Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-296 Luspatercept

Stand: Januar 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Luspatercept **[Behandlung von Erwachsenen mit transfusionsabhängiger Anämie aufgrund von myelodysplastischen Syndromen (MDS)]** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Die allogene Stammzelltransplantation kommt grundsätzlich als nicht-medikamentöse Behandlung im vorliegenden Anwendungsgebiet in Betracht.[1]
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Luspatercept: Beschluss vom 2. November 2023
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

[1] Zu dieser Behandlungsmethode wurde bisher keine Methodenbewertung durchgeführt.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Luspatercept B03XA06 Reblozyl	Geplantes Anwendungsgebiet: Reblozyl wird angewendet für die Behandlung von erwachsenen Patienten mit transfusionsabhängiger Anämie aufgrund von myelodysplastischen Syndromen (MDS) mit sehr niedrigem, niedrigem oder intermediärem Risiko.
Antimetabolite	
Azacitidin L01BC07 Vidaza	Vidaza ist angezeigt zur Behandlung von erwachsenen Patienten, die für eine Transplantation hämatopoetischer Stammzellen (HSZT) nicht geeignet sind und eines der folgenden Krankheitsbilder aufweisen: - myelodysplastische Syndrome (MDS) mit intermediärem Risiko 2 oder hohem Risiko nach International Prognostic Scoring System (IPSS)
Eisenchelatoren	
Deferasirox V03AC03 Exjade	EXJADE ist auch angezeigt zur Behandlung der chronischen, transfusionsbedingten Eisenüberladung, wenn eine Deferoxamin-Therapie bei folgenden Patientengruppen kontraindiziert oder unangemessen ist: – bei Kindern im Alter zwischen 2 und 5 Jahren mit Beta-Thalassämia major mit Eisenüberladung auf Grund häufiger Transfusionen (≥ 7 ml/kg/Monat Erythrozytenkonzentrat), – bei Erwachsenen, Kindern und Jugendlichen im Alter von 2 Jahren oder älter mit Beta-Thalassämia major mit Eisenüberladung auf Grund seltener Transfusionen Transfusionen (< 7 ml/kg/Monat Erythrozytenkonzentrat), – **bei Erwachsenen, Kindern und Jugendlichen im Alter von 2 Jahren und älter mit anderen Anämien**.
Deferoxamin V03AC01 Desferal	Behandlung der chronischen Eisenüberladung, z. B. – Transfusionshämosiderosen, insbesondere bei Thalassaemia major, sideroblastischer Anämie, autoimmunhämolytischer Anämie **und anderen chronischen Anämien**; – […]

Erythropoese stimulierende Faktoren (ESF)	
Epoetin alfa B03XA01 Erypo	ERYPO wird angewendet zur Behandlung der symptomatischen Anämie (Hämoglobinspiegel ≤ 10 g/dl) bei Erwachsenen mit primären Niedrigrisiko Myelodysplastischen Syndromen (MDS) (niedrig oder intermediär-1) und niedrigen Erythropoetin-Serumspiegeln (< 200 mU/ml).
Epoetin zeta B03XA01 Retacrit	Retacrit wird angewendet zur Behandlung der symptomatischen Anämie (Hämoglobinspiegel ≤ 10 g/dl) bei Erwachsenen mit primären Niedrigrisiko Myelodysplastischen Syndromen (MDS) (niedrig oder intermediär-1) und niedrigen Erythropoetin-Serumspiegeln (< 200 mU/ml).
Tyrosinkinaseinhibitoren und Immunmodulatoren	
Imatinib L01EA01 Glivec	Imatinib ist angezeigt zur Behandlung: - von Erwachsenen mit myelodysplastischen/myeloproliferativen Erkrankungen (MDS/MPD) in Verbindung mit Genumlagerungen des PDGF-Rezeptors (platelet-derived growth factor).
Lenalidomid L04AX04 Revlimid	Myelodysplastische Syndrome Revlimid als Monotherapie ist indiziert für die Behandlung von erwachsenen Patienten mit transfusionsabhängiger Anämie infolge myelodysplastischer Syndrome mit Niedrig- oder Intermediär-1-Risiko in Verbindung mit einer isolierten Deletion 5q als zytogenetische Anomalie, wenn andere Behandlungsoptionen nicht ausreichend oder nicht angemessen sind.
Erythrozytenkonzentrate (EK)	
Erythrozyten-konzentrat n. a. n. a.	Anwendungsgebiete sind akute und chronische Anämien. Für die Indikation zur Erythrozytentransfusion lassen sich keine universell anwendbaren unteren Grenzwerte für Hämoglobin oder Hämatokrit festlegen. Die Ursache der Anämie soll möglichst geklärt werden und, falls möglich, eine kausale Therapie eingeleitet werden. Die Entscheidung für die Transfusion von Erythrozyten oder für eine andere, gleichwertige Therapie ist abhängig vom klinischen Gesamtzustand des Patienten.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-296 (Luspatercept)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	11. Dezember 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AML	akute myeloische Leukämie
ATG	Antithymocyte globulin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	ECRI Guidelines Trust
ESA	Erythropoiesis-stimulating agents
G-CSF	Granulocyte-colony stimulating factor
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
Hb	Haemoglobin
HCT	Hematopoietic Cell Transplantation
HCT-CI	Hematopoietic Cell Transplantation–Comorbidity Index
HgB	Hemoglobin
HMA	Hypomethylating agents
HSCT	hematopoietic stem cell transplantation
IPSS	International Prognostic Scoring System
LDAC	Low-dose cytarabine
LoE	Level of Evidence
MAC	myeloablative conditioning
MDS	Myelodysplastische Syndrome
MDT	Multidisciplinary team meeting
NICE	National Institute for Health and Care Excellence
OS	Overall survival
RBC	Red blood cell
RIC	reduced-intensity conditioning
SIGN	Scottish Intercollegiate Guidelines Network
TPO	Thrombopoietin
TPO-RA	Thrombopoietin receptor agonists
TRIP	Turn Research into Practice Database
TRM	transplant-related mortality
WBC	White blood cell
WHO	World Health Organization

1 Indikation

Erwachsenen Personen mit transfusionsabhängiger Anämie aufgrund von myelodysplastischen Syndromen (MDS)

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *myelodysplastisches Syndrom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.ecosia.org/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 14.11.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 331 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 2 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.3 Leitlinien

Killick S et al., 2021 [2].

British Society for Haematology guidelines for the management of adult myelodysplastic syndromes

Zielsetzung/Fragestellung

The objective of these guidelines is to provide healthcare professionals with clear guidance on the management of adult patients with MDS.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: Betroffene waren am Review der Leitlinie, allerdings nicht an deren Erstellung beteiligt.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche. Auswahl und Bewertung der Evidenz unklar: Laut Publikation basiert die Einschätzung der „quality of evidence“ auf einer Bewertung mittels GRADE. In diese Einschätzung fließt regelhaft eine Einschätzung des Biasrisikos ein. Ergebnisse der Biasrisikobewertung sind der Publikation nicht zu entnehmen.
- Formale Konsensusprozesse nicht beschrieben, externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Pubmed from 2012 to December 2020

LoE / GoR

The BSH Guidelines Committee uses the GRADE nomenclature for evaluating levels of evidence and assessing the strength of recommendations in all Guidance. Details are available at: http://www.gradeworkinggroup.org/index.htm

Quality of Evidence and criteria for assigning the quality of evidence
The quality of evidence is graded as high (A), moderate (B), low (C) or very low (D).

Type of evidence	**Randomized trial = high (A)** **Observational study = low (C)** **Any other evidence = very low (D)**
Decrease* grade if	• Serious or very serious limitation to study quality • Important inconsistency • Some or major uncertainty about directness • Imprecise or sparse data • High probability of reporting bias *Each quality criteria can reduce the quality by one or, if very serious, by two levels
Increase grade if	• Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) • Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2) • Evidence of a dose response gradient (+1) • All plausible confounders would have reduced the effect (+1)

In general:
(A) High: further research is very unlikely to change our confidence in the estimate of effect
(B) Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
(C) Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
(D) Very Low: any estimate of effect is very uncertain

Strength of Recommendation
Strong (grade 1): Strong recommendations are made if clinicians are certain that benefits do, or do not, outweigh risks and burdens. Grade 1 recommendations can be applied uniformly to most patients and words such as "recommend", "offer" and "should" are appropriate.

Weak (grade 2): Weak recommendations are made if clinicians believe that benefits and risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks. In addition, clinicians are becoming increasingly aware of the importance of patient values and preferences in clinical decision making. When, across the range of patient values, fully informed patients are liable to make different choices, guideline panels should offer weak recommendations. Grade 2 recommendations require judicious application to individual patients and words such as "suggest" and "consider" are appropriate.

Empfehlungen

Supportive care

Supportive care should be offered to all patients with MDS and symptomatic cytopenias (1A).

Red cell transfusions should be given to improve symptomatic anaemia (1A).

Policies for transfusion, including haemoglobin thresholds for red cell transfusion, should take clinical factors into consideration, including patient-related factors (1A).

Matching for Rh, K or additional antigens should be offered in line with current BSH Guidelines for patients expected to receive regular red cell transfusions (2C).

Local policies should be in place for the management of neutropenic sepsis (1A).

Patients with stable MDS not receiving intensive chemotherapy and without signs of bleeding should not be offered prophylactic platelet transfusions (1A).

TPO receptor agonists may be used to reduce bleeding events in thrombocytopenic patients with low or intermediate-1 risk MDS (1A).

Management of anaemia with transfusion

Red cell transfusion dependency is associated with decreased overall and leukaemia-free survival in MDS, and reduced quality of life (QoL).[5–7] Transfusion therapy is associated with well-recognised complications including risks of alloimmunisation. [8,9] Antibodies to Rh and K antigens appear the most common,[10] but the exact role and cost effectiveness of extended red cell phenotyping remains unknown and local practices vary.[11] Irradiated blood products are recommended after a stem cell transplant or treatment with antithymocyte globulin (ATG), in keeping with the current BSH Guidelines on the use of irradiated blood components.[12]

Although the severity of anaemia has a major impact on QoL in MDS patients,[13] the degree to which this may be ameliorated by different policies for red cell transfusion is not known. Clinicians may choose to apply a policy for red cell transfusion that is individualised and targeted to symptoms, although in practice specific haemoglobin (Hb) thresholds are often applied. A common haemoglobin threshold of around 80 g/l was identified by a UK national audit, a survey in Australia[14] and findings from the European MDS Registry (EUMDS).[13] The only randomised trial of transfusions in MDS patients compared two transfusion thresholds (80 g/l, to maintain Hb 85–100 g/l against 105 g/l, maintaining 110–125 g/l).[15] In an exploratory analysis, the five main QoL domains were improved for participants in the liberal compared to restrictive arm.

Management of neutropenia and infection

National Institute for Health and Care Excellence (NICE) has published guidelines for the prevention and management of neutropenic sepsis in cancer patients (CG151 published September 2012).[16] The use of prophylactic granulocyte-colony stimulating factor (G-CSF) may be considered in patients with recurrent infections who have low-risk MDS and may be used (with prophylactic antibiotics) to support the delivery of azacitidine in selected higher-risk patients.

Although a randomised centre study showed that in patients undergoing chemotherapy, posaconazole prevented invasive fungal infections more effectively than did either fluconazole or itraconazole and improved overall survival (OS),[17] there is no evidence to suggest that this should be routinely given to all patients with MDS. The American Society of Clinical Oncology and Infectious Diseases of America guidelines suggest that a mould-active triazole is recommended for patients who are at risk of profound, protracted neutropenia (defined as <01 9 109/l ≥ 7 days, or other risk factors).[18]

Management of thrombocytopenia and bleeding

There is common but variable practice of platelet transfusion in MDS. There are no similar studies in MDS, but a retrospective study in patients with stable chronic severe aplastic anaemia described a 'no-prophylaxis' platelet transfusion approach.[19–21] Avoiding unnecessary platelet transfusions in patients without signs of bleeding reduces the need for outpatient attendance improving QoL and may reduce the risk of platelet refractoriness. Patients with chronic thrombocytopenia presenting with bleeding of World Health Organisation (WHO) grade 2 or above should receive platelet transfusions.

Alternative agents to platelet transfusions include the antifibrinolytic drug tranexamic acid and should be considered as a symptomatic measure in mucous membrane bleeding in appropriate patients with MDS, although randomized trial evidence is lacking.[22]

Thrombopoietin receptor agonists (TPO-RA), specifically romiplostim and eltrombopag, have been evaluated in randomized placebo-controlled studies in both low-risk MDS and high-risk MDS (the latter in combination with either chemotherapy, hypomethylating agents or lenalidomide).[23–29] There were fewer bleeding episodes and fewer platelet transfusion episodes in the romiplostim arm in the Low/INT-1 study, although this study was halted prematurely because of concerns about increasing blast cell counts in patients receiving active drug.[25] A subsequent meta-analysis of several such studies did not find a significant difference in transformation to AML between intervention with TPO-RAs and placebo.[30] A moderate reduction in bleeding events compared with placebo controls was noted, but with no improvement in mortality. Ongoing studies are evaluating the safety and efficacy of eltrombopag in Low/INT-1 MDS with severe thrombocytopenia (<30 9 109/l), and interim analysis has shown platelet responses in 47% of the eltrombopag group compared to 3% in the placebo group.[31]

Although their use in high-risk MDS cannot be recommended, the results are promising for TPO-RA with platelet responses in low or intermediate-1 risk MDS (47–65%).[24,31] TPO-RA are not currently licenced for

use in MDS and although these agents should ideally be accessed within clinical trials, the overall safety data now with longer follow-up is reassuring.

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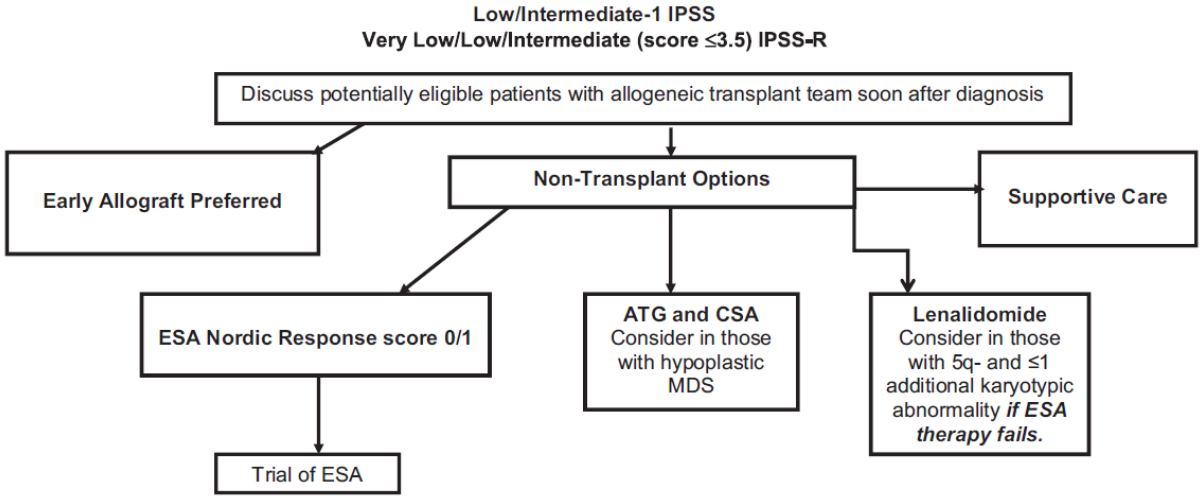
Management of low-risk MDS

Algorithm for the management of low-risk MDS



ATG, antithymocyte globulin; CSA, ciclosporin-A; ESA, erythropoiesis-stimulating agent; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome

Patients with IPSS Low and Intermediate-1 (or IPSS-R very low, low or intermediate with a score up to 3.5) MDS with symptomatic anaemia, or asymptomatic anaemia and Hb < 100 g/l and who fulfil the criteria for a high or intermediate predictive Nordic score for response should be considered for a trial of therapy with an ESA (1A).

For maximum benefit, ESA treatment should be started as soon as appropriate after diagnosis of MDS and before established transfusion dependence (for maximum benefit) (1B).

Patients should receive a maximum trial period of 24 weeks of therapy. This should comprise eight weeks at the starting dose of ESA, a further eight weeks at the higher doses, if required, and finally with the addition of G-CSF for a further eight weeks, before considering the patient to have failed ESA therapy (2B).

Patients achieving a complete or partial erythroid response by accepted criteria should continue on long-term therapy at the minimum dose of ESA required to maintain the response or until the response is lost (2B).

The haemoglobin concentration should not be allowed to rise above 120 g/l (2C).

Erythropoiesis-stimulating agents

It is only recently that randomised controlled trials for erythropoiesis-stimulating agents (ESAs) have been performed in the EU[32,33] and these have led to the European licence of EPO-a (Eprex), but not darbepoetin (Aranesp), for the treatment of symptomatic anaemia (haemoglobin ≤ 100 g/l) in adults with IPSS Low- or INT-1 primary MDS who have low serum EPO levels (<200 iu/l). There is a suggestion of survival advantage for responders to ESA therapy, especially if they are non-transfused prior to starting ESA,[34–36] and improvements in global QoL scores for responders.[32,37,38]
Who should be offered ESA therapy? ESA therapy is considered first-line standard of care for appropriately selected low-risk MDS patients who should have pretreatment variables that predict a response. The validated Nordic score, shown in Table I, has been widely used.[37] An alternative model is the ITACA scoring system.[39] As the Nordic model more effectively identifies likely non-responders, it remains the preferred model.
ESA therapy should be considered in patients with low or INT-1 IPSS (or IPSS-R very low, low or intermediate with a risk score of up to 3.5), in the context of symptomatic anaemia and Hb < 100 g/l. If patients are symptomatic from anaemia at a higher Hb, then starting an ESA is at the clinician's discretion. Patients should fulfil criteria predictive of response by the Nordic score (score 0–1). There are data to suggest that starting ESA therapy within six months of diagnosis improves response rates and delays the onset of transfusions (80 vs 35 months).[34,40] Patients with higher-risk MDS should not generally be considered for ESA therapy because of poor responses, short survival and the likely use of hypomethylating agents and stem cell transplantation, which require red cell transfusion support.

Initial treatment
Treatment should be initiated with EPO-a or darbepoetin alone in all patients. The recommended starting dose for EPO-a is 30 000–40 000 units subcutaneous once weekly for eight weeks (mds-europe.eu).[32,41] If there is no response at eight weeks, the dose can be increased to a maximum dose of 60 000 units/week (divided over one or two doses) for a further eight weeks. Doses of >60 000 units/week are not supported by scientific evidence. The starting dose for darbepoetin should be 300 µg once every 14 days or 150 µg once every seven days (mds-europe.eu).[42,43] This can be increased after eight weeks in non-responders to a maximum of 300 µg per week for a further eight weeks.[44] The starting dose in the randomised Phase 3 study33 was 500 µg once every three weeks. However, 81% of patients had an increase in the dose to 500 µg every two weeks in the open-label period leading to a higher erythroid response. The starting dose of EPO-a or darbepoetin in low body weight with stable anaemia and always in the case of reduced renal function should be lower (mds-europe.eu).
Finally, it is recommended that all patients receive incremental therapy with ESA alone for 16 weeks, as above, and G-CSF is then added to the higher dose in all non-responders for a final eight-week trial.[45,46] G-CSF should be given to approximately double the starting white cell count (WBC) if <1.5 x 10^9/l, or keep the WBC in the range 6–10 x 10^9/l. A starting dose of 300 µg per week or in 2/3 divided doses, rising to 300 µg three times per week in non-responders, is appropriate. However, the dosing regimen should be tailored to individual patients according to need and response. Response monitoring, criteria for response and long-term therapy. Response criteria for defining response[37] are as follows:

- Complete erythroid response: achievement of Hb > 115 g/l and transfusion independence.
- Partial erythroid response: >20 g/l increment in Hb and transfusion independence, but Hb remains <115 g/l.

Some patients may achieve potentially beneficial longer gaps between transfusions, although this is not a formally recognised response criterion.
The risk of thrombosis in MDS patients responding to darbepoetin has been estimated at 2%[42] and between 0.3 and 1.1% in meta-analysis.[45] However, in the randomised trial of EPO-a there were no grade 3–4 thrombo-embolic or stroke episodes in 85 treated patients.[32] In the darbepoetin randomized controlled trial,[33 24] weeks of darbepoetin produced no new safety signals and only one thromboembolic event (PE) in the darbepoetin group. Although the risk of thrombosis is low, it seems appropriate to temporarily interrupt ESA therapy if there is a rapid rise in haematocrit, or if the Hb rises above 120 g/l. Lower doses can then be introduced with careful monitoring of response parameters.

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Iron chelation in MDS

All suitable lower-risk patients (IPSS low and intermediate-1; IPSS-R low and very low) should be considered for iron chelation therapy at the time they have received 20 units of red cells, or when the ferritin is more than 1 000 lg/l (1B).

Iron chelation therapy should be considered in patients prior to stem cell transplant, if time allows (2C).

Expert opinion is that deferasirox (although only licensed second line in MDS) is the drug of choice based on tolerability, compliance and mature safety data (2C).

Deferiprone is not routinely recommended in MDS (2C).

Iron chelation therapy with deferasirox should be stopped if the ferritin falls below 500 lg/l and desferrioxamine should be stopped if the ferritin falls below 1 000 lg/l (2C).

Patients with MDS are at risk of developing iron overload from transfusion of red cells where iron build-up is inevitable (one unit of red blood cells delivers 200–250 mg iron), and there is also increased intestinal absorption of iron driven by ineffective erythropoiesis,[48] mostly relevant to MDSRS. Excessive iron ultimately leads to secondary end organ damage and cardiac disease remains the main non-leukaemic cause of death in MDS.[49,50]

Iron overload is associated with adverse outcome in MDS.
Retrospective studies have shown that OS is significantly shorter in transfusion-dependent MDS patients either through cardiac deaths, hepatic cirrhosis[51,50] or increased leukaemic progression.[50] The European LeukemiaNet MDS Registry showed that the risk of death in transfusion-dependent patients with detectable labile plasma iron levels is independent of risk of disease progression.[52] Iron overload also increases transplant-related mortality in haematopoietic stem cell transplantation (HSCT) in MDS patients[53] and total transfusion burden implied a worse prognosis in a European Society for Blood and Marrow Transplantation (EBMT) study.[54]

Measuring iron loading
Routine estimations of iron loading can be made by serial monitoring of ferritin and tracking of red cell units transfused. However, there is little correlation between units transfused, or serum ferritin, and the degree of organ iron deposition.
Magnetic resonance imaging (MRI) for R2 (liver proton relaxation rate),[55] or cardiac and liver T2* assessments[56] can be used to help quantify hepatic and cardiac iron loading and its impact on organ function.

Iron chelation can improve natural history
Effective iron chelation may improve haemopoiesis. The EPIC study[57] and the GIMEMA group[58] showed an International Working Group (IWG) erythroid response in 15–25% of patients although median response duration was only eight weeks in the EPIC study. Platelet and neutrophil responses were also reported.
Desferrioxamine has been shown to lower cardiac iron assessed by MRI measurements[59] and deferasirox has been shown to improve alanine transaminase (ALT) levels.[60] A German registry study showed that chelation therapy improved survival in almost 200 transfused lower-risk MDS patients,[61] supported by prospective data from the EUMDS registry.[62] Furthermore, it is now accepted that iron chelation prior to HSCT in congenital anaemia can improve transplant-related mortality.[53] Although this is not yet proven to be the case in haematological neoplasms including MDS, a recent EBMT joint expert panel recommended chelation in patients who have received more than 20 units of blood prior to HSCT.[63]

Choice of iron chelator
Desferrioxamine remains the most efficient iron chelator available and is given subcutaneously in overnight infusions, which may decrease the labile iron pool. However, many patients find it uncomfortable and cumbersome, reporting QoL issues. Deferasirox and deferiprone are given orally and are generally well tolerated, although deferiprone is associated with agranulocytosis in around 4% of patients. Deferiprone should not be used routinely in patients with MDS, and only after careful consideration with a haematologist experienced in treating MDS. It should be undertaken with very careful monitoring (weekly blood counts), and should not be used where the baseline neutrophils are $<1.5 \times 10^9$/l.
Deferasirox is the only iron chelator currently licensed for use in MDS patients with proven reduction in labile iron and improved haemopoiesis in some patients.[57,64]

Discussion of recommendations
Iron chelation in lower-risk MDS patients. It is recommended that all suitable lower-risk patients (IPSS low and intermediate-1; IPSS-R low and very low) should be considered for iron chelation therapy around the time they have received 20 units of red cells, or when the ferritin is more than 1 000 lg/l. Patients should have ferritin levels measured every 12 weeks and have ophthalmological and auditory examinations before commencing therapy and annually while on treatment. Iron chelation with deferasirox should be stopped if the ferritin falls below 500 lg/l and desferrioxamine should be stopped if the ferritin falls below 1 000 lg/l.

Iron chelation in higher-risk MDS patients
Patients who are considered suitable for HSCT should have iron levels monitored and iron chelation therapy given prior to transplant, if time allows.

Drug recommendations
Deferasirox is only licensed second line (after desferrioxamine) for the treatment of chronic iron overload due to blood transfusions in patients with anaemia, such as MDS. However, real-world experience is that deferasirox is better tolerated, compliance is far superior and safety data are now mature. For these reasons, expert opinion is that deferasirox is the drug of choice for transfusion-related iron overload in patients with MDS. Desferrioxamine remains an option in those resistant to or intolerant of deferasirox.
The two drugs may be combined in exceptional circumstances with heavy cardiac iron overload, but only under the supervision of a haematologist experienced in MDS treatment, although there are no data to support the combination.
There is no contra-indication to the use of iron chelation in combination with other disease-modulating treatments such as lenalidomide or azacitidine.

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MDS associated with del(5q)

Patients with IPSS Low or INT-1 or IPSS-R with a score <3.5 and MDS with del(5q) and symptomatic anaemia and who fulfil the criteria for a high or intermediate predictive score for response, should be first considered for a trial of therapy with ESAs (1B).

For transfusion-dependent patients unsuitable for a trial of ESAs, and for non-responders and patients losing their response to ESAs, who have IPSS Low or INT-1 MDS with del(5q), consider treatment with lenalidomide 10 mg daily for 21 days repeated every 28 days after careful discussion with the patient about risk and benefit (1B).

Selected MDS patients with del(5q) and IPSS Low/INT-1 or IPSS-R with a score <3.5 may be candidates for allogeneic stem cell transplantation. These include lenalidomide-treated patients who fail to achieve transfusion independence, those losing their response, and patients with transfusion dependence not considered suitable for lenalidomide (2B).

Lenalidomide is not currently recommended for patients with del(5q) and bone marrow blasts >5% or multiple (complex) cytogenetic abnormalities in addition to del(5q) (neither of which fall into this diagnostic category) or patients with IPSS INT-2/high (2B).

MDS with isolated del(5q) is a distinct diagnostic entity that features macrocytic anaemia, normal or high platelet count, characteristic non-lobulated megakaryocytes and <5% bone marrow blasts. A single additional cytogenetic abnormality other than -7 or -7q is permitted within this diagnostic category. It is associated with female preponderance and has a relatively indolent natural history, with a median survival of six years in those with an IPSS score of 0.65 Independent predictors for OS include transfusion dependence, age and thrombocytopenia.[66]

Responses of patients with del(5q) MDS to ESA are inferior to that seen in low-risk MDS patients lacking del(5q) (39% vs 52%).[67,68] Nonetheless, given the established safety and efficacy data for ESA, ESA should be first-line therapy for symptomatic anaemia in lower-risk MDS patients with del(5q).

The MDS004 study compared lenalidomide with placebo in low and INT-1 transfusion-dependent MDS with del(5q); 58%, 42% and 6% of patients receiving lenalidomide 10 mg, 5 mg or placebo, respectively, achieved transfusion independence.[69] Cytogenetic responses were also seen in the lenalidomide treatment groups. Lenalidomide is licensed for transfusion-dependent low/INT-1 MDS with isolated del(5q) (with up to one abnormality other than -7/7q) and is recommended for NHS commissioning (NICE TA322) for such patients who have failed or are unresponsive to ESAs.

Concerns about the risk of progression to AML with lenalidomide have not been confirmed in retrospective studies, [70,71] post-MDS-004 study monitoring,[72,73] or a recent meta-analysis.[74] Rather, improved survival and reduced risk of transformation have been shown. Nonetheless, the MDS-004 study showed that progression to AML was 40% at five years compared to historically reported data of 20%. Follow-up studies have demonstrated that clonal evolution from existing or acquired TP53 mutations result in higher rates of AML transformation in del(5q) MDS patients.[75–77] However, some TP53-mutated cases with del(5q) have durable (2–3 years) responses to lenalidomide. Thus, TP53 mutation is not a contra-indication to lenalidomide therapy, but requires careful discussion and monitoring in this subgroup. Thromboprophylaxis should be considered on an individual basis.

Selected patients may be candidates for allogeneic stem cell transplantation. Indications include:

- Intolerance to or unsuitable for lenalidomide.
- Lenalidomide-treated patients who fail to achieve transfusion independence.
- Those with TP53 mutation.
- Those with clonal or overt progression.
- Those with bone marrow fibrosis.

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Allogeneic haematopoietic stem cell transplant in MDS

All transplant-eligible MDS patients should be discussed with a transplant physician at a MDT both at diagnosis and at disease progression (2B).

Additional prognostic factors such as transfusion burden, depth of cytopenias, cytogenetics and BM fibrosis should be assessed when considering the optimal timing of transplant for lower-risk MDS patients (2B).

Higher-risk MDS patients with >10% blasts may be considered for cytoreductive therapy or hypomethylating agents prior to transplant (2B).

Up-front transplant may be considered in patients with 5–10% blasts with slowly progressive disease or in those with a hypocellular or fibrotic BM (2B).

Transplant is not routinely recommended for patients with TP53 mutation in association with a complex monosomal karyotype due to poor outcomes (2B).

Eligibility for transplant should be guided by HCT-CI and EBMT risk score (2B).

Performance status and age should be used to inform choice of myeloablative or reduced-intensity conditioning (2B).

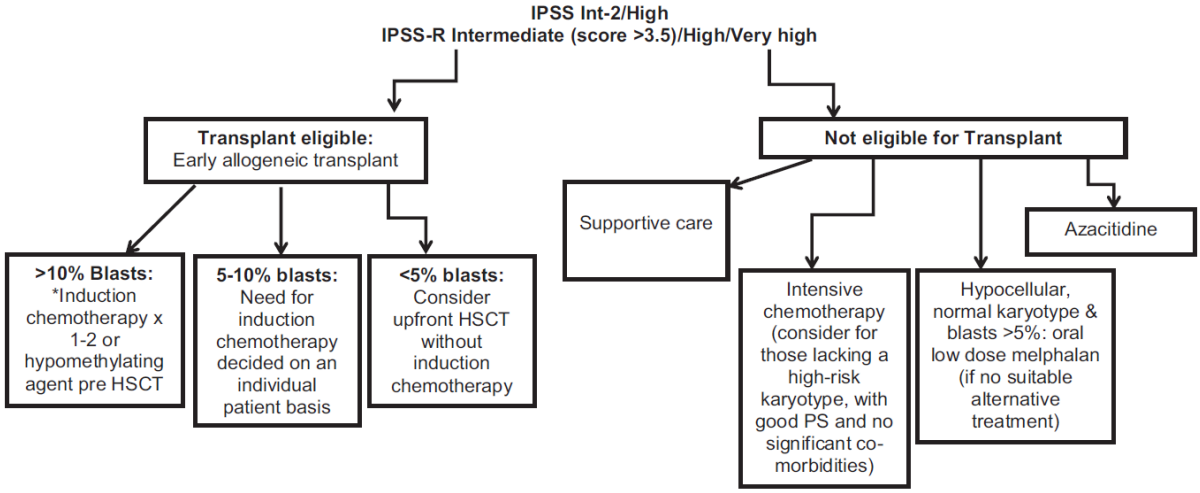
All transplant-eligible MDS patients should be discussed with a transplant physician at a MDT, both at diagnosis and with disease progression. The decision to transplant should be made on a case-by-case basis, evaluating patient, donor and disease factors known to influence transplant outcomes.[101]

Factors influencing timing and decision to transplant
Lower-risk MDS
The optimal time to transplant patients with lower-risk MDS remains an area of debate. Early transplant for the lowest-risk patients is generally not recommended due to subsequent reduction in life expectancy.[102–104]
To help guide decision-making, particularly in the IPSS INT-1 group, the ELN/EBMT guidelines[63] recommend the use of other poor prognostic factors such as transfusion dependency (≥2 units of blood per month),

significant cytopenias, e.g. platelet count <30 x 10^9/l, neutrophils <0.3 x 10^9/l, or very poor prognostic cytogenetics. Transfusion dependence, elevated ferritin and labile plasma iron levels correlate with increased transplant-related mortality (TRM) in MDS patients following transplantation.[50,105–107]
Transplant should be considered once the patient becomes transfusion-dependent, before iron overload occurs. However, if there is a delay to transplant then iron chelation should strongly be considered.
Patients with progressive disease such as increasing blast cells or acquisition of adverse cytogenetic abnormalities should be considered for transplant.[63] Therapy failures, for example to ESAs or lenalidomide, convey a worse prognosis and should prompt consideration of transplantation.[108,109] Furthermore, patients with isolated del(5q) and an associated TP53 mutation have a worse prognosis and greater chance of failing lenalidomide therapy.[75,77] Such patients should be considered for transplantation early in their disease course.[110]
Patients with MDS and severe bone marrow (BM) fibrosis experience worse outcomes following HSCT compared with mild/moderate fibrosis, or those lacking fibrosis.[111] As such, the presence of BM fibrosis should prompt early transplant consideration, ideally prior to progression to severe fibrosis.

Management of high-risk MDS

Algorithm for the management of high-risk MDS



IPSS, international prognostic scoring system; IPSS-R, IPSS-revised; HSCT, haematopoietic stem cell transplant; PS, performance status. *Where possible, patients should be offered entry into a clinical trial

High-risk patients NOT eligible for allogeneic transplant

Patients requiring treatment should be considered for any appropriate clinical trial.

In fit older patients lacking an adverse karyotype, the options of therapy with a hypomethylating agent versus intensive chemotherapy should be carefully discussed. Where intensive chemotherapy outside a clinical trial is planned, standard AML induction regimens should be used (2B).

Azacitidine is the preferred hypomethylating agent and is recommended as first-line therapy for patients ineligible for stem cell transplant with IPSS Intermediate-2 and high-risk MDS (IPSS-R Intermediate (score >3.5)/high/very high-risk groups) or AML with 20–30% blasts. Grade 1A (on the basis of a single randomised control trial).

The recommended dose of azacitidine is 75 mg/m2 daily for seven consecutive days but a 5–2–2 schedule (with a two-days weekend gap) is acceptable where it is not practical to offer seven consecutive days and outcomes with the two schedules appear comparable (2B).

Outcomes of patients treated with azacitidine in routine clinical practice show a considerably shorter OS than the pivotal clinical trial (12.4–18.9 months compared to 24.5 months). Patients should be made aware of this.

Responding patients should continue azacitidine while their response is maintained (1A).

The decision to stop or continue azacitidine in patients who fail to achieve any response after six cycles, but who have stable disease, is dependent upon clinician and patient preference (2B).

Patients failing therapy with hypomethylating agents should be considered for any appropriate clinical trial.

Intensive chemotherapy for patients ineligible for allogeneic HSCT

For patients not eligible for transplantation, intensive AML-style chemotherapy can be used in an attempt to achieve disease response and improve survival. Patients should be entered into clinical trials where possible. The advantages of intensive chemotherapy are the QoL improvement if complete remission (CR) is achieved, and the small possibility of long-term disease-free survival.

There have been reported cases of long-term survival (>4 years) in patients with high-risk MDS and lacking an unfavourable karyotype.[82] However, older patients frequently have comorbidities, making intensive regimens less well tolerated. Overall, remission rates are lower (40–60%) than in de novo AML, remission duration is often shorter (median duration 10–12 months) and therapy-related complications of marrow aplasia (infection and haemorrhage) more frequent.[82–85]

Analysis of 160 patients over the age of 60 years with high-risk MDS or AML showed an early death rate of 10% and an inability to deliver consolidation chemotherapy in 40 of the 96 (42%) patients who achieved CR.[84] Compared to those with a normal karyotype who had a median survival of 18 months, those with a high-risk karyotype (involving 3 or more unrelated abnormalities or chromosome 7 abnormality) had a median survival of four months. The largest study of intensive chemotherapy for high-risk MDS broadly supports these data.[86] For this reason, it is recommended that cytogenetic results are available before committing to intensive chemotherapy in older patients with MDS, as there is no evidence to suggest this delay in treatment would be detrimental.[87]

Disease-modifying agents in high-risk MDS

Hypomethylating agents (azacitidine, decitabine) offer an alternative to intensive treatment in high-risk MDS. They are not curative but may result in transfusion independence, improved QoL and survival benefit and are well tolerated in the elderly and in patients with comorbidities.

Azacitidine is recommended by NICE and the Scottish Medicines Consortium as a treatment option for adult patients with MDS not eligible for HSCT (IPSS INT-2 or High) and for AML with 20–30% blasts and lineage dysplasia. The recommended dose is 75 mg/m^2 for seven consecutive days, repeated at 28-day intervals.

The AZA001 study[88] showed that azacitidine significantly increased OS compared to conventional-care regimens (median OS 24.5 vs 15.0 months).[88] Azacitidine also resulted in haematological responses; 45% of patients became transfusion-independent compared to 11% receiving conventional care. In a subgroup analysis of patients ≥75 years, azacytidine also significantly improved two-year OS compared to conventional care (55% vs 15%), suggesting that this is the treatment of choice in older higher-risk MDS patients with good performance status.[89]

Even patients with poor-prognosis cytogenetic profiles may benefit from azacitidine treatment.[90] Reliable molecular predictors of response have not been identified, although patients with poor-prognosis indicators, including TP53 mutations, may respond. However, the presence of increasing numbers of mutations may be associated with a lower likelihood of response.[91]

Practical guidance for the delivery of azacitidine has been published.[92] Patients who receive less than six cycles or who fail to respond after six cycles have poor outcomes.[93,94] In the absence of progression and where azacitidine is tolerated, a minimum of six courses is recommended, with continued therapy for as long as response is maintained. Patients should have a marrow examination before starting treatment, after six courses (to assess response) and subsequently at clinician discretion should disease progression be suspected. In selected younger patients who achieve a CR with azacytidine and have good performance status, the option of HSCT should be re-visited.

Ongoing studies are exploring the combination of azacytidine with other agents in high-risk MDS.

The benefits of azacitidine have largely (but not uniformly) been confirmed in 'real-world' studies. However, OS in four large data sets has not matched that reported in the original pivotal trial.[88] The Canadian, Spanish and French Groups reported OS for azacitidine-treated patients with higher-risk MDS of 12.4, 13.4 and 13.5 months, respectively.[93–95]

Alternative dosing schedules for azacitidine include 75 mg/m^2 for five days, no treatment for two days, and two further days of treatment (5–2–2); 50 mg/ m^2 on a 5–2–5 schedule or 75 mg/m2 for five days.[96] In the Canadian real-world study of high-risk patients there was no difference in OS for patients treated with azacitidine for seven consecutive days compared with the 5–2–2 regimen,[94] and this is strongly preferred as the closest practical alternative if the licensed seven-day regimen is impractical.
Two Phase III studies comparing decitabine (15 mg/m^2 IV eight-hourly for three days every six weeks) with best supportive care in MDS have shown that some patients achieve CR, partial remission or haematological improvement. However, neither study showed significant improvement in OS.[97,98] In the ADOPT Phase II study of patients receiving decitabine 20 mg/m2 for five days every four weeks,[99] CRs/marrow CRs of 32% and red cell (33%) and platelet (40%) transfusion independence were observed. Median survival was 19.4 months.
No prospective randomised studies comparing azacytidine with decitabine have been reported in intermediate-2/high-risk MDS. Azacitidine is the preferred agent, and the only one approved for use in the UK.
Although low-dose cytarabine (LDAC) has activity in high-risk MDS, the superiority of azacitidine over LDAC in the AZA001 study renders LDAC therapy obsolete in high-risk MDS.
Low-dose oral melphalan therapy could be considered for selective use in a rare group of patients, namely those with an excess of blasts (>5%) in a hypocellular marrow with a normal karyotype, for whom no alternative active therapy is available and/or appropriate. The majority of such patients will achieve CR with typical remission duration of 12 months.[100] Re-treatment will usually achieve a second remission but for a shorter duration. At melphalan-refractory relapse, patients are usually chemotherapy-resistant.

Allogeneic haematopoietic stem cell transplant in MDS

All transplant-eligible MDS patients should be discussed with a transplant physician at a MDT both at diagnosis and at disease progression (2B).

Additional prognostic factors such as transfusion burden, depth of cytopenias, cytogenetics and BM fibrosis should be assessed when considering the optimal timing of transplant for lower-risk MDS patients (2B).

Higher-risk MDS patients with >10% blasts may be considered for cytoreductive therapy or hypomethylating agents prior to transplant (2B).

Up-front transplant may be considered in patients with 5–10% blasts with slowly progressive disease or in those with a hypocellular or fibrotic BM (2B).

Transplant is not routinely recommended for patients with TP53 mutation in association with a complex monosomal karyotype due to poor outcomes (2B).

Eligibility for transplant should be guided by HCT-CI and EBMT risk score (2B).

Performance status and age should be used to inform choice of myeloablative or reduced-intensity conditioning (2B).

All transplant-eligible MDS patients should be discussed with a transplant physician at a MDT, both at diagnosis and with disease progression. The decision to transplant should be made on a case-by-case basis, evaluating patient, donor and disease factors known to influence transplant outcomes.[101]

Factors influencing timing and decision to transplant
Lower-risk MDS
The optimal time to transplant patients with lower-risk MDS remains an area of debate. Early transplant for the lowest-risk patients is generally not recommended due to subsequent reduction in life expectancy.[102–104]
To help guide decision-making, particularly in the IPSS INT-1 group, the ELN/EBMT guidelines[63] recommend the use of other poor prognostic factors such as transfusion dependency (≥2 units of blood per month), significant cytopenias, e.g. platelet count <30 x 10^9/l, neutrophils <0.3 x 10^9/l, or very poor prognostic cytogenetics. Transfusion dependence, elevated ferritin and labile plasma iron levels correlate with increased transplant-related mortality (TRM) in MDS patients following transplantation.[50,105–107]
Transplant should be considered once the patient becomes transfusion-dependent, before iron overload occurs. However, if there is a delay to transplant then iron chelation should strongly be considered.

Patients with progressive disease such as increasing blast cells or acquisition of adverse cytogenetic abnormalities should be considered for transplant.[63] Therapy failures, for example to ESAs or lenalidomide, convey a worse prognosis and should prompt consideration of transplantation.[108,109] Furthermore, patients with isolated del(5q) and an associated TP53 mutation have a worse prognosis and greater chance of failing lenalidomide therapy.[75,77] Such patients should be considered for transplantation early in their disease course.[110]
Patients with MDS and severe bone marrow (BM) fibrosis experience worse outcomes following HSCT compared with mild/moderate fibrosis, or those lacking fibrosis.[111] As such, the presence of BM fibrosis should prompt early transplant consideration, ideally prior to progression to severe fibrosis.

Higher-risk MDS
Early allogeneic HSCT offers a survival advantage in higher-risk MDS and suitable patients should be referred promptly to a transplant centre.[102–104,112] Inferior survival outcomes for patients with excess BM blasts (>5%) at the time of transplant have been reported.[113] It remains unclear, however, whether cytoreduction prior to transplant improves outcomes (regardless of BM blast percentage) over up-front transplantation.[114] In the absence of prospective data, patients with >10% blasts may be considered for cytoreductive chemotherapy or hypomethylating agents (HMA) prior to transplant, particularly where immediate transplantation is not logistically possible.[63] Up-front transplantation should be considered where BM blasts are 5–10% in patients with slowly progressing disease, taking into account other patient- and disease-related factors. Patients with a hypocellular BM or presence of increased BM fibrosis with BM blasts up to 10% may also be considered for upfront transplant as prolonged cytopenia may occur with chemotherapy.

Induction chemotherapy vs HMA prior to allogeneic HSCT
Given the lack of available data from prospective, randomised trials, patients should be offered entry into a clinical trial, wherever possible. The ELN/EBMT support HSCT in suitable patients treated with HMA following attainment of CR.[63] However, emerging data from the VIDAZA ALLO study demonstrating early patient dropout due to treatment-related death or toxicity suggest that the number of HMA courses should be minimised.[115] For patients receiving induction chemotherapy, prolonged cytopenia may result; treatment should ideally be delivered once a donor has been identified (if a delay to commencing therapy is deemed acceptable).
Patients with a complex karyotype are more likely to exhibit TP53 mutation, contributing to their poor prognosis and therefore we recommend that all patients with complex karyotype are screened for TP53 mutation.[110,116,117] TP53 mutation is associated with resistance to conventional chemotherapy and early relapse.[116,117] In contrast, comparable response rates are observed following treatment with hypomethylating agents for MDS patients with TP53 mutation or wild-type TP53.[118–121] Patients with complex karyotype in the absence of TP53 mutation who require a reduction in blast count should be considered for clinical trials as there is no clear evidence to suggest whether intensive chemotherapy or HMA is better in this setting.[122]

Choice of conditioning regimen
The RICMAC trial showed no statistically significant difference in OS, relapse-free survival (RFS) or cumulative incidence of relapse at two years with reduced-intensity conditioning (RIC) or myeloablative conditioning (MAC).[130] A similar prospective trial demonstrated higher relapse rates for RIC versus MAC (48.3% vs 13.5%, $P < 0.001$) leading to early trial closure.[131] In keeping with ELN/EBMT guidance, high-risk patients with good performance status, lacking in comorbidity, may be candidates for MAC, reserving RIC for older, less fit patients.[63]

Management of relapse post transplant
Currently there are no standardised recommendations directing choice of therapy for relapse post HSCT and this is therefore not discussed further in this Guideline. Such patients may be best managed through accessing clinical trials where available.

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Bohlius J et al., 2019 [1].

Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update

Zielsetzung/Fragestellung

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche, Auswahl und Bewertung der Evidenz.
- Formale Konsensusprozesse nicht beschrieben, externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Regelmäßige Überprüfung der Aktualität gesichert: unklar.

Recherche/Suchzeitraum:

- PubMed and the Cochrane Library were searched for randomized controlled trials (RCTs) and meta-analyses of RCTs from January 31, 2010, through May 14, 2018

LoE / GoR

- Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases.

Empfehlungen

Clinical question 1

To reduce the need for RBC transfusions, should ESAs be offered to patients who have chemotherapy-associated anemia?

Recommendation 1.1

Depending on clinical circumstances, ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose HgB has declined to < 10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2

ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical question 2

To reduce the need for RBC transfusions, should ESAs be offered to anemic patients with cancer who are not receiving concurrent myelosuppressive chemotherapy?

Recommendation 2.1

ESAs should not be offered to most patients with nonchemotherapy-associated anemia (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).

Recommendation 2.2

ESAs may be offered to patients with lower-risk MDSs and a serum erythropoietin level ≤ 500 IU/L (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

In patients with MDS, one RCT evaluated the addition of epoetin beta to lenalidomide in 131 patients with RBC transfusion-dependent, low, or intermediate-1 risk (according to the International Prognostic Scoring System), ESA refractory, nondel(5q) MDS.[26] The combination of lenalidomide and epoetin beta increased the frequency of erythroid response relative to lenalidomide alone (39% v 23%; P = .04), but did not significantly affect duration of erythroid response (15 v 18 months; P = .64) or likelihood of transfusion independence (24% v 14%; P = .13). In subgroup analyses, patients with lower baseline serum erythropoietin levels had higher rates of erythroid response.
[…]
In patients with MDS, some studies suggest that patients with elevated baseline erythropoietin levels (> 500 IU/L) are unlikely to respond to ESA therapy.[37] Furthermore, a recent study has suggested that an even lower baseline erythropoietin level (< 200 IU/L) is associated with a better HgB response.[38] ESAs should be avoided in patients with MDS with elevated baseline erythropoietin levels (> 500 IU/L). Lower pretreatment RBC transfusion dependence (< 2 units per month) has also been associated with a higher likelihood of ESA response in patients with MDS.[39] Among the potential benefits of ESA therapy in patients with MDS is avoidance of secondary hemochromatosis, particularly for lower risk patients who may have years of survival.

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Clinical question 5

Among adult patients who receive an ESA for chemotherapy-associated anemia, do darbepoetin, epoetin beta and alfa originator, and currently available biosimilars of epoetin alfa differ with respect to safety or efficacy?

Recommendation 5

The Expert Panel considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to effectiveness and safety (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

[…]
A retrospective study of patients with MDS and refractory anemia evaluated 46 patients treated with biosimilar epoetin alfa and 46 patients with originator epoetin alfa. Median time to reach an HgB level > 12 g/dL was 10.5 weeks (range, 3 to 16 weeks) among patients treated with the biosimilar and 12 weeks (range, 4 to 18 weeks) among patients treated with the originator product.[31]
[…]

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Clinical question 6

Do ESAs increase the risk of thromboembolism?

Recommendation 6

ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Meta-analyses and individual RCTs consistently report a 50%[1,2] to 75%[16,25] increased risk of thromboembolism and vascular arterial events among patients receiving ESA therapy. The Expert Panel continues to urge caution in the use of ESAs for patients judged to be at increased risk for venous thromboembolism. Several risk scores for predicting venous thromboembolism have been developed; these are discussed in more detail in the ASCO guideline on venous thromboembolism.[42] Special attention should be given to patients with multiple myeloma who are being treated with thalidomide or lenalidomide and doxorubicin or corticosteroids since they are at particularly increased thrombotic risk.[43] There are no data from RCTs investigating concomitant use of anticoagulants or aspirin to lessen this risk.

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Clinical question 9

Among adult patients with chemotherapy-associated anemia who do not respond to ESA therapy (<1 to 2 g/dL increase in HgB or no decrease in transfusion requirements), does continuation of ESA therapy beyond 6 to 8 weeks provide a benefit?

Recommendation 9

ESAs should be discontinued in patients who do not respond within 6 to 8 weeks. Patients who do not respond to ESA treatment should be reevaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Given the known harms of ESAs, the exposure to ESAs should be minimized. In patients who have received appropriate ESA dosing and who do not respond, ESAs should be stopped and not continued.

Clinical question 10

Among adult patients with chemotherapy-associated anemia, does iron supplementation concurrent with an ESA reduce transfusion requirements?

Recommendation 10

Iron replacement may be used to improve HgB response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels is recommended (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: weak).

This recommendation changed from previous versions based on new information published after the last guideline. The Expert Panel believes that the use of iron supplementation in all patients receiving ESAs should be considered, independent of the iron status. This is based on evidence that iron supplementation reduces the risk for RBC transfusion. Additionally, in patients with evidence of iron deficiency, the cause of the deficiency should be investigated and corrected.
Oral and IV iron formulations are both acceptable options for iron supplementation. Choice of agents depends on patient and doctor preferences, formulation availability, cost, and comorbidities. IV iron preparations have the advantage of being able to deliver larger amounts of elemental iron in a single application and may also be more adequate in patients with poor oral intake or absorption problems. They have the disadvantages of being associated with more serious systemic reactions and higher costs. There is some limited evidence that IV iron is superior to oral iron based on improvement in HgB level. However, the results were not consistent across all other hematologic outcomes, and the quality of adverse outcomes reporting was poor.[15,20,22] Safety has been better studied in a systematic review and meta-analysis in patients with CKD, which showed no difference in mortality or serious adverse events in patients receiving intravenous iron, although there were more episodes of hypotension with IV iron.[44]

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2023) am 14.11.2023

#	Suchfrage
1	[mh "Myelodysplastic Syndromes"]
2	(myelodysplas* OR dysmyelopoie* OR GATA2 NEXT deficienc* OR (GATA NEXT 2 NEXT deficienc*) OR PNH):ti,ab,kw
3	(an*emia* AND (refractory OR sideroblast*)):ti,ab,kw
4	((paroxysmal OR nocturnal OR h*emoly*) AND (h*emoglobinuria)):ti,ab,kw
5	(marchiafava* OR stru*bing* OR strübing*):ti,ab,kw
6	#1 OR #2 OR #3 OR #4 OR #5
7	#6 with Cochrane Library publication date from Nov 2018 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 14.11.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	myelodysplastic syndromes[mh]
2	myelodysplas*[tiab] OR dysmyelopoie*[tiab] OR GATA2 deficienc*[tiab] OR GATA-2 deficienc*[tiab] OR PNH[ti]
3	(anemia*[tiab] OR anaemia*[tiab]) AND (refractory[tiab] OR sideroblast*[tiab])
4	(paroxysmal[tiab] OR nocturnal[tiab] OR hemoly*[tiab] OR haemoly*[tiab]) AND (haemoglobinuria[tiab] OR hemoglobinuria[tiab])
5	marchiafava*[tiab] OR struebing*[tiab] OR strubing*[tiab] OR Strübing[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR

#	Suchfrage
	overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
8	(#7) AND ("2018/11/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT "The Cochrane database of systematic reviews"[Journal]
10	(#9) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 14.11.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	myelodysplastic syndromes[mh]
2	myelodysplas*[tiab] OR dysmyelopoie*[tiab] OR GATA2 deficienc*[tiab] OR GATA-2 deficienc*[tiab] OR PNH[ti]
3	(anemia*[tiab] OR anaemia*[tiab]) AND (refractory[tiab] OR sideroblast*[tiab])
4	(paroxysmal[tiab] OR nocturnal[tiab] OR hemoly*[tiab] OR haemoly*[tiab]) AND (haemoglobinuria[tiab] OR hemoglobinuria[tiab])
5	marchiafava*[tiab] OR struebing*[tiab] OR strubing*[tiab] OR Strübing[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2018/11/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 14.11.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2023-B-296

Verfasser	
Institution	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
Sachverständige	
Datum	14. Dezember 2023

Indikation
Behandlung von erwachsenen Patienten mit transfusionsabhängiger Anämie aufgrund von myelodysplastischen Syndromen (MDS) mit sehr niedrigem, niedrigem oder intermediärem Risiko.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

MyeloDysplaStische Neoplasien (MDS, seit der WHO-Klassifikation 2022 wird der Begriff „Myelodysplastische Neoplasien“ verwendet [1], allerdings die Abkürzung „MDS“ beibehalten) sind klonale Erkrankungen der hämatopoetischen Stammzelle, die durch Dysplasien von Blut- und Knochenmarkzellen mit hämatopoetischer Insuffizienz und erhöhtem Risiko der Entwicklung einer akuten myeloischen Leukämie (AML) gekennzeichnet sind [2].

Basis der supportiven Therapie bei Patientinnen und Patienten (Pat.) mit transfusionsabhängiger Anämie ist die Symptom-getriggerte Transfusion mit Erythrozytenkonzentraten.

Der weitere Therapiestandard orientiert sich an definierten MDS-Subtypen:

- MDS-RS + SF3B1: Luspatercept
- MDS del(5q): Lenalidomid
- Hypoplastisches MDS: Immunsuppressive Therapie
- Alle anderen MDS-Subtypen (sEPO <500 U/l): Erythropoese-stimulierende Faktoren (ESF)
- Patienten mit einer Historie für Transfusion von Erythrozytenkonzentraten (EK, n>20) bzw. einer Transfusionsfrequenz von mehr als 2 EK alle 4 Wochen und einem Serum-Ferritinwert >1000 ng/ml: Eisenchelationstherapie

Fragestellung

Insbesondere die supportive Therapie und damit die Behandlung mit Erythrozytenkonzentraten ist bei den genannten Indikationen unverändert. Eine aktuelle Beratung für Studien und/oder für die Nutzenbewertung neuer Arzneimittel muss die WHO Klassifikation von 2022 berücksichtigen.

Stand des Wissens

Die MDS zählen mit einer Inzidenz von ca. 4-5/100.000 Einwohnern pro Jahr zu den häufigsten malignen hämatologischen Erkrankungen [3]. Im Alter über 70 Jahre steigt die Inzidenz auf >30/100.000 an. Das mediane Erkrankungsalter liegt bei ca. 75 Jahren, Frauen sind etwas seltener betroffen als Männer.

Die traditionell den MDS zugeordneten Typen werden in der aktuellen WHO-Klassifikation in 2 große Gruppen eingeteilt, siehe Tabelle 1. Neben den reinen MDS wird eine Gruppe von gemischten myelodysplastisch-myeloproliferativen Neoplasien abgegrenzt. Der von der akuten Leukämie diskriminierende Blastenanteil liegt in Blut und Knochenmark bei 20%. Der bis 2022 alleinig anwendbare Prognosescore für die MDS (IPSS-R) umfasst jedoch weiterhin Patientinnen und Patienten (Pat.) mit bis zu 30% Blasten [4]. Für eine klare Diagnosestellung und Therapieentscheidung beim MDS ist eine Chromosomenanalyse und ein Screening auf somatische Mutationen unerlässlich, weil nur damit die Prognose der Pat. so gut als möglich bestimmt werden kann.

Den Vorschlägen der WHO-Klassifikation aus dem Jahre 2022 liegt ein neues Prinzip zugrunde, nämlich die Einteilung der MDS in morphologisch definierte und genetisch definierte Typen [1]. Zudem wurden drei neue MDS-Typen erstmals als eigenständige Entitäten definiert. Andere Typen wurden unverändert aus den alten WHO-Klassifikationen übernommen. Periphere Zellzahlen haben nun weniger Gewicht in der Klassifikation.

Tabelle 1: Klassifikation der MDS nach den Vorschlägen der WHO 2022 [1]

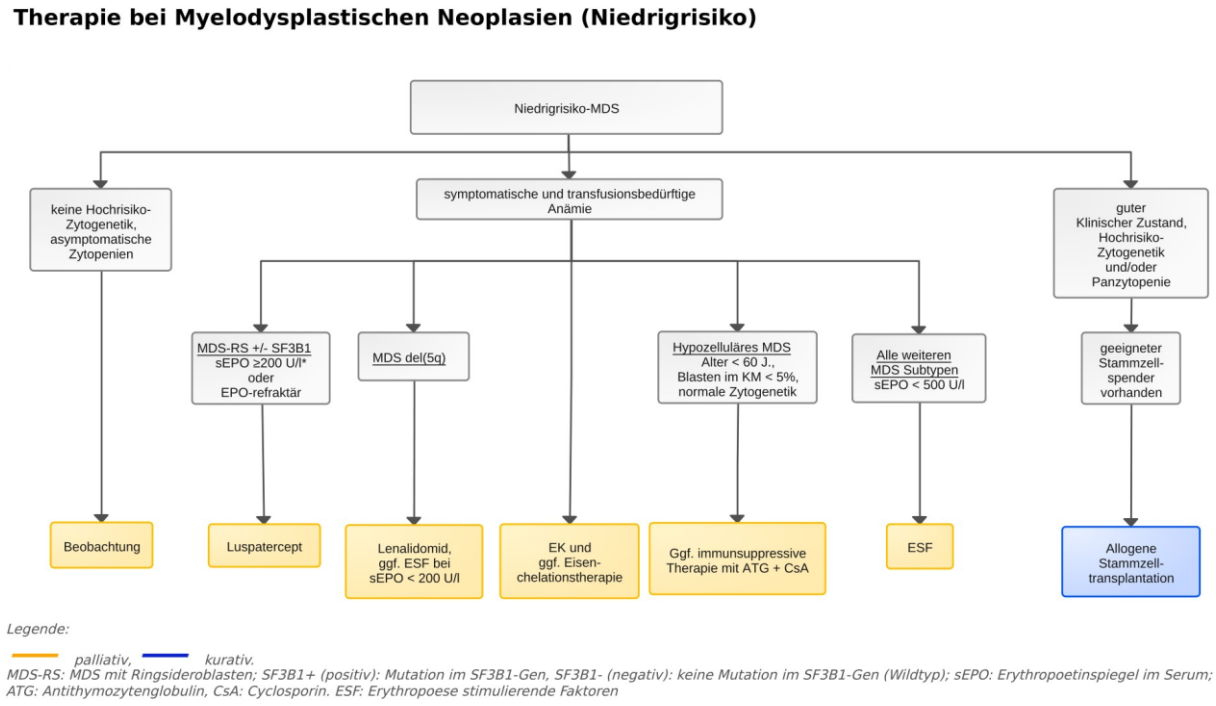
	Blastenanteil	Zytogenetik	Mutationen
Genetisch definierte MDS			
MDS mit niedrigen Blasten und isolierter Deletion (5q)	<5 % KM <2 % Blut	Deletion (5q) isoliert oder mit 1 anderen Anomalie außer Monosomie 7 oder Deletion (7q)	*SF3B1, TP53 möglich* **2 Subtypen** a) MDS del(5q) mit mono-allelischer *TP53* Mutation b) MDS del(5q) mit SF3B1 Mutation
MDS mit niedrigen Blasten und *SF3B1* Mutation[1]	<5 % KM <2 % Blut	Keine Deletion (5q), keine Monosomie 7, kein komplex aberranter Karyotyp	Fast immer *SF3B1*
MDS mit bi-allelischer *TP53* Inaktivierung	Jeglicher	Typischerweise hoch komplex aberrant mit >3 Aberrationen	2 oder mehr *TP53* Mutationen oder 1 Mutation + Verlust der Kopienzahl *von TP53*[5]
Morphologisch definierte MDS[2]			

MDS mit niedrigen Blasten			
MDS mit niedrigen Blasten[3]	<5% KM <2% Blut		
MDS, hypoplastisch[4]	<5% KM <2% Blut		
MDS mit erhöhten Blasten			
MDS mit erhöhten Blasten -1	5-9% KM, und/oder 2-4% Blut		
MDS mit erhöhten Blasten -2	10-19% KM und/oder 5-19% Blut		
MDS mit Fibrose	5-19% KM, und/oder 5-19% Blut		

[1] Nachweis von ≥15% Ringsideroblasten kann den Nachweis einer SF3B1-Mutation ersetzen
[2] ≥10% Dysplasiezeichen in mind. einer Zelllinie
[3] 2 Typen: MDS mit niedrigen Blasten und single lineage dysplasia (MDS-0-SLD); MDS mit niedrigen Blasten und multi lineage dysplasia (MDS-0-MLD)
[4] ≤25 % histologische Knochenmarkzellularität, altersadaptiert
[5] Kopienzahlverlust entweder zytogenetisch (durch Bänderungsanalyse oder FISH darstellbare 17p-Deletion) oder Kopienzahl-neutraler Verlust der Heterozygotie (darstellbar mittels Array-Analysen oder spez. NGS-Verfahren). Bei einer VAF von 50% oder höher besteht ebenfalls eine hohe Wahrscheinlichkeit für eine biallelische TP53-Inaktivierung.

Die Therapieempfehlungen für Pat. mit symptomatischer und transfusionsbedürftiger Anämie sind in Abbildung 1 graphisch dargestellt.

Abbildung 1: Therapie bei Myelodysplastischen Neoplasien (Niedrigrisiko) [2]



Bei Niedrigrisiko-MDS ist bei vielen MDS-Pat. aufgrund der geringgradigen Zytopenie zunächst eine „watch and wait"-Strategie ausreichend. Bei einem wesentlichen Teil der Fälle stellt jedoch die Anämie die häufigste Indikation zum Therapiebeginn dar. Eine Anämie führt vor allem bei älteren Pat. zu Fatigue, zu erhöhter Sturzhäufigkeit mit Frakturgefahr, zu verminderter Kognition und Lebensqualität sowie zu einem verkürzten Überleben.

Supportive Therapie - Erythrozytentransfusionen

Hauptbestandteil der supportiven Therapie ist die Transfusion von Erythrozytenkonzentraten in Abhängigkeit vom klinischen Zustand. Bei Pat. mit begleitender schwerer koronarer Herzerkrankung und/oder anderen schweren Begleiterkrankungen sollte ein Hb-Wert über 10 g/dl angestrebt werden.

Polytransfundierte Pat. sind längerfristig durch die begleitende sekundäre Hämochromatose (Kardiomyopathie) bedroht. Deshalb kann bei Pat. mit einer Lebenserwartung von mehr als 2 Jahren, die mindestens 20 Erythrozytenkonzentrate erhalten bzw. einen Serumferritinspiegel von >1000 ng/ml haben, eine Therapie mit Eisenchelatoren (Deferasirox, Desferoxamin) erwogen werden [2, 5]. Besonderen Stellenwert hat die Eisenchelation vor einer allogenen Stammzelltransplantation und wird dort bis zum Beginn der Konditionierung empfohlen, da die Eisenüberladung mit einer erhöhten Mortalität assoziiert ist.

MDS-RS + SF3B1

Die Inhibition von (bisher teilweise nur unzureichend charakterisierten) Suppressoren der Erythropoese bei Pat. mit MDS führt insbesondere bei der Subgruppe der Pat. mit MDS und RS und/oder SF3B1-Mutation zu einer Verbesserung der Differenzierung und Steigerung der Proliferation von erythrozytären Zellen und damit zur Verringerung des Transfusionsbedarfes. Luspatercept, ein Inhibitor des TGF-beta Signalweges, ist in der Lage, bei etwa 60 % dieser transfusionsabhängigen Pat. eine signifikante Reduktion der Transfusionsbedürftigkeit bis hin zu Transfusionsfreiheit zu erzielen. Pat. mit MDS-RS (<5 % KM-Blasten, ≥15 % Ringsideroblasten im KM bzw. ≥5 % Ringsideroblasten im KM und Mutation von SF3B1) und einer transfusionsbedürftigen Anämie sollten mit Luspatercept behandelt werden, wenn sie auf ESF nicht angesprochen haben oder keine hohe Wahrscheinlichkeit des Ansprechens aufweisen (Serum-Epo-Spiegel ≥200 U/l) [6, 7]. In dieser Zulassungsstudie wurde die Überlegenheit von Luspatercept gegenüber Placebo bei erwachsenen Pat. mit transfusionsabhängiger Anämie und MDS mit Ringsideroblasten mit sehr niedrigem, niedrigem oder intermediärem Risiko, die auf eine Erythropoetin-basierte Therapie nicht zufriedenstellend angesprochen haben oder dafür nicht geeignet sind, gezeigt. Die WHO 2022 Klassifikation führt formal das MDS mit Ringsideroblasten (MDS-RS) nicht mehr als eigene Entität auf, sondern hat die neue Entität MDS mit niedrigen Blasten und *SF3B1* Mutation (siehe Tabelle 1) eingeführt wegen der prognostischen (günstigen) Rolle der o.g. Mutation. Die große Mehrzahl der Pat. mit MDS-RS weist eine solche Mutation auf, jedoch können auch Pat. mit MDS-RS ohne diese Mutation auf Luspatercept ansprechen [8].

MDS del(5q)

Die Behandlung mit Lenalidomid führt bei etwa 60 % der MDS-Pat. mit einer singulären Deletion am Chromosom 5 und einer transfusionspflichtigen Anämie bei niedrigem Krankheitsrisiko zum Ansprechen mit dem Ergebnis einer Transfusionsunabhängigkeit sowie bei einem Teil der Pat. zu einer zytogenetischen

Remission. Pat. mit nur einer Zusatzaberration (außer von Chromosom 7) sprechen ähnlich gut an. Die minimale wirksame Dosis von Lenalidomid ist bis jetzt nicht definiert. Basierend auf einer randomisierten Studie [9] führt eine Dosierung von 10 mg/Tag zu einer höheren Rate an zytogenetischen Remissionen und sollte - mit entsprechender Anpassung der Dosis in Abhängigkeit der Thrombozytenzahl - zum Einsatz kommen. Bei älteren Pat. ist gelegentlich eine Initialdosis von 5 mg/Tag angezeigt. Sollte nach 4 Monaten keine Verbesserung der Transfusionspflichtigkeit eingetreten sein, sollte die Therapie beendet werden. Vor Beginn der Therapie sollte eine Bestimmung der TP53-Mutation durchgeführt werden. Pat. mit einer Mutation sollten regelmäßig im Rahmen von Knochenmarkpunktionen auf eine klonale Evolution überwacht werden. Die Effektivität von Lenalidomid bei MDS ohne Veränderungen am Chromosom 5 ist gering. Die Behandlung dieser Pat. mit der Substanz sollte hier streng abgewogen werden [10].

Hypoplastisches MDS

Die Behandlung mit immunsuppressiven Medikamenten (ähnlich zur Therapie der schweren aplastischen Anämie) beruht auf den positiven Erfahrungen bei einer Subgruppe von Pat., die wie folgt charakterisiert sind [11]:

- hypozelluläres Knochenmark
- MDS mit niedrigem Krankheitsrisiko
- geringe Transfusionsbedürftigkeit

Etwa 30% der Pat., die mit Antithymozytenglobulin und Cyclosporin behandelt wurden, erreichen Transfusionsfreiheit. Gute prädiktive Parameter für ein Ansprechen konnten bisher nicht identifiziert werden. Wegen der teilweise starken Nebenwirkungen und dem noch nicht klar definierten Patientengut sollte eine immunsuppressive Behandlung bei MDS ausschließlich an einem hämatologischen Zentrum durchgeführt werden.

Alle anderen MDS-Subtypen (sEPO <500 U/l)

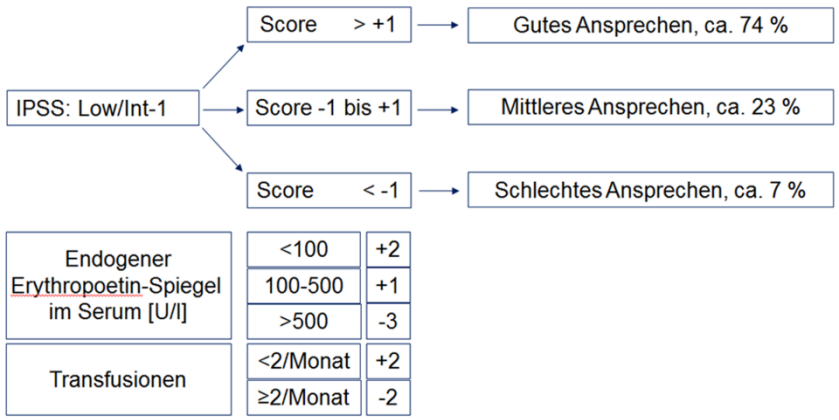
Die Therapie mit Erythropoese stimulierenden Faktoren (ESF, klassisch: subkutanes Erythropoetin 40.000 IE/Woche, bei unzureichender Wirkung ggf. steigern auf 80.000 IE/Woche, einmal pro Woche; Verzögerungserythropoetin: 300 µg wöchentlich bzw. 500 µg zweiwöchentlich subkutan) muss in Anlehnung an den sogenannten „Nordic Score“ [12] erfolgen, siehe Abbildung 1. Die Kombination mit niedrigen Dosen von G-CSF (100 µg G-CSF s. c. 1-2 mal pro Woche mit dem Hintergrund, die Wirksamkeit von ESF zu modulieren, nicht um die Leukozyten anzuheben – s. o.) kann die Wirkung von ESF, insbesondere bei Pat. mit nachgewiesenen Ringsideroblasten, die refraktär auf eine alleinige ESF-Behandlung sind, verbessern.

Unter Berücksichtigung der prädiktiven Faktoren

- Erythropoetinspiegel <200 (500) U/l,
- geringe Transfusionsabhängigkeit (maximal 2 EK in 8 Wochen),
- niedriges Krankheitsrisiko,

Es kann ein Ansprechen bei bis zu 75 % der entsprechend ausgewählten Pat. erreicht werden [13]. In der Regel ist das Ansprechen nach spätestens 6 Monaten Therapie zu erwarten. Bleibt es aus, sollte die Behandlung beendet werden. Ein Ansprechen ist bei einem Epo-Spiegel bis zu 500 U/l möglich.

Abbildung 1: Modifizierter Score der Nordic MDS-Group



Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ja, entscheidend ist der Subtyp des zugrundeliegenden MDS. Die Differenzialtherapie ist oben dargestellt.

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