Written by: Caroline Jones, PharmD
UVA Health

Positive Quality Intervention: Imetelstat (RYTELO®) in the treatment of low-to-intermediate-1-risk myelodysplastic syndromes (MDS)

Description:
The purpose of this PQI is to discuss clinical considerations around the use of imetelstat (RYTELO®) to optimize outcomes for patients with low-to-intermediate-1-risk myelodysplastic syndromes (MDS).

Background:
Imetelstat is FDA approved for the treatment of adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA). Imetelstat is an oligonucleotide that targets human telomerase (hTR). By binding to hTR, it inhibits the enzyme's activity and prevents the attachment of telomeres, thereby interfering with telomerase function. Continuous upregulation of telomerase function has been linked to the ineffective hematopoiesis seen in MDS.[1,2]
The IMerge trial was a phase 3, randomized, double-blind, placebo-controlled study evaluating the effectiveness of imetelstat in 178 patients with lower-risk MDS (118 in the imetelstat group and 60 in the placebo group).[3] Imetelstat 7.5 mg/kg (equivalent to imetelstat 7.1 mg/kg) was administered every 4 weeks via a 2-hour intravenous infusion. Efficacy was assessed following a median follow-up of 19.5 months for the imetelstat group and 17.5 months for the placebo group. In the imetelstat group, 40% of patients experienced a ≥ 8 consecutive week red blood cell transfusion independence (RBC-TI), compared to 15% in the placebo group. A minimum of ≥ 24 weeks RBC-TI was observed in 28% of imetelstat-treated patients vs 3.3% of patients receiving placebo. Imetelstat also led to improvement in patient-reported fatigue (assessed by the Functional Assessment of Chronic Illness Therapy Fatigue Scale [FACIT-Fatigue]). Fifty percent of imetelstat treated patients reported sustained meaningful improvement in fatigue in the FACIT-Fatigue scale (defined as an increase of at least three points on the FACIT-Fatigue for at least two consecutive cycles) compared with 40% of 57 patients treated with placebo.[3] Common side effects included decreased platelets and neutrophils, as well as fatigue and increased liver enzymes. The most frequent Grade 3/4 adverse events were neutropenia (68% of patients who received imetelstat vs 3% who received placebo) and thrombocytopenia (62% vs 8%). Rates of Grade 2/3 bleeding and infections were comparable. In patients receiving imetelstat, cytopenias were manageable, typically short-lived, and over 80% resolved to Grade 2 or lower within 4 weeks.[3]

PQI Process:[2]

- Review patient's chart for therapy appropriateness
  - Low-to-intermediate-1 risk MDS with transfusion-dependent anemia requiring 4 or more RBC units over 8 weeks who have not responded to, lost response to, or are ineligible for ESA
  - Verify pregnancy status prior to initiating treatment
- Confirm appropriate dose and schedule
  - Reconstitute lyophilized powder 0.9% Sodium Chloride for Injection
  - 7.1 mg/kg IV over 2 hours every 4 weeks
  - There are no recommended initial dose adjustments for *baseline* renal or hepatic impairment
  - Discontinue imetelstat if patient does not experience a decrease in RBC transfusion burden after 24 weeks (6 doses) or if unacceptable toxicity occurs
- Infusion reaction prevention and monitoring

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  - Administer pre-medications at least 30 minutes prior to imetelstat administration
    - Diphenhydramine (or equivalent) 25 mg – 50 mg, IV or PO
    - Hydrocortisone (or equivalent) 100 mg – 200 mg, IV or PO
  - Monitor patients for at least 1 hour after the completion of the infusion
  - See supplemental information for management of infusion reactions
- Common adverse reactions
  - Thrombocytopenia, neutropenia, infusion reactions, increased liver enzymes
    - Obtain complete metabolic panel prior initiation of imetelstat and prior to each cycle
    - Obtain complete blood counts with differential prior to initiation of imetelstat, weekly for the first two cycles, and prior to each cycle thereafter
    - Delay the next cycle if absolute neutrophil count (ANC) is less than 1 x 10^9/L or platelets are less than 50 x 10^9/L
    - If neutropenic, consider antimicrobial prophylaxis as appropriate
    - Administer platelet transfusions as needed
  - See supplemental information for additional recommendations for management and dose adjustments

Patient-Centered Activities:[2]

- Counsel patient on imetelstat with written materials
- Review adverse effects and instruct patient to report any symptoms
  - Neutropenia: fever, chills, sore throat
  - Thrombocytopenia: bleeding that doesn't eventually slow then stop
- Inform female patients of reproductive risk and importance of effective contraception during treatment and for 1 week after the last dose
- Advise female patients not to breastfeed during treatment and for 1 week after the last dose

References:

1. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT0259866.
2. Rytelo (imetelstat) Prescribing Information. Geron Corp;2024.
3. Platzbecker U, Santini V, Fenaux P, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024;403(10423):249-260.

Supplemental Information:[2]

Dose Reductions for Grade 3 and Grade 4 Adverse Reactions

Dose Reduction	Dose Every 4 Weeks
First dose reduction	5.6 mg/kg
Second dose reduction	4.4 mg/kg

Permanently discontinue imetelstat if the patient cannot tolerate the lowest dose level of 4.4 mg/kg

Dose Modifications for Adverse Reactions

Adverse Reaction	Severity Grade[a]	Occurrence	Treatment Modification
Thrombocytopenia	Grade 3	First	Delay imetelstat until platelets recover to 50 x 10^9/L; restart at same dose level
		Second and Third	Delay imetelstat until

			platelets recover to 50 x 10^9/L; restart at one dose level lower
		Fourth	Discontinue imetelstat
	Grade 4	First and Second	Delay imetelstat until platelets recover to 50 x 10^9/L; restart at one dose level lower
		Third	Discontinue imetelstat
Neutropenia	Grade 3	First	Delay imetelstat until ANC recovers to 1 x 10^9/L; restart at same dose level
		Second and Third	Delay imetelstat until ANC recovers to 1 x 10^9/L; restart at one dose level lower
		Fourth	Discontinue imetelstat
	Grade 4	First and Second	Delay imetelstat until ANC recovers to 1 x 10^9/L; restart at one dose level lower
		Third	Discontinue imetelstat
Infusion-Related Reactions	Grade 2 or 3	First and Second	Interrupt imetelstat infusion until resolution of adverse reaction or until the intensity of the reaction decreases to Grade 1; restart infusion at 50% of the infusion rate administered prior to adverse reaction
		Third	Grade 2: stop infusion. Resume at next cycle Grade 3: permanently discontinue imetelstat
	Grade 4	First	Stop infusion, administer supportive care, and permanently discontinue imetelstat
Other adverse reactions including elevated LFTs	Grade 3 or 4	First and Second	Delay imetelstat until recovery of adverse reactions to Grade 1 or baseline; restart at one dose level lower
		Third	Permanently discontinue imetelstat

[a] Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03