Myelodysplastic Syndromes and Acute Myeloid Leukemia: A Biological and Therapeutic Continuum

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in collaboration with
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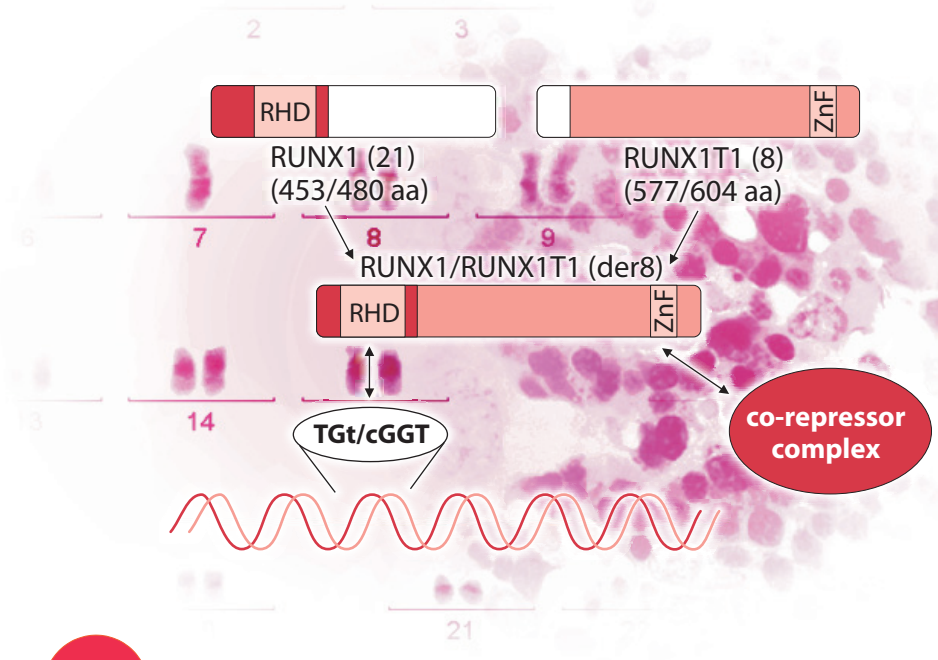

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UNI-MED Verlag AG, one of the leading medical publishing companies in Germany, presents its highly successful series of scientific textbooks, covering all medical subjects. The authors are specialists in their fields and present the topics precisely, comprehensively, and with the facility of quick reference in mind. The books will be most useful for all doctors who wish to keep up to date with the latest developments in medicine.

Preface and acknowledgements

The advent of genotype-driven treatment approaches, developed for the specific therapy of genetically defined subgroups of AML and - more recently - also MDS, has been boosted by the rapid and massive advances in high-throughput DNA sequencing technology. Thus at present the biological and therapeutic continuum existing between MDS and AML has become even more evident. This book has the goal of updating the reader on the epidemiological, morphological, cytogenetic and molecular aspects of both groups of disorders, pointing out the common themes and the distinctions between them. Furthermore, in separate chapters the different treatment options are reviewed: those with curative intent (standard chemotherapy, allografting) and the more recent treatment principles such as epigenetically active drugs, kinase inhibitors, differentiating agents and anti-angiogenic compounds among others. These non-intensive therapies may prove to be increasingly useful as well-tolerated "bridging" treatments prior to the curative approach of allografting. State-of-the-art functional and psycho-social assessment instruments used to determine the "fitness" of these often older patients are also reviewed, since they are increasingly applied prior to the choice of treatment modality.

The previous two editions of this book were authored by a group of experts in the fields of MDS and AML, joined in the German MDS Study Group and Competence Network "Acute and Chronic Leukemias". The present edition is also strongly supported by a number of international experts, many of them involved in the European LeukemiaNet - underscoring that with the increasingly differentiated diagnostics and treatment of the growing number of sub-entities, success is only possible within large, international networks.

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Chapter 9.

Contents

Epidemiology, classification and prognostic systems

1. Epidemiology, classification and prognostic systems

1.1. Epidemiology of myelodysplastic syndromes

Compared to many solid tumor, myelodysplastic syndromes (MDS) are rare. In older adults, however, they are among the most common hematological diseases. While they can appear in childhood and adolescence, their peak incidence rate occurs after the age of 80 years [1, 2].

Incidence and Prevalence

The actual incidence rate of MDS is unknown in many countries, but some progress has been made. Important reasons for these are:

- Unified recording of the disease has only been possible since 1982, after the French-American-British (FAB) group established uniform diagnostic criteria [10].
- Numerous causes of cytopenia remain undiscovered, particularly in advanced age, because a bone marrow examination often is not performed to determine the cause. Among patients with unexplained anemia, as many as 17% have a macrocytic anemia, leukopenia, or thrombocytopenia – peripheral blood findings typical of MDS.
- Central registries for recording new cases of MDS at a national level are not uniformly maintained around the world.

In 2001 the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute and the Centers for Disease Control and Prevention (CDC) started to track incidence rates of MDS. Based on these SEER data, collected from 2001-2003, the age-adjusted incidence rate of MDS in the United States (US) was estimated to be 3.4 per 100,000 people, which translates to approximately 10,000 new cases per year [3]. The incidence rate over these 3 years increased from 3.3 to 3.6, in large part likely due to improved reporting practices within cancer registries. Incidence rates were lowest for people less than 40 years of age at 0.14 per 100,000 and 36 per 100,000 for patients more that 80 years of age [4]. This figure is considered to be an underestimate. The incidence of MDS using a novel claims-based algorithm reported a high number of uncaptured cases by one cancer registry, and claimed an annual incidence of MDS of 75 per 100,000 persons 65 years or older, far higher than the 20 per 100,000 reported by SEER using the same sample [5]. Although Goldberg et al. reported the 2003 incidence rate among US Medicare Beneficiaries to be as high as 162 per 100,000, this is felt to be an overestimate related to inaccuracies in diagnostic coding [6]. The US incidence rate is similar to that reported in Western European countries such as England/Wales and Sweden 3.6/100,000, Germany 4.1/1000,000, and France 3.2 per 100,000 but higher than Japan's rate of 1.0/1000,000 [1, 7, 13, 14].

Prior to 2001, data on the incidence rate of MDS was recorded in local/regional registries, and did not represent the full scope of the disease. In addition, historic databases relied on the FAB MDS classification, rather than the WHO classification introduced in 1999 and revised in 2001 and 2008 [8, 9]. Therefore a precise comparison with older epidemiological studies is challenging, particularly when one factors in the difficulty of making the diagnosis pathologically, introducing the potential for misclassification. Despite all these uncertainties, there are some European regional registries that have allowed valid statements to be made regarding the incidence rate of MDS.

One large study from the United Kingdom [11] reported an incidence rate of 3.6/100,000 yearly, among 16 million people. People older than 80 years were not included in this study, and no central cytomorphological investigation of bone marrow blood was undertaken. A subsequent study in the UK over a 10-year period did include elderly patients, and found an incidence rate of 61/100,000 for male patients, 28/100,000 for females and 38/100,000 for both groups among patients 80 and older. Another large study from Düsseldorf, Germany recorded all new cases of MDS over two 10-year periods [1, 2]. The incidence rate was similar, at 4-5 new cases of the disease/100,000 of the population yearly, and a strong relationship with age was also identified. Moreover, the incidence rate of MDS was accurately tracked for a total of 26

years. Recently Neukirchen et al. reported a crude incidence rate of 4.15/100,000/year and the point prevalence per 100,000 persons of 7 based on data from the Düsseldorf MDS Registry [12].

While initially there was the impression that the incidence of MDS was increasing in Germany, since the end of the 1980s no further rise in the incidence of MDS has been found. This is primarily because the number of cytological investigations of bone marrow in elderly patients abruptly increased in the first few years of the survey, whereas since the end of the 1980s there has not been any further increase in the frequency of diagnostic procedures.

A Swedish study [13] found a similar incidence rate of 3.6/100,000, and three consecutive French studies [14, 16] reported an incidence rate of 3.2/100,000 of the population yearly. Another French study in the Basque region [17] found a somewhat higher incidence rate of 7.7/100,000, while a study from Bournemouth [18] showed the highest incidence rate, at 12.6 new cases of the disease per year, which may be due to the municipal region of Bournemouth having a large population of retired people (similar to the region in the U.S. study reporting an incidence rate of 75/100,000) [5]. Another British study [19] likewise estimated the incidence rate as being somewhat higher, at 9.3/100,000 of the population. A Japanese study [12] surprisingly showed a much lower incidence rate of 1/100,000 per year, but only reviewed a 1-year period and thus was unable to give any information about a possible change in the incidence rate.

Estimates as to the number of treatment-associated or secondary MDS (sMDS) are also fairly similar. Approximately 10% of MDS patients have secondary disease, most commonly following therapy with ionising radiation or cytotoxic drugs or leukaemogenic substances i.e. alkylating agents and topoisomerase inhibitors, for other cancers [1, 20, 21]. The latency period for sMDS after exposure to alkylating agents or radiation therapy is 5-7 years. The risk appears to be dose-dependent [22, 23], and is associated with unbalanced translocation involving chromosome 5 or chromosome 7, or complex cytogenetics [24]. MDS following topoisomerase inhibitors are less common, with a latency period of approximately 2 years [25], and is associated with a balanced translocation involving 11q23 (the MLL gene). Long-term prognosis is believed to be poor for either type of secondary MDS [26, 27].

It is difficult to identify accurate prevalence statistics for MDS i.e. the numbers of those living with the disease, as opposed to new diagnoses. Preliminary data from Germany reveals a prevalence rate of 12.4 per 100,000 people [28]. If we assume that the incidence, and thus the prevalence rates between the U.S. and Germany are similar, this would translate to approximately 60,000 people with MDS in the US. However, this is thought to be an underestimate. Guralnik et al. reported the prevalence of anemia in the U.S. in 2004, based on 2000 blood samples collected from people 65 years of age or older as part of the third National Health and Nutrition Examination Survey [29]. The overall prevalence of anemia was 10.6%. Within the category "unexplained anemia" 7% of people had a macrocytic anemia, leukopenia or thrombocytopenia – peripheral blood findings typical of MDS. This would translate to 170,000 people living with MDS in the U.S. Thus, while a prevalence of 170,000 can be assumed to be an overestimate, a rate of 60,000 people likely underestimates the impact of the disease.

Etiology

The etiology of the vast majority (>90%) of myelodysplastic syndromes is completely unclear. Pre-existing systemic hematological diseases such as aplastic syndrome or paroxysmal nocturnal hemoglobinuria (PNH) are identified in extremely rare cases. Genetic factors (Down syndrome, Noonan syndrome, Shwachman-Diamond syndrome, Fanconi anemia, and others) can be found in very few instances. While some case reports document MDS in advanced aged with a familial increase in incidence because of genetic constitutional abnormalities, e.g. of chromosome 5 and 7, these cases are rare enough to make the statement to patients that MDS does not run in families.

Environmental factors that can favor the development of MDS include ionising radiation, alkylating substances, and other chemotherapy agents as well as massive exposure to organic solvents and their derivatives. This has been well-described in patients working in the rubber and oil industries. Case-control studies confirm an increased risk of MDS from exposure to agricultural chemicals (insecticides, pesticides, herbicides or fertiliser, with