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ORIGINAL REPORT

Physician Characteristics and Variability of Erythropoiesis-Stimulating Agent Use Among Medicare Patients With Cancer

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This study used the linked Surveillance, Epidemiology, and End Results–Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

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ABSTRACT

Purpose
Drugs are usually approved for a specific indication on the basis of randomized trials. However, once approved, these treatments are often used differently than as tested in trials. We performed an analysis to determine the patterns of use of erythropoiesis-stimulating agents (ESAs).

Methods
We used the Surveillance, Epidemiology, and End Results–Medicare database to identify patients age 65 years or older with breast, lung, or colon cancer diagnosed between 1995 and 2005 who had one ESA and chemotherapy claim. Associations of patient, tumor, and physician-related factors with receipt of ESAs were analyzed.

Results
Of 21,091 patients analyzed, 5,099 (24.2%) received ESAs for 1 week or less (misuse), and 1,601 (7.6%) received ESAs for more than 14 weeks (prolonged use). Receipt of ESAs while not actively receiving chemotherapy (off label) occurred in 2,876 patients (13.6%). In a multivariable analysis, ESA misuse was associated with MD degree, female sex of physician, and earlier year of medical school graduation. Private practice physicians (odds ratio [OR], 0.78; 95% CI, 0.72 to 0.84) and high-volume physicians (OR, 0.78; 95% CI, 0.72 to 0.85) were less likely to use 1 week or less of ESA treatment. Treatment by high-volume oncologists (OR, 1.33; 95% CI, 1.14 to 1.55) and by oncologists who graduated from US medical schools (OR, 1.26; 95% CI, 1.12 to 1.42) predicted prolonged-duration ESA use, whereas female oncologists (OR, 0.79; 95% CI, 0.68 to 0.93) were less likely to prescribe prolonged ESA treatment. Private practice physicians (OR, 1.18; 95% CI, 1.02 to 1.38) and high-volume providers (OR, 1.58; 95% CI, 1.33 to 1.87) were more likely to prescribe more than 24 weeks of ESA treatment.

Conclusion
Our study demonstrated widespread variability in the use of ESAs. Physician characteristics exerted substantial influence on ESA use. Policies to discourage inappropriate use of cancer therapies are needed.

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INTRODUCTION

In 1993, the US Food and Drug Administration (FDA) approved the erythropoiesis-stimulating agent (ESA) epoetin alfa for patients with cancer.[1] Approval of the long-acting erythropoietin preparation darbepoetin followed in 2002.[2] FDA approval for both agents was granted based on reductions in transfusion requirements in placebo-controlled trials comparing 12 weeks of the respective ESA with placebo.[1,2] Both agents were approved for use in patients with cancer while they are actively receiving cytotoxic chemotherapy. Often, drugs are approved for a specific indication based on data from randomized clinical trials, in which the agents are tested for specific indications and for specific durations. However, once approved, these treatments are used in a manner different from that studied in the clinical trials. Off-label and inappropriate use—which can take the form of under-, over-, or prolonged use—of drugs places patients at risk for toxicity without any proven benefit and represents a major source of excess health care expenditures.[3-5]

Despite an increasing number of studies questioning the safety of ESAs, their use in the United States increased by 340% between 2001and 2006.[6-8]

It is estimated that annual Medicare expenditures for ESAs exceed $1 billion.[9] In 2007, prompted by emerging safety concerns, the FDA issued a black-box warning for ESAs. During the ESA review process, the FDA expressed significant concern regarding off-label and inappropriate use of ESAs. Although off-label use of oncologic drugs is common, the FDA review process for ESAs resulted in heightened scrutiny and changes in reimbursement.[8,10]

To facilitate appropriate ESA use, a number of professional societies have proposed guidelines for ESA administration.[11-14] The American Society of Clinical Oncology (ASCO) first published ESA guidelines in 2002, and the European Organisation for Research and Treatment of Cancer endorsed recommendations in 2004.[11,14] These guidelines have been regularly updated as emerging safety data have become available.[12,13] However, despite ongoing debate regarding appropriate use of ESAs, relatively little is known about the patterns of ESA use among oncologists. We performed a population-based analysis to determine the patterns of use of ESAs in the United States. We examined patient and physician characteristics associated with off-label and unconventional use of ESAs.

METHODS

Data Source

We analyzed data from the Surveillance, Epidemiology, and End Results (SEER) –Medicare database.[15] SEER provides information on tumor histology, location, stage of disease, treatment, and survival, along with SEER site at diagnosis and demographic and selected census tract-level information. The Medicare database includes Medicare A (inpatient) and B (outpatient) eligibility status, billed claims, and diagnoses. These two files are linked and provide the ability to determine who has been treated with ESAs and the dates of service. Exemption from the institutional review board of Columbia University was obtained.

Cohort Selection

We identified all individuals who were age 65 years or older, who had a pathologically confirmed primary diagnosis of breast, non–small-cell lung, or colon cancer[16] from January 1, 1995, to December 31, 2005, and who were treated with chemotherapy. These cancers were thought to represent common cancers for which ESAs are frequently used. We excluded patients who were enrolled in non-Medicare health maintenance organizations.[17] Patients who were enrolled in Medicare because of end-stage renal disease or dialysis as well as patients with other primary cancers were also excluded (Appendix Table A1, online only). Age at diagnosis was categorized into 5-year intervals. We recoded the SEER marital status variable as married, not married, or unknown.

Socioeconomic Status Score

We generated an aggregate socioeconomic status (SES) score from education, poverty level, and income data from the 2000 census tract data, as described previously by Du et al.[18] Patient scores were ranked on a scale of 1 to 5 by use of a formula incorporating education, poverty, and income weighted equally, with 1 being the lowest value.

Assessment of Comorbid Disease

To assess the prevalence of comorbid disease in our cohort, we used the Klabunde adaptation of the Charlson comorbidity index.[19,20] Medicare inpatient and outpatient claims were searched for diagnostic codes of the International Classification of Disease, Ninth Revision, Clinical Modification.[16] Each condition was weighted, and patients were assigned a score based on the Klabunde–Charlson index method.[20]

Physician Characteristics

We matched treating physician to ESA claim by use of the unique physician identification number (UPIN) on the ESA claim; this was required to have a match in the American Medical Association file and indicate a primary or secondary specialty in oncology. Primary and secondary specialty codes for oncologists were defined as oncologist, hematologist, hematologist/oncologist, radiation oncologist, and surgical oncologist. Ninety-five percent of ESA claims were linked to valid UPINs, and for each tumor type, 90% to 92% of physicians associated with UPINs had a primary or secondary specialty of oncology. Oncologists characteristics analyzed based on variables in the American Medical Association master file included sex, year of graduation, primary employment setting (private *v* government or academic), location of training (United States *v* other), and type of degree (medical degree *v* doctor of osteopathic medicine). Physician ESA volumes were analyzed. Those physicians with approximately the highest quartile of patients receiving ESAs were considered high volume, and the cohort was dichotomized as one to nine or 10 or more patients accordingly.

Treatment Characteristics

We extracted information on chemotherapy from date of diagnosis from the Medicare files by searching the Level II Healthcare Common Procedure Coding System; Current Procedural Terminology codes; International Classification of Disease, Ninth Revision, Clinical Modification, diagnostic codes; and procedure, diagnostic-related group, and center codes from physician claims files, hospital outpatient claims files, or Medicare provider review files. We searched for Level II Healthcare Common Procedure Coding System codes corresponding to ESAs erythropoietin and darbopoietin (Q0136-7, J0880-2, and J0885-6). All patients had at least one claim for ESAs, and we excluded patients who received their first ESA before they received chemotherapy. Use of ESAs was categorized by number of consecutive weeks of therapy, total number of weeks, and total number of claims. Continuous use of ESAs was defined as the length of time receiving ESAs with no more than 4 weeks between claims, starting with the first ESA. Continuous use was divided into three groups: 1 week or less (misuse), 2 to 14 weeks (standard use based on clinical trials), and more than 14 weeks (prolonged use). An ESA was defined as received with concurrent chemotherapy if a claim was filed within 8 weeks of the chemotherapy claim, as per the current guidelines, or as off label if claims continued beyond 8 weeks after completion of chemotherapy. Misuse, prolonged use, and off-label use were considered inappropriate use.

We classified patients into the following three groups: nonmetastatic (those who received chemotherapy only), metastatic (those who received chemotherapy only with metastatic or recurrent cancer), and both (those who

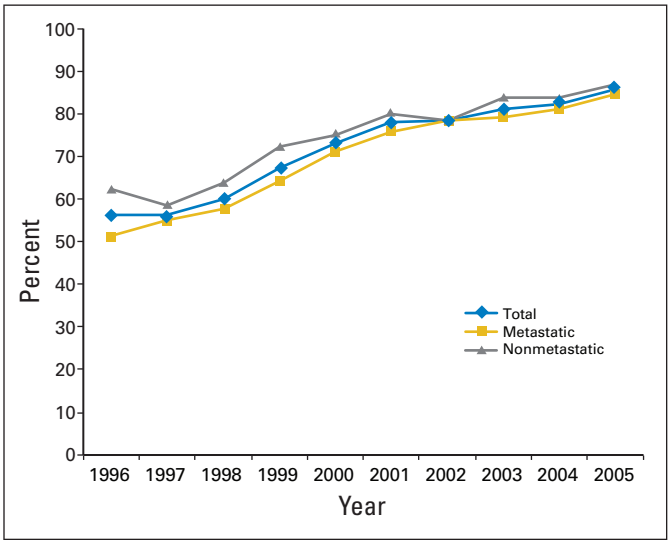

Fig 1. Percentages of patients with cancer treated with chemotherapy who also received erythropoiesis-stimulating agents, stratified by year of treatment (N = 24,112).

Table 1. Univariate Analysis of Factors Associated With Short- (≤ 1 week) and Prolonged-Duration (> 14 weeks) ESA Use

Factor	≤ 1 Week		2 to 14 Weeks			> 14 Weeks		
	No.	%	No.	%	*P**	No.	%	*P*†
Total	5,099	24.2	14,391	68.2		1,601	7.6	
Age at diagnosis, years					.28			.42
65-69	1,416	27.8	3,968	27.6		437	27.3	
70-74	1,647	32.3	4,829	33.6		564	35.2	
75-79	1,297	25.4	3,629	25.2		401	25.1	
> 80	739	14.5	1,965	13.7		199	12.4	
Race					.001			.15
White	4,333	85.0	12,546	87.2		1,403	87.6	
Black	433	8.5	1,036	7.2		127	7.9	
Hispanic	59	1.2	157	1.1		11	0.7	
Missing or other	274	5.4	652	4.5		60	3.8	
Year of diagnosis					.015			< .001
2005	880	17.3	2,183	15.2		178	11.1	
2004	883	17.3	2,320	16.1		193	12.1	
2003	799	15.7	2,397	16.7		226	14.1	
2002	700	13.7	2,042	14.2		250	15.6	
2001	619	12.1	1,904	13.2		256	16.0	
2000	559	11.0	1,641	11.4		220	13.7	
1999	203	4.0	591	4.1		77	4.8	
1998	155	3.0	436	3.0		60	3.8	
1997	121	2.4	372	2.6		58	3.6	
1996	90	1.8	268	1.9		52	3.3	
1995	90	1.8	237	1.7		31	1.9	
Residence					< .001			.13
Metropolitan	4,658	91.4	13,362	92.9		1,503	93.9	
Nonmetropolitan	441	8.7	1,029	7.2		98	6.1	
Marital status					.25			.68
Married	2,915	57.2	8,353	58.0		941	58.8	
Unmarried	2,039	40.0	5,619	39.0		619	38.7	
Unknown	145	2.8	419	2.9		41	2.6	
Socioeconomic status					< .001			.76
First (lowest) quartile	623	12.2	1,421	9.9		174	10.9	
Second quintile	902	17.7	2,573	17.9		283	17.7	
Third quintile	1,079	21.2	3,145	21.9		351	21.9	
Fourth quintile	1,145	22.5	3,324	23.1		370	23.1	
Fifth (highest) quartile	1,350	26.5	3,928	27.3		423	26.4	
Comorbidity score					.45			.02
0	4,294	84.2	12,170	84.6		1,361	85.0	
1	608	11.9	1,633	11.4		181	11.3	
> 1	197	3.9	588	4.1		59	3.7	
Tumor site					< .001			.017
Breast	1,489	29.2	4,478	31.1		445	27.8	
Colon	1,276	25.0	3,036	21.1		340	21.2	
Lung	2,334	45.8	6,877	47.8		816	51.0	
Tumor grade					.13			.06
High	1,957	38.4	5,369	37.3		603	37.7	
Low	1,829	35.9	5,311	37.0		531	33.2	
Unknown	1,313	25.8	3,711	25.8		467	29.2	
Treatment					.02			< .001
Recurrent/metastatic	2,708	53.1	7,374	51.2		992	62.0	
Early	2,391	46.9	7,017	48.8		609	38.0	
Oncologist training					.78			< .001
Non–United States	1,573	30.9	4,470	31.1		588	36.7	
United States	3,526	69.2	9,921	68.9		1,013	63.3	
Oncologist degree					< .001			.45
DO	150	2.9	581	4.0		71	4.4	
MD	4,949	97.1	13,810	96.0		1,530	95.6	

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Table 1. Univariate Analysis of Factors Associated With Short- (≤ 1 week) and Prolonged-Duration (> 14 weeks) ESA Use (continued)

Factor	≤ 1 Week		2 to 14 Weeks			> 14 Weeks		
	No.	%	No.	%	P*	No.	%	P†
Oncologist sex					.15			.002
Male	4,264	83.6	12,156	84.5		1,400	87.5	
Female	835	16.4	2,235	15.5		201	12.6	
Oncologist year of graduation					.07			.012
1990s	741	14.5	2,182	15.2		209	13.1	
1980s	1,788	35.1	5,267	36.6		554	34.6	
1970s	1,954	38.3	5,285	36.7		640	40.0	
1960s	616	12.1	1,657	11.5		198	12.4	
Oncologist practice setting					< .001			.87
Academic	1,224	24.0	2,875	20.0		317	19.8	
Private	3,875	76.0	11,516	80.0		1,284	80.2	
Patient volume					< .001			< .001
1-9	1,130	22.2	2,511	17.5		213	13.3	
> 10	3,969	77.8	11,880	82.6		1,388	86.7	

Abbreviations: DO, doctor of osteopathic medicine; ESA, erythropoiesis-stimulating agent; MD, doctor of medicine.
*Comparison of ≤ 1 week *v* 2 to 14 weeks of use.
†Comparision of > 14 weeks *v* 2 to 14 weeks of use.

received chemotherapy in both settings). Patients were classified as nonmetastatic if they had stage 1 to 3 breast, non–small-cell lung, or colon cancer when they were treated. They were classified as metastatic if they had stage 4 breast, non–small-cell lung, or colon cancer. If chemotherapy was administered after the first 12 months, the patient was categorized as having a recurrence.

Statistical Analysis

Treatment duration of ESAs was compared using χ^2 tests and univariate regression, with respect to clinical and demographic variables. We used Generalized Estimating Equations (GEE) methodology to account for the correlations of outcome measures among patients who had the same physician. Unit of analysis was the patient. For each patient, the UPIN was used as the clustering variable. GEE was used to analyze the association of underuse with standard use of ESAs with clinical variables, and then overuse with standard use of ESAs. A similar approach was taken to evaluate concurrent and off-label use of ESAs. We performed similar analyses to determine predictors of more than 12 weeks and more than 24 weeks of continuous ESA use. In the multivariate GEE analysis, we included physician characteristics, clinical characteristics, and demographic variables that we thought might be clinically significant in the model. All analyses were conducted with SAS, version 9.13 (SAS Institute, Cary, NC). All statistical tests were two sided.

RESULTS

A total of 21,091 patients were included in the duration-of-use analysis. During the years encompassed by the study, ESA use increased; 70.5% of patients who received chemotherapy in 1995 were treated with ESAs compared with 85.6% in 2005. Figure 1 displays yearly ESA use for all patients and also for patients within each disease stage. Overall, 5,099 patients (24.2%) received ESAs for 1 week or less. Table 1 lists demographic, clinical, and physician characteristics associated with duration of use. Clinical factors associated with misuse (≤ 1 week) included nonwhite race, treatment in the later years of the study, nonmetropolitan residence, lower SES, high-grade tumor, metastatic disease, and colon cancer ($P < .05$). Physician factors associated with ESA use of 1 week or less were MD degree, female sex, academic practice, and lower volume of ESA use ($P < .05$). In our multivariable model, the only clinical factors that remained associated with short duration were black race, year of diagnosis, colon cancer, nonmetropolitan area, lower SES, and presence of metastatic disease (Table 2). Physician characteristics associated with ESA misuse included MD degree (odds ratio [OR], 1.43; 95% CI, 1.18 to 1.73), female sex (OR, 1.10; 95% CI, 1.01 to 1.20), and earlier year of medical school graduation. In contrast, US medical school graduates (OR, 0.92; 95% CI, 0.85 to 0.99), private practice physicians (OR, 0.78; 95% CI, 0.72 to 0.84), and physicians who used high volumes of ESAs (OR, 0.78; 95% CI, 0.72 to 0.85) were less likely to administer ESAs for 1 week or less.

ESAs were administered for more than 14 weeks (prolonged use) in 1,601 patients (7.6%). Characteristics associated with prolonged use are listed in Table 1. In the adjusted model, year of diagnosis, treatment by a high-volume oncologist (OR, 1.33; 95% CI, 1.14 to 1.55), and treatment by a graduate of a US medical school (OR, 1.26; 95% CI, 1.12 to 1.42) significantly predicted prolonged-duration ESA use (Table 2). Female oncologists (OR, 0.79; 95% CI, 0.68 to 0.93) were less likely to prescribe prolonged ESAs, and patients with early-stage disease (OR, 0.71; 95% CI, 0.64 to 0.80) were less likely to receive prolonged ESAs. Figure 2 displays the temporal trends of misuse, standard use, and prolonged use of ESAs.

We then examined off-label use of ESAs (ESA use > 8 weeks after completion of chemotherapy; Table 3). Of the 21,091 patients included, 2,876 (13.6%) received off-label ESAs. Patient characteristics were strong predictors of off-label ESA use. Off-label use of ESAs was noted in 11.8% of patients age 65 to 69 years versus 15.6% of those age 80 years or older (adjusted OR, 1.40; 95% CI, 1.23 to 1.59). Likewise, black patients (OR, 1.42; 95% CI, 1.22 to 1.66) and patients with greater comorbidity (OR, 1.28; 95% CI, 1.05 to 1.55) were more likely to receive ESAs while off treatment. Physicians with high ESA claims volume (OR, 1.19; 95% CI, 1.07 to 1.33) were more likely to prescribe off-label ESAs.

Table 2. Multivariable Analysis of Factors Associated With Short- (≤ 1 week) and Prolonged-Duration (> 14 weeks) ESA Use

Factor	≤ 1 Week			> 14 Weeks		
	OR	95% CI	*P*	OR	95% CI	*P*
Age at diagnosis, years						
65-69		Referent			Referent	
70-74	0.96	0.89 to 1.05	.39	1.03	0.90 to 1.18	.63
75-79	1.00	0.92 to 1.10	.98	0.98	0.85 to 1.13	.77
> 80	1.02	0.92 to 1.14	.66	0.89	0.74 to 1.07	.21
Race						
White		Referent			Referent	
Black	1.17	1.02 to 1.33	.02	1.04	0.84 to 1.28	.74
Hispanic	0.99	0.73 to 1.34	.93	0.62	0.33 to 1.16	.14
Missing or other	1.12	0.95 to 1.31	.18	0.89	0.66 to 1.20	.44
Year of diagnosis						
2005		Referent			Referent	
2004	0.94	0.84 to 1.05	.30	1.00	0.81 to 1.24	.99
2003	0.82	0.74 to 0.94	< .001	1.09	0.89 to 1.34	.41
2002	0.84	0.74 to 0.94	.003	1.45	1.18 to 1.77	< .001
2001	0.80	0.71 to 0.90	< .001	1.55	1.27 to 1.90	< .001
2000	0.84	0.74 to 0.95	.006	1.52	1.23 to 1.88	< .001
1999	0.82	0.68 to 0.99	.03	1.56	1.16 to 2.09	.003
1998	0.83	0.68 to 1.02	.08	1.57	1.14 to 2.16	.006
1997	0.78	0.63 to 0.98	.03	1.77	1.28 to 2.45	< .001
1996	0.79	0.61 to 1.02	.07	2.25	1.59 to 3.18	< .001
1995	0.88	0.68 to 1.15	.37	1.52	1.01 to 2.30	.05
Residence						
Metropolitan		Referent			Referent	
Nonmetropolitan	1.32	1.14 to 1.51	< .001	0.81	0.63 to 1.04	.10
Marital status						
Married		Referent			Referent	
Unmarried	1.03	0.96 to 1.11	.37	0.98	0.88 to 1.10	.77
Unknown	0.97	0.80 to 1.19	.79	0.84	0.60 to 1.18	.32
Socioeconomic status						
First (lowest) quartile		Referent			Referent	
Second quintile	0.81	0.70 to 0.94	.005	0.95	0.74 to 1.20	.65
Third quintile	0.78	0.67 to 0.90	< .001	0.88	0.69 to 1.13	.32
Fourth quintile	0.79	0.68 to 0.92	.002	0.87	0.67 to 1.11	.26
Fifth (highest) quartile	0.79	0.67 to 0.91	.002	0.86	0.67 to 1.10	.23
Comorbidity score						
0		Referent			Referent	
1	0.97	0.87 to 1.08	.57	1.04	0.87 to 1.24	.66
> 1	0.84	0.71 to 1.00	.05	0.92	0.69 to 1.23	.59
Tumor site						
Breast		Referent			Referent	
Colon	1.24	1.12 to 1.36	< .001	1.01	0.86 to 1.19	.90
Lung	0.96	0.88 to 1.05	.40	1.08	0.94 to 1.24	.31
Tumor grade						
High		Referent			Referent	
Low	1.00	0.93 to 1.08	.98	0.89	0.79 to 1.02	.09
Unknown	1.04	0.94 to 1.14	.47	1.06	0.92 to 1.23	.43
Treatment						
Recurrent/metastatic		Referent			Referent	
Early	0.93	0.87 to 1.00	.04	0.71	0.64 to 0.80	< .001
Oncologist training						
Non–United States		Referent			Referent	
United States	0.92	0.85 to 0.99	.02	1.26	1.12 to 1.42	< .001
Oncologist degree						
DO		Referent			Referent	
MD	1.43	1.18 to 1.73	< .001	0.94	0.72 to 1.22	.63
Oncologist sex						
Male		Referent			Referent	
Female	1.10	1.01 to 1.20	.04	0.79	0.68 to 0.93	.005

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Table 2. Multivariable Analysis of Factors Associated With Short- (≤ 1 week) and Prolonged-Duration (> 14 weeks) ESA Use (continued)

Factor	≤ 1 Week			> 14 Weeks		
	OR	95% CI	*P*	OR	95% CI	*P*
Oncologist year of graduation						
1990s		Referent			Referent	
1980s	1.06	0.96 to 1.18	.24	0.97	0.82 to 1.16	.75
1970s	1.21	1.09 to 1.34	< .001	1.06	0.89 to 1.27	.49
1960s	1.24	1.09 to 1.42	.002	0.98	0.79 to 1.22	.85
Oncologist practice setting						
Academic		Referent			Referent	
Private	0.78	0.72 to 0.84	< .001	0.94	0.82 to 1.08	.40
Patient volume						
1-9		Referent			Referent	
> 10	0.78	0.72 to 0.85	< .001	1.33	1.14 to 1.55	< .001

NOTE. Models also adjusted for Surveillance, Epidemiology, and End Results site.
Abbreviations: DO, doctor of osteopathic medicine; ESA, erythropoiesis-stimulating agent; MD, doctor of medicine; OR, odds ratio.

Total (lifetime) ESA use for the cohort was then examined. A total of 4,432 patients (21.0%) received more than 12 weeks of ESA treatment, whereas 1,389 (7.1%) received ESAs for longer than 24 weeks. Year of diagnosis was a strong predictor of use for longer than 12 and longer than 24 weeks (Table 4). Patients in nonmetropolitan areas (OR, 0.69; 95% CI, 0.51 to 0.92), those with lung cancer (OR, 0.71; 95% CI, 0.61 to 0.83), and those with early-stage disease (OR, 0.34; 95% CI, 0.30 to 0.39) were less likely to receive ESAs for either more than 12 or more than 24 weeks. Patients treated by private practice physicians (OR, 1.18; 95% CI, 1.02 to 1.38) as well as those treated by high-volume providers (OR, 1.58; 95% CI, 1.33 to 1.87) were more likely to have had more than 24 weeks of treatment. Sensitivity analysis with removal of nonsignificant variables from the models did not result in any significant changes in associations between variables of interest and patterns of ESA use.

DISCUSSION

Our findings suggest that variability in use of ESAs is widespread. Nearly 25% of the patients in our cohort received 1 week or less of treatment, a dose that would provide negligible if any clinical effect. Likewise, we noted that 8% of patients received prolonged continuous ESA treatment for more than 14 weeks, and nearly 14% of the cohort continued to receive ESA treatment for more than 2 months after completion of chemotherapy. In addition to subjecting patients to toxicity, these patterns of use impose a significant financial burden to the health care system. Our findings raise concern in that actual use of ESAs deviates significantly from clinical trials and FDA labeling.

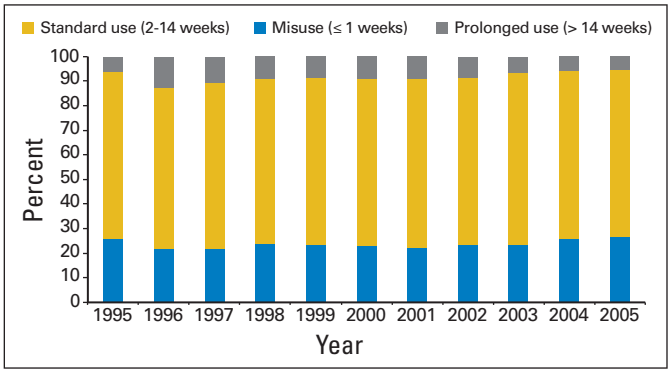

Fig 2. Use, misuse, and prolonged use of erythropoiesis-stimulating agents stratified by year of diagnosis.

The off-label use of drugs, particularly in oncology, is common.[3-5] One investigation noted that 38% of patients treated for bladder cancer in 2002 received an off-label agent, and 58% of men with hormone-refractory prostate cancer received an off-label drug.[4] Off-label use is particularly prevalent for new drugs entering the market. In the early 2000s, 22% of Australian women with metastatic breast cancer received off-label trastuzumab, and 75% of patients treated in the late 1990s with rituximab received the drug off label.[21,22] Inappropriate drug use also seems to be a problem for supportive care measures.[23,24] In a survey of the ASCO membership, Bennett et al[23] noted that many oncologists were using colony-stimulating factors in scenarios and dosing schedules that evidence and guidelines did not support.

Prior data examining the patterns of ESA use have predominantly focused on compliance with recommendations for target hemoglobin levels.[8,25-30] A majority of these studies have found fair to moderate compliance with recommended hemoglobin targets.[8,26-30] An evaluation of patients in the United States treated with ESAs between 2002 and 2006 noted that 24% of patients who received ESAs had hemoglobin levels greater than 12 gm/dL.[29] We focused our analysis on documenting use patterns that were clearly inappropriate and of questionable clinical utility. We noted that relatively large proportions of patients received either ultra-short courses of ESAs or prolonged-duration ESA therapy. An additional 14% of our cohort continued to receive ESA treatment well after completion of chemotherapy, treatment clearly at odds with current ESA labeling.

Although patient and tumor factors influence treatment decisions, it is becoming increasingly clear that physician characteristics are also important determinants of care.[31,32] In our analysis, physician characteristics including medical school training and physician sex,

Table 3. Multivariable Analysis of Associations Between Clinical, Demographic, and Physician Characteristics and Off-Label ESA Use

Characteristic	Off-Chemotherapy ESA Use				
	No. of Patients	%	Multivariable OR	95% CI	*P*
Total	2,876	13.6			
Age at diagnosis, years					
65-69	686	11.8	Referent		
70-74	960	13.6	1.20	1.08 to 1.33	< .001
75-79	777	14.6	1.30	1.16 to 1.45	< .001
> 80	453	15.6	1.40	1.23 to 1.59	< .001
Race					
White	2,430	13.3	Referent		
Black	269	16.9	1.42	1.22 to 1.66	< .001
Hispanic	33	14.5	1.00	0.69 to 1.47	.98
Missing or other	144	14.6	1.07	0.88 to 1.30	.51
Year of diagnosis					
2005	369	11.4	Referent		
2004	458	13.5	1.23	1.06 to 1.42	.007
2003	557	16.3	1.49	1.29 to 1.72	< .001
2002	44	13.7	1.23	1.05 to 1.43	.009
2001	403	14.5	1.30	1.11 to 1.52	< .001
2000	314	13.0	1.12	0.95 to 1.32	.17
1999	107	12.3	1.16	0.92 to 1.47	.22
1998	91	14.0	1.29	1.00 to 1.67	.05
1997	74	13.4	1.22	0.92 to 1.60	.16
1996	47	11.5	1.03	0.74 to 1.43	.87
1995	45	12.6	1.16	0.83 to 1.62	.40
Residence					
Metropolitan	2,682	13.7	Referent		
Nonmetropolitan	194	12.4	1.17	0.97 to 1.41	.10
Marital status					
Married	1,643	13.5	Referent		
Unmarried	1,147	13.9	0.97	0.89 to 1.06	.49
Unknown			1.20	0.94 to 1.52	.15
Socioeconomic status					
First (lowest) quartile	325	14.7	Referent		
Second quintile	484	12.9	1.17	0.97 to 1.42	.10
Third quintile	618	13.5	1.25	1.02 to 1.52	.03
Fourth quintile	652	13.5	1.25	1.02 to 1.52	.03
Fifth (highest) quartile	797	14.0	1.26	1.04 to 1.54	.02
Comorbidity score					
0	2,367	13.3	Referent		
1	368	15.2	1.12	0.99 to 1.27	.08
> 1	141	16.7	1.28	1.05 to 1.55	.01
Tumor site					
Breast	946	14.8	Referent		
Colon	661	14.2	0.84	0.75 to 0.95	.005
Lung	1,269	12.7	0.83	0.75 to 0.93	< .001
Tumor grade					
High	1,173	14.8	Referent		
Low	969	12.6	0.84	0.76 to 0.93	< .001
Unknown			0.93	0.83 to 1.05	.24
Treatment					
Recurrent/metastatic	1,569	14.2	Referent		
Early	1,307	13.1	0.87	0.80 to 0.95	.001
Oncologist training					
Non–United States	903	13.6	Referent		
United States	1,973	13.6	0.96	0.88 to 1.06	.42
Oncologist degree					
DO	119	14.8	Referent		
MD	2,757	13.6	0.85	0.69 to 1.05	.13

(continued on following page)

Table 3. Multivariable Analysis of Associations Between Clinical, Demographic, and Physician Characteristics and Off-Label ESA Use (continued)

Characteristic	Off-Chemotherapy ESA Use				
	No. of Patients	%	Multivariable OR	95% CI	*P*
Oncologist sex					
Male	2,389	13.4	Referent		
Female	487	14.9	1.11	0.99 to 1.24	.06
Oncologist year of graduation					
1990s	449	14.9	Referent		
1980s	1,014	13.3	0.92	0.81 to 1.04	.17
1970s	1,066	13.5	0.95	0.84 to 1.08	.40
1960s	347	14.0	0.99	0.84 to 1.16	.91
Oncologist practice setting					
Academic	624	14.1	Referent		
Private	2,252	13.5	0.94	0.85 to 1.04	.25
Patient volume					
1-9	482	12.5	Referent		
> 10	2,394	13.9	1.19	1.07 to 1.33	.002

NOTE. Model also adjusted for Surveillance, Epidemiology, and End Results site.
Abbreviations: DO, doctor of osteopathic medicine; ESA, erythropoiesis-stimulating agent; MD, doctor of medicine; OR, odds ratio.

volume, and practice setting all affected use of ESAs. A prior study of patterns of erythropoietin use noted that practice setting was the most important predictor of ESA use; those physicians in fee-for-service settings were more than twice as likely to use ESAs frequently.[25] We noted that oncologists in private practice settings were less likely to prescribe ESAs for 1 week or less and 20% more likely to administer ESAs for more than 6 months continuously.

Association between physician characteristics and ESA use is likely caused by a multitude of factors. Patients seen by private practice physicians are more likely to have commercial insurance, higher SES, and fewer medical comorbidities. Any or all of these factors may have influenced the prescribing patterns we noted. We also found a strong association between high practice volume and prolonged and off-chemotherapy ESA use. Finally, it also seems likely that economic considerations play a role in the allocation of ESAs. In the survey of oncologists reported by Adams et al,[25] 37% of US physicians reported that financial considerations affected their decision to use ESAs. In addition, physicians in fee-for-service settings were more likely to withhold ESAs because of reimbursement considerations. The current system in which private practice physicians purchase ESAs and generate profit from their administration has raised concerns regarding conflicts of interest.

Safety matters aside, misuse of ESAs is of concern, because ESAs represent a major source of drug-associated health care expenditures. It is estimated that Medicare expenditures for ESAs are more than $1 billion annually.[9] A recent study that modeled conservative use of ESAs reported that they were not cost effective, noting that the incremental cost per quality-adjusted life year gained with ESA treatment was $267,000.[33,34] Given the widespread misuse of ESAs that we found, the financial consequences surrounding ESA use are even greater in real-world practice.

Our findings of widespread variability in use of ESAs are somewhat surprising. Previous work examining guideline compliance by physicians has yielded mixed results.[24,35,36] In an effort to facilitate guideline compliance, ESA reimbursement has been limited in the United States, and the FDA has established a risk evaluation and mitigation strategy program to improve evidence-based use.[8,10] More work will be needed to monitor the efficacy of these efforts. Although ESAs are the only drugs currently being regulated in this way, our findings raise the question of whether other drugs should be more tightly regulated from the onset.

We acknowledge several important limitations of our study and of the SEER-Medicare database in general.[37] It is possible that not all patients who received ESAs were captured with Medicare claims. However, because of the substantial expense associated with ESAs, we believe that this would have occurred relatively infrequently. Patterns of ESA use may differ among younger patients and those with commercial insurance. The SEER-Medicare database lacks data on hemoglobin levels. As such, we could not calculate the number of patients receiving ESAs who had high hemoglobin levels. We used the overall number of patients treated with ESAs as a surrogate for physician prescribing volume. We recognize that this may not be representative of a physician's entire practice. As with any analysis of administrative data, it is impossible to determine individual patient and physician preferences that may have influenced patterns of use. Finally, given the widespread recognition of the safety concerns of ESAs, patterns of use have likely shifted in the last 5 years. More studies are clearly warranted to examine the influence of new regulations on ESA use.

Our study demonstrates widespread variability in use of ESAs in the United States. Short treatment duration providing little clinical efficacy and prolonged use were common. We noted that even after completing chemotherapy, a substantial number of patients continued to receive ESAs. Although patient-related factors affected patterns of ESA use, physician characteristics exerted substantial influence on the way ESAs were administered. Recent regulatory changes as well as limitations on reimbursement may drive more rational ESA use; however, further interventions to encourage guideline-based use of ESAs and other cancer-related drugs are needed.

Table 4. Multivariable Analysis of Factors Associated With Total ESA Use of > 12 Weeks and > 24 Weeks

Factor	> 12 Weeks			> 24 Weeks		
	OR	95% CI	*P*	OR	95% CI	*P*
Total						
No.		4,432			1,389	
%		21.0			7.1	
Age at diagnosis, years						
65-69		Referent			Referent	
70-74	1.07	0.98 to 1.17	.14	1.05	0.91 to 1.21	.53
75-79	1.01	0.92 to 1.11	.89	1.10	0.94 to 1.28	.24
> 80	0.99	0.88 to 1.11	.87	1.00	0.83 to 1.21	.99
Race						
White		Referent			Referent	
Black	1.23	1.08 to 1.41	.002	1.22	0.98 to 1.51	.08
Hispanic	1.31	0.96 to 1.79	.09	1.67	1.07 to 2.62	.03
Missing or other	1.09	0.91 to 1.30	.35	0.75	0.54 to 1.04	.09
Year of diagnosis						
2005		Referent			Referent	
2004	1.08	0.94 to 1.23	.29	1.38	1.06 to 1.79	.02
2003	1.47	1.29 to 1.67	< .001	2.08	1.63 to 2.65	< .001
2002	1.50	1.31 to 1.71	< .001	2.26	1.77 to 2.89	< .001
2001	1.71	1.50 to 1.95	< .001	2.49	1.95 to 3.18	< .001
2000	1.68	1.47 to 1.93	< .001	2.31	1.80 to 2.97	< .001
1999	1.62	1.34 to 1.96	< .001	2.20	1.58 to 3.05	< .001
1998	1.54	1.24 to 1.90	< .001	2.28	1.61 to 3.22	< .001
1997	1.72	1.38 to 2.14	< .001	2.69	1.90 to 3.81	< .001
1996	1.76	1.38 to 2.25	< .001	2.31	1.55 to 3.43	< .001
1995	1.46	1.11 to 1.91	.006	2.52	1.67 to 3.80	< .001
Residence						
Metropolitan		Referent			Referent	
Nonmetropolitan	0.84	0.72 to 0.99	.04	0.69	0.51 to 0.92	.01
Marital status						
Married		Referent			Referent	
Unmarried	0.95	0.88 to 1.02	.16	0.92	0.82 to 1.04	.17
Unknown	0.96	0.78 to 1.18	.70	0.87	0.61 to 1.24	.44
Socioeconomic status						
First (lowest) quartile		Referent			Referent	
Second quintile	1.02	0.87 to 1.19	.85	1.23	0.94 to 1.62	.13
Third quintile	0.99	0.84 to 1.17	.92	1.17	0.89 to 1.55	.27
Fourth quintile	1.00	0.85 to 1.18	.97	1.25	0.94 to 1.66	.12
Fifth (highest) quartile	0.99	0.84 to 1.16	.89	1.17	0.88 to 1.56	.28
Comorbidity score						
0		Referent			Referent	
1	1.09	0.98 to 1.22	.13	1.11	0.93 to 1.32	.27
> 1	0.94	0.79 to 1.13	.51	1.03	0.77 to 1.36	.87
Tumor site						
Breast		Referent			Referent	
Colon	1.04	0.94 to 1.15	.43	0.91	0.77 to 1.07	.26
Lung	0.88	0.80 to 0.96	.006	0.71	0.61 to 0.83	< .001
Tumor grade						
High		Referent			Referent	
Low	0.97	0.90 to 1.06	.53	0.92	0.80 to 1.05	.22
Unknown	1.13	1.03 to 1.25	.01	1.04	0.89 to 1.22	.60
Treatment						
Recurrent/metastatic		Referent			Referent	
Early	0.54	0.50 to 0.58	< .001	0.34	0.30 to 0.39	< .001
Oncologist training						
Non–United States		Referent			Referent	
United States	0.81	0.75 to 0.88	< .001	0.74*	0.65 to 0.83	< .001
Oncologist degree						
DO		Referent			Referent	
MD	0.95	0.79 to 1.13	.54	0.84	0.63 to 1.13	.25

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Table 4. Multivariable Analysis of Factors Associated With Total ESA Use of > 12 Weeks and > 24 Weeks (continued)

Factor	> 12 Weeks			> 24 Weeks		
	OR	95% CI	*P*	OR	95% CI	*P*
Oncologist sex						
Male		Referent			Referent	
Female	0.84	0.76 to 0.93	< .001	0.80	0.68 to 0.95	.01
Oncologist year of graduation						
1990s		Referent			Referent	
1980s	0.99	0.89 to 1.11	.92	0.92	0.76 to 1.12	.42
1970s	1.00	0.90 to 1.12	.99	1.07	0.89 to 1.30	.47
1960s	1.05	0.92 to 1.21	.47	1.07	0.85 to 1.34	.59
Oncologist practice setting						
Academic		Referent			Referent	
Private	1.11	1.01 to 1.21	.03	1.18	1.02 to 1.38	.03
Patient volume						
1-9		Referent			Referent	
> 10	1.48	1.35 to 1.63	< .001	1.58	1.33 to 1.87	< .001

NOTE. Models also adjusted for Surveillance, Epidemiology, and End Results site.
Abbreviations: DO, doctor of osteopathic medicine; ESA, erythropoiesis-stimulating agent; MD, doctor of medicine; OR, odds ratio.
**P* value < .05.

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