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Critical Reviews in Oncology/Hematology 56 (2005) 179–192

Critical Reviews in Oncology Hematology

www.elsevier.com/locate/critrevonc

Management of patients with higher risk myelodysplastic syndromes

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Accepted 20 April 2005

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Abstract

Higher risk myelodysplastic syndromes (MDS) include patients in the Intermediate-2 and high-risk categories of the International Prognostic Scoring System, as well as patients with MDS secondary to radiation or chemical exposure. Ideally, the goal of therapy is to alter the natural history of disease in these patients to achieve cure or durable remission. High-intensity chemotherapy can achieve moderate rates of complete remission, however, durability of remission and overall survival tend to be short. Hematopoietic stem cell transplantation (HSCT) offers the possibility of cure, with long-term disease-free survival inversely related to age. Patients who are elderly or have poor functional status are candidates for reduced intensity HSCT, although this is still an experimental modality. Azacitidine is a hypomethylating agent that is a reasonable option for many patients ineligible for high-intensity therapies. Other therapies, such as immunomodulatory agents, arsenic trioxide, and farnesyl transferase inhibitors have thus far shown limited usefulness in higher risk MDS. This paper reviews the various therapeutic options for higher risk MDS, providing rationale for specific management approaches for these patients.

Keywords: Myelodysplastic syndromes; MDS; Higher risk; Treatment; Chemotherapy; Hematopoietic stem cell transplantation; Hypomethylation; Azacitidine

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doi:10.1016/j.critrevonc.2005.04.006

1. Introduction

The myelodysplastic syndromes (MDS) are clonal disorders of hematopoietic stem cells characterized by ineffective hematopoiesis, peripheral blood cytopenias, and a propensity to evolve to acute myeloid leukemia (AML). Both the French–American–British (FAB) [1] and the World Health Organization (WHO) [2] systems categorize MDS according to morphology and the percentage of bone marrow blasts, with higher blast percentage correlating with more advanced disease. A notable difference between the two systems is the categorization of AML, which is defined as a blast count >30% in the FAB system and ≥20% in the more recent WHO system (Table 1). Bone marrow karyotype also plays an important role in the pathogenesis and prognosis of MDS, and specific cytogenetic abnormalities have been identified which correlate with outcome. Taking these issues into account, the International Prognostic Scoring System (IPSS) for MDS was developed [3], which stratifies patients into Low, Intermediate-1 (Int-1), Intermediate-2 (Int-2), and High-risk categories, according to three prognostic factors: bone marrow blast percentage, karyotype, and number of cytopenias (Table 2). This system has provided a valuable method for assessing survival and potential for AML evolution in patients with MDS, as shown in Table 3. To standardize the reporting of responses to MDS therapies, the International Working Group (IWG) proposed criteria for complete remission (CR), partial remission (PR), and hematologic improvement (HI) [4]. Use of IWG criteria is recommended for all MDS trials to facilitate comparisons of results across studies.

For prognostic purposes, MDS patients have been characterized as being relatively lower risk (IPSS Low and Int-1) or relatively higher risk (IPSS Int-2 and High). Therapy-related, or secondary MDS, which may occur several years after significant exposure to radiation or chemicals, such as chemotherapeutic agents, is also considered relatively higher risk MDS, with greater resistance to therapy and worse prognosis than primary MDS [5,6]. Whereas lower risk patients with stable disease can often be managed with observation or supportive care, higher risk patients, because of their increased morbidity and mortality due to bleeding and infections, increased risk of AML transformation, and decreased survival, require that the clinician consider initiation of treatment with more immediacy. The predominant goal of therapy in higher risk MDS patients is to alter the natural history of the disease, with the aim of cure or durable remission, as opposed to merely hematologic improvement in peripheral blood cell counts. This approach is often a challenge, however, as MDS tends to be a disease of older patients with median age 60–70 years, who may have co-morbidities and decreased functional status. Such patients are poor candidates for high-intensity therapies, such as induction chemotherapy or hematopoietic stem cell transplantation (HSCT). Thus, in addition to consideration of such high-intensity therapies,

Table 2
International Prognostic Scoring System (IPSS) for MDS [3]

Prognostic variable	Score value				
	0	0.5	1.0	1.5	2.0
Bone marrow blast (%)	<5	5–10	–	11–20	21–30
Karyotype[a]	Good	Intermediate	Poor		
Cytopenias[b]	0–1	2–3			

Risk category	Combined score
Low	0
Intermediate-1	0.5–1.0
Intermediate-2	1.5–2.0
High	≥2.5

This research was originally published in *Blood* [3]. ©The American Society of Hematology.

[a] Good, normal, -Y only, del(5q) only, del(20q) only; Poor, complex (≥3 abnormalities) or chromosome 7 abnormalities; Intermediate, other abnormalities.

[b] Absolute neutrophil count < 1800/μL; hemoglobin < 10 g/dL; platelet count < 100,000/μL.

Table 1
French–American–British (FAB) [1] and World Health Organization (WHO) [2] classifications of MDS

Bone marrow blast (%)	FAB	Bone marrow blast (%)	WHO
<5	Refractory anemia (RA)	<5	Refractory anemia (RA) Refractory cytopenia with multi-lineage dysplasia (RCMD)
	Refractory anemia with ringed sideroblasts (RARS)		Refractory anemia with ringed sideroblasts (RARS) Refractory cytopenia with multi-lineage dysplasia and ringed sideroblasts (RCMD-RS) Myelodysplastic syndrome with isolated del(5q) Myelodysplastic syndrome, unclassified (MDS-U)
5–20	Refractory anemia with excess blasts (RAEB)	5–9 10–19	Refractory anemia with excess blasts-1 (RAEB-1) Refractory anemia with excess blasts-2 (RAEB-2)
21–30	Refractory anemia with excess blasts in transformation (RAEB-T)	≥20	Acute myeloid leukemia (AML)
>30	Acute myeloid leukemia (AML)		
≤20	Chronic myelomonocytic leukemia (CMML)		Chronic myelomonocytic leukemia classified with myelodysplastic/myeloproliferative disorders