PQI IN ACTION

ERYTHROPOIETIN STIMULATING AGENT INELIGIBILITY IN MYELODYSPLASTIC SYNDROMES

NCODA’S POSITIVE QUALITY INTERVENTION IN ACTION
INTRODUCTION

In an effort to promote higher quality patient care NCODA created the NCODA Positive Quality Intervention (PQI) as a peer-reviewed clinical guidance resource for healthcare providers. By providing Quality Standards and effective practices around a specific aspect of cancer care, PQIs equip the entire multidisciplinary care team with a sophisticated yet concise resource for managing patients receiving oral or IV oncolytics. This PQI in Action is a follow up to the Erythropoietin Stimulating Agent Ineligibility in Myelodysplastic Syndromes PQI and explores how the medically integrated teams at Florida Cancer Specialists and Massachusetts General Hospital North Shore Cancer Center incorporate PQIs as part of their daily workflow. This article will discuss how utilizing the Erythropoietin Stimulating Agent Ineligibility in Myelodysplastic Syndromes PQI elevates patient care.

Florida Cancer Specialists & Research Institute (FCS) was founded in 1984 and utilizes a comprehensive, multidisciplinary approach to cancer treatment and care. Innovative clinical research, cutting-edge technologies, and advanced treatment therapies all contribute to their reputation of excellence and the exceptional and compassionate care they strive to deliver. Their mission, vision and values align closely with NCODA, including providing world-class cancer care, being patient-centered and working together as a team. With over 250 physicians, 220 nurse practitioners and physician assistants and nearly 100 locations in their network, FCS is committed to providing world-class cancer care in community-based settings throughout Florida. Currently, FCS serves patients on the Gulf Coast from Naples to Tallahassee, Central Florida and on the East Coast from Palm Beach County to Jacksonville. This PQI in Action highlights members of the FCS practices in Fort Myers, FL and Tallahassee, FL.

Massachusetts General North Shore Cancer Center is located in Danvers, MA and combines the talent and expertise of physicians from Salem Hospital with those from Massachusetts General Hospital. The multidisciplinary teams are nationally recognized for their expertise in cancer care including screening and prevention, diagnosis, medical, radiation and surgical oncology treatment and rehabilitation. Patients have access to tailored treatment regimens, including but not limited to, infusion, radiation and surgical treatments, comprehensive imaging, dedicated blood lab and pharmacy on-site, and comprehensive support programs including wellness services, support groups and a resource room.

THE PARTICIPANTS

Florida Cancer Specialists
Fort Myers, FL

Viralkumar Bhandari, MD
Medical Oncologist

Diane Cope, PhD, APRN, BC, AOCNP
Oncology Nurse Practitioner

Lauren Trisler, PharmD, BCOP
Clinical Oncology Pharmacist

Massachusetts General Hospital
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Stephanie Sanford, NP
Lead Oncology Nurse Practitioner

Brenna Rowen, PharmD, BCOP
Oncology Pharmacist Specialist

Anne Marie Haynes, RN, OCN, JD
Hematology/Oncology Nurse
The implementation of pharmacists as part of the medically-integrated team continues to add value as the complexity of cancer treatment evolves. This is especially important in the assessment and clinical review of therapy for myelodysplastic syndromes (MDS) and other disorders of the blood and marrow. As the care of patients with cancer continues to be challenged with high-cost therapies, medication shortages, regulatory requirements, and dwindling reimbursement, the oncology pharmacist is heavily relied on to provide support for the clinical team to improve overall cancer care and quality of life. Oncology pharmacists also play a key role in the education of patients and other health care providers, as they continue to be the experts on medication and side effect management.

Medically Integrated Pharmacy (MIP) teams continue to show that these models provide the best quality of care to oncology patients. In 2019 the Patient-Centered Standards for Medically Integrated Dispensing (MID): ASCO/NCODA Standards were published to provide standards for medically integrated dispensing of oral anticancer drugs and supportive care medications. Adoption of quality standards can help MID or MIP practices obtain optimal adherence and persistence rates, minimize the risk of toxicity with therapy, and positively affect patient health outcomes. The oncology pharmacists at Florida Cancer Specialists and Massachusetts General Hospital North Shore Cancer Center have adopted quality standards and best practices of their own to accommodate the needs of their patients and clinics, which are pivotal in assisting in the treatment plans of MDS patients.

Anne Marie Haynes, RN, OCN, JD at Massachusetts General Hospital North Shore Cancer Center finds tremendous benefit in having a pharmacist in her clinic. “I am SO grateful to our pharmacy group. The speed at which they can answer my questions, especially regarding drug-drug interactions and herbal interactions, allows me to get the information right back to the patient. I could not do my job without them.”

Viralkumar Bhanderi, MD at FCS comments on the MIP model at FCS “The benefit of having the integrated EMR system is priceless. The pharmacy can view our clinical notes and correct us if we are off. They are closely aligned with what we are doing and this is all excellent for the patient.” He continues “The counseling our pharmacy provides for these patients is superior to anything they receive filling with an outside pharmacy. We are able to connect with them right away, as soon as the medication is prescribed and dispensed, so the patient is aware when to start and what to expect.” Diane Cope, PhD, APRN, BC, AOCNP, also at FCS, adds “RX To Go tremendously improves the overall patient experience that FCS offers. The education alone that our pharmacy team provides the patient is unmatched by an outside pharmacy. Our team is very responsive to patients, ensuring timely delivery of drug, adherence to oral therapies and just building the personal relationship with the patients.”
Myelodysplastic syndromes (MDS) are a family of myeloid cancers with diverse genotypes and phenotypes characterized by ineffective hematopoiesis and risk of transformation to acute myeloid leukemia (AML).\textsuperscript{3} Most MDS cases are caused by randomly acquired somatic gene mutations, with more than 80\% of patients harboring at least one mutation, whose identity may often influence the prognosis of disease.\textsuperscript{4} Prognostic systems, such as the revised International Prognostic Scoring System (IPSS-R), help to categorize MDS mutations while also taking into account the varying degrees of bone marrow functionality, to determine risk groups that help guide treatment.\textsuperscript{3-8}

The Erythropoietin Stimulating Agent Ineligibility in Myelodysplastic Syndromes PQI provides a precise and concise overview of the treatment of lower risk MDS patients with symptomatic anemia, specifically those experiencing suboptimal responses or treatment failure with erythropoietin stimulating agents. The Description and Background sections of the Erythropoietin Stimulating Agent Ineligibility in Myelodysplastic Syndromes PQI include the purpose of the PQI and information on risk stratification using the IPSS-R system, treatment of MDS patients with erythropoietin stimulating agents (ESAs) and factors to consider when patients fail this treatment.

### REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R) IN MDS\textsuperscript{7}

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score 0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>3.0</th>
<th>4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow blast (percent)</td>
<td>≤2</td>
<td>&gt;2 to &lt;5</td>
<td>5 to 10</td>
<td>&gt;10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>≥10</td>
<td>8 to &lt;10</td>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (cells/microL)</td>
<td>≥100</td>
<td>50 to 100</td>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count (cells/microL)</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### IPSS-R MDS RISK GROUPS AND PROGNOSIS\textsuperscript{7}

<table>
<thead>
<tr>
<th>Risk group</th>
<th>IPSS-R score</th>
<th>Median overall survival (years)</th>
<th>Median time to 25 percent AML evolution (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>≤1.5</td>
<td>8.8</td>
<td>&gt;14.5</td>
</tr>
<tr>
<td>Low</td>
<td>&gt;1.5 to 3.0</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;3 to 4.5</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>&gt;4.5 to 6</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;6</td>
<td>0.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Upon diagnosis of lower risk MDS, 3 primary cytopenias are observed including anemia (80-85%), thrombocytopenia (30-45%) and neutropenia (40%). Supportive care including close observation, clinical monitoring of symptoms, psychosocial support and quality of life assessments should all be part of caring for these patients. Red blood cell (RBC) transfusions typically become standard care amongst lower-risk MDS patients with symptomatic anemia, but these chronic transfusions carry risks including infection, cardiac risks, increased morbidity and lower overall quality of life. Transfusions are also inconvenient to patients and caregivers as they are time consuming, often require admission to a hospital for increased monitoring (serum labs, iron chelation) and overall increasing costs to the medical system. Symptomatic anemia can also vary from patient to patient depending on risk factors, mutation status, age and other comorbidities. Transfusions should be ordered on a case by case basis and should not always be dependent on a lab value. Furthermore, patients should also be assessed following transfusions, not only by looking at lab values, but by asking them if they are feeling improvement from the transfusion. Haynes at Massachusetts General Hospital North Shore Cancer Center comments “We really should be asking patients how they feel and using this information more than just looking at the numbers. If the hemoglobin improves but the patient is not feeling better, this defeats the purpose of continually transfusing or giving drug therapy in these patients.” Brenna Rowen, PharmD, BCOP at Massachusetts General Hospital North Shore Cancer Center adds “We try to get patients to correlate their symptoms based on knowledge they have from what their normal looks like. These patients sometimes walk around with hemoglobin levels of 8.9 gm/dL, which looks like a lab we want to treat. But if they are not symptomatic, we should not always transfuse them based on a lab value. This is an area where we could all do better – having these conversations with these patients and empowering them to be involved in making treatment decisions.”

The IPSS-R charts shown here are included in the supplemental section of the Erythropoietin Stimulating Agent Ineligibility in Myelodysplastic Syndromes PQI and are referenced in the Background section of the PQI. In addition, the PQI Background reviews the treatment of these patients with ESA therapy, including agents such as epoetin and darbopoetin. Patient response to the ESA agents can be variable and impermanent, generally yielding an erythroid response of at least 1.5 g/dL increase in hemoglobin in 20-60% of MDS patients. Factors considered to be predictive of favorable response of MDS anemia to ESA agents include low baseline endogenous erythropoietin levels (< 500 mU/mL, preferably < 200 mU/mL), low (< 2 per month) or no RBC unit transfusion requirement, and disease cytogenetics (absence of del(5q)) and less than 2 somatic mutations. Patients with del(5q) disease, serum EPO levels > 500 mU/mL, or heavy transfusion dependence would commonly be considered ineligible for a trial of ESA therapy. Primary resistance to ESA therapy is possible in these patients, with initial responses waning in up to 70% of cases within 18 to 24 months of initiating therapy.
Patients with lower-risk disease, who make up two-thirds of the MDS population, suffer predominately from anemia. The PQI Process section of the Erythropoietin Stimulating Agent Ineligibility section displays an exceptional step-wise chart to walk the user through treatment options based on risk factors, mutations, EPO levels, etc.

### THE PQI PROCESS: ASSESSING THE LOW RISK MDS PATIENT FOR ANEMIA, TREATMENT SELECTION AND MONITORING PARAMETERS

#### TREATMENT ALGORITHM FOR SYMPTOMATIC ANEMIA IN LOWER RISK MDS PATIENTS

- If symptomatic anemia is present, proceed through the stepwise algorithm to determine treatment.
- Recommended starting dose of ESA:
  - Epoetin alfa or biosimilar 40,000–60,000 units subcutaneously 1-2 times per week
  - OR
  - Darbepoetin alfa 150-300 mcg subcutaneously weekly to every other week
- Assessment for ESA response by 6 to 8 weeks of treatment:
  - 1.5 g/dL rise in hemoglobin
  - And/or
  - Decrease in RBC transfusion requirements by 3-6 months of treatment
- Target hemoglobin range 10 to 11 g/dL; not to exceed 11g/dL
- If desired response not reached can consider add on therapy with agent such as lenalidomide or granulocyte-colony stimulating factor
- Luspatercept is a non-chemotherapy option in patients with ESA ineligibility/lack of response
  - Inject 1 mg/kg once every 3 weeks subcutaneously

**RS:** ring sideroblasts; **EPO:** erythropoietin; **ESA:** erythropoietin stimulating agent; **IST:** immunosuppressive therapy.
All participants collectively agreed that the stepwise algorithm portion of the PQI is extremely helpful. Once you know mutation status and have an EPO level, determination of treatment is effortless when following this chart. Lauren Trisler, PharmD, BCOP from FCS comments “I love the simplicity of the breakdown criteria on EPO levels and when ESA should be used. This section within the PQI Process is extremely helpful in determining treatment of our MDS patients.” Bhanderi continues “This PQI is a really great document to guide optimal therapy for these patients. It ensures that we are selecting the correct patient group for ESA therapy and also ensures that if patients are not responding that we are moving on to different therapies to ensure disease is not progressing.”

**PATIENT-CENTERED ACTIVITIES:**
**COUNSELING PATIENTS AND PROVIDING THE RESOURCES AND TOOLS THEY NEED FOR SUCCESSFUL TREATMENT**

With the patient always at the center of what we do, we follow the PQI Process section with Patient-Centered Activities. This section is key to what we want to tell the patients when they begin treatment on ESA therapy or luspatercept injection. It is important to stress to patients beginning ESA therapy that responses may take up to 8-12 weeks. Within around 3 months of therapy initiation, 30-60% of patients experience an erythroid response defined by hemoglobin increase of 1.5 gm/dL in transfusion-independent patients or significant reduction or disappearance of transfusion need in transfusion-dependent patients. Nevertheless, primary resistance to ESA therapy is frequent and most responders relapse in 70% of the cases most likely due to loss of sensitivity of erythroid progenitors to ESAs.

Luspatercept is a recombinant fusion protein made up of a modified extracellular domain of the human activin receptor type IIB linked to the human IgG1 Fc domain that binds transforming growth factor beta (TGF) ligands to reduce SMAD2 and SMAD3 signaling, which enables erythroid maturation. In April 2020, based on encouraging phase III data, the FDA approved luspatercept for the treatment of anemia in patients with lower-risk MDS with ring sideroblasts who have failed treatment with ESAs. For patients with lower-risk MDS and ring sideroblasts who require frequent RBC transfusions and are refractory or intolerant to ESAs, luspatercept remains an option.

Luspatercept is currently available in 25 mg and 75 mg vials for injection. Vials should be stored at refrigerated temperatures (2 – 8 degrees Celsius) and in the original container, protected from light until use. To prepare a dose for a patient, reconstitute with 0.68 mL (25 mg vial) or 1.6 mL (75 mg vial) of sterile water for injection to a final concentration of...
Heathcare providers continually look for ways to empower patients to own their disease and be active participants in their treatment choices and care decisions. This is particularly important in patients with lower-risk MDS, as they need to be able to recognize symptoms of anemia and alert their care teams to assist in making treatment decisions. Both teams at Florida Cancer Specialists and Massachusetts General North Shore Cancer Center provide treatment care plans upon completion of patient visits that summarize treatment given, monitoring parameters and dates for future appointments. Even with these references and resources given to patients, both centers agree that patients may need more and that specifically patients helping to track blood transfusion dates and times may be helpful.

When placing a patient on luspatercept for treatment of MDS anemia, it is recommended to follow the guidelines below:

- Advise patient of risk of increased blood pressure especially if patient has baseline history of hypertension
- Advise patient on signs/symptoms of venous thromboembolism, stroke, myocardial infarction and when to contact healthcare provider or proceed to ER for evaluation
- Counsel patient on most common side effects

When placing a patient on ESA therapy for treatment of MDS anemia, it is recommended to follow the guidelines below:

- Advise patient of risk of increased blood pressure especially if patient has baseline history of hypertension
- Advise patient on signs/symptoms of venous thromboembolism, stroke, myocardial infarction and when to contact healthcare provider or proceed to ER for evaluation
- Counsel patient to notify team of any upcoming surgical procedures as DVT prophylaxis is recommended in perisurgery patients
- Educate that response to ESA therapy typically takes at least 6–8 weeks but can take up to 12 weeks
- Counsel patient regarding risk of cutaneous reactions including rash but also severe reactions such as erythema multiforme and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)

When following the research in hematology and oncology, many clinicians already have an idea which patients will benefit from treatments that are showing encouraging results in clinical patient trials. The clinicians at Massachusetts General Hospital North Shore Cancer Center were eager to begin luspatercept treatment on their lower-risk MDS patients who were not responding to ESA treatment. Rowen at Massachusetts General Hospital North Shore Cancer Center saw the need for an improvement in the screening and treatment assessment for these patients and developed a Pharmacist-led Luspatercept Dose Monitoring Program. This program ensures that all patients receiving luspatercept are appropriately screened to begin therapy. Stephanie Sanford, lead nurse practitioner at Mass General Hospital North Shore Cancer Center comments on the initiation of this program. “When luspatercept was approved, we had 12 patients who were likely candidates for this medication. These patients had failed ESA therapy and were on supportive care. Brenna created a spreadsheet for us to track trends of these patients and monitor for the development of ringed sideroblasts, outside of our EMR system, which worked for us at this time to determine eligibility. Now she (Brenna) runs the show and just instructs us on what to do, as she has incorporated more into the program.”
Trisler at FCS discusses the possibility of a phone application where patients could enter and track information. “With everyone linked through technology these days, it might be as simple as developing an app for smartphones where patients can easily enter data and track symptoms and dates and times of blood transfusions. This data could then somehow be sent to the provider through a secure network or through email.”

As noted earlier, lower-risk MDS patients often have the burden of receiving consistent blood transfusions. When patients receive these transfusions outside of the oncology clinic, it is often difficult to locate exact times and infusion dates within EMR systems. The oncology teams are always looking for more helpful ways to house or track these infusions. If not recorded properly by the staff, the team often relies heavily on the patient to give them the infusion information to document in the EMR. Cope comments “There is no good way to identify when our patients received blood transfusions. We are consistently digging in several areas of the EMR chart for this information.” Sanford adds “Finding transfusion information in our EMR system is like bean counting. Trying to track when patients received transfusions and trends has always been tricky. This is definitely an area that could be improved upon.”

Patients are also encouraged to visit the patient resources sections of drug manufacturer websites for helpful information. For lower-risk MDS patients requiring treatment with Reblovyl® (luspatercept), the website offers detailed information in easy to understand formats for patients. Included in these resources, patients will learn about the treatment of luspatercept, how often it is given, what to expect following treatment and also information regarding patients who received this treatment in studies and how they responded. There are also pages included with helpful tracking information on hemoglobin levels, patient symptoms, RBC transfusions, and a section where patients can record notes if needed.

"WITH EVERYONE LINKED THROUGH TECHNOLOGY THESE DAYS, IT MIGHT BE AS SIMPLE AS DEVELOPING AN APP FOR SMART PHONES WHERE PATIENTS CAN EASILY ENTER DATA AND TRACK SYMPTOMS AND DATES AND TIMES OF BLOOD TRANSFUSIONS. THIS DATA COULD THEN SOMEHOW BE SENT TO THE PROVIDER THROUGH A SECURE NETWORK OR THROUGH EMAIL."
Lauren Trisler, PharmD, BCOP

“FINDING TRANSFUSION INFORMATION IN OUR EMR SYSTEM IS LIKE BEAN COUNTING. TRYING TO TRACK WHEN PATIENTS RECEIVED TRANSFUSIONS AND TRENDS HAS ALWAYS BEEN TRICKY. THIS IS DEFINITELY AN AREA THAT COULD BE IMPROVED UPON.”
Stephanie Sanford, NP

CONCLUSION: NCODA, THE MEDICALLY INTEGRATED TEAM AND BRIDGING THE GAP WITH THE ERYTHROPOIETIN STIMULATING AGENT INELIGIBILITY IN MYELODYSPLASTIC SYNDROMES PQI

The benefits of the medically integrated team continue to show us that this model is essential for the overall care of oncology patients. Rowen speaks on pharmacy being a key component to the medically integrated system. “Our pharmacy is at the forefront of making clinical decisions for these patients. We are often the most constant team members our patients interact with. I really feel like we are the glue between every member of the team and the patient to provide the optimal care.”

The Erythropoietin Stimulating Agent Ineligibility in Myelodysplastic Syndromes PQI provides the medically integrated team with a precise and concise reference docu-
ment that guides treatment selection when treating patients with lower-risk MDS. Cope at FCS comments on the PQI, “The PQI is an extremely helpful document. I love that it is quick, direct and clear information.” Empowering the team with the tools to effectively educate, counsel and treat onco-
logy patients with lower-risk myelodysplastic syndromes who fail ESA treatment meets NCODA’s Guiding Values of being Patient-Centered and Always Collaborative.

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12. Santini V. “Treatment of low-risk myelodysplastic syndromes.” He-
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16. Procrit (epoetin alfa) [prescribing information].
17. Reblozyl (luspatercept) [prescribing information].

ON THE COVER:

• Massachusetts General North Shore Cancer Center team members from left to right - Stephanie Sanford, NP, Brenna Rowen, PharmD, BCOP, Anne Marie Haynes, RN, OCN, JD.
Helpful Online Resources

- NCODA Website
- Positive Quality Interventions
- Oral Chemotherapy Education Sheets
- Erythropoietin Stimulating Agent Ineligibility in Myelodysplastic Syndromes PQI

PQI Principles:

1. Identify lower-risk MDS patients using the IPPS-R scoring system
2. Follow treatment algorithms for symptomatic anemia
3. Based on disease mutation or other factors, determine treatment for anemia
4. If patients become unresponsive to ESA treatment, consider other therapies per algorithm
5. Once treatment is determined, counsel patient on expectations and side effects of treatment
Practice panelist’s comments reflect their experiences and opinions and should not be used as a substitute for medical judgment.

Important notice: NCODA has developed this Positive Quality Intervention in Action platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional.

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