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Seminars in

Myelodysplastic Syndromes

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Seminars in Oncology

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Myelodysplastic Syndromes: Introduction

Donald C. Doll and Alan F. List

IN NEARLY 20 years of publication of *Seminars in Oncology,* this is the first issue devoted to the biology and management of the myelodysplastic syndromes (MDS). Although the terminology and classification of MDS is relatively new, the concept of such disorders is at least five decades old. In 1938, Rhoades and Barker' described 100 patients who had refractory anemia, 60 of whom had primary refractory anemia while the other **40** cases were secondary to an underlying illness. Eleven years later, Hamilton-Paterson' used the term "pre-leukemic anemia" to describe three cases of refractory anemia antedating acute myelogenous leukemia. Block and colleagues[3] later coined the term "preleukemia" in their 1953report describing **12** patients with refractory cytopenia(s), with evolution to acute leukemia.

Although this nosologic reference persists even to date, case studies revealed that both the hematologic presentation and natural history of the preleukemic states vary. Bjorkman[4] chronicled four cases of refractory anemia associated with ringed sideroblasts in the bone marrow in which leukemic conversion appeared to be uncommon. In 1963, Rheingold et al[5] described an apparent variant of acute leukemia characterized by a prolonged and often benign clinical course with a variable but comparatively lower percentage of marrow-blasts, which the authors termed "smoldering acute leukemia."

Not until the 1970s, however, was a unique preleukemic syndrome recognized distinguished by myeloproliferative features of excess monocytes and granulocyte production, designated chronic myelomonocytic leukemia."' Dreyfus'[9] seminal observation that patients with refractory anemia accompanied by an excess number of myeloblasts (>5%) in the bone marrow experience a more aggressive clinical course provided a prognostically useful means to discern differences in clinical behavior. A number of additional terms have been applied to describe the preleukemic states and are summarized in Table 1.

In 1976, the French-American-British (FAB) cooperative group initially defined refractory anemia with excess blasts and chronic myelomonocytic leukemia as preleukemic states.'' **Six** years later, the FAB group further refined this classification and adopted the term "myelodysplastic syndromes," which includes the five current subtypes: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), chronic myelomonocytic leukemia (CMML), refractory anemia with excess blasts (RAEB) and refractory anemia with excess blasts in transformation (RAEB-t).[19] Although the need and validity of this new scheme has been questioned[20-22] it has enjoyed widespread application because of its reproducibility and clinical relevance.

With the possible exception of CMML, the MDS are invariably associated with cytopenias. Controversy persists over the inclusion of CMML among the **MDS** because of its proliferative phase akin to chronic myelogenous leukemia (see article by Goasguen and Bennett). Indeed, many cases previously characterized as Ph-negative chronic myelogenous leukemia are in

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Table 1. Chronology and Terminology of the Myelodysplastic Syndrome

Term	Year	Author
Refractory anemia	1938	Rhoads and Barker[1]
Preleukemic anemia	1949	Hamilton-Paterson[2]
Preleukemia	1953	Block et al[3]
Refractory anemia with ringed sideroblasts	1956	Bjorkman[4]
Refractory normoblastic anemia	1959	Dacie et al[10]
Smoldering acute leukemia	1963	Rheingold et al[5]
Chronic erythemic myelosis	1969	Dameshek[14]
Preleukemic syndrome	1973	Saarni and Linman[16]
Subacute myelomonocytic leukemia	1974	Sexauer et al[13]
Chronic myelomonocytic leukemia	1974	Miescher and Farquet[6]
Hypoplastic acute myelogenous leukemia	1975	Beard et al[11]
Refractory anemia with excess myeloblasts	1976	Dreyfus[9]
Hematopoietic dysplasia	1978	Linman and Bagby[15]
Subacute myeloid leukemia	1979	Cohen et al[12]
Dysmyelopoietic syndrome	1980	Streuli et al[17]
Myelodysplastic syndromes	1982	Bennett et al[18]

fact unrecognized cases of CMML.[23-25] Progress in understanding the pathobiology of these disorders has shown that unique biologic features such as increased sensitivity to growth factor regulation appear to distinguish CMML from other MDS types (see articles by Greenberg and List and Jacobs in this issue).

The pathogenesis of these disorders remains unclear. However, recognition that both MDS and acute myeloid leukemia (AML) may develop following treatment with chemotherapy and/or radiotherapy[26-31] has provided a fertile area to investigate the pathobiology of these disorders. The risks associated with specific exposures are addressed by Levine and Bloomfield. Environmental exposure to potential leukemogens may also represent contributing factors. Nonetheless, the application of sensitive probes to assess clonality suggests that such exposures may enhance host susceptibility to malignant conversion by limiting stem cell reserve and restricting clonality, and inducing somatic mutations of cellular oncogenes (see article by List and Jacobs in this issue). Interaction with host factors such as age may determine susceptibility and influence disease expression.

Detection of nonrandom, cytogenetic abnormalities in MDS confirmed the clonal nature of these disorders, and provided important information regarding disease biology (see article by Nowell). The development of marrow culture techniques has shown that these disorders share a disturbance in progenitor growth and maturation, independent of FAB type (see article by Greenberg). Progress in the last decade suggests that the abnormalities in progenitor growth relate in large part to decreased responsiveness to cytokine stimulation. Supersaturating concentrations of hematopoietic growth factors and certain pharmacologic agents restore progenitor growth in vitro and provide new avenues for clinical applications (see articles by Greenberg, and Kizaki and Koeffler). Indeed, the introduction of recombinant hematopoietins into clinical trials has shown that this new class of agents hold particular promise to ameliorate the cytopenias in MDS.

For patients with high initial leukemic burden (eg, RAEB-T) and those patients experiencing leukemic conversion, induction chemotherapy offers the prospect for hematologic remission (see article by Cheson). The traditionally higher rate of induction failure due to primary chemoresistance may be less pronounced in patients with RAEB-T, but has limited success in patients with acute leukemia. Recognition that specific biologic phenotypes such as multidrug resistance (MDR) may contribute to treatment failure has provided new inroads for innovative protocol designs.

The myelodysplastic syndromes are an extremely heterogenous group of bone marrow disorders with unique biologic features. Further progress with the management of these disorders remains inextricably linked to continued developments in their biology. We hope that this issue of ***Seminars in Oncology*** will highlight present results of such efforts and stimulate further development.

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