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SIGNED: ________________________________________

APPROVAL BY MASTER’S PROJECT DIRECTOR

This Master’s Project has been approved on the date shown below:

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Clinical Associate Professor
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Myelodysplastic Syndrome (MDS) is a bone marrow disorder that is becoming increasingly prevalent in the older adult population; it is currently the most common hematologic malignancy in adults over 80 years of age. Primary care providers (PCPs) are almost always involved in the care of MDS patients, whether it be at time of diagnosis or management of co-morbidities during the disease process. Despite this, the literature rarely addresses PCPs regarding their role in the care of MDS patients.

The purpose of this project is the creation of a MDS educational module for PCPs based on current evidence that will guide them in the recognition, diagnosis, and management of MDS in the primary care setting. The educational module will be based on an extensive review of the literature and follow the theoretical framework of the adult learning theory. The project will conclude with plans for evaluation and discussion of the project’s strengths, limitations, and significance.
CHAPTER 1

Introduction

The Myelodysplastic Syndromes (MDS) embody a range of heterogeneous clonal hematopoetic stem cell malignancies characterized by bone marrow abnormalities and dysfunctional hematopoiesis. MDS is a potentially deadly disease, as one-third of all patients who have it will progress to Acute Myelogenous Leukemia (AML) (Kurtin, 2007). Approximately 10,000 to 15,000 new cases of MDS are diagnosed each year in the United States. Based on the average life expectancy post diagnosis, this proposes that 35,000 – 60,000 Americans have MDS at any point in time (Kurtin, 2008). It is currently the most common hematologic malignancy in individuals over 80 years of age (Jadersten & Hellstrom-Lindberg, 2008). The median age range of MDS patients is 65 to 70 years (Kurtin, 2007). It is important to note that many experts believe the number of MDS cases per year to be greatly underestimated because it was not until recently that MDS was added to the national cancer registries. It is also believed that many of the very elderly patients may not be referred for their cytopenias (Finn, 2008).

The initial hematologic problems associated with MDS are most often discovered in the primary care setting, and following appropriate work-up, a hematology referral is made. Primary care providers (PCPs) also manage the comorbid conditions of MDS patients (Kurtin, 2007). It is evident that PCPs play an important role in the diagnosis and care of MDS patients; however there is a lack of resources available to them, and their role is ill-defined in the literature.
Statement of the Purpose

The purpose of this project is the creation of a MDS educational module for PCPs. It will guide PCPs in the recognition, diagnosis, and management of MDS and focus on recognizing signs and symptoms, referral to hematology, disease complications, treatment and side effects, and patient quality of life. The project will conclude with plans for evaluation and discussion of the project’s strengths, limitations, and significance.

Significance of the Problem

In 1970, the percentage of the United States population over the age of 65 was 20%, with an increase by 2006 to 38% (Hellmich, 2008). The median age range of MDS patients is 65 to 70 years (Kurtin, 2007). With an aging population, the number of MDS patients will continue to rise, which presents a higher likelihood that primary care providers will see these patients in their offices. It is also likely that MDS is underdiagnosed; the true prevalence may be much higher than those cases that are actually reported (Chabner et al., 2008). Although there is not currently a cure for MDS aside from bone marrow transplant, it is important that potential MDS patients are recognized and referred to hematology for further workup to avoid potential complications of the disease. Fatal complications of the cytopenias associated with MDS are not uncommon, especially infections that arise in the neutropenic patient (Steensma & Bennett, 2006). PCPs play a key role in the recognition and referral process and can also help with quality of life issues. In a recent qualitative study of quality of life in MDS patients, a significant number of patients reported feeling as though their PCPs had
limited knowledge regarding their disease, which led to decreased confidence in these providers (Heptinstall, 2008). With the aging population, the likelihood that primary care providers will be managing the comorbid conditions of patients with MDS is also increasing. They should be armed with a general knowledge base on MDS pathophysiology, diagnosis, and treatment.

Definitions of Relevant Terms

The following terms are used in this paper:

- **Absolute Neutrophil Count (ANC):** The actual number of white blood cells that are neutrophils. Commonly used in assessment of neutropenia. Neutropenia is present when ANC is less than or equal to 1000/mm3 (Polovich et al., 2005).

- **Alkylating Agents:** A type of drug that is used in the treatment of cancer. It interferes with the cell's DNA and inhibits cancer cell growth (National Cancer Institute, 2008).

- **Allogenic:** Taken from different individuals of the same species (i.e. a bone marrow transplant where one person gets cells from a donor) (National Cancer Institute, 2008).

- **Auer Rods:** Auer rods are clumps of granular material found in leukemic blast cells, part of the diagnosis of leukemia. The presence of Auer rods is generally considered to be associated with acute myelogenous leukemia (AML). They look like elongated, bluish-red rods inside the blast cell when you look at them under a microscope (Sherry, 2006).

- **Cytogenetics:** The study of chromosomes and chromosomal abnormalities (National Cancer Institute, 2008).
- **Cytopenia:** A condition in which there is a lower number of certain types of blood cells (National Cancer Institute, 2008).

- **Dysplasia:** Cells that look abnormal under a microscope but are not necessarily cancer (National Cancer Institute, 2008).

- **Flow Cytometry:** A method of measuring the number of cells in a sample, the percentage of live cells in a sample, and certain characteristics of cells, such as size, shape, and the presence of tumor markers on the cell surface. The cells are stained with a light-sensitive dye, placed in a fluid, and passed in a stream before a laser or other type of light. The measurements are based on how the light-sensitive dye reacts to the light (National Cancer Institute, 2008).

- **Hematopoiesis:** The formation of new blood cells and formed elements (National Cancer Institute, 2008).

- **Immunohistochemistry:** Demonstration of specific antigens or cell markers in tissues by the use of markers that are either fluorescent dyes or enzymes (Kumar et al., 2005).

- **Myelosuppression:** A condition in which bone marrow activity is decreased and production of platelets, red blood cells, and white blood cells is limited (National Cancer Institute, 2008).

- **Performance Status:** A measure of how well a patient is able to perform ordinary tasks and carry out daily activities (National Cancer Institute, 2008).

- **Petechiae:** Pinpoint, unraised, round red spots under the skin caused by bleeding. May be a sign of thrombocytopenia (National Cancer Institute, 2008).
- **Refractory Anemia:** Progressive anemia that is not associated with nutritional deficiency, renal insufficiency, hemolysis, vitamin deficiency, medication causes, or alcohol and is unresponsive to therapy other than transfusion (Tefferi, 2003).

- **Ringed Sideroblasts:** Red blood cells with iron deposits encircling the red cell nuclei that show up on a Prussian blue stain of a sample of bone marrow (McPhee & Papadakis, 2008).

- **Stem Cell:** A cell from which other types of cells develop. All blood cells develop from blood-forming stem cells (National Cancer Institute, 2008).

**Summary**

The myelodysplastic syndromes present a range of hematologic abnormalities that are usually discovered in the primary care setting. It is a disease that affects primarily older adults, who represent a growing percentage of the U.S. population and often present with several comorbid health issues. PCPs play a key role in the care of MDS patients in the identification of the disease, management of comorbid conditions throughout the MDS disease process, and monitoring quality of life. Current MDS literature and education is aimed towards the specialist is not well suited for PCPs, despite their roles in MDS diagnosis and management. An educational module for PCPs regarding the Myelodysplastic Syndromes will provide relevant and helpful information for the care of the patient with MDS.
CHAPTER 2

Introduction

This chapter will focus on the theoretical framework used to guide this project and will provide a comprehensive literature review. Malcolm Knowles’ Theory of Adult learning will provide the theoretical framework. Knowles developed this framework as a way to understand and guide the principles of adult learning. The first section of this chapter explains how the Theory of Adult Learning relates to this project. Subsequently, a literature review will be presented which includes etiology and pathogenesis, epidemiology, clinical features, diagnosis and classification, management, and psychosocial factors associated with MDS.

Theoretical Framework

Knowles Theory of Adult Learning is based on the concept of andragogy, which is defined as “the art and science of adult learning” (Knowles, 1974). This differs from pedagogy, which focuses on children/youth learning. It is considered a process model because it focuses on providing resources and procedures to assist learners in acquiring information, understanding, skills, attitudes, and values (Knowles, 1974).

Knowles bases his model on seven principles associated with andragogy.

- The Need to Know: For adults to get involved in a learning experience, they need to know the purpose of the learning experience and how it will benefit them (Misch, 2002).
- The Learner’s Self-Concept: Mature adults generally develop a self-concept that focuses on self-direction and self-reliance rather than dependence on others. They
prefer to feel in control of and responsible for their own lives. In educating adults, it is important that they feel like an equal in the educational experience (Misch, 2002).

- The Role of the Learner’s Experiences: Adults often enter educational situations with a variety of life experiences that shape their learning capacity (Misch, 2002). Their experiences should be welcomed as they bring versatility to the learning experience (Woodward, 2007).

- Readiness to Learn: Adults are usually eager to learn material that will be helpful in their every-day life and work situations (Misch, 2002). They tend to value those learning experiences that are relevant to their daily practices (Kaufman, 2003).

- Orientation to Learning: Adults are usually task-oriented or problem centered in regards to learning. They are more motivated to learn material to the extent that the material will benefit them in issues that confront them regularly (Misch, 2002).

- Motivation: Adults respond to internal motivators to learn (e.g. need for greater job satisfaction, self-esteem, quality of life) (Misch, 2002). It is important to involve adult learners in the diagnosis of their learning needs. This tends to further internal motivation (Kaufman, 2003).

- Involvement in Evaluation: Adult learners should be included in the evaluation of their learning experiences as this can further their competency of critical reflection (Kaufman, 2003).

Concepts from this model have been used to create an MDS educational module for primary care providers. Each of the above principles can be applied to the creation and implementation of the educational module.
• The Need to Know: Prior to beginning the content of the educational module, learners will be provided with pertinent information as to why further knowledge on MDS will benefit them.

• The Learner’s Self-Concept: The educational module will be provided for the learners complete on their own and at their own pace. It is a resource that will be available in their offices for immediate and future reference.

• The Role of the Learner’s Experiences: The learners in this setting will be a group of primary care providers, so it will be important to gear the content towards people who have a high level of education and a strong medical background. Experiences that primary care providers are familiar with will be incorporated into the learning to increase relevance.

• Readiness to Learn & Orientation to Learning: The module will present the information in a manner that makes it applicable to daily practice.

• Motivation: Learners will be given examples of how the educational content can increase job satisfaction (will broaden knowledge on hematologic abnormalities) and improve patient care (more thorough work up and proper management of MDS patients).

• Involvement in Evaluation: The learners will evaluate the educational module after completion to identify strengths, weaknesses, helpfulness, and applicability to practice. PCPs involved in the educational module will have access to the author or a representative via e-mail in order to ask questions or discuss the topic. This will keep the learners involved in the experience and promote a safe learning environment.
Literature Review

Etiology and Pathogenesis

The Myelodysplastic Syndromes (MDS) represent a group of heterogeneous clonal hematopoietic stem cell malignancies characterized by bone marrow abnormalities and dysfunctional hematopoiesis (De Angelo & Stone, 2005; Kurtin, 2007; Kumar et al., 2005; Nimer, 2008; Steensma & Bennett, 2006). This bone marrow dysfunction manifests as one or more peripheral blood cytopenias, particularly anemia, neutropenia, and thrombocytopenia with a variable risk of transformation to Acute Myelogenous Leukemia (AML) (First Consult, 2007; Kurtin, 2007; Steensma & Bennett, 2006; Nimer, 2008). The exact cause of MDS is unknown in the majority of patients. Defects in hematopoietic cells and the bone marrow microenvironment are thought to play a primary role in the pathogenesis of MDS (Chabner et al., 2008; Kurtin, 2007). Genotoxic substances, such as benzene and other solvents, radiation exposure, and mutagenic toxins such as chemotherapeutic agents, particularly alkylating agents or topoimerase inhibitors, have been identified as contributing factors (Chabner et al., 2008; Kurtin, 2007). The majority of MDS cases to date are de novo (primary) and are associated with variable prognosis. Treatment related MDS (T-MDS) have an especially poor prognosis with frequent transformation into AML (Chabner et al., 2008; First Consult, 2007; Lichtman & Liesveld, 2006).

Ineffective hematopoiesis is the key pathophysiologic mechanism in MDS. In MDS, the bone marrow is partially or completely replaced by the clonal descendents of a mutant pluripotent stem cell that maintains the ability to differentiate into erythrocytes,
granulocytes, and platelets. However, this differentiation takes place in a futile and
disorderly manner, which often manifests as cytopenias of the peripheral blood (Chabner
et al., 2008; De Angelo & Stone, 2005; Kumar et al., 2005; Lichtman & Liesveld, 2006).
MDS is characterized by amplified cellular proliferation of they myeloid lineage
accompanied by increased apoptosis (cellular death). It is likely that along with
ineffective cell differentiation, increased apoptosis plays a role in peripheral blood
cytopenias (Chabner et al., 2008; De Angelo & Stone, 2005; Kumar et al., 2005;
Lichtman & Liesveld, 2006). Increased apoptosis is likely due to aberrations in the bone
marrow microenvironment including increased circulation of inflammatory cytokines. In
MDS patients, the bone marrow fibroblasts and macrophages secrete higher than normal
levels of tumor necrosis factor (TNF) and interleukin-6, leading to increased apoptosis
(Chabner et al., 2008; De Angelo & Stone, 2005; Lichtman & Liesveld, 2006).

Cellular genetic abnormalities of nonrandom origin of are a factor in many MDS
cases. “Clonal genetic abnormalities are observed in the bone marrow of 50% of patients
with de novo MDS and 80% of patients with secondary MDS” (Chabner et al., 2008, p.
292). For example, in patients with T-MDS, karyotypic derangements may include
partial or total deletions of chromosomes –5, -7, 7q-, 13q-, 17p-, and –18 (Chabner et al.,
2008; Lichtman & Liesveld, 2006). The most frequent single genetic abnormality in
MDS is the 5q-Interstitial deletion, which occurs on the long arm of chromosome 5. This
may or may not be accompanied by other cytogenetic abnormalities. When present as a
single cytogenetic abnormality, 5q- holds a favorable prognosis (Chabner et al., 2008,
Kurtin, 2007).
**Epidemiology**

MDS is primarily a disease of older adults. The median age at diagnosis is 65 years, however, it can affect people of any age. Most cases in adults younger than age 50 occur due to previous chemotherapy or radiotherapy. One-third of cases in children are related to Down’s Syndrome (Cazzola & Malcovati, 2005; Chabner et al., 2008; First Consult, 2007; Kurtin, 2007; Steensma & Bennett, 2006). In the United States, it is estimated that approximately 35,000 to 60,000 individuals have MDS at any given time, and 10,000 to 15,000 new cases will be diagnosed each year. In people over the age of 65, it is expected that anywhere from 20 to 50 per 100,000 people will be affected by this disease. Current data shows that MDS is slightly more predominant in males (Cazzola & Malcovati, 2005; Chabner et al., 2008, First Consult, 2007, Steensma & Bennett, 2006). It is suggested that the true prevalence of MDS is higher than reported due to underdiagnosis and failure of cancer registries to capture all cases. Given its reported prevalence, MDS is as common as Chronic Lymphocytic Leukemia (CLL), which is the most highly diagnosed form of leukemia in Western countries (Cazzola & Malcovati, 2005; Chabner et al., 2008; Steensma & Bennett, 2006).

**Clinical Features**

The main symptoms associated with MDS are related to peripheral blood cytopenias. It is not uncommon, however, for patients to be asymptomatic with disease status discovered on a routine CBC (Bridges & Pearson, 2008; Cazzola & Malcovati, 2005; Chabner et al., 2008; De Angelo & Stone, 2005; First Consult, 2007; Kurtin, 2007; Nimer, 2008; Silverman, 2001).
Anemia occurs in 85 to 90% of individuals affected by MDS at some time during their diagnosis. It is generally normocytic or macrocytic but refractory to vitamin B12 and folate treatment. Symptoms associated with anemia include light-headedness, fatigue, shortness of breath, dyspnea, angina, dizziness, and palpitations (Cazzola & Malcovati, 2005; Chabner et al., 2008; Kurtin, 2007; Larson, 2008; Steensma & Bennett, 2006). Leukopenia is present in 40 to 50% of MDS patients at some point during their diagnosis. Neutropenia is generally the major type of leukopenia and is associated with infections that often manifest in the lungs, skin, and sinuses (Bridges & Pearson, 2008; Cazzoli & Malcovati, 2005; Chabner et al., 2008; Steensma & Bennett, 2006).

Thrombocytopenia is the least common cytopenia, but still occurs in 25 to 40% of patients with MDS. Symptoms related to thrombocytopenia include easy bruising, bleeding, petechiae, hematuria, epistaxis, and hematochezia (Bridges & Pearson, 2008; Cazzoli & Malcovati, 2005; Chabner et al., 2008; Steensma & Bennett, 2006). Other potential complications that may arise in MDS patients include hepatosplenomegaly, cutaneous vasculitis, peripheral neuropathies, polyarthritis, polymyositis, lupus-like symptoms, and Coomb’s positive hemolytic anemia (De Angelo & Stone, 2005; First Consult, 2007; Larson, 2008).

**Diagnosis and Classification**

The diagnostic evaluation of MDS has several components. A detailed history and physical, including current medications and the presence of comorbidities that may limit treatment options, are key components. A systematic baseline physical exam will be important to detect any underlying cardiopulmonary disease, skin abnormalities, such as...
petechiae or pallor, and skin infiltrates. Peripheral blood should be carefully examined. A CBC with differential, platelet count, and reticulocyte count will provide information about cytopenias, blast cells, cellular morphology, and character of bone marrow response to anemia (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008; Steensma & Bennett, 2006). Evaluation of serum iron, ferritin, TIBC, folate, and B12 will reveal other potential causes of anemia. Coombs test, LDH, haptoglobin, LDH, and reticulocyte count will provide information about possible underlying hemolysis. Serum erythropoietin helps to determine the role of growth factors in supportive treatment (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008; Steensma & Bennett, 2006).

Other labs that may be helpful in the diagnosis of MDS include thyroid, renal, and hepatic profiles. A thyroid profile should be checked as hypothyroidism may cause anemia and fatigue and may develop during therapy with immunomodulatory drugs. A renal and hepatic profile provide information about functional status and whether or not patients will be able to tolerate certain active therapies for MDS. Renal and hepatic toxicity are associated with several MDS treatments (Kurtin, 2007). In patients with specific risk factors, HIV testing may be necessary (NCCN, 2008; Steensma & Bennett, 2006). Bone marrow biopsy and aspiration provides is essential to confirm the diagnosis of MDS. Bone marrow aspirate should contain spicules (microscopic material in bone that forms a meshwork of spaces that are filled with bone marrow) and have adequate cellularity to examine at least 500 cells. Examination reveals information about cell morphology, cellular abnormalities, blast percentage, ringed sideroblasts, monocytes, and dysplasia. Bone marrow biopsy should be approximately 1 to 2 cm in size for adequate
assessment. It provides information about overall cellularity, immature precursors, and tissue structure. It also assists in the exclusion of other hematologic malignancies or bone marrow disorders (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008; Steensma & Bennett, 2006). The use of flow cytometry is more recent and may provide confirmation of immunophenotype, particularly in hypocellular specimens (Chabner et al., 2008; NCCN, 2008; Steensma & Bennett, 2006). Cytogenetics of the bone marrow aspirate should be performed to assess the presence of nonrandom chromosomal aberrations (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008).

Diagnostic criteria for MDS are complex and based on criteria that characterize the several different sub-types of the disease (see WHO criteria in Table 2). The National Comprehensive Cancer Network recommends the following minimum diagnostic criteria for MDS: 1.) Stable cytopenia that has been present for 6 months or greater; 2.) Other possible causes of the dysplasia and cytopenias have been ruled out; 3.) At least one of the following: dysplasia (> 10% in at least one of the three bone marrow lineages); blast cell count of 5 to 19%; and an MDS-type karyotype (e.g. del(5q), del(20q), +8, or –7/del(7q)) (NCCN, 2008; Steensma & Bennett, 2006).

There are several different forms of MDS and two current classifications systems: the French American British (FAB) classification system and the World Health Organization (WHO) classification system. The WHO system is more specific as it identifies disease subtypes. The International Prognostic Scoring System (IPSS) and the World Prognostic Scoring System (WPSS) provide risk stratification of the disease
Table 1: FAB Classification of MDS

<table>
<thead>
<tr>
<th>FAB Subtype</th>
<th>Peripheral Blood</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory Anemia (RA)</td>
<td>&lt; 1% blasts</td>
<td>&lt; 5% blasts</td>
</tr>
<tr>
<td></td>
<td>Cytopenia of the erythroid cell line</td>
<td>Normocellular or hypocellular marrow with dysplastic changes</td>
</tr>
<tr>
<td>Refractory Anemia with Ringed Sideroblasts (RARS)</td>
<td>&lt; 1% blasts</td>
<td>&lt; 5% blasts</td>
</tr>
<tr>
<td></td>
<td>One or more cytopenias</td>
<td>Dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ringed sideroblasts make up more than 15% of all nucleated cells</td>
</tr>
<tr>
<td>Refractory Anemia with Excess Blasts (RAEB)</td>
<td>&lt; 5% blasts</td>
<td>5-20% blasts</td>
</tr>
<tr>
<td></td>
<td>Cytopenia of two or more blood cell lineages</td>
<td>Dysplastic changes of all three blood cell lineages</td>
</tr>
<tr>
<td>Refractory Anemia with Excess Blasts in Transformation (RAEB-t)</td>
<td>≥5% blasts</td>
<td>21-30% blasts</td>
</tr>
<tr>
<td></td>
<td>One or more cytopenias</td>
<td>Possible Auer Rods in blast cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysplastic changes</td>
</tr>
<tr>
<td>Chronic Myelomonocytic Leukemia (CMML)</td>
<td>&lt; 5% blasts</td>
<td>5-20% blasts</td>
</tr>
<tr>
<td></td>
<td>Monocytosis (&gt; 1,000 monocytes/mcL blood)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>WHO Subtype</th>
<th>Peripheral Blood</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory Cytopenias with: Unilineage Dysplasia (RCUD) Refractory Anemia (RA) Refractory Neutropenia (RN) Refractory Thrombocytopenia (RT)</td>
<td>Unicytopenia or bicytopenia. No or rare blasts (&lt;1%)</td>
<td>Unilineage dysplasia; ≥ 10% of the cells of the affected lineage are dysplastic &lt; 5% blasts &lt;15% of the erythroid precursors are ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory Anemia with Ringed Sideroblasts (RARS)</td>
<td>Anemia; no blasts</td>
<td>Erythroid dysplasia only &lt; 5% blasts &gt; 15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory Cytopenia with Multilineage Dyplasia and Ringed Sideroblasts (RCMD-RS)</td>
<td>Bi-or pancytopenia No or rare blasts No Auer rods; Monocytes &lt; 1,000/ul</td>
<td>Multilineage dysplasia &lt; 5% blasts ≥ 15% ringed sideroblasts No Auer rods</td>
</tr>
<tr>
<td>Refractory Anemia with Excess Blasts – 1 (RAEB-1)</td>
<td>Cytopenias &lt; 5% blasts No Auer rods &lt; 1,000/ul monocytes</td>
<td>Uni- or multilineage dysplasia 5-9% blasts No Auer rods</td>
</tr>
<tr>
<td>Refractory Anemia with Excess Blasts-2 (RAEB-2)</td>
<td>Cytopenias 5-19% blasts ± Auer rods Monocytes &lt; 1,000/ul</td>
<td>Uni- or multilineage dysplasia 10-19% blasts ± Auer rods</td>
</tr>
<tr>
<td>Myelodysplastic Syndrome,</td>
<td>Cytopenias</td>
<td>Unequivocal dysplasia in</td>
</tr>
</tbody>
</table>
Along with the FAB and WHO classification systems, the International Prognostic Scoring System (IPSS) is used to assess patient prognosis. In this system, there are three categories in which a score can be assigned: percentage of bone marrow blasts, cytogenetics, and the number and degree of cytopenias. The scores are added to calculate one of four IPSS categories: Low, Int-1, Int-2, and High (Chabner et al., 2008; NCCN, 2008; NCI, 2008; Steensma & Bennett, 2006). “The median survival for patients with Low, Int-1, Int-2, and High-risk disease is 5.7, 3.5, 1.2, and 0.4 years respectively” (Chabner et al., 2008, p. 291). It must be noted that the IPSS system only applies to those patients with de novo MDS. The IPSS system is very useful in clinical decision-making and is the current standard for risk assessment in MDS. However, it does not include the more recently recognized prognostic information for MDS with transfusion dependency.
or multilineage dysplasia. This led to the WPSS, which acknowledges five different prognostic groups that range from very low risk to very high risk. The WPSS has a slight advantage because it includes prognostic information for subtypes of MDS with multilineage dysplasia and RBC transfusion dependence. Also, WPSS prognostic information is applicable throughout the course of the disease, while IPSS information is only applicable at the time of diagnosis (Jadersten & Hellstrom-Lindberg, 2008; Kurtin, 2008).

Management

Management of MDS varies considerably and is dependent on the characteristics of the individual patient, including, including IPSS score, hematologic presentation, age, comorbidities, performance status, and lifestyle (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008; Steensma & Bennett, 2006). The major objectives of MDS treatment include quality of life improvement, limited treatment toxicity, decreased frequency and number of transfusions, decreased infections, and increased survival (Chabner et al., 2008; Kurtin, 2007).

Supportive care provides a foundation in MDS management. Quality of life evaluation, observation, growth factors for cytopenias, antibiotics for infection, iron-chelation therapies for iron overload, and transfusions represent the current standards of care in supportive therapy (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008; Steensma & Bennett, 2006). MDS related cytopenias result from dysfunctional and unproductive proliferation of bone marrow cells. Cytopenic effects of active MDS therapy often compound this direct disease effect. There are specific therapeutic options to counteract
the detrimental effects of cytopenias and stimulate the bone marrow to proliferate in an effective manner. In cases of anemia, which is present in 90% of individuals with MDS, treatment is initiated with the use of erythroid growth factors such as epoetin alfa (Procrit) and darbepoetin alfa (Aranesp). For those patients with endogenous erythropoietin (EPO) levels greater than 500 mU/ml, response to exogenous forms of EPO is usually insignificant and patients require intermittent support with packed red blood cell (PRBC) transfusions (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008).

Neutropenia is common in MDS. This occurs when the absolute neutrophil count (ANC) is less than 1500 cells/mm³. A decreased neutrophil count places patients at higher risk of infection, especially in older adults. Similar to the treatment of anemia, there are growth factors available to stimulate the effective production of neutrophils (filgrastim, (Neupogen); sargramostin, (Leukine); pegfilgrastim, (Neulasta)). Although available, these growth factors have shown little utility when used in prophylactic manner, so they are often reserved for use in the setting of an active infection or treatment-induced neutropenia. Due to the potential for resistance and drug interactions, antibiotics are not recommended for infection prophylaxis (Chabner et al., 2008; Kurtin, 2007; Steensma & Bennett, 2006).

Thrombocytopenia is generally treated with platelet transfusions when platelet count is less than 10,000 cells/μl. Careful attention must be paid to signs of bleeding, such as petechiae and excessive bruising, which may indicate that transfusions are necessary at higher platelet levels (20,000 to 30,000 cells/μl) (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008). Chronic platelet transfusions may result in patients forming
resistance to the transfusion. In these cases, alternative therapy such as aminocaproic acid or other antifibrinolytic medications represent possible options (Chabner et al., 2008; Kurtin, 2007). Treatment with fibrinolysis agents, such as aminocaproic acid, tranexamic acid, and danazol can improve bleeding symptoms, especially bleeding from mucous membranes. A new thrombopoiesis agent, Romiplostim, was just approved by the Food and Drug Administration for the treatment of immune-mediated thrombocytopenic purpura (ITP) and is currently being investigated for efficacy in MDS (Jadersten & Hellstrom-Lindberg, 2008).

As discussed earlier, many MDS patients receive frequent PRBC transfusions due to anemia. Chronic transfusions are associated with iron overload with high levels of iron in the liver, heart, and adrenal glands. Patients are often asymptomatic until worrisome organ damage has already occurred (Chabner et al., 2008; Kurtin, 2007). Signs and symptoms of iron overload include increased liver enzymes, symptoms of congestive heart failure, onset of diabetes, and vague abdominal distension. In an MDS patient who receives chronic transfusions, these symptoms warrant consideration of an MRI of the liver or an echocardiogram. All MDS patients should have a baseline and periodic ferritin levels checked, as a ferritin level greater than 1000 mg/ml is clinically significant for iron overload (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008). Iron chelation agents can effectively bind tissue and serum iron and subsequently promote excretion in the body’s urine and bile to reduce systemic iron overload. Two such drugs that are FDA approved are desferoxamine (Desferal), which is given via intravenous infusion, and deferasirox (Exjade), which is taken orally in a dissolved solution.
Treatment should be introduced when blood ferritin levels exceed 1000 μg/L (Kurtin, 2007; NCCN, 2008).

Decisions regarding active therapy in MDS are dependent on patient age, IPSS score, performance status, the presence of an additional hematological disorder, patient wishes, quality of life, and the availability of an HLA-matched stem cell donor. There are both low-intensity and high-intensity therapies available, with the only current cure being allogenic bone marrow transplant (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008; Steensma & Bennett, 2006).

Low-intensity therapy includes hypo-methylating agents and biologic response modifiers/immunosuppressive therapy. The hypo-methylating agents include 5-azacytidine (Vidaza) and decitabine (Dacogen). Thus far, clinical trials have shown that these drugs have similar efficacy in treating MDS patients with progressive and higher risk disease. These two drugs have very similar side effect profiles, including myelosuppression, diarrhea, nausea, pyrexia, fatigue, and constipation (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008). Vidaza and Dacogen are both recommended for use in IPSS Low-Intermediate 1 and Intermediate 2-High categories (Kurtin, 2007; NCCN, 2008). Biologic response modifiers, another form of low-intensity MDS therapy, are drugs such as anti-thymocyte globulin (ATG), cyclosporin, thalidomide, and lenalidomide. ATG therapy has shown specific efficacy in treating patients with the histocompatibility type HLA-DR15 (Chabner et al., 2008; Kurtin, 2007; NCCN, 2008). Lenalidomide has shown efficacy in those patients with a del(5q) chromosomal abnormalities and has recently been approved by the FDA for this purpose (Chabner et
al., 2008; NCCN, 2008). Side effects associated with lenalidomide include myelosuppression, diarrhea, pruitis, rash, urticarial dermatitis, and fatigue (Kurtin, 2007).

High-intensity therapy in MDS consists of intensive chemotherapy or hematopoietic stem cell transplantation (HSCT). Both of these options have the potential to alter the natural disease course, but they are associated with a much greater risk of treatment related morbidity and mortality (Chabner et al., 2008; NCCN, 2008; Steensma & Bennett, 2006). Given the advanced age, and common co-morbidities of many MDS patients, high-intensity therapy is not a feasible option (Kurtin, 2007; Steensma & Bennett, 2006). It is recommended that most high-intensity treatment regimens take place in a clinical trial setting (NCCN, 2008).

Table 3: Treatment Guidelines for MDS

<table>
<thead>
<tr>
<th>Therapeutic Goals</th>
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<tbody>
<tr>
<td>Individualize therapy to each patient</td>
</tr>
<tr>
<td>Keep toxicity at a minimum</td>
</tr>
<tr>
<td>Increase quality of life</td>
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<tr>
<td>Recover blood counts (fewer transfusions, fewer infections)</td>
</tr>
<tr>
<td>Lengthen survival</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Basis For Treatment</th>
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</thead>
<tbody>
<tr>
<td>IPSS score and disease classification</td>
</tr>
<tr>
<td>Comorbidities</td>
</tr>
<tr>
<td>Performance status</td>
</tr>
<tr>
<td>Treatment side effects/toxicities</td>
</tr>
<tr>
<td>Frequency of clinic or hospital visits</td>
</tr>
<tr>
<td>Financial status</td>
</tr>
<tr>
<td>Psychosocial support</td>
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<tr>
<td>Quality of life</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Treatment Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>If patient is stable and asymptomatic with an IPSS score in the Low-Intermediate 1 range, a period of observation is recommended.</td>
</tr>
<tr>
<td>Age &lt; 60 years with good performance status and IPSS score in the Low-Intermediate 1 range, evaluation for stem cell transplant is recommended.</td>
</tr>
<tr>
<td>If patient is HLA-DR15 positive, treatment with ATG should be considered.</td>
</tr>
</tbody>
</table>

Low-Intermediate 1
- Del (5q) – Lenalidomide for initial therapy
- Serum EPO level ≤ 500 mU/mL – Initial therapy with erythropoietin or darbepoietin
- Clinical trials
- Azacitadine
- Decitabine
- Thalidomide
- Chemotherapy
- Cyclosporine-A

### Intermediate 2-High
- Clinical trials
- Growth Factors
- Azacitadine
- Decitabine
- Arsenic trioxide
- Chemotherapy (younger patients)

### Any IPSS with Complex Comorbidities and/or Poor Performance Status
- Supportive Care
  - Growth Factors
  - Transfusion support
  - Chelation therapy
  - Antibiotics
- Psychosocial Support

- Supportive care and continuous evaluation of quality of life is recommended in all risk groups.
- Clinical trials are recommended to encourage further enhancement of treatment options.


### Psychosocial Factors

“MDS is a puzzling, life-threatening group of diseases of the bone marrow for which there are no easy cures or quick remedies” (MDS Foundation, 2008, p. 24). The majority of patients diagnosed with MDS have never heard of the disease before. MDS and its management exert a profound physical and emotional burden on patients and their families. The frequent bloodwork, RBC and platelet transfusions, clinic visits, and high levels of fatigue all contribute to decreased quality of life in MDS patients (Heptinstall,
Patients are encouraged to utilize support systems to help with both the physical and emotional aspects of their disease. Along with family members, patients are challenged to learn new coping mechanisms to deal with the impact this disease has on relationships, spirituality, and life in general (ACS, 2008; Heptinstall, 2008). According to the MDS Foundation’s US and European Patient Forums, some of the negative impacts that MDS imparts on quality of life include decreased physical and mental functioning; fatigue; lethargy; depression; loss of independence; difficulty sustaining relationships; diminished role in family; anxiety; anger; helplessness; concern about the future; fear of prognosis; vast amount of time spent in clinical setting; and changing employment status (Heptinstall, 2008). Given the immense effects that MDS can have on patients’ lives, it is important for clinicians to continually assess quality of life in all MDS patients in order to get a complete clinical picture and determine the impact of therapy (Demakos, 2008; Heptinstall, 2008).

**Summary**

MDS is a complex disease process with several key concepts important to complete understanding. Knowles’ Theory of Adult Learning will help to guide the creation of an MDS educational module for primary care clinicians. Principles of andragogy will shape the module into one that is relevant, interesting, and applicable to daily practice. It is a disease that is characterized by ineffective hematopoiesis and blood cytopenias that may progress to AML. Approximately 55,000 to 100,000 Americans have MDS at any point in time (Chabner et al., 2008). It typically manifests in adults over the age of 60, but may occur in younger individuals. Several treatment options have become available over
the past five years, none of which are curative. Currently the only possible cure is allogenic bone marrow transplant (Kurtin, 2007).
CHAPTER 3

Introduction

This project is an educational module for all primary care providers who may encounter MDS patients in their practice. All of the content in this chapter is based on current literature and the latest guidelines published regarding MDS. Educational material has been organized into nine sections, each consisting of learning objectives, educational content, and learner review questions to evaluate module comprehension. Primary care providers can use each section of this module to guide their care of MDS patients. The last section of the educational portion summarizes information from each previous section of the module to create a list of clinical pearls for primary care providers in the management of MDS patients. Lastly, the implementation of the project will be discussed in detail.

Use of Adult Learning Theory Concepts

In fulfilling “the need to know” and learner motivation, the module will be introduced with information for PCPs on how completion of this activity will benefit their practice. The educational module is a self-paced learning activity. Participants will complete it independently in their own time frame, consistent with Knowles’s principle of “self-concept.” Participants’ health care knowledge and expertise will not be discounted. Each of the nine sections of this module is geared towards individuals with a high level of education and strong clinical background. This module presents information applicable to daily practice and recommendations on the implementation of this knowledge. Participants will be encouraged to be involved in the evaluation of the
educational module. They will have the opportunity to provide feedback immediately after module completion to offer suggestions for improvement.

Project in Detail

Introduction

MDS is a potentially deadly disease, as one-third of all patients who have it will progress to Acute Myelogenous Leukemia (AML) (Kurtin, 2007). PCPs play a key role in the recognition and referral of MDS patients. With the aging population, the likelihood that primary care providers will be managing the comorbid conditions of patients with MDS is steadily increasing. This educational module will prepare participants for their potential involvement in the diagnostics and management of MDS patients. The content presented is that which is relevant to a primary care setting.

Section I: Basic Pathophysiology

Learning Objectives

1. Define MDS.

2. Identify the potential factors that constitute MDS pathogenesis.

3. Identify possible causes of MDS.

Content

MDS is a heterogeneous group of hematopoietic stem cell disorders characterized by ineffective hematopoiesis and resulting in varying degrees of anemia, neutropenia, and thrombocytopenia (Hellstrom-Lindberg & Malcovati, 2007). These disorders arise in the bone marrow due to a defect in the myeloid stem cell line and decrease the bone marrow’s ability to produce functioning mature blood cells. Advanced disease is
associated with the potential to transform into AML (Kurtin, 2008). Disease pathogenesis is not completely understood, but is thought to be a combination of many factors, including cytogenetic abnormalities, epigenetic DNA changes, medullary angiogenesis, stromal dysregulation, and an imbalance of cellular apoptosis and proliferation (Kurtin, 2007; Kurtin, 2008).

MDS may arise de novo or secondary to previous treatment with chemotherapy or radiotherapy. It usually strikes patients greater than 60 years of age, but it is possible in younger patients. There are several different sub-types of the disease based on the morphologic characteristics of the cells (NCI, 2008).

**Learner Review Questions**

1. How is MDS defined as a disease?
2. What are the proposed factors of MDS pathogenesis?
3. What are the major causes of the pathogenesis of MDS?

**Section II: Signs and Symptoms of MDS**

**Learning Objectives**

1. Identify the major signs and symptoms associated with MDS.
2. List the signs of MDS that indicate the need for evaluation beyond the primary care level.

**Content**

The initial signs and symptoms of MDS are often very subtle and nonspecific (Silverman, 2001). Those symptoms that often provoke patients to see their primary care providers include fever, fatigue, infection, bruising, bleeding, exercise intolerance,
palpitations, dizziness, and headaches (Kurtin, 2007; Silverman, 2001; Steensma & Bennett, 2006). However, it is not uncommon for the patient to be initially asymptomatic with the disease process discovered with routine lab work (Cazzola & Malcovati, 2005). Major signs include anemia, neutropenia, and/or thrombocytopenia on peripheral blood examination. Hepatosplenomegaly is a possible sign, but is rare (First Consult, 2007). Approximately 90% of patients with MDS will present with anemia either initially or at some point during the disease process. Anemia is generally normocytic or macrocytic (Kurtin, 2007). Peripheral blood cytopenias, monocytosis of unknown origin, erythrocyte macrocytosis, or cellular dysplasia and abnormalities on peripheral blood smear are all signs that reveal the necessity for further evaluation (Steensma & Bennett, 2006).

**Learner Review Questions**

1. What are the major signs and symptoms MDS?
2. What combination of signs indicate the need for further patient evaluation?

*Section III: Diagnostic Evaluation at the Primary Care Level*

**Learning Objectives**

1. Identify the diagnostics of MDS that can be performed at the primary care level.
2. Describe why it is important for primary care providers to perform these tests.

**Content**

MDS can arise with no apparent cause or it can result from previous chemotherapy, radiotherapy, or other environmental exposures (Steensma & Bennett, 2006). For this reason, it is important to obtain a detailed and accurate health history from the patient.
The health history also helps to eliminate other etiologies of the patient’s signs and symptoms (Kurtin, 2006).

There are several diagnostic tests that can be performed by the primary care provider, mainly in the form of peripheral blood work.

- CBC, differential, platelet count, reticulocyte count: Provide information on cytopenias, presence of peripheral blasts, cell abnormalities, and response of bone marrow to anemia (Kurtin, 2007).
- Serum iron, ferritin, TIBC (total iron binding capacity), folic acid, B12 level: Evaluate all possible causes of anemia (Kurtin, 2007).
- LDH (lactate dehydrogenase), haptoglobin, reticulocyte count, Coombs test: Examine the possibility of underlying hemolysis (Kurtin, 2007).
- Thyroid profile: Evaluate for hypothyroidism. Hypothyroidism can cause anemia, fatigue, and exercise intolerance (Kurtin, 2007).
- Serum testosterone: Fatigue is a major symptom of hypogonadism (Kurtin, 2007).
- Renal and hepatic profile: Evaluate for renal and hepatic insufficiencies. Renal failure can be a potential cause of anemia (Kurtin, 2007). Chronic liver disease may be a co-morbid condition with MDS (First Consult, 2007).
- Serum Erythropoietin level: This can help to determine the type of anemia and evaluate the performance of erythropoiesis-stimulating hormones (Kurtin, 2008).

Performing these tests is important for the primary care provider to rule out any potential differential diagnoses and get a clearer picture of the disease process that is occurring.
Learner Review Questions

1. What are the MDS diagnostics that can be performed at the primary care level, and how is each performed?
2. Why should primary care providers perform these tests?

Section IV: Referral

Learning Objectives

1. Identify the point at which a Hematology/Oncology referral is necessary.
2. Name the test that the oncologist would perform to confirm diagnosis.

Content

If the above test results point to a possible MDS diagnosis, it is important for the primary care provider to refer to hematology/oncology. Signs on a peripheral blood sample, such as unexplained monocytosis, unexplained cytopenias, macrocytic erythrocytes, atypical cellular composition, and cellular dysplasia warrant further evaluation by a hematologist/oncologist. Any one of these signs alone is not specific for MDS, but the combination of these attributes is very indicative of the disease (Steensma & Bennett, 2006). Any unexplained abnormalities on a peripheral CBC should prompt referral to hematology/oncology. Once a patient is referred, the next important step is for the oncologist to perform a bone marrow aspirate and biopsy to further evaluate the bone marrow and any cellular abnormalities (Steensma & Bennett, 2006).

Learner Review Questions

1. When is it necessary to refer to hematology/oncology?
2. What is the likely first step that the oncologist will take to make a diagnosis of MDS?

Section V: Treatment and Side Effects

Learning Objectives

1. Discuss the major factors that go into choosing a treatment modality for MDS patients.

2. Review the treatment options available for MDS patients.

3. Identify the side effects and drug interactions associated with each treatment.

Content

Choosing a treatment modality for patients with MDS is challenging and depends on many factors, including patient performance status, disease subtype, risk category, physiological age, comorbid conditions, and way of life (Kurtin, 2007). “The primary goals of therapy are to improve quality of life, minimize treatment toxicity, decrease transfusions, decrease infections, and prolong survival” (Kurtin, 2007, p. 43). An oncologist will prescribe all treatments, but it is important for the primary care provider to know the treatments and their side effects because they will manage patients’ comorbid conditions in the primary care setting. Below is a list of several treatment options along with potential toxicities and side effect profile.

- Period of observation: This is appropriate for low to intermediate risk patients whose blood counts may remain stable over several months. Observation with blood work every 2-4 months will help to determine a patient’s “clinical stability” (Kurtin, 2007,
p. 44). Once patients in this category develop further cytopenias or dependence on transfusions active treatment will be considered (Kurtin, 2007).

- **Red blood cell transfusions:** About 90% of MDS patients require regular transfusions at some point in the course of the disease. Packed red blood cell (PRBC) transfusions provide temporary increases in hemoglobin and may help with fatigue and other symptoms of anemia (Kurtin, 2007). Some potential complications of chronic transfusions include volume overload, iron overload, increased infections, and the development of antibodies to donor blood (Kurtin, 2007).

- **Recombinant erythropoietic growth factors:** In MDS patients with low levels of endogenous erythropoietin, recombinant erythropoietic growth factors may be used to decrease transfusion dependence (Kurtin, 2007). These drugs are given as a subcutaneous injection or an intravenous injection no more than once per week. Potential adverse effects include thromboembolic events (rare), peripheral edema, rash, headache, dizziness, and fever (Wilkes & Barton-Burke, 2006). With any anemia treatment, hemoglobin levels should surpass 12 g/dL, as this is associated with heart failure, thromboembolism, and potential death in patients with chronic renal disease (Kurtin, 2007).

- **Platelet transfusions:** Many MDS patients become thrombocytopenic at some point during the course of the disease. Platelet counts below 10,000 per microliter of blood indicate the need for transfusion. Patients with complicating comorbid conditions may require transfusions at higher platelet levels (Kurtin, 2007). Potential adverse
effects associated with platelet transfusions include bacterial infection, pruitis, rash, fever, chills, and becoming refractory to transfusions (Heddle et al., 2008).

- **Aminocaproic Acid**: If a thrombocytopenic MDS patient becomes refractory to platelet transfusions, aminocaproic acid can be used to decrease bleeding tendencies (Kurtin, 2007). Aminocaproic acid is given via IV infusion and is usually well tolerated. Some potential side effects include edema, headache, malaise, anaphylaxis, bradycardia, hypotension, thrombosis, agranulocytosis, leukopenia, myalgia, nausea, vomiting, diarrhea, dizziness, pruitis, rash, and tinnitus (Rx List, 2009).

- **Antibiotics**: MDS patients are at increased risk for developing infections. Antibiotics are not recommended for use prophylactically, but are recommended for active infections (Kurtin, 2007).

- **G-CSF and GM-CSF**: MDS patients may become neutropenic during the course of their disease either from the disease itself or from certain active therapies. G-CSF and GM-CSF are growth factors that stimulate the bone marrow to produce more white blood cells (NCCN, 2008). Both of these drugs are given as a subcutaneous injection. Possible side effects include bone pain, headache, myalgia, abdominal pain, and arthalgia (Wilkes & Barton-Burke, 2006).

- **Deferoxamine and deferasirox**: MDS patients who are RBC transfusion dependent are at risk for iron accumulation in the heart, liver, and adrenal glands. This can lead to cardiac failure, infection, hemorrhage, and hepatic cirrhosis. Deferoxamine and deferasirox are both approved as iron chelation therapies. Deferoxamine is given either subcutaneously or as an IV infusion, while deferasirox is given orally. They
both act to remove excess iron in the circulation and tissues. Potential toxicities include mild neutropenia, vision and hearing abnormalities, elevation of hepatic enzymes, and elevated creatinine levels (Kurtin, 2007).

- **5-Azacitadine (Vidaza):** Vidaza is an antineoplastic therapy that is used to actively treat MDS. It is given as a subcutaneous injection or as an IV infusion. It is approved in the United States for treatment of all subtypes of MDS. Potential toxicities include nausea, vomiting, anemia, thrombocytopenia, pyrexia, leukopenia, diarrhea, fatigue, injection-site erythema, neutropenia, and ecchymosis (Siddiqui & Scott, 2005). There are no specific drug interactions known for Vidaza (Wilkes & Barton-Burke, 2006).

- **Decitabine (Dacogen):** Dacogen is an active MDS therapy that acts to induce apoptosis of neoplastic cells. It is administered via IV infusion. The most common adverse effect is myelosuppression. Other potential adverse effects include fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia (McKeage & Croom, 2006). The only drug interactions are other specific chemotherapeutic and biotherapeutic agents (Wilkes & Barton-Burke, 2006).

- **Lenalidomide (Revlimid):** Revlimid is an active MDS treatment indicated for patients with low-risk MDS. It has anti-angiogenesis properties and induces growth arrest and apoptosis of abnormal cells (Shah & Tran, 2007). It is available in an oral form. Potential side effects include myelosuppression, rash, fatigue, lightheadedness, leg cramps, and diarrhea. When given with other myelosuppressive agents, there may be increased myelosuppression (Wilkes & Barton-Burke, 2006).
• Thalidomide: Thalidomide is an active MDS treatment with antiangiogenesis and immunomodulatory actions. It is given orally (Wilkes & Barton-Burke, 2006). Potential adverse effects include myelosuppression, peripheral neuropathy, sedation, rash, pruitis, constipation, fluid overload, bone pain, and thrombosis (Kurtin, 2007; Wilkes & Barton-Burke, 2006). Drug interactions include barbiturates, alcohol, chlorpromazine, and reserpine with the major effect being increased sedation (Wilkes & Barton-Burke, 2006).

• Anti-thymocyte globulin (ATG): ATG is an active treatment in certain subtypes of MDS. It is an anti-immune therapy that is administered by IV infusion (NCCN, 2008). It is often given in combination with Cyclosporin. Possible side effects include hypersensitivity reactions, myelosuppression, sepsis, urinary tract infections, cytomegalovirus (CMV) infections, fever chills, bacterial infections, viral infections, fungal infections, nausea, diarrhea, dyspnea, headache, peripheral edema, and fatigue. ATG has an added immunosuppressive effect when combined with other immunosuppressant agents (Steensma & Bennett, 2006).

• Cyclosporine: Cyclosporine is used in combination with ATG as an immunosuppressive regimen in MDS (NCCN, 2008). It may be administered orally or as an IV infusion. Potential adverse effects include nausea, vomiting, gastritis, mouth sores, pancreatitis, myelosuppression, anaphylaxis, edema, chest pain, fever, seizures, anxiety, depression, fatigue, ataxia, renal dysfunction, pruritius, hepatotoxicity, tinnitus, muscle pain, blurred vision, infection, and joint pain (Spratto & Woods, 2006). Cyclosporine has several drug interactions, which include
allopurinol, aminoglycosides, amiodarone, amphotericin B, androgens, azathioprine, bupropion, calcium channel blockers, carbamazepine, carvedilol, chloramphenicol, cimetidine, clarithromycin, clindamycin, colchicines, corticosteroids, cyclophosphamide, diclofenac, digoxin, diltiazem, Echinacea, erythromycin, etoposide, fluconazole, fluoroquinolones, HIV protease inhibitors, imipenem-cilastin, isoniazid, itraconazole, ketoconazole, lovastatin, melphalan, methotrexate, methylphenidate, methylprednisolone, metclopramide, naproxen, nifedipine, octeotride, oral contraceptives, Phenobarbital, phenytoin, ranitidine, rifampin, simvastatin, St. John’s Wort, sulfamethoxazole-trimethoprim, sulindac, tacrolimus, vancomycin, and verapamil (Spratto & Woods, 2006).

- Arsenic Trioxide (Trisenox): Trisenox is an antineoplastic agent that is thought to act on dysfunctional cells by inducing apoptosis or programmed cell death. It is administered as an IV infusion. Potential side effects include myelosuppression, nausea, vomiting, diarrhea, alterations in cardiac function, fever, DIC, bleeding, headache, chest pain, fatigue, bone pain, arthralgias, myalgias, hypokalemia, hypomagnesemia, hyperglycemia, edema, parasthesias, dizziness, tremor, insomnia, hypoxia, pleural effusion, cough, dyspnea, and skin irritation. Trisenox can prolong the QT interval, so it should not be given with any other drugs that cause QT prolongation (certain antiarrhythmics). It may also cause severe electrolyte imbalances, so other drugs that have this action should be avoided (e.g. diuretics, amphotericin B) (Wilkes & Barton-Burke, 2006).
- Allogenic Bone Marrow Transplant: Allogenic bone marrow transplant is currently the only cure for MDS, but the age and performance status of most patients prevents them from this option (Kurtin, 2007). In an allogenic stem cell transplant, the patient’s bone marrow is obliterated by intensive chemotherapy and total body radiation. Functional cells from a donor whose stem cell type is nearly identical to the patient’s replace the dysfunctional bone marrow cells. This treatment has serious side effects and is usually attempted only in patients who are younger and have good performance status (American Cancer Society, 2008). Side effects can be immediate or can arise after a period of years after the transplant. Early side effects are consistent with those of chemotherapy and radiation therapy. Other complications that may take place long after the transplant include graft vs. host disease, shortness of breath, damage to reproductive organs, thyroid damage, and cataracts. Graft vs. host disease can manifest as problems with the integumentary system, the liver, the gastrointestinal tract, the mouth, and several other organs (American Cancer Society, 2008).

Learner Review Questions

1. How are treatment modalities individualized to each patient?
2. What are the different types of treatment available for MDS patients?
3. What are some of the major side effects of available treatments?
4. What are some drug interactions important to a primary care setting?
Section VI: Complications Relevant to Primary Care

Learning Objectives

1. List the major complications that may arise in MDS patients.
2. Identify the causes, signs, and symptoms of major complications.
3. Discuss PCP’s involvement in the care of MDS complications.

Content

Infections

Infections in MDS patients can arise due to neutropenia secondary to the disease process or neutropenia secondary to a myelosuppressive MDS treatment (Mayo Clinic, 2007). At this time, infections are the leading cause of death in MDS patients (Steensma & Bennett, 2006). Regardless of the cause of infection, it is imperative that primary care providers realize the prevalence and implications of infection in the MDS patient.

The literature does not provide a list of infections that are specific to MDS; however, infections that often affect the elderly population can be expected to be prevalent in MDS patients (Kurtin, 2007). Some examples of infection that frequently affect the older adult include pneumonia, urinary tract infections, influenza, herpes zoster, methicillin-resistant staphylococcus aureus, and vancomycin-resistant enterococcus (Mouton et al., 2001). Providers should be prepared to evaluate for a wide range of infectious processes in MDS patients.

As a general guideline, MDS patients are not treated with antibiotics on a prophylactic basis, but any active infection warrants treatment with the appropriate antibiotic or antifungal (Kurtin, 2007). Although the oncologist may be the primary
manager of infection in MDS patients, it is important for primary care providers to be
aware of increased infection in MDS patients and assess for signs and symptoms of
infection at each patient visit. If the primary care provider suspects a new infection,
phone consultation with the patient’s oncologist would be appropriate to decide course of
action.

Iron Overload

Many MDS patients may be develop PRBC transfusion dependence during the
course of their disease (Kurtin, 2007; Kurtin, 2008; NCCN, 2008; NCI, 2008; Nimer,
2008; Steensma & Bennett, 2006). One major adverse effect of frequent transfusions is
iron overload, also known as hemosiderosis. Oncologists generally begin iron chelation
therapy at a serum ferritin > 1000 (Kurtin, 2008).

Iron overload adversely affects many different organs and physiologic processes in
the body. A surplus of iron most often accrues in the heart, liver, and adrenal glands.
Signs and symptoms are frequently indistinct and may not manifest until the patient has
severe organ damage (Kurtin, 2008). Some signs and symptoms to look for include
elevated liver enzymes, congestive heart failure (CHF) symptoms, development of
diabetes, or development of abdominal bloating and/or pain. If the patient presents with
any of these issues, it is reasonable to order imaging studies, such as MRI of the liver or
echocardiogram (Kurtin, 2008).

It is important for the primary care provider to recognize the signs and symptoms
of iron overload. If an MDS patient presents with any of these manifestations, it would
be important to consult the oncologist and potentially order the appropriate imaging tests.
**Bleeding**

A significant percentage of MDS patients deal with thrombocytopenia and its effects during the course of their disease (Steensma & Bennett, 2006). Severe thrombocytopenia and chronic bleeding has proven to be a significant problem in the MDS population and is correlated to decreased survival time and worsened quality of life. Platelet transfusions are currently the main treatment modality to relieve bleeding tendencies secondary to thrombocytopenia, but the effect is transient and will not prevent symptoms over the long run (Hellstrom-Lindberg & Malcovati, 2007).

Oncologists monitor platelet count and bleeding tendencies regularly, but it is important for primary care providers to monitor for bleeding tendencies as well. Providers must be aware of any medication they prescribe that may have anti-platelet or bleeding effects (Kurtin, 2007), such as aspirin products, anticoagulants, and NSAIDS (Spratto & Woods, 2006). It is very appropriate for primary care providers to reinforce to their MDS patients education on bleeding precautions, emergent management of bleeding, and the signs and symptoms of bleeding (Kurtin, 2007). Patients should be instructed to report the onset of signs and symptoms of bleeding, such as frank blood, frequent bruising, and petechiae, to their oncologist or primary care provider.

**Fatigue**

Fatigue is a major complication in MDS patients. It can arise from the disease itself, from anemia, or from MDS treatment. Fatigue is a side effect of most of the active therapies available for MDS (Mayo Clinic, 2008). Many patients find they have diminished physical capabilities, spend more time in bed, and cannot tolerate their usual
daily activities. Fatigue is one of the most significant contributors to decreased quality of life in MDS patients (Heptinstall, 2008).

PCPs should assess MDS patients for fatigue at regular intervals. The cause of the fatigue should be determined. PCPs should recognize that causes of fatigue are often multifactorial in MDS patients. Patients should be encouraged to participate in desired activities as tolerated and allow adequate periods for rest. The clinician’s sympathetic listening is often therapeutic in this patient population (McPhee & Papadakis, 2008).

**Learner Review Questions**

1. What are some common complications of MDS and its treatment that PCPs should be aware of?
2. In regards to complications, what signs and symptoms should PCPs watch for?
3. What is the role of the PCP in management of MDS complications?

**Section VII: Comorbidities**

**Learning Objectives**

1. Identify the effect that aging has on number of patient comorbidities.
2. List the specific comorbidities that complicate MDS diagnosis.
3. Identify how PCPs can encourage therapeutic management of both MDS and its comorbidities.

**Content**

MDS occurs primarily in an elderly population, many of whom are affected with various non-hematological comorbidities (Porta et al., 2006). Older MDS patients tend to
have a worse prognosis and performance status than their counterparts due to age-related health problems and multiple comorbidities (Deschler et al., 2006).

Some specific comorbidities that tend to have a major effect on MDS treatment and survival include cardiac disease, liver disease, pulmonary disease, kidney disease, and arthritis. Extra-hematological comorbidities have the potential to significantly worsen the disease course in MDS patients (Porta et al., 2006). It is important for PCPs to be aware of patients’ comorbidity profile and continually monitor for worsening of comorbidity disease states and symptoms. If certain disease symptoms worsen, providers should collaborate with the oncologist to create a more therapeutic management strategy.

Table 4: Common Comorbidities in MDS Patients

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Effect</th>
<th>Intervention by PCP</th>
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| Cardiac Disease   | • Many MDS patients get frequent blood transfusions, which can lead to volume overload, especially in CHF patients.  
• Some of the active treatments for MDS are potentially cardiotoxic; more dangerous in an already diseased heart.  
• Frequent PRBC transfusions can lead to iron build-up in the heart, which can worsen cardiac disease (especially CHF).  
• Certain cardiology medications, such as warfarin and ASA can worsen bleeding profile in thrombocytopenic patients. | • Cardiac status should be closely monitored. Worsening disease states must be discussed with the oncologist so a therapeutic management plan can be worked out. |
### Liver Disease
- Many of the medications for MDS are potentially hepatotoxic, so impaired liver function limits treatment options.
- Iron overload from frequent transfusions often manifests in the liver, which would worsen already impaired liver function.

### Pulmonary Disease
- Patients with known pulmonary disease may have increased shortness of breath/dyspnea due to anemia and may develop lung infections more easily due to neutropenia.

### Kidney Disease
- Preexisting kidney disease may worsen the anemia profile in MDS patients.
- Decreased kidney function may also contribute to volume overload with frequent transfusions.
- Kidney disease can limit MDS treatment options, as many active MDS treatments may impair renal function.

### Diabetes
- Diabetes often causes renal impairment, which limits MDS treatment options.
- Iron overload from frequent PRBC transfusions can also manifest in the adrenal

| MDS patients. | Both PCPs and oncologists should monitor liver function. If patient becomes symptomatic with possible liver etiology, an MRI of the liver is indicated. |
| Pulmonary Disease | PCPs should monitor patients for worsening pulmonary symptoms and manage based on symptoms. If upper respiratory infection is present, this should be treated with appropriate antibiotics. |
| Kidney Disease | PCPs and oncologists should monitor renal function regularly to assess for decrease. If worsening renal impairment, PCPs and oncologists must collaborate to create therapeutic management plan. |
| Diabetes | Known diabetics must be monitored closely. Patients who receive frequent transfusions should be monitored for new onset diabetes. |
glands, which can lead to a new diagnosis of diabetes or worsen preexisting diabetes.

| Arthritis                       | • Arthritis is a common problem in the elderly, which is the main population affected by MDS.  
|                                | • Fatigue and physical debility from arthritis may be worsened with added fatigue and decreased physical function from MDS.  
|                                | • NSAIDS and aspirin products, which are important drugs with arthritis, are strongly cautioned against in MDS due to increased bleeding risk.  
|                                | • PCPs should encourage the use of acetaminophen products for arthritic pain.  
|                                | • Other therapeutic options such as heat, ice, topical arthritic creams, and physical therapy, should be explored.  

(Kurtin, 2007; First Consult, 2007; Kurtin, 2008; Porta et al., 2006; Steensma & Bennett, 2006)

Learner Review Questions

1. What is the relationship between aging, comorbidities, and performance status?
2. What comorbidities have a significant effect on MDS and/or its treatment?
3. What step can PCPs take to encourage therapeutic management of comorbidities in MDS patients?

Section VIII: Quality of Life

Learning Objectives

1. Give one definition of quality of life.
2. Explain how MDS can affect quality of life.
3. Discuss approaches PCPs can take to improve quality of life in MDS patients.

*Content*

Quality of life can be “defined as an individual’s estimation of personal well-being including physical, mental, social, and spiritual aspects” (Deschler et al., 2006, p. 1518). MDS and its management take a heavy physical toll on patients. The repeated need for blood work, blood transfusions, and physician visits, along with the incapacitating fatigue experienced by many patients, often leads to a decreased quality of life (Heptinstall, 2008).

The MDS Foundation performed a patient forum in both the United States and Europe to get MDS patients’ perspectives on how their quality of life was affected by MDS. Some of the most common negative effects include:

- Decreased physical and mental capabilities that interfere with daily functioning.
- Decreased physical energy making it difficult to work or perform normal daily activities.
- Loss of independence.
- Strain on relationships with friends and family members.
- Change in role within family.
- Feelings of anger, depression, anxiety, concern for future, fear, and helplessness.
- Significantly increased amount of time spent on health care.
- Change in employment status.

(Heptinstall, 2008).
Patient forums also revealed that MDS patients would appreciate physicians’ attention to the quality of life issues associated with their disease. Patients appreciate a thorough assessment of physical aspects of their disease, but would like physician’s to discuss their mental, social, and emotional well being regularly (Heptinstall, 2008).

Many MDS patients report having a high confidence level in their hematologists/oncologists, but view their relationships with their primary care providers in a negative manner because they feel that primary care providers have a lack of knowledge about MDS (Heptinstall, 2008). Primary care providers can improve this image by having a solid knowledge base on MDS and discussing quality of life issues with their MDS patients at each visit. A wider knowledge base of MDS that includes quality of life issues is important for any provider caring for a MDS patient (Heptinstall, 2008).

**Learner Review Questions**

1. What are some possible components of quality of life?

2. How can MDS affect patient quality of life?

3. What measures may improve quality of life for patients with MDS?

**Section IX: Key Learning Points**

1. When a patient presents with non-specific symptoms that could be characteristic of MDS, a full history, physical examination, and laboratory profile should be performed to rule out any other causes of the symptoms. Laboratory work should include CBC with differential, serum ferritin, serum iron, TIBC, folic acid, B12,
LDH, thyroid profile, testosterone, renal profile, hepatic profile, and serum erythropoietin.

2. Primary care providers should have a basic and broad knowledge base regarding MDS so they can effectively communicate with patients regarding the disease and its many manifestations.

3. A complete medication profile should be known, including any MDS treatments the patient is taking. Providers should be aware of any interactions between primary care drugs and MDS drugs, as well as the potential side effects of MDS treatments.

4. Patients with CHF who receive frequent transfusions may experience CHF exacerbations that could require adjustments of CHF medications and diuresis with transfusions (Kurtin, 2008).

5. It is important to monitor transfusion dependent patients for iron overload both subjectively (reported symptoms) and objectively (lab values and scans if necessary).

6. The use of anticoagulation therapies, such as aspirin, aspirin products, and warfarin, should be avoided or must be monitored very carefully.

7. Iron overload may cause the development of diabetes, so patients should be monitored regularly for clinical manifestations of diabetes.

8. Kidney and liver function should be checked on a regular basis and monitored by oncology and primary care.

9. Psychosocial needs of MDS patients should be addressed at each visit.
10. It is appropriate for the primary care provider to collaborate with the oncologist to create a therapeutic health care regimen for each individual MDS patient.

Implementation of Educational Module

This educational module will be offered as a self-paced learning module. The module will be offered in print form that can be accessed online or as a hard copy. The content will be evaluated by MDS experts and pilot tested prior to implementation. Once pilot testing is complete and revisions have been made, the module will be made available in print and electronically to all PCPs who are interested in participating. In order to provide incentive for PCPs to participate, the project author will work to get this module approved for continuing education (CE) credits. As advances in medicine and research will undoubtedly bring future changes to the management of MDS, this module will be updated as necessary to reflect the most current and evidence-based knowledge on the topic.

Summary

This chapter discusses how the theoretical framework guides project contents, presents the educational module in detail, and explains how the module will be implemented. The educational module focuses on the major points of MDS and its management that are relevant to primary care providers. Upon completing this module, providers should have a better understanding of MDS and its manifestations, diagnosis, treatment, complications, quality of life issues, and comorbidities. The information presented should increase primary care providers’ knowledge on how to manage MDS.
patients in the primary care setting. It is suggested that this module be evaluated yearly to determine any changes in practice that would alter the module contents.
CHAPTER 4

Introduction

This chapter will cover a proposed plan for evaluation of this project, which includes the use of expert opinion and project participants. Strengths and limitations of the project will be discussed and explained in detail. Suggestions for future research are also covered. Lastly, the significance of this project will be addressed, followed by project conclusion.

Proposed Evaluation Plan

Before this educational module can be made available to PCPs, it needs to be evaluated by hematology/oncology providers, as they play the main role in MDS management. Prior to the module being released to the pilot group of participating PCPs, it would be important to present it to a board of hematologist/oncologists, who are content experts. Ten local hematology/oncology providers, from different practices around Tucson, will be recruited to review the content of the educational module prior to releasing it to the pilot group of PCPs. Then, fifty PCPs in the Tucson area will be recruited to complete this module. The group of PCPs will consist of nurse practitioners, physicians, and physician’s assistants. Each of the PCPs will complete all portions of the module within a one-month time span and return the module along with answered questions and feedback to the project committee. The project committee will then evaluate participant understanding of the module based on answers to learning questions. They will take participant feedback into consideration and determine the need for revision. Of note, participants after this pilot group will not have a time limit to complete
the module, but it is necessary in the first group in order for the author and project committee to get feedback in a timely manner. Their input and feedback will help to validate and improve the content before it is accessed by all PCPs.

PCPs will have the option to evaluate the module. Directly after completion, participants will submit their thoughts on strengths, limitations, and any general feedback regarding the project. Revisions will be made based on suggestion.

Strengths of Project

With the aging population, health care will continue to focus on care of the older adult. This project covers an important health problem that is becoming more prevalent as the population ages. It provides useful information to PCPs who are likely to encounter MDS patients in their practice at some point. Additionally, no other learning modules that address MDS have been found in the literature.

The educational portion of this project has the potential to impact how PCPs manage the care of patients with MDS. PCPs will have evidence-based knowledge on how to manage MDS patients, which will likely increase patients’ confidence in their providers. Patient confidence in provided care is one aspect that can lead to an increased quality of life.

The design of the educational module is theoretically driven using Adult Learning theory. Strategies used to educate adults are different than those used to educate children. This project focuses on information that is applicable to the every-day practice of PCPs. Participants will have the freedom to complete the module at a self-paced rate and will be
given the option to evaluate the material when they are done. This project uses concepts that are paramount in educating the adult population.

The information presented in this educational module is based on the most recent and evidence-based research on MDS. It focuses on factual and relevant information that can be used in every day practice. Each participant will receive a hard copy of the information covered so they can reference the module for review at any time. Since the information will be presented in a written form, it will be easy to update and revise this module as future research and literature becomes available.

This project will be relatively easy to implement. The module will be a self-paced activity available as written material. There will not be the need to plan a presentation, rent space, find presenters, and fund the utilities and workforce that would be necessary to give the presentation. Participants will have the opportunity to complete the module independently, which saves them from missing work or other obligations to attend a presentation. A large number of people can partake in this educational experience at any given time, as there will be no concerns of the amount of physical space available for participants.

Limitations of Project

One limitation of this project is the lack of information in the literature about what is vital for PCPs to know regarding MDS. Virtually all of the literature available is geared towards hematology/oncology providers. In educating PCPs about MDS, a major goal is to improve patient care. Since this is the first attempt to increase PCP awareness
of and involvement in MDS care, it is unknown whether this knowledge will increase disease detection and ultimately improve patient outcomes.

It may be difficult to recruit the initial fifty PCP participants. Ultimately this educational experience will be self-paced, but the pilot group of participants will have a one-month time limit so the author and project committee can get feedback in a timely manner. Due to the reasons discussed in the preceding paragraph, along with lack of incentive and the proposed time limit, PCPs may be reluctant to participate.

It may also be difficult to find a group of hematology/oncology providers to serve on the evaluative board of this project. As with the majority of medical providers, these professionals are likely very busy with their daily practice. This would be an additional time commitment for which they might feel there is little incentive.

Significance

Nurse practitioners, physicians, and physician’s assistants who practice primary care will all likely manage the comorbidities of patients who also have MDS. MDS is primarily a disease of the elderly, and the elderly population is steadily increasing. The elderly population is also more likely to have a higher number of co-morbidities that require management by primary care. Currently, the literature does not address or direct PCPs in the detection and management of MDS. This will be the first project to focus specifically on information about MDS that is relevant to primary care. It will give PCPs direction on the diagnostics and management of MDS that they will be involved in. It will be reviewed by MDS experts prior to release and encourages participants to provide feedback for project improvement. The self-paced nature of the module takes into
consideration the busy lifestyles of most medical providers. Once the module is completed, participants will have the opportunity to reference it any time in the future as needed. As MDS research develops, the educational module will be revised to reflect the most current literature. It is the author’s hope that this project will increase PCPs knowledge on an important disease, promote increased communication between PCPs and hematology/oncology providers, and as a result, improve the overall quality of care that MDS patients receive.

Suggestions for Future Research

There is currently very little information in the literature regarding PCPs’ role in the management of MDS. It is inevitable that many PCPs will manage the co-morbidities of MDS patients and encounter the complications of MDS and its treatment. The author suggests that further research be undertaken to determine a more defined role of the PCP in MDS management and an evaluation of whether this module impacted practice with improved patient outcomes. In compliance with Knowles’ Theory of Adult Learning, it may be helpful in the future to research what the best possible delivery method is for this module. Evaluation from participants will be helpful in this process. The development of clinical guidelines for PCPs regarding this disease could provide evidence-based recommendations for care and ultimately improve patient care and increase collaboration between PCPs and hematology/oncology providers. The author also suggests the creation of a fast facts sheet based on the educational module content to provide users with a quick reference to the key points of MDS management in primary care.
Conclusion

MDS is among the most prevalent hematopoietic malignancies in patients older than the age of 80. Given the aging population, PCPs will most likely encounter and care for MDS patients in their practice. It is important that these providers have a general knowledge base regarding the diagnosis and management of MDS in order to improve both physiologic care and quality of life in MDS patients. The educational module proposed in this project is designed to provide PCPs with the knowledge necessary to manage MDS patients in a primary care setting. Further research is suggested to create more definitive clinical guidelines on MDS for PCPs. The author produced this project with the major goal of improving the care of MDS patients and ultimately improving patient outcomes.
REFERENCES


