# MYELODYSPLASTIC SYNDROMES TREATMENT REGIMENS (Part 1 of 3)

**Clinical Trials:** The National Comprehensive Cancer Network recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

## First-Line Treatment[1]

**Note:** All recommendations are Category 2A unless otherwise indicated.

### Relatively Lower-Risk Patients[a,b]

#### Symptomatic Anemia With del(5q) ± One Other Cytogenetic Abnormality (except those involving chromosome 7)

| REGIMEN | DOSING |
|---|---|
| **Lenalidomide**[2-5,c] | **Days 1–21:** Lenalidomide 10mg orally once daily.<br>Repeat cycle every 28 days (or 28 days monthly). Assess response 2–4 months after initiation of treatment. |

#### Symptomatic Anemia Without del(5q) and Serum Erythropoietin ≤500mU/mL

| | |
|---|---|
| **rHu-Epo ± G-CSF**[6-11] | rHu-Epo 40,000-60,000 subcutaneous units 1–2 times weekly.<br>Repeat cycle 6–8 weeks. Add G-CSF if no response occurs during treatment.<br>G-CSF 1–2mcg/kg subcutaneously daily 1–2 times weekly.<br>Repeat cycle for 6–8 weeks. If no response observed after this treatment course, discontinue treatment. |
| **Darbepoetin alfa ± G-CSF**[8-15] | Darbepoetin alfa 150–300 mcg subcutaneously every other week.<br>Repeat cycle for up to 24 weeks. Add G-CSF if no response occurs during treatment.<br>G-CSF 1–2mcg/kg subcutaneously daily 1–2 times weekly.<br>Repeat cycle for 6–8 weeks. If no response observed after this treatment course, discontinue treatment. |

#### Symptomatic Anemia Without del(5q), Serum Erythropoietin >500mU/mL, Good Probability to Respond to IST[d]

| | |
|---|---|
| **ATG ± Cyclosporine A**[16-19] | **Days 1–4:** ATG (rabbit or equine) 40mg/kg IV daily, **plus**<br>Cyclosporine 5–6mg/kg (initial dose) orally twice daily, and adjusted for blood levels between 100–300ng/mL per institutional guidelines. |

#### Symptomatic Anemia Without del(5q), Serum Erythropoietin >500mU/mL, Poor Probability to Respond to IST[e]

| | |
|---|---|
| **Azacitidine**[20-23] | **Days 1–7:** Azacitidine 75mg/m² IV infusion or subcutaneous injection once daily.<br>Repeat cycle every 4 weeks. After 2 cycles, dose can be increased to 100mg/m² if no beneficial effect is seen and no toxicity other than nausea and vomiting has occurred. Patients should be treated for a minimum of 4–6 cycles. Complete or partial response may require additional treatment cycles. |
| **Decitabine**[24-26] | **Days 1–3:** Decitabine 15mg/m² IV infusion over 3 hours, repeated every 8 hours.<br>Repeat cycle every 6 weeks for minimum of 4–6 cycles.<br>**OR**<br>**Days 1–5:** Decitabine 20mg/m² IV infusion daily over 1 hour.<br>Repeat cycle every 4 weeks for minimum of 4–6 cycles. |
| **Lenalidomide**[2-5] | **Days 1–21:** Lenalidomide 10mg orally once daily.<br>Repeat cycle every 28 days (or 28 days monthly). Assess response 2–4 months after initiation of treatment. |

### Higher-Risk Patients[b,f]

#### Transplant Candidate With Available Donor Stem Cells[g]

| | |
|---|---|
| **Allogeneic HCT**[27-29] | HLA-matched sibling is preferred donor, but HLA-matched unrelated donor can be considered. High-dose conditioning is typically used for younger patients, whereas reduced intensity conditioning is generally used for older patients (≥60 years). |
| **High-Intensity Chemotherapy + HCT**[30,h] | **Days 1–3:** An anthracycline (daunorubicin 60–90mg/m² IV infusion OR idarubicin 12mg/m²), **plus**<br>**Days 1–7:** Cytarabine 100–200mg/m² IV infusion.<br>**AND**<br>HCT upon reduction of bone marrow blast count. |

*continued*

# MYELODYSPLASTIC SYNDROMES TREATMENT REGIMENS (Part 2 of 3)

## First-Line Treatment[1] (continued)

### Higher-Risk Patients[b,f]

#### Transplant Candidate With Available Donor Stem Cells[g]

| REGIMEN | DOSING |
|---|---|
| **Azacitidine + HCT**[20-23,h] | **Days 1–7:** Azacitidine 75mg/m² IV infusion or subcutaneous injection once daily. Repeat cycle every 4 weeks. After 2 cycles, dose can be increased to 100mg/m² if no beneficial effect is seen and no toxicity other than nausea and vomiting has occurred. Patients should be treated for a minimum of 4–6 cycles. Complete or partial response may require additional treatment cycles.<br>**AND**<br>HCT upon reduction of bone marrow blast count. |
| **Decitabine + HCT**[24-26,h] | **Days 1–3:** Decitabine 15mg/m² IV infusion over 3 hours, repeated every 8 hours. Repeat cycle every 6 weeks for minimum of 4–6 cycles.<br>**OR**<br>**Days 1–5:** Decitabine 20mg/m² IV infusion daily over 1 hour. Repeat cycle every 4 weeks for minimum of 4–6 cycles.<br>**AND**<br>HCT upon reduction of bone marrow blast count. |

#### Transplant Candidate With No Available Donor Stem Cells or Not a Transplant Candidate[i]

| | |
|---|---|
| **Azacitidine (Category 1)**[20-23] | **Days 1–7:** Azacitidine 75mg/m² IV infusion or subcutaneous injection once daily. Repeat cycle every 4 weeks. After 2 cycles, dose can be increased to 100mg/m² if no beneficial effect is seen and no toxicity other than nausea and vomiting has occurred. Patients should be treated for a minimum of 4–6 cycles. Complete or partial response may require additional treatment cycles. |
| **Decitabine**[24-26] | **Days 1–3:** Decitabine 15mg/m² IV infusion over 3 hours, repeated every 8 hours. Repeat cycle every 6 weeks for minimum of 4–6 cycles.<br>**OR**<br>**Days 1–5:** Decitabine 20mg/m² IV infusion daily over 1 hour. Repeat cycle every 4 weeks for minimum 4–6 cycles. |

*Abbreviations: ATG:* antithymocyte globulin; *EPO:* erythropoietin; *ESA:* erythropoiesis-stimulating agent; *G-CSF:* granulocyte-colony stimulating factor; *HCT:* hematopoietic cell transplantation; *HLA:* human leukocyte antigen; *IPSS:* International Prognostic Scoring System; *IPSS-R:* International Prognostic Scoring System-Revised; *IST:* immunosuppressive therapy; *rHu-Epo:* recombinant human erythropoietin; *WPSS:* Work Health Organization Prognostic Scoring System.

a Includes patients classified as IPSS Low or Intermediate-1; IPSS-R Very Low, Low, or Intermediate; or WPSS Very Low, Low, or Intermediate.

b Patients classified as IPSS-R Intermediate can be treated using the regimens for either risk group, depending on additional risk factors such as age, performance status, and serum ferritin and serum lactate dehydrogenase levels.

c Lenalidomide should be avoided in patients with a clinically significant decrease in neutrophil or platelet counts. An initial trial of ESAs can be considered instead of lenalidomide in patients with serum erythropoietin <500mU/mL.

d Factors associated with a higher likelihood of a good response include age ≤60 years; ≤5% marrow blasts or hypocellular marrows; HLA-DR15 positivity; PNH clone positivity; or presence of STAT-3 mutant cytotoxic T cell clones.

e Patients lack features associated with features listed in footnote d.

f Includes patients classified as IPSS Intermediate-2 or High; IPSS-R Intermediate, High, or Very High; or WPSS High or Very High.

g High-intensity chemotherapy, azacitidine, or decitabine are administered before HCT when tumor burden needs to be reduced before performing HCT.

h Even a partial remission following treatment might be sufficient to enable HCT.

i Patients who show clinical benefit with azacitidine or decitabine should continue treatment with a hypomethylating agent as maintenance therapy.

## References


1. NCCN Clinical Practice Guidelines in Oncology™. Myelodysplastic Syndromes. v 1.2016. Available at: http://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed June 21, 2016.
2. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med.* 2006;355(14):1456–1465.
3. Revlimid [package insert]. Summit, NJ: Celgene Corporation; 2015.
4. Revicki DA, Brandenburg NA, Muus P, et al. Health-related quality of life outcomes of lenalidomide in transfusion-dependent patients with low- or intermediate-1-risk myelodysplastic syndromes with a chromosome 5q deletion: results from a randomized clinical trial. *Leuk Res.* 2013;37(3): 259–265.
5. Oliva EN, Latagliata R, Laganà C, et al. Lenalidomide in International Prognostic Scoring System Low and Intermediate-1 risk myelodysplastic syndromes with del(5q): an Italian phase II trial of health-related quality of life, safety and efficacy. *Leuk Lymphoma.* 2013;54(11):2458–2465.


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## References (continued)


6. Greenberg P. The role of hemopoietic growth factors in the treatment of myelodysplastic syndromes. *Int J Ped Hem-Onc*. 1997;4:231–238.
7. Hellström-Lindberg E. Efficacy of erythropoietin in the myelodysplastic syndromes: a meta-analysis of 205 patients from 17 studies. *Br J Haematol*. 1995;89(1):67–71.
8. Negrin RS, Stein R, Doherty K, et al. Maintenance treatment of the anemia of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor and erythropoietin: evidence for in vivo synergy. *Blood*. 1996;87(10):4076–4081.
9. Hellström-Lindberg E, Ahlgren T, Beguin Y, et al. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. *Blood*. 1998;92(1):68–75.
10. Casadevall N, Durieux P, Dubois S, et al. Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. *Blood*. 2004; 104(2):321–327.
11. Hellström-Lindberg E, Negrin R, Stein R, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. *Br J Haematol*. 1997;99(2):344–351.
12. Mannone L, Gardin C, Quarre MC, et al. High-dose darbepoetin alpha in the treatment of anaemia of lower risk myelodysplastic syndrome results of a phase II study. *Br J Haematol*. 2006;133(5):513–519.
13. Musto P, Lanza F, Balleari E, et al. Darbepoetin alpha for the treatment of anaemia in low-intermediate risk myelodysplastic syndromes. *Br J Haematol*. 2005;128(2):204–209.
14. Giraldo P, Nomdedeu B, Loscertales J, et al; Aranesp in Myelodysplastic Syndromes (ARM) Study Group. Darbepoetin alpha for the treatment of anemia in patients with myelodysplastic syndromes. *Cancer*. 2006;107(12):2807–2816.
15. Stasi R, Abruzzese E, Lanzetta G, Terzoli E, Amadori S. Darbepoetin alfa for the treatment of anemic patients with low- and intermediate-1-risk myelodysplastic syndromes. *Ann Oncol*. 2005;16(12):1921–1927.
16. Sloand EM, Wu CO, Greenberg P, Young N, Barrett J. Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. *J Clin Oncol*. 2008;26(15):2505–2511.
17. Passweg JR, Giagounidis AA, Simcock M, et al. Immunosuppressive therapy for patients with myelodysplastic syndrome: a prospective randomized multicenter phase III trial comparing antithymocyte globulin plus cyclosporine with best supportive care—SAKK 33/99. *J Clin Oncol*. 2011;29(3):303–309.
18. Molldrem JJ, Caples M, Mavroudis D, et al. Antithymocyte globulin for patients with myelodysplastic syndrome. *Br J Haematol*. 1997;99(3):699–705.
19. Deeg HJ, Gotlib J, Beckham C, et al. Hematologic responses of patients with MDS to antithymocyte globulin plus entanercept correlated with improved flow scores of marrow cells. *Leuk Res*. 2004;28(11):1177–1180.
20. Vidaza [package insert]. Summit, NJ: Celgene Corporation; 2015.
21. Silverman LR, Fenaux P, Mufti GJ, et al. Continued azacitidine therapy beyond time of first response improves quality of response in patients with higher-risk myelodysplastic syndromes. *Cancer*. 2011;117(12):2697–2702.
22. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al; International Vidaza High-Risk MDS Survival Study Group. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol*. 2009;10(3):223–232.
23. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol*. 2006;24(24):3895–3903.
24. Dacogen [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2014.
25. Kantarjian HM, O'Brien S, Shan J, et al. Update of the decitabine experience in higher risk myelodysplastic syndrome and analysis of prognostic factors associated with outcome. *Cancer*. 2007;109(2):265–273.
26. Kantarjian H, Oki Y, Garcia-Manero G, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood*. 2007;109(1):52–57.
27. Alyea EP, Kim HT, Ho V, et al. Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. *Blood*. 2005;105(4):1810–1814.
28. Laport GG, Sandmaier BM, Storer BE, et al. Reduced-intensity conditioning followed by allogeneic hematopoietic cell transplantation for adult patients with myelodysplastic syndrome and myeloproliferative disorders. *Biol Blood Marrow Transplant.* 2008;14(2):246–255.
29. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA*. 2011;306(17): 1874–1883.
30. Beran M, Shen Y, Kantarjian H, et al. High-dose chemotherapy in high-risk myelodysplastic syndrome: covariate-adjusted comparison of five regimens. *Cancer*. 2001;92(8):1999–2015.


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