

AHFS Final Determination of Medical Acceptance: Off-label Use of Lenalidomide in Transfusion-dependent Low-risk or Intermediate-1 Risk Myelodysplastic Syndrome without the Deletion 5q Chromosomal Abnormality

Drug/Drug Combination: Lenalidomide

Off-label Use: Treatment of transfusion-dependent low-risk or intermediate-1 risk myelodysplastic syndrome (MDS) without the deletion 5q chromosomal abnormality

Criteria Used in Selection of Off-label Use for Review:

- Periodic review of prior Final Determination for the purpose of updating medical acceptance. The current Final Determination supersedes the past review originally published in January 2009. At the time of the original review, the use of lenalidomide in transfusion-dependent low-risk or intermediate-1 risk myelodysplastic syndrome without the deletion 5q chromosomal abnormality was not fully established.

Strength of Evidence: Level 2 (Moderate strength/quality)

Strength of Study End Point(s): Hematologic improvement-erythroid (HI-E) response

Grade of Recommendation: Reasonable choice (Accepted, with possible conditions)

Narrative Summary:

Use in Myelodysplastic Syndrome without the Deletion 5q Chromosomal Abnormality:

Lenalidomide has been studied for the management of transfusion-dependent low-risk or intermediate-1-risk MDS in patients *without* the deletion 5q (del[5q]) chromosomal abnormality (non-del[5q])†.^{30,31} In a multicenter, phase 2, noncomparative clinical trial (MDS-002), 214 patients with transfusion-dependent anemia (i.e., requiring at least 2 units of red blood cells within 8 weeks prior to study treatment) secondary to low-risk or intermediate-1-risk MDS without the deletion 5q chromosomal abnormality received lenalidomide 10 mg once daily on days 1–21 of a 28-day cycle or 10 mg once daily continuously.³⁰ Treatment was administered cyclically upon initiation of the study, but the schedule was amended when data from a prior study in MDS suggested a faster onset of response to lenalidomide, with no apparent increase in toxicity, with continuous administration; patients were permitted to switch from cyclic to continuous treatment.³⁰ Sustained (for at least 8 weeks) hematologic improvement involving the erythroid cell line was reported in 43% of patients in this study, with 26% of patients achieving transfusion independence accompanied by an increase in hemoglobin concentration of at least 1 g/dL after a median of 4.8 weeks of treatment; the median duration of transfusion independence was 41 weeks.³⁰ An additional 17% of patients had a 50% or greater reduction in transfusions.³⁰ When the study data were analyzed to exclude minor responses and to use a more stringent definition of baseline transfusion dependence (transfusion of 4 or more units of red blood cells

in response to a hemoglobin concentration of 9 g/dL or less within 8 weeks prior to study treatment),^{30,33,34} 62% of patients had baseline transfusion dependence and 30% of those patients achieved a reduction in transfusion requirements equaling 4 or more units during any 8-week period during therapy.³⁰ In the subset of patients without baseline transfusion dependence, 37% achieved a sustained (for at least 8 weeks) increase in hemoglobin concentration of at least 1.5 g/dL during therapy.³⁰ Overall, 17 or 33% of patients achieved sustained (for at least 8 weeks) transfusion independence or hematologic improvement involving the erythroid cell line.³⁰ Grade 3/4 neutropenia and thrombocytopenia occurred in 30 and 25% of patients, respectively.^{30,31} There were no apparent differences in response and few differences in adverse effects between those who initiated therapy with cyclic administration and those who received only continuous daily dosing.³⁰ Efficacy of lenalidomide is being evaluated in a phase 3, placebo-controlled, clinical trial (MDS-005) in patients with low-risk or intermediate-1-risk MDS without the deletion 5q chromosomal abnormality who have transfusion-dependent anemia and are unresponsive to therapy with erythropoiesis-stimulating agents or have endogenous erythropoietin concentrations exceeding 500 mU/mL.³²

A post-hoc analysis of the MDS-002 and MDS-003 clinical trials demonstrated a correlation between treatment-related cytopenias and likelihood of achieving transfusion independence in patients with the deletion 5q chromosomal abnormality; however, no relationship between the development of treatment-related cytopenias and response could be established for lower-risk MDS patients without the deletion 5q abnormality.³¹

Use of lenalidomide for the treatment of transfusion-dependent low-risk or intermediate-1-risk MDS without the deletion 5q chromosomal abnormality is a reasonable choice (accepted, with possible conditions). However, randomized controlled studies in adequate numbers of patients are lacking; additional data are needed to further elucidate clinical benefit (i.e., hematologic improvement-erythroid response) and to assess the relevance of prognostic factors (e.g., transfusion requirement, baseline platelet count, duration of MDS, serum lactate dehydrogenase concentration) to lenalidomide response.

Dosage in Myelodysplastic Syndrome without the Deletion 5q Chromosomal Abnormality:

When used in adults for the treatment of transfusion-dependent low-risk or intermediate-1-risk MDS without the deletion 5q chromosomal abnormality, lenalidomide has been administered at a dosage of 10 mg once daily.³⁰

References:

30. Raza A, Reeves JA, Feldman EJ et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. *Blood*. 2008; 111:86-93. (PubMed 17893227)
31. Sekeres MA, Maciejewski JP, Giagounidis AA et al. Relationship of treatment-related cytopenias and response to lenalidomide in patients with lower-risk myelodysplastic syndromes. *J Clin Oncol*. 2008; 26:5943-9. (PubMed 19018091)
32. A study of lenalidomide versus placebo in subjects with transfusion dependent anemia in low risk myelodysplastic syndrome (MDS) without Del 5Q. From Clinical Trials (PDQ) database. Accessed 2013 Jan 30. (<http://www.cancer.gov/clinicaltrials/>)
33. Cheson BD, Bennett JM, Kantarjian H et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood*. 2000; 96:3671-4. (PubMed 11090046)

34. Cheson BD, Greenberg PL, Bennett JM et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006; 108:419-25. (PubMed 16609072) (doi: 10.1182/blood-2005-10-4149)

Oncology Expert Committee Voting Results:

Proposed Level of Evidence: Level 2 (Moderate strength/quality); hematologic improvement-erythroid (HI-E) response

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 1 vote

Reasonable choice (Accepted, treatment option): 4 votes

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Proposed Consensus Recommendation:

Use of lenalidomide for the treatment of transfusion-dependent low-risk or intermediate-1-risk myelodysplastic syndrome without the deletion 5q chromosomal abnormality is a reasonable choice (accepted, with possible conditions). However, randomized controlled studies in adequate numbers of patients are lacking; additional data are needed to further elucidate clinical benefit (i.e., hematologic improvement-erythroid response) and to assess the relevance of prognostic factors (e.g., transfusion requirement, baseline platelet count, duration of MDS, serum lactate dehydrogenase concentration) to lenalidomide response.

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

Oncology Expert Committee Members' Comments:

Comments in Support of Vote on Level of Evidence and Grade of Recommendation:

Reviewer #2: The MDS-002 study reported a possible correlation between transfusion burden less than 4 units RBC, baseline platelet count of 150,000 mm³ or higher, shorter duration of MDS, and an LDH less than or equal to the ULN, with higher rates of TI response. There would need to be further studies and stronger evidence of this correlation before these recommendations should be added to this review.

Reviewer #3: Needs additional study.

Comments on Draft Narrative Summary:

Reviewer #1: May consider giving the alternative dosing schedule of lenalidomide 10 mg daily for 21 days of a 28-day cycle since benefit and toxicity appears to be equal per phase II (Blood 2008).

Reviewer #2: I agree with this summary as written.

Reviewer #3: These data need a confirmatory study. Drug usually used in the single mutated 5q minus syndrome and less commonly with other mutations.

Comments on Proposed Consensus Recommendation:

None submitted.

Participants:

AHFS Staff Members (writing and editing): Lily Leu, Pharm.D., BCOP; Jane Miller, Pharm.D.

AHFS Oncology Expert Committee Members (reviewing and voting): Peter Rosen, M.D.; Mandy Gatesman, Pharm.D., BCOP; LeAnne Kennedy, Pharm.D., BCOP; Marc Earl, Pharm.D., BCOP; Christine Gegeckas, R.Ph., BCOP

External Consultants: None

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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