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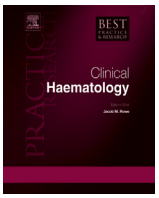

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More is better: Combination therapies for myelodysplastic syndromes

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The myelodysplastic syndromes (MDS) are a heterogenous collection of clonal hematopoietic malignancies that exist as a subgroup of the myeloid neoplasms as classified by the World Health Organization (WHO). They are characterized by ineffective hematopoiesis, subsequent cytopenias, transformation to acute myeloid leukemia (AML), and poor overall survival. There are currently three FDA-approved medications for MDS; lenalidomide, azacitidine, and decitabine. The role of these agents is to diminish the clinical impact of MDS and delay its progression to AML. However, despite known results with these monotherapies, recent clinical trials with a variety of combinations for MDS have demonstrated promising results. These trials include combinations of hypomethylating agents, histone deacetylase inhibitors, growth factors, and chemotherapy among others. In this paper we review the current literature on combination therapies in MDS, analyze on-going and concluded trials, and suggest future possibilities for combination strategies in MDS.

Introduction

The myelodysplastic syndromes (MDS) are a heterogenous collection of clonal hematopoietic malignancies that exist as a subgroup of the myeloid neoplasms as classified by the World Health

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Organization (WHO) [1]. MDS is the most common of these myeloid neoplasms, with a yearly incidence rate of 4.5 per 100,000 people in the U.S. This rate increases with age, reaching 28/100,000 among septuagenarians and 52 per 100,000 in patients 80 years and older [2]. MDS most commonly arises de novo, but can occur as a consequence of prior cytotoxic chemotherapy, radiation, environmental exposures, or genetic abnormalities in approximately 10% of patients [3,4]. The clinical impact of MDS results from ineffective hematopoiesis and the subsequent systemic signs and symptoms of anemia, thrombocytopenia, and leukopenia. In addition to the inherent challenges and consequences of these cytopenias, patients with MDS also face a varied risk of AML transformation.

MDS patients are classified into risk groups on the basis of dysplastic cell lines, percentage of bone marrow (BM) blasts, cytogenetics, and WHO MDS subtypes, among others. These factors have given rise to the development of multiple prognostic models that serve as tools for treatment decisions [5]. A more detailed analysis of these tools is discussed elsewhere in this journal. Briefly, the most commonly used prognostic tool is the International Prognostic Scoring System (IPSS), which incorporates cytogenetics, cytopenias, and proportion of BM blasts to categorize patients into low, intermediate-1 (Int-1), intermediate-2 (Int-2), and high-risk groups with varying median survival and risk of AML evolution [6]. In general terms, however, patients with MDS can be dichotomized into higher-risk (Int-2 and High) lower-risk (Low and Int-1) groups [7,8]. The revised IPSS (IPSS-R) incorporates additional chromosomal abnormalities, the degree of individual cytopenias, and modifies the impact of blast percentage in identifying five risk groups compared to the four risk groups in the IPSS [9]. Although the IPSS-R has been validated by numerous international groups [10,11] and is gradually gaining more widespread acceptance, the IPSS remains the current default scoring system still used in most clinical trials and practice guidelines [5].

Our understanding of the pathogenesis of MDS has undergone a recent revolution, with an explosion in identification of molecular and genetic factors driving the heterogeneity of the disease course and risk of AML transformation [12,13]. These are discussed in detail elsewhere in this journal but a brief review relevant to therapy. Appropriate methylation of CpG promoter regions of tumor suppressor genes (TSGs) is crucial in the expression of TSGs. Hypermethylation of these regions, however, leads to TSG suppression, resulting in tumor expression [14]. In MDS, this aberrant methylation process is thought to be a dominant epigenetic driver of disease manifestation and its progression to AML [12,15]. A variety of other bone marrow microenvironment factors, including the interplay between pro-apoptotic cytokines such at TNF-α and TNF-related apoptosis inducing ligand (TRAIL) have been implicated in the premature apoptosis of hematopoietic stem cells and the development and progression of MDS [13]. The increase in apoptosis and stem cell depletion leads to an emergence of abnormal clones and the conversion of myeloid progenitors (MP) to abnormal myeloid progenitors (aMP), which are at high risk of leukemic transformation [12].

Similarly, the cytogenetics and molecular genetics of MDS play a critical role in risk stratification, outcome, and treatment decisions. The most common chromosomal abnormalities in MDS are 5q-, -7/7q-, Trisomy 8, 20q-, -Y, and complex cytogenetics, with three or more chromosomal abnormalities [16]. More recently, somatic mutations affecting oncogenes, TSGs, and methylation have been identified, including *TET2, IDH 1* and *2, RUNX1, ASXL1, SF3B1, and DNMT3A* among others [17–20]. Recognition of these lesions is critical to understanding the pathobiology of MDS, its evolution to AML, and the discovery of novel as well as combination therapies.

The decision of how and when to treat patients with MDS takes into account the prognostic scoring systems, age, performance status, and a variety of other molecular and clinical factors not incorporated in formal prognostic scoring systems [21]. Ultimately, patients are stratified into higher-risk and lower-risk, with treatment of lower-risk patients focused on symptom management, immunosuppression, and maximizing hematopoietic production, and treatment of higher-risk patients involving modifying therapies designed to target the epigenetic dysregulation driving MDS, to delay AML transformation and improve overall survival. Regardless of risk, the only curative treatment for MDS is hematopoietic cell transplantation.

It is precisely the ability to oversimplify the stratification of patients into two risk categories that justifies combination therapeutic options, as there is significant overlap among patients in both groups. Combination therapies have multiple advantages over monotherapies, including multiple mechanisms of action (MOA), synergism between MOA, and the ability to identify appropriate combination based