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Myelodysplastic syndrome (MDS), diagnosis, prognosis and the best available treatment

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Introduction

Myelodysplastic syndrome (MDS) is a stem cell disorder characterized by ineffective hematopoiesis and bone marrow dysplasia that, in many cases, progresses to acute myeloid leukemia [1]. Treatment for MDS is variable and applied according to the risk classification based on the International Prognostic Scoring System (IPSS) [2,3]. Approximately 10–20% of patients with myelodysplastic syndrome (MDS) present with autoimmune diseases (AD) which can be challenging to recognize. The autoimmunity is believed to be triggered by the increased apoptosis in the dysplastic bone marrow. Recent evidence suggests that both diseases are characterized by dendritic and T-cell abnormalities. AD presentation varies from clinical syndromes such as vasculitis, lupus and rheumatoid arthritis to laboratory abnormalities such as thrombocytopenia, hemolytic anemia and autoantibodies [4]. The association of AIM and MDS was first described in 1982 as AIHA one year after the diagnosis of MDS. 6 Subsequently, multiple cases and studies have been published emphasizing the relationship between autoimmunity and MDS [5].

Prognostic markers and survival benefit

Myelodysplastic syndrome (MDS) with isolated deletion of chromosome 5q is part of a group of clonal disorders in myeloid stem cells with ineffective hematopoiesis which is manifested by morphologic dysplasia in hematopoietic cells and single or lineage Cytopenias. It is the only MDS subtype defined cytogenetically in the World Health Organization classification system [6].

MDS with isolated Del (5q) is present in <5% of MDS cases, it occurs more often in women than in men, male: female ratio 7: 3, with a median age of diagnosis at 65 to 70 years. Patients suffering from MDS with isolated Del (5q) present with macrocytic anemia, normal or increased platelet count and absence of significant neutropenia in their peripheral blood [7]. The incidence of bleeding and infections is therefore low in these patients because of the absence of significant neutropenia and thrombocytopenia. Blood transfusion dependency is seen in patients with severe anemia at diagnosis but also can develop in other patients. According to the Revised International Prognostic Scoring System (IPSS-R), MDS with isolated Del (5q) are defined as Low- or Intermediate -1- risk subtypes and usually have an indolent course [8].

Trisomy 21 and risk of transformation

Trisomy 21 (+21) is well known in the context of Down's syndrome, associated with a marked risk to develop AML during childhood. However, besides this hereditary disease, +21 may also occur as a clonal somatic abnormality in several hematologic disorders. In adult de novo AML, trisomy 21 occurs in around 3% of patients. In MDS, +21 as a single abnormality is occurring more rarely. In a series of 968 patients published by Sole et al. [9], isolated +21 was detected in 0.8% of patients and showed a significant association with CMML, where 3.5% of patients showed +21 as sole abnormality. 54 Further publications found a comparable incidence, calculated as 1.1% of patients showing +21 within a non-complex karyotype. Based on a cohort of 2,901 patients, the incidence of +21 as an isolated abnormality was 0.3%, assigning this abnormality to the group of rare abnormalities in MDS. Based on nine patients, the authors described an association with a low ANC (median 1.9/nl) and a slightly decreased platelet (median 105/nl) and hemoglobin (9.1 g/dl) level. The median blast count in these patients was 6%, indicating an association with higher risk MDS. The median OS was 100.8 months in +21 within a non-complex karyotype. Other publications stated a median OS of 13.9 months and **21.5 months** respectively, for patients showing isolated +21.

The median time to AML evolution was 100.7 months in the publication of Schanz et al. Solé et al. stated a cumulative AML risk of 25% after one year and 50% after five years. Taken these results together, the prognostic impact of an acquired, isolated +21 in patients with MDS remains unclear und has to be stated as intermediate until a higher number of patients were analyzed.

Molecular factor affecting the survival

The molecular background of patients showing +21 in myeloid malignancies remains undefined as yet. RUNX1 (=AML1), located on chromosome 8q22, commonly involved in t (8; 21)/RUNX1-RUNXT1 in AML, was shown to be also point mutated in patients with myeloid malignancies like AML, MDS and MPN with +21. A Japanese group found a poor prognostic impact of intragenic RUNX1 mutations in MDS but did not describe a correlation with +21. [10].

Available treatment modalities

Therefore, these findings suggest that 5--Azacitidine, a cytidine nucleoside analog, is a demethylating agent that was approved by the

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U.S. Food and Drug Administration for the treatment of high-risk MDS in 2004 [11-13]. In an international multicenter Phase III study (the Aza-001 study), 5-azacitidine was found to achieve a better overall survival in patients with high-risk MDS compared to conventional Therapies [11,14,15]. Almost all patients were treated with more than one cycle and approximately half achieved a first response after two or more cycles [16] Azacitidine therapy should be continued after obtaining a response.

In the post hoc analysis of the AZA-001 study, Silverman et al. reported that a median of two cycles (range, 1-16) of 5-azacitidine treatment was efficacious in achieving a first response with a hematological improvement [17]. Furthermore, The US Cancer and Leukemia Group B reported a median time to the initial response of 64 days for 5-Azacitidine therapy, although the time to a response in the subjects treated with a single cycle of therapy was unclear [10]. Therefore, late responses to 5-azacitidine treatment remain to be investigated.

Currently the only therapy with proven curative potential for MDS is hematopoietic stem cell transplantation (HSCT) [18], with long-term survival rates between 25% and 70%. However, HSCT carries a risk of toxicity and potentially fatal complications, particularly in older patients.

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