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Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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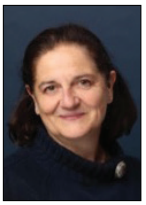
Using Imetelstat for Lower-Risk Myelodysplastic Syndromes



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H&O Who is eligible for treatment with imetelstat?

VS Imetelstat (Rytelo, Geron) is approved for use in adults with myelodysplastic syndromes (MDS) of low to intermediate-1 risk who have transfusion-dependent anemia requiring 4 or more red blood cell (RBC) units over 8 weeks and who have not responded to, have lost their response to, or are ineligible for erythropoiesis-stimulating agents (ESAs).

H&O What unmet medical need was imetelstat designed to address?

VS When MDS become refractory to ESAs, patients frequently become transfusion dependent. Transfusion dependence decreases both quality of life and survival, so the unmet clinical need was (and still is) to find a treatment that could improve the hemoglobin levels of these patients. Not only is imetelstat effective in patients at lower risk and with MDS refractory to or ineligible for treatment with ESAs; it also can be used in patients who have already received an agent such as luspatercept (Reblozyl, Celgene/BMS). The eligibility of luspatercept is similar to that of imetelstat, but imetelstat has the important advantage of being active in patients who have a high transfusion burden (>6 RBC units in 8 weeks).

H&O What is the mechanism of action of imetelstat, and why is telomerase inhibition relevant in MDS pathogenesis?

VS Imetelstat is a direct and competitive oligonucleotide inhibitor of telomerase, although we are not certain that telomerase inhibition is the mechanism responsible for the clinical response in MDS. Telomerase activity is increased in dysplastic hematopoietic stem cells, which allows the expansion of dysplastic clones in MDS, but other factors are at play as well. I am currently involved in a study to examine what mechanism of action of imetelstat is inducing improvement of erythropoiesis in MDS. We may find that a noncanonical activity or pathway that we did not explore earlier is responsible, or it could indeed be the inhibition of telomerase that creates the clinical response. We would also like to know which cells are targeted. The data we have produced from the IMerge clinical registration study are indicative of disease modification, showing a decrease in the burden of mutations, a cytogenetic complete response in parallel with an increase in hemoglobin, and transfusion independence. Further data are needed for us to be able to correlate telomerase inhibition with the clinical activity of the drug.

H&O Could you discuss the design and results of the IMerge trial that led do the approval of imetelstat?

VS IMerge was a double-blind, placebo-controlled phase 3 trial that took place across 17 countries.[1] It enrolled 178 adults with ESA-relapsed, ESA-refractory, or ESA-ineligible MDS of low or intermediate-1 risk by International Prognostic Scoring System (IPSS) criteria. Patients were randomly assigned in a 2:1 ratio to receive imetelstat at

7.5 mg/kg or a placebo. Treatment was administered as a 2-hour intravenous infusion every 4 weeks until progression of disease, unacceptable toxic effects, or withdrawal of consent. Patients were stratified by previous transfusion burden and IPSS risk group. The primary endpoint was transfusion independence lasting more than 8 weeks, evaluated at week 24.

A total of 118 patients were assigned to imetelstat and 60 were assigned to placebo between September 11, 2019, and October 13, 2021. More than half of the participants (62%) were male, and the median age was 72 years in the imetelstat group and 73 years in the placebo group. The percentage of patients who discontinued treatment by the data cutoff was 77% in the imetelstat group and 75% in the placebo group.

After a median follow-up of 19.5 months in the imetelstat group and 17.5 months in the placebo group, transfusion independence lasting at least 8 weeks was achieved in 40% of those in the imetelstat group vs 15% of those in the placebo group. The rate of transfusion burden greater than 6 RBC units in 8 weeks was 48% in the imetelstat arm vs 45% in the placebo arm. The great majority of the patients treated had received previous ESA therapy and lost response. Only 22% had serum erythropoietin levels above 500 U/L, a value that correlated with lack of response and ineligibility for ESA treatment. Grade 3 or 4 treatment-emergent adverse events occurred in 91% of the patients on imetelstat and 47% of the patients on placebo. The most common grade 3/4 treatment-emergent adverse events in patients taking imetelstat were transient neutropenia (68% of patients who received imetelstat vs 3% of patients who received placebo) and transient thrombocytopenia (62% vs 8%, respectively), with no treatment-related mortality.

H&O How do the results of IMerge compare with those of previous research?

VS IMerge achieved its primary endpoint of transfusion independence lasting longer than 8 weeks in a patient population with a median age of 72 years. If we compare the results of IMerge with those of a similar study, the phase 3 MEDALIST study of luspatercept,[2] the rates of transfusion independence are equivalent. In the IMerge study, 40% of patients receiving imetelstat achieved transfusion independence for longer than 8 weeks, whereas in the MEDALIST study, 37.9% of the luspatercept-treated patients achieved RBC transfusion independence (RBC-TI) lasting at least 8 weeks vs 13.2% of placebo-treated patients at weeks 1 to 24 of treatment.[2] When patients were assessed during the entire treatment period, a longer period of evaluation and follow-up than that of IMerge, a greater proportion of patients achieved transfusion independence with luspatercept (47.7%). A total of 40% of the patients in the IMerge study were ring sideroblast–negative, however, and imetelstat was equally active in these patients, so these results cannot be compared directly with those of MEDALIST, in which all patients had ring sideroblasts (MDS-RS). In addition, I want to stress that the majority of patients in IMerge had a high transfusion burden of more than 6 units in 8 weeks. Luspatercept does not have activity in MDS with a high transfusion burden.

Patients who have the longest responses to imetelstat, lasting more than a year, show in parallel a significant decrease in the variant allele frequency of somatic mutations.

H&O What is the safety profile of imetelstat, especially regarding thrombocytopenia and neutropenia?

VS Imetelstat can lead to myelosuppression that induces both thrombocytopenia and neutropenia. When these adverse events occur, delaying administration of the drug and decreasing the dose cause them to resolve. None of my patients with MDS who are taking imetelstat have required specific treatment for thrombocytopenia or neutropenia, and few infections have occurred. What I recommend to the treating physician is to be cautious in using imetelstat if the patient is severely thrombocytopenic or neutropenic at baseline.

H&O How do you define and measure transfusion independence in clinical practice?

VS We keep track of each patient's transfusion records, which we receive directly from the blood banks and blood centers, so we always know when a patient has received a transfusion, how many units have been transfused, and how much time has elapsed between transfusions. The hemoglobin threshold for administering a transfusion

must be maintained constantly to evaluate for possible improvements—that is, the policy of transfusion should be unmodified.

H&O What is the optimal duration of imetelstat treatment?

VS We need to administer treatment for at least 6 months to judge response. If a patient is responding to the agent, we continue until loss of response or progression.

H&O How do you monitor for response to imetelstat?

VS We monitor blood counts, hemoglobin level, and number of transfusions. During the clinical trial, a bone marrow aspiration was performed every 6 months. Outside clinical trials, I would evaluate bone marrow only in case of loss of response or suspected progression.

H&O How does imetelstat fit into the current treatment algorithm for patients with ESA-refractory, lower-risk MDS?

VS Imetelstat can be used in transfusion-dependent patients, especially if they have a ring sideroblast–negative subtype and a high transfusion burden, as I mentioned earlier. Imetelstat can also be used in patients with MDS who have a third-line need for treatment, such as those who have lost their response to luspatercept. In addition, evidence is accumulating for imetelstat activity after lenalidomide. A recent analysis of 226 patients from IMerge showed that patients could respond to imetelstat even if they had previously received luspatercept, lenalidomide, or a hypomethylating agent.[3]

H&O Is there anything you would like to add or emphasize?

VS We have observed that patients who have the longest responses to imetelstat, lasting more than a year (18% of patients treated with imetelstat), show in parallel a significant decrease in the variant allele frequency of somatic mutations (ie, the burden of acquired DNA mutations). With these data, the IMerge study showed for the first time that imetelstat does modify the dysplastic clone. This is different from what is observed with luspatercept, which does not affect the mutation burden. In addition, a cytogenetic response is present in approximately 35% of patients treated with imetelstat, providing further evidence of the disease-modifying effect of this drug.

The duration of response is also very important. Patients treated with imetelstat achieve responses that can be very long lasting. My personal experience is that patients can tolerate imetelstat very well for many years.

The last thing I would like to add is the fact that patients who are on imetelstat not only become transfusion dependent but also achieve normal or nearly normal levels of hemoglobin of up to 13 g/dL.

Disclosures

Dr Santini has served on the advisory boards of AbbVie, Ascentage Pharma, Bristol Myers Squibb, Geron, GSK, Servier, Novartis, Kura Oncology, Keros Therapeutics, and Jazz Pharmaceuticals.

References

1. 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.

2. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med*. 2020;382(2):140-151.

3. Komrokji RS, Santini V, Zeidan AM, et al. Effect of prior treatment (tx) on the clinical activity of imetelstat (IME) in transfusion-dependent (TD) patients (pts) with erythropoiesis-stimulating agent (ESA), relapsed or refractory (R/R)/ineligible lower-risk myelodysplastic syndromes (LR-MDS) [ASCO abstract 6569]. *J Clin Oncol*. 2025;43(16)(suppl).