

# Insights and Perspectives in the Clinical and Operational Management of Cancer-Related Anemia

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## Key Words

Cancer-related anemia, blood products management, erythropoiesis stimulating agents, ESA, blood products utilization

## Abstract

Management of anemia in patients with cancer presents challenges from clinical, operational, and economic perspectives. Clinically, anemia in these patients may result from treatment (chemotherapy, radiation therapy, or surgical interventions) or from the malignancy itself. Anemia not only contributes to cancer-related fatigue and other quality of life issues, but also affects prognosis. From the operational perspective, a patient with cancer who is also anemic may consume more laboratory, pharmacy, and clinical resources than other patients with cancer. (*JNCCN* 2010;8[Suppl 7]:S38–S55)

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Over the past several years, new paradigms have emerged for the treatment of cancer- and chemotherapy-induced anemia, specifically in the context of using erythropoiesis stimulating agents (ESAs), blood transfusions, and iron supplementation to maintain hemoglobin levels in patients with cancer. Each of these interventions has complexities and, in some cases, controversies. Moreover, anemia and the interventions used to counter it can have significant implications in terms of cost and revenue.

## Cause of Anemia in Patients With Cancer

As noted in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer- and Chemotherapy-Induced Anemia, 30% to 90% of patients with cancer experience anemia.<sup>1</sup> Anemia may originate from decreased production of red blood cells (RBCs), increased destruction of RBCs, or blood loss, and is characterized by a decrease in hemoglobin concentration or RBC count.<sup>2</sup> Normal hemoglobin levels specified by the NCI are 14 to 18 g/dL for men and 12 to 16 g/dL for women. In patients with cancer, anemia may occur as a result of treatments (e.g., from myelosuppression associated with cytotoxic chemotherapy) or from the cancer disease process itself, which may interfere with hematopoiesis, reduce the life span of RBCs, or interfere with serum iron levels. Renal insufficiency and other underlying or comorbid factors may contribute to or exacerbate chemotherapy- or cancer-induced anemia.

Because the effects of anemia, including fatigue and reduced QoL, can be severe, the general clinical approach in the oncology setting is, when possible, to treat symptomatic anemia through interventions that raise or

## Executive Summary

### The Challenge:

- Managing anemia in the oncology population is a complex issue with clinical, operational, and economic implications.
- Key interventions for anemia management in cancer patients include erythropoiesis stimulating agents (ESAs), supplemental iron products, and blood transfusions.

### The Shifting Landscape:

- Use of ESAs, which remained high in the late 1990s and early 2000s as an approach to management of chemotherapy-induced anemia, has decreased because of both clinical concerns and a CMS National Coverage Determination (NCD) restricting their reimbursement.
- Published data and NCCN survey results indicate that as ESA use has decreased in oncology in the United States, the frequency of blood transfusions to manage anemia is increasing. Management of blood products is expensive and resource-intensive for health care facilities.
- Use of supplemental iron, a widely available and relatively inexpensive intervention, is likely not optimized among oncology patients. This may be because of lower physician comfort levels with using iron or a lower level of understanding about how iron, especially parenteral formulations, can play a role in the management of cancer- and chemotherapy-induced anemia.

### Moving Ahead:

Institutions are pioneering new methods for optimizing blood product use. A case study from the University of Alabama at Birmingham describes how they reduced their blood products utilization rates by more than 20%.

- Programs that optimize use of supplemental iron, whether in conjunction with the prescription of ESAs or alone, may have the potential to bring clinical benefit and greater efficiencies in the oncology setting.
- Clearly defining institutional ESA policies in light of the NCD and the myriad reimbursement policies may provide opportunities to optimize reimbursement for clinically appropriate use of these agents to manage anemia in patients with cancer.

seek to restore hemoglobin levels. The primary clinical interventions are the administration of ESAs and transfusion with packed RBCs as supportive care measures. The use of supplemental iron, delivered either orally or intravenously, continues to garner attention. When clinically indicated and deemed appropriate, iron is used in conjunction with the other therapies mentioned, particularly when a patient's iron stores are low.

## The Operational Challenges of Anemia Management

Anemia in patients with cancer has the potential to impact hospital operations and can be associated with significant expense. A patient experiencing cancer- or chemotherapy-induced anemia may not be able to undergo scheduled chemotherapy, impacting infusion room and infusion pharmacy operations,

and potentially necessitating the consumption of additional laboratory, pharmacy, or blood bank resources. Patients with anemia may be transfused in infusion areas, slowing throughput for other chemotherapy patients. Other undesirable operational consequences include wasted chemotherapy doses and/or the admission of patients with severe anemia to the inpatient service. Apart from these considerations, patients with anemia may experience complications, suboptimal outcomes of radiation or chemotherapy treatment, lower performance status, or decreased QoL.

A primary challenge in the management of anemia from a hospital operations perspective is the need to balance clinical, operational, and financial objectives in an environment where evidence and best practice are in flux. Although a decade ago ESAs were seen as the primary and optimum intervention for the management of anemia in patients with can-

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cer, their use is becoming ever more controversial as emerging data raise serious patient safety concerns and suggest potentially undesirable outcomes in patients with cancer. At the same time, blood product supplies continue to be constrained, and transfusions are not without risk to patients. Some clinicians are emphasizing the use of supplemental iron as a means of reaching better outcomes in anemia management, but approaches to iron use have not been universally adopted among the oncology community.

## ESAs: Clinical and Operational Impact

### Historical Perspective: Use of ESAs in Oncology, 1980s Through Early 2000s

ESAs were originally studied in chronic kidney disease, with the first publications examining their use in a nephrology setting appearing in 1986.<sup>3,4</sup> ESAs first came to market with the introduction of epoetin alfa in 1989, which was initially approved by the FDA for the treatment of anemia in patients with end-stage renal disease undergoing dialysis. The agent was marketed as Epogen by Amgen for the dialysis market and as Procrit by OrthoBiotech for other markets, including cancer and HIV/AIDS. In 1993, the FDA added an indication for cancer-related anemia as a label supplement for epoetin alfa (Epogen/Procrit), specifying that the treatment of patients with nonmyeloid malignancies undergoing concomitantly administered chemotherapy was an indicated use.<sup>5</sup> Approval in Europe for a similar indication followed in 1994.

Throughout the 1990s and early 2000s, ESAs were widely featured in both the nephrology and oncology literature. For patients with cancer- and chemotherapy-related anemia, data indicated that use of ESAs lowered dependence on transfusions, improved QoL, and reduced symptoms of fatigue.<sup>3,6</sup>

In 2001, darbepoetin alfa, marketed by Amgen as Aranesp, came to market after a September approval by the FDA for the treatment of anemia associated with chronic renal failure. Darbepoetin alfa had already been approved in June 2001 by the European Medicines Agency (EMA) for the chronic renal failure indication and the treatment of chemotherapy-induced anemia. To date, these 2 ESAs are the only agents available in the United States market, although various “biosimilar” (often referred to in the United States as “follow-on biologic”) ver-

sions of ESAs, including epoetin alfa, epoetin beta, and epoetin zeta biosimilars have been approved by the EMA since 2007.

The pharmacologic rationale for ESA use in the oncology setting is not as straightforward as the rationale for use in nephrology patients. For a patient with chronic kidney disease, erythropoietin production is diminished and ESAs act as a replacement hormone. In treating cancer- and chemotherapy-related anemia, the differing and occasionally multifactorial origin of the anemia translates into a less-certain response from ESAs and greater complexity regarding their appropriate clinical use.

Although the FDA indications for ESAs in patients with cancer are somewhat limited to treating anemia related to concomitant chemotherapy administration, ESAs were used beyond the FDA label for patients who continued to experience anemia after chemotherapy or who were not undergoing chemotherapy but had cancer-related anemia of a different origin. Publications such as the 2002 paper by Crawford et al.<sup>7</sup> described improved QoL for patients with cancer when hemoglobin levels reached 10 to 12 g/dL through ESA use. At the same time, direct-to-consumer advertisements were emphasizing the ability of ESAs to improve QoL and reduce fatigue in patients. With increased patient demand and growing evidence showing QoL improvement, ESAs became even more widely used in oncology settings. However, starting in 2004, ESA use came under scrutiny from the FDA, Centers for Medicare & Medicaid Services (CMS), and the clinical community, as concerns grew regarding potential safety and outcome issues, possible overuse, and the structure of reimbursement models that could cause potentially undesirable incentives.

### Reimbursement and Business Implications of ESAs in Cancer

Separating business and reimbursement elements from clinical concerns surrounding ESAs is a difficult task. In the mid- to late 1990s and early 2000s, ESAs were considered a large potential source of revenue in both the nephrology and oncology settings. As an injectable, erythropoietin alfa was purchased by oncology practices from the manufacturer, then billed to Medicare and private payors under the “buy and bill” payment mechanism. ESAs were among the most expensive drugs used in oncology at the time, with a 6-month course costing approximately \$10,000. The

net profits recouped by oncology practices from ordering and administering ESAs in their offices were far from insubstantial, stemming not only from excellent reimbursement by public and private payors but also from lower acquisition costs due to manufacturer rebates based on bulk purchasing. According to a 2007 article in *The New York Times*, one group practice of 6 oncologists that prescribed \$9 million worth of ESAs in 2006 received rebates of \$2.7 million.<sup>8</sup> Overall, sales of ESAs resulted in approximately \$10 billion in the United States in 2006.

Both clinical and reimbursement models for the use of ESAs began to change significantly starting in 2004. On the FDA side, a 2004 Oncology Drugs Advisory Committee (ODAC) meeting examined data from 2 studies that had been published in *The Lancet* and *The Lancet Oncology* during the previous year.<sup>9,10</sup> Data from these studies, the ENHANCE head and neck trial and the BEST breast cancer study, showed higher mortality rates in patients who were treated with ESAs. Several other oncology studies had been halted within a similar time frame because of increased thromboembolic events that seemed to be associated with ESA use. By the time ODAC next met in 2007, additional studies had shown decreased survival in patients with cancer who were treated with ESAs and were titrated to relatively high hemoglobin levels.<sup>11,12</sup> In March 2007, the FDA required manufacturers of ESAs to add a black box warning to these products.<sup>13</sup> Between November and December of that year, NCCN, American Society of Hematology (ASH), and ASCO restricted their recommendations for use of ESAs in practice guidelines. In March 2008, ODAC again convened to discuss ESA safety, and as a result of ODAC recommendations, the FDA decided to again change the product label, specifying that ESAs are not indicated for patients “receiving potentially curative treatments.”<sup>14</sup> Currently, providers prescribing ESAs must engage patients in an informed-consent process via REMS before the drugs can be administered.

### Blood Transfusions: Clinical and Operational Impact

One effect of ESA use was a decreased need for transfusion in patients with anemia when their hemoglobin levels could be adequately maintained on these agents. In light of increasing restrictions on the

use of ESAs, renewed attention has been given to transfusion of RBCs as an intervention for anemia in patients with cancer. Transfusions, like ESAs, are not without risk. The management and use of blood products also result in significant costs for health care institutions, both in terms of the acquisition cost of blood products and the cost of maintaining blood banks and other operations to properly obtain, collect, store, and deliver blood to patients.

In the oncology setting, efficient use of blood products poses unique clinical effectiveness, patient safety, operational, and financial challenges. Patients with cancer may require transfusions or other blood products because of treatment-related factors (e.g., chemotherapy-related anemia and fatigue, surgery) or to treat a precipitous drop in hemoglobin because of hemorrhage or other disease-related factors. In the cancer center, for both inpatients and outpatients, blood products management strategies must be developed to ensure clinically effective and safe use of blood products while maximizing operational efficiency.

Data from a 2009 abstract presented at the 51st ASH Annual Meeting that examined blood use related to chemotherapy-induced anemia before and after the 2007 National Coverage Determination (NCD) regarding ESAs showed that the odds of a patient receiving a blood transfusion were significantly higher in the time frame after the NCD.<sup>15</sup> In this study, 88% of patients pre-NCD were treated with ESAs, whereas only 56% of patients post-NCD underwent this treatment. After the NCD, patients not only were more likely to receive a transfusion (19.1% of patients post-NCD vs. 15.3% pre-NCD) but also were likely to receive more units of blood (mean units transfused per patient of 0.55 units post-NCD vs. 0.36 units pre-NCD). The abstract also concluded that after controlling for demographic, clinical, and chemotherapy factors, the odds that a patient received a transfusion because of chemotherapy-induced anemia were 1.4 times higher in the time frame after the NCD.

### Blood Products Management as a Priority Area in the Cancer Center

Delivery of blood transfusions is a relatively high-risk, high-cost procedure. In 2006 (the most recent year for which data are available), more than 14 and



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15 million units of whole blood and RBCs, respectively, were transfused in the United States.<sup>16</sup>

Blood transfusions for all patient groups, including those with cancer, have associated risks. Although the public often perceives that transmission of infection is a large risk in blood transfusion, it is actually a rare occurrence. The most common risks include allergic and febrile reactions that are rarely life-threatening. Other significant and more serious risks include contamination of platelets, acute transfusion-related lung injury, and errors related to incorrect matching or infusion to the incorrect patient. The frequency of adverse events seen with transfusions varies directly with the number of units or overall amount of blood transfused. Transfusions require clinicians to complete an informed-consent process with the patient, outlining the spectrum of potential risks associated with receiving transfused blood. In this regard, ordering and delivery of a blood transfusion can be just as or more complex than the ordering and administration of an ESA.

Blood products also come at a significant cost. In 2006, the mean price paid for one unit of leukocyte-reduced RBCs was \$213.94.<sup>16</sup> Price may have significant regional variations, with hospitals in the northeastern United States paying significantly more than the national mean, and hospitals in the southwestern and central United States paying significantly less.<sup>16</sup>

In the cancer center, an evolving body of knowledge surrounding optimal management of cancer-related anemia has brought a new focus to addressing blood product management. For example, recent studies indicate that a higher hematocrit achieved through means such as transfusions or pharmacologic intervention may actually be associated with higher risk of death for some high-risk patients, including those in intensive care.<sup>17,18</sup> Appendix A provides a case study illuminating the challenges related to blood transfusions.

### Supplemental Iron Use in Oncology

Despite several studies that have shown a better response to ESAs in patients with cancer receiving intravenous supplemental iron, and/or a reduction in transfusions for oncology patients receiving intravenous iron during therapy, no unified practice exists regarding the use of supplemental iron products in the oncology setting. The NCCN Guidelines for

Cancer- and Chemotherapy-Induced Anemia address supplemental iron.<sup>2</sup> For patients with cancer undergoing myelosuppressive chemotherapy without curative intent who are asymptomatic and with risk factors for the development of symptomatic anemia, observation or iron studies, including iron panel (serum iron, total iron binding capacity, serum ferritin), is recommended. If a patient has an absolute iron deficiency (ferritin < 30 ng/mL and transferrin saturation < 15%), intravenous or oral iron supplementation is recommended, with the note that intravenous iron seems to have superior efficacy and should be considered for supplementation rather than oral iron, which has been more commonly used but is less effective. For patients with functional iron deficiency (ferritin ≤ 800 ng/mL and transferrin saturation < 20%), intravenous iron supplementation should be considered along with erythropoietic therapy after patient counseling regarding risks and benefits of ESAs. These guidelines also address parenteral iron preparations, stating that “these products are helpful in treating iron deficiency in patients intolerant or unresponsive to oral iron therapy, and in treating functional iron deficiency as seen in chronic renal failure patients, and cancer patients who are receiving ESAs.”

The primary intravenous iron products available on the market, iron dextran, iron sucrose, and sodium ferric gluconate, are not specifically approved for the oncology context and are associated with various risks. A survey of NCCN pharmacy directors, described in detail later, indicated that, from the pharmacist perspective, iron is underused by oncologists for various reasons. The prevailing perception is that oncologists have a lower comfort level with and lower level of knowledge and understanding regarding intravenous supplemental iron use for treating or preventing anemia compared with use of either ESAs or blood transfusions. Another NCCN survey indicated that oncologists themselves are concerned about the risks of infusion-related reactions with intravenous iron, to the point that some are unwilling to prescribe certain iron products. Additionally, because supplemental iron policies are not as prevalent as policies surrounding ESA and transfusion use, iron studies may not be routinely assessed as part of an anemia management strategy for oncology patients.

An abstract presented at the 2007 ASCO Annual Meeting examined the effect of intravenous iron

supplementation in conjunction with darbepoetin administration. For patients with a hemoglobin lower than 10 g/dL, 94% of those receiving intravenous supplemental iron along with darbepoetin reached their target hemoglobin, whereas only 73% of the control group, which received darbepoetin with no or oral iron, reached the target. Moreover, 31% of the control group required transfusion, whereas only 11% of those receiving intravenous iron required the same. In patients with a baseline hemoglobin of 10 g/dL, differences were less pronounced, with 94% of the study group and 92% of the control group reaching the target hemoglobin. However, only 8% of the study group required a transfusion, compared with 14% in the control group.<sup>19</sup>

Another 2007 study focusing solely on patients with cervical cancer examined the use of intravenous iron without ESAs and found that administration of intravenous iron sucrose to patients undergoing chemoradiotherapy reduced the need for transfusion. In that study, published in *Gynecologic Oncology*, 40% of patients in the study group required transfusion, whereas 64% of patients in the control group (no intravenous iron) required transfusion. Patients in the study group also required fewer units of blood on average than did patients in the control group (1.87 vs. 3.58 units, respectively).<sup>20</sup> A 2008 editorial in the *Journal of Clinical Oncology* raised the provocative question of whether the restrictions in ESA coverage and reimbursement recently imposed by CMS and other payor groups might be partially influenced by suboptimal use of intravenous iron, which the editorial's author interprets as a suboptimal use of ESAs.<sup>21</sup>

A clinical explanation for the apparent effect of intravenous iron in improving the ability of ESAs to raise hemoglobin levels, even in patients with sufficient baseline iron stores, is that mobilization of iron from existing stores may not be able to keep pace with RBC production when an ESA is administered. One pharmacist provided the layman's analogy of ESAs as a "gas pedal" and iron as the "tank of gas." Iron must be mobilized from iron stores to the labile iron pool before it can be incorporated into hematology groups for RBC production. Administration of an ESA quickly stimulates the production of RBCs, but the production rate may exceed the rate at which stored iron can be mobilized into the labile iron pool. If this scenario occurs, the process can "run out of gas" even when sufficient iron stores ex-

ist, because stored iron is not being released quickly enough to meet RBC production demand (termed *functional iron deficiency*). Oral iron supplementation is less effective than intravenous supplementation in this scenario because of limitations in the absorption rate of oral iron formulations. Additionally, oral iron products generally cause undesirable side effects, such as gastrointestinal pain and constipation, which reduce adherence to oral iron regimens.

Use of intravenous iron has a somewhat controversial history, primarily because of the serious risks that were associated with the administration of intravenous iron in past decades. Before the availability of low molecular weight iron dextran (i.e., Infed), iron sucrose (i.e., Venofer), and sodium ferric gluconate (i.e., Ferrlecit), high molecular weight iron dextran (i.e., Dexferrum) was the sole product available for intravenous iron supplementation. This product was associated with a much higher rate of serious adverse reactions, including allergic/anaphylactoid reactions, hypotension, cardiac arrest, and death, when compared with low molecular weight iron dextran. These rates appear especially higher when compared with nondextran-containing products, such as iron sucrose and sodium ferric gluconate.

A study using FDA MedWatch data from 2001 to 2003 estimated the rate of life-threatening adverse reactions to be 0.6, 0.9, 3.3, and 11.3 per million for iron sucrose, sodium ferric gluconate, low molecular weight iron dextran, and high molecular weight iron dextran, respectively.<sup>22</sup> Both high and low molecular weight iron dextran have a "black box" warning for life-threatening anaphylaxis, and the labeling requires a test dose be given before the first therapeutic dose is administered.

Despite concerns about the serious infusion-related reactions, the overall rate of these major adverse events is low, and has decreased, compared with that reported in an earlier analysis of FDA MedWatch data from 1998 to 2000.<sup>23</sup> This may be partly because of a higher percentage of use of non-dextran products in 2001 to 2003 versus 1998 to 2000 (69% vs. 5%, respectively). Regardless, the historical use of high molecular weight iron dextran and the high rates of serious adverse events may have instilled a misguided sense of fear in practitioners concerning the use of intravenous iron preparations.<sup>24</sup> This may especially be the case for low molecular weight iron dextran, which some may mistakenly believe has the

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same rate of adverse events as the high-molecular weight product.

An NCCN survey regarding intravenous iron preparations (discussed in detail later) seems to confirm this thinking. A higher percentage of clinicians will not prescribe iron dextran because of the perceived risk of infusion-related reactions compared with nondextran products. However, a small number of clinicians are also unwilling to prescribe the non-dextran products.

Any anemia management strategy that includes intravenous iron must take into account the severity of the anemia and the potential for adverse events, such as serious infusion-related reactions. The data from the NCCN survey indicate that physicians are differentiating between iron dextran, iron sucrose, and ferric gluconate in terms of their risk levels. Additionally, NCCN pharmacy directors overall favor the use of iron sucrose or sodium ferric gluconate as the preferred parenteral intravenous iron preparation on formulary. It is important to note that formulary substitution policies should not allow high molecular weight iron dextran to be substituted for low molecular weight iron dextran because of the much higher rates of serious adverse events with the former.

### Data From 3 NCCN Surveys: The Changing Landscape of Anemia Interventions

In 2009, NCCN conducted 3 surveys regarding oncology clinicians' approaches to treating anemia. The first 2 surveys focused on the 21 NCCN Member Institutions, which are all large academic and research cancer centers in the United States. The third survey took a different approach and gathered responses from more than 1800 individuals in the United States and globally. These surveys pertained to the use of ESAs, outpatient blood transfusions, and supplemental iron as interventions in cancer- and chemotherapy-related anemia.

#### Survey 1: Blood Product Management

The first NCCN study, conducted in May and June of 2009, specifically examined blood products and transfusion operations. Among the 21 NCCN Member Institutions, 15 participated in this study; 11 of the respondents were directors, medical directors, or managers with direct oversight of transfusion/

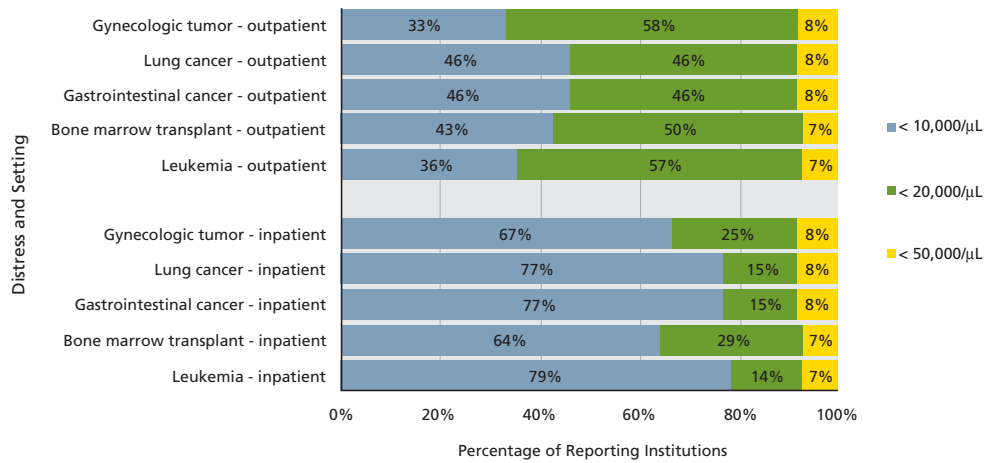
blood bank services, and the remaining 4, each with a high level of involvement in transfusion services, were medical directors or administrators responsible for laboratory, medical operations, and/or oncology units. Of the reporting institutions, 14 convened their own Blood Utilization Committees, and 1 institution's blood management activities were managed in a collaborative format with another institution. Thirteen of the institutions reported that they had instituted a comprehensive blood management program based on evidence-based transfusion guidelines. All of the reporting institutions stated that over the past 5 years, their institutional expenses associated with blood products had increased.

Varying models of blood product utilization management emerged, with institutions implementing various means to better manage use of blood products and reduce unnecessary use. Slightly more than half of the responding institutions reported that they require a reason for transfusion to be included on the order. However, most reporting institutions also allow prescribers to order a transfusion with multiple activations, and only 4 institutions reported that transfusion orders expired in less than a week. Other institutions reported that transfusion orders can remain open or standing for 3 weeks or more.

Institutions were asked to report threshold levels that would trigger a transfusion order for various diseases in both the inpatient and outpatient settings (Figure 1). Institutions were generally more aggressive in starting a prophylactic transfusion at a lower platelet count for inpatients than for outpatients, with most institutions reporting a threshold platelet count of less than 10,000/ $\mu$ L as a trigger for infusions in the inpatient setting for all listed diseases. For all listed diseases in the outpatient setting, most institutions reported using a platelet count of less than 20,000/ $\mu$ L as a threshold for prophylactic infusion. One institution reported a threshold platelet count of less than 50,000/ $\mu$ L for all listed scenarios. However, not all institutions reported for all tumor types, accounting for this latter institution representing 7% to 8% of the total depending on the scenario.

These thresholds were variable for all institutions, with 100% of the reporting cancer centers ( $n = 14$ ) stating that the threshold would change for actively bleeding patients. Most reporting centers also stated that thresholds would change in scenarios involving a patient who has high-risk features or if

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**Figure 1** At what platelet count does your medical staff initiate a prophylactic transfusion to a patient?

the patient required anticoagulation (Figure 2).

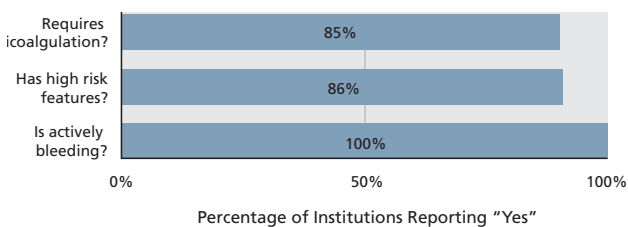
Varying thresholds for transfusion were described in several manners. Several institutions had a higher threshold, at a platelet count of less than 50,000/ $\mu$ L, for patients on active anticoagulation, patients who were actively bleeding, patients with active infections, or other higher risks. Other institutions had 2 levels of increased thresholds, setting one at less than 50,000/ $\mu$ L for active bleeding and full anticoagulation and a second at less than 20,000/ $\mu$ L for fever, sepsis, uncontrolled infections, a blood urea nitrogen of greater than 70, or veno-occlusive disease. One institution with a usual threshold of less than 10,000/ $\mu$ L increases this threshold to less than 20,000/ $\mu$ L for patients who have associated hemostatic defects. The highest threshold mentioned by any institution was less than 100,000/ $\mu$ L in instances of a head bleed. Eight institutions stated that thresholds can be altered per clinical discretion, occasionally in conjunction with discussions between the clinician and the medical director of the blood bank.

All of the institutions that were able to name a threshold platelet count above which interventional

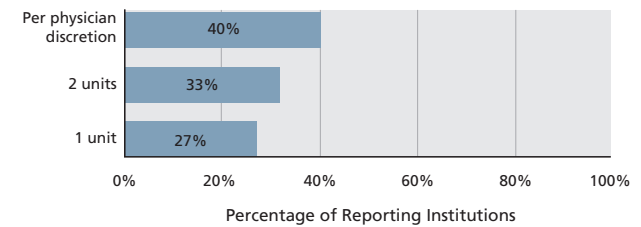
radiology would deem safe for a line placement put this threshold at greater than 50,000/ $\mu$ L.

Fewer than a third of institutions had set a policy allowing only 1 unit of RBCs to be ordered in an initial order. Slightly more than a third (36%) had a policy or practice of initially ordering 2 units, whereas 43% allowed for physician discretion in the number of units originally ordered (Figure 3). Although a change in policy from a 2-unit ordering standard to a 1-unit ordering standard was a key component of the University of Alabama at Birmingham (UAB) Health System process improvement in blood products utilization (see case study, Appendix A), these data indicate that a policy such as this is not necessarily accepted as a best practice in the oncology environment.

When asking about policies governing the use of ESAs and iron, several of the blood bank and transfusion directors noted that these policies were beyond the purview of the blood bank, and therefore the individuals were unable to report details of policies. This potential disconnect between the blood bank, which supervises transfusions, and the



**Figure 2** Does your transfusion threshold change if the patient requires anticoagulation, has high risk features, or is actively bleeding?



**Figure 3** When red cells are ordered for a transfusion, what is your policy on the number of units that should be initially ordered?



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pharmacy, which manages ESAs and iron, indicates an opportunity for improvements in the efficiency of anemia management.

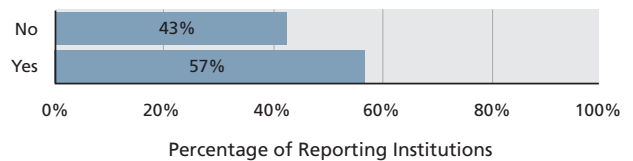
Of the institutions, 14 reported data on their use of programs or policies aimed at minimizing the impact of diagnostic phlebotomy on the development of anemia; more than half indicated that they had put these policies in place (Figure 4). Respondents were asked to provide specific examples of measures taken in this area if the institution had adopted such a program. The methods included reducing specimen volumes for clinical testing; conducting more testing in-house to allow use of one specimen tube for multiple tests; establishing a formal policy to limit the number of blood draws and the amount of blood drawn per draw; guidelines on volume requirement for all tests; and using pediatric tubing. Three institutions specifically mentioned policies pertaining to children, infants, and/or neonates to limit potential blood loss from diagnostic phlebotomy.

Fourteen institutions also reported on programs for encouraging autologous blood donation in the oncology context when clinically appropriate (Figure 5). One institution maintained these policies across disease states and specialty areas. Another institution offered autologous donation to low-risk elective surgical oncology patients. A third had instituted a policy of routine autologous donations for patients undergoing radical prostatectomy and bone marrow donors for allogeneic transplantation.

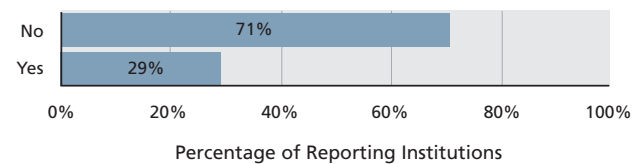
A slight majority of reporting institutions had an on-site blood donation facility or donor collection center (Figure 6). Incorporating a strategy for on-site donation/collection was a key component of the UAB Health System program to reduce its dependence on blood supplies from vendors and particularly out-of-state sources.

### Survey 2: NCCN Pharmacy Directors and Survey 3: Practicing Oncology Clinicians

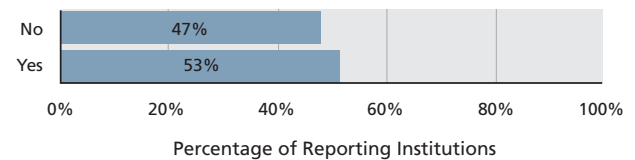
The second and third studies asked similar questions to 2 different samples: clinical pharmacy directors at NCCN institutions, and a large group of oncology clinicians worldwide. Both groups were asked to estimate the change over the past 2 years in use of ESAs, outpatient blood transfusions, and supplemental iron as treatment interventions for anemia in patients with cancer. In the survey of NCCN institution pharmacy



**Figure 4** Has your institution developed programs or policies to minimize the impact of diagnostic phlebotomy on the development of anemia (e.g., decreased frequency, use of small-volume sample tubes, etc.)?



**Figure 5** Does your institution have policies surrounding autologous blood donation specifically in the oncology context?

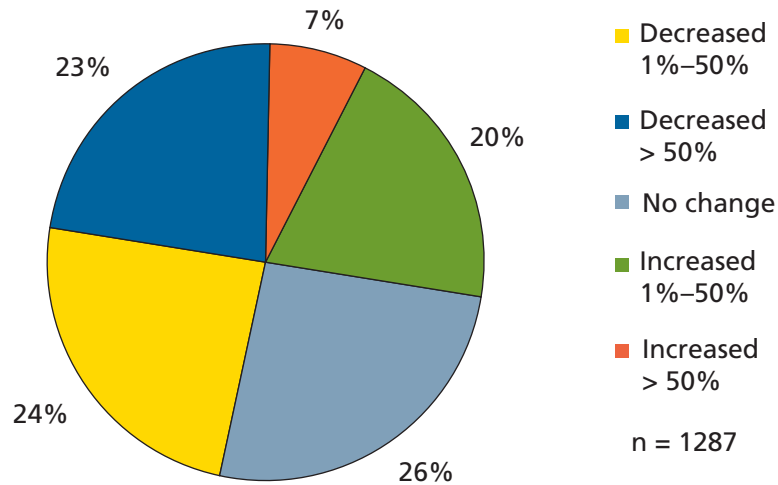


**Figure 6** Do you have an on-site blood donor collection center at your institution?

directors (conducted in September 2009), 15 of 21 institutions responded. Of 15 pharmacy directors who participated in the survey, 7 reported a decrease in ESA use of greater than 50%, whereas 7 reported a decrease of 1% to 50%. Only 1 institution reported seeing an increase in ESA use of 1% to 50%. Of the same respondents, 10 reported an increase in outpatient blood transfusions over the same period. No institution reported a decrease in the number of outpatient blood transfusions over the past 2 years. Eight pharmacy directors reported an increase in the use of supplemental iron. Of these, 5 attributed this increase specifically to changes in policies regarding ESA use.

Data from the larger survey on anemia, also conducted in September 2009, garnered responses from 1589 clinician respondents. Of these, nearly half (47%) reported that their ESA use had decreased over the past 2 years, whereas 26% did not see a change and 27% saw an increase in ESA use for patients with cancer and anemia. Of those who saw a decline in ESA use, half reported a decrease of greater than 50% (Figure 7). Results were segmented heavily among geographic lines, with clinicians in

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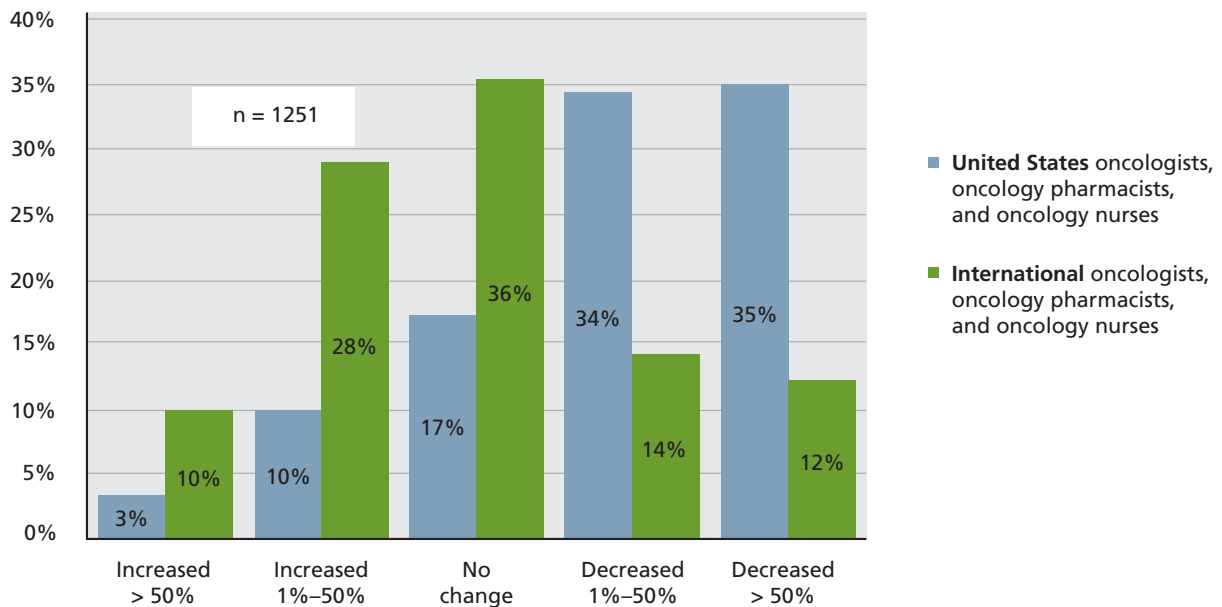
**Figure 7** Reported changes in use of ESAs in cancer patients over past 2 years.

the United States reporting significant decreases, and international clinicians primarily reporting increases or no change in the use of ESAs. Approximately 70% of United States oncologists reported a decrease in ESA use over the past 2 years, whereas only 16% of international oncology clinicians reported the same (Figure 8). These respondents' observations are congruent with anecdotal reports and expectations of decreased use of ESAs in the United States after these events as the emergence of new safety data about the use of ESAs in patients with cancer, the Medicare NCD changing reimbursement

for the use of these agents, and changes in clinical practice guidelines including those from NCCN.

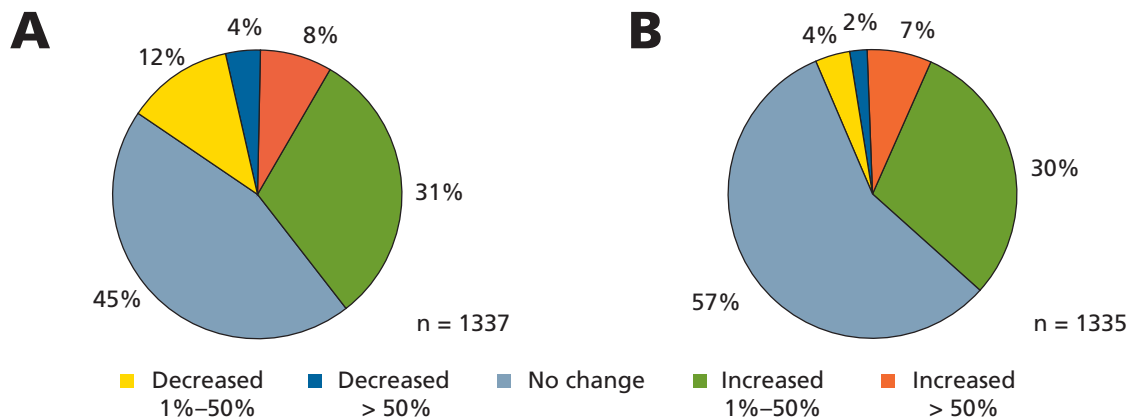
The survey of 1589 clinicians also queried respondents as to whether they had seen changes in the use of outpatient blood transfusions and supplemental iron as approaches to managing anemia in patients with cancer (Figures 9 and 10). For supplemental iron, most clinicians (56%) reported seeing no change and 37% reported an increase in iron use; few clinicians (6%) reported a decrease.

Nearly 40% of the 1589 reporting clinicians indicated that they had seen an increase in the use of



**Figure 8** Reported changes in use of ESAs in cancer patients over past 2 years: United States and international comparison.

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**Figure 9** (A) Reported changes in use of outpatient blood transfusions in cancer patients over past 2 years. (B) Reported changes in use of supplemental iron in cancer patients over past 2 years.

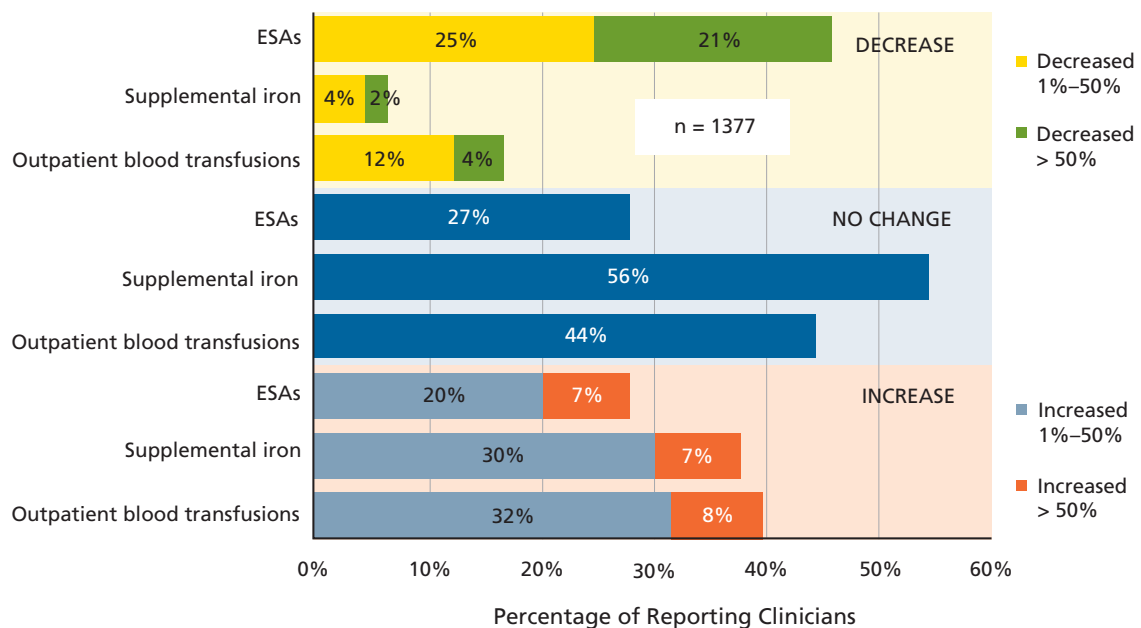
outpatient blood transfusions for patients with cancer and anemia. However, 45% reported that the use of transfusions had not changed.

In the smaller survey of 15 NCCN pharmacy directors, 8 (53.3%) reported an increase of 1% to 50% in the use of outpatient blood transfusions, and 2 (13.3%) reported an increase in transfusions of greater than 50% over the past 2 years.

The survey of pharmacy directors also examined policies related to supplemental iron, including which iron products could be found on formulary and which, if any, had a “preferred” status among prescribers and pharmacists at the institution. For-

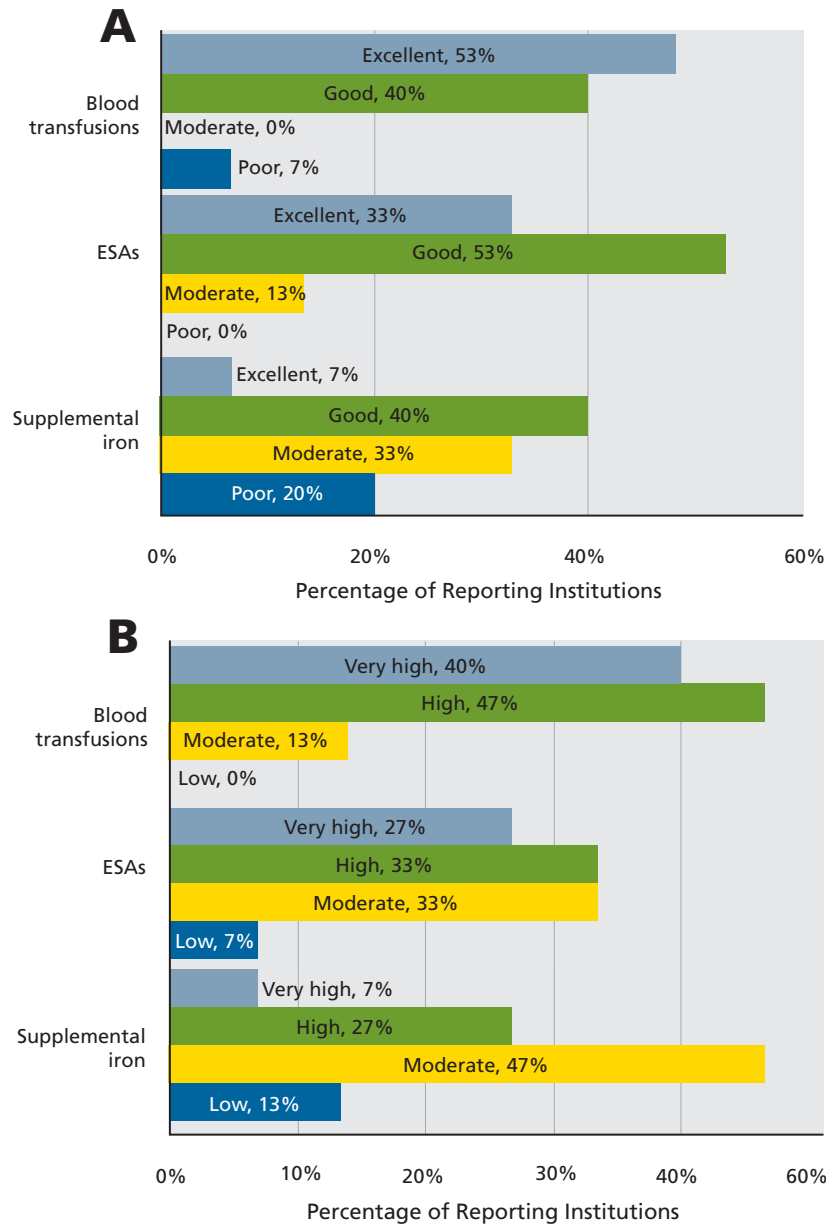
mularies at 13 institutions include iron dextran, 11 include iron sucrose, and 8 include sodium ferrous gluconate. At 7 institutions, iron sucrose is the “preferred” supplemental iron agent, whereas sodium ferrous gluconate is preferred at 5 institutions and iron dextran at 2. Seven institutions had a specific policy in place regarding the use of supplemental iron in their institutions. In most cases, this policy or program is led by the pharmacy.

Pharmacy directors were also asked to characterize their perceptions of “physician knowledge and understanding” and “physician comfort level” regarding various anemia interventions (Figure 11).



**Figure 10** Reported changes in use of ESAs, supplemental iron, and outpatient blood transfusions among all reporting practicing oncology clinicians.

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**Figure 11** (A) Pharmacist perspective: characterizing physician *knowledge and understanding* of cancer-related anemia treatment options. (B) Pharmacist perspective: characterizing physician *comfort level* with cancer-related anemia treatment options.

Although most respondents characterized knowledge of transfusions and ESAs as excellent or good, knowledge and understanding of supplemental iron was characterized as only “moderate” by 30% of the respondents and “poor” by 20%. Likewise, comfort level with transfusions and ESAs was generally higher than comfort level with iron.

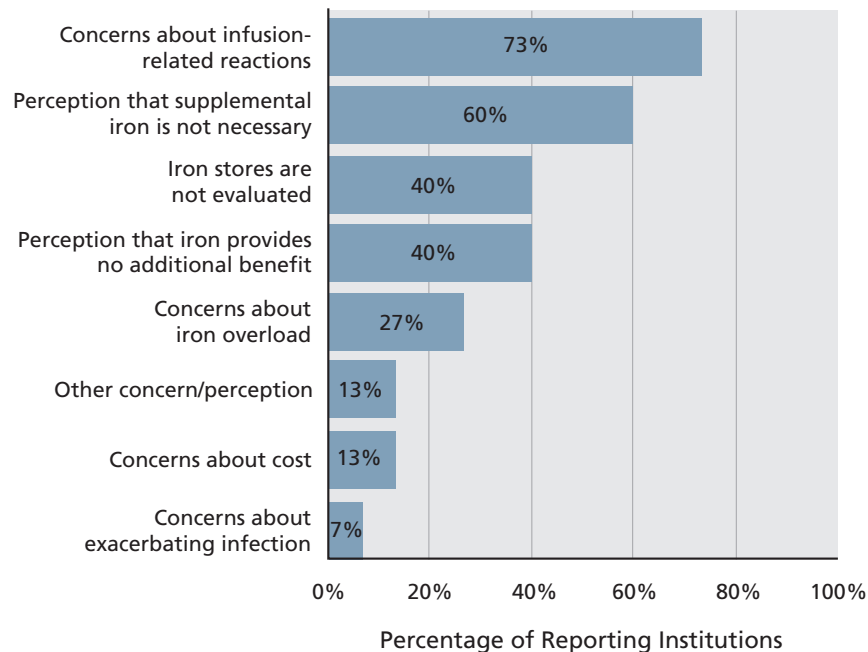
The most commonly cited reason for suboptimal use of supplemental iron in oncology was that prescribers are concerned about infusion-related reactions (Fig-

ure 12). Pharmacy directors also thought that prescribers perceived supplemental iron as not necessary or that it would offer no additional benefit to the patient. One respondent stated that iron was not deemed an “important issue” among clinicians at that institution.

The larger survey of practicing oncology clinicians also indicated some level of concern with the prescription of supplemental iron (Figure 13). Clinicians had the highest level of concern regarding infusion-related reactions with iron dextran. For all



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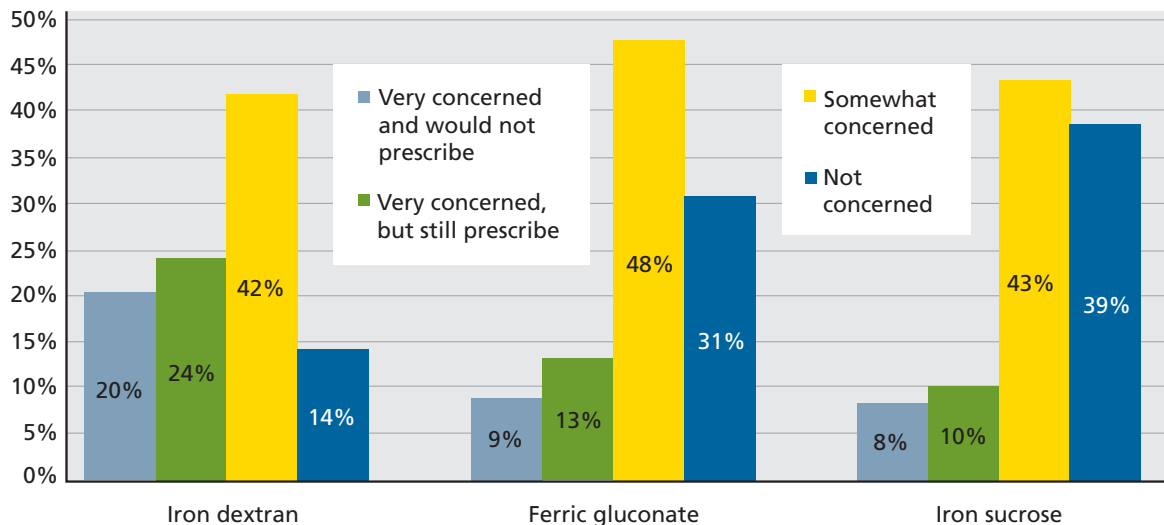


**Figure 12** Pharmacist perspective: factors accounting for suboptimal use of IV iron supplementation in oncology patients.

3 supplemental iron products listed, however, more than 40% of responding clinicians indicated that they were “somewhat concerned” about the risk of infusion-related reactions. Concern was generally lower for iron sucrose than for the other 2 products, falling in line with the pharmacy director survey that indicated more institutions used iron sucrose as their “preferred” supplemental iron product compared with iron dextran and ferric gluconate.

Among the pharmacy directors, policies surrounding ESAs were much more straightforward

than those for iron use. For example, all of the reporting institutions have a policy in place for discontinuation of ESAs after therapy is initiated. Some follow the ESA NCD guidelines, whereas others have multiple target points, including timelines and target hemoglobin levels that signal therapy should be discontinued. In most cases, these guidelines do not differ according to whether a patient is covered by Medicare or by another payor source, but 2 institutions indicated that their practices do differ for Medicare patients to ensure reimbursement accord-



**Figure 13** Practicing clinician perspective: rating level of concern for infusion-related reactions.

ing to CMS policies. One institution reported that it had attempted to put differential policies in place but no longer was doing so. Another institution had many different templates to accommodate use of ESAs in patients according to both payor and indication so that “various and inconsistent requirements” could be accommodated.

The pharmacy directors also commented on perceived differences between the approaches to anemia management in academic settings, such as NCCN Member Institutions, and those in the wider practicing community. Although some thought that approaches were “probably comparable” because of Medicare policy, others thought that academic physicians are “more cautious and concerned about potential tumor growth and adverse events from ESAs.” The perception was also that academic clinicians are “quicker to transfuse” because “the logistics are easier,” because blood products are in proximity to the clinic or hospital as part of the academic medical center, and access to laboratory services may also be easier. Several pharmacy directors mentioned the use of “strong” or “strict” guidelines for ESA use and stated that “the approach to the use of ESAs” has become “largely driven” by reimbursement concerns, including CMS and FDA regulations. Another said that hemoglobin levels are “tightly regulated” and that academic centers tend to give lower doses of ESAs compared with community practitioners. However, another pharmacy director thought that academic institutions had “a more liberal approach” without a “hard stop.” Although institutions have guidelines for ESA use, guidelines for “iron supplementation and transfusions are needed.” One pharmacy director stated:

“I think physicians in general are much more cautious/considerate about starting an ESA and tend to stop at 10 [g/dL], rather than 12 [g/dL] as previously done. We are seeing more blood transfusions here, and colleagues express the same trends at their institutions/practices. I know many places are using more [intravenous] iron. We are doing a better job at assessing iron as hemoglobin is dropping, but [doctors] are still more comfortable with oral iron when supplementation is needed.”

## Strategies for Operational Efficiency and Clinical Effectiveness in Anemia Management

Controversies surrounding the treatment of anemia in oncology populations are likely to become more common. Paradigms for ESA use in the United States and internationally may continue to diverge as coverage for their administration becomes further restricted in domestic markets. At the same time, pressure to use blood supplies efficiently and effectively remains a concern of blood bank managers and administrators who recognize the high cost of transfusions and blood management operations. Overall, transfusion should be seen as an essentially useful intervention but one that should be considered very carefully when possible because of the associated costs and potential risks to the patient. The following paradigms may serve as a course for improving processes surrounding anemia management in the cancer center while taking into account varying practice patterns.

### Implementing a Blood Products Management Program That Emphasizes Clinical Appropriateness and Operational Efficiencies

A robust blood products management program cannot be effective without both clinical and administrative “buy-in,” especially because any changes in blood products ordering or use is likely to significantly impact clinical practice. For example, in an institution in which clinicians routinely order 2 units of RBCs, a sudden policy shift to a 1-unit standard would likely lead to pushback from clinical teams. Before any revised blood products management program is implemented, a comprehensive audit of blood use should be conducted. This audit should examine elements such as reasons for transfusion orders, the number of units used by various clinical groups, the location and circumstances of transfusions (are patients being transfused in infusion room chairs?), and the supply/sources of blood products used at the institution.

Components of a successful policy include clinical input to identify target hemoglobin levels and transfusion trigger levels for various disease states and scenarios, policies regarding the number of units to be initially ordered, the number of activations that can be included in a single order, and guidance on timelines and expirations for orders. As examples from survey data, institutions were found to generally take 1 of 2 approaches to improve management

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of blood products ordering. One model restricts the ordering process at the front end, requiring orders to include reason for transfusion and limiting orders to few activations while allowing for orders with longer expiration times (and therefore reducing the need to write additional orders if a patient meets the same criteria again in a given period). The second model generally allows for more liberal ordering with multiple activations, for instance, but the orders usually expire with a much shorter period.

Apart from policies surrounding blood ordering, institutions may consider blood supply sources and programs to encourage local donation or allow for autologous donation when it might be clinically appropriate. However, autologous donation should be carefully considered to avoid significant numbers of patients donating blood that is never used. A strategy that includes autologous donation, perhaps in subsets of presurgical patients, must be closely monitored for waste, because some estimates indicate that as much as half of blood collected for autologous donation is wasted. Wider donation programs, such as those that encourage blood donations from institutional staff or family and friends of patients, may slightly reduce dependence on “imported” blood supply and therefore lead to lower costs. At the same time, the overhead for implementing a program like this or for the expansion of a donor center must be considered in the overall picture. For a program with limited space or other constraints, expansion of facilities for greater collection of blood products on-site may not be feasible or may negatively impact operations and revenue.

Lastly, because anemia is a clinical issue that involves medical, pharmacy, and blood bank stakeholders, any policy changes should be accompanied by educational components that use “change champions” across these multidisciplinary groups. As evidenced by comments that blood bank and pharmacies do not necessarily communicate in a routine fashion, even though cancer- and chemotherapy-related anemia crosses into both of these areas, educational initiatives that simultaneously engage these functions may improve efficiencies and reduce barriers to institutions’ process improvement efforts.

#### **Examining Policies for Supplemental Iron use and Identifying Areas Where Iron May Be Used Suboptimally**

Although clinical evidence supports the use of intravenous iron supplementation in an oncology context,

many clinicians remain resistant to routine ordering of iron, whether as an adjunct to ESA use or alone, or are forgetful of assessing patient iron stores. From the pharmacy perspective, missed opportunities exist in this arena. These shortfalls may be attributed to lack of knowledge and understanding of the benefits of supplemental iron, misconceptions about the safety of iron products (especially newer products vs. high molecular weight iron dextran), and long-standing practice patterns that did not include supplemental intravenous iron as a regular approach to anemia management in oncology. In institutions without policies or guidelines for supplemental iron use, clinical education and examination of current practices is a logical first step. Any discussion of supplemental iron use in oncology should involve clinical pharmacy and include consideration of available iron products and their safety profiles.

#### **Instituting Clearly Defined ESA Policies With Input From Medical, Pharmacy, and Reimbursement Teams**

Managing ESA reimbursement in an environment in which most payors are particularly scrutinizing the use of these costly products is an immediate challenge. Many institutions and practices have opted to build policies around Medicare criteria for coverage and reimbursement of ESAs because these are, in most cases, the most restrictive set of regulations, and doing so reduces the administrative burden of dealing with multiple policies. However, oncology practices that segment policies by payor and take payor policies into account on a patient-by-patient basis may have the flexibility to be reimbursed for ESA use that extends beyond what Medicare would pay for under the current coverage determination. Because many clinical guidelines are not as restrictive in recommendation as the Medicare NCD, segmenting approaches according to payor may allow physicians greater freedom to make decisions regarding ESA use based on clinical rather than financial criteria. Admittedly, this type of system can add considerable burden to the practice in administrative overhead.

#### **Adopting Nonpharmacologic Strategies for the Prevention of Anemia When Possible and Appropriate**

Although nonpharmacologic strategies for the prevention and reduction of anemia may have a modest impact, they are not resource-intensive and can

## Management of Cancer-Related Anemia

be adopted quickly. One example would be reducing the impact of diagnostic phlebotomy, especially in inpatient settings. The amount of blood taken for diagnostic phlebotomy can be reduced through extending the amount of time between draws when clinically appropriate, using smaller tubing (often pediatric sized), or using one tube for blood samples that can be used for more than one diagnostic test.

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## UNIVERSITY OF ALABAMA AT BIRMINGHAM

In 2007, the University of Alabama at Birmingham (UAB) Health System was the 4th largest purchaser of blood from the American Red Cross in the United States. At that time, the University Hospital needed to contract with 4 blood products suppliers to meet demand. The health system was also faced with semi-frequent shortages of blood products, necessitating prioritization of blood use within the hospital at those times. The heavy use of blood products and occasional shortages were not only causing a large expense but also increasingly frustrating operational challenges as the system struggled to meet demand.

When an analysis of blood products use at UAB showed that use had increased by more than 70% between 1997 and 2007, whereas the average national increase in blood products was substantially lower, leadership at UAB and the American Red Cross decided to take action to ensure blood products were being used efficiently and appropriately.

The occasional shortages of blood products gave UAB impetus to address the stability of the blood supply in the UAB Health System. The goals established were twofold: 1) decrease use through incorporating the increasing medical evidence showing that improved outcomes occur when a more conservative blood transfusion policy is adapted, and 2) conserve blood resources and increase local collections, thus decreasing the need to import blood from outside Alabama.

The Health System established several organizational principles in this effort, including education of clinicians/prescribers, a multidisciplinary/multimodal approach, an attention to detail that borrowed from process improvement, use of evidence-based guidelines and clinical best practices, patient safety/advocacy, and proactive patient management systems.

The American Red Cross acted as a partner in the UAB Health System's efforts to develop a comprehensive blood management program, facilitating a blood use audit and benchmarking report by an external consultant, Strategic Blood Management. The benchmarking

audit included data on blood use trends, blood use oversight, BloodStat benchmarking, blood bank operations, nursing practices, blood management systems, surveys of clinicians (including nurses and medical technicians), risk management, and finance.

The improvement process engaged key stakeholders to include not only top users of blood in the medical and surgical subspecialties but also nursing, blood bank, and laboratory personnel, perfusionists, and hospital administration.

One of the first steps in the improvement process was to negotiate a new contract with a blood vendor. As a result, UAB Health System reached an agreement that helped contain blood acquisition costs. A marketing collaboration aimed at increasing donations was also arranged with the American Red Cross.

As a part of this arrangement, the UAB Health System agreed to provide optimal space within their hospital complex for a new American Red Cross donor center. Location was paramount to the success of the new blood donation center at the hospital. It was positioned in one of the newest and most heavily used wings of the hospital complex. Most visitors pass the center coming to and from parking areas, and it is strategically placed adjacent to retail establishments to which coupons are given as incentive for blood donation. Additionally, a center advocate personally recruits family members from the surgical waiting rooms.

Although visitor donations are strongly encouraged, UAB Health System believes that its employees will be critical to the long-term success of the program. Additionally, UAB exceeded target goals for units donated by employees over the past year. Champions within individual departments are being identified, and barriers to donation have been limited through encouraging donations while on shift, extending the donor room hours, and expanding the donor room by 2 beds. Individual incentives are also provided through a program called UAB TouchPoints.

The primary goal in the development of UAB's

Timeline	2007				
	JULY/AUGUST	OCTOBER	NOVEMBER		
	Strategic Blood Management Group site visit and audit	Blood audit report received and presented	Medical and surgical Grand Rounds, 10 additional departmental presentations	Blood implementation plan received and "Capstone" seminar to engage stakeholders	Blood donor center completed

## Case Study

## Appendix A

blood management program was to ensure that every unit of blood transfused is appropriate. A 1999 study published in *The New England Journal of Medicine* showed that a restrictive transfusion approach, adopting a goal of transfusion for hemoglobin of 7.0 g/dL with a goal to maintain the hemoglobin between 7.0 and 9.0 g/dL, was as effective as and possibly superior to a more liberal transfusion policy (hemoglobin 9.0-12.0 g/dL). Despite this, a 2005 survey of critical care specialists showed that 40% of physicians still adhered to a general practice of transfusing to hemoglobin of 10.0 g/dL. Although these studies are not specific to oncology, the Health System used this literature to help formulate its policy for all specialties of practice.

A key component of the program was changing the criteria under which red blood cells (RBCs) could be ordered. As part of this effort, ordering policies attempted to shift clinicians away from the “2-unit custom,” wherein 2 units of packed RBCs are often initially ordered. A new policy stated that RBCs should be ordered as single units for most inpatient indications under a “transfuse and reassess” strategy, excepting patients with ongoing blood loss or hemodynamic instability. Critically ill patients, including those who were postoperative, were to be transfused with RBCs only if the hemoglobin decreased to within a range of 7 g/dL, and the target for hemoglobin maintenance in these patients became 7 to 9 g/dL.

Patients, clinical staff, and providers were educated about potential transfusion risks, with the more common and/or serious potential risks associated with infusion emphasized over those that are less common and/or lower-risk. This approach helped mitigate patient concerns regarding rare adverse events, such as infection with HIV, hepatitis B, or hepatitis C. As an example, education materials indicated that a fever may occur with an incidence of 1 in 300 transfusions, and HIV or hepatitis C infection occurs with an incidence of 1 in 2 million. Other methods of reducing the need for transfusion included the use of smaller volume tubes for diagnostic phlebotomy and eliminating any subsequent diagnostic phlebotomies that may not be

immediately necessary, especially for patients who were already experiencing anemia.

As a result of these actions, UAB reduced RBC use by approximately 20% by the end of October 2009. Continuing reductions in RBC use also resulted in a 29% decrease in use by the end of the 2009 calendar year. RBC units transfused per discharge fell from 0.94 units between October 2006 and May 2007 to 0.84 units between October 2007 and May 2008, for a reduction of 11%. These improvements continue, and by the end of the 2009 calendar year, RBC units per discharge had fallen to 0.65 units per patient. Total blood products costs decreased from \$12.2 million in fiscal year 2005 to \$9.8 million in fiscal year 2008, for a total savings of \$2.4 million.

Providing education to clinicians regarding these policy changes and sustaining the effort through continued feedback and educational opportunities is ongoing. The plan for strategically managing the UAB Health System blood supply was first introduced to key stakeholders at a retreat session intended to address performance gaps and programmatic aspects of blood management. The retreat was designed to ensure that participants left with a clear sense of immediate and long-term action items. As the initiative was rolled out through the UAB Health System, CME talks were held to gain buy-in among clinicians. Further education came in the form of the creation and distribution of laminated cards that briefly outlined transfusion policies. After the new policies were implemented, a plan for disseminating feedback to clinicians was developed. Audits reviewed the use of RBCs, platelets, fresh frozen plasma, and other blood products. These data were reported to the blood utilization management committee, and reports were distributed to individuals with a letter to both the attending and the resident.

In the future, individual variances in blood product utilization among clinicians will be reported to Division Chairs and Program Directors. Other future initiatives include nursing education and audits, incorporating blood policies into standardized computerized order entry systems, increasing on-site donations of blood products, and improving preoperative anemia assessment.

2008			2009	
JANUARY	FEBRUARY	SEPTEMBER	(ONGOING)	
Launched donor recognition program	Reformation of blood utilization management committee	Employee blood program	Continuing education of clinical staff and management	Expansion of donor center