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Chapter

Myelodysplastic Syndromes: An Update on Pathophysiology and Management

Wanxing Chai-Ho and Gary J. Schiller

Abstract

Myelodysplastic syndromes (MDS) comprise a set of clonal hematopoietic stem cell (HSC) disorders characterized by ineffective hematopoiesis that manifest as cytopenia of variable severity. The result often is an increased risk of infection, transfusion dependence, and a potential to transform to acute myeloid leukemia (AML). For the past decade, hypomethylating agents remain the only FDA-approved therapy. Given that MDS is more prevalent in the elderly who often have comorbid conditions, supportive care remains the mainstay of therapy. Curative treatments are restricted to younger, healthy individuals with histocompatible-matched donors for allogeneic transplant able to tolerate more intensive chemotherapeutic treatment. Understanding of the pathophysiology of MDS advanced over the past decade, which leads to an increasing array of new agents under clinical investigation. This review focuses on our recent enhanced understanding of MDS molecular biology, and promising novel agents that go beyond the hypomethylating agent.

Keywords: myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), bone marrow transplant, hypomethylating agent, somatic mutation

1. Introduction

The myelodysplastic syndromes (MDS) comprise an heterogeneous group of malignant hematopoietic stem cell disorders characterized by dysplastic and ineffective blood cell production and a variable risk of transformation to acute leukemia. Based on the United States Surveillance, Epidemiology, and End Results (SEER) Program, the incidence of MDS is about 4.1–4.6 cases per 100,000 population per year, with approximately 86% of patients aged ≥60 years at time of diagnosis (median age 76 years). The incidence rate is higher in men than women. [1] The prevalence is slightly lower in Europe with reported 1.24–3.7 cases per 100,000 population per year, also with observed male predominance.[2, 3] With an aging population and improved awareness of disease, it is likely that the number of new patients diagnosed with MDS each year will increase in the future.

Pathogenesis of MDS is incompletely understood. Studies have revealed age, male gender, alcohol, cigarette smoking, ionizing radiation, chemotherapy such as alkylating agents and topoisomerase II inhibitor, immunosuppressive therapy, viral infection, benzene and other environmental/occupational exposures as possible implicating factors. [4–8] However, disease caused by these risk factors are estimated

to account for only 20–30% of cases, which are described as secondary MDS, with remainders as primary MDS [4]. The major subsets of secondary MDS are therapy-related MDS (t-MDS) and MDS with predisposition to familial myeloid neoplasm.

The risk for MDS and AML is increased in certain familial predisposition syndromes, such as inherited bone marrow failure disorders like Diamond-Blackfan syndrome, Fanconi anemia, dyskeratosis congenital, Shwachman-Diamond syndrome, and Down syndrome, Noonan syndrome/Noonan syndrome-like disorders and neurofibromatosis [9]. Accurate diagnosis and recognition of these syndromic disorders allows opportunities to improve clinical care. Genetic counseling should be offered to family members of affected individual. One should avoid using heterozygous sibling as bone marrow transplant donor. Recently, a growing number of germline mutations including CEBPA, DDX41, ANKRD26, ETV6, GATA2, RUNX1 were identified to associate with familial thrombocytopenia and development of MDS and acute leukemia in up to 40% of patients [10, 11]. Special attention should be noted that many patients with familial MDS and acute leukemia predisposition syndromes develop disease in adulthood rather than childhood. To increase awareness of this entity of disease, myeloid neoplasm with above mentioned germline predisposition was incorporated into the updated WHO 2016 classification [12].

2. Diagnosis

2.1 Clinical presentation

MDS usually presents as cytopenia in one or more lineage. Fatigue, dyspnea on exertion, infection, easy bruising or bleeding are the most common symptoms. Lymphadenopathy and hepatosplenomegaly are infrequent and should raise suspicion for chronic myelomonocytic leukemia (CMML) [13, 14]. It has been estimated that various autoimmune features such as subacute vasculitis, fever, arthritis, peripheral edema, and pulmonary infiltrates, may be present in up to 10% of patients [15–18]. Certain autoimmune syndromes have correlated with distinct cytogenetic abnormalities; including Behcet's disease with trisomy 8, Sweet's syndrome and pyoderma gangrenosum with del(5q) [19]. Acquired hemoglobin H disease has been documented in approximately 8% of cases of MDS [20–22]. An acquired somatic mutation of ATRX, an X-linked gene encoding a chromatin-associated protein, has been linked to this entity, [21] as have acquired deletions of the alpha globin loci.

2.2 Pathology evaluation and WHO criteria

Bone marrow aspiration and biopsy are critical to the diagnosis of MDS. In general, the marrow is normo- or hypercellular due to ineffective hematopoiesis. However, up to 20% of MDS patients have hypocellular marrow, making it difficult to distinguish from aplastic anemia or paroxysmal nocturnal hematuria [23, 24]. Dysplastic neutrophils are commonly found in the peripheral blood smear. These cells may demonstrate reduced segmentation, increased size, the so-called pseudo-Pelger-Huet cell [25], often accompanied by reduced or absent granulation [26], and are associated with del(17)p [27]. Hypersegmentation with greater than 5 nuclear lobes is another feature of neutrophil dysplasia [28]. Red cells are usually normocytic or macrocytic, although ring sideroblasts, ovalomacrocytosis, teardrops, stomatocytes or acanthocytes may be seen [28]. Platelet morphology is usually normal, but micromegakaryocytes, mononuclear megakaryocytes, dumbbell-shaped nuclei, multinuclearity with multiple isolated nuclei ("Pawn ball" changes) may be seen [29].

Classification of MDS has been a challenge. In 1982, the French-American-British (FAB) Cooperative Group published the first seminal classification system that distinguished five subcategories of MDS based on marrow morphological criteria and myeloblasts proportions: refractory anemia, refractory anemia with ring sideroblasts (RARS), refractory anemia with excess of blasts (RAEB), RAEB "in transformation" (RAEB-T), and chronic myelomonocytic leukemia (CMML) [30]. Presence of more than 30% blasts in the bone marrow was defined as AML.

In 2001, World Health Organization (WHO) published new classification system on myeloid malignancy with modifications to the FAB system: The diagnosis of AML requires 20% myeloblasts. RAEB-T is classified as AML, and CMML is categorized as a new entity of myeloid neoplasms with both MDS and myeloproliferative features. In addition, MDS with isolated del(5q) is acknowledged as distinctive features in forms of disease with a low blast count, severe anemia and thrombocytosis (5q- syndrome) [31]. The revised 2008 WHO criteria maintained these modifications [32]. In the absence of definitive morphologic features of MDS, MDS-defining cytogenetic abnormalities were included in the diagnostic criteria (**Table 1**). The presence of chromosome 7, Y, or del(20q) does not meet criteria as an MDS-defining abnormality.

The 2016 revision of WHO (**Table 2**) incorporated rapidly accumulating molecular genetic information into the classification [12]. The same cytogenetic abnormalities listed in the 2008 WHO classification remain MDS-defining in a cytopenic patient. Given recent data showing 1 chromosomal abnormality in addition to the del(5q) poses no adverse effect [33–35], the entity "5q- syndrome" may be diagnosed if there is 1 additional cytogenetic abnormality besides the del(5q), unless that abnormality is monosomy 7 or del(7q). Mutations like SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53, and EZH2 can be found in 80–90% MDS patients [36, 37]. Importantly, acquired clonal mutations identical to those seen in MDS can occur in the hematopoietic cells of healthy older individuals without MDS, so-called "clonal hematopoiesis of indeterminate potential" (CHIP), or patients with mild cytopenia but without dysplastic changes or specific cytogenetic and/or genetic abnormalities considered as presumptive evidence of MDS (idiopathic cytopenia of undetermined significance, ICUS) [38, 39]. Although some CHIP and ICUS subsequently develop MDS, there have not been sufficient data to support using the presence of aforementioned mutations as surrogate diagnostic marker of MDS. Based on the link between ring sideroblasts and an SF3B1 mutation, MDS

Unbalanced abnormalities	Balanced abnormalities
−7 or del(7q)	t(11;16)(q23;p13.3)
−5 or del(5q)	t(3;21)(q26.2;q22.1)
i(17q) or t(17p)	t(1;3)(p36.3;q21.1)
−13 or del(13q)	t(2;11)(p21;q23)
del(11q)	inv(3)(q21q26.2)
del(12p) or t(12p)	t(6;9)(p23;q34)
del(9q)	
idic(X)(q13)	

Complex karyotype (3 or more chromosomal abnormalities) involving one or more of the above abnormalities.

Table 1.
Recurring chromosomal abnormalities considered as presumptive evidence of MDS in the setting of persistent cytopenia or undetermined origin in the absence of definitive morphologic features of MDS, according to World Health Organization 2008 and 2016 criteria.

Myeloproliferative neoplasms
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) Chronic myelomonocytic leukemia(CMML) Atypical chronic myeloid leukemia (aCML), BCR-ABL1 Juvenile myelomonocytic leukemia (JMML) MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) MDS/MPN, unclassifiable
Myelodysplastic syndrome MDS with single lineage dysplasia MDS with ring sideroblasts (MDS-RS) MDS-RS and single lineage dysplasia MDS-RS and multilineage dysplasia MDS with multilineage dysplasia MDS with excess blasts MDS with isolated del(5q) MDS, unclassifiable *Provisional entity: Refractory cytopenia of childhood*
Myeloid neoplasms with germline predisposition
Acute myeloid leukemia (AML) and related neoplasms Includes AML with myelodysplasia-related changes and therapy-related myeloid neoplasms
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
B-lymphoblastic leukemia/lymphoma
T-lymphoblastic leukemia/lymphoma

Table 2.
Classification of myeloid neoplasms and acute leukemia, according to World Health Organization 2016 criteria.

with ring sideroblasts and multilineage dysplasia, marked thrombocytosis, lacking excess blasts or an isolated del(5q) abnormality is included into the category of MDS with ring sideroblasts, and correlates with a favorable prognosis [40–43].

2.3 Differential diagnosis

MDS must be distinguished from other marrow dysplasia secondary to reversible causes, such as folate and vitamin B12 deficiency, viral infections (e.g. HIV), antibiotics, benzene, ethanol, or lead poisoning. Other primary bone marrow disorders presenting as pancytopenia, such as aplastic anemia, paroxysmal nocturnal hematuria, hairy cell leukemia, large granular lymphocytic leukemia can be distinguished by marrow morphology, flow cytometry features and gene mutation profile [8].

2.4 Risk stratification

The natural history of MDS in patients varies. The heterogeneity reflects both known and unknown differences in the pathophysiology of specific disease subtypes and patient related characteristics. Several prognostic scoring systems were developed and validated for MDS patients. In 1996, the International Prognostic Scoring System (IPSS) was developed by the International MDS Risk Analysis Workshop based on FAB classification [44]. Based on percent bone marrow blasts, specific cytogenetic abnormalities, and the number of cell lines involved with dysplasia and cytopenia, individual patient are placed into 4 groups: low,

intermediate-1, intermediate-2, and high. The median survival in these four risk categories is 5.7 years for low risk, 3.5 years for intermediate-1 risk, 1.2 years for intermediate-2 risk, and 0.4 year for high risk.

In 2012, a revised IPSS (IPSS-R) was developed based upon data from 7012 patients with primary MDS diagnosed using the FAB or WHO classifications [45]. It incorporated new cytogenetic categories [35], and differentially weighed the degree of cytopenias in newly diagnosed patients. Patient age is an optional variable that can be incorporated to predict overall survival, but not evolution to AML. Individual patient was categorized into five risk groups: very low, low, intermediate, high and very high risk, that translates into median survival of 8.8, 5.3, 3.0, 1.6 and 0.8 years respectively. IPSS-R is simple to use, and is perhaps the most commonly used prognostication system today. However, there are several potential limitations to the IPSS-R. Both IPSS and IPSS-R were developed using data from patients who were observed without treatment. While outcomes might be different now that a variety of interventions are available, an analysis of a separate population suggested that the predictive value of the IPSS-R also applies to those treated with lenalidomide and azacitidine. [46] The prognosticating system only considered patients with *de novo* MDS. It is well recognized that patients with secondary MDS are more likely to have shorter survival. Much of this reflects the association between secondary MDS and "unfavorable cytogenetics". In addition, the IPSS-R seems to be most reliable at predicting outcomes at initial disease diagnosis, as the hazards in mortality and leukemia transformation diminishes over time in higher-risk but remains stable in lower-risk patients [47]. With increasing knowledge of MDS clonal genetics, the future risk stratification system might incorporate the prognostic value of mutation profile, which will be discussed in the next section.

WHO prognostic scoring system (WPSS) was designed to include information on red blood cell (RBC) transfusion need and cytogenetic information [48]. A subset of patients in the study cohort had data from multiple time points for a time-dependent analysis, therefore had the advantage over the IPSS of being able to be used at any time during the disease course.

The MD Anderson Cancer Center (MADCC) MDS model was developed based on a retrospective analysis of 856 patients with *de novo* or therapy-related MDS [49]. Age, cytogenetics, degree of anemia and thrombocytopenia, bone marrow blast percentage were identified as prognostic markers. Subsequently it was prospectively validated in 1915 patients, accounted for the duration of MDS and prior therapy [49]. One should take note that the MDACC model should only be applied to the population of patients with lower-risk (low or intermediate-1 IPSS) MDS, and patients who received various of MDS treatment, from which it was derived [50].

3. Pathogenesis

The pathogenesis of MDS is considered as a multistep process involving sequential acquisition of oncogenic mutations [51, 52]. The interplay between genetically altered HSCs and an abnormal bone marrow microenvironment may allow for selection of a predominant dysplastic clone [51–56].

3.1 Clonal heterogeneity and evolution

MDS is driven by a multistep process characterized by recurrent mutations affecting basic cellular pathways, including RNA splicing, epigenome regulation, myeloid transcription coordination, DNA damage response and growth factor signaling. It has been long recognized that HSC with certain pathogenic alterations

has a competitive advantage and drives clonal expansion at the stem cell level. Clonal cytogenetic abnormalities are detected in up to 50% of *de novo* MDS cases and 80% of therapy-related cases [57, 58]. Over the past decade, a number of large, MDS-focused sequencing studies further demonstrated that MDS is a genetically complex and heterogeneous disease [36, 37, 42, 59–61].

However, clonality alone is not sufficient to cause or diagnose disease, because increased clonal hematopoiesis can remain functionally intact [38, 39]. Recently published data on a large cohort of cytopenia (ICUS) patients delineated the natural history of patients with clonal vs. nonclonal cytopenia [62]. Patients with clonal ICUS had a much higher rate of progression than patient with nonclonal ICUS. Spliceosome gene mutations such as SF3B1 SRSF2 and U2AF1 and co-mutation patterns involving TET2, DNMT3A or ASXL1 had clinical characteristics resemble low-risk MDS patients, and higher progression to myeloid neoplasm when comparing with patient with somatic TET2, DNMT3A and ASXL1 mutation alone [39].

The diversity of clinical MDS phenotypes associated with specific mutations may be related to differential coregulation of the HSC self-renewal and lineage-specific differentiation capacity. Accurate prediction of the natural history of individual patient is certainly of high clinic interest. Our growing knowledge suggests that individual mutations occur in highly stereotyped order and strong patterns of co-mutation association and exclusivity (**Figure 1**) [36, 60, 63]. Mutations affecting epigenetic modifier genes (DNMT3A, TET2, ASXL1, EZH2, etc.) or RNA spliceosome components (SF3B1, SRSF2, and U2AF1) tend to arise in the initiation and early progression phase of MDS and rarely occur at the time of transformation. By contrast, mutations in growth factor signaling pathways (NRAS, KRAS, PTPN11, FLT3, etc.) are rarely found in early phase of disease, and instead, they are frequently acquired and expanded in subclones at time of progression to high-grade MDS or secondary AML [63–66]. A recent study [67] suggested that at the time of

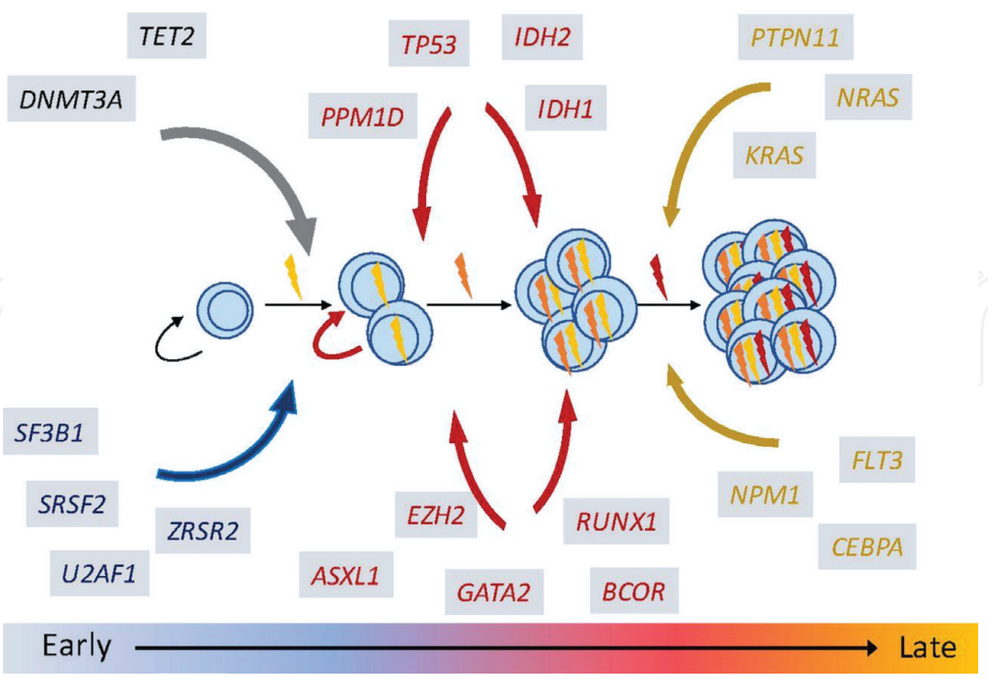

Figure 1.
Gene mutations have stereotyped positions in the MDS clonal hierarchy. Recent knowledge suggests that individual mutations occurs in highly stereotyped order and strong patterns of co-mutation association and exclusivity (Mutations affecting epigenetic modifier genes (DNMT3A, TET2, ASXL1, EZH2, etc.) or RNA spliceosome components (SF3B1, SRSF2, and U2AF1) tend to arise in the initiation and early progression phase of MDS and rarely occur at the time of transformation. Mutations in growth factor signaling pathways (NRAS, KRAS, PTPN11, FLT3, etc.) are frequently acquired and expanded in subclones at time of progression to high-grade MDS or secondary AML.

secondary AML transformation, the founding clone persisted at high variant allele fraction, but there was selective emergence and dominance of at least one genetically distinct subclone. In t-MDS, mutations in PPM1D or TP53 were present in 46% of patients, and they were the only gene mutations that were significantly associated with t-MDS [63, 68–71].

Various studies have also assessed the value of risk stratification based on MDS mutation profile [36, 42, 72]. TP53, ETV6, ASXL1, EZH2 and RUNX1 mutation confers adverse outcomes that are independent of IPSS risk assessment. SF3B1, which is frequently mutated in patients with ring sideroblasts, is associated with distinct and favorable clinical features [37, 38, 40].

3.2 Bone marrow microenvironment

HSC and genetically altered HSC all reside in a highly complex and dynamic cellular microenvironment in the bone marrow, that is composed of endothelial cells, multipotent mesenchymal stem cells, and sympathetic nerve fibers. There have been many *in vivo* studies demonstrated the concept of niche-induced disease initiation of MDS [73, 74] or AML [75, 76]. Evidence to support this in humans is mainly based on the not-so-rare occurrence of donor-derived leukemia in bone marrow transplant recipients, where changes in the preexisting niche in the host is thought to be leukemogenic [77]. In the review by Pleyer et al., [78] a variety of functional and molecular alterations were observed in *ex vivo* expanded mesenchymal stromal cells from MDS and AML patients, including their differentiation potential and HSC supportive activities, as well as chromosomal aberrations, transcriptional, and epigenetic changes. *In vivo* evidence also suggested that endothelial cells-specific gene alterations causes myeloproliferative disorders [79, 80].

3.3 Dysregulated immune pathways

Regulators of inflammation and innate immunity have always been thought to play an important role in pathogenesis of malignancies, but only until recent have the specific immune effectors and their cell-intrinsic functional roles in MDS stem cell biology been elucidated [81, 82]. Therapeutic targeting of over-activated innate immune components such as Toll-like receptors [83], IL-1 receptor–associated kinase/tumor necrosis factor receptor–associated factor-6 [84], IL8/CXCR2 [85], and IL1RAP [86] signaling pathways in MDS HSCs is being attempted pre-clinically.

4. Treatment

Treatment for MDS is guided by clinical symptoms, disease risk classification, patient age, comorbidities and performance status. Supportive care with transfusion and timely treatment of infection with antibiotics are important adjuncts for all MDS patients. Incorporating iron chelation therapy for patients requiring chronic transfusion and all candidates for allogeneic stem cell transplant is being increasingly emphasized to prevent cardiac and liver damage from iron overload [87, 88]. Pharmacologic treatment is usually reserved for symptomatic patients. Treatment goal for lower-risk MDS patients is to minimize symptoms, improve quality of life, and avoid toxicity from therapy. Erythropoiesis stimulating agent (ESA) can be used for symptomatic anemia and a low serum erythropoietin [89–92]. Together with low-dose G-CSF, hemoglobin improvement can be seen in up to 40% of lower-risk patients [93, 94]. Immunosuppressive therapy with antithymocyte globulin and cyclosporine A can produce response in a selected subset of

patients. Those most likely to benefit are younger than 60 years, with less than 5% bone marrow blasts, hypoplastic MDS, presence of a paroxysmal nocturnal hemoglobinuria clone, trisomy 8, human leukocyte antigen DR15 positive, and with short duration of transfusion dependence [95]. Low-dose lenalidomide at 10 mg daily is FDA-approved for lower-risk MDS characterized as the 5q- syndrome. Transfusion independence was achieved in 67% of patients in the phase 2 trial [96], and 56% in the phase 3 trial [97]. For ESA refractory lower-risk MDS patients without 5q- syndrome, lenalidomide in combination with ESA also demonstrated efficacy at reducing transfusion need [98–100]. So far, the only FDA approved therapies for higher-risk MDS are the HMAs azacitidine and decitabine. The use of these agents results in complete (CR) and partial response (PR) each in 10–20% patients, with median duration of response about 10 months [101–104]. An additional 20–30% patients achieve hematologic improvement without an objective response. Despite survival benefit demonstrated with azacitidine in high-risk patients [101], HMAs are not curative. For young and fit patients, allogeneic stem cell transplant is the only curative treatment option. Therefore, there remains a significant unmet therapeutic need beyond HMAs. Novel agents under clinical investigation and the use of allogeneic stem cell transplant will be discussed here.

4.1 Next-generation hypomethylating agents

HMAs are S-phase specific. Conventional HMAs all have a very short half-lives (less than 30 min) due to rapid clearance of azanucleoside by cytidine deaminase. The focus of newer generation HMA development has been to meet the need of prolonged drug exposure, allowing greater drug incorporation into DNA.

Oral film-coated azacitidine (CC-486) was first studied in an open-label pilot trial. It demonstrated 17% mean bioavailability after a single dose at 80 mg [105]. In a subsequent phase 1 dose finding study in MDS, CMML and AML patients, overall response rate was 73% in previously untreated patients, and 35% in previously treated patients [106]. Extended dosing schedule of CC-486 for 14 or 21 days is being evaluated in a phase 3 trial (NCT01566695) in lower-risk MDS [107]. CC-486 is also being studied in combination with immune check point inhibitor in the second line setting (NCT02281084).

ASTX727 is a novel formulation of oral decitabine paired with an oral cytidine deaminase inhibitor E7727 to overcome the rapid clearance from cytidine deaminase in gut and liver. In the early phase studies with intermediate- or high-risk MDS, ASTX727 (35 mg decitabine, 100 mg E7227) successfully emulated the pharmacokinetic profile of intravenous decitabine [108, 109]. In the phase 2 trial, clinical benefit was observed in 62% patients, with 16% CR, 28% marrow complete response (mCR), and 18% hematologic improvement [109].

Another strategy to circumvent the rapid degradation of azanucleotide is to develop a novel formulation that is relatively resistant to cytidine deamination. Guadecitabine (SGI-110) is a novel dinucleotide of decitabine and deoxyguanosine, linked by a phosphodiester bond, that leads to a slower release of the active decitabine moiety, prolonging cellular exposure to the drug [110]. In the phase 2 study with guadecitabine in intermediate and high risk MDS and CMML patients, CR was observed in 7/49 treatment naïve patients (14%) while CR + mCR were observed in 11/53 previously treated patients (21%) [111].

4.2 Histone deacetylase inhibition

Both DNA-promoter hypomethylation as well as post-translational modification of histone tails (e.g., deacetylation) lead to transcriptional silencing of tumor-suppressor

genes and genes involved in differentiation and apoptosis [112, 113]. Histone deacetylase inhibitors (HDACi) have limited single-agent efficacy in both high risk MDS and AML [114–116]. Preclinical evidence supported synergy between HMAs and HDACi [117]. However, a few phase 2 randomized clinical trials failed to demonstrate improvement in response rates or survival when azacitidine was combined with HDACi entinostat, vorinostat, valproic acid, or pracinostat [118–122]. Currently, a few clinical trials in MDS are ongoing using HDACi in combination with other novel agents such as immune checkpoint inhibitors (NCT 02936752) or pracinostat in combination with azacitidine using different dosing scheme (NCT 03151304). At this moment, how to best incorporate HDACi in MDS treatment remains uncertain.

4.3 Other epigenetic modification agents

Beyond targeting DNA methylation and HDAC recruitment, there has also been an increasing effort to develop epigenetic modification agents targeting posttranslation or posttranscription pathways, to mitigate malignant myeloid transformation in MDS.

Bromodomain and extraterminal (BET) proteins are epigenetic readers that recognize acetylated lysine tails of histones, and thus areas of open chromatin structure. It has been suggested that AML relies on BET protein BRD4 [123, 124], therefore led to great interest in utilizing BET inhibitors in myeloid malignancy. Various clinical trials are investigating the use of JQ1, the first selective BET inhibitor, in myeloid malignancy including MDS (NCT 02158858, NCT 02308761).

Overexpression of the mono and dimethyl lysine demethylase, LSD1 has been implicated in myeloid malignancies [125]. Clinical trials are ongoing evaluating LSD1 inhibitors in combination with ATRA or HMA in previously treated AML and MDS patients (NCT02273102, NCT02717884, NCT02929498).

4.4 Immune checkpoint inhibition

Upregulation of immune checkpoint molecules like PD-1/PDL-1 and CTLA4 is commonly observed in many malignancies, including AML and MDS [126, 127] to evade immune surveillance. However, preliminary experience suggested limited activity of immune checkpoint inhibitor use as single agent after HMA failure in MDS patients [128]. Several clinical trials are ongoing evaluating the efficacy of immune checkpoint inhibitors plus HMAs or HDACis (NCT02530463, NCT03092674, NCT02775903, NCT03094637, NCT02599649).

4.5 Other targeted therapies: extrapolating experience from AML

Based on the mutation profile, FLT3 inhibitor and IDH1/2 inhibitors are now FDA approved for AML. However, these mutations are less common in MDS [129]. The early phase ½ studies of IDH1 and IDH2 inhibitors included MDS patients, with reported response [130, 131]. Especially given their tolerability profile and single agent activity, these agents deserves further investigation in MDS.

Spliceosome mutations, such as SF3B1, SRSF2 and U2AF1 are the most common mutations in MDS [37]. Based on the encouraging activity in preclinical study [132], there is now a phase 1 study in myeloid malignancies including MDS, with splicing modulator H3B-8800, an oral modulator of the SF3B complex (NCT02841540).

Venetoclax, a selective BCL-2 inhibitor was granted breakthrough designation by FDA in combination with decitabine in 2017 for treatment–naive AML patients age greater than 65 years. This decision was based on result from two ongoing phase ½ clinical trials [133]. This combination is now being evaluated in higher-risk MDS in both frontline and HMA failure settings (NCT02966782, NCT02942290).

4.6 Management of anemia in lower-risk MDS

Luspatercept and sotatercept are modified activin receptor type II (ActRII) chimeric fusion proteins that consist of the modified extracellular domain of ActRIIB and ActRIIA respectively, trap TGF-β superfamily ligands to promote late-stage erythropoiesis [134, 135]. In the phase 2 trial of luspatercept for patients with lower-risk MDS who were ineligible for or refractory to ESAs, RBC transfusion independence was seen in 38% patients, and 63% hematologic improvement [136]. Similar efficacy was seen in the phase 2 trial for sotatercept, with 47% hematologic response in patients with high transfusion burden, and 58% with low transfusion burden [137]. Ongoing phase 3 clinical trial is evaluating the efficacy of ActRII antagonist in lower-risk MDS and MDS with ring sideroblasts who require regular RBC transfusions (NCT 02631070).

Rigosertib is a PI3K and polo-like kinase pathways small-molecule inhibitor. In the recent phase 2 study for transfusion-dependent lower-risk MDS patients, 20 of 62 (32%) patients achieved transfusion independence lasting for more than 8 weeks [138]. Validation of these results in future clinical trials is anticipated.

Roxadustat is a drug which acts as a HIF prolyl-hydroxylase inhibitor and thereby increases endogenous production of erythropoietin, which stimulates production of hemoglobin and RBCs. Roxadustat is shown to be safe and effective as anemia treatment for patient with underlying chronic kidney disease, not on dialysis [139]. A phase 3 trial is ongoing to evaluate the efficacy of roxadustat in low-risk MDS patients with low transfusion burden (NCT03263091).

4.7 Allogeneic stem cell transplant

Allogeneic stem cell transplant is the only curative therapy for MDS, but restricted to younger and fit patients. Disease free survival rates are approximately 30–50%. Treatment failure is attributed by transplant-related mortality in low-risk patients, and relapse in higher-risk patients [140]. In general, bone marrow transplant is offered to intermediate-2 and high-risk MDS patients. Over the past decade, reduced-intensity conditioning transplant made more older patients eligible for transplant [141].
An ongoing clinical trial is comparing the efficacy of reduced intensity allogeneic stem cell transplant to HMA in patients aged 50–75 with higher-risk disease [142]. In the study by Della Porta et al. [143], IPSS-R was prognostic for outcomes of patients in the high and very high-risk groups, but not in the low- and intermediate-risk groups.

There have been emerging data on the prognostic value of mutation profile and minimal residual disease pre- and post-transplantation. It was shown that only a minority of patients with MDS was in deep hematologic remission by flow cytometry minimal residual disease (MRD) and cytogenetic analysis before transplant [144]. For myeloablative conditioning, MRD positive and MRD negative patients had similar post-transplant outcome. However, relapse rate was higher for MRD positive patient who received non-myeloablative conditioning. Multiple studies have shown that TP53 mutation is an independent marker for short survival post-transplant [59, 61, 145]. EZH2, ETV6, RUNX1, ASXL1, JAK2, and mutations in the RAS signaling pathway have all been implicated to associate with short relapse-free interval post-transplant [59, 61, 145, 146].

5. Conclusion

Over the past decade, knowledge was gained in understanding the pathogenesis of MDS. However, many gaps remain to change the natural history of MDS. With

increasing number of novel treatments under investigation, it is likely that we are getting closer to more therapeutics options for MDS in the near future.

Conflict of interest

Wanxing Chai-Ho reports no conflict-of-interest.

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