Nephrology Rounds: The Role of the Pharmacist in the Management of Anemia in Chronic Kidney Disease Patients

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CASE 1a, Bill

Bill is a 55-year old office worker with stage G4 A3 CKD secondary to type 2 diabetes mellitus who is seen in the nephrology clinic for routine follow up of his CKD. His history also includes hypertension and heart failure with preserved ejection fraction. He complains of frequent fatigue and shortness of breath but denies chest pain. Medications include: lisinopril 40 mg PO daily, carvedilol 12.5 mg PO twice daily, empagliflozin 100 mg PO daily, metformin 1000 mg PO twice daily, and furosemide 40 mg PO daily. His physical exam reveals blood pressure 148/92 mm Hg and 2+ pedal edema, but is otherwise unremarkable. Laboratory data include normal electrolytes, blood urea nitrogen (BUN) 45 mg/dL, creatinine 2.4 mg/dL, estimated GFR (eGFR) 22 ml/min/1.73 m^2, Hb 8.9 g/dL, normal white blood cell (WBC) and platelet counts.

CASE QUESTIONS

1. What clinical manifestations of anemia does Bill have?

Faculty Response: This patient presents with both fatigue and shortness of breath that can be attributed to his anemia. It's important to remember that he does have heart failure and so shortness of breath could be also a sign of pulmonary edema form the heart failure. But in looking at the case, he does have some pedal edema which could indicate some mild volume overload, but there was no mention of pulmonary edema on physical exam, and therefore, it's more likely his shortness of breath is also attributed to his anemia. Secondarily, given that his hemoglobin is 8.9 g/dL, that has a significant effect on the cardiovascular system, and so the manifestations he's presenting with could likely be contributing to his decline in cardiovascular health overall.

2. What are the likely mechanisms of anemia in Bill?

Faculty Response: With chronic kidney disease as the glomerular filtration rate, GFR, decline below about 45 mL/min, the patients can start to develop anemia, typically as a result of a decreased production of erythropoietin, which is normally produced by the kidney. This patient's GFR is 22, indicating that he has less than 25% renal mass remaining, and therefore, it's most likely that a lack of production of erythropoietin is the main mechanism of anemia. However, we know that anemia in CKD is multifactorial and one of the other causes is a dysregulation of iron metabolism. This is likely driven by an increase in hepcidin, which is cleared by the kidney, and therefore, as GFR declines, the hepcidin increases, which decreases the oral iron absorption, both from diet and supplemental sources, but it

also decreases the functional utilization of iron for erythropoiesis. So, he likely has a component of iron deficiency along with a lack of erythropoietin production, both of which are contributing to his anemia.

3. What other laboratory parameters would be useful to evaluate Bill's anemia?

Faculty Response: Certainly, an iron panel would be useful in this patient because we would be worried about iron deficiency, and so we would mostly focus on the transferrin saturation, or the iron available for erythropoiesis, as well as the ferritin, which reflects the storage form of iron. Both of those are the treatment targets per the KDIGO guidelines on anemia from 2012. Additionally, any patient being worked up for anemia should be evaluated for gastrointestinal sources of blood loss, and so a fecal occult blood test should also be recommended. Vitamin B12, folate and methylmalonic acid could also be checked if there were megaloblastic red cells present, but there is no real difference in terms of patients with CKD compared to patients without CKD in the development of megaloblastic anemia.

4. What long-term complications of anemia is Bill at high risk of developing?

Faculty Response: I would be most worried about two complications. The first is progression of his underlying cardiomyopathy, given that anemia, over time, can worsen left ventricular hypertrophy and this patient already has heart failure with preserved ejection fraction. The progression of his underlying cardiomyopathy would be an essential concern for this particular patient. One of the goals of treating his anemia would be to try to slow that left ventricular hypertrophy that can develop. The other complication is present in all patients with chronic kidney disease, and that is the need for blood transfusion. As chronic kidney disease progresses to end-stage renal disease, the ultimate cure of that condition is a renal transplantation. However, when patients receive blood transfusions, they become sensitized to the various blood antigens present, and become allosensitized, which increases their risk of rejection of kidney transplants in the future. So, one of the major goals in treating anemia in both chronic kidney disease and end-stage renal disease is to reduce the risk of blood transfusions to try to minimize that allosensitization that can occur.

CASE 1b, Bill, Continued.

Bill was evaluated for his anemia and found to be iron deficient (TSAT 12%, serum ferritin 112 ng/mL). Therapy with ferrous sulfate 325 mg by mouth every other day was initiated. He returns to clinic 3 months later and continues to complain of fatigue and shortness of breath despite an increased dose of furosemide, and repeat Hb was 8.8 g/dL.

In response to this finding, the pharmacist in the CKD clinic recommends initiating intravenous iron therapy and discontinuing the oral iron. Bill begins iron sucrose 100 mg intravenously twice per week for 10 doses. Four weeks later, Bill's hemoglobin is 9.5 g/dL, and shortness of breath is resolved, but his fatigue is not significantly improving.

CASE QUESTIONS

1. What dose of oral iron would you have recommended for Bill? Why?

Faculty Response: When first deciding on iron supplementation for this patient, I think it's critical to evaluate both the degree of anemia, as well as the degree of iron deficiency. Because he is a chronic kidney disease patient not on dialysis, the KDIGO guidelines for anemia management from 2012 recommend that a trial of oral iron could be considered. Therefore, I would recommend to start this patient on oral iron. However, the dose that he was started on was low, and this is unfortunately happening in a lot of the CKD patients in clinic – that the alternate dosing recommendations are filtering in for patients with chronic kidney disease. As we discussed in the text, there is evidence that giving oral iron less frequently can increase the fractional absorption, however, in patients such as this that have clinically relevant anemia, as well as a significant iron deficit, they really need an increase in the absolute amount of iron that they're receiving in order to address both their anemia and their iron deficiency. So, given that information, I would have recommended starting the patient on 200 mg of elemental iron a day, divided in 2 to 3 doses. That could be achieved with ferrous sulfate, 325 mg, 3 times a day. Again, this would decrease the fractional iron absorbed over time given that it will increase hepcidin production, however, the absolute amount of iron absorbed would be necessary to be increased, which is what the 3 times a day regimen would achieve compared to every other day.

2. How long after initiation of oral iron would you reassess therapy? When would you re-check iron studies? What are your goal iron parameters?

Faculty Response: A 1- to 3-month trial of oral iron is recommended before reassessing therapy. So, after 1 to 3 months in this patient, I would recheck their iron studies, as well as their hemoglobin, and determine how they are improving, and whether or not an additional therapy needs to be initiated at that time. When rechecking the iron studies, the goal transferrin saturation is above 30% and the goal ferritin is above 500, per the KDIGO guidelines.

3. How should you monitor Bill during the iron infusions?

Faculty Response: It's important to monitor patients during intravenous iron infusions for potential infusion reactions. Iron dextran was the first intravenous iron product available and it had a high risk of infusion reactions, which could range from mild all the way through severe anaphylactic reaction. The more current iron products have a much lower rate of anaphylaxis or sever iron infusion reactions. However, patients still need to be monitored during the infusion. Monitoring parameters include vital signs, such as blood pressure and heart rate, as well as any patient symptoms that can range from mild discomfort and pruritus up to chest pain, shortness of breath, and even anaphylaxis, though again, that is exceedingly rare with conventional products. The patient should also be monitored for about a half hour after the end of the infusion in clinic before they are sent home to ensure that no reactions develop after the iron has been infused.

4. When would you consider starting an ESA for Bill?

Faculty Response: When deciding to start an erythropoiesis stimulating agent, or an ESA, for any patient it's important to think about two factors. The first is, are they iron replete? So for this patient, it would be important to recheck his iron studies after the intravenous iron is administered. If the patient is iron replete, that is, the transferrin saturation is above 30% and the ferritin is above 500, but they continue to have anemia, meaning their hemoglobin is below goal, you could consider starting an ESA. The KDIGO guidelines recommend to start that ESA, again, when the patient is iron replete, and the hemoglobin is between 9 and 10. The purpose here of starting between 9 and 10 is to prevent the hemoglobin from declining below 7, which is when a transfusion would be necessary, but also to minimize the risk of ESAs, which is thromboembolic events, particularly as the hemoglobin climbs above 11. Starting at between 9 to 10 allows us to kind of find the "sweet spot" where the patient doesn't dip too low with their hemoglobin, and by 4 to 6 weeks, once the ESA has started working effectively, that hemoglobin starts to slowly trend back up towards that 10 to 11 range, which is the target hemoglobin, in the United States at least, for end-stage renal disease patients.

CASE 2, Jim

Jim is a 44-year old male (68 inches, 150 pounds) who is on chronic hemodialysis secondary to type 1 diabetes mellitus. His past medical history also includes peripheral vascular disease status post right total metatarsal amputation (6 months ago) and left below knee amputation (2 years ago), chronic osteomyelitis of the right lower extremity, stage 3 sacral decubitus ulcer, peripheral neuropathy, chronic pain, and orthostatic hypotension. Most recent labs show a hemoglobin 7.8 g/dL, TSAT 22%, ferritin 1552 ng/mL, C-reactive protein 88.5 mcg/mL and erythrocyte sedimentation rate 72 mm/hour. Jim has been receiving escalating doses of epoetin alfa which was increased 4 weeks prior from 12,000 units IV three times per week to 15,000 units IV three times per week. He also receives intravenous ferric gluconate 62.5 mg once weekly.

CASE QUESTIONS

1. What would you do with Jim's epoetin alfa dose: continue unchanged, increase or decrease, and why?

Faculty Response: This is a very difficult case, and so it's important to discuss both epoetin alfa as well as intravenous iron dosing in this patient. His epoetin alfa has been escalating, the most recent dose increase was 4 weeks ago and was a 25% increase. However, his hemoglobin has not improved, and so it's always important to evaluate both the trend in hemoglobin as well as the trend in ESA dose when determining the next steps. For this patient I think there are two options. The first option is to increase his epoetin alfa dose. If you look at most centers' anemia management protocols, they follow an empiric algorithm for dose adjusting any ESA, and that is after 4 to 6 weeks of a dose change, if the hemoglobin is not improved, increase the dose by another 25%. I think that's a reasonable step in this patient – to increase his epoetin alfa by an additional 25%. However, when evaluating this patient maybe more holistically, it's evident that the patient is not responding very well to the epoetin alfa therapy. So this patient would have something in the literature called either ESA hyporesponsiveness or ESA resistance, and that is again, that they are not increasing their hemoglobin in response to multiple escalating doses

of epoetin alfa. His weekly epoetin alfa dose is greater than 500 units per kg, which again, is a marker of ESA hyporesponsiveness. In these patients, it's important to further evaluate the causes of that hyporesponsiveness, and address those causes before escalating the doses of epoetin alfa. So my recommendation for this patient would actually be to do that – to evaluate for the hyporesponsiveness and address those underlying causes before increasing his dose of epoetin alfa.

2. What would you do with Jim's IV ferric gluconate dose: continue unchanged, increase or decrease, and why?

Faculty Response: Again, this is a difficult decision to make clinically. When evaluating his iron panel, his transferrin saturation is 22%, which is below target of 30%. However, his ferritin is about 1500, which is way above target of 500. Ferritin above 1200 is suggestive of iron overload, and it's not recommended to give further doses of intravenous iron to patients above 1200.; and that's where we're sort of stuck between these two laboratory values. Ferritin, though, is also an acute phase reactant and is elevated in patients that have sources of inflammation. For this patient, he has chronic osteomyelitis, a stage 3 sacral decubitus ulcer, and recent amputations. He also has other laboratory results such as C-reactive protein and erythrocyte sedimentation rate, which are also reflective of inflammation. Therefore, it's reasonable to assume that his elevated ferritin is more a result of inflammation, and not necessarily reflective of iron overload. However, it is still difficult to administer a higher dose of intravenous iron to a patient that has a high ferritin due to that underlying risk of iron overload. Given that his transferrin saturation is low, but not critically ow, it's still pretty close to the 30% target, and his ferritin is very elevated, I would recommend not changing his IV iron dose at this time. He would remain on what we would consider maintenance intravenous iron dosing, which is a once-weekly dose of around 50 to 100 mg of elemental iron. This allows the patient some iron in his system available for erythropoiesis from the concomitant ESA therapy. I would not, however, increase it, given that his TSAT is close to normal, but his ferritin is well above target.

3. What other interventions might be appropriate to increase Jim's hemoglobin?

Faculty Response: For me, this question is the most critical one for this patient case. Addressing this patient's underlying cause of inflammation would be the most critical step in evaluating and providing care for his anemia. He has a number of sources of inflammation, again, osteomyelitis, sacral decubitus, bad peripheral vascular disease, even the procedure of hemodialysis can increase inflammation, and so all of those sources need to be addressed. Certainly, that is a lot easier said than done, those are also chronic disease states that will require close follow-up and monitoring by a number of different specialists. But those sources of inflammation really need to be addressed before this patient will adequately respond to other therapies such as intravenous iron and ESAs.

4. Might Jim be a candidate for a HIF stabilizer agent if one or more receive FDA approval Why or why not?

Faculty Response: I will speculate a little bit here since none of the HIF-stabilizers are currently approved by the FDA so discussing them in the context of a patient case is, in a sense, discussing them off label. But if HIF-stabilizers become available, I think this patient would be an excellent candidate for one of those agents. That is because this patient has both functional iron deficiency and hyporesponsiveness to ESAs. Now both of these are very troubling clinical problems that we see all too often in our chronic hemodialysis patients as they require escalating doses of epoetin alfa, as was present in this case, and a lot of intravenous iron. Both of these can be potentially detrimental to the patients as they are both associated with serious chronic adverse effects. The HIF-stabilizers could provide this patient with improved iron metabolism, as well as a more complete erythropoiesis response that uses endogenous erythropoietin more effectively. Therefore, it could address some of the underlying causes of this patient's anemia. However, again, this is not an FDA-approved therapy, and my comments on it are a bit speculative at this time.

CASE 3, Margie

Margie is a 55-year old African American female (65 inches, 204 pounds) who works part-time at a local school. She presents to her routine nephrology clinic appointment with no complaints. Margie has a past medical history of type 2 diabetes mellitus, chronic kidney disease stage IIIB A3, hypertension, atrial fibrillation, and heart failure with reduced ejection fraction of 30-35%. Physical exam reveals a blood pressure of 152/88 mm Hg, heart rate of 105 beats per minute, 1+ pedal edema, irregularly irregular heart rhythm and is otherwise unremarkable. Recent labs show a hemoglobin A1C of 9.2%, eGFR 38 ml/min/1.73 m^2, TSAT 18%, ferritin 112 ng/mL, hemoglobin 10.7 g/dL.

Medications: aspirin 81 mg daily, apixaban 5 mg twice daily, labetalol 400 mg twice daily, nifedipine ER 90 mg once daily, glyburide XL 10 mg daily in the morning, metformin 1000 mg twice daily, esomeprazole 40 mg daily.

You are the pharmacist in the nephrology clinic reviewing this patient's chart to address her anemia.

CASE 3 QUESTIONS

1. What is your next step in addressing Margie's anemia?

Faculty Response: This patient presents without any complaints, and so has asymptomatic anemia since she is a female with a hemoglobin less than 12 and has chronic kidney disease, and therefore meets the KDIGO diagnostic definition of anemia. In further evaluating her lab work, she also has iron deficiency; her transferrin saturation is 18% and ferritin 112, both below targets for patients with chronic kidney disease. Therefore, the next step would be to evaluate iron supplementation in this patient. Given that she has stage 3 CKD, and is not on dialysis, a trial of oral iron is suggested for 1 to 3 months. Therefore. I'd recommend starting the patient on an oral iron supplement at a dose of approximately 200 mg of elemental iron per day in divided doses. It is important to note that this patient is also taking esomeprazole, which is a proton pump inhibitor, which will dramatically increase the gastric pH and that lessens the bioavailability of oral iron product. So it's important to evaluate the patient for adequate oral iron therapy given that she takes a PPI. You could consider adding ascorbic acid or vitamin C to her

oral iron therapy to try to enhance absorption, as well as discuss with the patient the indication for the PPI and determine if alternate acid-suppressing therapy could be considered.

2. What other services can a pharmacist provide Margie during this encounter? What would you prioritize?

Faculty Response: There is a long list of things that a pharmacist can provide this patient just in this encounter alone. Some medication therapy management, medication reconciliation, adherence assessments and counseling, lifestyle and dietary counseling, as well as immunization assessment and potential administration of immunizations are all things that would be critical for a pharmacist to provide. What I would prioritize to the top of my list, though, would be comprehensive medication management with a focus on achieving guideline-directed medical therapies and guideline-directed targets of therapies, particularly for her heart failure, diabetes, and hypertension. For diabetes and hypertension, these are the main drivers of her chronic kidney disease progression, and it's critical that she achieves the goal blood glucose targets, particularly an A1C less than 7%, and the goal blood pressure targets, that being less than 130/80 in order to slow the progression of her chronic kidney disease. As you can see from the case, she is not achieving either of those targets yet. She is not on optimal therapy for either her blood pressure or her chronic kidney disease, which would be an ACE inhibitor or an angiotensin receptor blocker. I think a pharmacist could offer a really critical service to the patient at this time by performing comprehensive medication management and addressing some of these chronic comorbidities to ensure that she has guideline-directed medical therapy to achieve the best outcomes.

3. What kind of patient education would you provide for Margie?

Faculty Response: Again, here I think there is a long list of things a pharmacist can educate this patient about. Dietary lifestyle modifications, decreased salt intake in her diet, home monitoring of blood pressure and blood glucose would all be important. However, what I would prioritize to the top of the list would be adherence. The patient is currently receiving a number of medications, to which we are probably adding 1 or 2 at this visit, and it would be critical to discuss how this patient self-administers medications, how she ensures she's adherent to medications, and discuss any potential barriers she has to adherence. That would be the number one thing that a pharmacist should focus on with this patient, especially given her polypharmacy and her multiple comorbid conditions.