 (14)
Lung	58 (13)	103 (11)	171 (11)
Genitourinary	48 (10)	74 (8)	135 (9)
Gynecologic	23 (5)	39 (4)	68 (5)
Other[c]	32 (7)	69 (8)	104 (7)
Disease stage, n (%)			
I	15 (3)	43 (5)	60 (4)
II	67 (15)	149 (16)	232 (16)
III	86 (19)	227 (25)	339 (23)
IV	243 (53)	409 (45)	706 (47)
Patients receiving platinum-based chemotherapy, n (%)	151 (33)	307 (33)	499 (33)
Baseline hemoglobin, g/dl, mean (SD)	9.3 (0.6)	10.5 (0.3)	10.1 (0.7)

[a]Sixty-six patients (4%) had a missing hemoglobin value at baseline, and 47 patients (3%) had baseline hemoglobin levels measured within 28 days of an RBC transfusion.
[b]May include acute and chronic lymphocytic leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and other lymphoma.
[c]May include bone sarcoma, soft tissue sarcoma, melanoma, head and neck cancer, and other tumors.
[d]Excludes small cell lung cancer patients.
Abbreviation: SD, standard deviation.

Table 2. Darbepoetin alfa dosing

	Baseline hemoglobin <10 g/dl (n = 462)	Baseline hemoglobin ≥10 g/dl (n = 918)	All patients (n = 1,493)
No. of weeks of dosing, mean (95% CI)	10.9 (10.5–11.2)	11.4 (11.2–11.6)	11.2 (11.0–11.3)
Average weekly dose administered, µg/week, mean (95% CI)	109.8 (107.4–112.1)	102.9 (101.1–104.6)	105.4 (104.0–106.7)
Average Q3W dose administered, µg/dose, mean (95% CI)	331.1 (325.8–336.3)	319.0 (315.5–322.6)	323.6 (320.8–326.4)
No. of doses received, mean (95% CI)	4.2 (4.1–4.4)	4.3 (4.2–4.3)	4.2 (4.2–4.3)
No. of patients with at least one dose withheld (%)[a]	52 (11)	175 (19)	242 (16)
No. of patients who had a dose increase (%)	207 (45)	336 (37)	585 (39)
No. of patients who had a dose increase because of an extra dose of darbepoetin alfa[b] (%)	36 (8)	77 (8)	116 (8)
No. of patients who had a dose decrease (%)	85 (18)	206 (22)	308 (21)

[a]The hemoglobin threshold of 13g/dl was reached in these patients.
[b]Including patients who received an extra dose at week 15 or 16 probably because of scheduling or administration errors.
Abbreviations: CI, confidence interval; Q3W, every 3 weeks.

Table 3. Summary of hemoglobin, transfusion, and quality-of-life end points

	Baseline hemoglobin <10 g/dl (n = 462)	Baseline hemoglobin ≥10 g/dl (n = 918)	All patients (n = 1,493)
Achievement of target hemoglobin (≥11 g/dl)[a]			
Patients who achieved target hemoglobin, crude percent (95% CI) [n]	66 (61–70) [462]	87 (85–90) [891]	79 (77–81) [1464]
KM time to target hemoglobin, weeks (95% CI) [n]	9 (8–10) [462]	3 (NE, NE) [891]	4 (4–5) [1464]
Maintenance of target hemoglobin			
Mean (SD) hemoglobin (g/dl) after achieving target [n]	11.5 (0.8) [304]	11.6 (0.8) [803]	11.6 (0.8) [1178]
No. of patients maintaining hemoglobin after achieving target (%)[b]			
<11 g/dl	74 (24)	186 (23)	275 (23)
–13 g/dl	215 (71)	589 (73)	858 (73)
>13 g/dl	15 (5)	28 (3)	45 (4)
Patients with a hematopoietic response, crude percent (95% CI) [n]	58 (54–63) [462]	66 (63–69) [918]	63 (61–66) [1380]
Patients with RBC transfusion from week 5 to end of study, crude percent (95% CI) [n]	28 (24–32) [431]	12 (9–14) [881]	18 (16–20) [1417]
Mean (95% CI) baseline FACT-F score [n][c]	27.3 (26.1–28.5) [418]	28.2 (27.4–29.1) [847]	27.9 (27.2–28.5) [1358]
Mean (95% CI) change in FACT-F from baseline to week 16 [n][d]	5.2 (3.7–6.7) [303]	4.4 (3.4–5.5) [647]	4.7 (3.9–5.6) [1012]
Crude percent (95% CI) of patients with ≥3-point change in FACT-F score at week 7 [n][d]	47 (42–52) [384]	43 (39–46) [780]	44 (41–47) [1,246]
Crude percent (95% CI) of patients with ≥3-point change in FACT-F score at week 16 [n][d]	58 (53–64) [303]	53 (49–57) [647]	55 (52–58) [1,012]

[a]Patients who had a hemoglobin value at or after baseline were eligible to achieve the target hemoglobin level. Patients who had hemoglobin values ≥11 g/dl at baseline were not eligible to achieve the target hemoglobin level.
[b]Percentages are based on the number of patients who achieved the target hemoglobin.
[c]FACT-F scores after baseline are summarized with a ± 1-week window.
[d]A ≥3-point change in FACT-F score is clinically significant [20].
Crude percent indicates the actual number of patients.
Abbreviations: CI, confidence interval; FACT-F, Functional Assessment of Cancer Therapy–Fatigue; KM, Kaplan-Meier; NE, not estimable; SD, standard deviation.

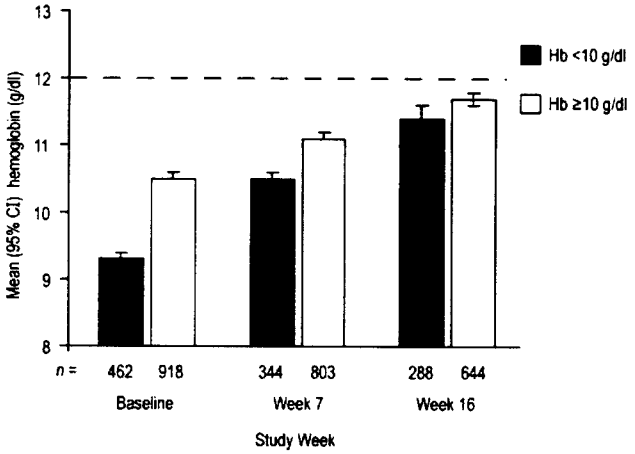


Figure 2. Mean hemoglobin (Hb) concentration at baseline, week 7, and week 16. Darbepoetin alfa at a dose of 300 μg every 3 weeks increased hemoglobin levels in patients with baseline hemoglobin <10 g/dl or ≥10 g/dl. By week 16, patients in both hemoglobin strata had achieved mean hemoglobin concentrations that were within the range recommended by current evidence-based guidelines (11–13 g/dl, shaded area). Mean hemoglobin was calculated using the available data approach. Bars represent 95% confidence interval (CI).

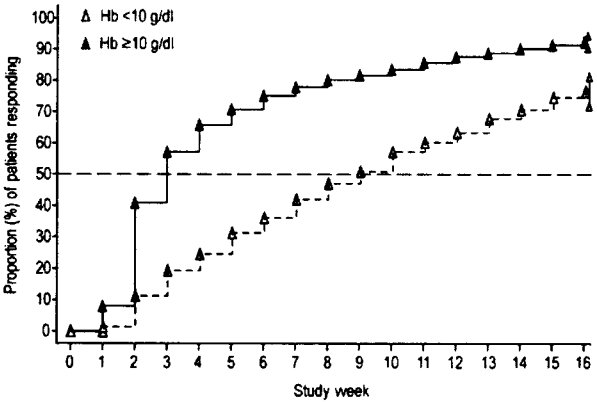


Figure 3. Time to target hemoglobin. The time taken to achieve the target hemoglobin (Hb) level was longer for patients with baseline hemoglobin <10 g/dl. The 95% confidence interval was determined from the last noncensored time point up to week 16 and is displayed at week 16.

strata, respectively) maintained hemoglobin concentrations within it; few patients (5% vs. 3%, respectively) had hemoglobin levels that exceeded the target range (Table 3).

The mean baseline hemoglobin level was 1.2 g/dl lower in the <10-g/dl stratum than in the ≥10-g/dl stratum (9.3 vs. 10.5 g/dl, respectively). The absolute increase in hemoglobin concentration from baseline to week 16 was higher in the <10-g/dl stratum (2.1 g/dl vs. 1.2 g/dl for the <10-g/dl and ≥10-g/dl strata, respectively, using available data). In both strata, the mean change in hemoglobin was lower using the more conservative LVCF approach (1.5 g/dl vs. 0.9 g/dl for the <10-g/dl and ≥10-g/dl strata, respectively). A higher percentage of patients with a baseline hemoglobin level ≥10 g/dl achieved a hematopoietic response (Table 3).

Fewer patients in the ≥10-g/dl stratum than in the <10-g/dl stratum required transfusions during the study. A lower proportion of patients in the ≥10-g/dl stratum received transfusions from week 5 to the end of the study compared with the <10-g/dl stratum (12% vs. 28%, respectively). In the first month of the study, the percentages of patients who received transfusions were 5% (95% CI, 4%–6%) and 22% (95% CI, 18%–26%), for the ≥10-g/dl and <10-g/dl strata, respectively (Fig. 4). By the last month of the study (month 4), the transfusion requirements were further reduced: 3% (95% CI, 1%–5%) versus 3% (95% CI, 2%–4%) (Fig. 4).

Improvement in FACT-F score from baseline to the end of the study was associated with increased hemoglobin concentration. By week 16, patients in both hemoglobin strata had clinically significant improvements in their mean FACT-F score (Table 3). By week 7, 47% and 43% of patients in the <10.0-g/dl and the ≥10.0-g/dl strata, respectively, reported clinically significant improvements in FACT-F score (Table 3). By week 16, clinically significant improvements in FACT-F scores were reported by more than 50% of patients (58% and 53%, respectively) (Table 3).

Predictors of Clinical Response

Fifty percent (95% CI, 47%–53%) of patients had a ≥1-g/dl rise in hemoglobin concentration during the first 4 weeks of treatment: 53% (95% CI, 48%–57%) in the <10-g/dl stratum and 49% (95% CI, 45%–52%) in the ≥10-g/dl stratum. Sensitivity and specificity were calculated to determine if a ≥1-g/dl rise in hemoglobin during the first 4 weeks of darbepoetin alfa therapy was predictive of whether patients required an RBC transfusion or achieved the target hemoglobin concentration. Sensitivity and specificity were 56.2% and 80.4% for RBC transfusions, and 58.0% and 90.4% for achievement of the target hemoglobin concentration. The relatively low sensitivity suggests that a ≥1-g/dl rise in hemoglobin during the first 4 weeks is a poor predictor of clinically meaningful patient end points.

Safety

A total of 420 patients (28%) reported at least one serious adverse event, including 168 patients (36%) in the <10-g/dl stratum and 220 patients (24%) in the ≥10-g/dl stratum. No obvious differences in any given system organ class were observed between the two strata. The most commonly reported serious adverse events were febrile neutropenia (2%), pneumonia (1%), and pyrexia (1%); none of these were reported to be related to darbepoetin alfa use. In addition, 3% of patients reported a venous or arterial thrombotic event. Ten patients reported at least one treatment-related serious adverse event: four patients with deep vein thromboses, two patients with pulmonary emboli, and one patient each with phlebothrombosis, cerebral artery occlusion, cerebrovascular accident, and acute myocardial infarction.

A total of 387 patients (26%) did not complete the study. Of these, 78 (5%) died, including 34 (7%) in the <10-g/dl stratum and 36 (4%) in the ≥10.0-g/dl stratum. The primary reasons for death were the underlying tumor, disease progression, or complications such as sepsis or pneumonia.

Assay results for neutralizing antibodies to darbepoetin alfa were available for 1,169 patients; none developed neutralizing antibodies to darbepoetin alfa during the study.

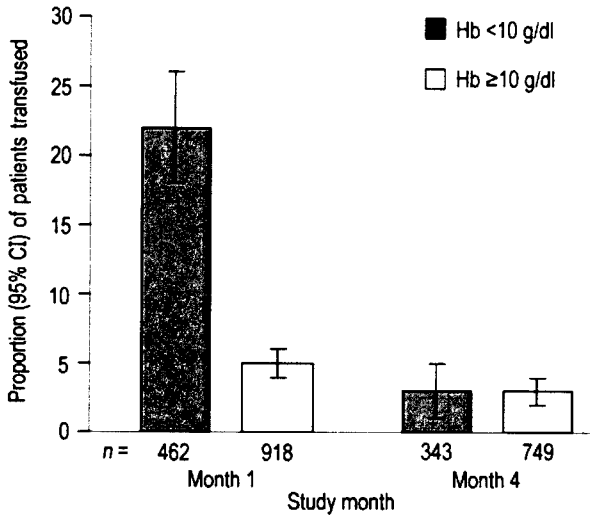


Figure 4. Incidence of RBC transfusion. In month 1, the percentage of patients who required RBC transfusions was about fivefold greater in the <10-g/dl baseline-hemoglobin stratum than in the ≥10-g/dl baseline-hemoglobin stratum. Over the course of the study, darbepoetin alfa at a dose of 300 μg every 3 weeks reduced the requirement for RBC transfusion; by month 4, the percentage of patients who required RBC transfusions was 3% in both hemoglobin strata. Data points are the crude percentage of patients determined at the beginning of each month, and the lines represent the 95% confidence interval (CI).

Discussion

This study showed that administration of darbepoetin alfa at a fixed dose (300 μg) Q3W appears to be well tolerated and effective for the treatment of cancer patients with CIA. A high proportion of the total patient population (79%) achieved the target hemoglobin concentration (≥11 g/dl), and the median time to target hemoglobin was 4 weeks. Treatment with darbepoetin alfa at a dose of 300 μg Q3W also reduced the requirement for RBC transfusion and led to clinically significant improvements in FACT-F scores.

The results of this study emphasize the benefits of initiating erythropoietic therapy when patients' hemoglobin concentrations are ≥10 g/dl rather than <10 g/dl. Intervening in the treatment of CIA while hemoglobin was ≥10 g/dl, that is, on-time intervention, resulted in more patients achieving the target hemoglobin by week 16, rather than waiting until hemoglobin was <10 g/dl, that is, late intervention (a 20% difference: 66% with late intervention vs. 87% with on-time intervention). The median time to achieve the target hemoglobin range when intervening on time was threefold shorter than when intervening late (3 weeks vs. 9 weeks). Patients receiving on-time intervention required fewer RBC transfusions between week 5 and the end of study than patients receiving late intervention. By study month 4, however, similar percentages of patients in the two groups (3%) received transfusions.

As mean hemoglobin concentration increased from week 7 to the end of the study, there was an increase in the percentage of patients in both baseline-hemoglobin strata who reported a clinically meaningful improvement (≥3-point change) in FACT-F score, with >50% of patients in both strata reporting clinically meaningful improvements in FACT-F scores. These observations are consistent with previous studies that demonstrated an association between hemoglobin level and patient-reported quality-of-life outcomes [8, 21, 22].

More than 50% of patients in each baseline-hemoglobin strata had a ≥1-g/dl rise in hemoglobin concentration during the first 4 weeks of treatment, similar to the incidence reported for epoetin alfa administered weekly [23]. Others have suggested that this end point is a useful predictor of clinically meaningful response to erythropoietic therapy in patients with CIA [23]. However, in the present study, sensitivity and specificity analyses suggest that a ≥1-g/dl rise in hemoglobin during the first 4 weeks is not a good predictor of the requirement for RBC transfusion or achievement of target hemoglobin in patients with CIA. This finding agrees with previously published data on predictors of response from trials using epoetin alfa [24].

The dose titration rules employed in this study were effective in achieving and maintaining hemoglobin concentrations within the range recommended by current evidence-based guidelines [15–17]. More than 70% of patients who achieved the target hemoglobin maintained an average hemoglobin level within this range; only 4% of patients had a mean hemoglobin concentration that exceeded the threshold (13 g/dl). This result is important given recent safety concerns over adverse survival outcomes for clinical studies using epoetin alfa [25, 26] and epoetin beta [27], in which hemoglobin levels were allowed to exceed 13 g/dl. In the present study, darbepoetin alfa at a dose of 300 μg Q3W was well tolerated; there was a low incidence of treatment-related serious adverse events and no treatment-related deaths.

In summary, administration of darbepoetin alfa Q3W may simplify the treatment of CIA in the oncology practice and minimize disruption to the lives of patients and their caregivers by synchronizing erythropoietic therapy with chemotherapy.

Acknowledgments

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Disclosure of Potential Conflicts of Interest

Peter Silberstein has acted as a consultant for Amgen; Drs. Ralph Boccia, Tom Lillie, and Dianne Tomita have a financial interest in Amgen; and Drs. Tom Lillie and Dianne Tomita are employees of Amgen.

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Recombinant Human Erythropoietin and Overall Survival in Cancer Patients: Results of a Comprehensive Meta-analysis

Julia Bohlius, Simon Langensiepen, Guido Schwarzer, Jerome Seidenfeld, Margaret Piper, Charles Bennett, Andreas Engert

Background: **Anemia associated with cancer and cancer therapy is an important clinical and economic factor in the treatment of malignant diseases.** ***Methods:*** **We conducted a systematic literature review to assess the efficacy of erythropoietin to prevent or treat anemia in cancer patients with regard to red blood cell transfusions, hematologic response, adverse events, and overall survival. We searched the Cochrane Library, Medline, EMBASE, and other databases for relevant articles published from January 1985 to December 2001. We included all randomized controlled trials that compared the use of recombinant human erythropoietin (plus transfusion, if needed) with no erythropoietin treatment (plus transfusion, if needed). Relative risks (RRs) and 95% confidence intervals (CIs) were calculated under a fixed-effects model. Clinical and statistical heterogeneity were examined with sensitivity analyses and meta-regression. Statistical tests for effect estimates were two-sided.** ***Results:*** **We identified 27 trials involving 3287 adult patients. Patients treated with erythropoietin had a lower relative risk of having a blood transfusion than untreated patients (RR = 0.67, 95% CI = 0.62 to 0.73). Erythropoietin-treated patients with baseline hemoglobin levels lower than 10 g/dL were more likely to have a hematologic response than untreated patients (RR = 3.60, 95% CI = 3.07 to 4.23). The relative risk for thromboembolic complications after erythropoietin treatment was not statistically significantly increased (RR = 1.58, 95% CI = 0.94 to 2.66) compared with that of untreated patients. There is suggestive but inconclusive evidence that erythropoietin may improve overall survival (adjusted data: hazard ratio [HR] = 0.81, 95% CI = 0.67 to 0.99; unadjusted data: HR = 0.84, 95% CI = 0.69 to 1.02).** ***Conclusions:*** **Erythropoietin treatment may reduce the risk for blood transfusions and improve hematologic response in cancer patients. However, our favorable survival outcome is in contrast to two large (N = 351 and 939) recently published randomized controlled trials in which erythropoietin-treated patients had statistically significantly worse survival than untreated patients. Possible reasons for the disparity with our results include differences in study population and design, higher target hemoglobin levels and higher risk of thromboembolic complications, and concerns that erythropoietin may stimulate tumor growth.** **[J Natl Cancer Inst 2005;97:489–98]**

Anemia, defined as an inadequate number of hemoglobin-containing red blood cells, is a widely prevalent complication among cancer patients and varies by type of neoplasia and cytostatic treatment *(1)*. Apart from the physical symptoms *(2)* and diminished quality of life *(3)* patients with anemia experience, there is some evidence that anemia, with the consequence of increased tumor hypoxia, might result in a poorer response to radiotherapy or chemotherapy *(4–8)*. On the basis of these observations, researchers have hypothesized that strategies to diminish cancer-related anemia might not only alleviate anemia-related symptoms and improve quality of life but also improve tumor response and possibly extend overall survival time. However, randomized controlled trials testing this hypothesis have generated conflicting evidence. Results of a phase III trial showed that patients treated with erythropoietin had statistically significantly improved disease-free survival compared with untreated patients *(9)*; however, two recently published trials reported statistically significantly worse tumor control and survival rates *(10,11)*.

Historically, blood transfusion has been the treatment of choice for severe cancer-related anemia. Severe anemia, which is defined as a hemoglobin level less than 8 g/dL, is usually treated, whereas mild-to-moderate anemia (hemoglobin level of 8–11 g/dL) is left untreated in most patients. Although blood transfusion is the fastest means to alleviate symptoms associated with anemia, there are short- and long-term risks associated with this treatment, such as transmission of infectious agents, transfusion reactions, alloimmunization, and overtransfusion *(12)*. The development of increasingly more aggressive antineoplastic treatments that may lead to anemia has increased the need for blood transfusions and has prompted oncologists to weigh the advantages and disadvantages of transfusion. Two forms of recombinant human erythropoietin (rHuEpo), epoetin alfa and epoetin beta, both with similar clinical efficacy *(13,14)*, are available to treat anemia and have been tested in randomized controlled trials. Recently, a novel long-acting erythropoietin variant (novel erythropoiesis stimulating protein [NESP] or darbepoetin alfa) has been introduced into clinical practice *(15,16)*.

Evidence-based guidelines and several systematic reviews on erythropoietin in cancer patients that concentrate on specific underlying malignancies, such as myelodysplastic syndromes *(17)* and solid tumors *(18)* or specific clinical outcomes such as quality of life *(19)* or methodologic issues *(20)*, have been

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See "Notes" following "References."

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published. A systematic review of erythropoietin treatment published by the Agency for Health Care Research and Quality (AHRQ) provides the most comprehensive summary of clinical trials to date *(21,22)*. Although the AHRQ report provides evidence that erythropoietin significantly reduces blood transfusion requirements, the critical question, whether erythropoietin affects overall survival, could not be addressed using the published data available at that time. In collaboration with authors of the AHRQ report, we here present the results of our systematic review of erythropoietin treatment with respect to hematologic response, red blood cell transfusion need, adverse events, and overall survival. This report is part of the Cochrane Review, in which additional outcomes (tumor response, quality of life, and fatigue) are being addressed. An updated Cochrane Review that includes randomized studies of darbepoetin alfa is being planned *(23)*.

Methods

Literature Search

Trials were identified by searching the Cochrane Controlled Trials Register, Medline, EMBASE, and Internet databases of ongoing trials. We manually searched the conference proceedings of the American Society of Hematology, the American Society of Clinical Oncology, and the European Society of Medical Oncology for clinical trial information. Experts in the field at academic institutions and at pharmaceutical companies were contacted to provide information about their study. Citations of all trials identified in the search were checked for additional references. We searched for articles published from January 1985 through December 2001. No language restrictions were used. The full search strategy is published in the Cochrane Library *(23)*.

Inclusion Criteria

Only randomized controlled trials among patients of any age with a histologically or clinically proven malignancy were included in this analysis, regardless of type or stage of disease or previous therapy. Other causes of anemia, such as hemolysis or iron deficiency, had to be ruled out. Epoetin alfa or epoetin beta had to be administered subcutaneously or intravenously at doses of at least 300 U/kg of body weight per week and given for at least 4 weeks to prevent or reduce anemia in cancer patients treated with or without nonmyeloablative antineoplastic therapy. Dose adaptation of erythropoietin, depending on hematologic response, was allowed. The control group had to receive identical antineoplastic and supportive treatment, e.g., iron supplementation and placebo or no experimental treatment. We included published and unpublished data. We excluded ongoing studies, interim analyses, crossover studies, quasi-randomized studies, and studies with 10 or fewer patients per study arm. Studies on long-acting substances, such as darbepoetin alfa, were not included in this review.

Study Selection, Quality Assessment, and Data Extraction

Study selection, quality assessment, and data extraction were carried out independently by two reviewers (S. Langensiepen and J. Bohlius). Any disagreement between the reviewers was resolved by discussion involving a third party (A. Engert, G. Schwarzer). Assessment of study quality included randomization, concealment of allocation, masking of patients and clinicians, documentation of dropouts and withdrawals, and intent-to-treat analysis. To obtain unreported data, we contacted the first author of the included trials. The investigators were also asked for details about the study design as well as aggregated patient data with respect to baseline characteristics, and several study outcomes, including hematologic response, initial and final hemoglobin levels, the number of transfused patients, the number of red blood cells transfused, and individual patient data regarding survival duration. Hematologic response was defined as an increase in hemoglobin level of 2 g/dL or more or an increase in hematocrit of 6% or more, unrelated to blood transfusion.

Data Analysis and Statistical Methods

Analyses were performed using Review Manager (RevMan, version 4.2.7 for Windows; Oxford, England): The Cochrane Collaboration 2004; the statistical software package R *(24)* was used for additional analyses not possible with RevMan. A fixed-effects model was assumed in all meta-analyses. For binary data, the relative risk was used to measure treatment effect; the Mantel–Haenszel method was used to pool relative risks. The estimated overall relative risk and a plausible value for baseline risk were used to estimate numbers of patients needed to treat. For continuous data, weighted mean differences were calculated. Overall survival was calculated as hazard ratios (HRs) and was based on individual patient data when possible. If individual patient data were not available, the hazard ratio was calculated from data obtained from published reports, using methods described by Parmar et al. *(25)* or derived from binary mortality data. The number of patients needed to treat for overall survival was calculated with data from trials with available individual patient data at arbitrarily chosen time points (at 60 and 150 days), based on methods described by Altman et al. *(26)*. The P value of the homogeneity test was used only to describe the extent of heterogeneity inherent in a meta-analysis. Potential causes of heterogeneity were explored by performing sensitivity and subgroup analyses (*see* below). The influence of a single large study on the pooled estimates was tested in a sensitivity analysis by including and excluding it. In meta-analyses with at least four trials, a funnel plot was generated and a linear regression test *(27)* was performed to examine the likely presence of publication bias in meta-analysis. A P value less than .1 was considered statistically significant for the linear regression test. Potential causes of heterogeneity were explored by performing sensitivity analyses to evaluate the effects of hemoglobin level at study entry, type of tumor, antineoplastic therapy given, duration of study, study quality, source of data, and the influence of single large studies on the effectiveness of erythropoietin treatment. In addition to subgroup analyses, a fixed-effect metaregression *(28)* was conducted for the outcome "patients receiving red blood cell transfusions." All covariates showing a statistically significant effect in univariate analysis were included in the multivariable analysis. A backward selection method was used for the model; the covariate with the largest P value was consecutively removed until only statistically significant covariates, according to the Akaike Information Criterion *(29)*, remained in the model. Statistical tests for heterogeneity were one-sided; statistical tests for effect estimates were two-sided.

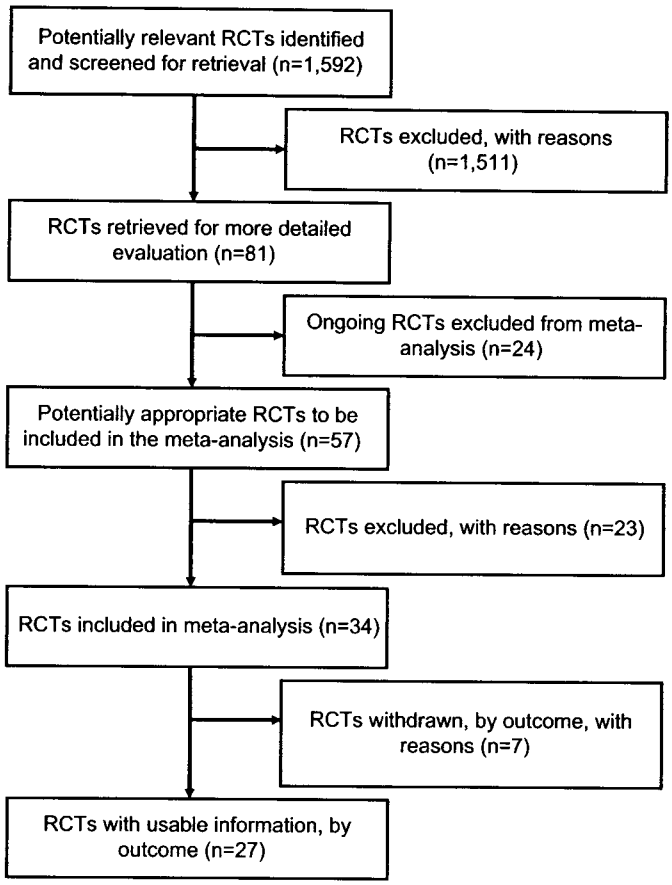

Fig. 1. Identifying and evaluating randomized controlled trials (RCTs).

Results

Description of Studies

A total of 1592 potentially relevant trials were screened for inclusion. Eighty-one studies were retrieved for more information. Of these, 54 were excluded because they did not meet the inclusion criteria (n = 30) or were still ongoing (n = 24). A flow diagram of the process used to identify and evaluate potentially relevant trials is displayed in Fig. 1.

A total of 27 randomized controlled trials involving 3287 patients were included in this systematic review (Table 1). Although the search was limited to studies published in year 2001 or earlier, we included one report that was published in 2002 *(30)* because unpublished data from that trial were available in 2001. Because the full-text report for that study was published shortly thereafter, it was used as the principal data source. All studies recruited adult patients. Thirteen studies included patients with solid tumors only, six studies focused on patients with hematologic tumors, two studies included patients with myelodysplastic syndrome, and six trials evaluated patients with various malignancies. All trials compared the effectiveness of erythropoietin treatment initiated at study entry (plus transfusions if necessary) compared with no erythropoietin treatment (plus transfusions if necessary). Transfusion of red blood cells was given when the patient's hemoglobin (Hb) level fell below a defined threshold or at the discretion of the treating physician. In most studies, the effectiveness of erythropoietin was measured with regard to hematologic response, transfusion requirements, and adverse events. Several studies also addressed quality of life. Studies were grouped by mean or median baseline hemoglobin level at study entry in intervention studies (Hb $\leq$ 10 g/dL, 16 studies; Hb 10–12 g/dL, six studies) and preventive trials (Hb > 12 g/dL, five studies). For 17 studies, final hemoglobin levels were reported or submitted by the investigators. In the erythropoietin-receiving groups, the hemoglobin level at week 12 ranged from 9.82 g/dL (standard deviation [SD] = 2.10) *(31)* to 13.9 g/dL (SD = 1.85) *(32)*. None of the trials directly compared the outcomes of initiating erythropoietin treatment at alternative hemoglobin thresholds. Epoetin alfa was given in 15 studies, and epoetin beta was given in eight studies. In four studies, the specific erythropoietin preparation given could not be clarified. In several studies, different erythropoietin dosages and schedules of administration were compared with one control group *(31–36)*; for each of these studies, we randomly assigned control patients to the corresponding number of separate control groups. If the erythropoietin dose was less than 300 U/kg of body weight per week in a single experimental arm, the data were excluded from analyses because of the possibility of an incomplete response *(33)*. Duration of treatment ranged from 6 weeks to more than 20 weeks.

Study Quality

Details of the studies are shown in Table 1. All included studies were described by the authors as randomized. In 17 of 27 trials, which covered 2490 (76%) of the patients included in the analysis, the method for concealing allocation was judged to be adequate. In 10 studies, the method for concealing allocation could not be determined. Fourteen trials were placebo controlled. Most of the studies included intent-to-treat calculations or excluded fewer than 10% of the participants from the analyses. Twenty-two studies were published as full text, and five were abstracts *(37–41)*. For 19 of the 27 trials, which covered 2930 (89%) of the patients, additional unpublished data were provided by investigators.

Patients Receiving Red Blood Cell Transfusions

Twenty-five trials with 3069 patients reported the percentage of patients who received red blood cell transfusions *(30–33,35–54)*. Investigators provided unpublished aggregated results for 1525 (49.7%) of the included patients *(30,31,38,40,43,44,48,51)*, whereas data from the remaining 1544 (50.3%) patients were taken from published reports *(32,33,35,36,39,41,42,45–47,49,50, 52–54,55)*. Patients treated with erythropoietin had a 33% lower risk of transfusion than untreated patients (relative risk [RR] = 0.67, 95% CI = 0.62 to 0.73, 25 studies; n = 3069, Fig. 2).

The funnel plot was asymmetric ($P<.001$), suggesting that negative results (i.e., no reduction of the proportion of patients transfused) were underreported. Whether studies with more than one experimental arm were analyzed with separated experimental arms or merged into one experimental arm did not influence the overall result (data not shown). There was statistically significant heterogeneity among the trials ($P = .0012$). Results of the meta-regression analysis showed that the treatment effects for hematologic malignancies and myelodysplastic syndrome were similar, whereas the treatment effect for solid tumors was markedly better. In addition, full-text publications and unpublished

Table 1. Summary of size of trial, patient characteristics, interventions, concealment of allocation, and publication form*

Study	N	Disease	Erythropoietin	Antineoplastic therapy	Allocation concealed	Source of data
Baseline Hb < 10 g/dL						
Abels 1993 *(42)*	124	Various	Alfa	None	Yes	Full text†
Cascinu 1994 *(42)*	100	Solid tumors	Alfa	Pb-CT	Yes	Full text†
Case 1993 *(44)*	157	Various	Alfa	CT	Yes	Full text†
Cazzola 1995 *(33)*	146	MM, NHL	Beta	CT	Unclear	Full text†
Coiffier 2001 *(38)*	262	Various	Beta	NR	Yes	Abstract†
Dammacco 2001 *(55)*	145	MM	Alfa	CT, some Pb-CT	Unclear	Full text†
Henry 1994 *(47)*	132	Various	Alfa	Pb-CT	Yes	Full text†
Italian 1998 *(48)*	87	MDS	Alfa	None	Yes	Full text†
Kurz 1997 *(49)*	35	Gynecolog.	Alfa	Pb-CT	Yes	Full text†
Littlewood 2001 *(50)*	375	Various	Alfa	CT	Yes	Full text†
Oberhoff 1998 *(51)*	218	Solid	Beta	Pb-CT	Yes	Full text†
Österborg 1996 *(31)*	144	MM, NHL, CLL	Beta	CT	Yes	Full text†
Österborg 2002 *(30)*	349	MM, NHL, CLL	Beta	CT	Yes	Full text†
Rose 1994 *(40)*	221	CLL	Alfa	CT	Unclear	Abstract†
Silvestris 1995 *(56)*	54	MM	Alfa	CT	Unclear	Full text
Thompson 2000 *(52)*	66	MDS	Alfa	None	Yes	Full text†
Baseline Hb 10–12 g/dL						
Carabantes 1999 *(37)*	35	SCLC, Ovarian	Alfa	Pb-CT	Unclear	Abstract
Henke 1999 *(34)*	50	Head and neck	Alfa or beta	RT	Unclear	Full text
Quirt 1996 *(39)*	56	Various	Alfa	NR	Unclear	Abstract
Ten Bokkel 1998 *(32)*	122	Ovarian	Beta	Pb-CT	Yes	Full text†
Throuvalas 2000 *(41)*	55	Cervix, bladder	NR	Pb-CT + RT	Yes	Abstract†
Wurnig 1996 *(54)*	30	Osteosarcoma	Beta	CT, some Pb-CT	Unclear	Full text
Baseline Hb > 12 g/dL						
Del Mastro 1997 *(45)*	62	Breast ca.	NR	CT	Yes	Full text†
Dunphy 1999 *(46)*	30	NSCLC, head and neck	NR	Pb-CT	Unclear	Full text
Kunikane 1997 *(35)*	72	NSCLC	Beta	Pb-CT	Yes	Full text
Thatcher 1999 *(36)*	130	SCLC	Alfa	Pb-CT	Yes	Full text†
Welch 1995 *(53)*	30	Ovarian	Alfa	Pb-CT	Unclear	Full text

*Hb = hemoglobin; MM = Multiple myeloma; NHL = non-Hodgkin lymphoma; MDS = myelodysplastic syndrome; CLL = chronic lymphatic leukemia; gynecol = ovarian and cervical carcinoma; NSCLC = non–small-cell lung cancer; SCLC = small-cell lung cancer; NR = not reported; CT = chemotherapy; RT = radiotherapy; Pb-CT = platinum-based chemotherapy.

†Additional unreported data from personal communication.

data yielded similar results, whereas publications restricted to abstracts only reported larger treatment effects than full-text publications. For each combination of type of allocation concealment, publication, and underlying disease, we used the information in Table 2 to calculate the relative risk of receiving a blood transfusion as follows. For example, the logarithm of the relative risk for an adequately concealed trial using unpublished data on patients with solid tumors is: Intercept + concealment adequate + unpublished + solid tumor = −.60 + 0.08 + 0.20 − 0.28 = −0.60. Accordingly, the relative risk is 0.55. For hematologic malignancies and myelodysplastic syndrome, analogous calculations yield relative risks of 0.86 and 0.80, respectively. Applying the overall relative risk of 0.67 to a hypothetical population with an estimated risk of 50% for transfusion, the number of patients needed to treat is 6.06 (95% CI = 5.26 to 7.41). Thus, approximately six patients would have to be treated with erythropoietin to spare one patient from transfusion. In a hypothetical population with an estimated risk of 70% for transfusion, the number needed to treat is 4.33 (95% CI = 3.76 to 5.29). Thus, in this group, four to five patients would have to receive erythropoietin to spare one patient from transfusion. These results show that the absolute effectiveness of erythropoietin depends on the baseline risk for transfusion.

Number of Red Blood Cell Units Transfused

Thirteen studies with 2056 patients were included in the analysis *(30–33,38,40,42–44,47,49,51,55)*. All included data were unpublished aggregated results provided by the investigators. The overall weighted mean difference between the amount of blood transfused in treated and untreated patients showed a statistically significant benefit for patients receiving erythropoietin (−1.00, 95% CI = −1.31 to −0.70, 13 studies, n = 2056). In other words, the erythropoietin-treated group received 1.00 unit of blood less on average than the control group, in which patients received an average of 3.57 units of blood. There was no statistically significant heterogeneity among the trials (P = .91), and sensitivity analyses did not show statistically significant differences. Whether studies with more than one experimental arm were analyzed with separated experimental arms or merged into one experimental arm did not influence the overall result (data not shown).

Hematologic Response

Data from 2347 patients with a baseline hemoglobin level below 10 g/dL from 14 trials were analyzed *(30,31,33,38,40,42,44,47–52,55)*. Investigators provided unpublished aggregated results for 1359 (58%) of the patients *(30,31,33,38,40,48,51)*, whereas data from 988 (42%) of the patients was taken from published reports *(42,44,47,49,50,52,55)*. Hematologic response was observed in 690 of 1338 patients (median = 48%, range = 9%–70%) in the erythropoietin group compared with 142 of 1009 patients (median = 11%, range = 0%–27%) in the control group, corresponding to a relative risk for hematologic response for erythropoietin versus control of 3.60 (95% CI = 3.07 to 4.23, 14 trials,

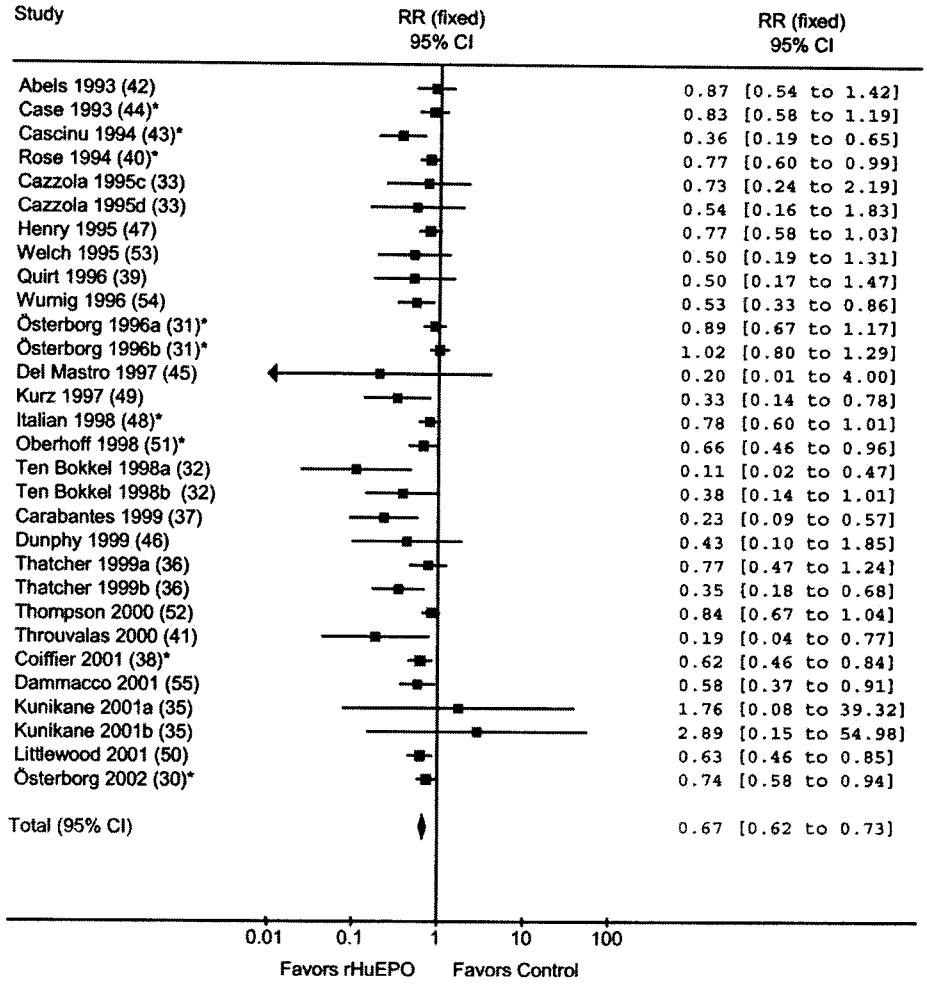

Fig. 2. Meta-analysis of the relative risk to receive red blood cell transfusions for cancer patients receiving erythropoietin or standard care. Risk estimates for the single studies (**solid squares**). The size of the squares is proportional to the sample size and the number of events. Horizontal lines denote 95% confidence intervals. Wide confidence intervals were truncated with an **arrow**. The confidence intervals for the pooled relative risks are shown (**diamonds**). Negative values indicate a relative risk reduction for red blood cell transfusions favoring the erythropoietin group. *Additional unreported data from personal communication. Cazzola 1995c: patients in treatment arm received 5000 IU daily; Cazzola 1995d: patients in treatment arm received 10000 IU daily; Österborg 1996a: patients in treatment arm received 10000 IU daily; Österborg 1996b: patients in treatment arm received 2000 IU daily, if Hb did not increase after 8 weeks, dose was increased to 5000 IU and 10000 IU daily after 12 weeks; Ten Bokkel 1998a: patients in treatment arm received 3 × 150 IU/kg three times a week; Ten Bokkel 1998b: patients in treatment arm received 3 × 300 IU/kg three times a week; Thatcher 1999a: patients in treatment arm received 3 × 150 IU/kg three times a week; Thatcher 1999b: patients in treatment arm received 3 × 300 IU/kg three times a week; Kunikane 2001a: patients in treatment arm received 3 × 100 IU/kg three times a week; Kunikane 2001b: patients in treatment arm received 3 × 200 IU/kg three times a week. Test for overall effect: z = 9.73, $P<.001$ (two-sided), test for heterogeneity chi-square = 57.8, degrees of freedom = 29, $P<.001$ (one-sided).

n = 2347). The funnel plot was asymmetric ($P = .01$), suggesting that negative results (i.e., no hematologic response) were underreported. Whether studies with more than one experimental arm were analyzed with separated experimental arms or merged into one experimental arm did not influence the overall result (data not shown). In addition, data from investigators' personal communications were statistically significantly ($P = .04$) more conservative (RR = 3.18, 95% CI = 2.61 to 3.88, seven trials, n = 1359) than data from full-text publications (RR = 4.23, 95% CI = 3.31 to 5.64, seven studies, n = 988). Other sensitivity analyses did not show statistically significant differences between the subgroups compared.

Table 2. Patients receiving red blood cell transfusions: results of the meta-regression analysis*

Category	Effect (log)	SE	95% CI	P†
Intercept	−0.60	0.11	−0.81 to 0.38	<.001
Concealment adequate	0.08	0.058	−0.034 to 0.19	.17
Concealment unclear	−0.08	0.058	−0.19 to 0.034	.17
Full-text publication	0.22	0.12	−0.0083 to 0.45	.059
Abstract publication	−0.42	0.22	−0.86 to 0.012	.057
Unpublished data	0.20	0.13	−0.042 to 0.45	.10
Solid tumors	−0.28	0.075	−0.43 to 0.13	<.001
Hematologic malignancies	0.16	0.075	0.016 to 0.31	.03
Myelodysplastic syndrome	0.097	0.075	−0.049 to 0.24	.19
Mixed tumors	0.02	0.073	−0.12 to 0.16	.78

*For each combination of type of allocation concealment, publication, and underlying disease, the relative risk can be calculated from the table. SE = standard error; CI = confidence interval.

†P values (two-sided) were determined using the Wald test.

Adverse Events

Based on 1738 patients in 12 trials, thromboembolic events, such as transient ischemic attacks, stroke, or myocardial infarction, were observed in 43 (4%) of 1019 of the erythropoietin group and in 14 (2%) of 719 of the control group *(30–32,36,41,43,44,47,48,50,52,53)*. The pooled relative risk was increased by 58% in the erythropoietin-treated group (RR = 1.58, 95% CI = 0.94 to 2.66, 12 trials, n = 1738), but the increase was not statistically significant. There was no statistically significant heterogeneity among the trials ($P = .99$). A funnel plot analysis revealed statistically significant asymmetry ($P = .003$), suggesting that negative results (i.e., no thrombotic event) were underreported. We excluded the study published by Littlewood et al. *(50)*, which contributed 46.6% to the weight of the overall result in a sensitivity analysis to explore the influence of this single large study. Exclusion of this study did not change the overall result (data not shown). No statistically significant differences were observed between subgroups with different hemoglobin levels at baseline (data not shown). Whether studies with more than one

Table 3. Adverse events reported most often: hypertension, thromboembolic and thrombopenic events, rash, and itching*

Outcome	No. of trials	No. of patients	rHuEPO group†	Control group†	Pooled RR (95% CI)
Thromboembolic events	12	1738	43/1019	14/719	1.58 (0.94 to 2.66)‡
Hypertension	12	1656	138/1009	64/647	1.19 (0.96 to 1.49)§
Hemorrhage, thrombocytopenia	8	1082	74/670	32/412	1.26 (0.85 to 1.86)‖
Rash, irritation, itching	8	675	21/395	11/280	1.17 (0.63 to 2.18)¶

*rHuEPO = recombinant human erythropoietin; RR = risk ratio; CI = confidence interval. Statistical tests for treatment effects were two-sided; statistical tests for heterogeneity were one-sided.

†Events/sample size.

‡Test for overall effect z = 1.73, test for heterogeneity chi-square = 3.29, df = 12; $P = .99$.

§Test for overall effect z = 1.56, test for heterogeneity chi-square = 15.45, df = 14; $P = .35$.

‖Test for overall effect z = 1.16, test for heterogeneity chi-square = 4.80, df = 9; $P = .85$.

¶Test for overall effect z = 0.50, test for heterogeneity chi-square = 8.32, df = 8; $P = .4$.

experimental arm were analyzed with separated experimental arms or merged into one experimental arm did not influence the overall result (data not shown).

Hypertension data were reported for 1656 patients from 12 studies *(31,32,35,36,40,43,44,47,50,53,55,56)*. The relative risk of developing hypertension was 19% higher in erythropoietin-treated patients than in untreated patients, but the increase was not statistically significant (RR = 1.19, 95% CI = 0.96 to 1.49, 12 studies, n = 1656, Table 3). There was no statistically significant heterogeneity among the trials ($P = .35$). Funnel plot analysis revealed statistically significant asymmetry ($P = .02$), suggesting that negative results (i.e., no hypertension) were underreported. Whether studies with more than one experimental arm were analyzed with separated experimental arms or merged into one experimental arm did not influence the overall result (data not shown).

No statistically significant differences between patients treated with erythropoietin and untreated patients were detected for other adverse events analyzed (hemorrhage/thrombocytopenia and rash, Table 3).

Overall Survival

Overall survival was compared among 2805 randomized patients from 19 studies *(30–33,36,38,40–47,49–52,55)*. Studies included patients with solid tumors only *(32,36,41,43,45,46,49,51)*, patients with hematologic malignancies only *(30,31,33,40,55)*, patients with both solid and hematologic malignancies *(38,42,44,47,50)*, or patients with myelodysplastic syndrome *(52)*. Fourteen studies included anemic patients with baseline Hb less than 10 g/dL, two studies assessed patients with baseline Hb from 10 to 12 g/dL *(32,41)*, and three prevention trials analyzed only patients with baseline Hb level greater than 12 g/dL *(36,45,46)*. For seven studies, including 1235 (44%) of 2805 of the data points analyzed, individual patient data were provided by the authors; for the other studies, the hazard ratio was either calculated as described by Parmar et al. *(25)* or from binary mortality data. For the Littlewood et al. *(50)* study, which contributed 50.9% weight to the overall analyses, both adjusted (Cox regression) and unadjusted (Kaplan–Meier) aggregated survival data were available, but individual patient data were not available. To test the influence of the two statistical methods used, we used both estimates in the analysis. The pooled hazard ratio was statistically significant (HR = 0.81, 95% CI = 0.67 to 0.99, 19 trials, n = 2805, Fig. 3) when we included the adjusted survival data from Littlewood et al. *(50)*, but not when we included the unadjusted survival data (HR = 0.84, 95% CI = 0.69 to 1.02, data not shown). There was no heterogeneity among the trials ($P = .6$). Whether studies with more than one experimental arm were analyzed with separated experimental arms or merged into one experimental arm did not influence the overall result (data not shown). On average, the median observation time of the included studies was 84 days [range = 42 days *(46)* to 7.17 years *(45)*]. Although the included studies were clinically heterogenous, sensitivity analyses for baseline hemoglobin level, tumor entity, different antineoplastic therapies, study quality, duration of follow up, and published versus unpublished data and funnel plot analysis did not reveal statistically significant differences among the studies. For seven studies with available individual patient data, survival probabilities in the control group were estimated by the Kaplan–Meier method for 60 and 150 days after treatment onset. Survival probabilities in the control group ranged from 0.82 to 1.00 at 60 days after treatment onset and from 0.73 to 100 after 150 days. Accordingly, to calculate the number of patients needed to treat, survival probabilities of 0.90 and 0.80 were assumed for 60 and 150 days, respectively. Given this information and the estimated hazard ratio of 0.81, the number of patients with a need to treat after 60 days was 55 (95% CI = 31.4 to 1,054). If we assume this calculated effect is real, 55 patients would have to be treated to prevent one death within 60 days of treatment onset. For the same patient population, the number needed to treat was 29 (95% CI = 16.4 to 559.6) after 150 days. Therefore, treating 29 patients with erythropoietin would prevent one death within 150 days of treatment onset.

Discussion

This systematic review analyzed the effectiveness of erythropoietin in the treatment of cancer patients. The primary findings of our study are that cancer patients treated with erythropoietin had a reduced need for red blood cell transfusion and an increased hematologic response compared with untreated patients. There is insufficient evidence to conclude that erythropoietin increases the risk of hypertension or thromboembolic events and suggestive but inconclusive evidence that erythropoietin may improve overall survival.

There is strong and consistent evidence that treatment with recombinant human erythropoietins may reduce the need for red blood cell transfusion and increase hematologic response rates. Patients treated with erythropoietin had a statistically significantly lower risk of blood transfusion and, on average, received statistically significantly fewer blood transfusions than control patients. Similarly, there was consistent evidence that patients with a mean hemoglobin level below 10 g/dL at study entry who were treated with erythropoietin had an increased frequency of hematologic responses than untreated patients, independent of transfusion. From a clinical point of view, sparing patients from red blood cell transfusion is meaningful. Among patients with a 50% risk of blood transfusion, the number needed to treat was

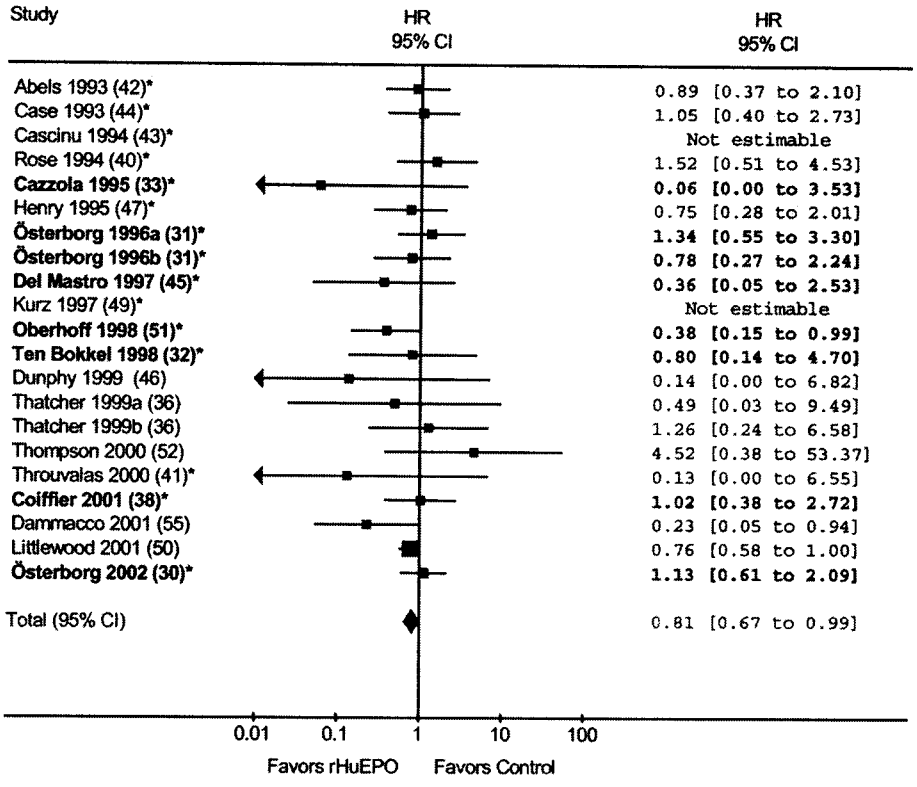

Fig. 3. Meta-analysis of the hazard ratio for overall survival for cancer patients receiving erythropoietin or standard care. Risk estimates for the single studies (**solid squares**). The size of the squares is proportional to the sample size and the number of events. Horizontal lines denote 95% confidence intervals. Wide confidence intervals were truncated with an **arrow**. The confidence intervals for the pooled hazard ratio are shown (**diamonds**). Negative values indicate a hazard ratio reduction favoring the erythropoietin group. Studies in which individual patient data were available are in **bold**. *Additional unreported data from personal communication. Österborg 1996a: patients in treatment arm received 10000 IU daily; Österborg 1996b: patients in treatment arm received 2000 IU daily, if Hb did not increase after 8 weeks, dose was increased to 5000 IU and 10000 IU daily after 12 weeks; Thatcher 1999a: patients in treatment arm received 3 × 150 IU/kg three times a week; Thatcher 1999b: patients in treatment arm received 3 × 300 IU/kg three times a week. Test for overall effect: z = 2.1, P = .04 (two-sided); test for heterogeneity chi-square = 15.88, degrees of freedom = 18, P = .60 (one-sided).

6.06 (95% CI = 5.26 to 7.41), suggesting that six patients would have to be treated with erythropoietin to prevent one patient from undergoing blood transfusion. The overall reduction in red blood cell units transfused seems to be less meaningful. It is unlikely that patients would care whether they received 3.6 or 2.6 units of blood on average. The relevance of this reduction for other health services, such as blood banks, will vary between institutions, depending on their case patient population. Results of a metaregression analysis for the risk of transfusions suggested that erythropoietin might be more effective in patients with solid tumors than in patients with hematologic malignancies or myelodysplastic syndrome. However, there was no evidence that baseline hemoglobin levels at the initiation of erythropoietin treatment (<10 g/dL versus 10–12 g/dL versus >12 g/dL) had a statistically significant influence on the risk of transfusion or the quantitative benefit of erythropoietin. Results of laboratory analyses of predictive factors, such as low baseline serum erythropoietin level, or a decreased ratio of observed-to-predicted erythropoietin levels *(31)*, were unavailable to permit a meta-analysis based on individual patient data.

The randomized controlled studies included in our analysis were of good methodologic quality. For example, the methods of concealing allocation were judged to be satisfactory for most of the studies, which included 76% of the patients randomly assigned. The meta-analysis of the specific outcomes showed a high proportion of studies with proper allocation concealment that ranged between 79.1% (transfusion risk) and 94.3% (overall survival). There was no evidence that performance bias affected the overall study results. We obtained additional unreported data for 19 of the 27 trials, representing 89% of the patients included. When we compared results obtained using published versus unreported data, the unreported dataset yielded more conservative pooled estimates than those based only on published data. Thus, any bias introduced into this meta-analysis by unreported data would have decreased rather than increased the apparent effectiveness of erythropoietin.

Studies with more than one experimental group created some methodologic problems because of the specific requirements of the software we used (RevMan version 4.2.5). In studies with more than one erythropoietin dose arm, the control arm had to be artificially divided into as many control arms as treatment arms, which decreased the apparent size of the control arm, reduced some groups to very small numbers, and thus affected the weighting of these studies. However, an alternative analysis (data not shown) that instead merged experimental arms yielded similar results.

This meta-analysis demonstrated suggestive but inconclusive evidence for improved overall survival among patients treated with erythropoietin (HR = 0.81, 95% CI = 0.67 to 0.99). The relevance of this finding is unclear because none of the trials included in the analysis of overall survival was designed or had adequate statistical power to determine whether erythropoietin increases overall survival. Also, this result was not robust to changes in the statistical methods used. Although the pooled hazard ratio was statistically significant when we included data from the largest study *(50)*, analyzed by Cox regression, and adjusted for confounders, it was no longer statistically significant if the same study was analyzed with the unadjusted raw data (HR = 0.84, 95% CI = 0.69 to 1.02). The computed effects would be clinically meaningful if they are real. On the basis of the available data and the relatively short follow-up, we estimated that it would be necessary to treat 55 (95% CI = 31.4 to 1054) patients for 60 days with erythropoietin to prevent one death. With a longer follow-up period of 150 days, the estimated number needed to treat was 29 (95% CI = 16.4 to 559.6). However, the confidence intervals around these estimates are wide, indicating substantial uncertainty surrounding these results.

These provocative findings on overall survival from our meta-analysis differ from results of two recently published clinical trials.

Henke et al. *(10)* reported that among 351 patients with head and neck cancer undergoing radiotherapy, those who received erythropoietin had a worse overall survival (RR = 1.39; 95% CI = 1.05 to 1.84, $P = .02$) than those who did not. Similarly, a multicenter trial that investigated the use of erythropoietin as an adjunct to chemotherapy among 939 patients with metastatic breast cancer undergoing first-line therapy was terminated early because survival at 12 months was worse in the group that received erythropoietin than the group that did not (70% versus 76%; $P = .017$), although the survival curves converged at 19 months *(11)*. Because our review included only studies published from 1985 through 2001, neither of these two studies *(10,11)* was included in this analysis. In the study by Leyland-Jones et al. *(11)*, the mortality rate during the first 4 months of study was explained in part by an increased incidence of thrombotic and vascular events in the erythropoietin group versus control (1% versus 0.2%) and in part by an increase in incidence of disease progression in the erythropoietin group versus control (6% versus 3%). In the study by Henke et al. *(10)*, vascular disorders, including hypertension, hemorrhage, venous thrombosis, pulmonary embolism and cerebrovascular events, were observed in 11% of patients in the erythropoietin group and in 5% of the placebo group when the data were analyzed on an intent-to-treat basis. Taken together, these studies raised concerns about the safety of erythropoietins, particularly when used in clinical trials aimed at raising the hemoglobin at a target level of 12–14 g/dL and higher. These safety questions were discussed during a comprehensive Food and Drug Administration hearing on May 4, 2004 *(57)*. The discussion at that meeting, at which results of company-sponsored meta-analyses on the safety of erythropoietins were presented, focused on the difference between the results of studies performed according to the current American Society of Hematology and American Society of Clinical Oncology guidelines and those of studies aimed at increasing hemoglobin to levels that exceed correction of anemia. Clinical studies aimed at maintaining a high hemoglobin level *(10,11)* seem to report that erythropoietin treatment was associated with a higher risk of thrombovascular events. This higher risk is further supported by the fact that three additional studies targeting hemoglobin levels between 14 and 16 g/dL were closed prematurely because of increased thromboembolic complications in the erythropoietin arm *(57)*. In addition, studies evaluating erythropoietin to maintain different hematocrit levels of end-stage renal failure patients with pronounced cardiovascular risk factors showed that patients with high hematocrit levels had an increased mortality due to thrombovascular events *(57,58)*. Taken together, the major difference between the Henke et al. *(10)* study and our systematic review is the substantially higher mean final hemoglobin levels in the former trial at the end of study (15.4 g/dL, SD = 1.7), which may have contributed to the higher number of thrombovascular events. Among the studies included in our analysis, the final hemoglobin levels ranged from 9.82 g/dL (SD = 2.10) *(31)* to 13.9 g/dL (SD = 1.85) *(32)*. Although the relative risk for thromboembolic events was increased by 58%, with 43 (4%) of 1019 thromboembolic events occurring in the erythropoietin group and 14 (2%) of 719 occurring in the control group, this difference was not statistically significant. Overall, the data evaluated in this systematic review are insufficient to conclude that erythropoietin increases the risk for thromboembolic complications in the clinical settings analyzed in our review.

The reduced tumor control associated with erythropoietin treatment reported in the studies published by Henke et al. *(10)* and Leyland-Jones et al. *(11)* raises additional pathophysiological considerations. Tumor tissue is often hypoxic, and hypoxia may be more prevalent in anemic patients than in patients with normal hemoglobin levels *(59,60)*. Tumor hypoxia may impair the effectiveness of chemotherapy and radiotherapy *(4–6,8)*. Studies using animal models have provided evidence suggesting that increasing the hemoglobin level with erythropoietin might improve tumor oxygenation *(61)*, and results of clinical studies indicate that erythropoietin may improve response to radiotherapy *(9)*. However, preclinical studies *(60,61)* have reported high levels of erythropoietin and erythropoietin receptors in breast cancer cells and other malignancies. Both endogenously produced or exogenously administered erythropoietin could theoretically promote the proliferation and survival of erythropoietin receptor–expressing cancer cells *(62–65)*. High hemoglobin concentrations may reduce the oxygen supply in the tumor, due to viscous resistance *(66)* or thromboembolic events within the tumor bed *(67)* and thus diminish tumor response to therapy. In addition, imbalances in baseline prognostic factors between the erythropoietin and control groups in the studies published by Henke et al. *(10)* and Leyland-Jones et al. *(11)* may also explain the poor tumor control in the erythropoietin-treated patients.

Our literature search ended in December 2001 because that was when the project protocol was finalized and when requests for unpublished data were sent to the investigators. As a consequence, studies published later were not included in this meta-analysis. In addition to the studies of Henke et al. and Leyland-Jones et al., another six studies with approximately 751 patients have been published as full-text articles since. Three of these studies reported survival or mortality data for 90 *(68)*, 144 *(69)*, and 330 *(70)* patients. There were no statistically significant survival differences observed between the erythropoietin group and the untreated patients *(68–70)*. An update of the Cochrane Review is being planned.

Other adverse events reportedly related to erythropoietin include hypertension and the production of anti-erythropoietin–specific antibodies. In patients with chronic renal failure, hypertension is the most common adverse effect of erythropoietin *(71)*. This analysis shows that erythropoietin is associated with a 19% increase (not statistically significant) in the relative risk of hypertension for cancer patients. There has been some discussion about whether neutralizing anti-erythropoietin–specific antibodies cause pure red cell aplasia in patients with chronic renal failure following treatment with erythropoietin *(72–74)*. The studies included in this review did not report any cases of erythropoietin antibody production, but only six of the included studies have addressed this subject *(30,32,36,42,47,51)*.

In view of the inconclusive evidence presently available, our results suggest that erythropoietin should not be used to increase overall survival outside clinical trials. Erythropoietin may be used routinely outside of clinical trials to increase hemoglobin levels and to reduce the need for transfusion in patients with falling hemoglobin levels approaching 10 g/dL. Adverse events such as thromboembolic complications and hypertension should be monitored.

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Notes

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Randomized, Double-Blind, Active-Controlled Trial of Every-3-Week Darbepoetin Alfa for the Treatment of Chemotherapy-Induced Anemia

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Background: **In the United States, darbepoetin alfa (Aranesp) is often used to treat patients with chemotherapy-induced anemia using weekly or every-2-week administration schedules. In Europe, darbepoetin alfa is used either weekly or in every-3-week dosing. The every-3-week schedule can be synchronized with many chemotherapy regimens, resulting in fewer visits and reducing burden to patients, but the safety and efficacy of this regimen have not been clear.** ***Methods:*** **A randomized, double-blind, double-dummy, active-controlled phase 3 trial was performed in 110 European centers. Eligible patients (age ≥18 years) were anemic (hemoglobin level <11 g/dL), had a nonmyeloid malignancy, and were to receive at least 12 weeks of chemotherapy. Patients were randomly assigned 1:1 to darbepoetin alfa treatment every 3 weeks (500-μg dose) or weekly (2.25-μg/kg) for 15 weeks. We compared red blood cell transfusion incidence among the two arms from week 5 to the end of the treatment phase using a noninferiority study design. Noninferiority was determined if the upper limit of the 95% confidence interval (CI) for the difference in blood transfusions between groups, calculated using Kaplan–Meier methods, did not exceed 12.5%, a margin based on previous placebo-controlled studies.** ***Results:*** **A total of 705 patients were randomly assigned, and 672 remained in the study at week 5. Fewer patients in the every-3-week arm than in the weekly arm received blood transfusions from week 5 to the end of the treatment phase (unadjusted Kaplan–Meier estimates = 23% versus 30%, difference = −6.8%; 95% CI = −13.6 to 0.1). Percentages of patients achieving the target hemoglobin level (≥11 g/dL, consistent with evidence-based practice guidelines) were 84% (every 3 weeks) and 77% (weekly). The frequency of cardiovascular/thromboembolic adverse events was 8% in both groups, and safety was comparable.** ***Conclusions:*** **Patients with chemotherapy-induced anemia can safely and effectively be treated with 500 μg of darbepoetin alfa every 3 weeks. [J Natl Cancer Inst 2006;98:273–84]**

Anemia is a frequent complication of malignant disease or chemotherapy and contributes to increased morbidity and reduced quality of life *(1)*. Recombinant human erythropoietin (rHuEPO) has been shown to be effective for treating anemia in patients who undergo chemotherapy by increasing hemoglobin concentrations and reducing or eliminating the need for red blood cell (RBC) transfusions *(2–8)*. In addition, patients have substantially less fatigue and better physical and functional well-being after treatment with erythropoietic therapy *(5,8–13)*.

Darbepoetin alfa is an erythropoiesis-stimulating protein with a unique amino acid sequence, greater sialic acid content, longer half-life (74 hours in cancer patients), and greater biologic activity than rHuEPO *(14,15)*. Because of differences in the pharmacokinetic properties of darbepoetin alfa and rHuEPO, darbepoetin alfa can be administered less frequently than rHuEPO without changes in efficacy and safety. Darbepoetin alfa was originally licensed for treatment of chemotherapy-induced anemia in many regions of the world, including the United States and Europe, based on a weekly 2.25-μg/kg dose *(16,17)*. However, the number of studies showing that darbepoetin is safe and effective when used less frequently is increasing *(2,15,18–23)*.

Administration of darbepoetin alfa every 3 weeks would coincide with many chemotherapy schedules and may be convenient to patients and their health care providers as well as improve health care resource use. A double-blind, placebo-controlled, dose-response study *(2)* evaluated several weight-based doses of every-3-week darbepoetin alfa (4.5, 6.75, 9, 12, 13, or 15 μg/kg). Darbepoetin alfa was shown to be effective at all every-3-week doses, with limited incremental benefit at doses greater than 6.75 μg/kg. A recent study of 81 anemic patients *(15)* provided further evidence of the effectiveness of darbepoetin alfa 6.75 μg/kg every 3 weeks for the treatment of chemotherapy-induced anemia. These data demonstrated the effectiveness of an every-3-week regimen of darbepoetin alfa irrespective of the timing of administration relative to concurrent chemotherapy. However, a study comparing the every-3-week regimen of darbepoetin alfa with the established weekly regimen has not yet been conducted.

Erythropoietic therapy has been shown to be effective and safe when administered as a fixed dose *(7,9,13,20)*. Recently, a phase

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2, randomized controlled trial of darbepoetin alfa *(24)* indicated that the efficacy profile was not affected if a fixed (versus weight-based) dose was used. This finding is consistent with the pharmacokinetic-pharmacodynamic modeling of darbepoetin alfa *(25)*, based on data from previous studies, which suggested that patient body weight is not a primary determinant of efficacy for this molecule. The fixed-dose approach adds convenience for clinicians and is consistent with current patterns of practice *(26)*.

This randomized, double-blind, double-dummy, active-controlled, phase 3 study compared the efficacy and safety of weekly and every-3-week regimens of darbepoetin alfa treatment. The primary hypothesis being tested was that cancer patients treated for chemotherapy-induced anemia with darbepoetin alfa using a fixed 500-μg dose every 3 weeks have an incidence of RBC transfusions that is comparable (defined as not inferior) to that of patients receiving the standard weekly (2.25 μg/kg) regimen of darbepoetin alfa. A description of the study may be found online (http://www.ClinicalTrials.gov, Identifier No. NCT00118638).

Subjects and Methods

Study Population

The independent ethics committee or central ethics committee for each of the 110 participating medical centers in 24 European countries approved the protocol. All patients gave oral and written informed consent before any study-specific procedures were initiated.

For entry into the study, patients were required to have a diagnosis of nonmyeloid malignancy and at least 12 additional weeks of planned cytotoxic chemotherapy (chemotherapy may have been ongoing at time of random assignment). Patients were eligible for the study if they were at least 18 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, and had adequate renal (creatinine level less than twice the upper limit of normal) and hepatic (alanine aminotransferase and aspartate aminotransferase levels less than five times the upper limit of normal) function. Patients were required to have anemia (i.e., a hemoglobin level of <11 g/dL within 24 hours of random assignment) secondary to malignancy and chemotherapy treatment. Patients were excluded if they were iron deficient; had received more than two RBC transfusions within 4 weeks of random assignment or any RBC transfusions within 14 days of the first dose of investigational product (i.e., study day 1); had received rHuEPO therapy within 4 weeks of random assignment; or were pregnant, breast-feeding, or not using adequate birth control measures. Patients were also excluded if they had a history of seizure disorders, active cardiac disease, uncontrolled hypertension, active infection, or any chronic inflammatory or hematologic disorder that could cause anemia.

Random Assignment

This was a phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled study. After registration, patients were randomly assigned in a 1:1 ratio to receive blinded darbepoetin alfa subcutaneously, either at a fixed dose of 500 μg every 3 weeks or a weight-based dose of 2.25 μg/kg weekly. Random assignment was stratified by tumor type (lung or gynecologic versus others), screening hemoglobin concentration (<10.0 g/dL versus ≥10.0 g/dL), and European region (Western versus Central and Eastern) to ensure a balanced allocation of patients to darbepoetin alfa every-3-week and weekly groups within each stratum.

All patients were randomly assigned up to 3 days before study day 1. A blood sample was drawn within 24 hours of random assignment at a local laboratory to confirm hemoglobin concentration less than 11 g/dL, as well as to provide hemoglobin concentration data for stratification. The random allocation sequence was obtained using an interactive voice response system after the screening hemoglobin concentration result was entered.

Treatment Schedule

The study consisted of a screening period of up to 7 days before random assignment, followed by 15 weeks of blinded study treatment and a 2-week follow-up period after the last dose of study drug. A double-dummy design was used to ensure that patients in each treatment group received the same schedule of blinded injections. The every-3-week group received darbepoetin alfa dosing at weeks 1, 4, 7, 10, and 13 and a weekly blinded placebo injection. The weekly group received darbepoetin alfa dosing weekly from weeks 1 to 15 and blinded placebo administered every 3 weeks.

Darbepoetin alfa (Aranesp; Amgen Inc., Thousand Oaks, CA) was prepared in a phosphate buffer, pH 6.2, as a human serum albumin–free, polysorbate formulation. Patients received the study drugs from identical 500-μg vials that contained either a dose of darbepoetin alfa or a placebo. The delivered volumes of drug and placebo were identical.

At any time during the study, the dose of blinded study drug was withheld if a patient's hemoglobin concentration was greater than 13 g/dL. After the patient's hemoglobin concentration decreased to 12 g/dL or less, administration of the study drug was then reinstated at 60% of the previous dose at the next administration visit. Consistent with the package insert for darbepoetin alfa in the United States *(16)*, patients were required to have a dose reduction if their hemoglobin concentration increased by 1 g/dL or greater over a 14-day period in the absence of RBC transfusion (during the previous 14 days); the dose of darbepoetin alfa was decreased to 60% of the previous dose. Further dose reductions proceeded in 40% dose decrements. A maximum of four dose reductions were permitted before the investigational product was to be discontinued.

To allow for regional- and center-based differences in transfusion policies, the protocol recommended, but did not mandate, transfusions for patients with hemoglobin concentrations of 8 g/dL or less. Transfusions were permissible for hemoglobin concentrations greater than 8 g/dL in symptomatic patients or as recommended by the physician.

LabCorp (Mechelen, Belgium) provided the central laboratory service for the analysis of hematology (except for hemoglobin), chemistry, and iron variables. Hemoglobin measurements on study were performed by local laboratories.

Efficacy Evaluation

The primary objective was to evaluate the efficacy of darbepoetin alfa administered as 500 μg every 3 weeks by showing that this dose and schedule are not inferior to darbepoetin alfa administered weekly as 2.25 μg/kg in the treatment of anemia

in patients with nonmyeloid malignancies receiving cyclic chemotherapy. The primary endpoint of this noninferiority study was the incidence of RBC transfusions; therefore, information on the incidence and number of RBC transfusions was collected throughout the study. Data from previous randomized, placebo-controlled trials indicate that the effects of rHuEPO on the incidence of RBC transfusion are not apparent until the second month of treatment *(5,9,27)*. Therefore, the proportion of patients receiving a transfusion was measured from week 5 to the end of the treatment phase, an endpoint that has been accepted by the regulatory agencies as sufficient for drug approval. However, because this study compared two active therapies, it was deemed appropriate to also evaluate the transfusion requirements over the entire course of therapy (week 1 to the end of the treatment phase) as well as the total number of RBC units transfused.

The effect of darbepoetin alfa treatment on hemoglobin concentration was an additional measure of efficacy. The therapeutic goals, with respect to hemoglobin levels, were the proportion of patients achieving a hemoglobin concentration of 11 g/dL or greater, and the proportion of patients subsequently maintaining hemoglobin levels in the 11–13 g/dL range. This target hemoglobin range is based on three well-recognized evidence-based practice guidelines for anemia management in cancer patients [National Comprehensive Cancer Network *(28)*, American Society of Hematology *(29)*/American Society of Clinical Oncology *(30)*, and European Organization for Research and Treatment of Cancer *(31)*], which recommend the attainment and subsequent maintenance of a target hemoglobin concentration between 11 and 13 g/dL to minimize transfusion requirements and maximize health-related quality of life benefits. In addition, the change in hemoglobin concentration was analyzed over time. Hemoglobin measurements made within 28 days of a RBC or whole blood transfusion were excluded from the analysis.

For this study, the primary health-related quality-of-life instrument was the Functional Assessment of Cancer Therapy (FACT)-Fatigue subscale, which has previously been validated in the oncology setting *(32)*, along with additional quality of life questionnaires (FACT-General and all its subscales, EQ-5D Health State Index, Brief Symptom Inventory Anxiety and Depression scales, and the number of caregiver hours). A change in the FACT-Fatigue subscale score equal to or greater than three points during intervention has been described as a clinically meaningful change *(33)*; hence, the proportion of patients achieving a change equal to or greater than three points in FACT-Fatigue was also assessed.

Safety Evaluation

A key objective of the study was to assess the overall safety of 500 μg of darbepoetin alfa given every 3 weeks and compare it with that of 2.25 μg/kg given weekly. The nature, frequency, severity, relationship to treatment, and outcome of all adverse events were measured. The safety of the fixed dosing regimen of darbepoetin alfa was evaluated by comparing the overall safety profile across weight and body mass index (BMI) groups of the standard weekly dose to the every-3-week dosing schedule. The safety profiles of the two treatment groups were evaluated with respect to changes in hemoglobin concentrations as follows: values greater than 13 g/dL at any time on study and increases of 2 g/dL or greater in a 28-day window or of 1 g/dL in a 14-day window.

Serum was collected before study drug administration, at week 10, and at the end of the treatment phase to screen for the presence of antibodies to darbepoetin alfa using a Biacore 3000 biosensor immunoassay (Biacore International, AB, Uppsala, Sweden). Any Biacore-positive sample (i.e., antibody concentration of ≥0.25 μg/mL) was routed for analysis using a bioassay to detect neutralizing antibodies and to characterize the antibody classes observed in the biosensor immunoassay. A central laboratory provided storage of samples for antibody testing. Anti-darbepoetin alfa antibody screening was done at MDS Pharma Services (St. Laurent, Quebec, Canada), and immunoassay characterization and bioassay were done at Amgen Inc. There was no data safety monitoring board for this study.

Statistical Analysis

The sample size of 705 randomly assigned patients provides 95% power to demonstrate noninferiority of the every-3-week regimen compared with the weekly regimen based on the primary endpoint of incidence of RBC transfusions from week 5 to the end of the treatment phase. A two-sided 95% confidence interval (CI) for the difference (every-3-week versus weekly regimens) in the proportion of patients experiencing at least one RBC transfusion from week 5 to the end of the treatment phase was calculated based on the unadjusted Kaplan–Meier estimates. Noninferiority of the every-3-week dosing schedule was declared if the upper limit of this confidence interval was less than or equal to 12.5%. The 12.5% cut point was based on an estimate of the 95% confidence interval for the difference in the rate of RBC transfusion between placebo and darbepoetin alfa groups obtained from two previous placebo-controlled, phase 3 studies *(3,4)*, both of which used a starting dose of 2.25 μg/kg weekly. In a combined unadjusted analysis of the two trials, the difference between darbepoetin alfa treatment and placebo was 23%, with a lower 95% confidence interval of 16%. This effect size is consistent with the recent meta-analysis of randomized, placebo-controlled trials of erythropoietic agents in cancer patients *(34)*. A noninferiority margin of 12.5% was selected to ensure that a substantial proportion of the treatment effect was maintained.

Analysis of the primary endpoint was based on the set of patients who were randomly assigned, received at least one dose of study medication, and were treated until at least day 29 (primary transfusion analysis set). Preplanned sensitivity analyses of the primary endpoint were performed using an alternate analysis set (per-protocol analysis set) and censoring mechanism (secondary censoring).

Statistical analyses were performed by the sponsor using SAS statistical software, version 8.2 (SAS Institute Inc., Cary, NC). Descriptive statistics included frequencies and means (with 95% confidence intervals or standard deviations [SDs]) for categorical and continuous variables, respectively. Changes in hemoglobin levels and FACT-Fatigue scores of each patient were analyzed using an analysis of covariance model including the stratification factors. Two analytical approaches—imputation (last-value-carried-forward) and available data—were used to account for missing hemoglobin data. Hemoglobin values within 28 days after a transfusion were considered to be missing; using the last-value-carried-forward imputation method, the pretransfusion hemoglobin value was used to impute all weekly hemoglobin values during the 28 days after a transfusion. Changes in hemoglobin were evaluated using both methods; achievement of target

hemoglobin was calculated using only the last-value-carried-forward method. Kaplan–Meier estimates for the proportion of patients achieving the target hemoglobin levels and for the proportion of patients achieving a clinically meaningful increase in FACT-Fatigue were adjusted for the baseline stratification factors of tumor type (lung or gynecologic versus others), screening hemoglobin concentration (<10.0 g/dL versus ≥10.0 g/dL), and European region (Western versus Central and Eastern). The adjusted Kaplan–Meier estimate is the weighted average of the Kaplan–Meier estimates obtained for each stratum. Primary analysis of transfusion-related endpoints was based on the unadjusted Kaplan–Meier estimates. In addition, transfusion results were examined using the adjusted Kaplan–Meier estimates, as well as an actuarial approach to estimate the crude proportion of patients receiving transfusions (crude estimates are not presented). Additional analyses of transfusion, hemoglobin, and safety endpoints were stratified by weight and BMI categories.

An exploratory piecewise mixed-effects model was developed to investigate the effect of dose reductions on hemoglobin levels *(35)*. The mixed-effects model allows the hemoglobin slope to change before and after the first dose reduction, ensuring that these two lines intersect at the time of titration. As with other hemoglobin endpoints, the analysis was adjusted for study stratification factors, and hemoglobin measurements within 28 days of a RBC or whole blood transfusion were excluded from the analysis.

Safety was evaluated in all patients who received at least one dose of study drug, according to the treatment they actually received. Adverse events were grouped by primary system organ class and by preferred term within the primary system organ class according to the MedDRA dictionary. The frequency and percentage distributions of adverse events to the study drug were summarized.

Results

Study Population

Of the 763 patients screened, 705 were randomly assigned. Enrollment was well distributed across study centers, with no center enrolling greater than 3% of patients. Patient disposition is outlined in Fig. 1. All 705 randomly assigned patients received darbepoetin alfa. Baseline demographics and clinical characteristics were similar in the two treatment groups (Table 1). A similar proportion of patients in each treatment group completed treatment: 75% in the 500 μg of darbepoetin alfa every-3-week group and 70% in the 2.25 μg/kg weekly group. Reasons for early discontinuation included death (31 patients [9%] in the every-3-week group and 39 [11%] in the weekly group), withdrawal of consent (17 [5%] in the every-3-week group and 28 [8%] in the weekly group), and adverse events (14 [4%] in each group). The distribution of patients across baseline stratification factors was balanced across both groups (data not shown).

Darbepoetin Alfa Dose

The mean numbers of darbepoetin alfa doses administered were 4.2 and 11.8 in the every-3-week and weekly groups,

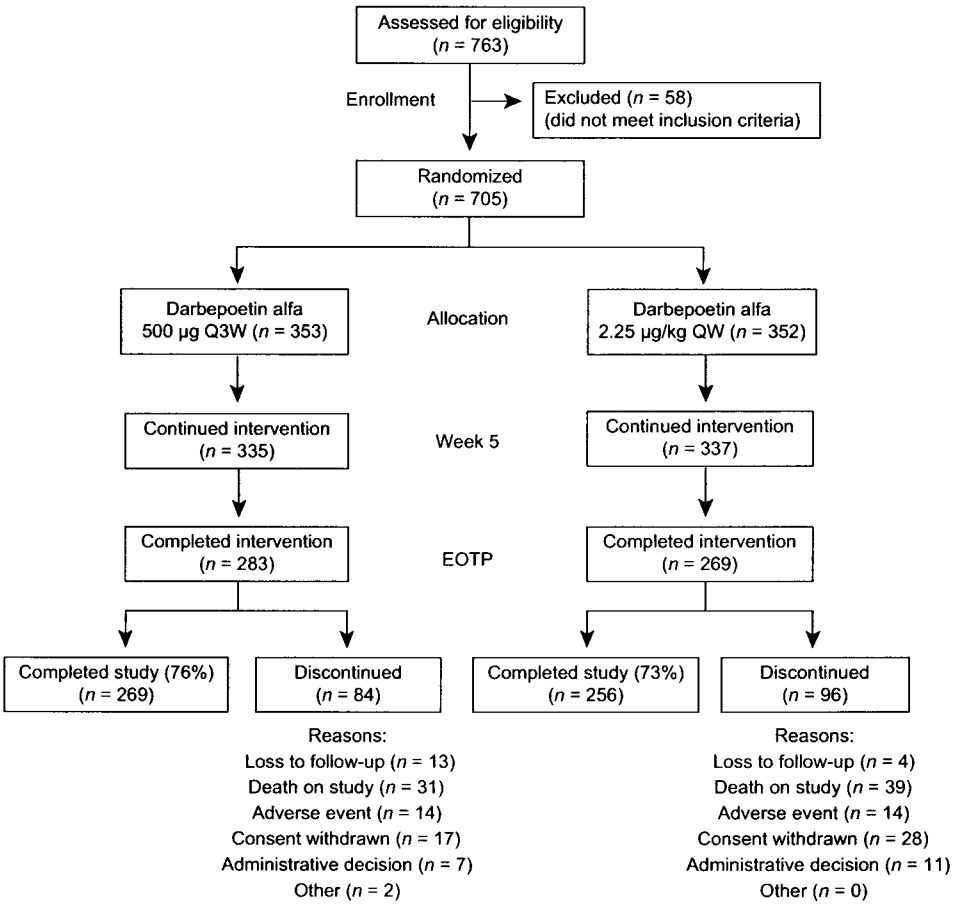

Fig. 1. CONSORT (Consolidated Standards for Reporting of Trials) diagram of patient disposition. The flow of patients screened and enrolled is shown in accordance with the CONSORT Statement for reporting clinical trials *(36)*. The total number of patients evaluated for the primary endpoint (red blood cell transfusions from week 5 to end of treatment phase) is shown at week 5. Q3W = every 3 weeks; QW = weekly; EOTP = end of treatment phase.

Table 1. Demographic and laboratory characteristics at baseline*

Characteristic	Darbepoetin alfa 500 μg every 3 weeks	Darbepoetin alfa 2.25 μg/kg weekly
Total No. of patients	353	352
Sex, No. (%)		
Men	167 (47)	155 (44)
Women	186 (53)	197 (56)
Age, y		
Mean (SD)	58.7 (13.1)	59.3 (12.3)
Geographic region, No. (%)†		
Western Europe	205 (58)	206 (59)
Central and Eastern Europe	148 (42)	146 (41)
ECOG performance status, No. (%)		
0 or 1	307 (87)	289 (82)
2	46 (13)	63 (18)
Hemoglobin, g/dL		
Mean (SD)	9.76 (0.95)	9.78 (0.85)
Hemoglobin category, No. (%)		
<10 g/dL	175 (50)	176 (50)
≥10 g/dL	178 (50)	176 (50)
Serum eEPO, mU/mL		
Mean (SD)	108.2 (179.6)	127.3 (258.6)
Median (Q1, Q3)	53.2 (31.9, 109.5)	59.0 (30.6, 111.5)
Ferritin, μg/L		
Mean (SD)	539.9 (694.19)	576.5 (785.71)
Median (Q1, Q3)	300.0 (111, 666)	298.0 (132, 754)
Transferrin saturation, %		
Mean (SD)	30.1 (25.3)	30.3 (26.0)
Median (Q1, Q3)	21.0 (12.0, 38.0)	21.0 (11.0, 40.5)
FACT-Fatigue score		
Mean (SD)	31.3 (11.6)	29.8 (11.6)
Weight, kg		
Mean (SD)	69.3 (13.71)	67.8 (13.83)
Common tumor types, No. (%)		
Solid tumors‡		
Breast	57 (16)	55 (16)
Large intestine/colon	65 (18)	51 (14)
Non–small-cell lung	34 (10)	32 (9)
Ovarian	16 (5)	11 (3)
Other solid tumor	96 (27)	126 (36)
Hematologic malignancies		
Chronic lymphocytic leukemia	13 (4)	10 (3)
Hodgkin's disease	11 (3)	9 (3)
Multiple myeloma	26 (7)	17 (5)
Non-Hodgkin lymphoma	33 (9)	38 (11)
Other	2 (1)	2 (1)
Disease stage at diagnosis, No. (%)§		
I, II, or III	188 (53)	186 (53)
IV	133 (38)	133 (38)
Other	20 (6)	20 (6)
Unknown or missing	12 (3)	13 (4)

*ECOG, Eastern Cooperative Oncology Group; eEPO = endogenous erythropoietin concentration; FACT, Functional Assessment of Cancer Therapy.

†Western European countries included Austria, Belgium, Denmark, Finland, France, Germany, Italy, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and United Kingdom; and Central and Eastern European countries included Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovak Republic, and Ukraine.

‡Lung or gynecologic cancer category for randomization includes non–small-cell lung, small-cell lung, ovarian, endometrial, and cervical primary cancers.

§TNM classification.

Table 2. Dosing of Darbepoetin alfa

Dose characteristic	Darbepoetin alfa 500 μg every 3 weeks (n = 353)	Darbepoetin alfa 2.25 μg/kg weekly (n = 352)
Total no. of doses		
Mean (SD)	4.2 (1.24)	11.8 (3.98)
Median	5.0	14.0
Duration of exposure, weeks*		
Mean (SD)	12.8 (3.6)	12.3 (3.9)
Median	15.0	14.0
Average planned weekly dose, μg/wk		
Mean (SD)	166.7 (0)	152.5 (31.1)
Average weekly dose, μg/wk†		
Mean (SD)	125.2 (37.1)	107.8 (42.2)
Weight-adjusted average weekly dose delivered†, μg/kg/wk		
Mean (SD)	1.87 (0.644)	1.59 (0.527)
Cumulative dose, μg		
Mean (SD)	1608.2 (582.4)	1349.3 (661.4)

*Number of weeks between first and last dose adjusted by frequency. SD = standard deviation.

†Includes 0 doses, i.e., doses withheld or missed.

respectively (Table 2). The average planned weekly doses (i.e., at time of random assignment, before dose adjustment) were 166.7 μg (i.e., the 500-μg starting dose) and 152.5 (SD = 31.1) μg for the every-3-week and weekly groups, respectively. Because of dose modifications, the average weekly doses (including the weeks with withheld or missed doses) over the entire study were 1.87 (SD = 0.644) μg/kg for the every-3-week group and 1.59 (SD = 0.527) μg/kg for the weekly group (difference = 0.28 μg/kg, 95% CI = 0.17 to 0.39 μg/kg).

Dose modification in this study resulted predominantly from the dose reduction rule in patients with a hemoglobin rise of 1 g/dL or greater within any 14-day period (in the absence of a transfusion during the previous 14 days). Overall, a high proportion of patients had their dose reduced to 60% of the previous dose (adjusted Kaplan–Meier estimates = 74%, 95% CI = 69% to 80% and 75%, 95% CI = 70% to 80%, in the every-3-week and weekly groups, respectively) with a median time to first dose reduction of 43 days for the every-3-week group and 36 days for the weekly group (Table 3). Similar patterns were observed within each regimen when the active and placebo drug dosing changes were compared (data not shown).

Efficacy Evaluations

RBC transfusions. The percentage of patients in the every-3-week group who had blood transfusions between week 5 and the end of the treatment phase was lower than that observed in the weekly group (unadjusted Kaplan–Meier estimates = 23% [95% CI = 19% to 28%] versus 30% [95% CI = 25% to 35%], difference = −6.8%; 95% CI = −13.6 to 0.1; Fig. 2, A). When the analyses were adjusted for stratification factors, results were consistent with the aforementioned unadjusted results. That is, fewer patients in the every-3-week arm than in the weekly arm received blood transfusions from week 5 to the end of the treatment phase (adjusted Kaplan–Meier estimates = 19% [95% CI = 15% to 23%] versus 28% [95% CI = 23% to 33%], difference = −6.7%, 95% CI = −13.2% to −0.2%).

The primary endpoint of RBC transfusions from week 5 to the end of the treatment phase was repeated using the per-protocol analysis set and the alternate (secondary) censoring approach, as described in "Subjects and Methods." These sensitivity analyses

Table 3. Dose withholding and dose reductions on study in the absence of red blood cell transfusions*

Characteristic	Darbepoetin alfa 500 μg every 3 weeks (n = 353)	Darbepoetin alfa 2.25 μg/kg weekly (n = 352)
Patients with maximum hemoglobin ≥13.0 g/dL at any time during the study, No. (%)	76 (21.5)	84 (23.9)
Excess rise in hemoglobin, No. (%)		
≥2.0 g/dL in 28 days	118 (33.4)	118 (33.5)
≥1.5 g/dL in 21 days	207 (58.6)	206 (58.5)
≥1.0 g/dL in 14 days	232 (65.7)	222 (63.1)
Patients with at least one dose reduction due to rapid rate of rise in hemoglobin concentration		
Kaplan–Meier percent (95% CI)	74 (69 to 80)	75 (70 to 80)
Crude percent (95% CI)	66 (61 to 71)	69 (64 to 74)
Median time to first dose reduction due to rapid rate of rise in hemoglobin concentration (study day) (95% CI)	43 (43 to 61)	36 (35 to 49)
Hemoglobin concentration at time of first dose reduction due to rapid rate of rise in hemoglobin concentration (g/dL)		
Total no. of patients	232	243
Mean (95% CI)	11.1 (11.0 to 11.3)	11.1 (10.9 to 11.2)

*CI = confidence interval.

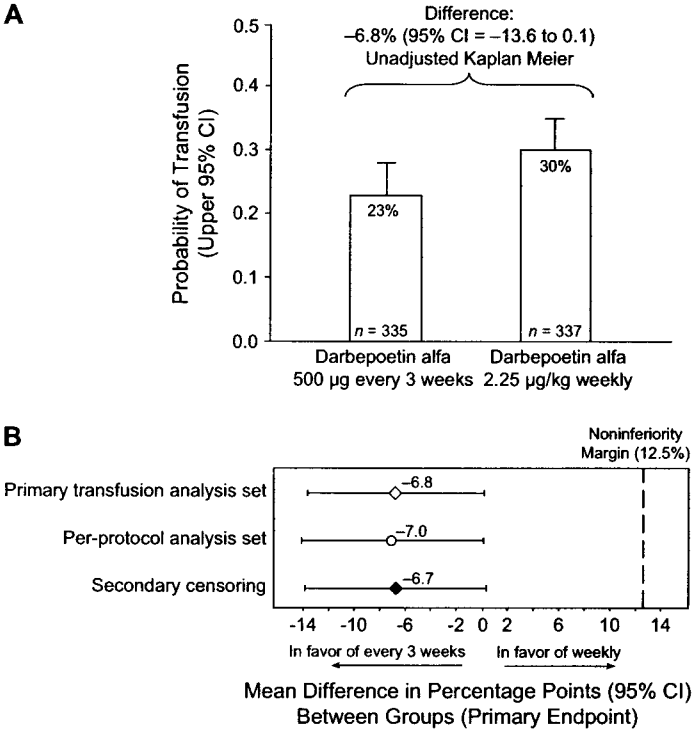

Fig. 2. Red blood cell (RBC) incidence of transfusions from week 5 to end of treatment phase (primary endpoint). **A)** Incidence of RBC transfusions from week 5 to the end of the treatment phase. Bars represent the unadjusted Kaplan–Meier estimates and error bars upper 95% confidence intervals. The total number of patients evaluated for the primary endpoint is shown at bottom of each bar, and the unadjusted Kaplan–Meier estimate of the percentage of patients receiving at least one RBC transfusion from week 5 to the end of the treatment phase is shown at the top of each bar. The difference in transfusion rates between groups is shown. **B)** Sensitivity analyses of incidence of RBC transfusions from week 5 to the end of the treatment phase: impact of analysis set and censoring approach. Analysis of the primary endpoint was based on patients who were randomly assigned, received at least one dose of study medication, and were in treatment until at least day 29 (primary transfusion analysis set, **open diamond**). Preplanned sensitivity analyses of the primary endpoint were performed using alternate approaches with respect to the analysis set (population effect) and censoring mechanism. The population effect was examined using an alternate analysis set (per-protocol analysis set, **open circle**). The per-protocol analysis set consisted of patients in the primary transfusion analysis set who: received 75% or more and less than 125% of the planned dose of study drug, received between 67% and 133% of the planned number of doses, and did not receive conditioning myeloablative chemotherapy or radiotherapy for stem cell transplant during the treatment period. Two methods for handling withdrawals were used in this study (primary and secondary censoring). The primary method censored patients who withdrew without having a RBC transfusion during the specified period as observed (**open symbols**). The secondary mechanism (**closed diamond**) assigned patients who withdrew prematurely because of withdrawn consent or loss to follow-up, without a RBC transfusion during the specified period as transfused. The noninferiority margin of 12.5% is shown as a **dashed line**.

generated similar results, namely, that the upper limit of the 95% confidence interval for the difference in transfusion rates between groups was well below the prespecified noninferiority margin of 12.5% (Fig. 2, B).

The percentage of patients receiving RBC transfusions from week 1 to the end of the treatment phase yielded results consistent with the analysis of the primary endpoint. That is, patients in the every-3-week treatment arm had fewer blood transfusions than those in the weekly arm (unadjusted Kaplan–Meier estimates = 29% [95% CI = 24% to 34%] versus 36% [95% CI = 30% to 41%], difference = −6.9%, 95% CI = −14.0% to 0.2%).

In the analysis of transfusion rates by weight, no statistically significant differences were observed between any of the weight categories in the every-3-week schedule, suggesting that treatment effectiveness did not decrease with increasing body weight when fixed dosing was used (Fig. 3). Similar results were obtained for transfusion results by BMI categories (data not shown).

In the analysis evaluating the subset of patients who received transfusions, the numbers of RBC units transfused from study day 1 to the end of the treatment phase were similar among the two treatment groups (mean = 1.64 [SD = 3.87] and mean = 2.07 [SD = 4.52] [standard unit = 250 mL] for the every-3-week and weekly groups, respectively).

Change in hemoglobin and hemoglobin target. The hemoglobin profiles over time were similar for the two treatment groups. Hemoglobin concentrations increased from a mean baseline level of 9.8 g/dL to approximately 11 g/dL in the initial 7 weeks of therapy and then stabilized at this level (Fig. 4, A).

As previously noted, most patients experienced a dose reduction at least once during the study because of increases in hemoglobin concentration of 1 g/dL or greater in a 14-day period. The mean hemoglobin concentrations at the time of the first dose reduction were the same for the every-3-week and weekly groups (11.1 g/dL). The median time to the first dose reduction was similar in the two groups and corresponded to the time at which the hemoglobin concentration profiles for both groups stabilized. A piecewise mixed-effects model was developed to further investigate the effect of these dose reductions on hemoglobin levels. A linear increase in hemoglobin concentration of 0.34 g/dL per week up to the first dose reduction was observed with hemoglobin concentration stabilizing after the first dose reduction (subsequent increase of 0.028 g/dL per week), suggesting that a 40% dose reduction for either schedule effectively sustains hemoglobin levels in the setting of continuing chemotherapy administration.

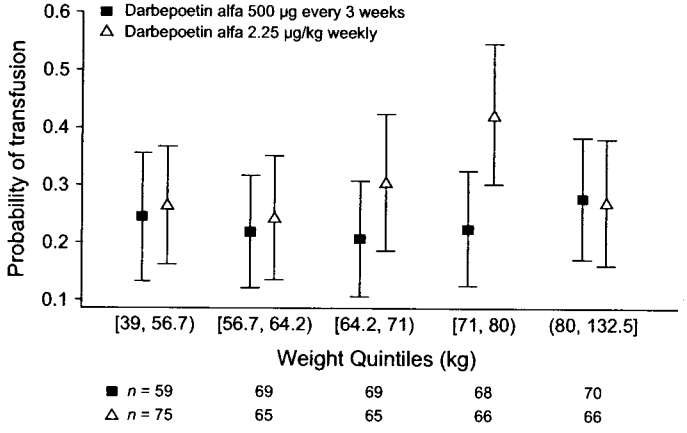

Fig. 3. Incidence of transfusions from week 5 to the end of the treatment phase by weight quintiles (kg) of patients in the two study arms. Unadjusted Kaplan–Meier estimates and 95% confidence intervals of RBC transfusion incidence from week 5 to the end of the treatment phase are shown (**squares**, 500 µg every 3 weeks; **triangles**, 2.25 µg/kg weekly). The total number of patients in each weight quintile is indicated below each plot. Quintile groups include the lower bound (denoted with **square bracket**) and exclude the upper bound (denoted with **rounded bracket**) with exception of upper quintile which includes both bounds.

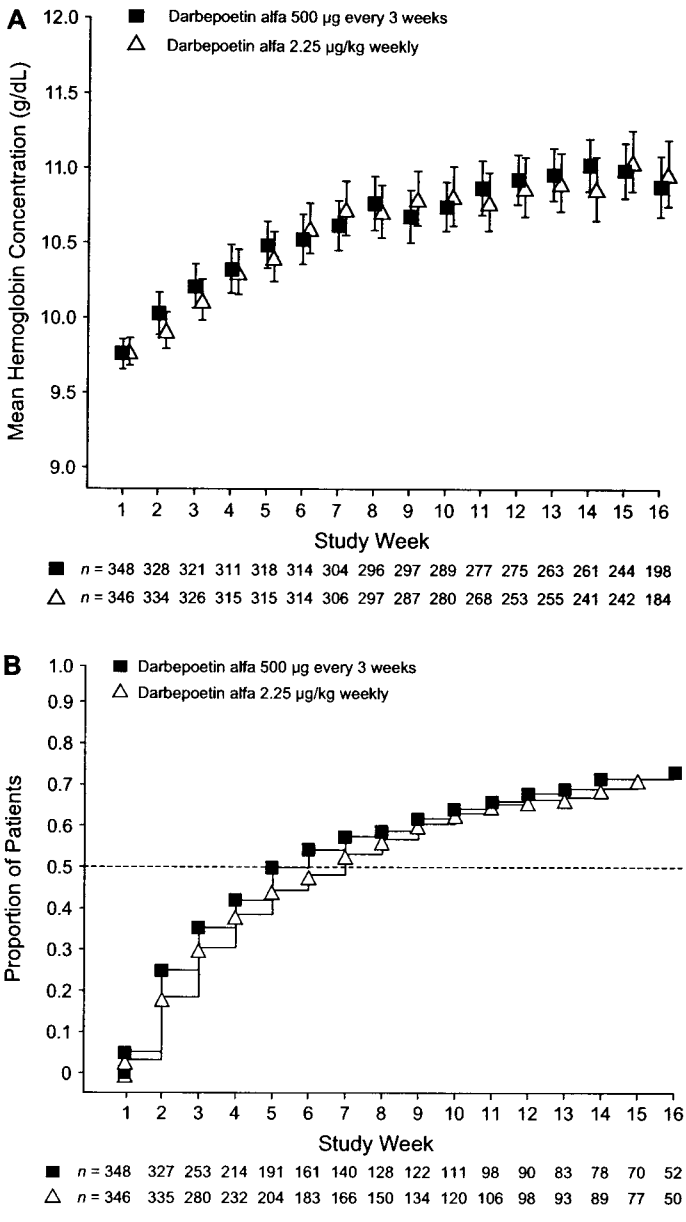

Fig. 4. Mean hemoglobin and achievement of target hemoglobin concentration. **A)** Hemoglobin concentration profiles over the study period. The mean hemoglobin concentration levels for the two treatment groups are shown with 95% confidence interval bars (available data approach). Patients with no hemoglobin value after baseline were excluded from the analysis. The total number of patients with hemoglobin values is shown by study week. **B)** Time to achievement of target hemoglobin concentration. The Kaplan–Meier plot displays the unadjusted proportion of patients achieving a target hemoglobin concentration of ≥11 g/dL. Patients with no hemoglobin value after baseline were excluded from the analysis. The number of patients remaining after censoring is shown by study week. **Squares**, 500 µg every 3 weeks; **triangles**, 2.25 µg/kg weekly.

Consistent with the hemoglobin over time profiles, no differences in change in hemoglobin concentration were observed between groups. This change was consistent, whether the analysis was based on available data or last-value-carried-forward (Fig. 5, A).

The target hemoglobin concentration was prespecified as 11 g/dL or greater. After adjustment for stratification variables, the Kaplan–Meier percentage of patients in the every-3-week and weekly groups achieving this target from week 1 to the end of the treatment phase was 84% (95% CI = 81% to 88%) and 77% (95% CI = 72% to 81%), respectively. The unadjusted Kaplan–Meier results were similar: 73% (95% CI = 68% to 78%) in the every-3-week group and 72% (95% CI = 67% to 77%) in the weekly group (Fig. 4, B). Median times to achievement of target hemoglobin levels were 36 and 43 days for patients in the every-3-week and weekly schedules, respectively. The proportion of patients in the two study groups who reached the target hemoglobin concentration at the end of the treatment phase was similar (Fig. 5, B).

After achievement of target hemoglobin levels, patients' mean hemoglobin concentration remained above 11 g/dL, consistent with evidence-based practice guidelines: 11.4 g/dL (95% CI = 11.3 to 11.5 g/dL) for the every-3-week group and 11.5 g/dL (95% CI = 11.4 to 11.6 g/dL) for the weekly group. The majority of patients subsequently maintained their hemoglobin levels in the target range of 11–13 g/dL.

Patient self-reported assessment of fatigue. Baseline FACT-Fatigue scores are shown in Table 1. Data from 295 (every 3 weeks) and 288 (weekly) patients who completed both the baseline and the end of the treatment phase FACT-Fatigue questionnaires were available for analysis. The mean changes in FACT-Fatigue subscale scores from baseline to the end of the treatment phase were similar for both treatment groups. More than half of the patients in each treatment group (adjusted Kaplan–Meier estimates = 57% and 58% in the every-3-week and weekly groups, respectively) had at least a three-point improvement in FACT-Fatigue subscale score from baseline by the end of the treatment phase (Kaplan–Meier difference between treatment groups = −0.9%, 95% CI = −9.7% to 7.8%). No statistically significant differences were observed between the two treatment groups for any other quality of life instruments.

Safety

In general, the incidence of adverse events was comparable in both groups (Table 4). Most adverse events were deemed by investigators to be unrelated to darbepoetin alfa treatment and were attributable to chemotherapy treatment or underlying malignancy. The most frequently reported adverse events were