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Integrating IV Iron into Cancer Care: An Expert Overview of Best Practices

Announcer:
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Dr. McDonough:
Did you know that cancer-related anemia affects more than a third of all patients with cancer before they even start treatment? That number more than doubles to nearly 70% once patients begin their care journey, largely consequent to the myelosuppressive and hyperinflammatory effects of chemotherapy, radiation and novel targeted therapeutics. The deleterious effects of cancer-related anemia and chemotherapy-induced anemia on both clinical and patient-reported outcomes are myriad and expansive, and therefore safe, effective and evidence-driven mitigation and management strategies are exigently needed.

This is CME on ReachMD. I'm Dr. Brian McDonough. Joining me to discuss the role of intravenous iron in cancer care are Dr. George Rodgers and Dr. Patricia Ford.

Dr. Rogers is a Professor of Medicine in the Division of Hematology, Hematologic Malignancy at the University of Utah School of Medicine. Dr. Rodgers, thanks for being here today.

Dr. Rodgers:
Happy to be here.

Dr. McDonough:
And Dr. Ford is a Clinical Professor of Medicine and Hematology Oncology at Penn Medicine and Pennsylvania Hospital, where she also serves as the Director of the Cellular Therapy and Transplant Program, as well as the Center for Transfusion-Free Medicine. Dr. Ford, it's great to have you with us.

Dr. Ford:
Thank you. I’m looking forward to joining the discussion.

Dr. McDonough:
We know that anemia is exceedingly common among patients with cancer, especially among those actively receiving treatment. Why is that? What are the principal causes of anemia in this patient population?

Dr. Rodgers:
As you mentioned, many patients with untreated cancer have anemia, which is made worse with treatment. The major cause of this anemia is inflammation. In response to cancer, the patient's immune system produces inflammatory cytokines such as interleukins 1 and 6, and tumor necrosis factor, which stimulate the liver to increase hepcidin levels. Hepcidin causes iron deficiency by blocking iron absorption in the GI tract and by also blocking iron utilization by red blood cells in the bone marrow. This iron block is called functional iron deficiency.

In addition to the cancer itself, treatments for cancer cause inflammation, including chemotherapy and radiation therapy. This further increases hepcidin levels and inflammation. In addition to inflammation, patients with cancer may have bleeding that contributes to their anemia. Other contributing factors include B12 or folate vitamin deficiencies, as well as pre-existing medical comorbidities such as heart failure or chronic kidney disease.

Dr. McDonough:
What best practices do you recommend for recognizing, diagnosing, and evaluating iron deficiency and iron deficiency anemia in your patients with cancer?

Dr. Rodgers:
Iron deficiency is associated with a wide constellation of signs and symptoms. The major clinical feature is fatigue and low energy. Patients may also have skin pallor, brain fog or fuzzy thinking, headaches, dry skin, restless legs, pica, depression, and even hair loss. Severe iron deficiency can cause hypotension and syncope.

In terms of laboratory diagnosis of iron deficiency, the two key lab tests are ferritin and transferrin saturation, usually abbreviated as TSAT. Ferritin is a measure of total body iron stores. TSAT is the serum iron value divided by the total iron binding capacity and measures how much iron is available for tissues, such as red blood cells. A low TSAT means that insufficient iron delivery is being made to the tissues.

We can distinguish absolute iron deficiency from functional iron deficiency with the ferritin and TSAT lab test. In absolute iron deficiency, both the ferritin and TSAT are low. In functional iron deficiency, the TSAT is low, but the ferritin is normal or increased. This clinical distinction is important because absolute iron deficiency and functional iron deficiency may require different treatments.

We can view the iron status of the patient as a spectrum using the ferritin and TSAT lab results. As you can see from the far lefthand side of the spectrum, we have absolute iron deficiency with low or very low ferritin and TSAT results. These patients should respond to iron monotherapy. Patients at the far righthand side of the spectrum have increased iron stores. These patients will not benefit from iron treatment but should respond to an erythropoiesis-stimulating agent such as the epoetin-alpha or darbepoetin.

Patients in the middle of the spectrum have functional iron deficiency with TSAT values between 20 and 50%, and ferritin values which are intermediate. These patients are candidates for IV iron, with or without an ESA to treat their iron deficiency.

Dr. McDonough:
How do iron deficiency and iron deficiency anemia impact the care journey for a patient with cancer? Do they impact clinical outcomes? What about patient reported outcomes like quality of life?

Dr. Rodgers:
Unfortunately, many cancer physicians do not address cancer-related anemia in their patients, which may result in negative clinical outcomes.

Anemia in cancer patients is associated with disease progression, an increased red cell transfusion burden, and an increased risk of death. Although red cell transfusion is an option to treat cancer-related anemia, there is strong evidence that transfusions are associated with more adverse events than seen with IV iron therapy when it's used to treat cancer-related anemia. Additionally, patient-reported outcomes, as measured by quality-of-life instruments, are negatively impacted by cancer-related anemia. Patients may experience the signs and symptoms of iron deficiency previously mentioned with fatigue, impaired cognition and exercise intolerance being of major importance. Lastly, clinical trials have shown a correlation between hemoglobin and quality of life scores.

Other studies have shown that correction of iron deficiency anemia in cancer patients improves quality of life.

Dr. McDonough:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Brian McDonough, and today I'm speaking with Dr. George Rodgers and Patricia Ford about best practices for intravenous iron in cancer care. We spoke a bit earlier about what causes cancer-related, or chemotherapy-induced anemia, how to recognize, diagnose, and evaluate it in your patients, and how it impacts both clinical and patient-reported outcomes. But now, let's shift over to the actual treatment of cancer-related anemia, with a focus on IV iron.

We learned earlier that inflammation and increased hepcidin levels are centrally implicated in the pathophysiology of cancer-related in chemotherapy-induced anemia. With that in mind, what is the rationale for using intravenous iron instead of oral iron or some other therapeutic option in these patients?

Dr. Ford:
Well, our therapeutic options certainly can include transfusion support, and we all know that the risks associated with transfusion range

from transfusion reactions to the immunosuppression-causing transfusion-related acute lung injury, increasing infections. So, when you look at it with transfusions, the risk of the transfusion is actually not only much more common, but much more serious than giving intravenous iron. So, then, we moved down to oral iron, and as Dr. Rodgers mentioned, oral iron is difficult for patients to take. So, when you address first the side effects, we find that anywhere from about 30 to upwards to 75% of patients are just noncompliant because of the difficulty taking it, it's inconvenience, and the side effects we discussed. And very importantly, is the fact that oral iron is just not effective.

So, when we look at functional iron deficiency, what we know about that is the fact that when we increase hepcidin, oral iron is just not going to be absorbed, so we have to bypass the gut, which is what parenteral iron does.

Number 2, and one of the major components of a functional hepcidin block actually, is that we're not going to move the iron where we need it. We're not going to recycle it; we're not going to get it into the erythroid progenitor cells. So, that's another distinct advantage of intravenous iron is, again, we're able to overcome that hepcidin block.

And then, when we talk a little bit about IV iron, as we said, it's also faster. It's not only more consistent, but it also gives us a more rapid response. So, it's faster than trying to make up iron stores with oral iron. When we talk a little bit about the safety about oral versus IV iron. So, when physicians are really hesitant to give intravenous iron, it's really because of the unfounded side effects that they're worried about. And we know many decades ago, we only had high molecular weight iron dextran and that's where you did see and cause black box warning for risks and also, anaphylaxis. That is no longer even available. So, now with our low-molecular weight irons and our new next-generation iron products, they have very low rates of hypersensitivity than the older formulations.

If you look at some of the studies, actually, a nice one with Avni looks at 100 trials, over 10,000 patients, so it's a large number of iron patients. And here, you can see the risks are well under 1%. If you look at minor infusion reactions, maybe 1 in 200. If you look at more serious iron infusion reactions, it's 1 in 200,000. And certainly, no deaths that could be directly attributed to parenteral iron, and no increased infection, which is another question we get asked over and over; is it safe to give iron, especially in someone who may have an infection?

So, in essence, here, we know that transfusions probably carry the biggest risk of everything we talked about, oral iron is ineffective in overcoming functional iron deficiency, and the advantage of IV iron include its rapid and its effective.

Dr. McDonough:
So, the pharmacology dictates that IV iron is a reasonable treatment option for CRA and CIA. What does the actual data say?

Dr. Ford:
So, there's a lot of data that's out there. If we look back to one of the first studies that was ever done, decades ago at this point, from Dr. Michael Auerbach, where he actually looked at no iron, oral iron and IV iron, that kind of kicked off doing these kind of clinical trials. And there was a definite advantage to oral iron, but even more so with intravenous iron. And since then, we've had a large number of systematic reviews. We've had meta-analysis to kind of corroborate what we've said in terms of the advantages of parenteral iron and the clinical utility.

So, just to look at a couple of them and to kind of demonstrate, what they all tend to show is an increase in hemoglobin levels. And when you look through the studies, it could be 1 to 2 grams at about 60% of patients. In all the studies, it decreases red cell transfusions. And the advantage, here, is that we can use iron by itself as monotherapy or in conjunction with ESA's.

So, I wanted to highlight two studies that were very practice-changing. I'll start first with the PROFOUND study. This was a randomized, noninferiority trial of iron isomaltoside versus oral iron and non-myeloid malignancies and anemia in patients who were receiving chemotherapy. A Phase 3 study looking at both efficacy and safety. And they looked at 350 patients in a 2 to 1 randomized fashion, and what they found with intravenous iron, this was a non-inferiority study, is that it was non inferior in the change of hemoglobin seen at 4 and 6 weeks. However, there was a faster onset of increase in hemoglobin. Importantly, there's a significant relief in fatigue or patient-reported outcomes, and it actually was better tolerated than oral iron for all the reasons we said. A number of patients just had to stop their oral iron because of the GI distress.

Another study I wanted to highlight was the IRONCLAD study. So, this was looking at efficacy and safety of ferric carboxymaltose infusion in reducing anemia in patients receiving chemotherapy for non-myeloid malignancies. This was a randomized placebo-control study looking at monotherapy, here. Looking at patients, double-blinded, for an 18-week period. Patients received two infusions. There was a cap in the amount of iron they could receive, but essentially two infusions, 7 days apart. To get on, just as Dr. Rodgers highlighted in our definition of functional iron deficiency, these patients had hemoglobins between 8 to 11, ferritin anywhere from 100 to 800, and TSATs under or equal to 35%. And the results, here, showed that 1: the percentage of patients who maintain their hemoglobin – so,

what they actually were looking at – the number of patients that did not decrease the hemoglobin more than 0.5g at week 18 was higher in the IV iron; 50 versus 35%. And although the main change in hemoglobin was similar between the two groups here, it definitely was higher in the IV iron group when the hemoglobin was under 9.9. And we'll remember that number, because 10 becomes important when we look at our consensus recommendations.

The increase in hemoglobin over 1 gram was also not just more in the IV iron 71 versus 54%, but also occurred faster in that group.

So, we have that clinical data that supports in randomized good studies and even in meta-analyses.

Dr. McDonough:
Dr. Ford, you mentioned expert consensus statements. What about expert consensus statements? Is IV iron guideline recommended? If so, in which clinical scenarios is it most important?

Dr. Ford:
So, we have a lot of guidelines that are out there and it ranges from NCCN, the National Comprehensive Cancer Network, to ASCO and ASH and ESMO. And I think the consensus recommendations, they all recognize the fact that transfusions are an option for certain patients and that ESA's are effective for the use in chemotherapy-induced anemia but it comes with significant adverse effects. So, recognizing there could be a safer alternative in terms of IV iron, they all start out, as was highlighted, by saying the first thing you got to do is just do a good anemia workup. You want to see why is that patient anemic? Are they low, nutritionally, in B12 folate, other than iron? Are they having ongoing blood losses? And then, after that, you want to look at the fact that we can use intravenous iron as monotherapy and we've seen that it decreases red cell transfusions. It's recommended to be used in conjunction with the ESAs; you'll enhance your response there. And the uses in most of these guidelines are for chemotherapy-induced anemia where treatment is not curable, so they are not recommending that you use this in any malignancy where there's a curative potential, except for MDS, or myelodysplastic syndrome.

Most of the recommendations highlight they should be considered when the hemoglobin is under 10 grams. And they do, in most of these, recommend the fact that you can use this upwards to a ferritin of 800, and over 800, there would be no use in iron either, oral or parenteral. But of course, they all end by saying end red cells are still an option in these patients.

So, I think the consensus recommendations in summary are, we can use this as monotherapy, we can use it even before ESA's, use it with the ESA's. It can be given with ferritins under 800. You want to decide what type of anemia you actually have here, and certainly, should always be considered when you're using ESAs. And they all highlight the fact that there needs to be ongoing monitoring to see if you have a response and ongoing evaluation of your iron studies.

Dr. McDonough:
Dr. Rodgers, do you have any practical clinical pearls you'd like to add?

Dr. Rodgers:
I'm happy to give a few pearls. First of all, I would encourage cancer physicians to use those routine ferritin and TSAT assays to monitor the iron status of their cancer-related anemia patients. The tests are very inexpensive, widely available, and highly predictive in who needs to be treated. And if you use that spectrum analogy that I described, it can accurately guide your treatment to treat either absolute or functional iron deficiency.

Another useful pearl is that IV iron has the advantage to treat both absolute and functional iron deficiency. So, if your cancer patient has anemia primarily due to bleeding and less-so to inflammation, IV iron will work perfectly. If they have functional iron deficiency due to their cancer and/or its treatment, with or without bleeding, again, IV iron monotherapy will be very helpful. And IV iron by itself may help you avoid the need for the use of ESA therapies, which have black box warnings and limitations, insurance restrictions, etcetera. IV iron has none of those limitations.

And then, lastly, I'd like to emphasize what Dr. Ford said about the adverse event rate, which causes a lot of unwarranted concern about the use of IV iron. As she mentioned, the adverse event rate with red cell transfusions is 10 times higher than the adverse event rate associated with the use of IV iron.

Dr. Ford, how about you? Do you have any practical clinical pearls that you would like to add?

Dr. Ford:
So, I wanted to add, maybe, a few more things than what Dr. Rodgers said, and I want to highlight this. It was just a coincidence that the patient I saw this afternoon will really highlight all of this.

So, this is a gentleman, and although he is a Jehovah Witness and won't allow transfusion support, I actually see a lot of Jehovah

Witness patients – He came to me from his oncologist who's not as familiar with chemotherapy-induced and cancer-related anemia, to kind of help him to treat the anemia. So, this is a gentleman who walked in with metastatic colon cancer. So, A: remember this is non curative, so certainly this would be an approved early use of ESAs and IV iron. Number 2: He walked in with a hemoglobin of 5, and I swear he looks as good as we do, meaning he has a performance status of 0. It just goes to show that we shouldn't be really, merely transfusing patients. It is amazing how well they can tolerate a low hemoglobin. It's not that I would suggest to hemoglobin of 5, but what I saw in this case was that the anemia was not addressed.

Now, he has a hemoglobin of 5, and when I looked back, there was never an iron study sent. Not one. So, that highlights the fact, you've got to think about this. And when I went through his history, he has three reasons why he is so anemic. Number one: His colon cancer is evading into the duodenum and he's bleeding, so he's having bleeding. So, as Dr. Rodgers said, if that was the only problem, parenteral iron is all you needed. Number two: He's been through FOLFOX chemotherapy recently and he has metastatic cancer. That highlights our functional anemia right there, and the ability to use IV iron and ESA to keep that hemoglobin up.

So, at this point, I'm going to recommend radiation to stop the bleeding to the duodenum, even with a hemoglobin of 5. And number two: He can now get chemotherapy, so the delay in treatment happens in all our patients, also, when we have this untreated anemia. His anemia should have been treated earlier. They could have used IV iron alone if it was just related to bleeding, but honestly, they should have started the ESA and the IV iron and I think that would have avoided this profound anemia.

What they did do was they had him on oral iron for the last 2 months. Ineffective, and as he said, was ripping out his digestive tract. So, I thought it was just a great highlight of just a coincidence that I had that patient this afternoon that really highlighted all the things we talked about today.

Dr. McDonough:
That's a great way to round out our discussion on this important clinical topic. I want to thank my guests for helping us better understand how to integrate IV iron into cancer care in accordance with the latest data and best practices.

Dr. Rodgers, Dr. Ford, it was great speaking with you both today.

Dr. Rodgers:
Thank you.

Dr. Ford:
Thank you.

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