


WATCHTOWER
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TO ALL HOSPITAL LIAISON COMMITTEES

Re: Updated information on use of ESAs and blood thinners

Dear Brothers:

We have received a number of technical inquiries regarding the safety of erythropoiesis-stimulating agents (ESAs) and also on reversal agents for anticoagulant agents or blood thinners. ESAs include all current forms of erythropoietin, such as epoetin alfa, epoetin beta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta. This letter provides current information on these two subjects.

Erythropoiesis-stimulating agents (ESAs): According to the medical literature, use of ESAs in the setting of chemotherapy-induced anemia helps to avoid blood transfusion and improves the functional status or quality of life of many cancer patients. However, in recent years clinicians have become hesitant to prescribe ESAs because of evidence that they increase the risk of thromboembolic complications (obstruction of blood flow in arteries by blood clots) in patients regularly receiving the drug for prolonged periods (e.g., those with kidney disease, cancer, or chronic illness). Moreover, in cancer patients, several studies suggest that ESAs may increase tumor progression or cancer recurrence and mortality, particularly those patients not on chemotherapy. Although the evidence is controversial, studies suggest there may be an elevated risk of using ESAs in patients with breast cancer, head and neck cancer, non-small cell lung cancer, uterine cervix cancer, or various lymphoproliferative malignancies or mixed nonmyeloid cancers when dosed to target hemoglobin levels greater than 12 g/dL (120 g/L) in patients on chemotherapy. Clinicians in many lands will not administer ESAs to patients who are not on chemotherapy. Most regulatory agencies have published revised guidelines regarding the use of ESAs, placing restrictions on their use in oncology as well as chronic kidney disease (renal failure) patients.

On the matter of thromboembolic complications, most authorities recommend that patients receiving ESAs who have an elevated risk for thrombosis or thromboembolism (e.g., cancer patients, those of advanced age, patients with a history of blood clotting disorders) should receive appropriate thromboprophylaxis using products such as unfractionated heparin, low-molecular-weight heparin, fondaparinux, or warfarin. Regarding patients in intensive care units at risk for bleeding, see section 2.C.1.a.-d. entitled “Cautious Thromboembolic Prophylaxis” in *Clinical Strategies for . . . Critically Ill Patients*.

Regarding use of ESAs in oncology, listed below are talking points from medical articles that may be helpful when you speak to doctors regarding the care of our brothers. These articles also discuss the safety and appropriateness of using ESAs up to a target hemoglobin of 12 g/dL in patients on chemotherapy, which is in accordance with guidelines set forth by leading professional oncology organizations (e.g., EORTC and ASH/ASCO).

- Cantrel and coauthors¹ concluded there was no correlation between ESAs and the rate of ovarian cancer progression or survival in patients who received ESAs within guidelines.
- Calabrich et al² reviewed the evidence and determined that when ESAs are used within current guidelines, they are valuable and safe drugs for anemia management in patients receiving radiotherapy and/or chemotherapy.
- A large meta-analysis study by Glaspy and co-investigators³ found no significant effect on mortality or disease progression with or without administration of ESAs. The mechanism behind the ESA-associated adverse events in some studies is unclear. Great variation exists in the progression endpoints measured and in the quality, consistency, and frequency of tumor assessments.
- Glaspy⁴ notes that the study by Bohlius (on which the ASH/ASCO [American Society of Hematology/American Society of Clinical Oncology] guidelines are based) focused on study mortality (that is, deaths during active treatment) as opposed to overall survival for the entire period following study enrollment, which included follow-up. Patients were included whether they received chemotherapy or did not.
- Aapro and coworkers⁵ state: “Although the safety of ESAs is being debated, there are no prospective randomized trials that have adequately tested blood transfusions as an alternative approach.” Although eight clinical trials of ESAs in oncology raise concern, the authors observe that these studies “have deficiencies and limitations in their design.”
- In a meta-analysis of the data, Aapro and colleagues⁶ conclude that ESAs in cancer patients showed no evidence for a significantly negative effect on survival or tumor progression.
- Arcasoy⁷ states there is no conclusive evidence that ESAs directly promote cancer progression.
- Allogeneic blood transfusion is associated with adverse effects in cancer patients.^{8,9}
- Calabrich and coauthors² state: “Blood transfusion is not a proven safe alternative to ESAs, as comparative studies have not been performed and, in contrast to ESAs, little is known about the potential long-term side effects.”

In Witness patients, and particularly those not receiving ESAs, anemia can be addressed through minimization of blood loss (i.e., restriction of phlebotomy for laboratory testing, blood conservation during surgery, prompt control of tumor-associated bleeding) and correction of nutritional deficiencies (e.g., iron, folic acid, vitamin B₁₂, or malnutrition).

Iron-restricted erythropoiesis, due to reduced iron stores or diminished access to storage pools, is frequently present in patients with cancer. There is evidence that intravenous (parenteral) iron may be more effective than oral iron in addressing absolute or functional iron deficiency. Intravenous iron preparations with a more favorable safety profile than the early high-molecular-weight iron dextran products have increased interest in the role of parenteral iron in managing anemia in patients with cancer.^{10,11,12} Intravenous iron is used alone or in combination with ESAs to treat anemia associated with cancer.

Preoperative ESA therapy continues to be associated with well-documented benefits to anemic surgical patients. There is relatively low risk of thromboembolic complications in otherwise healthy non-hospitalized patients scheduled for elective surgery.

Reversal of blood thinners: Anticoagulant and antiplatelet agents (so-called blood thinners) have been available for many years but are now more widely used than in previous years. Patients are given these drugs for various reasons. These drugs can lower the risk of a heart attack or a stroke by reducing the risk of formation of blood clots in blood vessels. Blood thinners are also given to patients who are prone to clot formation, have abnormal heart rhythms, have congenital heart defects, or have undergone heart-valve surgery.

For more than 50 years, warfarin (e.g., Coumadin[®]) has been used as an oral anticoagulant (tablet), but it requires regular blood tests to monitor the drug's effects. The effects of warfarin can be reversed with vitamin K and other agents, such as prothrombin complex concentrates (PCCs). Newer medications are equally (if not more) effective, and close monitoring is not required, which is convenient and reduces health care costs. Hence, the newer drugs, such as clopidogrel (Plavix[®]), rivaroxaban (Xarelto[®]), and dabigatran (Pradaxa[®]), have rapidly gained popularity among physicians and patients. For Witnesses, however, the main concern with these newer drugs is the lack of known, specific agents to reverse their effects.

Nonetheless, many of these drugs are prescribed by physicians for Witness patients. Our brothers may be unaware that if there is an emergency, such as a life-threatening bleed or a condition requiring an operation, there is no known way to reverse or neutralize the action of some of these newer agents and subsequently there is a potential for life-threatening bleeding. Even for patients on older drugs that can be reversed, doctors will likely want to administer blood transfusions (plasma or platelets) as first-line treatment, as many doctors are not aware of reversal agents that exist for some of these anticoagulants or antiplatelet agents. In some cases, blood fractions have been effectively used to arrest the bleeding quickly. But some brothers may forget to make doctors aware of their position on blood transfusion and blood fractions early in their treatment. Other brothers may not have decided whether to accept blood fractions or not. Still others conscientiously refuse all fractions.

In reality, doctors may not always clearly communicate the risks and benefits associated with the use of medications, and thus our brothers may not be aware of the serious bleeding risk. Some may simply hope the bleeding risks of such blood thinning medications will never affect them.

We desire to bring this to your attention, since many brothers often seek the assistance of the Hospital Liaison Committee (HLC) in medical emergencies involving the blood issue. Of course, it is not expected that the HLCs will attempt to conduct a campaign to warn the brothers regarding these matters. However, HLC brothers need to be aware of the view that some doctors hold regarding erythropoiesis-stimulating agents and the side effects associated with the newer blood thinning agents, and they need to be ready to render assistance to our brothers as they are able. (Prov. 17:17) We refer you to the links of the abstracts of the articles listed below.

This letter has been added to the list of permanent policy letters. Please update the HLC *Index to Letters* (hlc-4) at this time. We want to assure you of our warm Christian love and support for all your good work.

Your brothers,


OF NEW YORK, INC.

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Reversal of Blood Thinners

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