Current Treatment Strategies for Myelodysplastic Syndromes

A Compendium of Case Studies

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2. Describe evaluations of risk and prognosis in MDS.
3. Review approaches to various subtypes of MDS.

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Current Treatment Strategies for Myelodysplastic Syndromes

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The past few years have seen important advances in the medical care of patients with myelodysplastic syndromes (MDS). Since 2004, the US Food and Drug Administration (FDA) has approved three medications—azacitidine, lenalidomide, and decitabine—for MDS-related indications, expanding the potential treatment options for patients and the choices available to clinicians. In addition supportive care for anemic and red blood cell (RBC) transfusion–dependent patients is in evolution. There is concern and controversy about the potential harmful consequences of transfusional iron overload, and decisions about iron chelation therapy are more complex now that an oral iron chelator (deferasirox) is available. We have also gained a better understanding of which patients with MDS are most likely to respond to treatment with the erythropoiesis-stimulating agents (ESAs) epoetin and darbepoetin alfa. Finally, continued improvement in nonmyeloablative conditioning regimens for hematopoietic stem cell transplantation, coupled with growing experience with allogeneic transplantation in patients older than age 55 years, is increasing the number of patients who can now be considered eligible for the only potentially curative MDS therapy.

In this Case Study Compendium, five experienced clinicians discuss how they would approach a series of MDS cases. These clinical vignettes were chosen to demonstrate evolving treatment strategies and illustrate some of the practical considerations related to recently approved agents. For instance, with respect to treatment with azacitidine or decitabine, in what clinical settings is the risk:benefit ratio most favorable? Who are the best candidates for stem cell transplantation, and what is the optimal stem cell source and conditioning regimen? Lenalidomide has proved remarkably effective in MDS patients with acquired deletions of chromosome 5q31; how are the common adverse events associated with lenalidomide therapy, such as myelosuppression and skin rash, best managed?

Despite recent treatment advances, a large proportion of patients with MDS still do not benefit substantively from any of the available therapies. There is a long way to go before we can be satisfied with the level of progress in this group of diseases, which until recently were considered by many physicians to be a “backwater” of hematology practice, due to our limited understanding of MDS biology and the mediocre treatment options. The future appears more promising, but monetary and logistical support for aggressive development of genuinely novel drugs continues to be essential if we are to make real progress. Vigorous effort is also needed to eliminate obstacles to clinical trial enrollment. Importantly, the most exciting clinical trials must be easily accessible to community oncology practices, the setting where most patients with MDS currently receive care. MDS patients are mostly elderly and they frequently suffer from profound and debilitating fatigue, making travel to distant academic medical centers difficult.

When 2006 International Working Group (IWG) standard criteria are used to reassess response, approximately 15–20% of patients with MDS achieve a complete response (CR) or partial response (PR) to either azacitidine or decitabine therapy when the drugs are used in the doses and schedules specified in their package inserts. For both nucleoside analogs, the dose-limiting toxicity is myelosuppression, which can delay retreatment. It is not entirely clear whether these drugs are working via inhibition of DNA methyltransferase and alteration of epigenetic patterns with attendant changes in gene expression, or by a different mechanism. Combination trials, such as with histone deacetylase inhibitors, are ongoing at many centers.

There is some evidence that the FDA-approved doses and schedules for both azacitidine and decitabine are not ideal. For instance, the azacitidine package insert calls for 75 mg/m² administered subcutaneously for 7 consecutive days, but Gore and colleagues at Johns Hopkins University have observed encouraging results with a 10-day regimen of azacitidine 50 mg/m² daily, which is currently being tested in a large clinical trial by the Eastern Cooperative Oncology Group.
Clinical practices find weekend dosing problematic and administer azacitidine only on weekdays; support for this practice came from a pilot study exploring three schedules that avoid weekend dosing, which demonstrated hematologic improvement rates in the 40-60% range.\(^1\)\(^2\) Whereas formal equivalence between these 3 regimens and the label-specified 7-day schedule has not yet been demonstrated, and the recent study that showed a survival advantage with azacitidine in higher-risk MDS patients used the 7-day regimen,\(^1\) practical considerations mean that many clinical practices will continue to use the more convenient regimens. Similarly, with respect to decitabine, Kantarjian and colleagues at The University of Texas M. D. Anderson Cancer Center observed that an outpatient regimen of 20 mg/m\(^2\) administered intravenously over 1 hour daily for 5 consecutive days appeared superior to historical controls receiving the package insert dose (15 mg/m\(^2\) intravenously every 8 hours for 3 days for a total of 9 doses, a regimen suitable only for inpatient administration).\(^1\) A multicenter confirmatory study of outpatient decitabine therapy was reported in December 2007, and response rates were almost as high as in the single-institution trial (32% rate of CR or marrow CR; 51% overall response rate using IWG 2006 criteria).\(^1\)\(^6\)

Lenalidomide caused great excitement when, for biologic reasons that remain obscure, a striking 67% of treated patients in the lower-risk del(5q) subset achieved durable red cell transfusion independence, and 45% experienced complete cytogenetic remissions.\(^1\) Unfortunately, lenalidomide is not as effective in patients without del(5q): in the largest trial to date, which excluded patients with severe thrombocytopenia (≤50,000/µL) or neutropenia (≤500/µL), only 26% of non-del(5q) patients achieved transfusion independence, and responses lasted for a median of 41 weeks.\(^1\) Discovery of the peculiar lenalidomide response pattern in del(5q) was, it appears, blind luck, and there may be other special cytogenetic subsets yet to be detected. Regardless, the race is on to try to find the mechanism of lenalidomide’s effectiveness so that the relevant pathway can be exploited with more precisely targeted agents. A number of groups have proposed candidate genes for the del(5q) phenotype and this is an active area of investigation.

Interest also continues in the area of immunotherapy in MDS, with optimal patient selection the chief area of controversy at present.\(^1\)\(^9\)\(^2\)\(^0\) Although immune modulators such as antithymocyte globulin or antilymphocyte globulin are effective only in a minority of patients, when responses do occur they are usually quite durable, often lasting for more than a year.\(^2\) Another controversial area is the role of iron chelation in MDS. Interest in chelation received a boost from a study of prognostic variables that highlighted the risk from ferritin levels greater than 1,000 ng/mL in patients with low-risk MDS and another study that demonstrated a high risk from proceeding to stem cell transplantation with an elevated ferritin level.\(^2\)\(^2\)\(^2\) Unfortunately, whether iron chelation therapy reduces these risks or yields any other long-term benefits is unclear. Deferasirox is quite expensive, and there are important adverse events such as renal insufficiency, so the bar is high with respect to the benefits that need to be demonstrated before this agent can be more widely used in patients with MDS.\(^2\)\(^3\)

The availability of a growing number of therapies for MDS challenges the tradition of therapeutic nihilism towards these disorders, and also makes the physician’s role in choosing appropriate therapy more complex. Risk-based treatment is now in vogue, with lower-risk therapies targeted to patients with a good prognosis and higher-risk therapies reserved for those with a poorer outlook.\(^2\)\(^4\) Better definition of patient prognosis and an expanding roster of therapies should make for a more satisfying set of conditions in which to treat MDS in the near future.

References

Treatment and Evaluation of High-risk MDS

Kenneth Miller, MD, and German Pihan, MD

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Case Study

A 62-year-old man presents for evaluation of pancytopenia. He notes being in good health except for a 6-month history of progressive fatigue. He denies fevers or night sweats but notes a 1-month history of easy bruising with minor trauma. He denies weight loss or recent infections. He has no family history of hematologic disorders. His parents are both alive and in good general health. His past medical history reveals mild hypertension well controlled on a beta blocker. In addition, he takes 81 mg aspirin daily. He has a 50 pack/year history of cigarette smoking and stopped 3 years ago. He drinks alcohol socially. He denies exposure to known hemotoxins and works in computer sales. He has two brothers and a sister, who are alive and well. He is married and has two adult children.

Laboratory evaluation on presentation revealed the following: hemoglobin (Hb) 10.3 g/dL, hematocrit 31.4%, mean corpuscular volume (MCV) 106 fL, and platelets 85,000/µL. His white blood cell (WBC) count was 1,800/µL with a differential of 32% neutrophils/bands, 5% myelocytes/metamyelocyte, 2% blasts, 13% monocytes, and 48% lymphocytes. Liver function tests, serum B12, and folate were within normal limits; serum ferritin was 280 ng/mL and erythropoietin level was 420 U/L.

The peripheral blood smear showed marked anisopikilocytosis with frequent macrocytes and rare schistocytes (Figure 1A). Red cells with coarse basophilic stippling was noted. Neutrophils were hypogranulated with frequent pseudo–Pelger-Huet forms (Figure 1A, center and right inset), and rare blasts were present (Figure 1A, left inset). A bone marrow aspirate was hypercellular and erythroid precursor–dominant (M:E of 0.6). Erythroblasts exhibited megaloblastoid maturation and frequent dysplastic forms (“nuclear budding,” micronuclei, and binucleate erythroblasts with asymmetric nuclei; Figures 1B–1E). Myeloid precursors demonstrated left-shifted maturation with abnormal granulation/hypogranulation. Frequent giant myelocytes were present. Megakaryocytes were not decreased, but the majority were mononuclear or binucleate with only rare multinucleated forms present (Figures 1B and 1D). The differential count included 9% myeloblasts, 4% promyelocytes, 5% myelocytes, 8% metamyelocytes, 9% bands/neutrophils, 1% plasma cells, 13% lymphocytes, 44% erythroblasts, and 7%
monocytes. The core biopsy was hypercellular (60%) and demonstrated abnormal localization of immature precursors and numerous mononuclear micromegakaryocytes and dysplastic erythroblasts (Figure 1B). Cytogenetics demonstrated a complex karyotype: 47,XY,inv(3)(q21q26),der(7)t(1;7)(q10;q10)[13]/46,XY[3] in 13 of 16 metaphases. Of note, both inv(3) and t(1;7)—often unbalanced and equivalent to 7q- syndrome—are typical of MDS.

The patient was initially followed without treatment but told to avoid all aspirin-containing compounds considering his recent history of easy bruising. One month later his Hb was 9.8 g/dL, hematocrit 29.5%, and MCV 105 fl. His WBC count was 2,100/µL with 5% circulating blast forms. He complained of increased fatigue and was unable to work full time. Platelet count was 88,000/µL. The patient was started on decitabine 20 mg/m² daily administered intravenously for 5 consecutive days.

Therapy was tolerated well, without nausea or vomiting. After three cycles of decitabine, the patient’s WBC count rose to 2,300/µL, Hb to 11.3 g/dL, and platelet count to 103,000/µL. His symptoms of fatigue improved. Human leukocyte antigen (HLA) typing of the patient and his siblings revealed that his 68-year-old sister was an identical HLA match.

**Discussion**

The patient is a 62-year-old man with no prior hematologic or oncologic illnesses who presents for evaluation of pancytopenia. He poses a number of questions: 1) Why did I develop MDS? 2) What is my prognosis? 3) Will chemotherapy cure me? 4) What should I do next?

The most common presenting symptom of MDS is a macrocytic anemia. MDS disorders are characterized by impaired or ineffective hematopoiesis of one or more cell lineages and by varying degrees of proliferation. The clinical course is highly variable, with the majority of patients developing complications related to marrow failure (eg, recurrent infections, bleeding, and anemia), or as a consequence of transformation to acute myeloblastic leukemia. Our patient presents with no prior hematologic illness and his past medical history is unremarkable. The majority of patients with MDS present in a similar manner and should be considered to have primary MDS, also called de novo MDS, the cause of which remains unknown. Secondary MDS, which is usually therapy-related, develops after cytotoxic chemotherapy, ionizing radiation, or exposure to known hemotoxins such as benzene. The patient denies exposure to agents associated with the development of MDS but did have a long history of cigarette smoking. Cigarette smoking is associated with the development of both MDS and acute myelogenous leukemia (AML). Notably, benzene and a number of related agents including toluene, ethylbenzene, m-/p-xylene, o-xylene, styrene, isoprene, and acrylonitrile are present in cigarette smoke. However, the answer to our patient’s first question—Why did I develop MDS?—is that no single biologic or genetic factor has yet been identified that is consistently involved in the pathogenesis of most de novo MDS cases.

The answer to his second question—What is my prognosis?—is that several factors help in defining prognosis and treatment options. The histological subtype of his MDS, percent of blasts, and the complex karyotype are associated with a poor overall prognosis. There are two systems that are currently in use to classify MDS,
the French-American-British (FAB) classification system and the World Health Organization (WHO) classification system. The former divides MDS into five subcategories: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB), chronic myelomonocytic leukemia (CMML), and RAEB in transformation (RAEB-T). The WHO classification of MDS redefined RA and RARS to encompass cases with dysplastic features in the erythroid lineage only and added two new categories, refractory cytopenia with multilineage dysplasia (RCMD) and RCMD with ringed sideroblasts (RCMD-RS). In the WHO classification the FAB category of RAEB is subdivided into RAEB-1 and RAEB-2 based on the presence of 5–9% and 10–19% bone marrow blasts, respectively. In addition the WHO defines a separate subgroup of MDS, 5q- syndrome, which includes patients with less than 5% marrow blasts and an isolated interstitial deletion of the long arm of chromosome 5. The WHO also adds a subtype of unclassified MDS, recognized by unilineage myeloid dysplasia and less than 5% blasts in bone marrow. Two FAB subgroups were excluded from the WHO classification: RAEB-T (>20% blasts forms) is now included in the AML classification and CMML is now included in a new WHO category of mixed myeloproliferative/myelodysplastic syndromes. In addition, the WHO clearly segregates all MDS with a previous history of chemotherapy or radiation therapy to the new category of therapy-related MDS.

The WHO classification system is now widely accepted and is prognostically important. The difference in the percent blasts between RAEB-1 and RAEB-2 appears to be biologically meaningful as well. Considering their poor prognosis, younger patients with RAEB-2 (10–19% blasts) are now generally treated with intensive, AML-like therapy. The WHO classification does not specifically address some clinically well-recognized but less common subtypes of MDS, such as hypoplastic MDS, which shares several features with aplastic anemia and which may respond to immunosuppressive therapy, and MDS with marrow fibrosis, which has features of a myeloproliferative disorder and a generally poor prognosis. This patient presented with a hypercellular bone marrow with evidence of trilineage dysplasia and 5–10% blasts. He best fits the diagnosis of RAEB-1 by the WHO criteria.

**Prognostic Assessment in MDS**

Myelodysplastic syndromes are clinically heterogeneous, ranging from indolent, slowly progressive illness with a near-normal life expectancy to life-threatening cytopenia that rapidly progresses to AML and responds poorly to standard cytotoxic therapy. The assessment of the individual patient’s overall survival and risk of leukemic transformation is critical in defining the management of MDS patients. As with this patient, a risk-adapted treatment strategy is important. The International Prognostic Scoring System (IPSS), developed in 1997, remains an important predictive model to define prognosis for untreated patients with MDS. The model is based on three independent prognostic variables: karyotype, number of cytopenias, and percentage of bone marrow myeloblasts (Table 1). Each variable is given a score and patients are divided into four separate categories based on the combined score for each variable. These groups have different probabilities for survival and risk for progression to AML. The median survival times in the IPSS are 5.7, 3.5, 1.2, and 0.4 years for the low-, intermediate-1-, intermediate-2-, and high-risk groups, respectively. The prognosis and survival is also dependent on the age of the patient, with patients over or younger than 60 years of age having a different survival (Table 2). The IPSS has been extensively validated, is widely accepted, and is presently used in most trials to stratify patients and assign risk. Moreover, the cytogenetic risk stratification system of the IPSS has been used as an independent prognostic marker in studies of high-risk MDS and AML following MDS. Patients with primary MDS do not present with the typical balanced cytogenetic translocations seen in patients with

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**Table 1. International Prognostic Scoring System for Myelodysplastic Syndromes: Survival and Acute Myeloid Leukemia Evolution**

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blasts (%)</td>
<td>0</td>
</tr>
<tr>
<td>Good</td>
<td>—</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Poor</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
</tr>
</tbody>
</table>

Scores for risk groups are as follows: 0=low; 0.5–1.0=int-1; 1.5–2.0=int-2; >2.5=high.

*Good=normal, 5q-, 20q-; Poor=>3 abnormalities, -7, multiple; Intermediate=all others.*
Table 2. International Prognostic Scoring System: Score, Age, and Survival

<table>
<thead>
<tr>
<th>Overall Score</th>
<th>Median Survival Age &lt;60 year</th>
<th>Median Survival Age ≥60 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0)</td>
<td>11.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Intermediate-1 (1.5–2.0)</td>
<td>5.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Intermediate-2 (1.5–2.0)</td>
<td>1.8</td>
<td>1.1</td>
</tr>
<tr>
<td>High (&gt;2.5)</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

de novo AML. A majority of the cytogenetic findings are unbalanced aberrations leading to loss of genetic material, most frequently involving chromosomes 5, 7, 20q, and 8. These cytogenetic abnormalities define clinically, biologically, and prognostically different groups (Table 3).

MDS is often divided into low- and high-risk groups, reflecting overall prognosis and the time to leukemic transformation. The low-risk group includes patients classified as low- and intermediate-1-risk according to the IPSS. The general aim of treatment for these patients is to improve blood counts (eg, with ESAs) and reduce symptoms through supportive care. Patients with high-risk MDS (ie, intermediate-2 and higher) have a poor prognosis and are usually treated with chemotherapy. The IPSS score for our patient was 2.0 based on poor-risk cytogenetics (>3 abnormalities) and trilineage cytopenias. This score places the patient in the intermediate-2 category of risk, with a predicted overall survival of approximately 12–14 months.

Treatment Strategies in High-risk MDS

“Will chemotherapy cure me?” The answer to this question is complex. For high-risk MDS, the hypomethylating agents azacitidine and decitabine are quickly gaining favor. Both drugs inhibit DNA methyltransferase, reduce DNA methylation, and may induce re-expression of key tumor suppressor genes in MDS. The effect of azacitidine was evaluated in a randomized phase III trial. Azacitidine-treated patients showed a better overall improvement compared to those treated with supportive care only (60% vs 5%) and a longer time to progression to AML or death, but no overall survival advantage. A confirmatory international phase III trial evaluating the effects on long-term outcome with azacitidine versus conventional care (ie, physician choice of low-dose cytarabine, standard chemotherapy, or best supportive care) has recently been completed; full results are pending but early analysis suggests a survival benefit for the azaciti-dine arm. Decitabine is a 10-fold more potent inhibitor of DNA methyltransferase than azacitidine and is associated with greater myelosuppression. Though the activity and side effects of the hypomethylating agents may be different, there are no studies directly comparing decitabine and azacitidine. Decitabine has been particularly effective in patients with high-risk MDS according to IPSS. A recently published phase III trial showed that patients treated with decitabine had a longer time to AML transformation or death compared to supportive care. The schedule of decitabine administration suggests that both the duration and dose of the infusion are important. Both azacitidine and decitabine require 3–6 treatment cycles to obtain an optimal therapeutic response, suggesting that the mechanism of action is more than just cytoceduction.

Our patient responded to treatment with decitabine. The use of lower doses of decitabine (20 mg/m² 3 5 days) facilitates the administration of more courses at more frequent intervals. In a study of three dosing schedules conducted by Kantarjian and colleagues this approach resulted in a CR rate of 34% versus 9% when decitabine was given at a higher dose with fewer and less frequent cycles. Nonetheless, patients with high-risk MDS are not cured with currently available chemotherapy.

The critical clinical decision now in our patient is whether to perform allogeneic stem cell transplantation, which is the only potentially curative therapy for him. The answer to the patient’s fourth question—What should I do next?—is, therefore, to proceed to reduced-intensity allogeneic transplantation from his HLA-matched sibling donor.

Although our patient has had a favorable response to decitabine, his overall prognosis with standard therapy remains poor. There is generally agreement that similar patients with high-risk MDS (eg, RAEB-1, poor cytogenetics, and an IPSS score of 2.0) will benefit from allogeneic stem cell transplantation from a HLA-identical sibling. The natural history of high-risk MDS is closer to that of AML than to indolent MDS. The use of reduced-intensity transplantation has decreased the mortality from transplantation in this high-risk group of patients.

References

Table 3. Characteristics of Cytogenetic Abnormalities in Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Karyotype/Genotype</th>
<th>Clinical/Lab Features</th>
<th>WHO MDS Subtype IPSS</th>
<th>Morphology, Morphologic Clues, Immunophenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosomy 5 Deletion 5q</td>
<td>-5/-5q; add -7/7q; add -7 in tr cases</td>
<td>60–80; 1:1, dn and tr (40% of all tr-MDS, 10% of dn-MDS) R: anemia W: ↓↓ P: ↓ to ↓↓↓</td>
<td>RA RCMD RAEB 1&amp;2&gt;AML IPSS: int to high</td>
<td>Trilineage dysplasia Mononuclear and hypolobated megakaryocytes Micromegakaryocytes</td>
</tr>
<tr>
<td>Monosomy 7 Deletion 7q</td>
<td>-7/del(7q); add -5/-5del5q in 20–30% of trMDS cases</td>
<td>60–80; 2:1, tr&gt;&gt;dn R: mild macrocytic anemia W: ↓ to ↓↓↓ P: ↓</td>
<td>RA (10) RAEB (80) CMML (10) IPSS: int to high</td>
<td>Trilineage dysplasia with micromegakaryocytes and increased myeloblasts</td>
</tr>
<tr>
<td>5q− syndrome*</td>
<td>del(5)(q13.3q33.1)</td>
<td>65–75: 1:4; dn R: mild macrocytic anemia W: nl or ↓ P: nl or ↑</td>
<td>RA (85) REAB (15) IPSS: low</td>
<td>Erythroid hypoplasia with mild dyspoiesis + mononuclear megakaryocytes with hyperchromatic nuclei (but not micromegakaryocytes)</td>
</tr>
<tr>
<td>Trisomy 8</td>
<td>+8</td>
<td>15–20 of all MDS 1.5 tr&gt;dn R: mild macrocytic anemia W: nl or ↓ P: nl or ↑</td>
<td>All subtypes; 30% of RARS IPSS:</td>
<td>Trilineage dysplasia</td>
</tr>
<tr>
<td>Deletion 20q</td>
<td>del(20q); add -7/7q or del(13q)</td>
<td>5% of MDS 60–80 dn&lt;tr R: mild macrocytic anemia W: nl or ↓ P: nl or ↑</td>
<td>RA (78–80) RAEB (10–20) IPSS: low; int to high with add cytogenetic abnormalities</td>
<td>Erythroid and megakaryocytic lineages preferentially involved</td>
</tr>
<tr>
<td>Deletion 11q</td>
<td>del(11q): MLL haploinsufficiency</td>
<td>1% of MDS trAML</td>
<td>RA RAEB &gt;&gt; AML</td>
<td>Trilineage dysplasia with frequent sideroblastosis</td>
</tr>
<tr>
<td>Inversion 3q21</td>
<td>inv(3)(q21q26) t(3;3)(q21;q26) ins(3;3)(q26q13q26) add -7/7q or -5/5q common</td>
<td>50s: 1:1; dn R: anemia W: neutropenia P: ↑↑↑ to nl</td>
<td>RAEB &gt;&gt; AML</td>
<td>Dyserythropoiesis and dysmegakaryopoiesis mononuclear-binuclear micromegakaryocytes</td>
</tr>
<tr>
<td>11q23 abnls</td>
<td>MLL fusion genes</td>
<td>Any age; tr&gt;&gt;dn follows exposure to topoisomerase II inhibitor chemotherapeutic agents</td>
<td>No preleukemia phase Rapid evolution to AML (should not be included)</td>
<td>Hypercellular marrow with increased blasts, often with monocytic differentiation</td>
</tr>
</tbody>
</table>

*Indicates isolated abnormality in an otherwise normal karyotype.

AML=acute myeloid leukemia; dn=de novo; IPSS=International Prognostic Scoring System; MDS=myelodysplastic syndromes; MLL=mixed lineage leukemia; P=platelet count; R=red blood cells; RA=refractory anemia; RARS=refractory anemia with ring syderoblasts; RCMD=refractory anemia multilineage dysplasia; tr=therapy related; W=WBC count; WHO=World Health Organization.

The Use of Hypomethylating Agents: Time to Response and Myelosuppression

Elias Jabbour, MD

Case Study

A 68-year-old white man presented with a history of slowly progressive fatigue and dyspnea on exertion. He underwent evaluation recently for a 1-year history of anemia and was treated with growth factors and packed RBC transfusion requiring 2 units every 2 weeks. His parents are deceased and he has no siblings. His past medical history is unremarkable except for lower back discomfort. He does not smoke and drinks only an occasional alcoholic beverage.

Physical examination of the patient revealed some bruising on his thighs and upper arms, no hepatosplenomegaly, and no palpable adenopathy. Laboratory findings included the following: WBC 1,800/µL, Hb 9 g/dL, platelet count 40,000/µL, and MCV 105 fL. Peripheral blood smear showed macrocytosis and hypogranular neutrophils with Pelger-Huet nuclei. Vitamin B12 and folate levels were normal, as were serum iron levels and total iron-binding capacity; erythropoietin level was 1,200 IU/L.

Bone marrow biopsy revealed hypercellular marrow with 18% blasts and multiple dysplastic features in megalakaryocytic and myeloid precursors. Cytogenetics showed trisomy 8, 20q-, and monosomy 7.

Based on the patient's history and laboratory findings, he was diagnosed with MDS, subtype RAEB-2. His IPSS score of 3 placed him in the high-risk category: 1.5 for percentage of blasts (18%), 1.0 for karyotype (complex karyotype with additional chromosome 7 abnormalities), and 0.5 for cytopenias (pancytopenia).

The patient was started on decitabine 20 mg/m² intravenously over an hour daily for 5 days, Monday through Friday. He continued the RBC transfusion support as required and was placed on prophylactic levofloxacin therapy. The patient was monitored biweekly with a complete blood count (CBC). He received 4 units of packed RBCs over 4 weeks. His performance status was 1. His CBC showed a WBC count of 1,000/µL, Hb level of 10 g/dL, and platelet count of 28,000/µL. Bone marrow biopsy revealed 20% blasts. The patient resumed the second course of decitabine at the same dosage; at day 28 of the second cycle his WBC count was 1,000/µL, Hb 10 g/dL, and platelet count 30,000/µL. Bone marrow biopsy revealed 5% blasts. The patient had no fever. He was given growth factor support (filgrastim) 480 µg twice a day for two doses. The repeated CBC 48 hours later revealed a WBC count of 2,000/µL and absolute neutrophil count (ANC) of 1,000/µL. He was started on the third course of decitabine at the same dosage. During the third course, his Hb level remained stable around 11 g/dL without transfusion support. He was taken off antibiotic therapy. At day 28 of the third course his WBC count was 2,500/µL, ANC 1,200/µL, Hb 11g/dL, and platelet count 150,000/µL. Bone marrow biopsy showed 3% blasts, and cytogenetic analysis revealed diploid karyotype. Therefore, after three courses of therapy, the patient achieved a complete remission. He is currently undergoing his 15th cycle of decitabine at the same dosage with a sustained complete remission. He is off antibiotic and growth factor support and remains transfusion-independent. He is followed by a weekly CBC and a bone marrow biopsy every three cycles.

Discussion

Hypomethylating agents like azacitidine and decitabine have demonstrated anti-MDS activity, and both are now approved for the treatment of MDS and CMML. However, response rates to these agents remain low, with CRs observed in fewer than 10% of patients in randomized phase III studies.

In a phase II trial of decitabine in MDS testing both dose intensity and subcutaneous route of administration, patients received a total dose of 100 mg/m² per course and were randomized in a Bayesian design to one of three arms: 1) 10 mg/m² intravenously over 1 hour daily for 10 days; 2) 20 mg/m² intravenously over 1 hour daily for 5 days; and 3) 20 mg/m² subcutaneously daily (administered as 2 doses) for 5 days. Cycles were repeated every 4 weeks; response or lack of response was evaluated only after at least three cycles were given. Ninety-five patients...
(median age, 67 years) were treated, 77 with MDS and 18 with CMML. Thirty-two percent had secondary MDS and 66% had intermediate-2– or high-risk disease. The median number of cycles was 7+ (range, 1–18 cycles). Overall, 32 patients (34%) achieved CR and 69 (73%) had an objective response according to the new modified IWG criteria. The 5-day intravenous schedule, which had the highest dose intensity, yielded a remarkably high response rate (39% CR) in a poor-prognosis group of patients and was therefore selected as optimal. This treatment was well tolerated with few nonmyelosuppressive complications. In addition, decitabine induced a better survival when compared to chemotherapy in matched cohort populations (median 22 vs 11 months; estimated 2-year survival rate 47% vs 25%; P<.001).

There are three key components of the 20 mg/m² IV over 1 hour daily 3 5 regimen that may account for its success: 1) The timely delivery of decitabine courses every 4 weeks (rather than 6–8 weeks), as long as there were no myelosuppression-related prohibitive complications (eg, pneumonia, severe infections or bleeding, severe organ dysfunction) or prolonged myelosuppression (no evidence of MDS in a hypocellular marrow with <5% cellularity). Our patient had persistent disease after the first courses and received the following courses without delay. He received two injections of growth factor before the third course to accelerate his recovery. 2) The delivery of at least three courses of decitabine before judging response. Our patient’s response would have been considered a failure after the first course; however the administration of additional courses led to a CR after three courses of therapy. 3) The reduced decitabine dose from 135 mg/m² to 100 mg/m² alleviated further myelosuppressive complications and optimized hypomethylation induction. The CR rate was 39% versus only 9% in the pivotal decitabine randomized study. Our patient did not experience any significant toxicity. He achieved a complete remission and became transfusion-independent by the 4th cycle of therapy.

In conclusion, decitabine given at low doses every 4 weeks is effective in patients with MDS. At least three courses are needed to achieve effect. The benefit is related to quality of response (CR; other) as well as long-term treatment.

References
Treatment of Lower-risk MDS Patients With Hypomethylating Agents

Mikkael A. Sekeres, MD, MS

Dr. Sekeres is Assistant Professor of Medicine in the Department of Hematologic Oncology and Blood Disorders, at Cleveland Clinic Taussig Cancer Center in Cleveland, Ohio.

Case Study

A 72-year-old retired film professor presented to his primary care physician with nonspecific complaints of fatigue, and said, “I feel like Orson Welles at the end of Citizen Kane.” A CBC was obtained, revealing a WBC count of 3,400/µL, Hb of 7.9 g/dL, platelet count of 123,000/µL, and ANC of 900/µL. His MCV was within normal range, and red cell distribution width was 16.9%. Subsequent iron, vitamin B12, folate, and thyroid studies were all within normal limits, and colonoscopy and esophagogastroduodenoscopy were negative for any lesions. His medical history was significant only for hypertension for which he was treated with hydrochlorothiazide, he had no known medication allergies, and his family history was significant only for coronary disease. His review of systems revealed a weight loss of 10 pounds in the past 3 months and, on further questioning, some dyspnea on exertion when walking across the parking lot to the cineplex. Physical examination was remarkable for pallor, most notable in his conjunctiva, and no hepatosplenomegaly.

He was referred to a hematologist/oncologist, who performed a bone marrow biopsy. This showed a hypercellular bone marrow for age at 70%, dysplastic erythroid precursors in 30% of cells, dysgranulopoiesis with hypogranular forms, pseudo–Pelger-Huet cells, hypolobated megakaryocytes, and 3% myeloblasts. Metaphase cytogenetics returned 2 weeks later, revealing -Y and +8 abnormalities in 18 of 20 cells analyzed. Additionally, a serum erythropoietin level returned at 670 U/L. He was given a diagnosis of RCMD.

The patient was started on recombinant humanized erythropoietin at a dose of 40,000 units weekly, but after 6 weeks his Hb fell to 7.5 g/dL and he received a transfusion of packed RBCs. The dose was increased to 60,000 units weekly, without a response, and he and his physician decided to try decitabine, dosed at 15 mg/m² every 8 hours over 3 days, with repeat cycles every 6 weeks. Within the first 4 weeks of therapy his cytopenias worsened; he required two subsequent RBC transfusions and was placed on a prophylactic ciprofloxacin when his ANC fell below 500/µL. Following his second treatment course he required a RBC transfusion only once, and following his third treatment cycle his blood counts started to improve: his WBC count increased to 6,500/µL, Hb to 11.4 g/dL, and platelet count to 174,000/µL. His ANC rose to 2,900/µL. He continued therapy for a total of 6 cycles, with a repeat bone marrow biopsy showing persistent dysplasia, but in the setting of normal blood counts. At that point the patient opted to stop therapy, as his quality of life was outstanding, and he said, “I feel like a rose, bud!”

Discussion

This patient has what would be considered lower-risk MDS: his IPSS score, based on his blast percentage of 3%, his bicytopenia, and intermediate-risk cytogenetics, would be 1.0, placing him in the intermediate-1 category.1 Alternatively, he could be classified according to the recently-published WHO Prognostic Scoring System (WPSS), which takes into account the WHO pathologic diagnosis, cytogenetics, and transfusion needs.2 Using the WPSS, he would receive a score of 2, based on having RCMD and intermediate cytogenetics, but no transfusion needs. Either would predict for a median survival of approximately 3.5 years.

The decision of which initial therapy to use for patients with lower-risk MDS is not straightforward. In the absence of transfusion needs or profound cytopenias, a watch-and-wait approach is entirely reasonable. No study has ever demonstrated a survival advantage to initiating therapy earlier rather than later in the lower-risk MDS disease course. The focus at this stage in the disease should be on maximizing quality of life, which ought not be significantly compromised in the absence of symptoms or transfusion needs.3 Once a patient starts to develop cytopenias requiring correction, physicians often consider treatment with growth factors, such as ESAs with or without granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor.
dictors of the likelihood of responding to ESAs have been published. Patients with low transfusion needs and a low serum erythropoietin level have a 74% chance of responding, whereas those with high transfusion needs and a high (>500 U/L) erythropoietin level have a low (7%) chance of responding. Those who have a mixed picture have a 23% chance of responding. Median response duration is approximately 2 years, and there may even be a survival advantage among all comers for ESAs compared to non–growth factor therapies.

The patient depicted here has a mixed picture: no transfusion needs but an erythropoietin level of 670 U/L. The question then arises of whether or not it is worth a trial of ESAs given the modest response rate. A decision analysis addressing this question explored whether a patient with lower-risk MDS should be treated initially with ESAs or non–growth factor approaches, incorporating data on response rates, overall survival, and quality of life. It found that patients who fall into the group with a good chance of responding to ESAs should generally be treated with ESAs, those who fall into the group with a poor chance of responding to ESAs should be treated with non–growth factor therapies, and those with a mixed picture should be treated with non–growth factor therapies, as long as those therapies have a response rate of greater than 14%.

Thus, it would be reasonable here to treat this patient with a non–growth factor therapy. Drugs approved by the FDA include lenalidomide for transfusion-dependent lower-risk MDS patients with a del(5q) abnormality, and two hypomethylating agents, azacitidine and decitabine, for all subtypes of MDS. Lenalidomide has been explored in one phase I/II study in MDS patients and in two phase II studies of transfusion-dependent lower-risk MDS patients: one for patients with the del(5q) abnormality and one in those without the abnormality. Dosing was 10 mg daily for 21 or 28 days of a 28-day cycle. Focusing on the study in patients without the abnormality, 214 patients were enrolled, with a median age of 72 years. More than 1 in 4 (26%) achieved transfusion independence, lasting a median of 41 weeks (range, 8 to >136 weeks). Grade 3 or 4 neutropenia and/or thrombocytopenia occurred in 20–25% of patients.

Both azacitidine and decitabine have been studied in phase III trials with the control arm being supportive care. In the azacitidine study, the CR plus PR rate (when analyzed using IWG criteria) for patients receiving azacitidine was 16%, with an overall response rate of approximately 47%. The overall response rate (CR + PR + hematologic improvement [HI]) in patients with lower-risk MDS was approximately 27%. Dosing was 75 mg/m² daily for 7 days of a 28-day cycle, and azacitidine significantly prolonged the time to AML transformation or death in all patient subtypes. In the decitabine study, dosing was 15 mg/m² every 8 hours 3 days, administered every 6 weeks. The CR + PR rate was 17% and the overall response rate (CR + PR + HI) was 30%. In lower-risk MDS patients, the response rate (CR + PR) was 16%. Decitabine significantly prolonged the time to AML transformation or death in higher-risk patients. Major toxicities to both drugs were grade 3 or 4 cytopenias, which occurred in approximately half of the patients. These two drugs are thought to have similar efficacy, with differences in response rate in pivotal trials due to variations in subjects enrolled and to the fewer numbers of cycles of decitabine given compared to azacitidine. An alternative dosing schedule for decitabine has been proposed, 20 mg/m² daily 3 days, which appears to provide responses at least equivalent to those achievable with the FDA-approved dosing schedule. Interestingly, in this study, subjects received a median of five or more treatment cycles of decitabine. Two multi-institution studies exploring various dosing approaches to both hypomethylating agents should be reporting results soon, providing further guidance to the optimal approach to this difficult disease.

References

The Use of Lenalidomide in MDS With Deletion of Chromosome 5q31

Larry D. Cripe, MD

Dr. Cripe is Associate Professor in the Division of Hematology/Oncology, School of Medicine, and the Indiana University Melvin and Bren Simon Cancer Center, in Indianapolis, Ind.

The recent approval of lenalidomide for the treatment of patients with low- to intermediate-1–risk MDS with a del(5q31) anomaly complicated by RBC transfusion–dependence provides the opportunity for the clinician to more rationally select therapy for a subset of people with MDS. The purpose of this case presentation is to highlight some of the issues associated with prescribing lenalidomide.

Case Study

The patient is a 75-year-old white woman with chronic obstructive pulmonary disease who presented with increasing dyspnea on exertion. A CBC demonstrated an Hb level of 8.5 g/dL with a low reticulocyte count and an elevated MCV (106 fL), a total WBC count of 3,600/µL with no immature forms, and a platelet count of 938,000/µL. A bone marrow aspirate demonstrated a marginally adequate specimen with few particles that revealed increased megakaryocytes, many of which were monolobated. There was evidence of erythroid and myeloid dysplasia; the percent myeloblasts was 4%. The patient received two units of packed RBCs and was initiated on an ESA. Metaphase cytogenetics were reported two weeks after the marrow aspirate and demonstrated the following: 46,XX,del(5)(q13q33)[13]/46,XX[7].

There was no reduction in transfusion frequency with ESA after 8 weeks and it was discontinued. The patient was initiated on lenalidomide 10 mg daily; Table 4 is a summary of selected peripheral blood values over time. There was a prompt reduction in her platelet count and resolution of the transfusion dependence. Unfortunately she developed a diffuse erythematous pruritic rash that was refractory to aggressive antihistamine and topical and systemic corticosteroid therapies, and, therefore, the lenalidomide was discontinued. She remains transfusion-independent at 6 months; sustained responses to lenalidomide after discontinuation have been reported.

Discussion

MDS With a Deletion of 5q31

One of the more common recurrent cytogenetic abnormalities observed in MDS is an interstitial deletion of the long arm of chromosome 5.1 Although the size of the deletion is variable, it appears that the critical deletion involves 5q31 to 5q32. There is a characteristic clinical presentation that may alert the clinician to the diagnosis. The 5q- syndrome is more common in women and the presentation typically includes a hypoproliferative macrocytic anemia and normal-to-elevated platelet count. The marrow aspirate usually reveals increased megakaryocytes, many of which are hypolobated, and less than 5% blasts. The prognosis has classically been considered favorable although the presence of an increased blast percentage or other karyotypic abnormalities portends a less favorable prognosis.2 Based upon the patients enrolled in the pivotal trial (known as MDS-03) of lenalidomide in MDS with del(5q31), discussed below, it is clear that the majority of patients with del(5q31) do not meet criteria for the syndrome.

Lenalidomide in Patients With MDS and del(5q31)

Lenalidomide was approved based upon a single-arm international multicenter study in patients with IPSS low- to intermediate-1–risk MDS with 5q31 deletions.
Table 4. Sequential Peripheral Blood Values in a Patient with MDS and del(5q) Treated With Lenalidomide

<table>
<thead>
<tr>
<th>Day</th>
<th>Hb, g/dL</th>
<th>ANC, per µL</th>
<th>PLT, ≥ 1,000 per µL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>1,800</td>
<td>1,143</td>
<td>Receiving PRBC transfusions Lenalidomide 10 mg daily</td>
</tr>
<tr>
<td>7</td>
<td>8.1</td>
<td>900</td>
<td>983</td>
<td>Received 2 units PRBC Lenalidomide dose held</td>
</tr>
<tr>
<td>14</td>
<td>10</td>
<td>600</td>
<td>96</td>
<td>Hb increasing without transfusion Lenalidomide dose held</td>
</tr>
<tr>
<td>28</td>
<td>9.7</td>
<td>750</td>
<td>115</td>
<td>Lenalidomide resumed at 5 mg daily</td>
</tr>
<tr>
<td>35</td>
<td>10.8</td>
<td>1,000</td>
<td>98</td>
<td>Rash and pruritus improved Lenalidomide resumed at 5 mg daily</td>
</tr>
<tr>
<td>49</td>
<td>11.4</td>
<td>1,300</td>
<td>256</td>
<td>Rash recurs, refractory to antihistamines and oral prednisone Lenalidomide discontinued</td>
</tr>
<tr>
<td>63</td>
<td>12.5</td>
<td>3,000</td>
<td>283</td>
<td>Rash resolved Lenalidomide discontinued</td>
</tr>
<tr>
<td>119</td>
<td>13.3</td>
<td>3,600</td>
<td>416</td>
<td>On observation</td>
</tr>
<tr>
<td>168</td>
<td>12.6</td>
<td>3,400</td>
<td>403</td>
<td></td>
</tr>
<tr>
<td>288</td>
<td>13.6</td>
<td>3,100</td>
<td>319</td>
<td></td>
</tr>
</tbody>
</table>

ANC=absolute neutrophil count; Hb=hemoglobin; MDS=myelodysplastic syndromes; PLT=platelet count; PRBC=packed red blood cells.

complicated by RBC transfusion–dependence. Analysis of a prior phase I trial of lenalidomide had indicated the response rate in this subgroup was higher than anticipated. Additional eligibility criteria included a platelet count greater than 50,000/µL and a neutrophil count greater than 500/µL. The primary endpoint was to assess the rate of red cell transfusion independence. Table 5 is a summary of selected outcomes and observed adverse events.

One hundred forty-eight patients were enrolled to receive lenalidomide 10 mg daily on either a 21-out-of-28-day schedule (n=46) or on a continuous basis (n=102). At the protocol-specified 6-month evaluation, 112 patients had a response to treatment; 96 patients were transfusion-independent. This rate of red cell transfusion independence is far superior to that observed with ESAs. At 1 year, 61 patients remained independent of transfusions; thus, the median duration of transfusion-independence has not been reached. The median time to response was 4.6 weeks (range 1–49 weeks). In addition to the hematologic response, 38 of 85 evaluable patients achieved a complete cytogenetic response.

Thus, lenalidomide produces a rapid, sustained, and clinically meaningful benefit for the majority of patients with MDS with 5q31 deletions. As discussed below, the most common adverse event was myelosuppression.

Table 5. Selected Outcomes Observed in the 148 Red Blood Cell Transfusion–dependent Patients with Low- or Intermediate-1–risk Myelodysplastic Syndromes Associated With del(5q31) Treated With Lenalidomide

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of red blood cell transfusion–independence</td>
<td></td>
</tr>
<tr>
<td>Number (%)</td>
<td>99 (67%)</td>
</tr>
<tr>
<td>Median time to response (range)</td>
<td>4.6 weeks (1–49)</td>
</tr>
<tr>
<td>Complete cytogenetic remission</td>
<td>48/85 evaluable (45%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
</tr>
<tr>
<td>Neutropenia (&lt;1,000/µL)</td>
<td>54.7%</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;50,000/µL)</td>
<td>54.7%</td>
</tr>
<tr>
<td>Total deaths (possibly related)</td>
<td>11 patients (3)</td>
</tr>
<tr>
<td>Dose modifications</td>
<td></td>
</tr>
<tr>
<td>Number (%) of patients</td>
<td>124 (84%)</td>
</tr>
<tr>
<td>Median time to modification (range)</td>
<td>22 days (2–468)</td>
</tr>
<tr>
<td>Premature discontinuation of treatment</td>
<td>30 (20%)</td>
</tr>
</tbody>
</table>
Modification of Dose and/or Schedule of Lenalidomide in Anticipation of Myelosuppression

A frequently asked question is whether the initial dose or schedule of lenalidomide should be modified given the observation that grade 3 or 4 neutropenia (ANC <1,000/µL) and thrombocytopenia (platelet count <50,000/µL) was seen in 55% and 44% of patients, respectively. Approximately two thirds of patients experienced these adverse events within 8 weeks of initiation of lenalidomide. It is important to note that only 4.1% of the patients developed fever while neutropenic. Thus, it was well tolerated. Three of 11 deaths observed in study participants were due to neutropenic sepsis. The remaining deaths were assessed as unrelated to study medication.

There are no data on initial dose reductions, as all patients enrolled on MDS-03 received 10 mg of lenalidomide. Thus far, I have for the most part refrained from a dose reduction given the possibility that there is a threshold dose required to effectively suppress the malignant hematopoiesis sufficiently to allow normal hematopoiesis to resume in full vigor. Clearly however, the vast majority of patients will require dose reduction. In MDS-03, 80% of the patients had at least one protocol-specified dose reduction (to 5 mg daily or, for a second adverse event, to 5 mg every other day). At the 24-week evaluation 40 patients (27%) were receiving 10 mg daily, 54 patients (36%) were receiving 5 mg daily, and 54 patients (36%) were receiving 5 mg every other day. The discontinuation of lenalidomide for rash observed in this case has, thus far, not been associated with relapse of her disease. This finding has been observed by others.

There is slightly more information available about the effect of the schedules. One hundred two of the 148 patients were scheduled to receive lenalidomide daily without interruption. The remaining 46 received drug for 21 days of every 28-day cycle. Grade 4 neutropenia (ANC <500/µL) was less common among patients receiving 21-day dosing versus 28-day dosing (17% vs 44%; P<.001). The reverse was true for grade 4 thrombocytopenia. Thus, if neutropenia is the particular concern, a 21-day dosing schedule may be prudent.

References

1. What percentage of patients with MDS typically achieve a complete or partial response to therapy with azacitidine or decitabine used at standard doses, according to a re-assessment of the data using iWG 2006 criteria?
   a. 10–15%  
   b. 15–20%  
   c. 20–25%  
   d. 25–30%

2. In which subset of patients with MDS is lenalidomide most effective?
   a. deletion 5q  
   b. trisomy 8  
   c. deletion 20q  
   d. monosomy 7

3. According to a study cited by Drs. Miller and Pihan, azacitidine-treated patients experienced a better overall improvement compared to patients treated with supportive care only by what percentage?
   a. 60% vs 5%  
   b. 50% vs 5%  
   c. 45% vs 5%  
   d. 40% vs 5%

4. What independent prognostic variables constitute the IPSS?
   a. del(20q), trisomy 8, monosomy 7  
   b. karyotype, del(5q), presence of refractory cytopenias  
   c. less than 5% blasts in marrow, unilineage myeloid dysplasia, isolated interstitial deletion of the long arm of chromosome 5  
   d. karyotype, number of cytopenias, percentage of bone marrow myeloblasts

5. Which of the following doses was NOT one used in the randomized phase II trial of decitabine described by Dr. Jabbour?
   a. 10 mg/m² intravenously over 1 hour daily for 10 days  
   b. 20 mg/m² intravenously over 1 hour daily for 5 days  
   c. 20 mg/m² subcutaneously administered as two doses for 5 days

6. What significant toxicities did the patient in the case study by Dr. Jabbour experience while receiving decitabine?
   a. emesis  
   b. bleeding  
   c. neutropenia  
   d. none of the above

7. In the case study by Dr. Sekeres, what were the WBC counts at presentation and after the third cycle of decitabine, respectively?
   a. 3,400/µL and 6,500/µL  
   b. 6,500/µL and 3,400/µL  
   c. 3,000/µL and 6,000/µL  
   d. 900/µL and 2,900/µL

8. Which patients have a high chance of responding to ESAs once they have developed cytopenias requiring correction?
   a. Patients with low transfusion needs and a high serum erythropoietin level.  
   b. Patients with low transfusion needs and a low serum erythropoietin level.  
   c. Patients with high transfusion needs and a high serum erythropoietin level.  
   d. Patients with high transfusion needs and a low serum erythropoietin level.

9. The 5q- syndrome typically includes which of the following?
   a. increased megakaryocytes  
   b. hypoproliferative macrocytic anemia and normal-to-elevated platelet count  
   c. less than 5% blasts  
   d. all of the above

10. What was the most common adverse event in patients treated with lenalidomide for MDS characterized by deletion 5q31 in the trial described by Dr. Cripe?
    a. myelosuppression  
    b. fever  
    c. bleeding  
    d. alopecia
Evaluation Form

Current Treatment Strategies for Myelodysplastic Syndromes

Initial release date: March 15, 2008; material expires one year from release date: March 15, 2009.

Please complete the CME post-test, the CME Certificate Request Form, and this evaluation form and return to: CME Consultants 94 Main St., Wakefield, RI 02879. Answers should be submitted no later than March 15, 2009. Please read the instructions below.

This activity is designated for 1.0 AMA PRA Category 1 Credit(s)™. In order to receive your CME credit(s) you are requested to review the material in full and take the post-test on page 19. Once you have completed the quiz, please note in the space provided on the Certificate Request Form the amount of time it took you to complete the entire activity, including the post-test and evaluation.

Thank you for completing the evaluation form. Your evaluation of the activity and comments are important to us and will remain confidential.

Please answer the following questions by circling the number that best reflects your view.
(Scale: 1 = poor; 2 = fair; 3 = satisfactory; 4 = good; 5 = excellent)

1. Please rate how effectively you are able to:
   a. Describe current treatment strategies for MDS. 1 2 3 4 5
   b. Describe evaluations of risk and prognosis in MDS. 1 2 3 4 5
   c. Review approaches to various subtypes of MDS. 1 2 3 4 5

2. Activity/Topic:
   a. The extent this program met your continuing professional development goals 1 2 3 4 5
   b. The overall quality of the activity 1 2 3 4 5
   c. The overall format of the activity 1 2 3 4 5
   d. The applicability/usefulness of the material to your practice Not in practice 1 2 3 4 5

3. Based on your previous knowledge and experience, this activity was:
   Too basic [ ]  Appropriate [ ] Too complex [ ]

4. Do you feel that the activity was objective, balanced, and free of commercial bias? Yes No
   If no, why? __________________________________________

5. Based on this activity, how might you change your practice management or patient care?

6. Please list any speakers and/or topics you would like in future programs.

7. Would a periodic review of this or related material be appropriate? Yes No

8. We welcome your comments

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