nature reviews disease primers

https://doi.org/10.1038/s41572-022-00402-5

Primer

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Myelodysplastic syndromes

Huan Li[1,4], Fang Hu[1,4], Robert Peter Gale[1,2], Mikkael A. Sekeres[3] & Yang Liang[1]

Abstract

Myelodysplastic syndromes (MDS) are a family of myeloid cancers with diverse genotypes and phenotypes characterized by ineffective haematopoiesis and risk of transformation to acute myeloid leukaemia (AML). Some epidemiological data indicate that MDS incidence is increasing in resource-rich regions but this is controversial. Most MDS cases are caused by randomly acquired somatic mutations. In some patients, the phenotype and/or genotype of MDS overlaps with that of bone marrow failure disorders such as aplastic anaemia, paroxysmal nocturnal haemoglobinuria (PNH) and AML. Prognostic systems, such as the revised International Prognostic Scoring System (IPSS-R), provide reasonably accurate predictions of survival at the population level. Therapeutic goals in individuals with lower-risk MDS include improving quality of life and minimizing erythrocyte and platelet transfusions. Therapeutic goals in people with higher-risk MDS include decreasing the risk of AML transformation and prolonging survival. Haematopoietic cell transplantation (HCT) can cure MDS, yet fewer than 10% of affected individuals receive this treatment. However, how, when and in which patients with HCT for MDS should be performed remains controversial, with some studies suggesting HCT is preferred in some individuals with higher-risk MDS. Advances in the understanding of MDS biology offer the prospect of new therapeutic approaches.

Sections

[1]Department of Hematologic Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, P.R. China. [2]Haematology Research Centre, Department of Immunology and Inflammation, Imperial College London, London, UK. [3]Division of Hematology, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA. [4]These authors contributed equally: Huan Li, Fang Hu. e-mail: liangyang@sysucc.org.cn

Introduction

Myelodysplastic syndromes (MDS; also known as myelodysplastic neoplasms) encompass a spectrum of related, phenotypically and genotypically diverse myeloid cancers. MDS are characterized by ineffective haematopoiesis in one or several myeloid lineages and a risk of progression to acute myeloid leukaemia (AML)[1–3]. Some epidemiological data suggest an increasing incidence of MDS[4,5], predominately in older persons, and that MDS incidence is increased in cancer survivors receiving prior chemotherapy and/or radiation therapy[6]; however, these incidence data are controversial[7–9]. The nomenclature and classification of MDS are complex and have a long, complicated history[10]. The gold standard and most commonly used classification system, the 2022 revision of the fifth edition of the WHO Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms, introduces the term 'myelodysplastic neoplasms' (also abbreviated MDS) to replace the term 'myelodysplastic syndromes' and classifies these cancers on the basis of genetic abnormalities and histological features, highlighting the neoplastic nature of these cancers and harmonizing terminology with myeloproliferative neoplasms[11] (MPN; the overproduction of myeloid lineage cells).

In some subtypes of MDS, there is overlap with AML and other disorders in genotypic and phenotypic features; consequently, accurate diagnosis is sometimes difficult or even impossible. Differential diagnoses for MDS include other causes of bone marrow failure and ineffective haematopoiesis and some forms of AML[12]. Challenging differential diagnoses include increased blood or bone marrow blasts, especially when there is only mild dysplasia, as well as mild and moderate bone marrow hypoplasia.

Moreover, in some classification systems, MDS and AML are distinguished on the basis of the proportion of myeloblasts in bone marrow, a threshold that is imprecise and arbitrary as it lacks a biological basis and ignores imprecision in quantifying the number of myeloblasts in different bone marrow sites and over time[13]. Another challenge is obtaining an adequate bone marrow sample for analysis, especially in individuals with mild bone marrow fibrosis. The fifth edition of the WHO Classification reconsiders the boundary between MDS and AML while retaining the formal boundary of 20% myeloblasts in bone marrow.

The diagnosis of MDS is based on analyses of bone marrow histology and cytogenetic and molecular genetic analyses. However, as cytopenias and dysplasia are not specific to MDS, other causes of cytopenias and histological changes need to be excluded. An MDS differential diagnosis also includes 'precursor' states, including idiopathic cytopenias of undetermined significance (ICUS), idiopathic dysplasia of undetermined significance (IDUS) and clonal cytopenia of undetermined significance (CCUS). Some current prognostic scoring systems that have been widely accepted to predict outcomes and direct therapeutic interventions are discussed below.

Treatment of MDS depends on the risk category of MDS and the urgency of treatment. Therapies include improving haematopoiesis (providing symptom relief), hypomethylating drugs (potentially extending survival) and allogeneic haematopoietic cell transplantation (HCT; a potential cure). Research into the aetiology, biology and therapy of MDS is increasing but many questions remain, for example, how to translate the current understanding of the pathogenesis of MDS into effective clinical management, and how to develop curative and tolerable strategies to manage patients with high-risk MDS and those who relapse or are resistant to initial treatment. In this Primer, we discuss MDS epidemiology, biology, pathophysiology, diagnosis, screening and prevention, therapy, and quality of life (QOL), and review recent progress in the field of MDS with a focus on pathophysiology, diagnosis and treatment as well as future research directions.

Epidemiology

Prevalence and incidence

The available epidemiological data on MDS incidence and prevalence are of poor quality, with prevalence and incidence estimates ranging by tenfold in different countries or regions[4,9,14–32] (Fig. 1 and Supplementary Table 1). Most accurate studies are from resource-rich countries/regions such as the USA, Europe and Scandinavia. Obtaining reliable data is confounded by evolving definitions and classifications (for example, the fifth edition of the WHO Classification), incomplete reporting and surveillance biases. The Surveillance, Epidemiology, and End Results (SEER) programme reported an age-adjusted annual incidence of MDS of 3.28 cases per 100,000 population in 2001 and of 5.6 cases per 100,000 population in 2010, a 60% increase[4,9,33,34]. Whether this is an accurate estimate is questionable[35–37]. Data from the HAEMACARE study report a low incidence of MDS in Eastern Europe, which likely reflects the aforementioned biases[38].

In the SEER dataset, white individuals with non-Hispanic surnames have the highest incidence rate of MDS and Asian and Pacific Islander individuals have the lowest incidence rate of MDS (an average of 4.8 versus 3.2 cases per 100,000 population, respectively, for the 2011–2015 interval)[14].

The seemingly increased incidence rate of MDS for 2011–2015 contrasts with decreasing incidence rate during the period 2001–2010 (3.3–5.6 versus 4.7–4.1 cases per 100,000 population, respectively); the reasons for this disparity are unknown but include changing diagnostic criteria, disease classification and coding, different statistical models, a changing arbitrary boundary between MDS and AML, and surveillance biases[39]. Interestingly, a study employing a complete blood cell count and bone marrow biopsy claims-based algorithm reported an annual incidence of MDS of 75 cases per 100,000 population ≥65 years of age, much higher than the 20 cases per 100,000 population reported by the SEER programme for the same age cohort[36]. However, claims-based algorithms are potentially confounded by physician over-reporting of MDS to gain approval for the use of anaemia drugs such as erythropoietin.

MDS is uncommon in children and adolescents[40] but incidence increases with age; however, age is a risk factor for MDS and not a cause, probably reflecting the accumulation of driver mutations over time. No difference in MDS incidence based on sex has been observed in patients <40 years of age, whereas there is a marked male predominance in those >40 years of age, consistent with different forms of MDS and/or different aetiologies at different ages[34]. The causes of most cases of MDS are unknown[41].

Risk factors

Factors reported to be associated with MDS include exposures to ionizing radiation (Fig. 2), chemicals such as benzene, some anticancer drugs (including mechlorethamine, procarbazine, chlorambucil, cyclophosphamide, ifosfamide, etoposide, teniposide, doxorubicin, daunorubicin and mitoxantrone), and hereditary disorders such as Fanconi anaemia, Shwachman–Diamond syndrome, Diamond–Blackfan anaemia, familial platelet disorder with a propensity to myeloid cancers, severe congenital neutropenia and dyskeratosis congenita[42–49]. People with a family history of leukaemia, in some cases a genetically identical twin or a sibling, are at increased risk of developing MDS as are people with aplastic anaemia[50–55]. The impact of exposure to

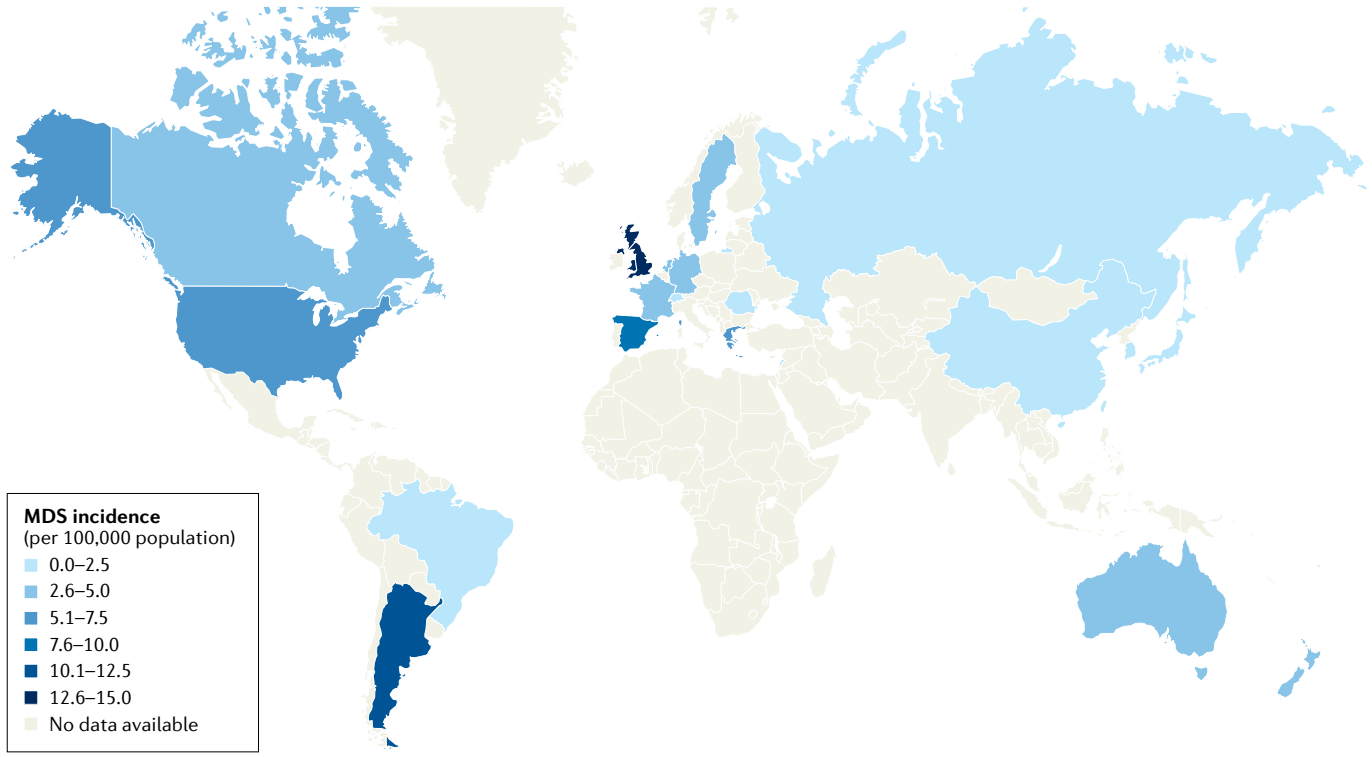

Fig. 1 | Epidemiology of MDS. This map depicts the incidence of myelodysplastic syndromes (MDS) in each country/region based on available epidemiology data (see Supplementary Table 1). Epidemiological data are lacking for some countries/regions.

agents such as insecticides and herbicides and of lifestyle covariates, such as cigarette smoking, obesity, and red meat, fruit and vegetable consumption, on MDS risk are controversial[44,56].

People with aplastic anaemia receiving immune-suppressive therapy have a 5-year actuarial probability of developing MDS and/or AML of 2–4% and a 10-year risk of about 15–25%[57] (Fig. 2a). Immune abnormalities can occur at diagnosis or at any time over the course of MDS. Conversely, there is an increased risk of MDS in people with immune abnormalities such as dysfunction of T cells, natural killer cells and/or dendritic cells, aberrant antibody and/or cytokine production, abnormal neutrophil function, and hypogammaglobulinaemia and/or hypergammaglobulinaemia[58]. MDS risk is also increased in individuals with autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren syndrome, and vacuoles, E1-activating enzyme, X-linked autoinflammatory somatic (VEXAS) syndrome[59–61].

Many patients with MDS are older and many will have had age-related somatic mutations referred to as clonal haematopoiesis of indeterminate potential (CHIP), which may be unrelated to the development of MDS in some cases. By contrast, many cases of MDS in children and younger adults and in some older persons are associated with a germline genetic predisposition[62–64]. Because there are no phenotype differences between inherited and sporadic disease, genetic testing is needed to identify these cases. This MDS category is discussed in the 2022 fifth edition of the WHO Classification and the International Consensus Classification (ICC) of Myeloid Neoplasms and Acute Leukaemia. The presence of an inherited genetic predisposition should now be indicated in the diagnosis. Genes commonly mutated include *DDX41*, *SAMD9*, *SAMD9L* and *GATA2* (refs.[65–67]). These mutations occur in several other myeloid neoplasms and, if found, require familial genetic testing to identify persons at risk.

Mechanisms/pathophysiology

Relationship between aplastic anaemia, PNH, MDS and AML

A complex, unanswered question is the relationship between the four disorders: aplastic anaemia, paroxysmal nocturnal haemoglobinuria (PNH), MDS and AML. It is unclear whether these are different manifestations of one disorder, different disorders or a variable combination of different disorders[52,68], and whether these diagnoses are mutually exclusive or whether someone can have more than one disorder synchronously or metachronously. Historically, aplastic anaemia, PNH, MDS and AML are typically considered different disorders with distinct genotypes, phenotypes and pathophysiologies (Table 1). Aplastic anaemia is characterized by bone marrow failure and has diverse causes, including hereditary factors, environmental exposures, infections and/or autoimmunity. The uniting feature is damage to haematopoietic stem and/or progenitor cells; however, often, an aetiology has not been identified. PNH is another bone marrow failure disorder characterized by haemolytic anaemia (often not nocturnal) resulting from an acquired mutation that leads to a deficiency of glycosylphosphatidylinositol-anchored proteins that normally protect erythrocytes from destruction by complement-mediated lysis. Both aplastic anaemia and PNH can undergo clonal evolution to MDS or AML, either by natural selection or in response to treatment[51]. The proportion of people diagnosed with aplastic anaemia who actually have MDS or AML is unclear and distinguishing between mild aplastic anaemia and MDS may be difficult or impossible[52]. This is mainly because mild aplastic anaemia and MDS

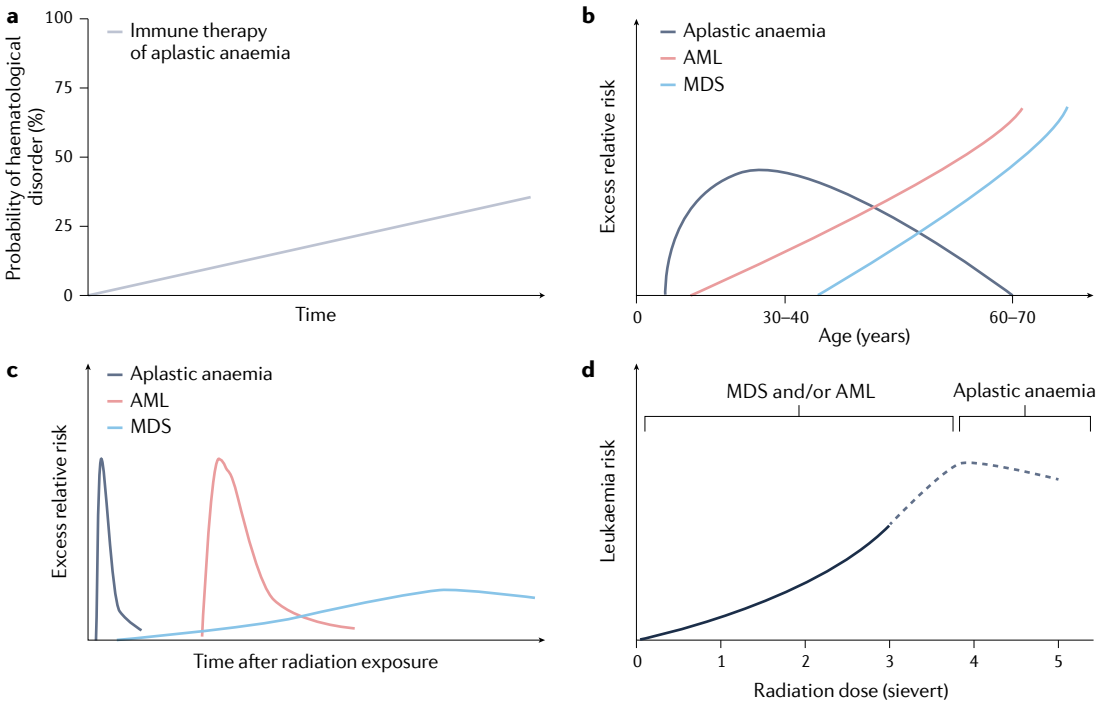

Fig. 2 | Drivers of the development of aplastic anaemia, MDS and AML. **a**, Probability of developing a clonal haematological disorder in individuals with aplastic anaemia receiving immune suppression. **b**, Incidence of aplastic anaemia, acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) as a function of age. **c**, Time course of development of aplastic anaemia, AML and MDS in individuals exposed to ionizing radiation from atomic bombs. **d**, Relationships between risks of MDS, AML and aplastic anaemia by radiation dose.

can have similar histological features and overlapping cytogenetic or molecular changes, which may reflect the early-stage nature of skewed haematopoiesis. Furthermore, some studies suggest that immune mechanisms in aplastic anaemia can also operate in some cases of MDS, especially mild MDS[69–71]. Furthermore, ~50% of people with aplastic anaemia have a PNH-like clone, although this proportion varies from 1% to 10% in different studies of people with MDS[72,73]. Some patients with PNH develop features of aplastic anaemia and/or AML as their disease evolves, and 10–20% of patients with MDS have a hypoplastic bone marrow (that is, containing few myeloid cells) at diagnosis, termed hypoplastic MDS (MDS-h; also referred to as hypocellular MDS) in the fifth edition of the WHO Classification[11].

Several factors could explain the overlap between these disorders in genotype, phenotype, aetiology, pathogenesis and pathophysiology. Different degrees of penetrance and expressivity of genetic alterations likely explain some of this overlap[74]. However, there are distinct differences in the frequencies of some cytogenetic abnormalities and mutations in these disorders. Cytogenetic abnormalities are detected in up to 15% of people with aplastic anaemia, the most common of which are trisomy 6, trisomy 8, trisomy 13 and del(7/7q)[57,75]. Cytogenetic abnormalities typical of PNH include trisomy 6, trisomy 8, del(5q) and del(7), and these alterations are present in 25% of patients[76]. About 60% of patients with MDS have cytogenetic abnormalities, including del(5/5q), del(7/7q), trisomy 8, del(17p), del(20q) and del(Y)[77]. Sometimes, these cytogenetic abnormalities are associated with specific mutation topographies[78]. Common cytogenetic abnormalities in AML include t(8;21), t(15;17), inv(16), t(6;9), inv(3)/t(3;3), 11q23 rearranged, del(5q/5), del(7q/7), del(17p) and complex/monosomal karyotype[11]. Translocations are common in AML but rare in these seemingly related disorders (Fig. 2).

MDS/MPN overlap syndromes

MDS and MPN overlap syndromes (MDS/MPN) are characterized by overlapping phenotypic and genotypic features of both entities. Chronic myelomonocytic leukaemia (CMML), a typical example of MDS/MPN, is characterized by persistent blood monocytosis. Common somatic mutations include those in spliceosome genes such as *SRSF2*, epigenetic regulators such as *TET2* and signal transduction genes such as *RAS*. The 2022 fifth edition of the WHO Classification provides an update on the diagnostic criteria for MDS/MPN. Two new subtypes of CMML, myelodysplastic CMML (white blood cell (WBC) count $<13 \times 10^9$/l) and myeloproliferative CMML (WBC count $\geq 13 \times 10^9$/l), are defined based on phenotype and genotype. Myeloproliferative CMML is associated with mutations in the *RAS* signalling pathway and has a poor prognosis. Previous subtypes of CMML-0 (a category for cases with <2% blood blasts and <5% bone marrow blasts) have been eliminated. Atypical chronic myeloid leukaemia is renamed MDS/MPN with neutrophilia to avoid confusion with typical chronic myeloid leukaemia associated with the *BCR::ABL1* fusion gene. MDS/MPN with ring sideroblasts (erythroblasts with a perinuclear concentration of iron-laden mitochondria that appear as a 'ring' by Prussian blue staining), thrombocytosis and *SF3B1* mutation is now classified as MDS/MPN with *SF3B1* mutation and thrombocytosis. A third category is MDS/MPN not otherwise specified.

Mutation topographies of these diseases also differ (Fig. 3). For example, mutations in RNA splicing genes, such as *SF3B1*, *SRSF2*, *U2AF1* and *ZRSR2*, are common in some forms of MDS (for example, *SF3B1*

and *SRSF2* mutations in MDS with ring sideroblasts and CMML) but are rare in aplastic anaemia, whereas the opposite is true for mutations in *BCOR1* and *PIGA*[79]. Common mutations in PNH include those in *BMPR2*, *F8*, *ITGA2B*, *THBD* and *THBS1* (ref.[80]). Mutations in *NPM1*, *FLT3* and *DNMT3A* are common in AML but uncommon in the other disorders[81,82].

Progression of a bone marrow failure disorder, such as PNH, to aplastic anaemia, MDS and/or AML may be associated with clones with similar or different cytogenetic abnormalities and mutation topographies[51]. However, the dominant clone in AML may have cytogenetic abnormalities and mutations unrelated to the antecedent MDS clone[83]. There are several possible explanations for these discordances. One is a clonal shift, whereby a mutant haematopoietic stem cell might give rise to subclones with different phenotypes (that is, aplastic anaemia and MDS subclones). Over time, as a consequence of therapy or chance, an initial dominant subclone is replaced by another and the disease genotype and phenotype may change[79,84]. An alternative hypothesis is a clone whose phenotype, and perhaps genotype, evolves from aplastic anaemia to MDS. As discussed above and elsewhere, it is sometimes difficult or impossible to distinguish mild aplastic anaemia from hypocellular MDS[52]. Getting the correct diagnosis (if there is one) is less important than receiving appropriate therapy. When there is ambiguity, immune suppression should be administered first as it is less likely to be fatal than HCT. MDS-h is recognized as a distinct MDS subtype in the fifth edition of the WHO Classification and is associated with immune-mediated bone marrow failure. MDS-h, PNH, aplastic anaemia and CCUS can share features and are sometimes difficult to accurately distinguish.

In summary, it is difficult to determine whether aplastic anaemia, PNH, MDS and AML are the same or different diseases. The genotypes and phenotypes of these disorders unavoidably overlap. In some people, these disorders can be considered one, evolving disease whereas, in others, they are distinct. We suggest that diagnosis should be probabilistic rather than deterministic and that physicians accept and acknowledge diagnostic uncertainty.

The 2022 WHO and ICC revised classifications of MDS

In 2022, the WHO and ICC proposed revised classifications of MDS[11,85] (Table 2). MDS are renamed myelodysplastic neoplasms (but continue to be abbreviated MDS) in the WHO Classification but not in the ICC; clonal haematopoiesis is recognized as a precursor disorder and CHIP and CCUS as clonal haematopoiesis in the WHO Classification whereas, in the ICC, pre-malignant clonal cytopenias are distinct entities, including CCUS. MDS genetic subtypes described in the WHO Classification include MDS with low blasts and isolated del(5q) (MDS-5q), MDS with low blasts and *SF3B1* mutation (MDS-*SF3B1*), and MDS with biallelic *TP53* inactivation (MDS-bi*TP53*), referred to in the ICC as MDS with del(5q), MDS with mutated *SF3B1*, and MDS with mutated *TP53*, respectively. In the WHO Classification, MDS is subdivided into MDS with low blasts (MDS-LB) or with increased blasts (MDS-IB), MDS with excess blasts 1 (MDS-EB1) and MDS-EB2 are renamed MDS-IB1 and MDS-IB2, and hypoplastic MDS and MDS with fibrosis are added as new MDS subtypes, whereas the ICC retains the 'MDS-EB' category.

In the WHO Classification, MDS in children is a new entity subdivided into childhood MDS-LB (cMDS-LB) or childhood MDS-IB (cMDS-IB). cMDS-LB replaces 'refractory cytopenia of childhood'. In the ICC, refractory cytopenia of childhood is included in a new subsection of paediatric and/or germline mutation-associated disorders. This new category for MDS in children and adolescents includes individuals with hypocellular bone marrow, somatic mutations in *SETBP1*, *ASXL1* and *RUNX1*, and abnormalities in the RAS–MAPK signalling pathway.

The WHO Classification suggests a balanced approach to distinguishing between MDS and AML with bone marrow blast percentage cutoffs for most AML subtypes. The WHO Classification retains a 20% blast cutoff between MDS and AML but allowing a 10% cutoff for MDS/AML, which is considered an overlapping entity. Notably, the 20% blast requirement is also eliminated for AML subtypes with defining genetic abnormalities except for AML with *BCR–ABL1* or *CEBPA* mutations. The WHO Classification does not include an MDS/AML entity. There is agreement in both classifications that people with ≥10% blasts can be considered equivalent to having AML in the context of therapy and for inclusion in clinical trials.

MDS, unclassifiable (MDS-U) is no longer a distinct entity in either the WHO Classification or the ICC. The ICC introduces two distinct entities. The first is 'AML with myelodysplasia-related gene mutations', which includes MDS without *TP53* mutations but which has mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1* and/or *ZRSR2*. These mutations are considered associated with secondary AML with prior MDS or MDS/MPN. The second category is a new one: 'AML with myelodysplasia-related cytogenetic abnormalities', which includes cases previously classified as AML with myelodysplasia-related changes (AML-MRC) based on MDS-associated cytogenetic findings but without *TP53* mutation or MDS-related mutations.

Molecular pathophysiology of MDS

Frequent genetic events associated with the development of MDS are displayed in Figs. 4 and 5. Among individuals with MDS, 80–90% have a somatic mutation in more than 1 of >40 recurrently mutated

Table 1 | Similarities and differences between aplastic anaemia, paroxysmal nocturnal haemoglobinuria and myelodysplastic syndromes

Condition	Phenotype	Aetiology	Pathogenesis and pathophysiology	Cytogenetic alterations	Molecular genetic alterations
Aplastic anaemia	Pancytopenia, hypoplasia and increase in non-haematopoietic cells, non-heterocyst	Genetic alterations, immune disease, environmental factors and idiopathic causes	Autoimmune condition	Trisomy 6, trisomy 8, trisomy 13, del(7/7q), del(20q) and del(Y)	Mutations in *PIGA*, *BCOR* and *BCORL1*
Paroxysmal nocturnal haemoglobinuria	Haemolytic anaemia, haematuresis, thrombosis, icterus and megalosplenia	Genetic alterations	Bone marrow failure disorder	Trisomy 6, trisomy 8, del(5q) and monosomy 7	Mutations in *BMPR2*, *ITGA2B*, *THBD* and *THBS1*
Myelodysplastic syndromes	Refractory cytopenia, ineffective haematopoiesis, increase in primitive cells and abnormal cells	Ageing, ionizing radiation, chemical exposure, irradiation, immune abnormalities	Peripheral blood cytopenia and myelodysplasia or dysplasia	del(5/5q), del(7/7q), trisomy 8, del(17p), del(20q) and del(Y)	Mutations in *TP53*, *ASXL1*, *TET2* and *DNMT3A*, *SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*

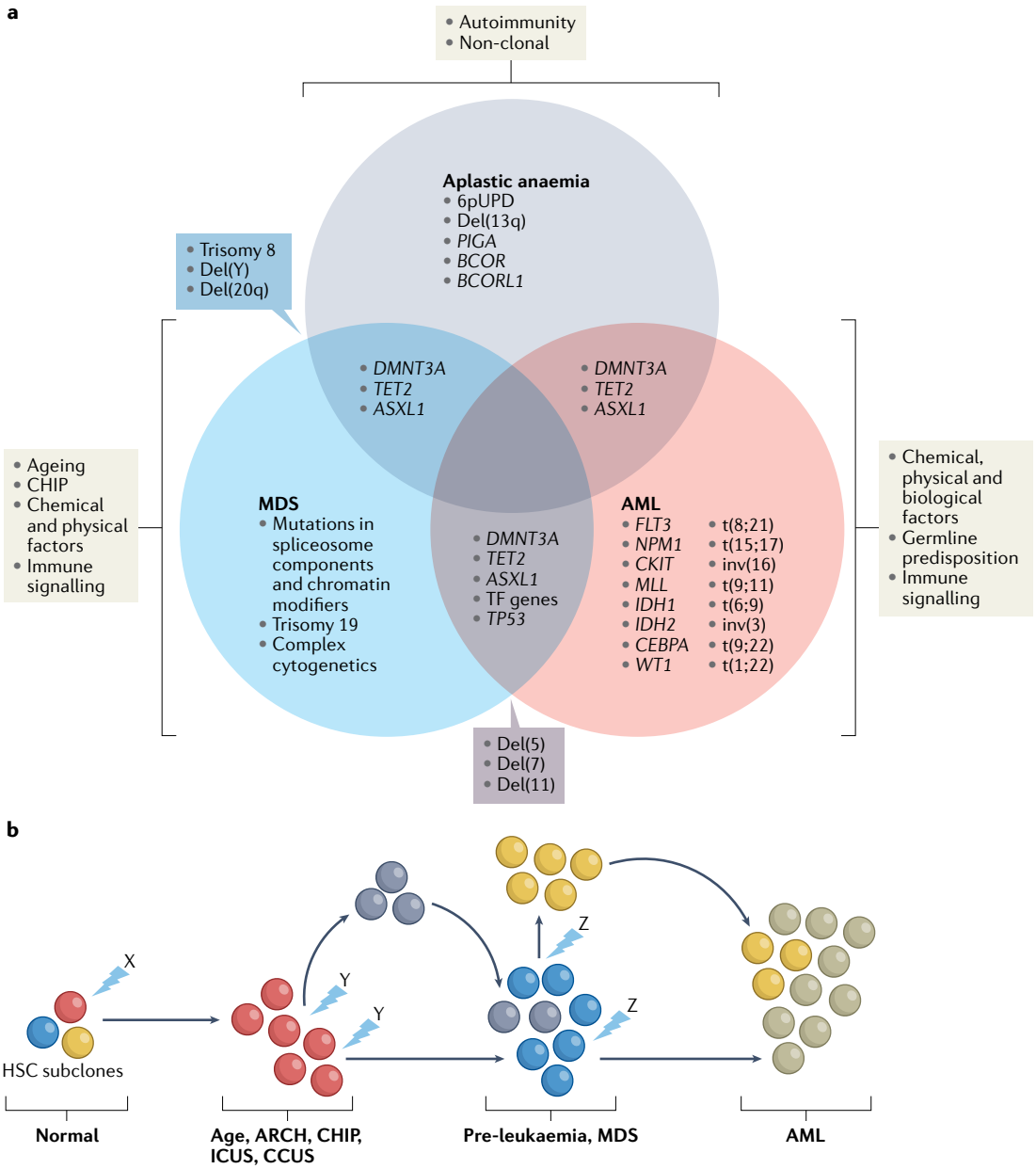

Fig. 3 | Relationship between aplastic anaemia, MDS and AML. a, Inter-relationships between aplastic anaemia, myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML). The factors driving mutagenesis in these conditions and the common cytogenetic abnormalities and mutations in each condition are depicted. **b**, Clonal evolution of MDS and AML. A normal haematopoietic stem cell (HSC) acquires one or more somatic mutations from intrinsic or extrinsic factors (X), resulting in clonal expansion with (idiopathic cytopenias of undetermined significance (ICUS), clonal cytopenia of undetermined significance (CCUS)) or without (age-related clonal haematopoiesis (ARCH), clonal haematopoiesis of indeterminate potential (CHIP)) haematopoietic abnormalities. Subsequent mutations, intrinsic or extrinsic (Y and Z), can expand the clone or subclones, resulting in further clonal expansion that can lead to a pre-leukaemia state, MDS and, eventually in some instances, AML. TF, transcription factor.

genes[78,86–88]. The most common mutations are in genes encoding epigenetic regulators, namely *DNMT3A, TET2, IDH1* and *IDH2*, the chromatin modifiers *EZH2* and *ASXL1*, the transcription regulators *ETV6*, *RUNX1* and *BCOR*, the cohesin complex components *STAG2*, *CTCF* and *SMC1A*, the DNA repair gene *TP53*, the spliceosome components *SF3B1*, *U2AF1*, *SRSF2* and *ZRSR2*, and the signal transduction genes *JAK2*, *KRAS* and *CBL*[78,89,90] (Table 3). A study reported race as an important consideration in the genomic classification of MDS with different prediction accuracies[91]. Different mutations are preferentially associated with specific MDS phenotypes and with diverse clinical outcomes, and the specific mutation has implications for therapeutic choice. A study used machine learning algorithms to identify patterns of co-occurrence

among genotypic and phenotypic features of MDS and to identify potential interactions[92]. People with similar histological or mutation topographies clustered into five histological profiles (for example, the majority of the higher-risk MDS cohort is enriched in profile 1 while patients at lower risk cluster into the remaining four profiles) and eight mutational profiles (for example, groups A, B, G and H contain *TET2*, coexisting *TET2* and *SRSF2*, *SF3B1*, and *BCORL1* mutations, respectively, whereas groups C–F contain more heterogeneous features), suggesting an association with specific morphological profiles. Importantly, this study interrogated these categories with clinical outcomes.

The specification of previous MDS subtypes with specific mutations in the fifth edition of the WHO Classification (that is, MDS-5q, MDS-*SF3B1* and MDS-bi*TP53*) will either illustrate the low-risk nature of some MDS cases and have implications for their effective treatment (for example, lenalidomide for MDS-5q and luspatercept for MDS-*SF3B1*) or indicate the aggressive disease course such that early administration of hypomethylating drugs plus HCT intervention is recommended, if applicable, or individuals with these subtypes are included in clinical trials.

MDS-5q is a special entity that is treatable with lenalidomide. The efficacy of this drug is thought to be due to its ability to alter the target specificity of the E3 ubiquitin ligase CUL4–RBX1–DDB1–CRBN so that casein kinase 1 isoform-α (CK1α; encoded by *CSNK1A1*) is ubiquitylated and undergoes proteasomal degradation, thereby correcting a defect in ribosomal protein[93,94]. *CSNK1A1* present within the region deleted in MDS-5q and *CSNK1A1* haploinsufficiency sensitize cells to lenalidomide.

MDS-*SF3B1* is a new entity in the WHO Classification and ICC that responds to luspatercept-aamt, a recombinant fusion decoy protein that binds to several endogenous TGFβ superfamily ligands to reduce SMAD2 and SMAD3 signalling, thereby promoting the maturation of late-stage erythroid precursors.

Therapy-related MDS and MDS-bi*TP53* are associated with poor response to conventional treatments and dismal outcome. These two disease categories frequently include patients with prior exposure to anticancer treatments. It is now clear that MDS-bi*TP53* is a distinct molecular entity and that the *TP53* allelic state has major implications for genome stability, clinical presentation and outcomes in patients with this subtype.

Biallelic but not monoallelic *TP53* mutations are an important prognostic co-variate in MDS. A study by the International Working Group for MDS Molecular Prognostic Committee reported that people with MDS and complex cytogenetics and somatic mutations who have a *TP53* mutation have a worse prognosis than similar people without a *TP53* mutation[95]. A study of patients with a *TP53* mutation reported that allelic imbalance correlates with complex cytogenetics, few co-mutations and other high-risk features[96]. Biallelic *TP53* mutations are also an independent adverse risk factor in the revised International Prognostic Scoring System (IPSS-R) model[96] whereas monoallelic *TP53* mutations are not[95].

The cohesin complex is a multisubunit protein complex that forms a ring-like structure around DNA and is an important transcription regulator that is also involved in DNA damage repair. Mutations in the main genes encoding the cohesin complex, namely *STAG2*, *RAD21*, *SMC1* and *SMC3*, are present in some patients with MDS or MDS/MPN, including CMML. Cohesin complex mutations alter the self-renewal, differentiation, lineage commitment and genomic integrity of haematopoietic stem cells[97–100].

Mutations in *DNMT3A, TET2* and *ASXL1*, which encode regulators of DNA methylation, are detected in some patients with MDS but are also present in otherwise healthy people of comparable age, in which case they are termed CHIP and CCUS[101]. These mutations are necessary but not sufficient to cause MDS and the presence of some of these can be considered a pre-MDS condition. People with CHIP have a cumulative risk of developing a haematological cancer of 0.5–1% per year[102,103]. People with CCUS with two or more typical MDS-related mutations have a very high likelihood of developing a myeloid neoplasm within a median of 2 years and a cumulative risk of developing MDS of 10–20%

Table 2 | Comparison of the WHO Classification, fifth edition, and International Consensus Classification of MDS

Category	WHO Classification, fifth edition	International Consensus Classification
Category 1: 'Precursor' state	Clonal haematopoiesis: CHIP, CCUS	CCUS
Category 2: Myelodysplastic neoplasms/syndromes	MDS with defining genetic abnormalities; MDS with low blasts and isolated 5q deletion (MDS-5q); MDS with low blasts and *SF3B1* mutation (MDS-*SF3B1*); MDS with biallelic *TP53* inactivation (MDS-bi*TP53*); MDS, morphologically defined; MDS with low blasts; MDS, hypoplastic; MDS-IB: MDS-IB1, MDS-IB2, MDS with fibrosis	MDS with mutated *SF3B1*; MDS with del(5q); MDS with mutated *TP53*; MDS NOS:MDS NOS without dysplasia; MDS NOS with single lineage dysplasia; MDS NOS with multilineage dysplasia; MDS with excess blasts
Category 3: Myelodysplastic/ myeloproliferative neoplasms	CMML; CMML subtyping criteria: myelodysplastic CMML, myeloproliferative CMML; CMML subgrouping criteria: CMML-1, CMML-2; MDS/MPN with neutrophilia; MDS/MPN with *SF3B1* mutation and thrombocytosis; MDS/MPN, NOS	CMML; clonal cytopenia with monocytosis of undetermined significance; clonal monocytosis of undetermined significance; atypical chronic myeloid leukaemia; MDS/MPN with thrombocytosis and *SF3B1* mutation; MDS/MPN with ring sideroblasts and thrombocytosis, NOS; MDS/MPN, unclassifiable
Category 4: Paediatric MDS	Childhood MDS: Childhood MDS with low blasts; hypocellular; NOS; childhood MDS with increased blasts	Paediatric and/or germline mutation-associated disorders: juvenile myelomonocytic leukaemia; juvenile myelomonocytic leukaemia-like neoplasms; Noonan syndrome-associated myeloproliferative disorder; refractory cytopenia of childhood; haematological neoplasms with germline predisposition
Category 5: MDS/AML	Not applicable	MDS/AML with mutated *TP53*; MDS/AML with myelodysplasia-related gene mutations; MDS/AML with myelodysplasia-related cytogenetic abnormalities; MDS/AML, NOS

AML, acute myeloid leukaemia; CHIP, clonal haematopoiesis of indeterminate potential; CCUS, clonal cytopenia of undetermined significance; CMML, chronic myelomonocytic leukaemia; MDS, myelodysplastic syndromes; MDS-IB, MDS with increased blasts; MPN, myeloproliferative neoplasm; NOS, not otherwise specified.

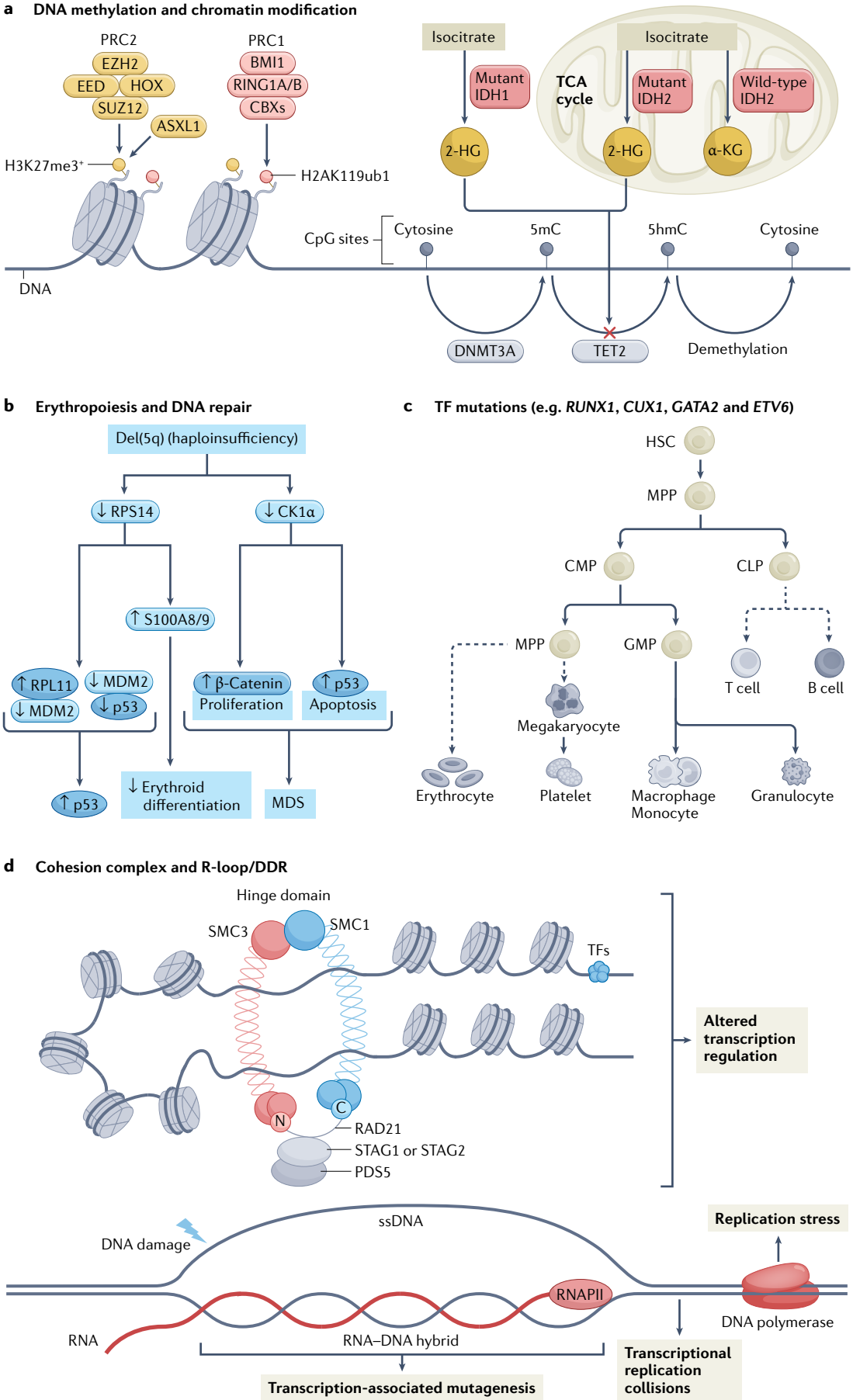
a DNA methylation and chromatin modification
PRC2
EZH2
EED
HOX
SUZ12
ASXL1
PRC1
BMI1
RING1A/B
CBXs
H3K27me3+
H2AK119ub1
DNA
Isocitrate
Mutant IDH1
2-HG
TCA cycle
Isocitrate
Mutant IDH2
2-HG
Wild-type IDH2
α-KG
CpG sites
Cytosine
5mC
5hmC
Cytosine
DNMT3A
TET2
Demethylation
b Erythropoiesis and DNA repair
Del(5q) (haploinsufficiency)
↓ RPS14
↓ CK1α
↑ S100A8/9
↑ RPL11
↓ MDM2
↓ MDM2
↓ p53
↑ β-Catenin
Proliferation
↑ p53
Apoptosis
↑ p53
↓ Erythroid differentiation
MDS
c TF mutations (e.g. RUNX1, CUX1, GATA2 and ETV6)
HSC
MPP
CMP
CLP
MPP
GMP
T cell
B cell
Megakaryocyte
Erythrocyte
Platelet
Macrophage
Monocyte
Granulocyte
d Cohesion complex and R-loop/DDR
Hinge domain
SMC3
SMC1
TFs
Altered transcription regulation
N
C
RAD21
STAG1 or STAG2
PDS5
ssDNA
DNA damage
Replication stress
RNAPII
DNA polymerase
RNA
RNA–DNA hybrid
Transcriptional replication collisions
Transcription-associated mutagenesis

Fig. 4 | Frequent mutations affecting transcription, erythropoiesis, and DNA repair and conformation in MDS. a, DNA methylation and chromatin modification abnormalities in myelodysplastic syndromes (MDS). An impaired tricarboxylic acid (TCA) cycle as a result of mutations in *IDH1* or *IDH2* leads to epigenetic changes that alter transcription. **b**, Del(5q) results in aberrant erythropoiesis and DNA repair in MDS by dysfunctional p53 function. **c**, Mutations in multiple transcription factor (TF) genes (*RUNX1* is depicted as an example) can result in aberrant haematopoiesis aspects (such as decreased gene expression) in MDS. **d**, Mutations in cohesion complex-related genes (such as *STAG2*) and formation of R-loop/DNA damage response (DDR) cause altered transcriptional programming in MDS. 2-HG, 2-hydroxyglutarate; C, carboxyl terminus; CK1α, casein kinase 1 isoform-α; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte-monocyte progenitor; HSC, haematopoietic stem cell; MPP, multipotent progenitor; N, amino terminus; RNAPII, RNA polymerase II; ssDNA, single-stranded DNA. Part **a** adapted with permission from ref.[99], Elsevier. Part **b** adapted from ref.[108], Springer Nature Limited. Part **d** adapted with permission from ref.[99], Elsevier, and from ref.[100], Springer Nature Limited.

per year. The WHO Classification defines CHIP and CCUS as precursor conditions to developing myeloid malignancies. A functional *TP53* mutation has been detected in some healthy older people[104], suggesting that age-related mutations can even precede diagnosis. Preclinical studies show that haematopoietic stem and progenitor cells bearing age-related *TP53* mutations are resistant to chemotherapy, expand preferentially following treatment, and are typical characteristics of patients with therapy-related AML or therapy-related MDS[104]. In addition, a large cohort study of 4,229 individuals detected cases of inherited CHIP. Interestingly, these germline genetic variations reconstruct haematopoietic stem cell destiny and lead to CHIP that links to clonal haematopoiesis and cause somatic mutations across different tissues[105].

MDS is characterized by genome-wide hypermethylation that results in silencing of gene expression by transcription inhibition[106,107]. However, hypermethylation in patients with MDS is more widespread than can be accounted for by mutations in epigenetic regulator genes. These mutations probably do not cause MDS but are associated with clonality and set the stage for MDS development, interact with other mutations and impact prognosis[108]. Among different genetic alterations identified in MDS, there are therapeutic implications for some druggable mutations such as those in *IDH1*, *IDH2, JAK2, TP53* and spliceosome component genes (Table 3). For example, the *IDH1* and *IDH2* inhibitors ivosidenib and enasidenib are active in people with high-risk MDS who carry *IDH1* and *IDH2* mutations[109,110].

Mutations in RNA splicing factors, such as *SRSF2*, *SF3B1*, *U2AF1* and *ZRSR2*, are common in some forms of MDS[89]. For example, *SRSF2* mutations result in skewed binding affinity and specificity of SRSF2 with its RNA consensus motif and decreased RNA splicing efficacy[111]. Mis-spliced RNAs can be degraded by the biological surveillance system nonsense-mediated decay or are translated into dysfunctional proteins. These effects might partially explain cytopenias and/or ineffective haematopoiesis in MDS[112]. *SF3B1* mutations are especially common in people with ring sideroblasts with erythroid dysplasia, who respond preferentially to luspatercept and lenalidomide[113–117]. The responsiveness to these two drugs is significant because it helps to alleviate the transfusion burden and decreases related iron removal costs and/or other potential harm of iron overload (for example, increased risk of transformation to AML). MDS with an *SF3B1* mutation is proposed as a distinct entity by the International Working Group for the Prognosis of MDS and is associated with anaemia, myelodysplasia with or without presence of ring sideroblasts and a blast count <1% and <5% in the blood and bone marrow, respectively[117].

Mutations in *U2AF1* are associated with a poor prognosis[118,119] and typically occur at amino acids S34 and Q157 within zinc finger domains, causing a selection bias at 3′ splice sites[120]. *U2AF1* mutations result in mis-splicing of the autophagy gene *ATG7*, resulting in inhibition of autophagy and leading to mitochondrial dysfunction and genome instability. These effects predispose cells to additional mutations that may result in transformation[121]. Some studies suggest that mutations in *U2AF1* and *SF3B1* induce the expression of targetable 'active' isoforms of IRAK4 and provide a genetic link to the activation of innate immune signalling observed in MDS[122,123].

Individuals with *ZRSR2* mutations typically present with isolated neutropenia and increased bone marrow blasts and have a high risk of transformation to AML[124]. *ZRSR2* is involved in assembly of the minor (U12-dependent) spliceosome. Short hairpin RNA-mediated knockdown of *ZRSR2* results in impaired splicing of U12-type introns. Furthermore, RNA sequencing of bone marrow cells from individuals with MDS indicates loss of *ZRSR2* expression in those with *ZRSR2* mutation, resulting in increased mis-splicing[125]. *ZRSR2*-deficient cells also have a reduced proliferation potential and a marked decrease of burst-forming unit–erythroid cells and an increase of colony-forming unit–macrophages in vitro[125].

Splicing factor mutations are typically mutually exclusive but single-cell analyses indicate that ~1% of patients with MDS have two or more splicing factor mutations[126]. These double splicing factor mutations are characterized by selection against the most common alleles (that is, *SF3B1*^{K700E} and *SRSF2*$^{P95H/L/R}$) and for less common alleles (that is, *SF3B1* non-K700E mutations, rare amino acid substitutions at *SRSF2*^{P95} and combined *U2AF1*$^{S34/Q157}$ mutations). This allele-specific difference is crucial in regulating the effects of these mutations on splicing factor function[126].

As discussed above, the two most common sites of mutations in MDS are epigenetic regulator genes and RNA splicing genes. How these interact is unknown but may be central to the pathogenesis of some cases of MDS. Studies suggest that the co-occurrence of *SRSF2* and *IDH2* mutations results in increased self-renewal and, in mice, a phenotype different from that of either mutation alone[127]. Functional study data indicate that *SRSF2* and *IDH2* double-mutant cells have aberrant splicing and decreased expression of *INTS3*, which drives the development of myeloid cancers in concert with *IDH2* mutation and with abnormal binding of SRSF2 to *cis*-elements in the *INTS3* mRNA, resulting in increased *INTS3* methylation and, as a consequence, reduced INTS3 expression[127]. *SRSF2* mutations also promote leukaemia development in *IDH2*-mutated cells[127].

Diagnosis, screening and prevention

Clinical features

MDS was previously termed *il morbo di Guglielmo* (Di Guglielmo disease), refractory anaemia, pre-leukaemia, idiopathic acquired sideroblastic anaemia and smouldering acute leukaemia[128–130]. The modern classifications of MDS started with 2 categories of 'dysmyelopoietic syndromes' in the 1976 French–American–British (FAB) classification[131], 5 categories of 'myelodysplastic syndromes' in the 1982 FAB classification[132], 10 MDS categories in the third edition of the WHO Classification (1999–2001)[133,134], 11 MDS categories in the fourth edition of the WHO Classification (2008)[135], and the integration of haematological, histological, cytogenetic and molecular covariates in the updated fourth edition of the WHO Classification (2016)[136]. The 2022 fifth edition of the WHO Classification distinguishes 8 subtypes of MDS, grouped as 3 subtypes that are defined by genetic abnormalities (MDS-5q, MDS-*SF3B1* and MDS-bi*TP53*) and 5 subtypes that are defined histologically (MDS-LB, MDS-h and three MDS-IB subtypes). Of note, the diagnosis and category of MDS is based on the proportion of immature myeloid cells

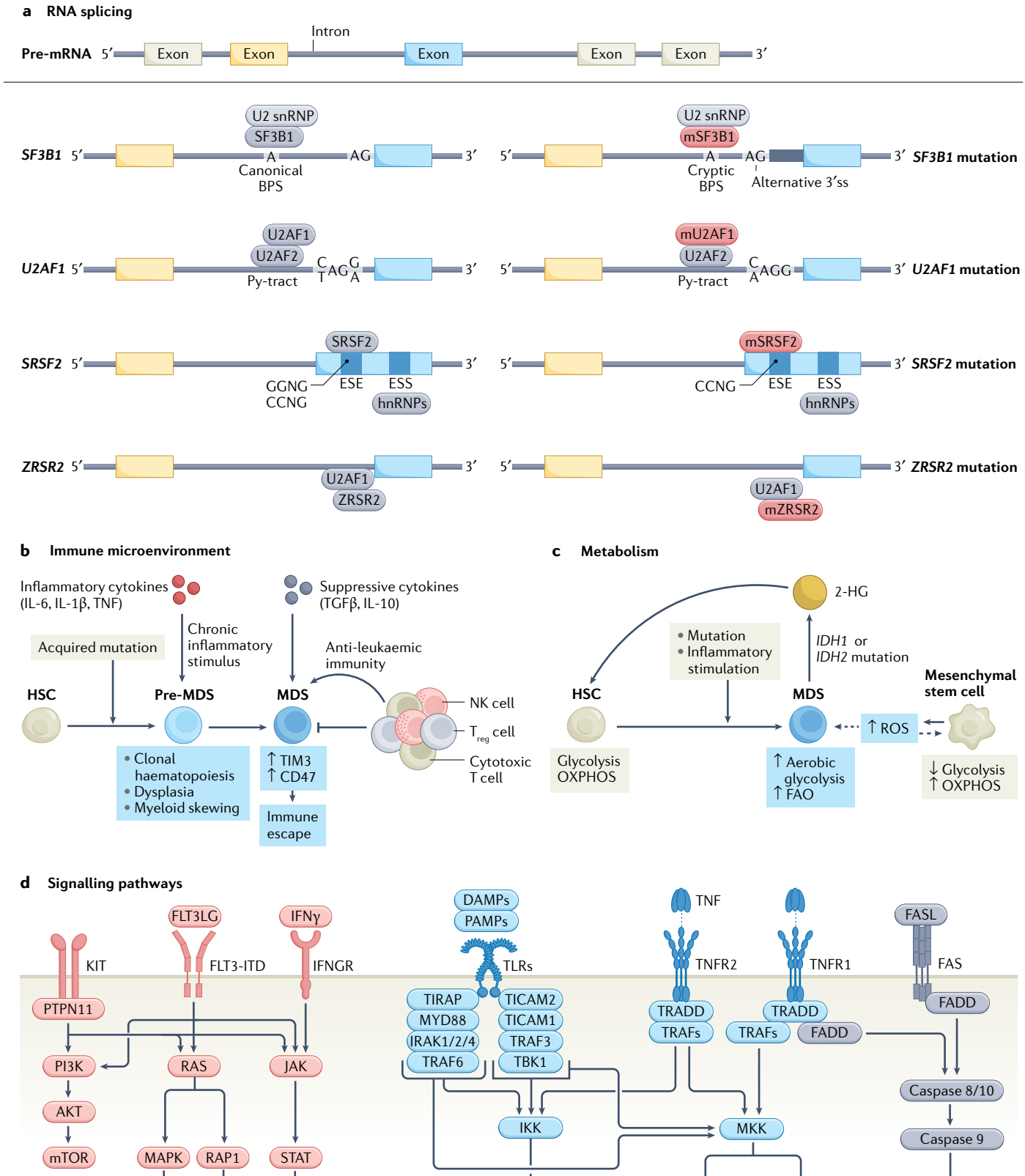
a RNA splicing
Pre-mRNA 5′
Exon
Exon
Intron
Exon
Exon
Exon
3′
SF3B1 5′
U2 snRNP
SF3B1
A
AG
Canonical BPS
3′
5′
U2 snRNP
mSF3B1
A
AG
Cryptic BPS
Alternative 3′ss
3′ SF3B1 mutation
U2AF1 5′
U2AF1
U2AF2
Py-tract
C T AG G A
3′
5′
mU2AF1
U2AF2
Py-tract
C A AGG
3′ U2AF1 mutation
SRSF2 5′
SRSF2
GGNG CCNG
ESE
ESS
hnRNPs
3′
5′
mSRSF2
CCNG
ESE
ESS
hnRNPs
3′ SRSF2 mutation
ZRSR2 5′
U2AF1
ZRSR2
3′
5′
U2AF1
mZRSR2
3′ ZRSR2 mutation
b Immune microenvironment
Inflammatory cytokines (IL-6, IL-1β, TNF)
Suppressive cytokines (TGFβ, IL-10)
Acquired mutation
Chronic inflammatory stimulus
Anti-leukaemic immunity
HSC
Pre-MDS
MDS
NK cell
Treg cell
Cytotoxic T cell
• Clonal haematopoiesis
• Dysplasia
• Myeloid skewing
↑ TIM3
↑ CD47
Immune escape
c Metabolism
2-HG
• Mutation
• Inflammatory stimulation
IDH1 or IDH2 mutation
HSC
MDS
Mesenchymal stem cell
↑ ROS
Glycolysis
OXPHOS
↑ Aerobic glycolysis
↑ FAO
↓ Glycolysis
↑ OXPHOS
d Signalling pathways
KIT
FLT3LG
FLT3-ITD
IFNγ
IFNGR
DAMPs
PAMPs
TLRs
TNF
TNFR2
TNFR1
FASL
FAS
PTPN11
TIRAP
MYD88
IRAK1/2/4
TRAF6
TICAM2
TICAM1
TRAF3
TBK1
TRADD
TRAFs
TRADD
TRAFs
FADD
FADD
PI3K
RAS
JAK
AKT
mTOR
MAPK
RAP1
STAT
IKK
MKK
Caspase 8/10
Caspase 9
Caspase 3
MAPK8
p38
Cytoplasm
Nucleus
TF
NF-κB
NF-κB
AP1
TF
Apoptosis

Fig. 5 | Frequent mutations in RNA splicing, immune function and metabolism in MDS. a, Mutations in RNA splicing factors alter exon inclusion, resulting in mis-splicing of pre-mRNA (right panel) and leading to the production of aberrant proteins with potentially pro-oncogenic functions or effects. **b**, Immune factors, such as dysfunctional immune cells, skewed cytokine production and/or stromal cell disruption, alter the myelodysplastic syndrome (MDS) microenvironment, potentially contributing to tumour development and progression. **c**, Metabolic dysregulation of haematopoietic stem cells (HSCs) and niche cells might contribute to MDS development. **d**, Deregulation of innate immune, inflammatory and other signalling pathways might contribute to MDS development. 2-HG, 2-hydroxyglutarate; 3′ss, 3′ splice site; BPS, branch point sequence; DAMPs, damage-associated molecular patterns; ESE, exonic splicing enhancer; ESS, exonic splicing silencer; FAO, fatty acid oxidation; hnRNPs, heterogeneous nuclear ribonucleoproteins; NK, natural killer; OXPHOS, oxidative phosphorylation; PAMPs, pathogen-associated molecular patterns; Py-tract, pyrimidine tract; ROS, reactive oxygen species; snRNPs, small nuclear ribonucleoproteins; TF, transcription factor; T_{reg}, regulatory T. Part **c** adapted from ref.[86], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **d** adapted from ref.[87], Springer Nature Limited.

(myeloblasts) in the bone marrow (≥20% myeloblasts in AML and <20% myeloblasts in MDS) and in peripheral blood, the extent of dysplasia, and the presence of ring sideroblasts[11].

The median age at diagnosis for MDS is 70 years but diagnosis can occur at any age[4]. The usual presentation involves signs and/or symptoms resulting from bone marrow failure, including fatigue, pallor, infection and bleeding. Laboratory abnormalities include low haemoglobin and granulocyte and/or platelet concentrations. Some individuals with MDS are diagnosed based on abnormalities detected on a routine blood examination or one performed for an unrelated medical condition. An enlarged spleen and lymph nodes are uncommon in MDS and should lead one to consider other diagnoses. Some individuals with MDS improve when given immunosuppressive drugs such as anti-thymocyte globulin or cyclosporine. Some of these cases may have been aplastic anaemia rather than MDS but this is controversial as some data suggest efficacy of these drugs in MDS.

MDS is uncommon in children, with an incidence of 1–2 cases per million population[11,137]. The disease is biologically distinct from MDS in adults. It is often associated with an inherited bone marrow failure syndrome and germline mutations, such as *GATA2* and *DDX41*, instead of acquired somatic mutations (discussed below). Differential diagnoses for MDS in children include infection, juvenile myelomonocytic leukaemia, myeloid proliferation associated with trisomy 21 (Down syndrome), and hereditary bone marrow failure syndromes such as Fanconi anaemia, Shwachman–Diamond syndrome and Diamond–Blackfan anaemia.

Histology

A bone marrow aspirate and/or biopsy is essential for accurate diagnosis and classification of MDS. Increased bone marrow cellularity is common in MDS, although hypocellularity is also consistent with a diagnosis of MDS. The fifth edition of the WHO Classification of myeloid neoplasms requires that 10% of cells have abnormal histology within a lineage to be designated as dysplasia[11].

Red blood cell (RBC) abnormalities are common in MDS. Erythrocytes tend to have a normal or high mean corpuscular volume. Other typical RBC changes include basophilic stippling, multinucleation, nuclear budding, karyorrhexis (nuclear fragmentation), irregular chromatin condensation, and asynchronous maturation of the nucleus and cytoplasm. Ring sideroblasts characterize some subtypes of MDS[90,117].

Abnormalities in neutrophils and granulocytes are also common in MDS, including hypogranular granulocytes and pseudo-Pelger–Huët anomaly (bilobed instead of the normal trilobed nuclei in neutrophils)[138]. Excess myeloblasts may be present, with a phenotype similar to that in AML (for example, frequent infections, skin looking pale or 'washed out', tiredness, and unusual and frequent bleeding such as bleeding gums or nosebleeds). A left shift in the differential WBC count should raise the prospect of MPN. Accurate enumeration of myeloblasts is essential to distinguish MDS from AML. Abnormal localization of blast clusters in bone marrow slides sometimes complicates analyses. We discuss arbitrariness and related considerations below.

Megakaryocyte changes consist of widely separated nuclear lobes or small size with absent nuclear lobation or hypolobation, including micro-megakaryocytes, mononuclear megakaryocytes, dumbbell-shaped nuclei, hypersegmentation and multinuclearity with multiple isolated nuclei. Giant platelets and platelet anisotropy are also common in MDS[139].

Immune phenotype

The value of analysing data on immune phenotype in MDS is controversial and, if used, should be integrated with histological, cytogenetic and molecular data for an accurate diagnosis. Abnormalities include overexpression, underexpression, aberrant and/or asynchronous antigen expression of myeloid cell markers and lineage infidelity (loss of original identity in differentiated haematopoietic cells and either de-differentiation to an earlier stage or transdifferentiation to a different cell type in the same or an entirely different haematopoietic lineage). Some studies suggest that the immune phenotype can be used to distinguish MDS from other causes of bone marrow failure but this is controversial[140,141].

Cytogenetic analysis

Cytogenetic changes are considered 'macrostate' changes that reflect genetic abnormalities, which are 'microstate' changes. Multiple techniques for detecting chromosomal abnormalities in MDS have been developed in past decades, among which metaphase cytogenetics or karyotyping, fluorescence in situ hybridization, spectral karyotyping, genotyping, and array-based comparative genomic hybridization have been widely used in clinical practice. Diagnosis of MDS is sometimes supported by conventional cytogenetic analyses (for example, karyotyping and fluorescence in situ hybridization), which can inform about clonality but is less sensitive than clonality defined by next-generation sequencing. Abnormalities associated with MDS are divided into five risk categories (Table 4). Clonal cytogenetic abnormalities associated with a very good prognosis include del(Y) and del(11), which occur in <5% of MDS cases. Cytogenetic abnormalities associated with a favourable prognosis include normal cytogenetics, del(5q), del(12p), del(20q) and the presence of >1 abnormality including del(5q), which are detected in about 70% of individuals with MDS. Cytogenetic abnormalities associated with an intermediate prognosis include del(7q), trisomy 8, trisomy 19, isochromosome 17q (loss of 17p and duplication of 17q), and any other single or double chromosomal aberration, which occur in 15–20% of MDS cases. Cytogenetic abnormalities associated with an unfavourable prognosis include del(7), inv(3), t(3q), del(3q), >1 abnormality including del(7//7q), and the presence of three abnormalities, which occur in about 5% of cases[142,143]. Cytogenetic abnormalities associated with very poor outcomes include more than three abnormalities, which are detected in 5–10% of individuals with MDS[142,143]. None of these cytogenetic abnormalities is specific to MDS. For example, many occur in individuals with AML and other haematological cancers (for example, myeloma and lymphoma) and related diseases discussed above (PNH, aplastic anaemia and CCUS). Furthermore, cytogenetic analysis does not capture the full extent of genetic changes in MDS. For example, individuals with complex cytogenetic abnormalities often have a *TP53* mutation[144–148], ~60% of individuals with MDS and

normal cytogenetics have mutations detected by next-generation sequencing[77,78], and copy number alterations are common in MDS[149].

Prognostic risk models and scores

As discussed earlier, MDS includes heterogeneous genotypes and phenotypes with diverse aetiologies, pathogeneses, pathophysiologies and prognoses, requiring different therapeutic strategies with different target end points such as reversing anaemia or preventing transformation to AML. Consequently, developing an accurate prognostic score is challenging. Nevertheless, several such scores have been developed and are widely used to predict outcomes and direct therapeutic interventions, including the International Prognostic Scoring System (IPSS)[150], IPSS-R[142], and systems that use artificial intelligence or machine learning algorithms to incorporate molecular mutations into prognostication[151] such as the Personalized Prediction Model and the IPSS-Molecular[152]. Furthermore, the WHO Classification-based Prognostic Scoring System (WPSS) is also used[153,154], although not as widely as IPSS and IPSS-R. Covariates included in these systems and risk cohorts are displayed in Table 5.

Table 3 | Mutation frequency, prognostic impact of mutation topography and targeted drugs in MDS

Mutated genes	Frequency	Prognostic impact	Targeted therapies[a]
Epigenetic regulators			
TET2	20%	No impact on survival, mutant *TET2* may predict better response to HMD	HMD
DNMT3A	5–10%	Unfavourable indicator, especially in *SF3B1* co-mutated MDS-RARS	HMD
IDH1 and *IDH2*	5–10%	Unfavourable	Ivosidenib and enasidenib
Chromatin modifiers			
ASXL1	10–20%	Unfavourable	BAP1 inhibitor
EZH2	10%	Unfavourable	Tazemetostat
Transcription regulators			
RUNX1	15%	Unfavourable	BET inhibitor or Menin inhibitors
ETV6	2–5%	Unfavourable	NA
BCOR	5%	Unfavourable	NA
Cohesin complex components			
STAG2	<10%	Unfavourable	NA
CTCF	<5%	Unfavourable	NA
SMC1A	<5%	Unfavourable	NA
Spliceosome components			
SF3B1	20% in MDS and 65% in MDS-RS	Favourable	Luspatercept or IRAK inhibitors
SRSF2	10–20%	Unfavourable	NA
U2AF1	<10%	Unfavourable	IRAK inhibitors
ZRSR2	<10%	Unfavourable	NA
Signal transduction genes			
JAK2	50% in RARS-T	Unfavourable	Ruxolitinib
KRAS	2–5%	Unfavourable	Antroquinonol
CBL	2–5%	Unfavourable	NA
DNA repair genes			
TP53	5–10%	Unfavourable	Eprenetapopt

HMD, hypomethylating drug; MDS, myelodysplastic syndromes; MDS-RS, MDS with ring sideroblasts; MDS-RARS, MDS with refractory anaemia and ring sideroblasts; NA, not available; RARS-T, refractory anaemia with ring sideroblasts associated with marked thrombocytosis. [a]Note that most targeted agents are of unproven impact.

The IPSS uses bone marrow blast percentage, cytogenetics and numbers of cytopenias to define four risk cohorts: low, intermediate-1, intermediate-2 and high risk[150]. The IPSS-R adds more precisely defined haemoglobin, platelet and neutrophil concentrations to identify five risk cohorts: very low, low, intermediate, high and very high risk[142]. A comparison revealed differences in the concordance (C)-statistic for IPSS and IPSS-R for survival (0.69, 95% CI 0.68–0.70 versus 0.72, 95% CI 0.71–0.73; $P<0.001$, respectively) and transformation to AML (0.74, 95% CI 0.73–0.76 versus 0.76, 95% CI 0.75–0.78; $P<0.001$, respectively)[142]. In heterogeneous disorders such as MDS, the increase of concordance from 0.69 to 0.72 is clinically relevant. Despite the IPSS-R being developed and validated using untreated populations, this system has the prognostic ability to discriminate among subsets of patients treated and at lower risk[155,156]. Both IPSS and IPSS-R have shortcomings: they were developed and validated in untreated individuals with MDS, are not dynamic and do not always accurately predict response to therapy.

Like the IPSS-R, the WPSS adds WHO histology and the requirement for RBC transfusion to define five cohorts. All these prognostic scoring systems are fundamentally similar but with some claimed differences. In multivariable analyses, the WPSS is a more accurate survival predictor compared with the IPSS but this conclusion needs validation[157]. Another study comparing prediction accuracies of the WPSS and IPSS-R reported a high correlation (Kendall tau = 0.72; $P<0.001$). The Dxy is a concordance coefficient varying between −1 and 1, with 0 representing no predictive power and 1 representing perfect concordance of ascribed risk. Dxy values of the WPSS and IPSS-R for survival are 0.43 and 0.46, respectively, and 0.53 and 0.54 for AML transformation, respectively. These data indicate no substantial difference in prediction accuracies of different prognostic models and scores.

However, there are discordances between these prognostic scores in identifying persons with lower-risk MDS. The WPSS but not the IPSS identifies a cohort of persons with a very low risk of MDS progression who do well with no intervention. Another discordance is that histology-defined myelodysplasia is subjective, often not replicable, and does not correlate well with the severity of cytopenias or with bone marrow blast percentage. Additionally, haemoglobin concentration <90 g/l in men and <80 g/l in women is given greater predictive weight in the WPSS than in the IPSS-R. The WPSS can identify persons in a very-low-risk cohort but adding cytogenetics data does not increase prediction accuracy because unfavourable cytogenetics are rare in this cohort. The relative prognostic weight assigned to high-risk cytogenetics is greater in the WPSS than in the IPSS[158]. Importantly, the IPSS and IPSS-R were developed and validated in untreated persons with MDS, are not dynamic and do not accurately predict therapeutic responses. The integration of machine learning and artificial intelligence has been reported to improve accuracy but needs validation[159–161].

Most of these scoring systems are based on data from study or registry participants and may not have similar accuracy in real-world populations. A large population-based study compared prognostic accuracies of the IPSS, IPSS-R and WPSS for survival and risk of AML

transformation[22]. The IPSS-R was more accurate than the IPSS ($P < 0.001$) and the WPSS ($P = 0.05$). The WPSS was more accurate than the IPSS ($P = 0.07$). The IPSS-R was more accurate than the IPSS and the WPSS in individuals ≤70 years of age[22]. Based on these data, we recommend using the IPSS-R in most instances. However, we emphasize that the C-statistics associated with these prognostic scores are low, implying considerable inaccuracy, especially when used in individuals with MDS.

None of these prognostic scores considers response to interventions, as is done in Markov and Bayesian modelling. For example, individuals with low-risk MDS and anaemia at diagnosis sometimes receive erythropoietin, lenalidomide and/or luspatercept. Some respond whereas others do not, but these interventions eventually fail in most patients. However, prognostic risk scores do not account for these data. These data have been used to improve prediction accuracy, such as by Markov modelling[162], with this analysis indicating that delaying a bone marrow transplant (BMT) for low-risk and intermediate-1-risk MDS and immediate BMT for intermediate-2-risk and high-risk MDS is associated with maximal life expectancy.

Another strong prognostic co-variate excluded from these prognostic risk scores is the adverse impact of MDS that is considered to be related to therapy[22,163]. However, as we discuss elsewhere, this attribution is probabilistic and entails considerable uncertainty[163,164]. As such, caution is necessary when using this designator to estimate prognosis.

More recently, the integration of clinical, histological and molecular data using artificial intelligence has improved the accuracy of the IPSS and IPSS-R and can be applied throughout a patient's disease course[159–161]. These systems continue to include clinical, histological and cytogenetics data identified as prognostic in the IPSS and IPSS-R and add mutation topography. Interestingly, optical genome profiling for MDS reveals cryptic aberrations that are used to predict prognosis and even to help identify therapies[165].

The Personalized Predictive Model was developed based on data from 1,471 individuals and validated in 465 individuals treated in a clinical trial and/or receiving a BMT[151]. Covariates associated with survival were age, blood cell concentrations, including bone marrow blast percentage, cytogenetics and number of mutations.

The IPSS-M was developed in a cohort of nearly 3,000 individuals and validated in a cohort of 754 individuals. Important survival covariates include blood cell concentrations, bone marrow blast percentage, IPSS-R cytogenetic risk categories, and mutations in 16 'main effect' genes and 15 'residual genes'. Biallelic *TP53* mutations as well as *FLT3* and *MLL*-partial tandem duplication mutations are adverse risk covariates. The IPSS-M model identifies the need to distinguish genetic subsets of *SF3B1* mutations by co-mutation pattern. IPSS-M risk cohorts range from very low risk, with a median predicted survival of 10.6 years, to very high risk, with a median predicted survival of 1 year.

Screening

There are no screening recommendations for MDS in any clinical practice guideline or consensus statement, or from the US Preventative Diseases Task Force. However, screening is sometimes performed in high-risk populations, such as in individuals who are occupationally exposed to hazardous chemicals (for example, benzene) or ionizing radiation and individuals with cancer who have been previously treated with DNA-damaging drugs and/or radiation therapy. Some physicians recommend screening for individuals with CHIP detected in settings unrelated to signs or symptoms associated with a haematological abnormality such as participants in genetic screening programmes; whether this is of value has not been confirmed. Screening for MDS is sometimes appropriate in individuals with the hereditary haematological disorders discussed earlier and in those with a family history of these disorders, MDS or related haematopoietic disorders.

Table 4 | Characteristics of IPSS-R risk cohorts of MDS[a]

Risk cohort	Cytogenetic abnormality	Frequency	Median survival (years)
Very good	Del(11q), del(Y)	<5%	5.4
Good	Normal, del(5q) alone or with one other anomaly, del(12p) or del(20q)	65–75%	4.8
Intermediate	Del(7q), trisomy 8, trisomy 19, isochromosome 17q, and any other single or double abnormality not listed	15–20%	2.7
Poor	Abnormal 3q, monosomy 7 and del(7q), double abnormalities including monosomy 7 and del(7q), and complex cytogenetics with three abnormalities	5%	1.5
Very poor	Complex cytogenetics with more than three abnormalities	5–10%	0.7

IPSS-R, revised International Prognostic Scoring System. [a]Data from refs.[142,143,150].

Prevention

The only preventive measure to reduce the risk of developing MDS is avoidance of exposures associated with increased risk such as cigarette smoking, some chemicals and ionizing radiation. The potential future risk of developing MDS may affect the decision of how to treat some cancers, such as Hodgkin lymphoma and breast cancer, because of the frequent application of radiation therapy in these diseases.

Management

Therapeutic goals and strategies

The most important consideration in deciding if, when and what therapy an individual with MDS should receive is to define the therapeutic goal. Some individuals do not require therapy because their symptoms are mild, because their cytopenias are not severe, and/or because they are older and/or with important comorbidities that are more likely to bring them harm than MDS. Other individuals might benefit from a therapeutic intervention but are not appropriate candidates because the anticipated benefit-to-risk ratio is unfavourable. In addition, there are people in whom the therapeutic goal is to reverse cytopenias, such as anaemia, granulocytopenia and/or thrombocytopenia, and improve QOL and not to eradicate MDS. These interventions may or may not be successful or might succeed only transiently. Finally, there are people for whom the therapeutic goal is to eradicate MDS, either because the aforementioned strategies are not working and/or because the goal is to decrease the likelihood of transformation to AML.

MDS can be viewed in several ways. One is that some forms of MDS are similar to conditions in which immature cells predominate. As such, a potential therapeutic approach is to use drugs designed to encourage differentiation, as is done in acute promyelocytic leukaemia, or to prevent transformation to AML[166–168], a potential mechanism of action of hypomethylating drugs.

Therapeutic goals for lower-risk MDS include improving disease-related symptoms, decreasing the frequency of RBC and platelet transfusions, and improving QOL. It is important to weigh any potential adverse impact of therapy against consequences of the disease, the

Table 5 | Prognostic scoring systems for MDS

Classification or score	Covariates	Survival prediction accuracy	AML transformation prediction accuracy
IPSS[150]	Bone marrow blast percentage; numbers of cytopenias; cytogenetic analyses[a]	Fair	Fair
IPSS-R[142]	Bone marrow blast percentage; haemoglobin concentration; platelet concentration; neutrophil concentration; cytogenetic risk[a]	Good	Good
IPSS-M[152]	Bone marrow blast percentage; minimum platelet concentration; haemoglobin concentration; IPSS-R cytogenetic category; gene main effects (17 variables, 16 genes); gene residuals (1 variable, 15 genes)	Good	Good
WHO Classification-based Prognostic Scoring System[153,154]	WHO category; cytogenetic risk[a]; haemoglobin <90 g/l in men or <80 g/l in women	Good	Good

AML, acute myeloid leukaemia; IPSS, International Prognostic Scoring System; IPSS-M, IPSS-Molecular; IPSS-R, revised IPSS; MDS, myelodysplastic syndromes. [a]We use the term cytogenetic rather than karyotype as this more correctly reflects modern practices such as fluorescence in situ hybridization.

time and cost related to receiving therapy, and the estimated likelihood, magnitude and robustness of efficacy. Therapeutic goals for higher-risk MDS are similar but also aim to prevent or delay transformation to AML and increase survival. Achieving these goals requires a delicate, often imperfect balance between benefits (real or perceived) and therapy-related adverse events. The balance between estimated risks and benefits is different in individuals with higher-risk MDS given their estimated shorter life expectancy.

Therapeutic options for MDS comprise supportive care (for example, transfusion), including human DNA recombination technology-based, molecularly cloned haematopoietic growth factors to alleviate pancytopenia, luspatercept to improve erythropoiesis, hypomethylating drugs to target the highly methylated genome status in MDS[169,170], immune modulators such as lenalidomide, chemotherapy drugs, low-dose cytarabine and the potential curative therapy allogeneic HCT. As discussed above, some individuals with seemingly mild MDS may be candidates for immunosuppression[52]. Other therapies being studied include immune-checkpoint inhibitors, such as PD1, PDL1 and CTLA4, anti-CD47 antibodies, and BCL-2 inhibitors[171]. Most treatment algorithms, such as those from National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology and several textbooks, suggest classifying individuals with MDS into lower-risk and higher-risk cohorts that require different and/or personalized therapeutic strategies[172–175].

Therapy for lower-risk MDS

The therapeutic goal in people with lower-risk MDS is to improve haematopoiesis and/or QOL (Fig. 6). Interventions are largely based on the dominant cytopenia or cytopenias. People with severe anaemia typically receive molecularly cloned haematopoietic growth factors such as erythropoietin[176]. People with del(5q) and ring sideroblasts typically receive lenalidomide and/or luspatercept, and those with granulocytopenia may receive molecularly cloned myeloid growth factors such as granulocyte–colony-stimulating factor (G-CSF) or granulocyte–macrophage colony-stimulating factor (GM-CSF). Patients with hypoplastic bone marrow and/or multiple cytopenias may receive cyclosporine and/or anti-thymocyte globulin under the hypothesis of an immune basis or hypomethylating drugs, while those with severe thrombocytopenia might receive molecularly cloned thrombopoietin analogues such as romiplostim or eltrombopag. HCT is rarely considered in persons with lower-risk MDS and only after other interventions have failed. Participation in clinical trials of new therapies and/or supportive care are options throughout the spectrum of lower-risk MDS. Iron-chelating drugs, such as deferoxamine, are a controversial intervention in terms of a survival benefit in people with low-risk MDS who are likely to live sufficiently long to receive many RBC transfusions. People in whom there is uncertainty of whether the correct diagnosis is mild aplastic anaemia or lower-risk MDS should receive a trial of immunosuppressive therapy with anti-thymocyte globulin and/or cyclosporine[52].

Erythropoiesis-stimulating agents (ESAs), which promote earlier stages of erythropoiesis, have been commonly used in lower-risk MDS for decades. In a 2007 study of 1,587 individuals enrolled in clinical trials with standardized response criteria, the anaemia response rate was 40%[177]. A randomized, blinded, placebo-controlled trial of darbepoetin in 147 individuals performed in 2017 reported an anaemia response rate of 15% with darbepoetin (increasing to 35% with longer follow-up) compared with 0% with placebo[178].

People with anaemia with ring sideroblasts and/or an *SF3B1* mutation[179] often receive luspatercept, which improves anaemia by reducing SMAD2 and SMAD3 signalling in late erythropoiesis[180]. In a randomized, blinded, placebo-controlled study of luspatercept, RBC transfusion independence occurred in ~40% of patients and lasted a median of 8 weeks[181].

Lenalidomide is approved in many countries to treat anaemia in people with del(5q). In a phase III trial of lenalidomide, the RBC transfusion-independence response rate was ~50%, with a median response duration of >2 years. Grade 3 or 4 neutropenia occurred in >70% of participants and thrombocytopenia occurred in >30% of participants. Patients with severe thrombocytopenia were more likely to respond to the drug[182].

Romiplostim and eltrombopag (a thrombopoietin analogue and thrombopoietin receptor agonist, respectively) are growth factor drugs that increase platelet concentrations[183–185]. A randomized study of romiplostim in individuals with platelet concentrations <20 × 10^9/l reported a marked decrease in platelet transfusions[185]. Another randomized study of eltrombopag reported a 47% platelet response rate in those receiving eltrombopag[184]. In both studies, the rate of AML transformation was increased, especially in people with excess myeloblasts; therefore, romiplostim and eltrombopag should be avoided in this setting.

The hypomethylating agents azacitidine, decitabine and decitabine/cedazuridine are sometimes given to people with multiple cytopenias. Their precise mechanisms of action are unknown but their biochemical effects include the inhibition of DNA methyltransferase, thereby favouring differentiation and cytotoxicity[186]. Single-arm studies report complete or partial responses or haematological improvement per international working group criteria of 30–40%[187], with a median response duration of 1–1.5 years[188,189]. People with

multiple cytopenias also sometimes receive immunosuppressive drugs such as anti-thymocyte globulin and cyclosporine, with studies finding a response rate of ~30% and a median response duration of 1–1.5 years[190,191].

The use of iron-chelating drugs in highly RBC-transfused persons with relatively long expected survival is controversial. A randomized, placebo-controlled trial of deferasirox in individuals with iron overload reported improvement in event-free survival and that the drug was safe[192].

In people with IPSS-R intermediate risk, the therapeutic choice is influenced by age, Eastern Cooperative Oncology Group (ECOG) performance score, comorbidities, cytogenetics, mutation topography and other covariates[95,96,193,194] (Fig. 7). Individuals with lower IPSS-R scores failing prior interventions are sometimes operationally defined as being at higher risk. We propose the following: no intervention in asymptomatic people until symptoms appear or disease progression occurs; administration of erythroid-stimulating drugs in those with symptomatic anaemia or risk of iron overload and serum erythropoietin concentration <500 U/l; consideration of luspatercept in those failing with erythroid-stimulating drugs and who have ring sideroblasts and/or del(5q) and lenalidomide in those failing with erythroid-stimulating drugs and in people with del(5q), unless they have a *TP53* mutation[195]; consideration of hypomethylating drugs and/or immunosuppression in those failing with lenalidomide; and consideration of immunosuppression, hypomethylating drugs, lenalidomide or HCT (see below), or participation in a clinical trial in people with an erythropoietin concentration ≥500 U/l. There is an important role for supportive care in individuals for whom it is appropriate, such as those unwilling to receive drugs or who have progression-related symptoms requiring intervention.

Consensus guidelines and strength of evidence for interventions in lower-risk MDS are summarized in the NCCN Guideline Version 3.2022 Myelodysplastic Syndromes[196].

Therapy for higher-risk MDS

The therapeutic goal for individuals at higher risk (IPSS intermediate-2 risk and high risk; IPSS-R intermediate risk, high risk or very high risk; or WPSS high risk or very high risk) in most guidelines is to delay disease progression, prevent or delay AML transformation, prolong life, improve QOL and, if possible, attempt cure (Fig. 6). Hypomethylating drugs, anticancer drugs and HCT are the modalities most often considered. For example, azacitidine is one of the major hypomethylating drugs approved by the FDA and the EMA for MDS treatment. A phase III trial (NCT00071799) reported that azacitidine increased survival by 9 months compared with best supportive care, low-dose cytarabine or intensive chemotherapy (survival HR 0.58, 95% CI 0.43–0.77)[197]. A phase II

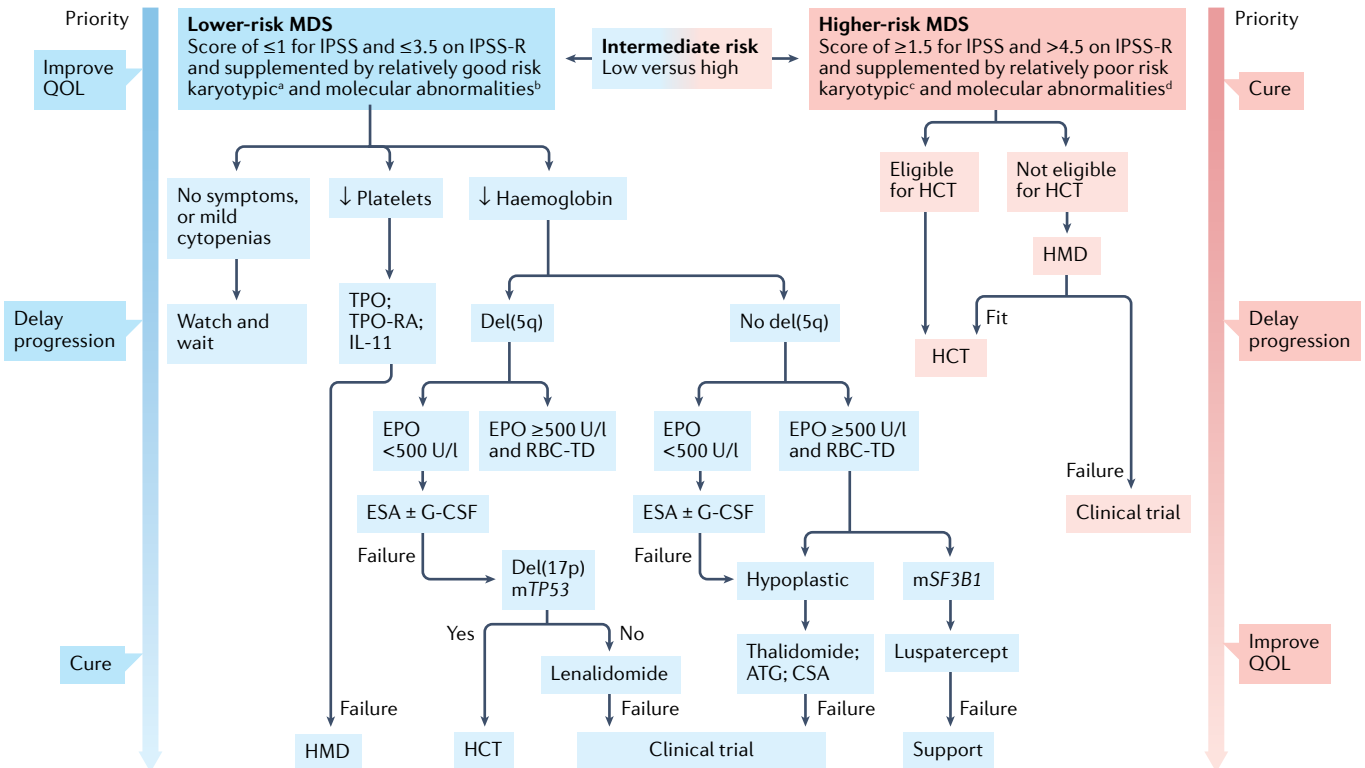

Fig. 6 | Proposed algorithm for the treatment of MDS. The algorithm depicts the treatment recommendations for lower-risk and higher-risk myelodysplastic syndromes (MDS). [a]Good-risk karyotypic abnormalities: del(11q), del(Y), normal, del(20q), del(5q) alone or with one other anomaly, del(12p). [b]Good-risk molecular abnormalities: *SF3B1* mutation. [c]Poor-risk karyotypic abnormalities: abnormal 3q, monosomy 7, double abnormality including del(7)/del(7q), complex karyotypes with three or more abnormalities. [d]Poor-risk molecular abnormalities: *TP53*, *RUNX1*, *EZH2*, *ASXL1* and *ETV6* mutations. ATG, anti-thymocyte globulin; CSA, cyclosporin; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; HCT, haematopoietic cell transplantation; HMD, hypomethylating drug; IPSS, International Prognostic Scoring System; IPSS-R, Revised IPSS; m*TP53*, mutated *TP53*; m*SF3B1*, mutated *SF3B1*; QOL, quality of life; RBC-TD, red blood cell transfusion dependence; TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonist. Adapted with permission from ref.[175], Elsevier.

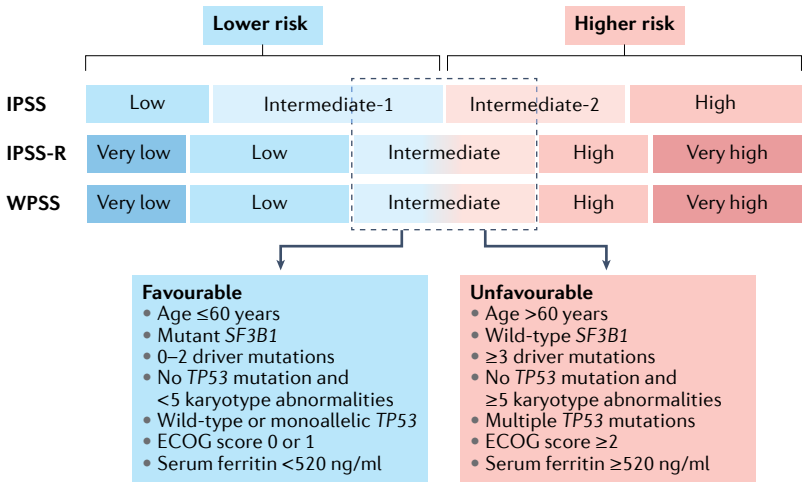

Fig. 7 | Prognostic factors for different outcomes in intermediate-risk MDS. People with Revised International Prognostic Scoring System (IPSS-R) intermediate risk are divided into lower-risk (score ≤3.5) and higher-risk (score >3.5) cohorts. Covariates, such as age, Eastern Cooperative Oncology Group (ECOG) performance score and mutation topography, are prognostic and important in therapy decisions. Favourable or unfavourable prognostic factors determine whether the therapy regimen for lower-risk or higher-risk myelodysplastic syndromes (MDS) should be followed. IPSS, International Prognostic Scoring System; WPSS, WHO Prognostic Scoring System.

trial (NCT01462578) reported that azacitidine therapy prevented or substantially delayed relapse in individuals who were positive for minimal residual disease after achieving a histological complete remission following intensive chemotherapy or HCT but this study lacked a concurrent placebo control[198]. Analyses of the Grupo Español de Síndromes Mielodisplásicos (GESMD) and Groupe Francophone des Myélodysplasies (GFM) observational data bases reported a time-dependent benefit of azacitidine therapy in individuals with high-risk MDS and del(7/7q) or with complex cytogenetics compared with best supportive care[199]. The sum of these data suggests the safety and efficacy of azacitidine in this population. However, real-world data suggest that the effect size might be smaller than that reported in clinical trials[197,200–202].

A phase III trial compared low-dose decitabine with best supportive care in older individuals with higher-risk MDS[203]. There was no substantial improvement in survival yet better progression-free survival and a lower risk of AML transformation were observed. Similar data are reported from another phase III study (NCT00043381)[204]. Whether decitabine significantly increases survival is controversial and may reflect trial design rather than different efficacies of azacitidine and decitabine[203,204]. However, it is important to acknowledge that the mechanisms of action of these drugs differ. Decitabine acts only on DNA whereas the predominant effects of azacitidine are on RNA[205,206]. Two studies reported that decitabine is effective in individuals with *TP53* mutation[207,208]. Some studies claim that hypomethylating drugs are a bridge to HCT but these data indicate that a bridge treatment as a prerequisite for HCT may not be necessary[162,209–211]. Decitabine/cedazuridine, a combination of decitabine and the cytidine deaminase inhibitor cedazuridine, is a new oral form of hypomethylating drug that was approved for MDS treatment by the FDA based on pharmacokinetic and pharmacodynamic data without a comparative clinical trial (see below)[189].

Haematopoietic cell transplantation

There are three fundamental questions regarding HCT for MDS: who, if anyone, should receive HCT; when should the procedure take place; and which approach is most appropriate?

Allogeneic HCT is the only cure for MDS[212–223]. However, HCT is performed in fewer than 10% of patients with MDS for diverse reasons, including inaccurately estimating prognosis without or with HCT, older age, frailty, comorbidities related or unrelated to MDS (often confounded), and financial and other considerations. Improved supportive care, development of reduced-intensity conditioning (RIC) regimens preferred in older persons, increased donor availability, especially HLA haplotype-matched relatives and use of post-HCT cyclophosphamide to prevent graft-versus-host disease explain the increasing numbers of HCTs for MDS and improved outcomes. However, it is impossible to know how much of this improvement results from patient-selection biases[224]. Another reason for the increase in HCT in the USA is a government payment for HCT in individuals >65 years of age. However, real-world data on the frequency or outcome of HCT for MDS are few.

Outcomes of HCT vary widely but large observational databases from the Center for International Blood and Marrow Research and the European Bone Marrow Transplant group report 2–3-year survival rates of ~50%[225–231]. Recipient-related covariates that correlate with transplantation outcomes include age and the transplantation co-morbidity index. MDS-related covariates include pre-transplantation haematological parameters such as platelet concentration and blood and/or bone marrow blast percentage, MDS risk category, therapy-related MDS (discussed earlier) and mutation topography, especially mutations in *TP53*, *RAS* and *JAK2*. Transplantation-related covariates include pre-transplantation conditioning intensity (that is, the dosage of chemotherapy and radiotherapy before HCT) and donor type, with the best outcomes reported among recipients of RIC transplants from HLA-identical siblings, HLA-matched unrelated donors and HLA haplotype-matched relatives with post-transplantation cyclophosphamide. Some but not all of these predictive covariates are validated (reviewed elsewhere[225,227,230]). Whether transplantation outcomes derived from transplantation registries reflect so-called real-world outcomes is unknown.

Deciding which individuals should receive HCT and when is a complex issue and there is no correct answer. One widely cited study

used a Markov model to optimize timing, the conclusions of which were mostly confirmed in other analyses and in an observational study[223]. A biological assignment trial based on the availability of a related or unrelated HLA-identical donor in individuals 50–75 years of age with an MDS risk score of IPSS intermediate-2 or higher from the Blood and Marrow Transplant Clinical Trials Network (CTN 1102; NCT02016781) compared a RIC allogeneic HCT with hypomethylating drugs or supportive care[227]. In an intention-to-treat analysis, leukaemia-free survival at 3 years was 36% (95% CI 30–42%) for donor arm (received transplant) compared with 21% (95% CI 13–29%; $P = 0.003$) for non-donor arm (received hypomethylating therapy or best supportive care) and adjusted survivals of 50% (95% CI 41–54%) and 27% (95% CI 18–36%; $P = 0.0001$), respectively, were observed. The results remained significant in sensitivity analyses that censored individuals who died before they could receive a transplant. Although these data indicate an advantage of transplantation, many individuals in the non-transplantation cohort received suboptimal therapy with, for example, hypomethylating drugs, and many individuals in the transplantation cohort also received these drugs. Furthermore, the outcomes in both cohorts remain unsatisfactory. Importantly, a leukaemia-free survival benefit was reported only in individuals in the IPSS-R intermediate-2-risk cohort and a survival advantage was reported only in individuals in the IPSS-R high-risk cohort. In addition, these data in selected individuals cannot be reliably applied to people with MDS, most of whom would not have met the study eligibility criteria. The several MDS and transplantation-predictive models and scores are imprecise, with C-statistics of about 0.75, implying considerable uncertainty, especially at the individual level (discussed earlier). Furthermore, few of these models and scores consider an individual's prior therapy exposure and responses or physician and/or potential recipient risk-taking tolerance. In several studies, there seemed to be no advantage or even a disadvantage with pre-transplantation azacitidine[232,233].

Several expert consensus statements and clinical practice guidelines address which individuals with MDS are suitable for transplantation and when it should occur[172,230,234–241] (Supplementary Table 2), none of which are based on data from randomized controlled trials (the CTN 1102 study used biological randomization). Above, we discuss our reservations regarding the accuracy of such recommendations. We think the decision about who should receive a transplant and when remains more an art than a science. We suggest that transplantation be considered at diagnosis in people with higher-risk MDS, especially in those with adverse mutations and in those with lower-risk MDS who need therapy but other interventions have failed, especially in those with adverse mutations. Risk–benefit analyses are complicated and should weigh prognostic covariates and response to prior interventions, in concert with the person's goals and support network. Most survival prognostic factors for conventionally treated MDS also operate in transplantations[225].

Currently, there are several transplantation-related controversies. For example, should people receive hypomethylating drugs before or after transplantation? Should mutation topography data be used to select appropriate transplantation candidates and/or determine transplantation timing? What is the role of pre-transplantation iron-chelating therapy? None of these questions is definitively answered nor are they likely to be.

Approved drugs

Only five drugs are approved by the FDA for the treatment of MDS. Azacitidine and decitabine are approved in lower-risk and higher-risk MDS including all subtypes (decitabine is not approved for MDS by EMA because it did not show a survival benefit in randomized controlled trials, discordant from the FDA approval)[203]. Decitabine/cedazuridine is a fixed-dose combination of decitabine and cedazuridine, a cytidine deaminase inhibitor that prolongs exposure to decitabine and presumably decreases genome-wide hypermethylation. Decitabine/cedazuridine is approved by the FDA for previously treated or untreated adults with de novo and secondary MDS with refractory anaemia, with or without ring sideroblasts or with excess blasts, and in IPSS intermediate-1-risk, intermediate-2-risk and high-risk cohorts. A randomized phase III pharmacokinetics and pharmacodynamics study (NCT02103478) reported comparable systemic decitabine exposure, de-methylating activity and safety in the first two cycles of oral decitabine/cedazuridine compared with standard intravenous decitabine in individuals with intermediate-1-risk, intermediate-2-risk or high-risk MDS[189]. Lenalidomide is approved for use by individuals who are RBC transfusion dependent with isolated del(5q) and with a low or intermediate-1 risk IPSS score. Luspatercept is approved for adults with ring sideroblasts or MDS/MPN with ring sideroblasts and thrombocytosis in whom erythropoiesis-stimulating drugs fail or who are unlikely to respond to one of these drugs and require two or more RBC transfusions over 8 weeks.

The reasons why there are so few FDA-approved and EMA-approved drugs for MDS are complex. The most obvious reason is the diverse causes and pathophysiology of MDS. For example, as discussed earlier, therapy-related MDS is probably the result of somatic mutations, whereas other MDS cases may result from or be aggravated by an abnormal bone marrow microenvironment, an abnormal immune response or a combination of these factors[87,242,243]. Furthermore, individuals with the same phenotype may have discordant genotypes and vice versa. Another challenge is the clinical heterogeneity of MDS, making the design and execution of clinical trials difficult. Most signs and symptoms of MDS are an indirect effect of the cancer. In addition, the mechanism of action of MDS pharmacotherapies is unclear, even for approved drugs such as azacitidine and decitabine. For example, the target genes of these drugs are uncertain and there is not a good correlation between the degree of genome-wide hypermethylation, post-therapy hypomethylation and response[244–246]. Another obstacle is the controversy over which individuals with MDS, especially those with lower-risk MDS, should be treated.

Other drugs are often used to treat complications of MDS such as anaemia (erythropoiesis-stimulating drugs and androgenic steroids) and thrombocytopenia (eltrombopag and romiplostim). Below, we discuss examples of these drugs.

Erythropoiesis-stimulating agents: luspatercept. Luspatercept is a decoy fusion protein for TGFβ superfamily ligands that inhibits SMAD2 and SMAD3 signalling and increases late-stage erythropoiesis. In a phase III trial in 229 individuals with ring sideroblasts and very-low-risk to intermediate-risk MDS who were RBC transfusion dependent, luspatercept therapy resulted in RBC transfusion independence for ≥8 weeks in ~40% and for ≥12 weeks in ~30% of individuals[181]. Based on these data, luspatercept was approved by the FDA in adults with anaemia in whom erythropoiesis-stimulating agents fail and who are receiving two or more RBC transfusions over 8 weeks, those with very-low to intermediate IPSS-R risk MDS with ring sideroblasts, or those with MDS/MPN with ring sideroblasts and thrombocytosis.

Thrombocytopenia therapies: romiplostim. Romiplostim is a peptibody (Fc-peptide fusion protein) designed to increase platelet

production. A small phase I/II trial (NCT00303472) reported that romiplostim was safe and effective in individuals with MDS and thrombocytopenia[247]. Another phase II study (NCT00303472) reported an effective starting dose[248]. A randomized phase II study (NCT00614523) in individuals with lower-risk MDS reported that romiplostim increased platelet concentrations, decreased bleeding events and decreased the frequency of platelet transfusions compared with placebo[185]. However, the study was halted early because of concern about a higher incidence of AML transformation in the romiplostim arm[185]. Because of this concern, romiplostim should not be used in individuals with MDS with excess blasts[185,249,250].

Quality of life

In the absence of disease-modifying interventions, an important goal in MDS therapy is to improve health-related QOL (HRQOL), and a structured evaluation of QOL is recommended in most MDS therapy guidelines. Much of the disease burden of MDS, especially in lower-risk MDS, is a decreased QOL which causes disease-related symptoms (for example, fatigue) and psychosocial sequelae[203,235,251,252]. Several validated instruments exist to quantify HRQOL in individuals with MDS, including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), the Functional Assessment of Cancer-Anaemia (FACT-An), Haematological Malignancy Patient-Reported Outcome (HM-PRO) scale, the Quality of Life in Myelodysplasia Scale (QUALMS) and the Quality of Life E (QOL-E) scale[253–257]. Other instruments that quantify fatigue include the Multidimensional Fatigue Inventory (MFI) and the Brief Fatigue Inventory (BFI)[258,259]. Generic HRQOL instruments, such as the 36-item Short Form (SF-36), the 12-item Short Form (SF-12), the 5-item European Quality of Life Five Dimensions (EQ-5D) and the European Quality of Life Visual Analogue Scale (EQ-VAS), are also used[260–262]. The plethora of HRQOL instruments suggests that no single instrument is entirely adequate. For example, it is difficult to reach conclusions about whether drugs that improve fatigue do so by increasing haemoglobin concentration, decreasing RBC transfusion frequency or a combination of both[263–266]. Unfortunately, few randomized controlled trials have included HRQOL as an end point[267].

Outlook

Challenges

MDS is a complex, heterogeneous cancer that is increasing in incidence and prevalence and is expected to continue doing so as populations age and more individuals with cancer exposed to DNA-damaging drugs and radiation therapy live longer. The aetiology (or aetiologies) is in most cases unknown but some cases are related to or associated with antecedent haematological conditions. Other cases develop after exposure to mutagenic and/or carcinogenic drugs and ionizing radiation, often in the context of anticancer therapy (Fig. 3). With a few exceptions, the pathogenesis and pathophysiology of MDS are poorly understood. Despite the existence of several survival prognostic and predictive models/scores for MDS, none of these is especially accurate at the individual level and most are of modest value in directing therapy. Consensus statements and clinical practice guidelines are useful but again of limited value at the individual level (reviewed elsewhere[268]). Only five drugs are approved by the FDA for the treatment of MDS but several others are used to treat MDS-associated bone marrow failure. Drug development in MDS has been slow because of the substantial disease heterogeneity, and there is also a limited understanding of how most approved drugs work.

Drugs in development

Clinical trials of drugs being developed for MDS are under way (those registered with ClinicalTrials.gov are presented in Supplementary Fig. 1). Most studies are uncontrolled and unblinded, with few heterogeneous individuals and diverse prior therapies and prognoses. As such, it is impossible to critically comment on drug safety and/or efficacy. Some drugs in development are discussed below.

Emavusertib. Preclinical data suggest that the IRAK4 inhibitor emavusertib (CA-4948) is active in MDS cells with spliceosome mutations, including *U2AF1* and *SF3B1*, and this drug is being evaluated in a clinical trial, alone or in combination with azacitidine or venetoclax in individuals with higher-risk MDS and AML (NCT04278768).

IDH1 and IDH2 inhibitors. *IDH1* or *IDH2* mutations occur in 5% of MDS cases[269]. The prognostic significance of these mutations is controversial and is affected by other co-varieties, including co-mutations[270,271]. Several trials of ivosidenib[272] (a small-molecule inhibitor of IDH1, NCT04493164) and enasidenib[273] (an IDH2 inhibitor, NCT03383575) included individuals with high-risk MDS. Some trials were in individuals with advanced MDS and/or AML whereas others were in untreated individuals. Some are single drug studies whereas others are combination studies[109,110,269,274]. Ivosidenib and enasidenib have only been tested in individuals with the relevant mutation and neither is approved by the FDA or EMA for individuals with MDS. Given the lack of suitable trials, it is too early to comment on their safety and efficacy in MDS.

Eltrombopag. Eltrombopag, a thrombopoietin receptor agonist, was tested in a randomized phase II trial in individuals with low-risk or intermediate-1-risk MDS and platelets $<30 \times 10^9$/l (ref.[184]). Platelet concentration improved in ~50% of individuals and severe bleeding episodes were reduced. Other studies report similar data[275,276]. In another randomized phase II study in individuals with intermediate-2-risk or high-risk MDS and platelets $\leq 25 \times 10^9$/l, individuals receiving eltrombopag had considerable fewer clinically relevant thrombocytopenic events[277]. Eltrombopag is not approved by the FDA for the therapy of MDS and has a warning of an increased risk of death and of progression of MDS to AML[278].

Magrolimab. Magrolimab, an anti-CD47 monoclonal antibody, is intended to reverse the CD47 macrophage 'don't eat me' signal[279–281]. Combining magrolimab with azacitidine should increase the induction of apoptosis of MDS cells by macrophages. In a phase Ib trial, 95 individuals with intermediate-risk to very-high-risk MDS received magrolimab with azacitidine, with an overall response rate of 75% and a complete response rate of ~33%. Responses were highest in people with a *TP53* mutation (40% complete remission, median overall survival 16.3 months)[282].

Venetoclax. The BCL-2 inhibitor venetoclax has been tested in combination with azacitidine in a phase Ib study (NCT02942290) in 57 individuals with untreated high-risk MDS[283]. This study reported an overall response rate of ~80% and a ~40% complete remission rate. Median response duration was 15 months and median progression-free survival was 18 months. However, 97% of individuals had grade 3 or higher adverse events. Another phase Ib study (NCT02966782) enrolled 46 individuals with advanced MDS who received venetoclax with or without azacitidine[284]. The overall response rate was ~50% and the complete response rate was ~13%. Progression-free survival at

6 months was ~75%[284]. Individuals with biallelic *TP53* mutations did not respond[285]. It is impossible to know from these data whether venetoclax is safe and effective in MDS or whether there is an advantage of adding venetoclax to hypomethylating drugs.

Basic research

Progress in treating MDS could be accelerated if our understanding of its aetiology, biology and pathophysiology were substantially increased. Progress is being made albeit slowly. In the interim, treatment of MDS is predominately symptomatic rather than disease modifying, with the possible exception of hypomethylating drugs and transplantation. The pace of research in MDS has been dramatic and, hopefully, a better understanding and new therapies are on the horizon (Supplementary Fig. 2).

Perspectives

In summary, substantial progress is being made in our understanding of the biology of MDS, in classifying MDS and in predicting outcomes. Progress, albeit less impressive, is also being made in expanding and improving MDS therapy. Several new drugs are in development and there is renewed interest in HCT in individuals with high-risk MDS. Furthermore, progress is occurring in the establishment of international collaborative studies, which should accelerate therapy advances. Nevertheless, more is needed to reach the important goals of a thorough understanding of MDS pathogenesis and personalized treatment of this syndrome.

Published online: 17 November 2022

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Acknowledgements

Y.L. is supported, in part, by Sun Yat-sen University Cancer Center Start-Up Funding (No. 201603), the National Natural Science Foundation of China (81873428) and the Programme for Guangdong Introducing Innovative and Entrepreneurial Teams (2017ZT07S096). R.P.G. acknowledges support from the National Institute of Health Research (NIHR) Biomedical Research Centre funding scheme. Y.L. and R.P.G. acknowledge support funding from the Ministry of Science and Technology of China (84000-51200002). E. Hellström-Lindberg (Karolinska Institute) and D. Steensma (Novartis Corp.) kindly reviewed the typescript.

Author contributions

Introduction (Y.L., R.P.G. and H.L.); Epidemiology (H.L. and R.P.G.); Mechanisms/pathophysiology (R.P.G., F.H. and M.A.S.); Diagnosis, screening and prevention (M.A.S., H.L., Y.L. and R.P.G.); Management (Y.L., M.A.S. and R.P.G.); Quality of life (Y.L., R.P.G. and F.H.); Outlook (Y.L. and R.P.G.); Overview of the Primer (M.A.S., R.P.G. and Y.L.).

Competing interests

R.P.G. is a consultant to NexImmune Inc. and Ananexa Pharma Ascentage Pharm Group, Antengene Biotech LLC; Medical Director, FFF Enterprises Inc.; partner, AZAC Inc.; Board of Directors, Russian Foundation for Cancer Research Support; and Scientific Advisory Board: StemRad Ltd. M.A.S. is on advisory boards for BMS, Novartis, Syros and Kurome. Y.L., H.L. and F.H. declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41572-022-00402-5.

Correspondence should be addressed to Yang Liang.

Peer review information *Nature Reviews Disease Primers* thanks G. Borthakur, J. Bennett and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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