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PHARMACY PRACTICE NEWS

pharmacypracticenews.com

Special REPORT

FEBRUARY 2004

Developing Guidelines For Treating Cancer-Related Anemia

Introduction

Cancer patients frequently have anemia as a result of their disease or treatment. Anemia has a profound impact on quality of life (QOL)^{1,2} and is also a predictor of high cost of treatment.³ The introduction of erythropoietic agents in the early 1990s made it possible to treat anemia in most patients, especially those with mild to moderate levels of anemia. Several organizations have published best-practices guidelines for the use of these growth factors in order to maximize cost-effectiveness.^{4,5} However, each institution must set its own policies regarding the use of these agents. Here we will review the biology, causes, and treatment of cancer-related anemia, and then describe how 3 institutions developed guidelines for the use of erythropoietic agents to treat anemia in cancer patients. The anemia guidelines from the 3 institutions, as well as from other institutions, are available at the University Pharmacotherapy Associates Web site (www.UPA-LLC.com).⁶

Epidemiology, Biology of Anemia

Anemia has been reported to occur in 25% to 70% of all cancer patients, depending on the particular scale used and level of anemia reported. The highest has been reported in patients with colorectal and gynecologic tumors,^{7,8} and is more frequent in women than in men.⁷ Although mild to moderate anemia was once thought to be of little consequence and was rarely treated, in recent years it has become clear that even mild anemia can affect both clinical outcomes and QOL for patients with cancer.

Anemia can produce a range of symptoms, including palpitations, nausea, chest pain, headache, and impaired cognitive function. However, the most prominent symptom of anemia is fatigue,⁹ caused by a reduction in the delivery of oxygen to the cells and tissues of the body. Under normal circumstances, low levels of oxygen (hypoxia) stimulates the peritubular cells of the kidney to produce the endogenous hormone erythropoietin, which, in concert with cofactors such as iron, folic acid, and vitamin B₁₂, stimulates the differentiation and proliferation of red blood cell precursors in the bone marrow.¹⁰ The increased numbers of red blood cells then increase tissue oxygenation. Eventually this process is turned off by a negative feedback mechanism once the hypoxia is corrected.

Anemia is usually defined in terms of serum hemoglobin (Hgb) concentrations or hematocrit. The lower limit of the normal Hgb concentration varies somewhat among the definitions established by different organizations. Definitions from the World Health Organization and the National Cancer Institute are the most frequently used (Table 1, page 2).

Cancer-Related Anemia

The etiology of anemia in cancer patients is multifactorial. Metastasis of the tumor into the bone marrow can destroy stem cells or change the milieu of growth factors and cytokines that affect erythropoiesis.⁹ Cancer patients have been shown to have low erythropoietin levels in relation to their degree of anemia,¹¹ and may suffer from the "anemia of chronic disease" (ACD), a syndrome common to many diseases

Table 1. Grading Systems for Anemia

Severity	World Health Organization	National Cancer Institute
Grade 0 (WNL)	≥11.0 g/dL	WNL
Grade 1 (mild)	9.5–10.9 g/dL	10.0 to WNL
Grade 2 (moderate)	8.0–9.4 g/dL	8.0–10.0 g/dL
Grade 3 (serious/severe)	6.5–7.9 g/dL	6.5–7.9 g/dL
Grade 4 (life-threatening)	<6.5 g/dL	<6.5 g/dL

WNL, within normal limits: 12.0–16.0 g/dL for women, 14.0–18.0 g/dL for men. Adapted from reference 2.

that is due to the suppression of endogenous erythropoietin production and blunted erythropoiesis by inflammatory cytokines. Bleeding from a gastrointestinal insult, infections, or nutritional deficiencies can also be contributing factors. Since iron is a necessary cofactor for the production of red blood cells, an absolute iron deficiency can also limit erythropoiesis; however, anemia can occur even in the presence of adequate iron stores if the ability of the body to mobilize this iron is compromised, a condition called functional iron deficiency (FID). FID may be present in half of anemic cancer patients.¹² Serum ferritin and transferrin saturation (TSAT) levels reflect iron stores and iron delivery function, respectively, and should be routinely measured in cancer patients. However, it is important to remember that ferritin levels may be generally elevated in patients with ACD or other inflammatory conditions.¹³

As mentioned earlier, the myelosuppressive effects of chemotherapy and/or radiotherapy play a significant role in the development of anemia in cancer patients. Retrospective reviews have estimated that about 60% of cases of anemia in cancer patients occur during active chemotherapy. The incidence of chemotherapy-induced anemia (CIA) varies according to the inherent myelosuppressive activity of the agent(s). Platinum-based regimens have been reported to have the highest rates of CIA, secondary to their interference of EPO production, by damaging the peritubular cells in the kidneys.⁹ Also, the effects of combination therapy and repeated cycles are cumulative.² Radiotherapy to regions containing large amounts of bone marrow, such as the pelvis or spine, can be myelosuppressive and/or cumulative with concomitant chemotherapy.

Clinical Outcomes, Quality of Life

Improvements in cancer treatments have led to longer survival, in some cases transforming cancer into a chronic disease. As a result, there has been increased focus on QOL issues. A number of validated scales are available for measuring anemia-related symptoms, including the Linear Analog Scale Assessment (LASA), the Functional Assessment of Cancer Therapy–Anemia (FACT-An), and the FACT-Fatigue (FACT-F).¹⁴ Fatigue seems to have the largest effect on QOL.² Cancer-related fatigue can affect a patient’s ability to perform daily activities or to hold a job, and can lead to frustration or depression.^{1,2} Family members or caretakers are also affected.^{1,15} Often times, they will need to interrupt their own activities to help the patient or take the patient for treatment.

Anemia can also have significant clinical effects. The effectiveness of radiotherapy and some forms of chemotherapy is dependent on the production of oxygen-free radicals and may be limited by tumor hypoxia.^{7,16} In patients with cervical cancer, nadir Hgb levels seem to predict treatment outcome in patients receiving radiotherapy¹⁷ and chemoradiotherapy.¹⁸ At least one systematic review, by Caro et al, found that the overall risk of death (adjusted hazard risk ratio) was increased by 65% in anemic cancer patients relative to those without anemia.¹⁶

Treatment Options

Transfusion—and hematinic treatments—were once the only options for treating chemotherapy-related anemia. Throughout the 1970s, transfusions were given fairly freely. Inherent risks of transfusion, including infection, transfusion reaction, and immunosuppression, have become more apparent. In addition, the blood supply began to be viewed as a limited resource, and transfusions were limited to those with serious anemia (Hgb <8 g/dL) and/or who showed physiologic symptoms such as tachycardia or dyspnea.^{2,4} The introduction of epoetin alfa in the early 1990s provided a pharmacologic option for the treatment of anemia in cancer.

Epoetin alfa is a recombinant molecule that is chemically identical to endogenous human erythropoietin. Epoetin alfa is distributed in the United States under 2 brand names, Epogen (Amgen) and Procrit (Ortho Biotech). Epoetin alfa was approved by the US Food and Drug Administration (FDA) in 1993 for use in nonmyeloid malignancies, after an earlier indication for use in chronic renal disease.

In 2001, a second erythroid growth factor (EGF), darbepoetin alfa (Aranesp, Amgen), was approved by the FDA for use in anemia associated with chronic renal failure. Darbepoetin alfa is a recombinant molecule that is very similar to epoetin alfa, but contains 2 additional carbohydrate side chains and 8 additional sialic acid residues. These modifications increase the molecule’s biological activity and half-life in the serum without changing its mechanism of action.⁹ Darbepoetin alfa was also FDA-approved for the treatment of chemotherapy-induced anemia in patients with nonmyeloid malignancies.

EGFs have been shown to be effective in increasing Hgb levels^{5,19,20}; reducing the need for transfusions in patients receiving chemotherapy⁴; and improving patient QOL.⁹ Studies have shown epoetin alfa and darbepoetin alfa to be therapeutically equivalent at standard doses in most patient populations.^{21,22}

Developing Guidelines for EGF Use

EGFs are among the most commonly used drugs in oncology centers. Several organizations—including the National Comprehensive Cancer Network (NCCN) and, jointly, the American Society for Clinical Oncology (ASCO) and the American Society of Hematology (ASH)—have developed evidence-based guidelines for the use of EGFs through evaluation of published reports of clinical outcomes and evolving standards of practice.

Whereas the goal of these organization-based guidelines is to assess the balance of evidence to determine best treatment practice, additional needs are reflected in the guidelines developed by individual healthcare institutions. These institution-specific guidelines have been developed to: 1) identify anemic patients; 2) identify when to initiate therapy; 3) dose the agent(s) appropriately; 4) institute monitoring parameters while on therapy; and 5) identify those patients who need dose modification or discontinuation. Practitioners must also understand the institution’s particular policies and regulations.

Because anemia is so common in cancer patients, Hgb concentrations should be measured routinely. Physiologically, the normal homeostatic response increases endogenous erythropoietin production as hemoglobin levels drop below 12 g/dL. This value of 12 g/dL also appears to be optimal for patient QOL.⁴ However, the organizational guidelines differ somewhat on when to initiate treatment. The NCCN recommends considering EGF therapy when the Hgb concentration is between 10 and 11 g/dL, whereas the ASCO/ASH guidelines do not recommend therapy until the Hgb concentration drops below 10 g/dL or in symptomatic patients where the Hgb is between 10 g/dL and 12 g/dL. Comorbid conditions, such as cardiovascular or pulmonary disease, should also be taken into account, as anemia presents a greater risk to patients with these conditions.²³ Before EGF therapy is started, the causes for the anemia other than disruption of erythropoietin production should be considered. For example, EGF therapy is not appropriate for treating iron deficiency anemia, other nutritional deficiencies, or chronic bleeding. If FID is suspected, treatment with intravenous iron may alleviate the anemia, avoiding the need for an EGF.¹²

If an EGF is deemed appropriate, a decision has to be made about which one to use. Because epoetin alfa and darbepoetin alfa are considered therapeutically equivalent in the oncology patient, the decision is usually based on cost or convenience. Currently, darbepoetin is not FDA-approved for use in myeloid malignancies, such as myelodysplastic syndromes (MDS), or for use in patients with human immunodeficiency virus (HIV) or the surgical patient. Therefore, each institution must decide on which EGF(s) to have on formulary, for which indications to use them, and whether one EGF is preferred over the other.

Once an EGF has been chosen, there is the issue of dosing. Package labeling recommends that epoetin alfa initially be given 3 times a week and darbepoetin alfa be given once weekly.²⁴⁻²⁶ However, the standard of practice is to use epoetin alfa in a weekly dose and darbepoetin alfa every 2 weeks for outpatient therapy and weekly for inpatient therapy; other schedules are under investigation.^{27,28} These practices reflect an evolving standard of care, which is supported by a growing body of data from clinical trials and retrospective reviews, as well as the new NCCN guidelines.⁴ Flexible dosing schedules may increase compliance, as frequent injections can present a burden to patients or caregivers.¹⁵

Deciding when to adjust or suspend care is another important issue. Studies of EGF therapy in patients with chemotherapy-induced anemia report response rates of 61% to 84%. Response is defined as either an increase in hemoglobin of 2 g/dL from baseline or hemoglobin correction to >12 g/dL.^{20,29-31} The first step should be to identify, if possible, the reason for the lack of response. Iron levels should always be a first consideration in this regard, because the EGF treatment, and the resultant burst of erythropoiesis, can itself deplete iron stores or outpace the ability of the body to mobilize the stores. Serum ferritin and TSAT levels should be measured during therapy, and if they are low, oral or intravenous iron supplementation should be started. If an iron deficiency is not the problem, the dose might need to be escalated, although it is important to note that there can be a lag of several weeks between the initiation of EGF therapy and an increase in Hgb concentration or an improvement in symptoms.^{25,26} Finally, if the patient does not respond after 4 to 6 weeks at an increased dose, EGF treatment should be discontinued, as it is an ongoing expense that is unlikely to provide any benefit.⁵ Treatment should also be adjusted if the Hgb concentration rises too quickly (≥ 1 g/dL in 2 weeks) or becomes higher than 12 g/dL.²⁵ A too rapid rise in Hgb may lead to an increase in adverse cardiovascular events.

In the following sections, the anemia treatment guidelines of 3 institutions are profiled. An emphasis is placed on how the guidelines were developed, implemented, and assessed in light of clinical and economic outcomes and evolving standards of care.

SAINT BARNABAS HEALTH CARE SYSTEM, NEW JERSEY

The Saint Barnabas Health Care System (SBHCS) is the largest healthcare system in New Jersey, with 9 acute-care hospitals (3,900 beds) and 9 long-term care facilities (1,500 beds). Each of the 9 acute-care hospitals has its own formulary, but all are coordinated by a Central Corporate Pharmacy Director for Clinical Services, Robert Adamson, PharmD, and Corporate Pharmacy Biotechnology Fellow, Indu Lew, PharmD. The hospitals have hematology/oncology sections, and 5 have outpatient facilities.

Erythropoietic therapy had been identified as one of the 10 most costly drug expenditures in the Saint Barnabas system, and

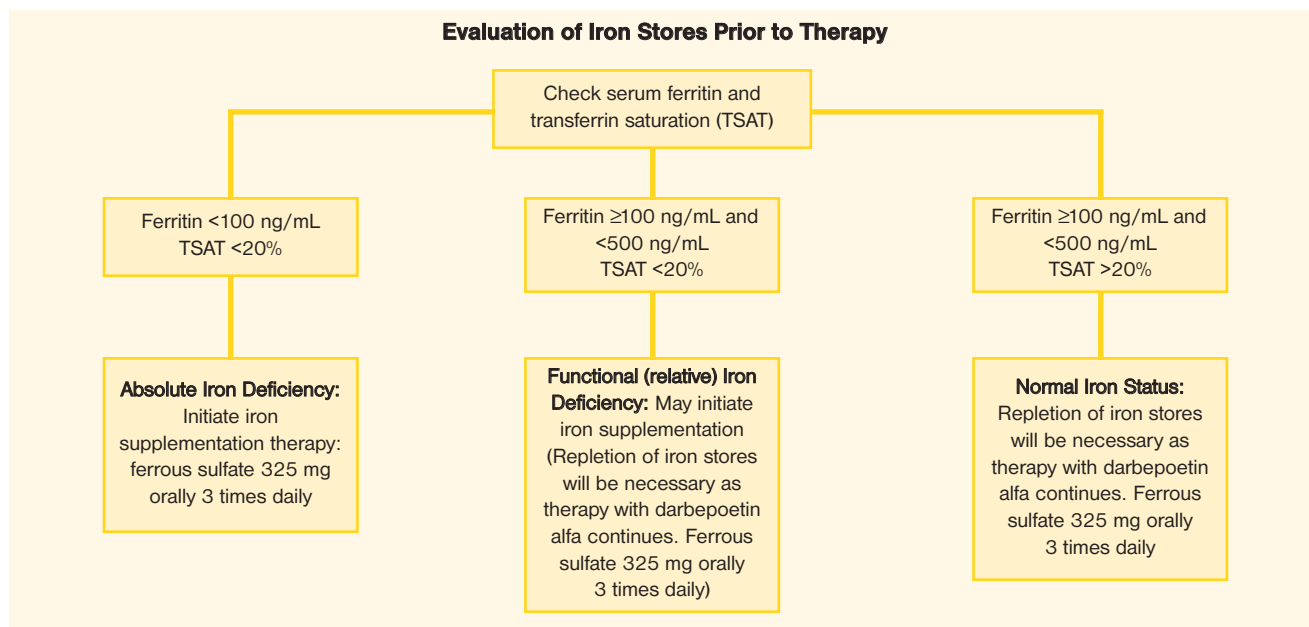


Figure 1. Saint Barnabas guidelines for evaluation and treatment of iron deficiency.

a study was initiated to determine whether epoetin alfa was being used appropriately. It was discovered that, in fact, many aspects of erythropoietic therapy were not being performed properly; for instance, physicians were not always prescribing concomitant iron when appropriate, nor were they routinely checking Hgb levels. Because no erythropoietic agent would work optimally under these circumstances, the guidelines were designed “to fix a process, not to select an agent,” according to Dr. Adamson.

The pharmacy staff at SBHCS made an early decision to include the end users of the guidelines in the development process. These end users, whether physicians, nurses, or pharmacists, need a compelling reason to change their practice, and are unlikely to adopt guidelines solely to fill a regulatory need. Furthermore, for these users “the buy-in is patient-centric, not economic,” said Dr. Adamson; that is, the quality of patient care is of the utmost importance.

When it became clear that current practice regarding EGF use was not up to the desired standards, the medical staff had a reason to participate in the process of developing guidelines. Information from clinical trials establishing the efficacy of a given EGF agent was important, but it was also important to the staff to see how it would work in *their* patient population. Therefore, SBHCS patients and practices were studied, and those writing prescriptions for EGFs were consulted as to what was working in the clinical setting and what was not. When such input was incorporated into the guidelines, they were more relevant to the staff and had a high degree of acceptance at their initial implementation.

One of the problems identified in the initial needs assessment was the inadequate testing for iron availability and use of iron supplementation. Because response to EGFs is dependent on adequate iron stores, specific guidelines for when to use iron supplementation were provided (Figure 1, page 3), along with an explanation of the rationale.

During the development of the guidelines, darbepoetin alfa was approved by the FDA for use in oncology patients. As a result, SBHCS decided to evaluate whether to use epoetin alfa or darbepoetin alfa as its primary EGF. Early on, caregivers needed to be convinced that they should even consider a switch in agents. However, the results of the study for the SBHCS patient population suggested that such a switch would be advantageous in terms of cost and the convenience of less frequent dosing.

Prompted by the findings from the study, SBHCS instituted new anemia guidelines in 2003, with darbepoetin alfa as the primary (preferred) EGF for oncology and nephrology patients. Epoetin alfa continues to be used in the outpatient HIV and hepatitis C clinics and for critical-care patients. In practice, however, critical care represents a very small portion—approximately 2%—of the population needing EGFs.

Separate but similar guidelines were developed for outpatient and inpatient treatment, and, importantly, they were linked. Having the nursing and pharmacy staffs checking the outpatient records to identify patients who had recently received an EGF in the outpatient setting prevents adverse events associated with overdosing and limits expenditures. However, dosing is slightly different for the outpatient and inpatient populations. In fact, what doses to recommend was one of the difficult issues in developing the guidelines, since actual practice varies considerably, said Dr. Lew.

The decision was made to initiate darbepoetin alfa 200 mcg subcutaneously (SC) every 2 weeks in the outpatient oncology areas. If the response is not adequate (Hgb increase <1 g/dL in 6 weeks, or Hgb <10 g/dL in the presence of adequate iron stores), the dose is raised to 300 mcg every 2 weeks. If this increased dose does not result in an increase of Hgb >1 g/dL, therapy is discontinued at week 12. Conversely, if there is an Hgb increase >2 g/dL in 2 weeks or less, the therapy is de-

creased to 200 mcg SC every 3 weeks. Therapy is withheld if the Hgb rises above 12 g/dL, and when the Hgb falls below 12 g/dL, therapy is restarted at 200 mcg SC every 3 weeks. Anecdotal and published evidence indicates that clinical practice is moving towards darbepoetin alfa 300 mcg SC every 3 weeks to match chemotherapy regimens.³²

For inpatients, an every-2-week dosing regimen is impractical, however, because the length of stay is usually less than 2 weeks. Therefore, the guidelines were adjusted to give darbepoetin alfa 100 mcg SC per week for inpatients, rather than 200 mcg every 2 weeks. However, Dr. Adamson said that before making any changes to the guidelines to reflect this practice, his department will evaluate the clinical evidence, the current practice within the SBHCS, and the associated outcomes.

The guidelines were introduced in the second quarter of 2003. The most important step in implementation was to provide scheduled lectures followed by question-and-answer periods. This training format gave the staff comprehensive education and a forum to address remaining questions and concerns. Although the core content of the education that was provided to each of the SBHCS facilities was the same, the presentations were tailored to focus on the areas of primary relevance for physicians, nurses, or pharmacists.

The SBHCS pharmacy is instrumental in enforcing the inpatient guidelines. Any medication order that is written for epoetin alfa is automatically converted to darbepoetin alfa, unless written justification by the physician is provided. Furthermore, the EGF order form has checkboxes for the physician to order iron supplementation, iron studies, and Hgb and hematocrit testing. The pharmacist is also provided with a form containing dose conversions from epoetin alfa to darbepoetin alfa, and a guide to the appropriate action to take in response to the laboratory values for iron and Hgb levels. Scripts are provided for the pharmacist to use when entering into discussions with the practitioner regarding appropriate anemia management. For example, pharmacists initiate dialogue with the physicians when patients are not on iron supplementation or discontinuation of the erythropoietic agents is needed, when the patient's Hgb exceeds 12 g/dL. All clinical interventions are documented. This system can also be used to track which physicians are not adhering to the guidelines, so that they can be provided with further education. As a result of the early input from caregivers and this tracking system, adherence is now almost 100%. A large cohort study is also being conducted to formally measure adherence.

Implementing these guidelines, as well as switching from epoetin alfa to darbepoetin alfa, has had a large impact on the treatment of anemia at SBHCS. Economically, the savings are on the order of \$147,000 per month, based on a comparison of purchases from the same month in the year before the switch. The savings have remained consistent from month to month and are due to darbepoetin's lower acquisition cost per dose when compared to Procrit. Furthermore, switching from an every-week or 3-times-a-week protocol with epoetin alfa to administering darbepoetin alfa once every 2 or 3 weeks has freed up practitioners to see more patients and perform other duties. The switch also has enabled SBHCS to offer a patient-friendly dosing schedule and has made it easier for patients to get an appointment with an oncologist, thereby improving patient care.

This was Saint Barnabas' second time using a guideline development process centered around the end user, and the first time for such a high-volume, high-complexity, high-cost product, but Dr. Adamson said he would do it again “in a heartbeat.” Although the process can be labor-intensive and tedious, he noted, in the end it was relatively easy to implement because prescribers did not have to be convinced to go along with it.

To that end, Dr. Adamson's advice is to "please tell the people why!" Study the problem and explain the rationale for the guidelines, he said, and then give the end users feedback on how the guidelines are working and how well the staff is implementing them. Also, said Dr. Adamson, conserve your energy. Too often a lot of information is thrown at the users in the first month of implementation, and then they hear nothing more about it. Periodic reminders and feedback about how the process is going keep everyone motivated and involved.

THE UNIVERSITY OF PITTSBURGH MEDICAL CENTER CANCER CENTERS

The University of Pittsburgh Medical Center (UPMC) Cancer Centers have 42 offices in southwestern Pennsylvania and Ohio. Although the outpatient practice is composed primarily of private practice physicians, there are hospital-based clinics as well as university-affiliated physicians within the network. UPMC Cancer Centers include 80 medical oncologists/hematologists, seeing approximately 25,000 to 30,000 newly diagnosed cancer patients per year, making it one of the largest centers in the country.

Erythropoietin-stimulating agents are the No. 1 drug expenditure within UPMC Cancer Centers, as they are in many healthcare

facilities. The need to control costs and to ensure appropriate use of the agents prompted UPMC Cancer Centers to revise their guidelines on EGFs 4 years ago. Approximately 90% of EGF usage occurs within the physician offices and hospital-based clinics. Thus, separate inpatient and outpatient guidelines were devised.

One concern about the use of EGFs within UPMC Cancer Centers was that iron stores were not being measured as often as required. In part this was for logistical reasons: in the outpatient setting these tests have to be sent to outside facilities, greatly increasing the time before the results are available. For this reason, the evaluation of iron stores is emphasized in the dosing guidelines (Figure 2), and intravenous or oral iron replacement is recommended until serum ferritin and TSAT levels are within normal limits. It is also recommended that Hgb concentrations be measured at 6 weeks and 8 weeks so that doses can be adjusted if necessary and nonresponders can discontinue therapy.

The guidelines were developed centrally by the Director of Pharmacy Operations, John Mucenski, PharmD. One of the private practice groups within UPMC Cancer Centers is a member of US Oncology, a publicly traded company that includes more than 850 oncologists in 30 states.³³ US Oncology had developed guidelines for using darbepoetin alfa. These guidelines were

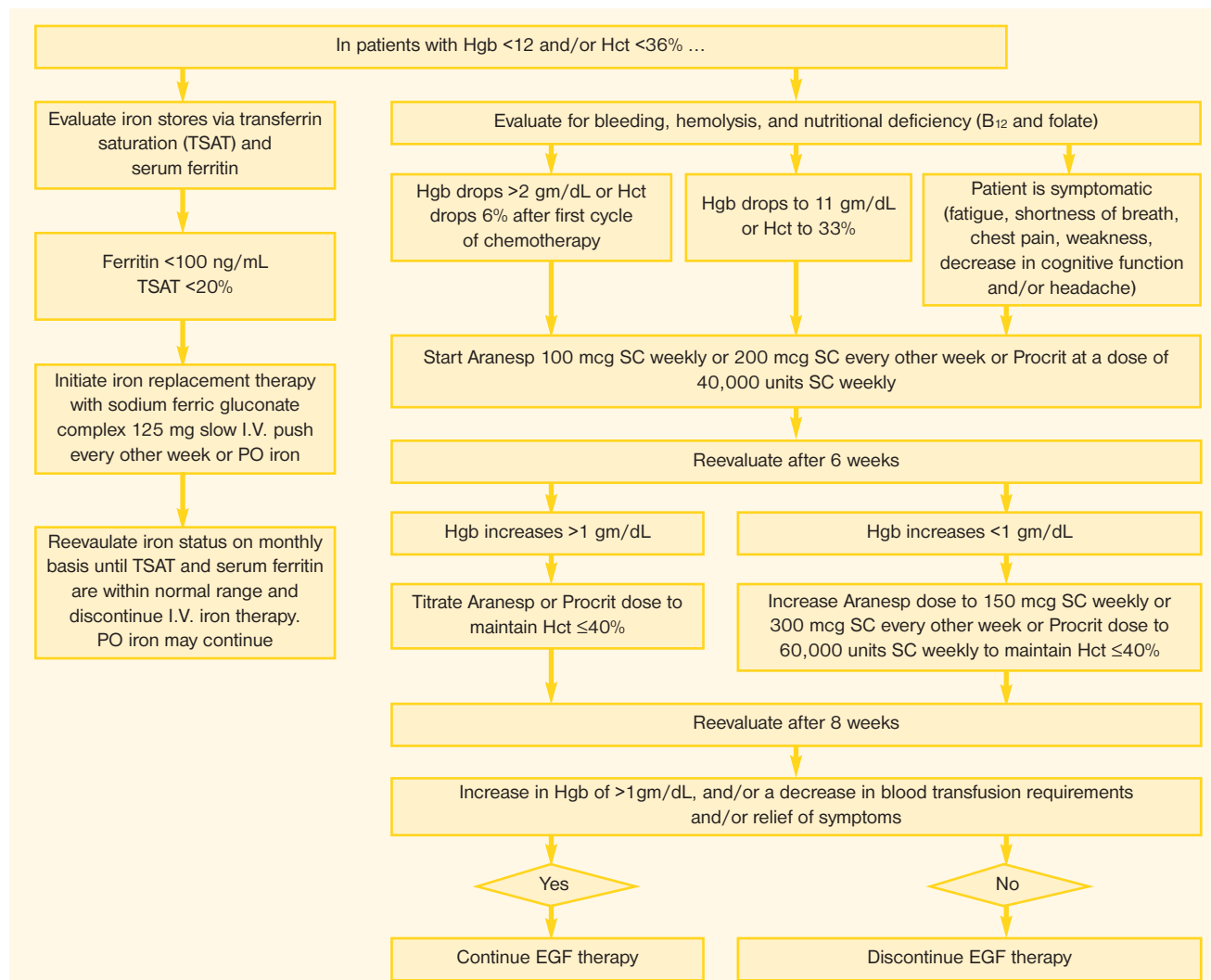


Figure 2. Erythropoietin (Aranesp/Procrit) dosing guidelines for the University of Pittsburgh outpatient cancer care.

based on the darbepoetin alfa package insert, which suggests that the minimally effective dosage of the agent is 1.5 mcg per kilogram per week. Dr. Mucenski used these guidelines as a starting point for the UPMC Cancer Centers guidelines. One goal was to keep the guidelines simple and easy to follow in the outpatient setting. The draft guidelines were reviewed and approved by the physicians on UPMC's Joint Policy Board. Once approved, the guidelines were disseminated at a quarterly physicians' meeting and then e-mailed to the physicians. Reminders were sent out periodically for 6 months.

The UPMC Cancer Centers were among the first institutions to approve guidelines for switching patients to darbepoetin alfa from epoetin alfa on an outpatient basis. There was some initial resistance from the oncology staff, due to concerns over the maturity of the literature supporting every other week darbepoetin dosing. However, darbepoetin alfa was chosen as the preferred agent for 3 reasons: the clinical evidence; convenience for patients and physicians; and, in a minor role, pharmacoeconomics.

Clinically, the data from the SOAR (Successful Outcomes in Anemia Research) trial were particularly influential, in part because of the large number of subjects (n=1,173). Data from this open-label trial support the effectiveness of darbepoetin alfa given every 2 weeks in improving physiological and QOL measures.²⁰ Eighty-four percent of patients taking darbepoetin alfa had a hematopoietic response, defined as a rise in Hgb concentration of at least 2 g/dL or attainment of Hgb \geq 12 g/dL, and the need for transfusions decreased by 64%.²⁰ Improvement was also seen in measures of fatigue and energy, and these improvements correlated with increases in Hgb levels.²⁰

The administration of darbepoetin alfa once every 2 or 3 weeks is also more convenient for both patients and physicians than the weekly or thrice-weekly dosing of epoetin alfa, according to James Natale, PharmD, a Clinical Pharmacy Specialist at UPMC. Indeed, one of the major benefits of the switch to darbepoetin alfa has been the "decompression" of the offices—that is, a freeing-up of physicians, nurses, and office staff to perform other essential duties, Dr. Natale noted. Additional benefits included increased convenience for the patient by synchronizing the administration of chemotherapy and EGFs. The switch also reduced the strain on the patient's family or other caregivers, who may have to take a day off of work every time the patient needs to come into the office for an injection.

Acceptance of the guidelines by physicians at the UPMC Cancer Centers was helped by presenting them as "guidelines, not commandments," Dr. Mucenski said. Although darbepoetin alfa is listed as the preferred agent, physicians are free to choose whichever drug they feel is most appropriate for their patient. Also, there is flexibility in the guidelines for prescribers to choose weekly or every-2-week dosing of darbepoetin alfa. Research into synchronized dosing of darbepoetin on an every-3-week schedule with chemotherapy is currently under way.

Adherence to the guidelines isn't formally monitored, in part because the UPMC Cancer Centers lacks the staff to do so, but Dr. Natale said that he has not gotten any negative feedback on the guidelines from the physicians. Furthermore, any unusual EGF usage, such as a patient on a particularly high dose, is usually caught by the billing office. This information can be used to track aberrant dosing patterns and to follow up with additional education for these prescribers.

According to Drs. Natale and Mucenski, positive feedback from patients regarding the decreased frequency of darbepoetin administration probably helped to smooth the transition to the newer EGF. Now that the guidelines are in place, more physicians are conducting iron studies to ensure maximal effectiveness of these agents, and more patients are being discontinued from EGFs when their Hgb concentrations are

sufficiently high, or if they are nonresponders. Thus, by focusing on clinical data and patient convenience, it is possible to influence prescribing patterns.

HUMILITY OF MARY HEALTH PARTNERS, OHIO

The Humility of Mary Health Partners (HMHP) runs 2 facilities in Ohio. St. Elizabeth Health Center, in Youngstown, Ohio, is a tertiary, teaching, Level 1 trauma center with an average census of 356 patients. St. Elizabeth has a small outpatient oncology service, with 2 oncologists who see 15 to 30 patients daily. St. Joseph Health Center, in Warren, Ohio, is a community teaching health center with an average census of 117 patients. St. Joseph has a significant outpatient oncology service, with 5 oncologists who see 30 to 40 patients daily. Most of the EGF use within HMHP takes place at the St. Joseph Oncology Service.

The Pharmacy Director, Barry Shick, MS, RPh, played a central role in the development of HMHP's anemia guidelines, which were introduced in 2003 after 10 months of development. In this institution, pharmacoeconomics was one of the driving forces behind the new guidelines.

In 2002, epoetin alfa was the No. 1 drug expenditure for HMHP, at \$1.1 million. Darbepoetin alfa was also available, although it was only indicated for use in patients with chronic renal failure and was not competitively priced. However, a 3-month trial was planned for the inpatient dialysis unit to test the clinical use of darbepoetin alfa within the HMHP system; the results were compared with historical records of epoetin alfa use. This trial, which ran from November 2002 through January 2003, found that darbepoetin alfa was safe, effective, and therapeutically equivalent to epoetin alfa in this population with renal failure. Just over half of patients in both groups were discharged with Hgb \geq 11 mg/dL (53% for darbepoetin alfa vs 51% for epoetin alfa), and 21% of patients receiving darbepoetin alfa needed blood transfusions, compared to 37% of those receiving epoetin alfa. No adverse events were seen in the darbepoetin alfa group. In addition, there was increased compliance with the darbepoetin alfa dosing schedule relative to the epoetin alfa schedule, and average cost savings of 38% were achieved.

Several other notable events occurred during the planning and implementation of the nephrology trial. In July 2002, darbepoetin alfa received an indication for use in oncology. Also, clinical data were emerging that showed equivalence for epoetin alfa and darbepoetin alfa in cancer patients,^{22,34} and in

Table 2. Humility of Mary Health Partners Therapeutic Interchange for Darbepoetin Dose* in Chemotherapy-Induced Anemia: A Modified, Weight-Based, Fixed-Dose Algorithm

Patient's Weight	Every-1-Week Dosing @ 1.5 mcg/kg	Every-2-Week Dosing @ 3 mcg/kg
<55 kg	80 mcg (2 x 40-mcg vials)	150 mcg/1-mL vial
55–90 kg	100 mcg/1-mL vial	200 mcg/1-mL vial
>90 kg	150 mcg/1-mL vial	300 mcg (2 x 150-mcg vials)

*The above oncology darbepoetin doses are initial dosing recommendations that may vary based on the patient's clinical needs. Depending upon each patient's needs and response, dosage adjustments (up or down) may be required after 4 weeks of initial therapy. Based on the patient's response, darbepoetin may be administered as infrequently as once every 3 or 4 weeks.

November 2002, the CMS determined that epoetin alfa and darbepoetin alfa are “functionally equivalent” and would be reimbursed accordingly.³⁵ Then, in December 2002, Amgen Inc. came out with competitive pricing for darbepoetin alfa.

EGF guidelines were developed for inpatient and outpatient groups, and for nephrology, oncology, surgery, and critical care. The heart of the guidelines is a therapeutic interchange, which allows for easy switching between epoetin alfa and darbepoetin alfa. A fixed-dose conversion of 400 units epoetin alfa:1 mcg darbepoetin alfa is used for weekly dosing in most nonnephrology patients, but the guidelines for chemotherapy-induced anemia are based on a modified, weight-based, fixed-dose algorithm, with lower doses for patients under 55 kg, and higher doses for patients above 90 kg (Table 2, page 6). There is flexibility for the physician to use weekly or every-2-week dosing or to adjust the dose up or down. To date, few physicians have gone to every-3-week schedules. Inpatient therapy is typically prescribed for administration on a weekly dosing schedule.

In February 2003, following completion of the nephrology study, the new guidelines went to the Pharmacy and Therapeutics (P&T) Committee for review. Because the guidelines had the support of oncologists and the data from the nephrology study,

they were approved by the P&T Committee in March, and by the Medical Executive Committee in April 2003.

The guidelines (Figure 3) recommend dosing of 1.5 mcg/kg every week or 3 mcg/kg every 2 weeks, with a dose increase of 50% for nonresponders (ie, for those who don't have an increase of ≥ 1 g/dL Hgb after 5 weeks). Dose escalation is an issue that needs to be considered in cost evaluations; however, only 10% to 20% of patients in this institution actually receive the higher doses.

A crucial step in developing and implementing the guidelines was to pull together the published data to show to the physicians and the approval committees. The recent reports of clinical trials and the endorsement of the CMS of the equivalence of epoetin alfa and darbepoetin alfa provided important support for switching to darbepoetin alfa, and the HMHP pharmacy was able to argue for the use of darbepoetin alfa in patients other than those in the nephrology and oncology services, such as for those in intensive care, cardiology, and surgery. The nurses in particular were concerned whether the dosing suggested by the guidelines was appropriate, because they recommended dosing at 1.5 mcg/kg per week, whereas the package insert recommends 2.25 mcg/kg per week. However, the nurses accepted the lower

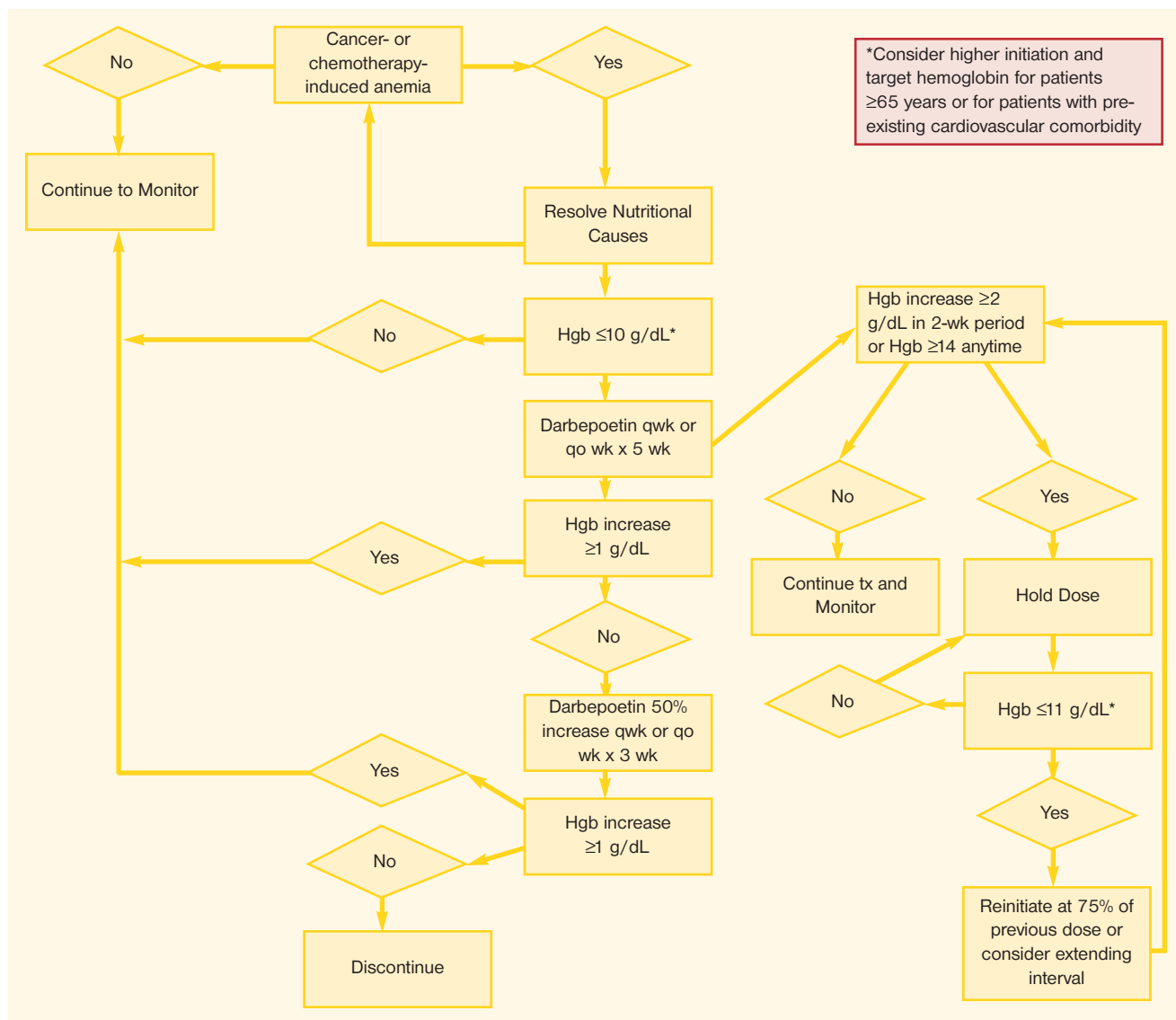


Figure 3. Humility of Mary Health Partners anemia therapy flowchart.

initial dosing when shown that it is supported in the literature.^{34,36}

To implement the guidelines, the Clinical Pharmacy Department sent representatives to the cancer care centers to provide in-services for the nurses and physicians reviewing the evidence on the costs and benefits. Costs were a major area of concern for the end users, in part because conflicting information was provided by the representatives of different drug companies. The nurses also expressed a concern about loss of revenue. Revenue from injections goes directly to the nursing department, and switching from once-a-week or thrice-weekly injections of epoetin alfa to every-2-week injections of darbepoetin alfa might have significantly reduced this source of income. However, when they became aware that expenses would also be reduced, with savings realized in the department and passed on to the patients, the nurses came on board. "Once nurses and physicians are all on the same page, everything works well," Mr. Shick said.

To aid with compliance, epoetin alfa was pulled from the cancer care centers and was made available only in the pharmacy. Now 98% of prescriptions for EGFs are filled with darbepoetin alfa. It is still possible to prescribe epoetin alfa, as long as the prescription specifies "dispense as written," and epoetin alfa remains the preferred drug for use in patients with MDS, and for Jehovah's Witnesses, because the formulation of darbepoetin available in the United States contains albumin, a

human blood product. An additional switch was made from using vials to using prefilled syringes, which is appealing to patients because of the smaller volume of injection.

The impact of the guidelines on the HMHP has been primarily economic. At St. Joseph's the prescribing volume has increased 30% without any concomitant increase in cost; at St. Elizabeth's the savings are about \$14,000 per month. The switch to darbepoetin alfa is one of the main reasons why the HMHP was able to meet its budget this year, Mr. Shick said, and because epoetin alfa and darbepoetin alfa provide equivalent patient outcomes, there has been no negative impact on patient care.

Conclusion

Anemia is a frequent and serious complication of cancer and cancer therapy, but it can be effectively treated with erythropoietic agents. Outcomes can be improved within individual institutions by assessing current practice, identifying clinical and economic needs, and working to develop institutional guidelines that best meet the needs of the pharmacy staff, practitioners, and patients.

Additional guidelines examples have been posted by University Pharmacotherapy Associates, LLC, an independent consulting and continuing education organization, at www.UPA-LLC.com.

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