Abstract

The NCCN Guidelines for Myelodysplastic Syndromes (MDS) comprise a heterogeneous group of myeloid disorders with a highly variable disease course that depends largely on risk factors. Risk evaluation is therefore a critical component of decision-making in the treatment of MDS. The development of newer treatments and the refinement of current treatment modalities are designed to improve patient outcomes and reduce side effects. These NCCN Guidelines Insights focus on the recent updates to the guidelines, which include the incorporation of a revised prognostic scoring system, addition of molecular abnormalities associated with MDS, and refinement of treatment options involving a discussion of cost of care. (J Natl Compr Canc Netw 2015;13:261–272)

Please Note

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Overview

Refinements to the method of prognosis and stratification of patients with myelodysplastic syndromes (MDS) and to the treatment regimens are indicated by the revisions to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Myelodysplastic Syndromes.\(^1\) Previously, the International Prognostic Scoring System (IPSS) and WHO Prognostic Scoring System (WPSS), which are based on morphology, cytogenetics, and the presence of cytopenias in patients with MDS, were the most frequently used.\(^2,3\) Recently, in a joint multinational study, termed the IWG-PM project, the IPSS was revised (IPSS-R)\(^4\) and has shown improved prognostic capability. This has initiated a transition from earlier scoring systems to the IPSS-R.

Conventional karyotyping remains the cornerstone for diagnosis of MDS;\(^5,6\) however, refined cytogenetic categories have been given greater weight in the IPSS-R,\(^7\) adding credence to the importance of
Frequent Mutations in MDS-Associated Genes Likely to Indicate Clonal Hematopoiesis

<table>
<thead>
<tr>
<th>Mutated Gene†</th>
<th>Typical Somatic Mutation Type and Locations§‡</th>
<th>Overall Incidence</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>TET2</td>
<td>Nonsense or Frameshift mutations: any in codons 134-144 or 1842-1921</td>
<td>20%–25%</td>
<td>Associated with normal karyotypes. More frequent in CMML (40%–60%).</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>Frameshift or Nonsense mutations: any in codons R682, 1593, R692, R696, Y666, K666, K700E, I704, G740, G742, D781</td>
<td>12%–18%</td>
<td>Associated with a poor prognosis.</td>
</tr>
<tr>
<td>TP53</td>
<td>Frameshift or Nonsense mutations: any codon except P475R and P72R</td>
<td>8%–12%</td>
<td>Independently associated with a poor prognosis. More frequent with complex karyotypes (50%) and del(5q) (15%–20%). May predict resistance or relapse to lenalidomide.</td>
</tr>
<tr>
<td>SF3B1</td>
<td>Missense: P935</td>
<td>4%–7%</td>
<td>Associated with poor prognosis. More frequent in CMML and JMML (7%).</td>
</tr>
<tr>
<td>SRSF2</td>
<td>Missense: P95</td>
<td>10%–15%</td>
<td>More frequent in CMML (40%–50%) and associated with a poor prognosis.</td>
</tr>
<tr>
<td>U2AF1</td>
<td>Missense: S34, Q157</td>
<td>8%–12%</td>
<td>Associated with a poor prognosis.</td>
</tr>
<tr>
<td>ZRSR2</td>
<td>Missense or Nonsense mutations: any in codons 974, 1156, 1226</td>
<td>5%–10%</td>
<td>Associated with a poor prognosis.</td>
</tr>
<tr>
<td>ASXL1</td>
<td>Nonsense or Frameshift mutations: any in codons 100–210</td>
<td>15%–25%</td>
<td>Independently associated with a poor prognosis in MDS and CMML. More frequent in CMML (50%).</td>
</tr>
<tr>
<td>RUNX1</td>
<td>Frameshift or Nonsense mutations: any in codons 424–432</td>
<td>10%–15%</td>
<td>Independently associated with a poor prognosis in MDS. May be familial in very rare cases.</td>
</tr>
<tr>
<td>EZH2</td>
<td>Nonsense mutations: any in codons 622–732 (except Y646)</td>
<td>5%–10%</td>
<td>Independently associated with a poor prognosis in MDS and MDS/MPN. More frequent in CMML (12%).</td>
</tr>
<tr>
<td>NRAS</td>
<td>Missense: G12, G13, G61</td>
<td>8%–10%</td>
<td>Associated with a poor prognosis, particularly in patients predicted to have lower risk MDS. More frequent in CMML and JMML (15%).</td>
</tr>
<tr>
<td>CBL</td>
<td>Missense, any in codons 366–420</td>
<td>&lt;5%</td>
<td>More frequent in CMML (10%–20%) and JMML (15%).</td>
</tr>
<tr>
<td>JAK2</td>
<td>Missense: V617F</td>
<td>&lt;5%</td>
<td>More frequent in RARS-T (30%).</td>
</tr>
<tr>
<td>SETBP1</td>
<td>Missense: E858, D686, S689, G870, I871, D860</td>
<td>&lt;5%</td>
<td>Associated with disease progression. More frequent in CMML (5%–10%) and JMML (7%).</td>
</tr>
<tr>
<td>IDH1</td>
<td>Missense: R132</td>
<td>&lt;5%</td>
<td>More frequent in AML.</td>
</tr>
<tr>
<td>IDH2</td>
<td>Missense: R140Q, R172</td>
<td>&lt;5%</td>
<td>More frequent in AML.</td>
</tr>
<tr>
<td>ETV6</td>
<td>Nonsense or Frameshift mutations: any in codons 1288, 1326</td>
<td>&lt;5%</td>
<td>Independently associated with a poor prognosis.</td>
</tr>
</tbody>
</table>

*Table: This table lists gene mutations likely to be somatic (acquired, not congenital/germline) and, therefore, indicative of clonal hematopoiesis. In the appropriate context (eg, cytopenias present without AML-defining criteria, no evidence of other malignancy), they could aid in the determination of diagnosis. However, no mutation is specific for MDS. There is insufficient evidence to support the use of somatic mutations as presumptive evidence of the disease when diagnostic criteria for MDS have not been met. Other disease-related mutations of the listed genes can occur in MDS, as can mutations in other genes, but these may have less certain significance (ie, possible germline variants or less specificity for MDS). Not all MDS patients will have a mutation in one of these genes, and the absence of non-clonal somatic mutations in non-hematopoietic tissues would be required to prove that they are acquired. Several of the genes listed can have congenital mutations that are disease-related in rare cases (eg, RUNX1, TP53, CBL). Known gene polymorphisms frequent in the population should be excluded from DNA sequencing results as they are likely germline variants and not evidence of clonal hematopoiesis. |

†Somatic mutations in several MDS-associated genes (eg, TET2, DNMT3A, and TP53) can occur in non-disease states and no gene mutation is diagnostic of MDS. Mutations in several genes can occur in neoplasms other than MDS, including lymphoid malignancies such as CLL and ALL. Mutations should not be used as presumptive evidence of MDS when diagnostic criteria for MDS have not been met. |

‡Mutation type definitions: *Frameshift* – a mutation that changes an amino acid codon into another (eg, K700E indicates that the lysine [K] at codon 700 changes to an glutamic acid [E]). *Missense* – a mutation that changes an amino acid into another (eg, R882Q indicates that the arginine [R] at position 882 can be mutated in more than one way). |

Universal Implementation of the IPSS-R

The IPSS-R was derived from analysis of a large dataset including 7012 patients from multiple international institutions. The IPSS-R defines 5 risk groups (very low, low, intermediate, high, and very high), versus the 4 groups in the IPSS, and provides more detailed cytogenetic abnormalities and subgroups (see MDS-5, page 263). Specifically, 16 cytogenetic abnormalities versus the previous 6 are identified, and the cytogenetic subgroups are refined to comprise 5 versus 3 risk groups. The newer classification separates the original designation of “marrow blasts <5%” into 2 subgroups, defined as “marrow blasts ≤2%” and “marrow blasts ≥2% to <5%.” Furthermore, the IPSS-R includes a depth of cytopenias measurement, defined with cutoffs for hemoglobin levels, platelet counts, and neutrophil counts. Age, performance status, serum ferritin, lactate dehydrogenase, and β2-microglobulin provide additional differentiating features related to survival but not for acute myeloid leukemia (AML) evolution. It should

developing diagnostic tests that determine genetic abnormalities. Additionally, these advances can aid in the design of future clinical trials.

The NCCN Guidelines are updated at least once per year, which is necessary to provide the most up-to-date treatments for clinical practice. One recent discussion regarding cancer treatment as a whole is the incorporation of risk/benefit and financial cost strategies. Although evaluation of the risks and benefits of individual treatments has always factored into strategies. Although evaluation of the risks and benefits of individual treatments has always factored into

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be noted that age is a more significant prognostic factor among lower-risk groups compared with higher-risk groups.9 Several retrospective studies have demonstrated the validity of the IPSS-R. In a database analysis of patients with MDS from a single institution (N=1088), median overall survival (OS) according to IPSS-R risk categories was 90 months for very low, 54 months for low, 34 months for intermediate 1, 21 months for high, and 13 months for very high (P<.005).9 The median follow-up in this study was 70 months. The IPSS-R was also predictive of survival outcomes among patients who received therapy with hypomethylating agents (n=618). A significant survival benefit with azacitidine was shown only for the high and very high IPSS-R risk groups compared with patients not receiving azacitidine (median survival, 25 vs 18 months; P<.028; median survival, 15 vs 9 months; P=.005, respectively). Significantly longer OS with allogeneic hematopoietic stem cell transplantation (HSCT) was only observed for patients at high risk (median survival, 40 vs 19 months without HSCT; P<.005) and very-high risk (median survival, 31 vs 12 months without HSCT; P<.005).9

Another multicenter study reviewed patients with MDS who received either best supportive care only (n=1314), induction chemotherapy (n=214), or allogeneic transplant (n=167) to compare the prognostic value of the IPSS-R with the IPSS, WPSS, and Dueseldorf score.10 The IPSS-R could clearly distinguish risk categories and was better than the 3 other scoring systems for identifying patient survival and risk of AML evolution. The distribution of patients among the IPSS-R groups was similar to that of the cohort in the original design of the IPSS-R. Overall, patients who had worse prognosis and were formerly categorized as lower risk by the IPSS could be identified as higher risk by the IPSS-R. Similarly, the IPSS-R ascribed to lower-risk category patients who had a more favorable prognosis than was predicted by the IPSS.10

As part of a larger study to identify predictive factors for patients receiving allogeneic HSCT, Della
Porta et al\textsuperscript{11} evaluated the ability of the IPSS-R to predict relapse and lower OS after transplant in 519 patients with MDS or oligoblastic AML. In a multivariate model, the IPSS-R significantly affected OS (hazard ratio [HR], 1.41; \textit{P}<0.001) and the probability of relapse (HR, 1.81; \textit{P}<0.001). The IPSS-R also showed the ability to identify posttransplantation outcomes. The study used the Akaike criterion and determined that the IPSS-R was more indicative of prognosis than the IPSS, especially during early-stage disease.\textsuperscript{11} One of the known limitations of the IPSS was the poor stratification of posttransplant outcome in patients with early-stage disease.\textsuperscript{12} This study has shown improvement of the IPSS-R over the IPSS in risk-stratifying this group.\textsuperscript{11}

Additional studies have confirmed the value of the IPSS-R in treated and untreated patients.\textsuperscript{9-11,13-18} Because more accurate risk stratification by the IPSS-R compared with the IPSS and WPSS has been demonstrated,\textsuperscript{16} the IPSS-R categorization is preferred. Although implementation of the IPSS-R has already occurred in many institutions, it has not fully transitioned into community practice, the drug approval process, or transplant decision applications. Community hospitals may find calculating the IPSS-R to be complex, particularly the inclusion of cytogenetic abnormalities; however, online calculators (http://advanced.ipss-r.com) and Smartphone apps are available for the IPSS-R to facilitate its use. A difficulty in universally adopting the IPSS-R to the drug approval process is that it could influence how drugs are used if they were originally approved under the IPSS. Lastly, the complication with applying the IPSS-R to the decision algorithms in terms of when to recommend transplant was discussed. These algorithms are currently based on the IPSS or WPSS.\textsuperscript{19,20} Although institutions are predicted to switch over to the IPSS-R as more data become available, a paucity of data remains regarding transplant. Recently, data were presented on the potential utility of using the
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SUPPORTIVE CARE

- Clinical monitoring
- Psychosocial support
- Quality-of-life assessment
- Transfusions:
  - RBC transfusions (leuko-reduced) are recommended for symptomatic anemia, and platelet transfusions are recommended for thrombocytopenic bleeding. However, they should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count <10,000/mm³. Irradiated products are suggested for transplant candidates.
  - Cytomegalovirus (CMV)-negative or leuko-reduced blood products are recommended whenever possible for CMV-negative transplant candidates.
- Antibiotics are recommended for bacterial infections, but no routine prophylaxis is recommended except in patients with recurrent infections.
- Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia.
- Iron chelation:
  - If >20 to 30 RBC transfusions have been received, consider daily chelation with deferoxamine subcutaneously or deferasirox orally to decrease iron overload, particularly for LOW/INT-1 and for potential transplant patients. For patients with serum ferritin levels >2500 ng/mL, aim to decrease ferritin levels to <1000 ng/mL.³ See Discussion
  - Patients with low creatinine clearance (<40 mL/min) should not be treated with deferasirox.
- Cytokines:
  - EPO: See Anemia Pathway (MDS-12)
  - G-CSF or GM-CSF:
    - Not recommended for routine infection prophylaxis
    - Consider use if recurrent or resistant infections in neutropenic patient
    - Combine with EPO for anemia when indicated See Anemia Pathway (MDS-12)
- Platelet count should be monitored

¹See NCCN Guidelines for Supportive Care.
²Avoid transfusions for arbitrary hemoglobin thresholds in the absence of symptoms of active coronary disease, heart failure, or stroke. In situations where transfusions are necessary, transfuse the minimum units necessary to relieve symptoms of anemia or to return the patient to a safe hemoglobin level. Hicks L, Bering H, Carson K, et al. The ASH Choosing Wisely campaign: five hematologic tests and treatments to question. Blood. 2013; 122:3879-3883.
³Clinical trials in MDS are currently ongoing with oral chelating agents.

IPSS-R for decision analysis of stem cell transplantation.²¹ The IPSS-R is currently being evaluated in therapy-related MDS, and preliminary data suggest that with additional modifications, the IPSS-R may be applicable to this distinct population of patients with MDS.²² Taken together, the NCCN Panel decided that it was premature to eliminate other scoring systems from the algorithm; however, the IPSS-R should be substituted when possible because of its greater accuracy.

During this transition period, before more uniform prognostic risk stratification is accepted by the field, keeping multiple prognostic scoring systems in the algorithms seems prudent. Therefore, each algorithm page that refers to treatment pathways based on prognostic category indicates category designations for IPSS, IPSS-R, and WPSS (see MDS-10 and MDS-11, pages 265 and 266, respectively). The algorithms address certain recommendations in the footnotes. For cases in which a patient is managed as lower risk but fails to experience response, the recommendation is to then move to a higher-risk management strategy.

Appropriate Incorporation of Frequent Mutations in Patient Evaluation

In recent years, several gene mutations have been identified among patients with MDS that may, partly, contribute to the clinical heterogeneity of the disease course, and thereby influence prognosis. A large variety of gene mutations will be present in most patients with newly diagnosed MDS, including most patients with normal cytogenetics. The NCCN Panel does not recommend molecular testing to establish a diagnosis of MDS. Comparable abnormalities have been described in apparently normal individuals. Also, in patients with a confirmed diagnosis of MDS using standard diagnostic criteria only, a limited number of the abnormalities have established prognostic significance. Several studies examining large numbers of MDS marrow or peripheral blood
samples have identified more than 40 recurrently mutated genes, with more than 80% of patients harboring at least 1 mutation. Frequent mutations in MDS-associated genes that are likely to be indicative of clonal hematopoiesis are listed in the NCCN Guidelines (see MDS-7, page 264). These genes can be categorized into several groups: (1) transcription factors (TP53, RUNX1, ETV6); (2) epigenetic regulators and chromatin-remodeling factors (TET2, DNMT3A, ASXL1, EZH2, IDH1/2); (3) pre-mRNA splicing factors (SF3B1, SRSF2, U2AF1, ZRSR2); and (4) signaling molecules (NRAS, CBL, JAK2, SETBP1).

The most frequently mutated genes were TET2, SF3B1, ASXL1, DNMT3A, SRSF2, RUNX1, TP53, U2AF1, EZH2, ZRSR2, STAG2, CBL, and NRAS, although no single mutated gene was found in more than a third of patients. Several of these gene mutations are associated with adverse clinical features, such as complex karyotypes (TP53), excess bone marrow blast proportion (RUNX1, NRAS, and TP53), and severe thrombocytopenia (RUNX1, NRAS, and TP53). Despite associations with clinical features considered by prognostic scoring systems, mutations in several genes hold independent prognostic value. Mutations of TP53, EZH2, ETV6, RUNX1, and ASXL1 have been shown to predict decreased OS in multivariable models adjusted for IPSS or IPSS-R risk groups in several studies of distinct cohorts.

Within IPSS risk groups, a mutation in 1 or more of these genes identifies patients whose survival risk resembles that of patients in the next highest IPSS risk group (eg, the survival curve for INT-1-risk patients with an adverse gene mutation was similar to that of patients assigned to the INT-2-risk group by the IPSS). When applied to patients stratified by the IPSS-R, the presence of a mutation in 1 or more of these 5 genes was associated with shorter OS for patients in the low- and intermediate-risk groups.

Thus, the combined analysis of these gene mutations and the IPSS or IPSS-R may improve on the risk stratification provided by these prognostic models alone. Mutations of ASXL1 have also been shown to carry independent adverse prognostic significance in chronic myelomonocytic leukemia. Other mutated genes have been associated with decreased OS, including DNMT3A, U2AF1, SRSF2, CBL, PRPF8, SETBP1, and KRAS. Mutations of SF3B1 have been associated with a more favorable prognosis, but this may not be an independent risk factor.

Mutations of TP53 are strongly associated with complex and monosomal karyotypes. However, approximately 50% of patients with a complex karyotype have no detectable TP53 abnormality and have an OS comparable to that of patients with noncomplex karyotypes. Therefore, TP53 mutation status may be useful for refining the prognosis of these patients typically considered to have higher-risk disease. Patients with del(5q), either as an isolated abnormality or often as part of a complex karyotype, have a higher rate of concomitant TP53 mutations. These mutations are associated with diminished response or relapse after treatment with lenalidomide. In these cases, TP53 mutations may be secondary events and are often present in small subclones that can expand during treatment. More sensitive techniques may be required to identify the presence of subclonal, low-abundance TP53 mutations before treatment.

Although several recurring genetic mutations have been identified in studies of patients with MDS and may be useful for assessing prognosis, their possible utility in diagnosing MDS has not been established. Some mutations may prove useful after further analysis, but many of the same mutations have been identified in elderly patients who do not have MDS, and thus their use for diagnosis is not currently recommended.

As noted in the algorithms, for patients categorized as intermediate risk by the IPSS-R, prognostic factors may affect treatment. This may be seen in patients who are initially treated on a lower-risk scale but do not experience a response to treatment. The presence of these mutations may direct the clinician to a higher-risk treatment strategy (see MDS-10, page 265). Other patients who may benefit from mutational analysis are those who experience no response to hypomethylating agents and move to a clinical trial. These tests may be useful in determining an appropriate clinical trial that targets the specific lesion.

Significant discussion occurred regarding how to appropriately include mutations into the NCCN Guidelines. Although mutational analysis is not recommended for use in routine clinical circumstances, additional testing could be useful in some clinical situations, as described earlier. For these circumstances...
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in which the identification of mutations would be clinically beneficial, the panel recommends the use of sites established for molecular analysis.

Cost-Effective Care

Patients with MDS require evaluation for short-term and long-term disease-related and treatment-related side effects, with continuous monitoring for disease progression or the development of complications, such as infections. Several therapeutic options are available for patients with MDS, depending on their specific clinical features as outlined in the NCCN Guidelines. The NCCN Guidelines for MDS should be consulted regarding criteria for treatment selection. However, occasionally clinicians must choose among these options based on individual patient factors. In these situations, it may also be appropriate to be aware of and consider cost-effective care. Optimization of treatment may often result in a concurrent reduction in cost.

One treatment that has received more recent analysis is the evaluation of red blood cell (RBC) transfusion practices in patients who develop symptomatic anemia. The recommendation to keep transfusions to the minimal amount of units necessary to relieve symptoms or restore normal hemoglobin levels was highlighted in an article from the ASH Choosing Wisely Campaign. Similar verbiage has been added to the 2015 NCCN Guidelines for MDS (see MDS-B, page 267). Furthermore, there are inherent risks associated with transfusions, including transfusion-related reactions, transfusion-associated circulatory overload, bacterial contamination and viral infections, and iron overload. Iron overload is a particular concern for patients with MDS who receive frequent transfusions over several years. In these patients, iron overload may occur, causing an excess of iron deposition in the liver, heart, skin, and endocrine organs, resulting in potential complications and the need to consider iron chelation medications to prevent or stabilize such adverse events (see MDS-B, page 267).

The standard method to attempt to decrease RBC transfusions in symptomatic anemic patients with MDS without del(5q) is the use of recombinant erythropoietin. Dosing and response prediction (ie, relatively low serum recombinant erythropoietin, clinical risk status) are important considerations for use of this drug. The cost-effectiveness can also be evaluated among hematopoietic cytokines, specifically erythropoietin alpha (EPO) and darbepoetin for the treatment of symptomatic anemia. Based on the 2009 NCCN Guidelines for MDS, the annual cost of EPO ranged from $26,076 to $52,176 compared with the cost of darbepoetin, which ranged from $41,904 to $87,300. The variability in cost reflects the spectrum of acceptable dosages. However, further studies have compared lower doses of darbepoetin with EPO and have shown that 200 mcg of darbepoetin every 2 weeks has equivalent effectiveness as 40,000 U of EPO. Using these values instead of a range, the cost of EPO would be approximately $18,824 compared with the cost of darbepoetin, which is estimated to be $15,132. Therefore, dosage is a significant consideration when comparing the cost. Furthermore, darbepoetin can be administered less frequently than EPO, providing a significant value in terms of quality of life. Because both of these drugs may be coadministered with a granulocyte colony-stimulating factor, the cost of the additional cytokine does not ultimately affect the comparison of these hematopoietic cytokines.

Another option for reducing RBC transfusions in patients with MDS is the use of lenalidomide. The FDA has approved lenalidomide for the treatment of transfusion-dependent anemia in patients with del(5q) classified as having low- or INT-1-risk MDS (see MDS-10, page 265). Clinical trial data have shown that lenalidomide treatment can result in transfusion independence in a substantial proportion of these patients (60%–70%). Studies have shown the relative safety of lenalidomide in these patients and improved quality of life outcomes in randomized clinical trials. Thus, lower-risk patients with del(5q) chromosomal abnormalities and symptomatic anemia should receive lenalidomide. However, lenalidomide should be avoided in those with a clinically significant decrease in neutrophil or platelet counts.

Although the cost of lenalidomide is higher than other treatment regimens, the expense is partially offset by the reduction in the number of transfusions and the duration of transfusion independence. The estimated annual cost for lenalidomide when given 21 days per month is $66,204, based on the 2009 NCCN Guidelines. A publication evaluating the cost-effectiveness of lenalidomide versus best supportive care from Goss et al also showed a similar cost for lenalidomide of $63,385. In this
study, the cost of best supportive care was approximately $54,940 annually. Factors that were included in the overall cost were the annual primary cost of the intervention, annual cost of transfusions when on the intervention, and annual cost of drug-related complications. Additionally, comparison for health outcomes showed that 67.0% of patients given lenalidomide were transfusion-free versus only 8.9% of patients receiving best supportive care. Although not quantifiable from a financial benefit, quality of life is generally greater with lenalidomide treatment because of a fewer number of treatments and the oral bioavailability of lenalidomide.

Another treatment cost associated with RBC transfusion includes the use of iron chelation drugs. The NCCN MDS Panel recommends consideration of deferoxamine subcutaneously for 5 to 7 days per week or daily deferasirox orally to decrease iron overload (aiming for a target ferritin level <1000 ng/mL) in the following IPSS low- or INT-1-risk patients: (1) those who have received or are anticipated to receive more than 20 RBC transfusions, particularly for lower-risk patients; (2) those for whom ongoing RBC transfusions are anticipated; and (3) those with serum ferritin levels greater than 2500 ng/mL (see MDS-B, page 267). Although both iron chelators are a category 2A recommendation, choosing between the 2 options may involve several factors. The prescribing information for deferasirox contains a black box warning pertaining to the increased risks for renal or hepatic impairment/failure and gastrointestinal bleeding in certain patients. It is recommended that patients on deferasirox therapy be closely monitored via measurement of serum creatinine and/or creatinine clearance and liver function tests before initiation of therapy, and regularly thereafter. The oral availability of this formulation makes it easier to administer than deferoxamine for most patients in terms of patient compliance. The subcutaneous administration of deferoxamine is more time-intensive and entails indirect costs associated with administration of the drug. The direct cost of deferasirox annually was estimated to be $46,008 per year compared with deferoxamine, which was estimated at $21,048 per year. However, although deferasirox has a higher direct cost, the associated indirect costs must be evaluated to determine overall financial burden. In a study from the United Kingdom, deferasirox was evaluated to be more cost-effective than deferox-amine in patients with lower-risk, transfusion-dependent MDS based on the cost of the drug, cost of administration and monitoring, and quality-of-life outcomes, with the last serving as the key driver for improved quality-adjusted life-years. Taken together, both iron chelators have advantages and disadvantages that must be considered for each patient before a treatment is determined.

Another treatment option that has been evaluated for cost-effectiveness involves the use of hypomethylating agents. Currently, azacitidine and decitabine are considered to be therapeutically similar, although the improved survival of higher-risk patients treated with azacitidine compared with control patients in a phase III trial supports the preferred use of azacitidine in this setting (see MDS-10 and MDS-11, pages 265 and 266, respectively). Azacitidine can be administered subcutaneously or intravenously compared with decitabine, which requires an intravenous infusion with clinic or hospital admission. Studies have shown that indirect costs for decitabine are higher (if the azacitidine is given subcutaneously), further adding to the expense. Indirect costs were calculated to include hospitalization, management of side effects, physician visits, and use of erythropoiesis-stimulating agents. Selection of the hypomethylating agent azacitidine may result in a lower expense but equivalent benefit if azacitidine is given subcutaneously.

Comparison between cancer treatments must evaluate whether any one treatment confers a benefit in survival or quality of life compared with another. If a benefit is observed, it should be weighed against the treatment cost. As discussed earlier, this does not necessarily mean a patient will be accepting a poorer prognosis or less valuable treatment. Historically, the NCCN Guidelines have excluded cost of a treatment from their deliberations on recommendations in order to provide an unbiased set of treatment options. However, this means that options in the current guidelines that are considered equivalent based on patient outcomes may not be equivalent when cost is a factor. Future iterations of the guidelines may involve cost evaluation, but until then, clinicians should be advised to consider cost, not in exchange for reduced care, but rather to prevent any undue financial burden to the patient.
Conclusions

The yearly revision of the NCCN Guidelines is a reflection of the rate at which cancer research advances treatment. However, the advances must be conveyed to clinicians and patients to allow integration into practice, and to enable patients to advocate regarding their own care. The most recent update has highlighted advances in the prognostic and diagnostic aspects of MDS. Treatment options have also been updated and modified to provide improved patient care. Future directions must endeavor to address the increasing cost of care. With the current state of health care, strategies to improve clinical treatment should also incorporate economic strategies.

References


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Posttest Questions

1. Which statement about the IPSS-R is false?
   a. “Marrow blasts <5%” was subdivided into 2 groups.
   b. Transition to the IPSS-R aids treatment decision-making.
   c. The NCCN Guidelines for MDS have eliminated other prognostic scoring systems, in favor of using the IPSS-R only.
   d. The IPSS-R has demonstrated an improved ability to distinguish prognostic risk categories compared with other scoring systems.

2. True or False: The inclusion of genetic mutational analysis can provide a diagnosis of MDS in the absence of clinically diagnostic information.

3. Which of the following may be considerations when evaluating cost-effective care?
   a. The costs of drug therapy compared with direct and indirect costs for RBC transfusions in MDS patients with symptomatic anemia
   b. The indirect costs of epoetin and darbepoetin in the treatment of symptomatic anemia
   c. The route of administration of iron chelation drugs
   d. The risk level of the patients in selecting a hypomethylating agent
   e. All of the above