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Myelodysplastic Syndromes: Aspects of Current Medical Care and Economic Considerations in Germany

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Key Words

Myelodysplastic syndromes · Erythrocyte transfusion · Geriatrics · Burden of illness · Quality of life

Summary

Myelodysplastic syndromes (MDS) are a heterogeneous group of diseases mainly affecting older people. The use of an increasing number of therapeutic options depends on a systematic risk stratification of the patients. A high percentage of MDS patients need blood transfusions as supportive care, which influence quality of life and cause a great part of the costs generated by MDS therapy. In this article which is based on a workshop about the burden of MDS held in October 2006 in Munich, MDS is discussed with regard to different aspects: current therapies, transfusion medicine, geriatrics, quality of life, and health economic aspects.

Schlüsselwörter

Myelodysplastische Syndrome · Erythrozytentransfusion · Geriatrie · Krankheitskosten · Lebensqualität

Zusammenfassung

Myelodysplastische Syndrome (MDS) sind eine heterogene Gruppe von Erkrankungen, die hauptsächlich ältere Menschen betreffen. Welche der inzwischen verfügbaren therapeutischen Optionen eingesetzt werden sollte, hängt von einer systematischen Risikostratifizierung der Patienten ab. Ein hoher Prozentsatz von MDS-Patienten benötigt Bluttransfusionen als unterstützende Therapie, welche die Lebensqualität beeinflussen und einen großen Teil der Kosten der MDS-Therapie verursachen. Dieser Beitrag basiert auf einem Workshop mit dem Titel «MDS – Burden of Disease» (Oktober 2006 in München), und befasst sich mit der Erkrankung unter therapeutischen, versorgungsrelevanten und gesundheitsökonomischen Gesichtspunkten.

Introduction

Myelodysplastic syndromes (MDS) encompass different hematological conditions characterized by chronic cytopenia (anemia, thrombocytopenia, neutropenia) and abnormal cellular maturation of hematopoiesis. Patients with MDS are at risk of symptomatic anemia, bleeding complications, and infections [1]. Another life-threatening factor is progression to acute leukemia in approximately 20% of the patients, which is often refractory to treatment compared to de novo acute myeloid leukemia (AML) [2, 3]. MDS are clonal disorders of the pluripotent hematopoietic stem cells resulting in different forms of cytopenia of peripheral blood cells. The bone marrow is at the same time hypercellular, normocellular, or, in rare cases, hypocellular, and often shows morphological changes in all cell lines. The contrast between peripheral blood cytopenia on the one hand, and normal or increased bone marrow cellularity on the other hand, is attributable to ineffective hematopoiesis, with a large proportion of precursor cells dying prematurely in the bone marrow. This mainly occurs through apoptosis. However, it is still unclear which intrinsic or external factors trigger the high rate of apoptosis. In more than 90% of cases, the etiology of the disease is unknown. Secondary MDS is linked to prior treatments with intensive chemo- or radio-

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Table 1. WHO classification of myelodysplastic syndromes (MDS) (based on [58])

Subtype	Blood	Bone marrow
Refractory anemia (RA)	anemia; no or rare blasts	erythroid dysplasia only, < 5% blasts; < 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	cytopenias (bicytopenia or pancytopenia); no or rare blasts; no Auer rods; $< 1 \times 10^9$/l monocytes	dysplasia in ≥ 10% of cells in ≥ 2 myeloid cell lines; < 5% blasts; no Auer rods; < 15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	anemia, no blasts	erythroid dysplasia only, < 5% blasts; ≥ 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	cytopenias (bicytopenia or pancytopenia); no or rare blasts; no Auer rods; $< 1 \times 10^9$/l monocytes	dysplasia in ≥ 10% of cells in ≥ 2 myeloid cell lines; < 5% blasts; no Auer rods; ≥ 15% ringed sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	cytopenias; < 5% blasts, no Auer rods; $< 1 \times 10^9$/l monocytes	unilineage or multilineage dysplasia; 5% to 9% blasts; no Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	cytopenias; 5–19% blasts; Auer rods ±; $< 1 \times 10^9$/l monocytes	unilineage or multilineage dysplasia 10% to 19% blasts; Auer rods ±
Myelodysplastic syndrome, unclassified (MDS-U)	cytopenias; no or rare blasts; no Auer rods	unilineage dysplasia in granulocytes or megakaryocytes; < 5% blasts; no Auer rods
MDS associated with isolated del (5q)	anemia; < 5% blasts; platelets normal or increased	normal to increased megakaryocytes with hypolobated nuclei; < 5% blasts; no Auer rods; isolated del (5q)

therapy. Chromosomal alterations, especially deletions of genes which are crucial for cell growth, differentiation, and signal transduction in hematopoietic stem cells (e.g. on chromosomes 1, 5, 7, 11, 13, 20), play an important role [4].

There are no typical early symptoms of MDS. Patients present with fatigue, petechial bleeding, or frequent infections due to the different forms of cytopenia. However, in elderly patients anemia and MDS are often diagnosed accidentally when patients are treated for a different disease. MDS is diagnosed by morphological and cytochemical analysis of peripheral blood and bone marrow, as well as cytogenetic and molecular biological analysis of the bone marrow aspiration. Bone marrow biopsy with immune histochemistry and immune phenotyping of the aspiration by fluorescence-activated cell sorting (FACS) are additional techniques. Other underlying causes resulting in the clinical picture of MDS such as alcohol and drug abuse, medication, or prior chemo- and or radiotherapy should be sought. Furthermore, vitamin B12, folic acid, and copper deficiency should be excluded [5, 6]. Patients with MDS have been classified into subgroups according to the French-American-British (FAB) consensus conference in 1982 [7]. The current form of classification is a modification of the FAB consensus by the World Health Organization (WHO) as shown in table 1.

Epidemiology and Risk Stratification

MDS are a relatively common hematological disorder. It is a disease of elderly patients, and it is rarely found in adolescents or young adults. The average age at diagnosis is between 65 and 70 years. The MDS registry at Düsseldorf has been collecting patient data in Germany for a long time. Reviewing this data base, an overall incidence of MDS of 5/100,000 inhabitants per year was revealed. The incidence increases rapidly in the older patient groups, and reaches 20–50 cases per 100,000 inhabitants in the group older than 70 years. These data are comparable to the estimated incidence in the industrialized world. Men develop MDS slightly more often than women and are even predominant in the older patient groups. Although the incidence in different age groups did not change when surveying a longer period of time, the future will bring an increase in the total number of MDS patients. The major contributing factor is the 'graying society', the increasing average age in the populations of the western world. Improved diagnostics (cytogenetics and molecular biological techniques) and a more precise diagnostic approach in anemic old or geriatric patients will possibly reveal formerly undefined MDS patients. Improvement and innovations in MDS therapy and supportive therapy may lead to a prolonged lifetime of these patients, linked with longer disease time and prolonged need for transfusions. Furthermore, there might be an increase in secondary MDS forms due to more aggressive chemotherapies in different malignant diseases.

The FAB classification and the WHO standard helped to systematically classify this heterogeneous disease but were less useful in determining the prognosis [8]. Reviewing the survival data from previous reported studies, variables were considered in a new way to form the 'International Prognostic Scoring System' (IPSS). The percentage of marrow blasts, specific cytogenetic abnormalities, and the number of cytopenias were used in combination to define 4 risk groups for overall survival and progression to AML: low, intermediate-1, intermedi-

Table 2a. International Prognostic Scoring System (IPSS): percentage of marrow blasts, specific cytogenetic abnormalities, and number of cytopenias were used in combination to define 4 risk groups for overall survival and progression to AML

Prognostic variable	Survival and AML evolution – score value				
	0	0.5	1.0	1.5	2.0
Marrow blasts, %[a]	< 5	5–10	–	11–20	21–30
Karyotype	good	intermediate	poor		
Cytopenia	0/1	2/3			

[a]Patients with 20–30% blasts may be considered as MDS or AML.
MDS = Myelodysplastic syndromes; AML = acute myeloid leukemia.

Table 2b. International Prognostic Scoring System (IPSS): resulting risk groups [13, 59]

Risk category	% of IPSS population	Score	Median survival in absence of therapy, years	25% AML progression in absence of therapy, years
Low risk	33	0	5.7	9.4
Intermediate risk-1	38	0.5–1.0	3.5	3.3
Intermediate risk-2	22	1.5–2.0	1.2	1.1
High risk	7	> 2.5	0.4	0.2

AML = Acute myeloid leukemia.

Table 3. Düsseldorf score: patient distribution in risk groups and survival (n = 1,636)

Risk	Patients, %	Survival, months
Low	15	71
Intermediate	57	27
High	28	7

ate-2, and high [9] (table 2a, b). The analysis of patient data from the MDS registry in Düsseldorf showed an average survival time of between 7 and 62 months depending on the risk stratification of the patients. On the basis of the collected data, other prognostic variables such as the lactate dehydrogenase (LDH) serum level were taken into account to develop the Düsseldorf score for the prognostic determination of MDS subgroups [10–12]. The Düsseldorf score (table 3) consists of 3 risk groups: low (0 points), intermediate (1–2), and high (3–4). The following 4 variables get 1 point if present: hemoglobin level < 90 g/l, platelets < 100 G/l, LDH elevated, blasts in marrow > 5%.

Due to a similar disease course and prognosis, patients with high-risk MDS according to IPSS can be considered as already having AML when it comes to treatment decisions. It is important to note that most patients with MDS, even those with IPSS intermediate risk-2, will die due to bone marrow failure rather than transformation to AML.

Treatment Options in MDS

Due to the fact that MDS comprises a very heterogeneous group of patients, treatment of MDS should be adjusted individually to every patient. There are 4 major therapeutic goals: control of symptoms caused by cytopenia, improvement of quality of life, improvement of overall survival, and decrease of progression towards AML [9]. The therapeutic approach should be based mainly on 3 features: age, performance status, and the IPSS-defined risk category [13].

Allogeneic hematopoietic stem cell transplantation (SCT) is the only curative chance for patients with MDS. Due to the aggressiveness of the treatment in the past, the age of the patient had to be below 60 years. New non-myeloablative regimens extended the approach into the group of 60–70-year-old patients. However, a lot of preconditions have to be fulfilled: age, performance status, a matched donor, general health status, and a risk group of intermediate-1 or higher. Only an estimated 5% of MDS patients are eligible for this approach. Despite the curative chance, transplantation- and relapse-related mortality is relatively high and results in a 5-year survival of between 40 and 60% [14]. If no donor is available, in younger patients at high risk, intensive chemotherapy according to an AML protocol is an alternative to SCT.

Supportive care is the central component for all MDS treatments, and it is the only essential option for the majority of the patients due to advanced age, comorbidities, and the chronic course of MDS. Cytopenia, especially anemia, is one of the major findings in MDS. At least 70% of patients will become transfusion-dependent during the course of the disease. If thrombocytopenic bleeding occurs, platelet transfusions are needed. Patients should be treated with antibiotics for infection especially when neutropenic. Supportive care also comprises the treatment of other concomitant problems (e.g. heart and lung disease).

Hematopoietic growth factors may be used in MDS, however, a low or decreasing responsiveness is seen in a lot of cases; e.g. recombinant human erythropoietin (EPO) alone leads to a response rate (defined as increasing or stable hemoglobin concentration without the need for transfusion) of only 10–20% of MDS patients [15]. However, the synergistic combination with granulocyte colony-stimulating factor (G-CSF) leads to elevated response rates in defined patient subgroups, e.g. 70% in patients with low endogenous EPO levels (< 200 mU/ml), low transfusion need, and an IPSS low or intermediate-1 [16–18]. Further, the Nordic MDS Group sees a potential benefit in combining the two growth factors in the defined subgroups [19]. One reason might be the change in the response criteria (IWG2000 vs. IWG 2006), but further studies are needed.

Immunosuppressive drugs such as antithymocyte globulin (ATG) and cyclosporine can be used in patients with hypocellular bone marrow. In these patients, immune-mediated marrow suppression might play a major role in the etiology of the disease [20–24].

Thalidomide has been used as an antiangionetic immunomodulatory drug with inconsistent effects, low response rates, and severe side effects (e.g. fatigue, neuropathy) [25, 26]. Lenalidomide is an orally administered immunomodulatory derivative of this substance without the typical side effects. In a phase II study with transfusion-dependent, erythropoietin-refractory patients, it has shown response rates of 56% (no transfusions or reduction of more than 50%). Most of the patients had an IPSS low or intermediate-1. The best results were seen in patients with del(5q), where even cytogenetic responses were achieved [27, 28].

Low and intermediate intensity chemotherapeutic agents are used in patients with intermediate or high IPSS. DNA methyltransferase (DNMT) inhibitors include azacitidine and decitabine. 5-azacitidine has been tested in a phase III trial and showed 7% complete response (CR), 16% partial response (PR), and hematological improvement in 36% of the patients [29]. Decitabine showed an overall response rate of 17% (including 9% CRs), and additionally 13% of hematological improvement in patients treated in a phase III trial. There was a trend towards longer median time to progression to AML [30]. Both substances exert their antineoplastic effect by hypomethylation of DNA and direct toxicity on hematopoietic cells. They are supposed to induce re-expression of tumor suppressor genes. The substances are tested in further trials. Cytarabine plays a minor role due to low remission rates.

New drugs have been introduced in trials and MDS therapy, including arsenic trioxide, oral farnesyltransferase inhibitor, inhibitors of tumor necrosis factor alpha, and anti-angiogenesis agents such as anti-VEGF as well as histone deacetylase (HDAC) inhibitors such as valproic acid [31, 32].

Several new drugs have been developed for the treatment of MDS, however, not all are yet approved in Europe for this indication. Although clinical trials could show promising results, further studies have to be conducted to show the long-term benefits regarding response rates, overall survival, and quality of life, as well as potential adverse effects and cost effectiveness.

Transfusion Medicine Focusing on MDS

Patients with MDS are a challenge for transfusion medicine. The previous chapter has shown that cytopenias are the result of ineffective dysplastic hematopoiesis. The majority of these patients need transfusions, especially of red blood cells (RBC). To guarantee an optimal supply for transfusion-dependent patients, a sufficient number of RBC units must be stored at any time in the transfusion center. Calculating an average need of 24 RBC units per MDS patient per year [33], the enormous need in this single patient group connected to relevant costs becomes obvious. While the number of MDS patients will increase in the next years, the supply of blood products will become more difficult, because blood products and donors are getting rare due to the demographic development. On the other hand, the aging population needs more transfusions, not only in MDS but in other chronic diseases and for surgical procedures. Since blood cannot be synthesized in the laboratory (yet), blood products remain 'special goods', and the indication for every single transfusion should be checked carefully. Consequently, from a general point of view, in transfusion medicine every therapy minimizing the need for transfusion in a certain indication is important to minimize the transfusion-related risks for the patient on one side, and on the other side to save valuable provisions of blood as an (emergency) supply for other patients.

Iron Overload

The safety of blood products has been increased over the past. In addition, leukoreduction combined with irradiation of the depleted product helped to minimize leukocyte-mediated complications of transfusions such as febrile transfusion reactions, platelet isosensitization, viral infections, and immunosuppression (even though irradiated erythrocyte concentrates are not recommended for MDS patients in general [34]). However, the iron overload in transfusion-dependent patients is one problem of the supportive therapy which cannot be abolished. The iron overload results in secondary hemochromatosis which can cause cardiac, hepatic, and endocrine malfunctions. Patients with an expected prolonged transfusion need, especially those with an IPSS low or intermediate-1, should be considered for iron chelation therapy [35]. In high-risk patients, the benefit will be minimal due to their short survival time. A serum ferritin level of > 1,000 µg/l, a high transfusion rate, and the expected duration of transfusion need are important parameters for the decision about treatment with iron chelators. Deferasirox, an easily applicable oral chelation therapy, is now available. It may be difficult to compare survival in patients with or without chelation therapy, since the relationship between iron overload, high ferritin, RBC transfusions, and shorter survival is not completely understood. Generally, it can be stated that long-term RBC transfusion has a negative effect on quality of life and survival in MDS patients [36].

MDS in Germany and Transfusion Dependency

Based on the data from a literature review, approximately 50% of MDS patients are transfusion-dependent across all risk groups [37]. In Germany, between 3,800 and 5,400 MDS patients needed transfusions in 2005. The number will increase due to an estimated increase in the number of MDS patients of approximately 6% per year. By the year 2010, the disease will occur in between 10,000 and 14,000 patients. Table 4 correlates the transfusion dependency of MDS patients in Germany with their IPSS score. Due to the lack of published

Table 4. MDS patients in Germany according to risk score and transfusion dependency; due to lack of published prevalence data for Germany, a lower [38] (scenario 1) and a higher scenario [39] (scenario 2) of patient numbers were calculated

Risk group	MDS patients			Transfusion-dependent MDS patients		
	Patients, % [13]	Scenario 1: patients, n	Scenario 2: patients, n	Patients, mean n [37]	Scenario 1: patients, n	Scenario 2: patients, n
Low	33	2,423	3,465	39	945	1,351
Int-1	38	2,790	3,990	50	1,395	1,995
Int-2	22	1,615	2,310	63	1,018	1,455
High	7	514	735	79	406	581
Total	100	7,343	10,500	51[a]	3,764	5,382

[a]Weighted average in % of transfusion-dependent MDS patients considering all risk groups; source: calculations by the Medical Economics Research Group (MERG), Munich, Germany. MDS = Myelodysplastic syndromes; Int = intermediate.

Table 5. Quality of life studies in myelodysplastic syndrome patients

Authors, year [Ref.]	Country	Study type	Sample size	Data source/methods	Results
Caocci et al., 2006 [49]	Italy	cross-sectional	33	QLQ-C30	QoL can be improved by lowering the amplitude of hemoglobin fluctuations
Stasi et al., 2005 [50]	Italy	phase II study	53	LASA FACT-AN	statistically significant correlation between increased hemoglobin levels and increased QoL for the responder group
Oliva et al., 2005 [51]	Italy	cross-sectional	39	Specific questionnaire QOL-E	QoL in MDS patients is influenced by transfusion dependency
Casadevall et al., 2004 [15]	France	randomized clinical trial	60	FACT-AN	QoL did not improve significantly under rHuE PO + RHuG-CSF
Clavio et al., 2004 [52]	Italy	prospective, open-label, unicentric, non-randomized	11	FACT-AN	erythroid response appeared to be clinically correlated with the improvement of QoL: higher hemoglobin levels increased QoL
Spiriti et al., 2004 [53]	Italy	open-label, prospective, multicenter trial	133	FACT-AN	QoL did improve under treatment with EPO
Hellstrom-Lindberg et al., 2003 [17]	Sweden	decision model	63	QLQ-C30	QoL did improve significantly under treatment
Jansen et al., 2003 [54]	The Netherlands	cross-sectional	50	SF36 MFI Euro QoL-5D VAS	the 3 internationally established methods proved to be useful in describing HRQoL in MDS patients

QoL = Quality of life; MDS = myelodysplastic syndromes; EPO = erythropoietin; rHuEPO = recombinant human erythropoietin; RHuG-CSF = recombinant human granulocyte colony-stimulating factor; HRQoL = health-related quality of life.

prevalence data for Germany, a lower [38] and a higher scenario [39] of patient numbers were calculated.

MDS and Geriatric Medicine

The elderly people in a population are a very heterogeneous group sharing the common features of a reduced life expectancy and reduced physiological organ function. The functional abilities are decreasing whereas the number of comorbidities is increasing with higher age. This results in different medications for different diseases, leading to a variety of pharmacodynamic and pharmacokinetic changes. Anemia, the unspecific finding at the beginning of a diagnostic process, is often incidentally diagnosed in routine blood tests. The prevalence of anemia is increasing with age: 8% of the people older than 65 years and 15–20% of those in the group older than 85 years are anemic. A variety of studies identified anemia as risk factor for mortality [40–44]. Not only is the prevalence of anemia increased in older age groups, but the risk for developing a malignant disease increases as well [45]. A study from a geriatric department has shown that in 5% of elderly patients with anemia, MDS is the underlying disease [46]: 'early forms' of MDS such as refractory anemia (RA) and refractory cytopenia with multilineage dysplasia (RMCD) are those predominant in geriatric patients [47]. Generally, anemia is a frequent finding in geriatric patients. A sufficient search for the cause is not always undertaken, so the number of MDS cases is actually probably underdiagnosed. This group of patients is not well studied, and literature describing outcome and quality of life is not available.

Table 6. Cost studies of transfusion in myelodysplastic syndrome patients

Authors, country, year [ref.]	Type of study	Scope	Study population	Perspective	Transfusion costs
Gupta et al., USA, 1999 [57]	retrospective record analysis	to assess the costs and potential complications of supportive (transfusion) care in MDS patients	50 male MDS patients diagnosed between 1992 and 1997	hospital	transfusion cost/patient/year during MDS phase US$ 1,614 (according to official procurement prices for American Red Cross blood products); US$ 4,877 (according to published average costs at US teaching hospitals)
Casadevall et al., France, 2004 [15]	clinical trial	to evaluate health, costs, and quality of life within 2 treatment groups of MDS patients	60 patients with low-grade MDS and serum EPO levels lower than 500 IU/l	French healthcare payer and hospital	treatment with rHuEPO + rHuG-CSF: € 6,200 transfusion cost and € 27,754 total cost per patient; best supportive care: € 7,148 transfusion cost and € 7,846 total cost per patient
Goss et al., USA, 2006 [60]	decision analytic model	cost-effectiveness study with a 1-year time horizon; comparison of lenalidomide with BSC without EPO vs. BSC with EPO	transfusion-dependent MDS patients	private payer in the US	annual cost per patient under lenalidomide treatment: US$ 7,574 transfusion cost and US$ 63,385 total treatment cost; under supportive care: US$ 18,101 transfusion cost and US$ 54,940 total treatment cost

MDS = Myelodysplastic syndromes; EPO = erythropoietin; rHuEPO = recombinant human erythropoietin; RHuG-CSF = recombinant human granulocyte colony-stimulating factor; BSC = best supportive care.

Focusing on Inpatient and Outpatient Treatment of MDS in Germany

Patients with either an unclear anemia or a supposed or already diagnosed MDS should be treated by a specialist for hematology and oncology. The therapy often requires cooperation between in- and outpatient departments for hematology/oncology at hospitals and hematologists in office-based practices.

As described earlier, patients often present with unspecific symptoms, or anemia is diagnosed in a routine blood analysis. A profound disease history and clinical examination is followed by a blood analysis. Different causes of anemia must be excluded; a bone marrow aspiration including a cytogenetic examination helps to find the diagnosis. If MDS has been diagnosed, the patient has to be risk stratified with IPSS, age, and performance status, and has to be informed about possible therapeutic strategies. Regarding the chronicity of the disease and the often limited life expectancy in MDS, the primary goal is to facilitate an outpatient treatment and minimize hospital admissions. However, a patient diagnosed with advanced-stage MDS spends 16% of his remaining life time in a hospital [48]. Red cell transfusions (RCT) and, if necessary, transfusion of platelets can be given in the outpatient departments of hospitals as well as in the office-based setting. The need for RCT is not strictly defined by a certain hemoglobin level, but is related to the subjective findings of the patient and dependents on comorbidities (e.g. heart disease). Due to strict laws and guidelines concerning the use and quality of blood products in Germany, this best supportive care for MDS patients is connected with high costs.

The Burden of MDS: Quality of Life and Health Economic Aspects

Existing quality of life studies in MDS patients use generic instruments due to the lack of a specially developed quality of life questionnaire covering MDS (table 5). Two aspects seem to be important for the quality of life of the patients: first, a higher hemoglobin level, which means probably less fatigue and a more active life; second, a decreased need for transfusions, which means fewer visits to the doctors' office and less restrictions in daily life [15, 17, 49–54]. Results of health utility interviews with MDS patients show that patients associate a high hemoglobin value with achieving transfusion independence, generating new health utility values to be used in economic evaluations that compare the health outcomes of therapies in quality-adjusted life years (QALYs) [55]. In elderly compared to younger cancer patients, presence of anemia is independently associated with poor quality of life in addition to poor performance status [56]. However, a more interven-

tion-specific research on quality of life of MDS patients is demanded to better meet patients' needs in the future [13].

Table 6 summarizes the very few international studies analyzing the costs of MDS, but focusing mainly on the direct costs of anemia and transfusion dependency [15, 57]. An RCT for an individual patient causes costs on every step of the production chain: donation-related direct and indirect costs, expenses for transportation and compatibility tests, costs for material and staff during the transfusion itself, costs for administration and organization of a transfusion medicine department, and expenses for the ongoing improvement and the guarantee of high quality standards. Adding up these costs, the current price of an RBC unit in Germany is 85–150 Euros. Consequently, the cost of RCTs for transfusion-dependent MDS patients in Germany ranges approximately between 7.8 and 20 million Euros per year, or from 1,500 to 5,300 Euros per patient and year. Analyzing these expenses in detail will reveal that MDS patients cause even more costs because of more frequent transfusion-related complications [57]. Additionally, it has to be taken into consideration that there are not only costs for the blood units but also in- or outpatient costs depending on hospitalization or ambulatory treatment for transfusions.

Identifying the real costs of MDS is difficult due to the complexity and heterogeneity of the disease. A first step should be an MDS cost analysis, identifying the resources used and the costs generated by MDS symptoms and therapies: i) anemia (including RCTs, adverse transfusion reactions and complications, iron overload and chelating therapy, the hematopoietic growth factors rHuEpo and G-CSF); ii) thrombocytopenia (therapy of bleeding complications and platelet transfusions); iii) neutropenia (diagnosis and therapy of infections with antibiotics and antifungal medication); iv) hematopoietic stem cell and bone marrow transplantation; v) intensive and intermediate chemotherapy and its side effects; vi) treatment of unwanted side effects of the primary intervention; vii) influence of MDS and its therapy on comorbidities (e.g. cardiac, pulmonary, vascular disease). All these aspects can only be realized in a complex economic model which does currently not exist for MDS. It could be an important step forward in optimizing the individual therapy of the patient, by treating the disease effectively, reducing the need for supportive care (especially transfusions), and improving quality of life. In a second step, cost effectiveness or cost utility analysis should be conducted, taking quality of life into account. These tools help to identify the advantages (benefit/value) and the disadvantages (costs) of a procedure in a defined period of time monetarily or in relation to quality of life. The results, such as costs per treatment or costs per QALY, can help decision makers, e.g. medical practitioners, hospital managers, or sickness funds, to decide rationally on their limited resources. Asking questions on effectiveness and using evaluation tools do not contradict good quality medical care but must be seen as instruments for fairer resource allocation. Particularly in oncology, innovative pharmacological treatment options which might seem expensive at first glance often offer the only chance to improve survival and quality of life of the patients.

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