5 Minute JournalClub

Myelodysplastic Syndromes

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CME INFORMATION

OVERVIEW OF ACTIVITY

Acute myeloid leukemia (AML) and the myelodysplastic syndromes (MDS) account for approximately 20 percent of all hematologic cancer and related hemopathies diagnosed on an annual basis. Emerging and continuing clinical research has resulted in an increased understanding of the heterogeneous nature of these diseases and in the availability of novel treatment strategies and options. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in AML and MDS. To bridge the gap between research and patient care, this CME activity will deliver a serial review of recent key presentations and publications and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for AML and MDS.

LEARNING OBJECTIVE

- Recognize the classification of myelodysplastic syndromes, the pathogenetic mechanisms underlying this heterogeneous disease and available treatment options.

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This program is supported by an educational grant from Celgene Corporation.

Last review date: November 2009
Expiration date: November 2010

Click to go directly to our slides and comments on the **recent review of myelodysplastic syndromes**, **a new proposed prognostic model for MDS**, **the effect of pre-HCT azacitidine therapy on post-transplant outcomes**, **the efficacy of decitabine on survival in elderly patients with higher-risk MDS**, and a **comparison of three alternative azacitidine treatment regimens**.

As we were about to hit the send button on this, our latest e-blast, I happened to be on PubMed and stumbled across a just e-published (Nov 5) *New England Journal* **review article on myelodysplastic syndromes** (MDS). Thinking that the paper might be an important addition to this project, I quickly poured over the work. As usual, our entire clinical team loved the *NEJM* graphics (best in the business!), and the science behind this instant classic by Ayalew Tefferi and James Vardiman was spectacular. Further examination revealed only one prior (1999) *NEJM* review article on MDS, in which for example, there was but a brief mention of an initial 29 patient report of 5-azacitidine — the only reference to demethylating agents. Lenalidomide was nowhere to be found in this "ancient" document by Mark Heaney and David Golde. So at the last minute, we bypassed our usual formal faculty review and integrated this serendipitous discovery into the enclosed activity.

The concluding statements of these two review articles separated by 10 years reflect first a hopeful wish (1999): "The next decade will probably see a marked improvement in our ability to manage myelodysplasias as well as AML" and then confidence (2009): "Increasing information on the identity and nature of transformed hematopoietic stem cells and advances in biotechnology are helping to create the 'perfect storm' for breaking the current stalemate in our understanding of this disease."

So where are we today in MDS? Our faculty — Gail Roboz, Steven Gore and Hagop Kantarjian — once again comment on four papers that were identified and prioritized as important to clinical practice. The first addresses a proposed new **prognostic model for MDS** that accounts for such important factors as prior therapy and adverse cytogenetic profiles. The paper's author, Dr Kantarjian, believes this new system is superior to IPSS, but only time will tell.

Paper 2 comes out of the Moffitt Cancer Center and is a retrospective review of 54 patients receiving hematopoietic stem cell transplant (HCT) for MDS or chronic myelomonocytic leukemia (CMML). The outcomes of 30 patients receiving pre-HCT treatment with 5-azacitidine were compared to and found to be very similar to the

outcomes of 24 patients who did not receive this agent, leading the authors to conclude that 5-azacitidine can be safely and effectively used to stabilize patients prior to transplant.

The third study examines the other available demethylating agent, decitabine, and demonstrates that in spite of a 34 percent response rate, no improvement in overall survival (OS) was observed compared to supportive care in this well-conducted trial completed in Europe. While the lack of OS benefit in this study may relate to suboptimal duration of treatment, a recent US national Patterns of Care study conducted by our education group in preparation for an upcoming **ASH satellite symposium** demonstrated that 80 percent of oncologists using an up-front demethylating agent for MDS chose 5-azacitidine, perhaps reflecting the OS benefit reported with this agent.

Finally we have **a report of three alternative doses/schedules** of 5-azacitidine in MDS that through indirect comparison appear to be as effective and well tolerated as the approved day 1-7 regimen that requires weekend infusions. We may need a head-to-head trial to be fully convinced but it seems like a more patient-friendly regimen may in fact be out there.

The publications and presentations in this short series testify to significant forward momentum in MDS and AML. However, the ultimate hope is that 10 years from now, the next *NEJM* review article on MDS or AML will describe the unraveling and elimination of these diseases that have for so long resisted research progress.

Coming up next on 5-Minute Journal Club: a Phase II trial of up-front clofarabine in older patients with AML, a review of prognostic and predictive markers in AML, a trial of decitabine in older patients with AML and finally a retrospective review of more than 1,000 patients with AML and MDS receiving HCT demonstrating similar efficacy and toxicity patterns regardless of patient age, up to 78.

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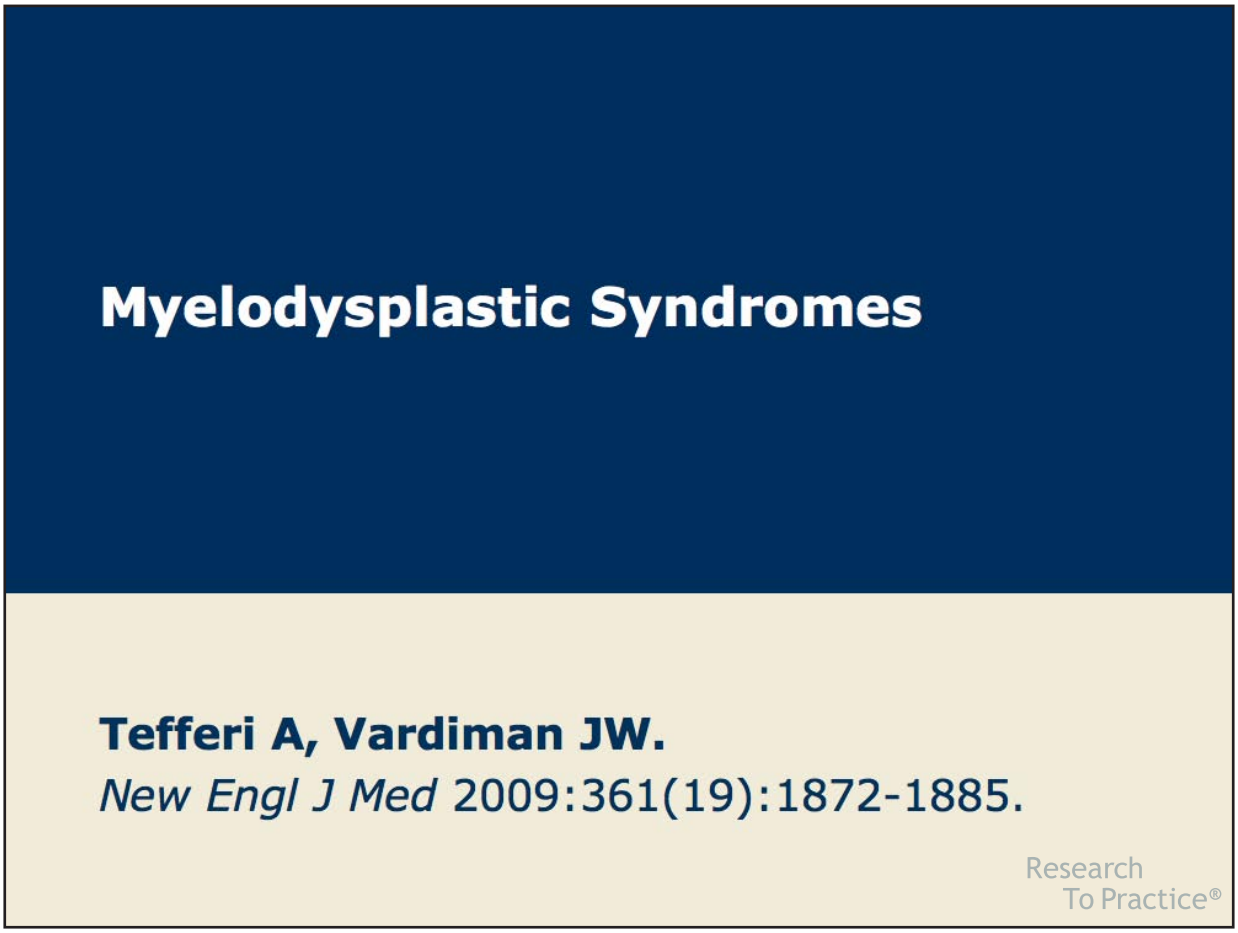
Myelodysplastic Syndromes

Presentation discussed in this issue:

Tefferi A, Vardiman JW. **Myelodysplastic syndromes.** *N Engl J Med* 2009;361(19):1872-85. **Abstract**

Slides from the journal article below



Introduction

- According to the 2008 World Health Organization (WHO) classification system for hematologic cancers, primary myelodysplastic syndromes are one of the five major categories of myeloid neoplasms (*Blood* 2009;114:937).
- The main feature of myeloid neoplasms is stem-cell-derived clonal myelopoiesis with altered proliferation and differentiation.
- Increasing evidence exists that the following contribute towards the development of myelodysplastic syndromes:
  - Haploinsufficiency
  - Epigenetic changes
  - Cytokine, immune system and bone marrow stroma abnormalities

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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Classification of Myeloid Neoplasms According to WHO Criteria

- Acute myeloid leukemia and related neoplasms, including therapy-related myelodysplastic syndromes
- Myelodysplastic syndromes
  - Refractory cytopenia with unilineage dysplasia (RCUD)
    - Refractory anemia
    - Refractory neutropenia
    - Refractory thrombocytopenia
  - Refractory anemia with ring sideroblasts (dysplasia limited to erythroid lineage and ring sideroblasts ≥15% of bone marrow [BM] erythroid precursors)
  - Refractory cytopenia with multilineage dysplasia (RCMD)

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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Classification of Myeloid Neoplasms According to WHO Criteria (continued)

- Myelodysplastic syndromes (continued)
  - Refractory anemia with excess of blasts (RAEB)
    - RAEB-1 (2-4% circulating blasts or 5-9% marrow blasts)
    - RAEB-2 (5-19% circulating blasts or 10-19% marrow blasts or Auer rods present)
  - Myelodysplastic syndrome (MDS) with isolated del(5q)
  - MDS (unclassifiable)
- Myeloproliferative neoplasm
- Myelodysplastic - myeloproliferative neoplasms
- Molecularly characterized myeloid or lymphoid neoplasms associated with eosinophilia.

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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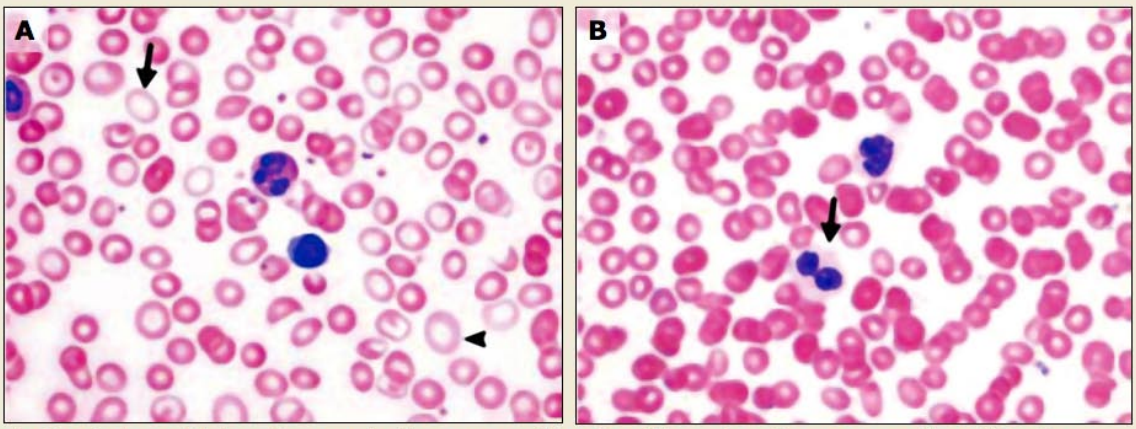
Morphologic Features of Peripheral Blood and Bone Marrow in Myelodysplastic Syndromes



A. Peripheral blood sample from a patient with refractory anemia with ring sideroblasts, with dimorphic red cells; some cells are hypochromic (arrow). Anisocytosis with occasional macroovalocytes is noted (arrowhead)
B. Peripheral blood sample from a patient with RAEB, demonstrating pseudo-Pelger-Hüet cells with hypercondensed chromatin, hypolobulated nuclei and virtually colorless cytoplasm (arrow).

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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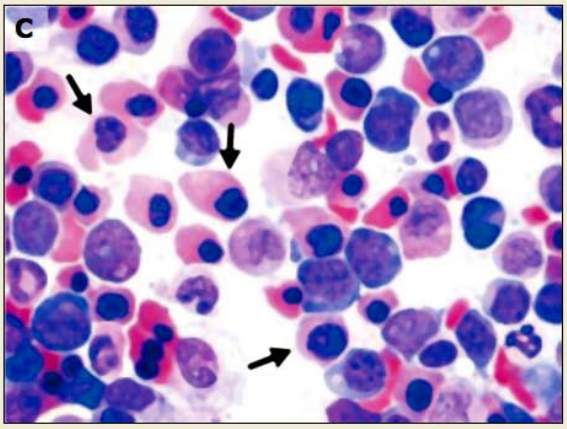
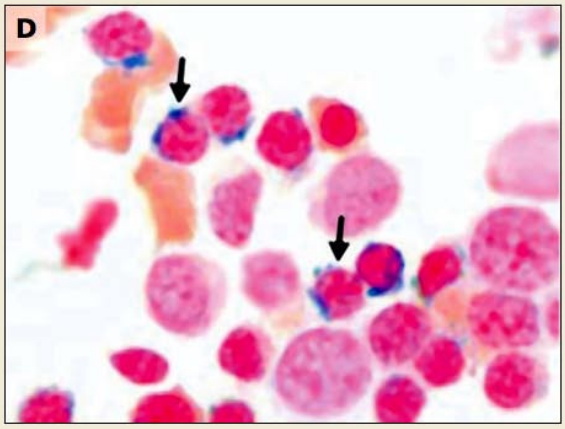
Morphologic Features of Peripheral Blood and Bone Marrow in Myelodysplastic Syndromes





C. Dyserythropoiesis (arrows) in a BM sample obtained from a patient with refractory cytopenia with multilineage dysplasia.
D. Ring sideroblasts (arrows) from a patient with refractory anemia. Ring sideroblasts are characterized by at least five granules of iron that encircle the nucleus of the erythroid precursor.

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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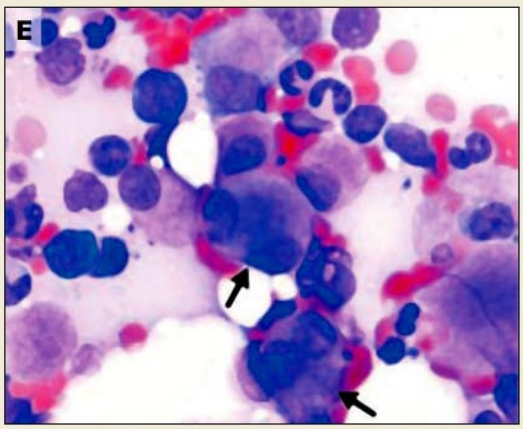
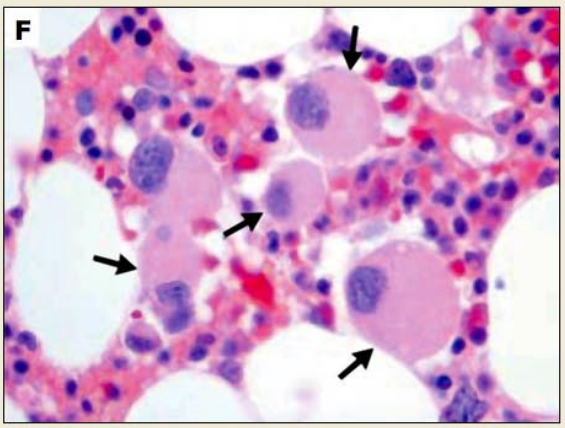
Morphologic Features of Peripheral Blood and Bone Marrow in Myelodysplastic Syndromes





E. Dysplastic small megakaryocytes (arrows) with monolobed or bilobed nuclei and mature granular cytoplasm in the aspirate smear of a patient with RAEB.
F. BM tissue section of a patient with MDS and isolated del(5q). The megakaryocytes are of medium size, with hypolobulated nuclei (arrows).

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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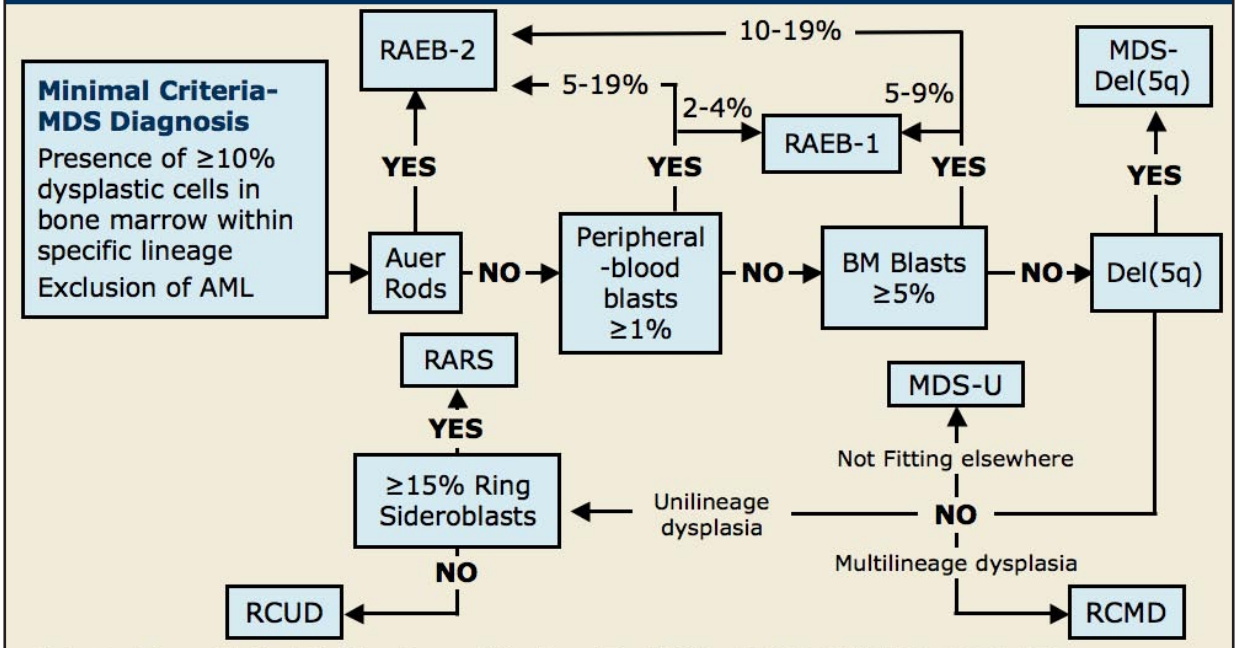
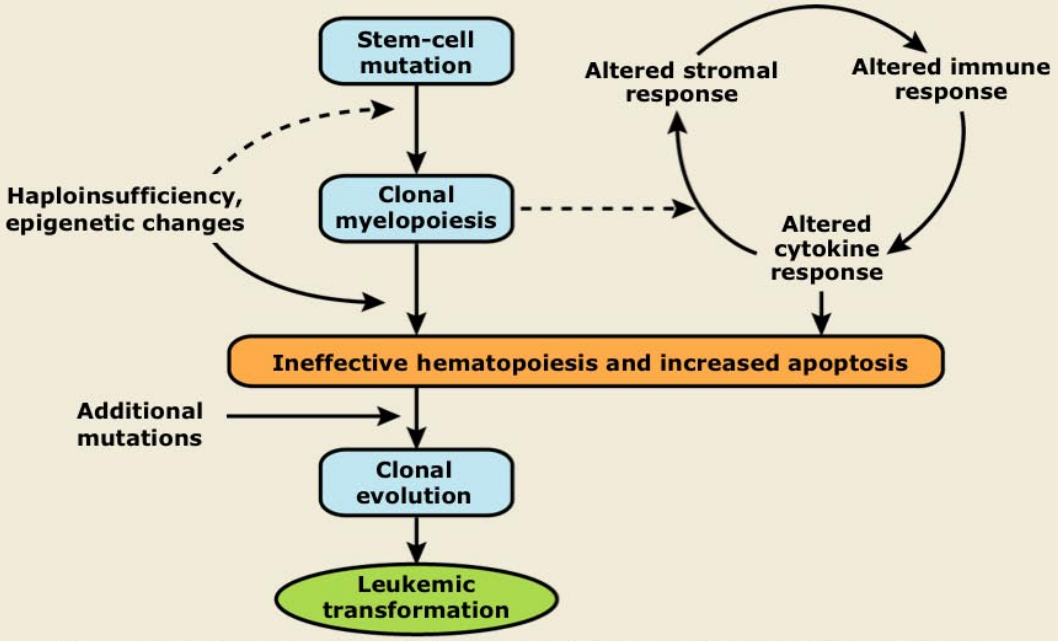
Classification Algorithm of Adult-Onset Primary MDS



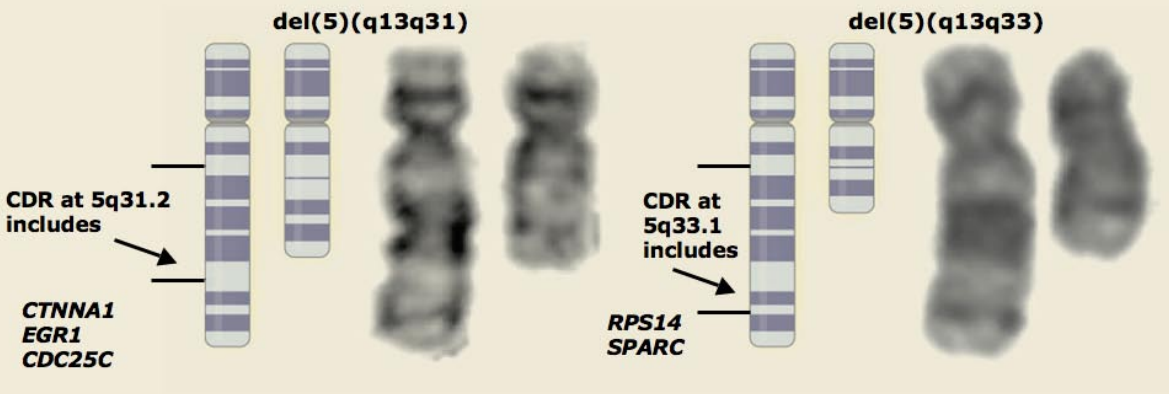
Adapted from Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

Putative Pathogenic Mechanisms and Their Interaction in the Myelodysplastic Syndromes



Adapted from Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

Ideograms and Commonly Deleted Regions Involving Del(5q)



In typical 5q minus syndrome, the commonly deleted region (CDR) has been mapped to 5q33.1 (at right), which contains the genes for osteonectin (*SPARC*) and ribosomal protein S14 (*RPS14*).
In the del(5q)-associated myelodysplastic syndrome—acute myeloid leukemia, the commonly deleted region has been mapped to 5q31.2 (at left), which contains the genes for catenin alpha 1 (*CTNNA1*), early growth response 1 (*EGR1*) and cell division cycle 25 homologue C (*CDC25C*).

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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Treatment Options

- Allogeneic hematopoietic stem-cell transplantation (AHCT)
  - The only treatment able to induce long-term remission in patients with MDS is AHCT, though it is not applicable to most patients because the median age of diagnosis is greater than 70 years and it is only recommended for patients with advanced stage disease.
  - Stem cell transplantation is associated with:
    - High rate of treatment-related death (39% at 1 year)
    - Suboptimal disease-free survival (29% at 5 years)
    - Chronic graft-versus-host disease (15% at 1 year)

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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Treatment Options (continued)

- Demethylating agents (azacitidine, decitabine) or low-dose cytarabine
  - Increased remission rates with these drugs versus supportive care
  - Complete remission rates achieved with azacitidine or decitabine (9%-17%) are similar to the rates obtained with low-dose cytarabine (11-18%).
    - Complete remission rates are lower than rates obtained with induction chemotherapy in patients with acute myeloid leukemia (>50%).
  - Use of these drugs may delay blastic transformation.

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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Treatment Options (continued)

- Lenalidomide
  - Lenalidomide can reduce the need for transfusion in about two-thirds of patients and can induce complete cytogenetic responses in almost half of the patients with low- or intermediate-1-risk MDS associated with del(5q).
  - The drug's effect is less on variants of MDS disease with karyotypes other than del(5q).
- Other drugs/treatment options
  - Erythropoiesis stimulating agents help anemic patients with low-risk disease and a serum erythropoietin level less than 200 mIU/mL.
  - Granulocyte stimulating growth factors are only cost-effective in patients with neutropenia and fever or overt infection.
  - Many patients can be treated effectively with red cell transfusion alone.

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.

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Conclusions

- Myelodysplastic syndromes appear to constitute several molecularly distinct entities that share common changes in blood and BM.
  - This heterogeneity poses a challenge for the creation of a unifying framework into which information about the molecular and biologic mechanisms of myelodysplastic syndromes can be incorporated.
- From a treatment standpoint, understanding the mechanisms of ineffective hematopoiesis and leukemic transformation may be as important as understanding the primary oncogenic events.
- Increasing information on the identity and nature of transformed hematopoietic stem cells and advances in biotechnology will help to better understand this disease.

Source: Tefferi A, Vardiman JW. *New Engl J Med* 2009;361(19):1872-85.