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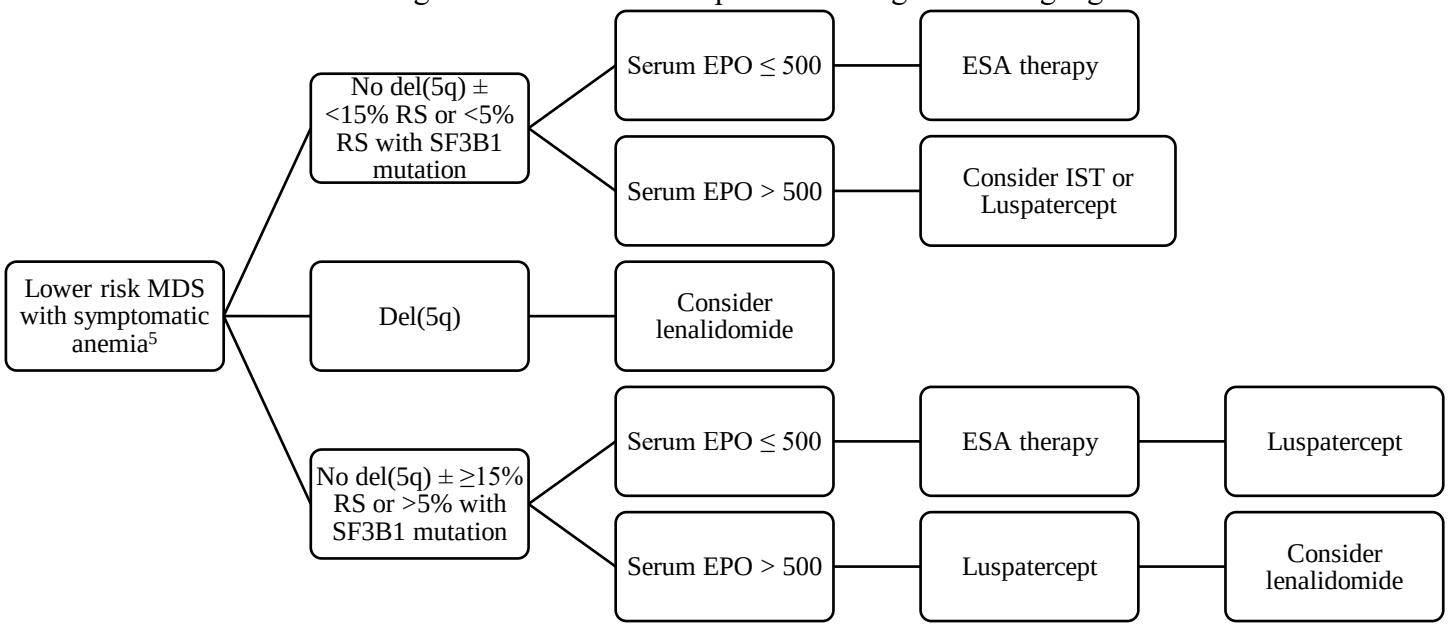
Positive Quality Intervention: Erythropoietin Stimulating Agent Ineligibility in Myelodysplastic Syndromes

Description: This PQI is centered on erythropoietin stimulating agent (ESA) ineligibility in patients with myelodysplastic syndromes (MDS), as well as understanding when an MDS patient fails ESA treatment or has a suboptimal ESA response.

Background: MDS are chronic disorders of clonal hematopoiesis leading to peripheral cytopenias, primarily anemia, which can ultimately progress to bone marrow failure and acute myeloid leukemia. Patients suffering from MDS are stratified by the revised International Prognostic Scoring System (IPSS-R) into risk groups ranging from very low to very high risk (Tables 1 and 2 in Supplemental Information).[4-5] The treatment of lower risk MDS is typically focused on optimizing patients' quality of life and providing support for symptomatic anemia. ESA agents, including epoetin and darbepoetin, are commonly used to treat MDS-associated anemia in lower risk disease to avoid chronic transfusions and the risk of iron overload, but patient response to these agents can be variable and impermanent.[3-6] Generally, administration of ESAs yields an erythroid response; at least 1.5 g/dL increase in hemoglobin or decrease in need for RBC transfusion, in 20-60% of MDS patients with anemia.[4,6] Factors considered to be predictive of favorable response of MDS anemia to ESA agents include low baseline endogenous erythropoietin (EPO) levels (< 500 mU/mL, but preferably < 200 mU/mL), low (< 2 per month) or no RBC unit transfusion requirement, and disease cytogenetics, namely absence of del(5q) and less than 2 somatic mutations.[2,4,6,8] Conversely, 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.[2,10] Primary resistance to ESA agents is possible, and, even if these patients do have an initial response to ESA therapy, in up to 70% of cases this response tends to wane within 18 to 24 months.[6-7]

PQI Process:

- Upon diagnosis or clinical review of a MDS patient, patient should be assessed for symptomatic anemia and evaluated for differential diagnosis and then should proceed through following algorithm:



RS: ring sideroblasts; EPO: erythropoietin; ESA: erythropoietin stimulating agent; IST: immunosuppressive therapy.

- ESA Eligible Patients
  - Characteristics
    - No del(5)q
    - EPO levels ≤ 500
    - No del(5)q with < 5% RS or <15% RS with SF3B1 mutation
      Or
    - No del(5)q with > 5% RS or >15% RS with SF3B1 mutation
  - Recommended starting dose of ESA[7]
    - 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[6]
    - 1.5 g/dL rise in hemoglobin
      And/or
    - Decrease in RBC transfusion requirements by 6-8 weeks of treatment
  - Target hemoglobin range 10 to 11 g/dL; not to exceed 11 g/dL[1,4,7,9]
  - If desired response not reached can consider add on therapy with agent such as lenalidomide or granulocyte-colony stimulating factor[2,4,6]
- ESA Ineligible Patients:
  - Characteristics:
    - No del(5)q
    - EPO levels > 500
    - No del(5)q with < 5% RS or <15% RS with SF3B1 mutation
      Or
    - No del(5)q with > 5% RS or >15% RS with SF3B1 mutation
  - IST or luspatercept
  - Lenalidomide for patients with del(5)q mutation
- Luspatercept is a non-chemotherapy option in patients with ESA ineligibility/lack of response
  - Inject 1 mg/kg once every 3 weeks subcutaneously
- Avoid use of ESAs in patients who also have concomitant diagnosis of solid tumor malignancy and are undergoing active treatment
  - ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with solid tumor malignancy
  - ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure[9]

Patient-Centered Activities:

- If patient is decided to start on ESA for treatment of MDS anemia
  - Advise patient of risk of increased blood pressure especially if patient has baseline history of hypertension[1,9]
  - Advise patient on signs/symptoms of venous thromboembolism, stroke, and 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)
- If patient is to start on luspatercept for treatment of MDS anemia
  - Advise patient of risk of increased blood pressure especially if patient has baseline history of hypertension[11]
  - Advise patient on signs/symptoms of venous thromboembolism, stroke, and myocardial infarction

and when to contact healthcare provider or proceed to ER for evaluation
- Counsel patient on most common side effects
  - Blistering, peeling, or loosening of the skin, red skin lesions, severe acne or a skin rash, sores or ulcers on the skin, or fever or chills

References:

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4. Fenaux P, Adès L. How we treat lower-risk myelodysplastic syndromes. Blood. 2013 May 23;121(21):4280-6. doi: 10.1182/blood-2013-02-453068. Epub 2013 Apr 10.
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7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myelodysplastic Syndromes V.3.2022. ©
8. Park S, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood. 2008 Jan 15;111(2):574-82.
9. Procrit® (epoetin alfa) [prescribing information].
10. Santini V. Treatment of low-risk myelodysplastic syndromes. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):462-469. doi: 10.1182/asheducation-2016.1.462.
11. Reblozyl® (luspatercept-aamt) [prescribing information].

Supplemental Information:

Table 1. Revised international prognostic scoring system (IPSS-R) in myelodysplastic syndrome[5]

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

Table 2. IPSS-R myelodysplastic syndrome risk groups and prognosis[5]

Risk group	IPSS-R score	Median overall survival (years)	Median time to 25 percent AML evolution (years)
Very low	≤1.5	8.8	>14.5
Low	>1.5 to 3.0	5.3	10.8
Intermediate	>3 to 4.5	3.0	3.2
High	>4.5 to 6	1.6	1.4
Very high	>6	0.8	0.7