Myelodysplastic Syndromes

Clinical and Biological Advances

Myelodysplastic Syndromes: Clinical and Biological Advances stands out as the definitive text on the genetics, pathophysiology, and clinical management of this wide-range of syndromes. Written by international experts, this book provides a state-of-the-art update of the current status and recent advances in the field. The chapters cover all aspects of the myelodysplastic syndromes, from an in-depth analysis of the multifactorial nature of this disease, including a careful assessment of stromal, immunological, and stem cell abnormalities, to a review of recent molecular and cytogenetic discoveries and insights. This book will be a valuable resource for clinicians and researchers who wish to learn more about myelodysplastic syndromes.

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To Suzanne, Sarah, Daniel, Miriam, and, of course, Simi, whose love, encouragement, and support have been critical beacons for my worlds; to my MDS colleagues for their spirited camaraderie and scientific stimulation; to my patients with MDS who have permitted me the privilege of participating in their lives and struggles, who have taught me much of the eternal odds they/we face. All have been vital for my ongoing exploration to better comprehend and treat this distinctively problematic disease.

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Preface

Myelodysplastic syndrome (MDS) is a particularly problematic disease. This myeloid clonal hemopathy is heterogeneous, with varying stages having differing clinical problems that require specific yet disparate therapeutic approaches. Major morbidity relates to the patients' symptomatic cytopenias and their potential for progression to acute myeloid leukemia (AML). The patients' generally elderly ages complicate management of the illness due to attendant comorbidities. Beyond standard supportive care with transfusions, virtually all treatments for MDS are currently experimental. This combination of characteristics has contributed to the difficulty in determining appropriate therapy for MDS patients. Fundamental to improving the care for these individuals is a more thorough clinical characterization and basic understanding of mechanisms causing the marrow hemopoietic dysfunction central to this disorder.

Given these features and the increasing incidence of MDS as our populations age, this book is quite germane in providing a comprehensive state-of-the-art update of the current status and recent advances in the field. It describes major treatises by an international group of MDS experts on the clinical classification, underlying pathogenetic mechanisms, and biologically targeted treatments of the disease. Each of the book's 10 chapters provides critical insights into specific topics, demonstrating interconnections between subjects.

Chapter 1 reviews the current clinical and prognostic categorizations of MDS, describing the complexity of establishing disease diagnosis and the critical clinical and biological features used to categorize MDS prognostically so that effective management strategies may be undertaken. Chapter 2 provides more extensive descriptions and photomicrographs of the major

criteria for the morphologic classifications of MDS, including those for both adult and pediatric patients.

In order to understand basic pathogenetic mechanisms underlying MDS, an indepth analysis of the multifactorial nature of the biological derangements causing marrow dysfunction in this disorder is provided in Chapter 3, including careful assessment of marrow stromal, immunologic, as well as stem cell abnormalities and dysregulation. Particular focus in this discourse depicts the changing patterns of the aberrant biology associated with evolving stages of MDS. This evaluation examines the molecular lesions and their influences which generate the initially slow but insidious course of the disease, with a subsequent frequent triggering to more active disease progression. The role of the senescence process in enhancing the vulnerability of aging itself for susceptibility to MDS is also discussed in detail.

Chapters 4 and 5 are critical extensions of the analysis of MDS pathobiology, evaluating recently determined major cytogenetic and molecular discoveries involved in the syndrome. These treatises review current insights into disease biology using novel investigative techniques, including microarray analysis of differential gene expression profiles.

A growing plethora of therapeutic options for MDS is becoming available, particularly using biologically specific targeted drugs for treating the disease. Clinical subsets of MDS patients have been defined and discussed in Chapter 6 wherein immunologic mechanisms and immune-modulating therapy may be effective. Chapter 7 comprehensively updates results of experimental clinical trials using the many and various new agents targeting specific pathogenetic features in MDS and the strategies being used for managing differing subtypes of MDS. Treatment with hemopoietic cytokines for management of the patients' symptomatic cytopenias is reviewed in Chapter 8. Due to recently improved appreciation of the negative clinical consequences of iron overload for multiply transfused MDS patients and the current availability of novel oral iron chelators, interest has been rekindled for use of iron chelation therapy. The current management of iron overload, as well as the biologic derangements caused by tissue siderosis, are also discussed in this chapter.

The only potentially curative therapy for MDS is hemopoietic stem cell transplantation (HSCT). However, age limitations for this high-intensity form of treatment and its relative toxicity require careful consideration of eligibility criteria prior to application of this procedure. Results of HSCT

investigations using risk-based categorization of MDS patients and the newer preparative regimens (including reduced-intensity conditioning) are discussed in Chapter 9.

The complexity of the disease's clinical course and the multiple options for management approaches engender an element of uncertainty in the minds of many, patients and clinicians alike. These disconcerting issues have a particularly prominent impact on each MDS patient's quality of life. Such effects on the various domains comprising this component of the patients' lives (functional, emotional, physical, spiritual, and social) are reviewed in Chapter 10.

An important property of this book is the interconnectedness between chapters, engendering cross-fertilization for improved understanding of this disease. Numerous unique aspects of MDS have been incorporated into each chapter and the co-authors provide proposals for major future directions for the field. These comprehensive features should permit valuable insights for the reader into this potentially life-threatening illness and its effective management.