Treatment Strategies for Myeloid Growth Factors and Intravenous Iron: When, What, and How?

Presented by Jeffrey Crawford, MD, and George M. Rodgers, MD, PhD

Abstract

Myeloid growth factors can reduce the risk of chemotherapy-induced neutropenia (CIN) and thus impact the survival of patients with cancer. Patients should be assessed for risk, taking into consideration patient-related risk factors and chemotherapy regimens. Patients stratified as having at least a 20% risk for CIN should be considered for prophylactic growth factors. The NCCN Guidelines for Myeloid Growth Factors provide category 1 recommendations for the daily use of filgrastim, tbo-filgrastim, and pegfilgrastim. Cancer-related anemia can be treated with erythropoiesis-stimulating agents, red blood cell transfusion, or intravenous iron. (*J Natl Compr Canc Netw* 2014;12:821–824)

Chemotherapy-induced neutropenia is hazardous for 2 reasons: it produces febrile neutropenia (FN), which may result in life-threatening infections and prolonged hospitalizations, and it can necessitate chemotherapy dose reductions and delays, which decreases the relative dose intensity of treatment. Both scenarios can be associated with reduced survival in patients with cancer, according to Jeffrey Crawford, MD, Chief, Division of Medical Oncology, Professor of Medicine, Duke Cancer Institute.

At the NCCN 19th Annual Conference, Dr. Crawford and George M. Rodgers, MD, PhD, Professor of Medicine, Huntsman Cancer Institute at the University of Utah, discussed the appropriate use of myeloid growth factors (MGFs) to prevent neutropenia and the value of using intravenous (IV) iron for cancer-related anemia.

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Preventing FN

FN, when brief and uncomplicated, has a low-risk mortality. However, the risk of death may increase to more than 20% in patients with major comorbidities.[1] Giving lower chemotherapy doses will reduce this risk. However, even relatively small differences in dose intensity (ie, 10%–15%) may impact survival outcomes in very chemosensitive settings.

Preventing neutropenia is important, beginning with the first cycle of chemotherapy. There are 2 main strategies for prevention: dose reductions and delays in chemotherapy, and the use of MGFs, which include granulocyte colony-stimulating factors (G-CSF; ie, filgrastim and tbo-filgrastim), granulocyte-macrophage colony-stimulating factors, pegfilgrastim, and biosimilars (not yet available in the United States).

An important change to the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia occurred in 2013, and was reinforced in the 2014 version: the addition of the first new growth factor in several years, the human G-CSF tbo-filgrastim, as a category 1 recommendation. Like other G-CSFs, tbo-filgrastim is indicated for reducing the duration of severe neutropenia in patients with nonmyeloid malignancies receiving my-

elosuppressive chemotherapy associated with a significant risk for FN. This recommendation was based on a recent summary of 4 studies in breast cancer, lung cancer, and non-Hodgkin lymphoma, which all showed tbo-filgrastim to be noninferior to filgrastim at numerous end points.[2]

Although tbo-filgrastim, filgrastim, and pegfilgrastim are all category 1 recommendations, prophylactic antibiotics are not routinely recommended for standard dose chemotherapy, Dr. Crawford said. They may lead to the development of resistant bacteria, and do not impact the depth and duration of neutropenia, which is the major risk factor for FN.

Risk Assessment Per NCCN Guidelines

Before the start of chemotherapy, patients should be evaluated for their risk of FN based on disease, patient risk factors, chemotherapy regimen and dose, and treatment intent (curative vs palliative). This stratifies patients into high-risk (>20%), intermediate-risk, (10%–20%), and low-risk (<10%) groups. The risk classification is then paired with the chemotherapy treatment intent to determine whether growth factors are warranted.

"These recommendations have not changed, but the level of evidence has changed somewhat," Dr. Crawford noted.

Patient-related risk factors are important and include older age (≥65 years); previous chemotherapy or radiation therapy; preexisting neutropenia, bone marrow involvement, infections, or open wounds; recent surgery; poor performance status; poor renal or liver function; and HIV infection.

A large prospective study by Lyman et al[3] in 2010 was helpful regarding individual risk assessment. In addition to the risk factors previously stated, risk was elevated in patients with small cell lung cancer (SCLC; vs other solid tumors), those on immunosuppressive treatments, and patients intended for full-dose chemotherapy. Alternately, the risk of FN was substantially reduced in patients who received primary G-CSF prophylaxis, Dr. Crawford said.

"From this real-world setting, we can tease out risk factors and identify the high- and low-risk populations. Approximately half our patients fall into the high-risk group," he said. These patients warrant prophylactic G-CSF in the first and all subsequent cycles of chemotherapy.

Lung Cancer: How I Manage Neutropenia

Dr. Crawford, a lung cancer specialist, described how he manages chemotherapy-related neutropenia in his patients. For patients with SCLC with limited disease receiving concurrent platinum and etoposide plus radiation therapy, he does not give growth factors because they can exacerbate neutropenia in this setting. He does administer growth factors to patients receiving chemotherapy cycles before or after radiation therapy (Table 1).

For patients with extensive SCLC, he prescribes primary prophylaxis to patients with a good performance status receiving platinum or etoposide, and to those with a poor performance status who also have a primary dose reduction. In the relapse setting, he gives primary prophylaxis for patients receiving topotecan and uses secondary prophylaxis or dose reduction when these patients receive other single agents.

For non-SCLC, age, comorbidities, and disease stage are important considerations in determining the need for growth factors (Table 2).

Using IV Iron for Cancer-Related Anemia

Dr. Rodgers discussed the use of IV iron to optimize erythropoietic growth factor therapy or to minimize the need for it. Cancer-related anemia can be treated

Table 1 Management of Chemotherapy-Related Neutropenia in SCLC

	Treatment	Prophylactic CSF
Limited SCLC		
PS 0–2	Platinum/etoposide and CRT	No CSF
	Platinum/etoposide before or after CRT	Primary
Extensive SCLC		
PS 0–1	Platinum/etoposide	Primary
PS 2	Initial dose reduction	Primary
Relapsed SCLC	Topotecan	Primary
	Other single agents (paclitaxel, vinorelbine)	Secondary or chemotherapy dose reduction

Abbreviations: CRT, concurrent radiation therapy; CSF, colony-stimulating factor; PS, performance status; SCLC, small cell lung cancer.

Table 2 Management of Chemotherapy-Related Neutropenia in NSCLC

	Treatment	Prophylactic CSF
Stage IB-IIIA NSCLC	Adjuvant platinum-based CT	
	Age ≤70, no comorbidities	Secondary
	Age ≥70 or comorbidities	Primary
Inoperable IIIA/B NSCLC	Concurrent platinum-based CT and radiation	No CSF
Stage IV NSCLC	Platinum-based chemotherapy	
	Age <70, no comorbidities	Secondary
	Age >70 or comorbidities	
	PS 0–1	Primary
	PS 2 (single agent)	Dose reduction
Relapsed NSCLC	Docetaxel	Consider CSF
	Other single agents	Dose reduction

Abbreviations: CSF, colony-stimulating factor; CT, chemotherapy; NSCLC, non–small cell lung cancer; PS, performance status.

with erythropoiesis-stimulating agents (ESAs), red blood cell transfusion, or IV iron.[4] These last 2 options are especially important for patients who are not candidates for ESAs—those not receiving myelosuppressive chemotherapy and those with curable disease.

"Anemia management has become more restricted and difficult over the past several years, related to concerns over the safety of ESAs and the hassles linked to reimbursement," he noted. "Red blood cell transfusion is not necessarily a safe substitute for ESAs. Under these circumstances, IV iron is a way to safely treat patients and get reimbursed."

The NCCN Guidelines Panel for Cancer- and Chemotherapy-Induced Anemia recommends 3 products: low-molecular-weight iron dextran, ferric gluconate, and iron sucrose. The panel does not recommend high-molecular-weight iron dextran (safety reasons) or ferumoxytol (lack of data in patients with cancer).

"The panel suggests considering using iron with or without ESAs. The advantages are that it's less controversial, lower in cost, and does not mandate a particular hemoglobin target for initiating or withholding IV iron," Dr. Rodgers said.

The goal is to identify iron-deficient patients early, before they receive myelosuppressive chemotherapy, to prevent anemia. Vitamin levels are checked, consent is obtained for using ESAs, and vitamin levels are repleted as necessary. If patients are still anemic, iron status is evaluated.[4,5]

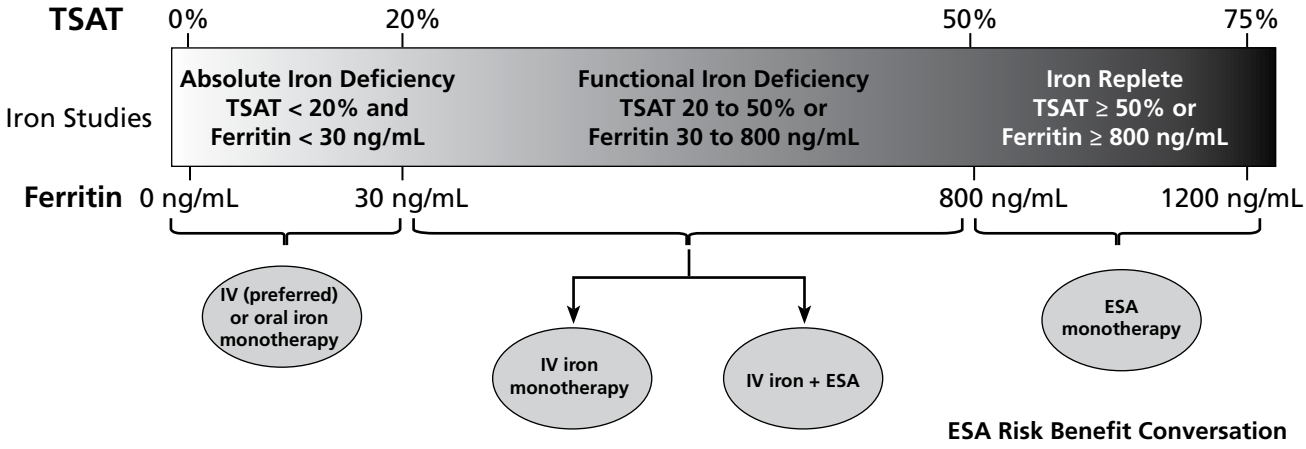

Figure 1 Patients with transferrin saturation (TSAT) and ferritin values on the left side of the iron spectrum have absolute iron deficiency and will only need iron monotherapy to treat anemia. Patients with laboratory values on the right side of the iron spectrum are iron replete or overloaded, and will only need erythropoiesis-stimulating agent (ESA) monotherapy. Patients with TSAT and ferritin values in the middle of the iron spectrum have functional iron deficiency and will likely benefit either from intravenous (IV) iron alone or IV iron plus an ESA. Reprinted with permission from Gilreath JA, Stenehjen DD, Rodgers GM: Am J Hematol 2014;89:203–212. Copyright © 2014 Wiley Periodicals Inc.

Iron deficiency can be absolute or functional, and it exists on a spectrum (Figure 1).[4] Absolute iron deficiency is defined by very low levels of transferrin saturation (<20%) and serum ferritin (<30 ng/mL). These patients should respond to iron replacement only, and ESAs are not needed. Patients with cancer usually have functional iron deficiency, which is usually associated with a transferrin saturation of 20% to 50%, and serum ferritin level of 30 to 800 ng/mL. They usually benefit from IV iron and an ESA; red blood cell transfusion is also an option.

References

1. Kuderer NM, Dale DC, Crawford J, et al. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106:2258–2266.
2. Hirsch BR, Lyman GH. Will biosimilars gain momentum? J Natl Compr Canc Netw 2013;11:1291–1297.
3. Lyman GH, Kuderer NM, Crawford J, et al. Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. Cancer 2011;117:1917–1927.
4. Gilreath JA, Stenehjem DD, Rodgers GM. Diagnosis and treatment of cancer-related anemia. Am J Hematol 2014;89:203–212.
5. Gilreath JA, Sajeser DS, Jorgenson JA, Rodgers GM. Establishing an anemia clinic for optimal erythropoietic-stimulating agent use in hematology-oncology patients. J Natl Compr Canc Netw 2008;6:577–584.