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THERAPY IN PRACTICE

Myelodysplastic Syndromes in the Elderly: Treatment Options and Personalized Management

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Abstract Myelodysplastic syndromes (MDS) are typical diseases of the elderly, with a median age of 68–75 years at initial diagnosis. Demographic changes producing an increased proportion of elderly in our societies mean the incidence of MDS will rise dramatically. Considering the increasing number of treatment options, ranging from best supportive care to hematopoietic stem cell transplantation (HSCT), decision making is rather complex in this cohort of patients. Moreover, aspects of the aging process also have to be considered in therapy planning. Treatment of elderly MDS patients is dependent on the patient's individual risk and prognosis. Comorbidities play an essential role as predictors of survival and therapy tolerance. Age-adjusted models and the use of geriatric assessment scores are described as a basis for individualized treatment algorithms. Specific treatment recommendations for the different groups of patients are given. Currently available therapeutic agents, including supportive care, erythropoiesis-stimulating agents (ESAs), immune-modulating agents, hypomethylating agents, and HSCT are described in detail and discussed with a special focus on elderly MDS patients. The inclusion of elderly patients in clinical trials is of utmost importance to obtain data on efficacy and safety in this particular group of patients. Endpoints relevant for the elderly should be integrated, including maintenance of quality of life and functional activities as well as evaluation of use of healthcare resources.

Key Points

Myelodysplastic syndromes (MDS) are typical diseases of elderly people.

Selecting the appropriate treatment for senior MDS patients is complex because of the heterogeneity of elderly individuals and the increasing number of available treatment options.

Age-adjusted models and geriatric assessment may be helpful in the design of individualized treatment algorithms.

1 Epidemiology of Myelodysplastic Syndromes (MDS) in Senior Patients

Myelodysplastic syndromes (MDS) are hematopoietic stem cell disorders characterized by ineffective hematopoiesis resulting in cytopenia and the symptoms thereof. Moreover, MDS carry an inherent risk of transformation to acute myeloid leukemia (AML) [1]. MDS are a typical disease of the elderly, displaying a median age of 68–75 years at diagnosis [2–4]. Whereas the total annual incidence of MDS is about four cases per 100,000 per year, this rate increases dramatically with advancing age to approximately 40 at the age of ≥70 years [5] and to 50 at ≥80 years [4]. Recent studies suggest a continuously

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increasing incidence of MDS over the last decades, which might be based on raised awareness as well as easier access to referral centers [6]. Importantly, with the aging of societies, the incidence of MDS will increase over the coming decades. In addition, the number of therapy-related MDS (t-MDS) following chemo- or radiotherapy of a primary tumor will increase in the future with the growing number of cancer survivors.

2 The Prevalence and Clinical Relevance of Cytopenias in Elderly

2.1 Anemia

Various cytopenias are a common finding in older individuals. Anemia is the most frequent condition, displaying a mean prevalence of 17 % in individuals aged ≥65 years, as defined by the World Health Organization (WHO) (hemoglobin [Hb] <120 g/L in women and <130 g/L in men [7]). Prevalence of anemia ranges from 12 % in community-dwelling individuals to 47 % in those living in nursing homes [8]. The prevalence rate increases with advanced age, reaching 31 % in individuals aged ≥80 years and 37 % in those aged ≥90 years [9], with men being more frequently affected [10]. Anemia is significantly correlated with increased mortality and hospitalization [11, 12] as well as impaired cognition and limited performance in activities of daily living (ADL) [13, 14]. An estimated 5.0–8.5 % of anemic patients [9, 15, 16] and 17 % of those with unexplained anemia [10] are suspected to suffer from as yet undiagnosed MDS. In light of the profound clinical impact of anemia in the elderly, a thorough diagnostic workup is essential to detect treatable nutritional deficiencies and MDS.

2.2 Thrombocytopenia

Data on the prevalence of thrombocytopenia in the general population are rare. A systematic review by Hui et al. [17] reported prevalence rates between 8 and 68 %. The wide discrepancy most likely resulted from the different thresholds applied in different studies. About 43 % of MDS patients have a platelet count $<100 \times 10^9$/L, and 7 % of such patients have a count of $<20 \times 10^9$/L. Importantly, low platelet counts are significantly associated with shortened survival [18].

2.3 Neutropenia

Neutropenia, defined as a neutrophil count $<1.5 \times 10^9$/L, has a mean prevalence of 1.2 % in a US general population [19]. In lower-risk MDS patients, neutropenia was observed in 7 % [20], and the prevalence of severe infection, defined as sepsis, was increased to 22.5 versus 6.1 % in a reference population [21].

3 Diagnosis of MDS

The diagnosis of MDS is mainly based on the morphologic examination of cells from peripheral blood and bone marrow. A bone marrow biopsy is strongly recommended, as it gives useful information about cellularity, the percentage and localization of CD34+ cells, and the degree of fibrosis [22]. Recommendations on the diagnostic workup and the relevance of laboratory parameters in MDS diagnosis have been summarized recently [22]. Chromosomal abnormalities as assessed by banding analysis are crucial for diagnosis and risk classification. Clonal cytogenetic abnormalities are observed in 50–80 % of MDS patients [23] and are the most relevant prognostic factor defined so far, both in the revised International Prognostic Scoring System (IPSS) IPSS-R [24] and the revised WHO classification-based prognostic scoring system (WPSS-R) [25]. In cases of insufficient bone marrow aspirate or a lack of metaphases, fluorescence in situ hybridization (FISH) can provide cytogenetic information [26]. Other additional tests, like flow cytometry analysis [27] or detection of acquired mutations by single nucleotide polymorphism (SNP) array karyotyping or whole genome sequencing, may provide additional information if MDS is the suspected diagnosis. The routine use of these techniques is not recommended so far.

The term 'idiopathic cytopenia of unknown significance (ICUS) has been introduced to classify cases that do not completely fulfill the criteria for diagnosis of MDS but reveal unexplained cytopenia (Hb < 110 g/L, granulocytes $<1.5 \times 10^9$/L, platelets $<100 \times 10^9$/L) [28]. The category 'idiopathic dysplasia of unknown significance' (IDUS) has been introduced for patients who are characterized by pronounced cellular dysplasia but lack marked cytopenia. Despite ICUS and IDUS being useful categories in the classification of cytopenias and dysplasias in the elderly in daily practice, these terms have not been used in the WHO classification [29] so far.

4 Classification

Classification of MDS is based on the WHO classification that was updated in 2008 [29] (Table 1). WHO subtypes characterized by multi-lineage dysplasia or high blast counts are characterized by an unfavorable outcome [22]. Therapy-related myeloid neoplasm,

Table 1 The World Health Organization classification of myelodysplastic syndromes 2008 [29]

Refractory cytopenias with unilineage dysplasia (RCUD)
Refractory anemia (RA)
Refractory neutropenia (RN)
Refractory thrombocytopenia (RT)
Refractory anemia with ring sideroblasts (RARS; ≥15 % BM ring sideroblasts)
Refractory cytopenia with multilineage dysplasia (RCMD)
Myelodysplastic syndrome unclassified (MDS-U)
MDS associated with isolated del(5q)
Refractory anemia with excess of blasts-1 (RAEB-1; 5–9 % bm blasts)
Refractory anemia with excess of blasts-2 (RAEB-2; 10–19 % bm blasts)

BM bone marrow

including MDS (t-MDS), AML (t-AML), and myelodysplastic/myeloproliferative neoplasms (t-MDS/MPN) are summarized in a distinct subgroup as they represent a unique clinical syndrome. Another subcategory of MDS/MPN includes chronic myelomonocytic leukemia (CMML) and MDS/MPN unclassifiable.

5 Risk Scoring

Prognostic scores provide information on estimated survival times and the risk of progression to AML and thus form the basis for individualized treatment algorithms. The IPSS was developed in 1997 and divides patients into four risk groups with significant differences in overall and progression-free survival [30]. The revised IPSS (IPSS-R) is currently the gold standard in prognostication (Fig. 1) [24]. One of the major achievements of IPSS-R is the refined classification of cytogenetic risk groups and the fact that cytogenetics now play a more relevant role than the other parameters [31]. In addition, thresholds for bone marrow blasts and the classification of cytopenia have been improved, resulting in five prognostic risk groups. An online tool for calculating the score is available at http://www.ipss-r.com. IPSS-R maintains its prognostic significance even at advanced age. Age has a major impact on survival, and this is more pronounced in lower-risk than in higher-risk patients (Fig. 1) [24]. Thus, age has been incorporated as a prognostic parameter, resulting in IPSS-RA (IPSS-R age). In daily practice and in clinical studies, IPSS-low, IPSS-int-1, IPSS-R very low, IPSS-R low, and IPSS-R intermediate are summarized as 'lower-risk MDS', whereas IPSS int-2, IPSS high, IPSS-R high, and IPSS-R very high constitute the 'higher-risk MDS' group.

The WPSS is another well-established predictive score [32]. Included predictive parameters are the WHO subtypes, cytogenetic abnormalities according to IPSS, and red blood cell (RBC) transfusion requirements or hemoglobin levels [33]. The advantage of the WPSS is that it was developed for dynamic use at any time during the course of the disease. An improved version of the WPSS was recently published that incorporates the IPSS-R cytogenetic risk groups [25].

Characteristics	Score values						
	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
Blasts BM, %	≤2	-	>2 - <5	-	5-10	>10	-
Hb (g/dL)	≥10	-	8-<10	<8	-	-	-
Platelets (G/l)	≥100	50-<100	<50	-	-	-	-
Neutrophils (G/l)	≥0.8	<0.8	-	-	-	-	-

Risk groups	Score values
Very low	≤1.5
Low	>1.5 – 3
Intermediate	>3 – 4.5
High	>4.5 - 6
Very high	>6

Age groups, y	Median survival (yrs) / IPSS-R category				
	Very low	Low	Inter-mediate	High	Very high
All	8.8	5.3	3.0	1.6	0.8
≤60	NR	8.8	5.2	2.1	0.9
>60-70	10.2	6.1	3.3	1.6	0.8
>70-80	7.0	4.7	2.7	1.5	0.7
>80	5.2	3.2	1.8	1.5	0.7

Fig. 1 The revised International Prognostic Scoring System [24]. *BM* bone marrow, *Hb* hemoglobin, *IPSS-R* Revised International Prognostic Scoring System

6 Age-Adjusted Models and Geriatric Assessment in MDS Patients

Age-adjusted life expectancy forms the basis for decision making in a given patient. Using survival data from local registries, the remaining life expectancy can be estimated and integrated in decision models [34]. Thus, life expectancy in MDS patients can be predicted by means of well-established prognostic scores like IPSS-R and compared with age- and sex-matched reference populations. In this way, it has been unequivocally shown that a majority of elderly MDS patients lose a considerable number of life-years [2]. However, patient subgroups with an excellent prognosis may be defined and reveal an outcome that is not inferior to that of reference populations [32]. Thus, comparisons of MDS- and age-related life expectancies are useful in the design of patient-orientated therapeutic decisions, ranging from a watch-and-wait strategy to a more aggressive disease-modifying therapy.

To date, prognostication in MDS has relied mainly on disease-related factors like cytogenetics or the percentage of blasts [24, 25, 30, 32]. The integration of patient-related parameters, including comorbidities, physical activities, or nutritional status has just begun. Several studies have analyzed the impact of comorbidities in MDS. Structured comorbidity scores have been applied in most studies, with the Charlson Comorbidity Index (CCI) and the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) being the most frequently used. Overall, comorbidities have been shown to display a high prevalence, with one comorbidity in 25 % and two or more comorbidities in 24 % of cases. The highest frequencies were detected for cardiovascular disease (28 %), diabetes (12 %), and prior tumors (10 %) [35]. Importantly, comorbidities have been shown to negatively impact the overall survival of MDS patients [35–42] and have thus been integrated in combined prognostic scores [38, 39]. Comorbidities have been found to increase the risk of non-leukemic death in lower-risk MDS patients, whereas the prognostic impact of the biology of the disease is of higher impact in higher-risk MDS patients. Comorbidities are relevant in higher-risk patients, as they impact clinical outcome by decreasing eligibility for stem cell transplantation (SCT) and tolerance of chemotherapy regimens [22]. Assessment of comorbidities using a validated score should thus be part of therapy planning and management of MDS patients.

The integration of geriatric assessment (GA) scores as a means of defining biological age and prognosis and predicting vulnerability and tolerance to therapy in MDS has only just begun. GA is a systematic procedure that employs validated tools to evaluate distinct dimensions like functional capacities (ADL [43], Instrumental Activities of Daily Living [44]), objective physical activities (Timed Up and Go [45]), mood (Mini-Mental State Examination [46]), or nutritional status (Mini Nutritional Assessment [47] and G8 [48, 49]). However, data on GA in MDS are rare to date [50]. Promising results concerning the prognostic impact of distinct parameters, namely function, mood, and cognition in MDS, on clinical outcome have been published by Deschler et al. [51]. Furthermore, evaluation by GA may be helpful in predicting toxicity and completion of chemotherapy [52] and in identifying targets for improving treatment tolerance [53]. Using the available evidence, an algorithm was proposed to assign patients to one of the three GA risk categories (fit, vulnerable, frail) [54, 55]. This concept enables clinicians to individually tailor treatment approaches (Table 2).

The individual needs and wishes of the elderly patient population should be integrated in future studies, as expectations and treatment goals may differ. Patient-reported outcomes (PROs), including health-related quality of life (HR-QOL) [56], the improvement and preservation of autonomy and functional capacities [57], and the use of healthcare resources, should be integrated as innovative and relevant clinical endpoints to improve personalized decision making in MDS in the future.

7 Treatment Options in Lower-Risk MDS Patients

The goal of therapy in lower-risk MDS is to treat cytopenias and improve quality of life (Fig. 2). Although the choice of available drugs has expanded considerably, the number of drugs approved for MDS is limited thus far (Table 3).

7.1 Red Blood Cell Transfusions and Iron Chelation

Anemia treatment in MDS is of major relevance, as some 90 % of all MDS patients suffer from anemia [58] and about half of them need RBC transfusions at initial diagnosis [4]. Increased RBC transfusion requirements are associated with dismal prognosis [22]. A recent retrospective study showed that lower hemoglobin levels were associated with reduced survival [33]. The main goal of RBC transfusions is to improve quality of life and avoid anemia-related symptoms. Therefore, specific thresholds for RBC transfusions cannot be recommended. An individual decision must be made for each patient. Hemoglobin levels of 80 g/L can be used as a benchmark. In the presence of comorbidities worsened by anemia, poor functional tolerance, or poor quality of life in still very active elderly patients, a threshold of even 90 g/L or 100 g/L can be used. The goal is to increase the hemoglobin level to

Table 2 Classification of elderly MDS patients based on geriatric assessment

Category	Parameter	Therapy
Go-go/fit	No functional limitation in ADL	Standard therapy similar to younger patients
	No functional limitation in IADL	
	No severe comorbidity	
	No geriatric syndromes[a]	
Slow-go/ vulnerable	No functional limitation in ADL	Attenuated, individualized therapy
	Limitation in ≥1 IADL	
	≤2 comorbidities with no limitation in daily life	
	Moderate impairments in nutritional status[b]	
	No geriatric syndromes[a]	
	Impaired G8 score [48] (≤14)	
No-go/frail	(Age ≅ 85 years[c])	BSC; palliative care; mild, symptom-oriented therapy
	Limitation in ≥1 ADL	
	Limitation in ≥3 IADL	
	≥3 comorbidities in CCI score or less but severe comorbidities with constant limitation in daily life	
	Severe impairments in nutritional status[d]	
	≥1 geriatric syndromes[a]	

Modified from Klepin et al. [53] and Balducci and Extermann [54]

ADL activities of daily living, *IADL* instrumental ADL, *BSC* best supportive care, *CCI* Charlson Comorbidity Index

[a] Geriatric syndromes: dementia, delirium, depression, failure to thrive, neglect or abuse, falls (modified from Sperr et al. [36])

[b] BMI <18 kg/m^2 or recent weight loss 1–3 kg, or moderate loss of appetite or 'at risk of malnutrition' as defined by Mini Nutritional Assessment

[c] A higher upper age limit might be considered

[d] BMI <16 kg/m^2 or recent weight loss <3 kg or severe loss of appetite or 'malnourished' as defined by Mini Nutritional Assessment

>100–110 g/L [59]. RBC transfusions should be kept to a minimum to avoid possible deleterious effects, including iron overload [60].

Iron overload may occur as a consequence of regular RBC transfusions. It has been shown that patients who received at least 70 RBC concentrates had a higher heart iron overload in magnetic resonance imaging (MRI) and an increased risk for heart failure [61]. Retrospective studies suggest that iron chelation therapy can improve survival [62] and even achieve hematologic responses [63]. However, no prospective data are available to date. Recommendations suggest that chelation therapy should be started in transfusion-dependent patients who need more than two RBC concentrates per month or who have stable serum ferritin levels of >1000–2000 ng/ml and a life expectancy of more than 2 years. Chelation is also proposed in patients already suffering from organopathy resulting from iron overload, which further reduces life expectancy [64]. Patients who are possible candidates for SCT should be chelated early, as iron overload before SCT is correlated with increased transplant-related mortality [65]. Administration of iron chelation is facilitated by the availability of oral therapy with deferasirox. However, caution is needed, since deferasirox therapy has been associated with gastrointestinal side effects in about 20 % of patients and with a possible increase in serum creatinine levels [66].

7.2 Erythropoiesis-Stimulating Agents and Other Growth Factors

Erythropoiesis-stimulating agents (ESAs) have demonstrated activity in numerous clinical trials and thus represent the first-line therapy in anemic patients without del(5q). Weekly doses of 30,000–80,000 units of recombinant human erythropoietin or 150–300 μg of darbepoetin alpha achieved erythroid responses in 27–58 % of patients with no evidence of a negative impact on AML transformation and are the treatment of choice [67–69] (Fig. 2). Higher dosages of ESAs (60,000–80,000 units of erythropoietin or 300 μg of darbepoetin alpha per week) showed even higher response rates. In clinical practice, higher doses should be administered in patients not responding to standard doses. An iron, B_{12}, or folate deficiency should be corrected before ESA therapy. Benefits of ESA therapy should be carefully weighed along with safety concerns, including thromboembolic events and arterial

Table 3 Drugs currently approved in myelodysplastic syndromes

Drugs	Approval status	
	EMA	FDA
ESAs	No	No
G-CSFs	No	No
GM-CSFs	No[a]	No
Thrombopoiesis-stimulating agents	No	No
Iron chelation		
Deferasirox	Yes	No
Deferoxamine	No[a]	Yes
Deferiprone	No	No
Hypomethylating agents		
Azacitidine	IPSS Int-2/high	Yes, for all subtypes[b]
Decitabine	No[a]	IPSS Int-1/Int-2/High[b]
Immunomodulating agents		
Lenalidomide	IPSS Low/Int-1 with isolated del(5q)[c]	IPSS Low/Int-1 with del(5q)[c]
Thalidomide	No	No
Immunosuppressive agents		
Cyclosporin	No	No
Anti-thymocyte globulin	No[a]	No

EMA European Medicines Agency, *FDA* US Food and Drug Administration, *ESAs* erythropoiesis-stimulating agents, *G-CSF* granulocyte-colony stimulating factors, *GM-CSFs* granulocyte–macrophage-colony stimulating factor, *int* intermediate, *IPSS* International Prognostic Scoring System

[a] These drugs have not been evaluated by the EMA, but may have been approved at a national level in several EU member states

[b] Indicated for all French–American–British subtypes

[c] In transfusion-dependent patients

hypertension. ESA therapy should continue for 8–12 weeks to evaluate response [70]. The median duration of response is about 2 years. Patients with a transfusion requirement of less than two RBC concentrates per month and an endogenous serum erythropoietin level <500 U/L are more likely to respond to ESAs [71, 72]. Likewise, the parameters <5 % bone marrow blasts and lack of multi-lineage dysplasia are predictive for higher response rates [59].

Addition of granulocyte colony-stimulating factor (G-CSF) can further improve the efficacy of ESAs [72]. A dose of G-CSF 300 μg per week divided into two or three doses should be added if no response is observed after a minimum of 8 weeks of ESA treatment. MDS with ring sideroblasts (RARS) respond exceptionally well to ESAs plus G-CSF and should thus be treated with the combination up front [71].

In MDS patients, neutropenia may occur as a manifestation of the disease per se or as a side effect of disease-modifying treatment modalities. In neutropenic infections, the use of G-CSF is recommended on an interventional basis. In addition, broad spectrum antibiotics should be used immediately when fever or other signs of infection occur.

7.3 Thrombopoiesis-Stimulating Agents

Severe thrombocytopenia is correlated with poor prognosis and shortened survival and limits the administration of effective drugs like lenalidomide or azacitidine [73]. Platelet transfusions are a relevant treatment option. Prophylactic administration is recommended in patients with transient platelet counts $<10 \times 10^9$/L or in patients with platelets $<20 \times 10^9$/L and any other risk factor for bleeding such as fever, infection, or invasive procedure. As platelet transfusions result in allo-immunization with subsequent loss of response, their administration should be limited [74]. Long-lasting and well-tolerated thrombocytopenia does not need prophylactic platelet transfusions [22].

As high immunogenicity limits the clinical use of recombinant thrombopoietin in thrombocytopenic patients, thrombopoiesis-stimulating agents (TSAs) have been

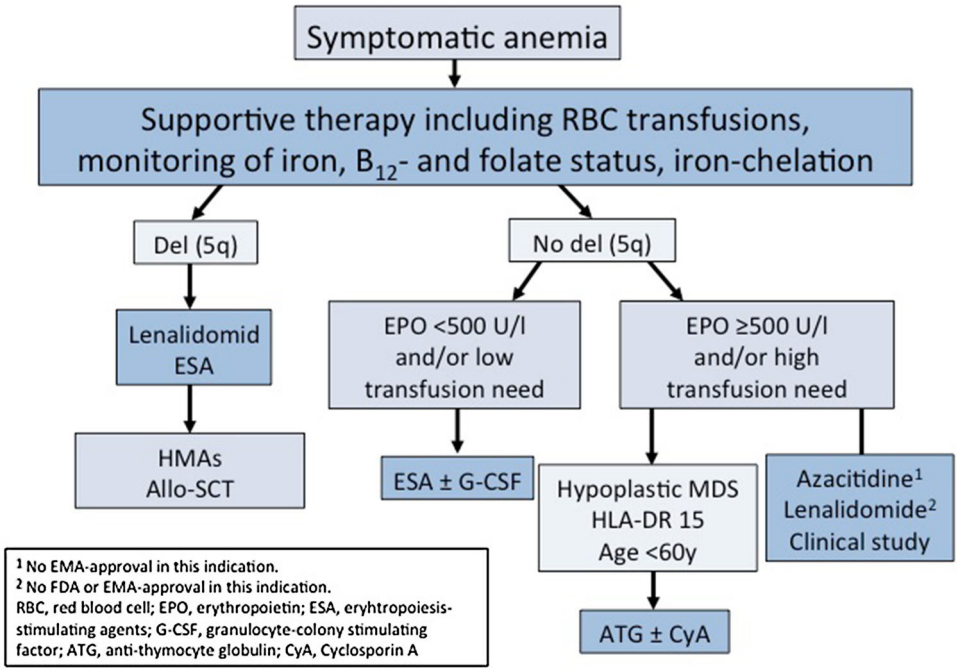

Fig. 2 Treatment options in senior lower-risk myelodysplastic syndrome patients (low to intermediate-1 IPSS; very low, low to intermediate IPSS-R). *ATG* anti-thymocyte globulin, *CyA* cyclosporin A, *EMA* European Medicines Agency, *EPO* erythropoietin, *ESA* erythropoiesis-stimulating agent, *G-CSF* granulocyte-colony stimulating factor, *HLA* human leukocyte antigen, *HMA* hypomethylating agent, *IPSS-R* revised International Prognostic Scoring System, *MDS* myelodysplastic syndrome, *RBC* red blood cell, *SCT* stem-cell transplant. *Number 1* indicates no EMA approval in this indication, *number 2* indicates no FDA or EMA approval in this indication

developed [75]. Romiplostim and eltrombopag are the most frequently administered drugs in MDS trials. TSAs are promising in MDS as monotherapy and as a concomitant therapy to facilitate the use of disease-modifying therapies. TSAs are effective in improving platelet counts and in reducing bleeding and transfusion requirements [76–79]. Interpretation of available data is currently complex, as the cohorts have been relatively small. Rising blast counts and the potential for AML transformation remain a concern and should be evaluated in clinical studies [75, 79]. Thus, the available evidence does not yet allow a general recommendation to be made on the use of TSAs in MDS. TSAs may be considered in patients no longer responsive to platelet transfusions who suffer from the clinical consequences of severe thrombocytopenia, so that a transient rise in blasts may be acceptable [75]. However, in vitro data suggest a dose-dependent anti-leukemic effect of eltrombopag. The first phase I trials using eltrombopag in AML patients are ongoing; further clinical studies are needed [80].

7.4 Lenalidomide

Lenalidomide is the treatment of choice in anemic lower-risk MDS patients with del(5q), as shown by better and longer-lasting responses than ESAs plus G-CSF [81]. An initial dose of lenalidomide 10 mg daily for 3 of every 4 weeks is recommended. Lenalidomide brought about RBC transfusion independence in 65 % of patients, with a median duration of 2.2 years. Cytogenetic response was observed in 72 % of patients, including 45 % complete cytogenetic responses. Positive predictors of survival and decreased risk for progression to AML include Del(5q) as the only cytogenetic abnormality, cytogenetic and/or hematological response, blasts <5 %, and a platelet count above 100×10^9/L [82]. Presence of a *TP53* gene mutation, which occurs in approximately 29 % of patients, is also associated with a higher risk for leukemic evolution as well as resistance to lenalidomide [83]. Grade 3 or 4 neutropenia and thrombocytopenia are the most frequent adverse events in the first weeks of treatment, with less than 20 % of patients discontinuing treatment as a result [84]. The number of adverse events subsequently decreased after the first two cycles [85]. During this time, close monitoring of blood counts with dose reduction and/or addition of G-CSF is strongly recommended.

Lenalidomide achieves RBC transfusion independence in about 25 % of ESA-refractory MDS patients without del(5q) [86, 87]. These response rates have been confirmed in a randomized phase III study [88] and will form the basis for registration for this indication. A higher percentage and a longer duration of response were observed in patients treated with lenalidomide plus ESAs [89, 90]. Prospective trials are needed to confirm these results. In all, lenalidomide is a valuable therapeutic option in anemic ESA-

refractory non-del(5q) patients, although it is not yet registered for this indication.

7.5 Immunosuppressive Drugs

Treatment of patients refractory to ESAs or lenalidomide poses a challenge. Anti-thymocyte globulin (ATG) with or without cyclosporine can yield erythroid responses in about 25–45 % of patients [91, 92]. The rate of responses was higher with ATG plus cyclosporine than with placebo or ATG alone [92]. Factors predictive of a better response to ATG were found to be age <60 years, short duration of RBC transfusion requirement, human leukocyte antigen (HLA)-DR15 phenotype, normal karyotype, <5 % marrow blasts, and hypo-cellular bone marrow [92, 93]. The relevance of ATG in elderly MDS patients is highly limited, because the prerequisites for the therapy are such that elderly patients hardly ever meet them.

7.6 Hypomethylating Agents

Azacitidine yields overall response rates in about 45 % and transfusion independence in 46–61 % of lower-risk MDS patients. It may thus be considered in selected cases of low-risk MDS [94]. However, for low-risk MDS, azacitidine has been registered to date exclusively by the US FDA (Table 3).

7.7 Treatment Options in Higher-Risk MDS Patients

Higher-risk MDS patients exhibit a dismal prognosis, with median survival between 0.4 and 1.5 years and a high risk for AML transformation [24, 30]. Therapeutic options (Fig. 3) should thus aim to modify the natural course of the disease.

7.8 Allogeneic Hematopoietic Stem-Cell Transplantation

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is the only procedure that can possibly cure the disease. Higher-risk disease with increased percentage of marrow blasts and high-risk cytogenetics is a clear indication for allo-HSCT. Low- and intermediate-risk disease with life-threatening cytopenia or transfusion dependency associated with the risk of iron overload can also prompt us to think about moving forward to allo-HSCT. But is allo-HSCT a reasonable therapeutic option for elderly MDS patients? Age per se should not serve as an exclusion factor for allo-HSCT, as new reduced-intensity conditioning regimens allow elderly patients to also be transplanted. More and more older patients—a few up to the age of 70 years—are being included in transplant studies [95]. These studies have shown no statistically significant difference between patients aged below or above 65 years, independent of conditioning regimen [96–98]. Nevertheless, only a very small proportion (<10 %) of patients aged >65 years are definitely going to be transplanted [99].

Outcome of allo-HSCT is strongly influenced by comorbidities [99, 100]. Comorbidities may be defined from assessment scores such as CCI or HCT-CI, although HCT-CI was found to be superior [101–103]. HCT-CI covers different clinical and laboratory-based definitions for a large number of comorbidities, and was found to discriminate different risk groups for prediction of non-relapse mortality, overall survival, and acute graft-versus-host disease (GvHD) and post-GvHD mortality [103, 104]. Co-morbid conditions as important predictors of outcome should be evaluated carefully prior to transplant, especially in elderly MDS patients. The use of performance scales is simple but recommended only in combination with HCT-CI during pre-transplant assessment [105]. Geriatric assessment and frailty measures appear to be of additional importance in determining whether or not a patient should be transplanted, although their prognostic significance has not been adequately tested in the transplant setting. The prospective use of geriatric and quality-of-life assessment in elderly MDS patients has been shown to be predictive of outcome. The combination of functional and symptom parameters measured by Karnofsky, ADL and 'fatigue', was associated with survival [51]. Prospective studies are needed, particularly in the transplant setting.

7.9 Remission-Induction Chemotherapy

Conventional chemotherapy regimens for AML are able to induce complete remissions in only about 35 % of patients with MDS [106, 107]. Long post-chemotherapy neutropenia causes lower remission rates in MDS patients compared with patients with primary AML due to increased rates of infection-related deaths [108]. Induction chemotherapy is thought to be a valid treatment option for patients aged <65 years who may not proceed to allogeneic stem-cell transplantation because of lack of a suitable donor. Additionally, patients should have more than 10 % bone marrow blasts and no adverse cytogenetic risk factors [22].

7.10 Low-Dose Chemotherapy

Low-dose cytarabine (ara-C [LDAC]) and low-dose oral melphalan achieve overall response rates of 30 and 40 %, respectively. However, existing evidence does not allow

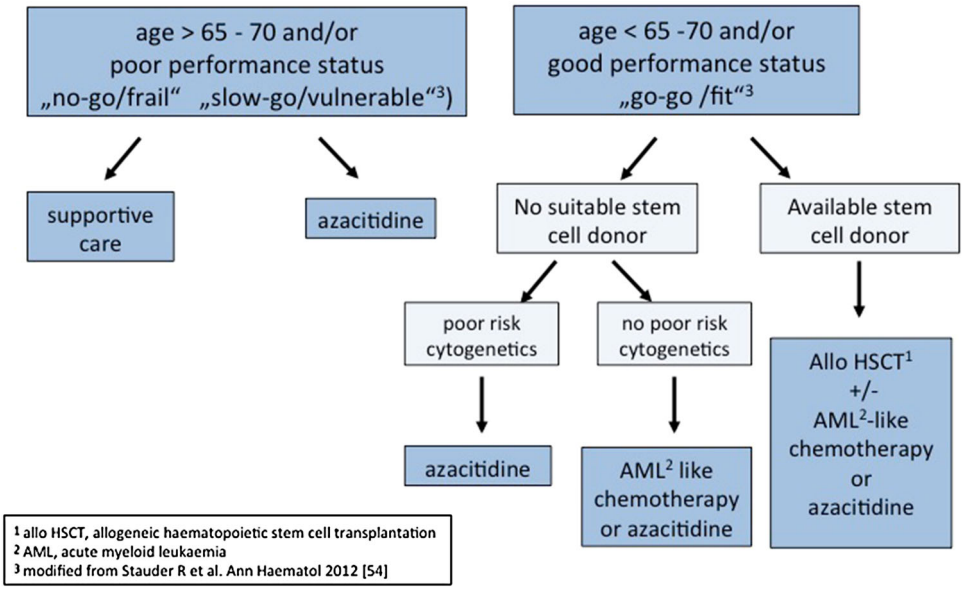

Fig. 3 Treatment options in senior higher-risk MDS patients (intermediate-2 to high IPSS; high to very high IPSS-R). *allo HSCT* allo hematopoietic stem-cell transplantation, *AML* acute myeloid leukemia. Reproduced and modified from Stauder [55]

for recommendation of routine use of these agents in MDS patients [109, 110].

7.11 Hypomethylating Agents

Hypomethylating therapy with azacitidine or decitabine (only FDA approved as yet) is recommended for all higher-risk MDS patients not eligible for allo-HSCT. Azacitidine is the standard of care in higher-risk elderly MDS patients.

Azacitidine was able to produce an overall survival benefit as compared with conventional care regimens (median survival 24.5 vs. 15 months) [111]. A subgroup analysis of elderly patients (>75 years) confirmed efficacy in this particular group. Tolerability of azacitidine is good [112]. Most common hematological grade 3/4 toxicities were cytopenias. Non-hematological toxicities were mainly nausea, vomiting, fatigue, and diarrhea, but these were generally easy to manage. Patients aged ≥80 years can be treated with azacitidine because of its favorable toxicity profile. Response is often achieved after several cycles of treatment, which means administration of at least four to six cycles of azacitidine is recommended before response evaluation. Not only complete or partial remission but also hematologic improvement and stable disease were shown to be associated with prolonged survival [113]. Azacitidine treatment beyond the first response may improve responses. It is therefore recommended that azacitidine be continued in responding patients. Azacitidine 75 mg/m^2 days is administered on days 1–7 of a 28-day cycle. Administration of azacitidine on weekends is often associated with logistic difficulties. Therefore, a regimen of 7 days with a 2-day break (5-2-2) is used. However, recently published data on high-risk patients compared the administration of azacitidine for 5 days (AZA 5) versus AZA 5-2-2 and azacitidine for 7 days (AZA 7). Median response rates and median overall survival seemed to be best in the AZA 7 arm [114]. An oral formulation of azacitidine has recently been developed and showed an overall response rate of 35 % in previously treated patients and 75 % in previously untreated patients [115]. Oral azacitidine is currently being tested in a phase III study.

Only 40–50 % of patients treated with hypomethylating agents achieve hematologic improvement; complete responses are seen in as few as 10–15 % of patients [103]. Therefore, effective methods for identifying those patients who are most likely to benefit from treatment with hypomethylating agents would be of great clinical and economic interest. Platelet count doubling after the first cycle of azacitidine was an early predictor of achieving objective response and overall survival [116, 117]. However, patients without platelet doubling after the first cycle (about 46 %) were also able to later achieve a partial or complete response. Therefore, early discontinuation of azacitidine cannot be recommended at that time. The association of *TET2* mutations with an increased response to hypomethylating agents was shown by Bejar et al. [118] and Itzykson et al. [119]. A prognostic score published by the Groupe Francophone des Myelodysplasies (GFM) showed previous LDAC treatment, bone marrow blasts >15 %, and abnormal karyotype to be associated with lower response rates to azacitidine treatment. Other factors associated with poorer overall survival were complex karyotype, performance status ≥2, intermediate- and poor-risk cytogenetics, presence of circulating blasts, and RBC transfusion dependency ≥4 units/8 weeks. Using these factors, three different subgroups of patients with a distinct prognosis under azacitidine treatment can be discriminated [120].

Nonetheless, patients with high-risk MDS continue to experience high mortality. Overall survival after relapse or failure of azacitidine treatment is still low at about 6 months [121]. The multi-kinase inhibitor rigosertib showed encouraging results in a phase I clinical trial in patients with MDS [122]. The first analysis of phase III data for rigosertib versus best supportive care in MDS patients who have progressed on or failed or relapsed after azacitidine or decitabine treatment seems to show a better median survival for patients in the rigosertib group [123]. No standard treatment is available for patients not responding to azacitidine or with diminishing response to azacitidine. Therefore, treatment within clinical trials is highly recommended. Decitabine achieved a longer median time to AML progression and death in patients with higher-risk MDS but was not able to show a survival benefit [124]. Retrospective comparative analyses demonstrated significantly better survival in patients treated with azacitidine than with decitabine [125, 126]. The use of decitabine is limited, as it is, as yet, not licensed by the European Medicines Agency (EMA) for the treatment of MDS patients (Table 3).

Efforts to improve treatment of higher-risk MDS are ongoing. A combination of multiple classes of medications (hypomethylating agents, histone deacetylase inhibitors, tumor necrosis factor [TNF]-alpha inhibitors, bortezomib, classical chemotherapeutic agents) in individual patients seems to produce promising results [127–131]. Randomized trials comparing standard monotherapy and combination therapies are needed to establish the significance and possible use of combinations, especially in elderly patients.

8 Future Aspects

Demographic changes in Western countries will cause the incidence of MDS to increase in the near future. Allo-HSCT, the only potentially curative treatment option, is available for only a minority of MDS patients. Reduced-intensity regimens and improved management of side effects may increase the proportion of elderly patients successfully transplanted. Instruments to better stratify patients for allo-HSCT versus supportive treatment are urgently needed. Prevention of cytopenia-related morbidity and preservation of quality of life are the main issues in MDS patients not fit for HSCT. Promising new drugs, including hypomethylating agents and growth factors, will improve the treatment options in elderly MDS patients. A new group of antagonists of activin receptor signaling (sotatercept, luspatercept, dalantercept) increases RBCs markedly in murine models as well as in healthy volunteers. First data in patients with MDS seem to be very promising. Phase III studies are currently planned.

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Compliance with Ethical Standards

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