IV IRON THERAPY AND THE MANAGEMENT OF DOCUMENTED IRON DEFICIENCY IN PATIENTS WITH CANCER: CASE STUDIES

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This article will identify effective anemia management practices for patients with cancer through the exploration of a pair of case studies. These case studies represent clinical and practical experience, and will discuss emerging information on iron, erythropoiesis stimulating agents (ESAs), and hematologic evaluations.

**IMPORTANCE OF IRON AND ESA IN ERYTHROPOIESIS**

**Case Study: Mrs. Smith**

Mrs. Smith is a 68-year-old female who was diagnosed with ovarian cancer. She presents with chronic kidney disease (CKD) stage 3, controlled hypertension, and a history of rectal bleeding due to hemorrhoidal disease. After debulking surgery, her oncologist has started her on platinum-based chemotherapy. Her Hb was 10.8 g/dL at diagnosis. After completing her first cycle of chemotherapy, Mrs. Smith returns for evaluation, during which a complete blood count (CBC) reveals that her Hb level has dropped to 9.8 g/dL. According to the National Comprehensive Cancer Institute (NCCN) Guidelines in Oncology, the patient is now demonstrating grade 2, or moderate, anemia.1

The treating oncologist is now presented several options for the initial management of the patient. Options include evaluating the causes of anemia, assessing the anemia symptoms and Mrs. Smith’s comorbidities, giving a blood transfusion, or giving ESA therapy.

On examination, several conditions may be contributing to Mrs. Smith’s anemia. These include chronic kidney disease (CKD), chemotherapy-induced anemia, and the inflammatory cytokine milieu caused by her cancer, as well as possible nutritional deficiencies such as iron, B12, or folate. Blood loss, iron deficiency, suppression of erythropoiesis and erythropoietin from chemotherapy, the production of inflammatory cytokines by her cancer, and renal impairment should be considered.

**According to NCCN Guidelines, oral iron has been more commonly used but is less effective. IV iron has superior efficacy and should be considered for supplementation for treatment of cancer patients receiving ESA therapy.**1
Upon patient assessment, the treating oncologist notes the following:

**Subjective**
- Fatigue
- Nausea
- Difficulty concentrating
- Pagophagia/pica

**Objective**
- Heart rate: 110 (sinus tachycardia)
- Blood pressure: 120/80
- Respiratory rate: 30 (rales in bases)
- Temperature: 97.8°F
- Pale skin
- Dry mucous membranes
- Positive stool guaiac
- Serum creatinine: 1.9
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- Respiratory rate: 30 (rales in bases)
- Dry mucous membranes
- Positive stool guaiac
- Serum creatinine: 1.9
- 15 lb weight loss

Mrs. Smith clearly has symptoms of anemia. Additionally, we also note that she may have symptoms of iron deficiency (pale skin, fatigue, irritability, weakness, shortness of breath, inability to concentrate, brittle nails, unusual food cravings). At this point, there are again several courses of action that can be taken. One option is to hold the patient’s chemotherapy cycle until her Hb increases normal; a second option is to start ESA therapy; a third option is transfusion; a fourth option is to perform a series of hematologic studies before initiating ESA therapy.

Hematologic evaluation of anemia reveals:

Based on these study results, one reasonable treatment option is to initiate iron therapy based on her low TSAT levels. In this scenario, the oncologist must decide between oral iron or IV iron, or oral iron first, followed by IV iron if the patient is intolerant or unresponsive. Oral iron, however, may be associated with troublesome gastrointestinal (GI) side effects, which may reduce therapy compliance and/or compound the GI side effects of radiation and chemotherapy. Additionally, it is believed that increased hepcidin levels associated with anemia of chronic diseases, which may occur in cancer patients, causes decreased oral iron absorption and bone marrow iron utilization. Conversely, according to NCCN recommendations, oral iron has been more commonly used but is less effective. IV iron has superior efficacy and should be considered for supplementation for treatment of cancer patients receiving ESA therapy. IV iron proved superior to oral iron in a study comparing incorporation in red blood cells (80% vs. 65%) and time to utilization in Hb formation (8 days vs. 34 days).

The approved IV iron products include: iron dextran, ferric gluconate, ferumoxytol, and ferumoxytol. Regarding iron dextran, the NCCN guidelines note that most adverse events associated with iron dextran occur with high molecular weight iron dextran (Dexferum). The recommended iron dextran product is low molecular weight iron dextran (InFeD). Iron dextran is indicated for treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.

### Lab Results

<table>
<thead>
<tr>
<th>Lab</th>
<th>Reference Range: Normal</th>
<th>Mrs. Smith</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ferritin</td>
<td>10-120 ng/mL (females)</td>
<td>211 ng/mL</td>
</tr>
<tr>
<td>Iron</td>
<td>60-150 µg/dL</td>
<td>48 µg/dL</td>
</tr>
<tr>
<td>TIBC</td>
<td>250-435 µg/dL</td>
<td>309 µg/dL</td>
</tr>
<tr>
<td>TSAT</td>
<td>15% - 50% (females)</td>
<td>14%</td>
</tr>
<tr>
<td>B12</td>
<td>4.72</td>
<td>7.2</td>
</tr>
<tr>
<td>Folate</td>
<td>10.2</td>
<td>11.3</td>
</tr>
</tbody>
</table>

Additional evidence for the efficacy of InFeD in place of oral iron are study results showing that the rate and degree of response is higher in patients receiving ESA therapy plus InFeD as compared to patients receiving ESA treatment only, or patients receiving ESAs and oral iron.

**Case Study: Mr. Jones**

Mr. Jones is a 60-year-old male who is scheduled for colon cancer surgery. His pre-operative lab results show WBC of 7,000, platelets of 475,000, and Hb of 10 g/dL. Serum ferritin is 400 ng/mL, and TSAT is 15%. At this point in patient management, several options exist, including: the immediate initiation of ESA therapy, since the patient may require this treatment after surgery, initiation of oral or IV iron therapy due to low TSAT, or no immediate treatment due to adequate Hb and serum ferritin levels.

Post-operatively, Mr. Jones returns as an outpatient to receive chemotherapy for stage III disease. Upon evaluation, Mr. Jones reports significant fatigue, poor appetite, and his face, hands, and gums show noticeable pallor. Additionally, Hb is now 9.4 g/dL. Preoperatively, he received no treatment. Possible contributors to Mr. Jones’ anemia include blood loss during surgery, post-operative inflammation or infection, and iron deficiency.

The management plan selected calls for ESA therapy to be initiated (40,000 U/week, without iron therapy). He also begins chemotherapy. One month later, lab results show an Hb level of 9.5 g/dL, serum ferritin of 675 ng/mL, and a TSAT of 13%. At this time, ESA therapy is increased to 60,000 U/week, but no iron is added. One month later, the patient still has not achieved a meaningful Hb response (Hb=9.3 g/dL; serum ferritin=650 ng/mL; TSAT=13%). At this time, it can be deduced that Mr. Jones may have ESA resistance due to iron-restricted erythropoiesis.

Iron-restricted erythropoiesis is different than absolute iron deficiency. Possible causes of absolute iron deficiency include increased blood loss and decreased iron absorption. The loss of iron then leads to the production of RBCs without adequate Hb. NCCN iron parameters for absolute iron deficiency are serum ferritin of <30 ng/mL and a TSAT of <20%.

**IN ONCOLOGY PATIENTS, AS IN THE CASE OF MR. JONES, THERE ARE MANY POTENTIAL BENEFITS OF IV IRON THERAPY. STUDIES HAVE SHOWN IV IRON TO IMPROVE THE HB RESPONSE TO ESA THERAPY IN PATIENTS WITH CHEMOTHERAPY-RELATED AND DOCUMENTED IRON DEFICIENCY ANEMIA.**

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**Drug Update Oncologistics**

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CONCLUSION

IV iron is more effective in some cancer patients with documented iron deficiency anemia who are intolerant to oral iron and receiving chemotherapy. It is essential to determine the reason why a patient fails to respond to ESA treatment.

IMPORTANT SAFETY INFORMATION

Anaphylactic-type reactions, including fatalities, have followed the parenteral administration of iron dextran injection. A test dose should be administered prior to the first therapeutic dose, followed by the full therapeutic dose if no signs or symptoms of anaphylactic-type reactions are seen. Resuscitation equipment and personnel trained in the detection and treatment of anaphylactic-type reactions must be readily available during all INFeD administrations. Patients should be observed for signs or symptoms of anaphylactic-type reactions during all INFeD administrations. Fatal reactions have followed the test dose and have also occurred in situations where the test dose was tolerated. Use INFeD only in patients in whom clinical and laboratory investigations have established an iron deficient state not amenable to oral iron therapy. Patients with a history of drug allergy or multiple drug allergies may be at increased risk of anaphylactic-type reactions.

INFeD should be used with caution in individuals with histories of significant allergies and/or asthma, and is contraindicated in patients with hypersensitivity to the product and patients with all anemias not associated with iron deficiency. INFeD should be used with extreme care in patients with serious impairment of liver function, and should not be used during the acute phase of infectious kidney disease. Unwarranted therapy with parenteral iron will cause excess storage of iron with the consequent possibility of exogenous hemosiderosis, which is particularly apt to occur in patients with hemoglobinopathies and other refractory anemias.

At this stage of treatment, considering Mr. Jones’ lack of response to ESA therapy, several options exist. The treating physician can increase the current ESA dose in the hope of eliciting a response; the current ESA dose can be maintained and IV iron can be initiated; or transfusion can be considered.

In oncology patients, as in the case of Mr. Jones, there are many potential benefits of IV iron therapy. Studies have shown IV iron to improve the Hb response to ESA therapy in patients with chemotherapy-related and documented iron deficiency anemia. Moreover, IV iron is shown to increase the proportion of patients reaching target Hb levels, and decrease the need for blood transfusions.

IV iron, in addition to ESA therapy, has efficacy in anemia of chronic disease. With IV iron treatment, iron is provided to the macrophages and is pulled out of the RES. IV iron promotes the continuous improvement of the iron loading of transferrin, and ensures that iron-transferrin is readily available for erythropoiesis. Additionally, ESA doses are diminished with the use of IV iron.