Chapter 4

Myelodysplastic Disorders, 5q-Syndrome

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Additional information is available at the end of the chapter

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Abstract

The myelodysplastic syndromes (MDSs) are characterized by ineffective erythropoiesis and progressive cytopenia and ultimately affected patients develop acute myeloid leukemia (AML) or die from advanced bone marrow (BM) failure.

Myelodysplastic syndrome (MDS) with isolated del (5q) is a common type of MDS with specific pathological and clinical manifestations including refractory anemia. It is usually treated by (1) supportive measures including blood transfusions that may cause iron overload that requires iron chelation therapy, (2) targeted therapies such as the immunomodulatory drug lenalidomide, and (3) hematopoietic stem cell transplantation (HSCT) in transplant eligible individuals. The establishment of the various prognostic systems, the discovery of the new genetic mutations, and the identification of new targets, in MDSs in general and in 5q-syndrome in particular, will hopefully translate into more pinpointed targeted therapies that will further improve the outcomes of patients having these disorders.

Keywords: myelodysplastic syndrome, 5q-syndrome, iron overload, lenalidomide, hematopoietic stem cell transplantation

1. Introduction

The MDSs are a group of clonal stem cell disorders that are characterized by ineffective erythropoiesis due to excessive apoptosis and progressive peripheral blood cytopenia culminating into acute myeloid leukemia AML or death from progressive BM failure [1–4]. MDS is primarily a disease of the elderly with a median age of 70 years [3]. The MDSs have been linked to several etiologies, risk factors, and environmental associations such as alcohol intake, tobacco use, Sweet's syndrome, vitamin deficiencies, cytotoxic chemotherapy, various hereditary disorders, and BM failure syndromes [5–12].

2. Pathogenesis of MDSs

The pathogenesis of MDS is poorly understood [5, 12]. However, several pathogenic mechanisms have been described and these include the following: (1) genetic mutations as the cell of origin has acquired multiple mutations that result in dysplasia and ineffective erythropoiesis; (2) MDS clonality: MDS is a clonal process thought to develop from a single-transformed hematopoietic progenitor cell. The inciting mutation is unknown for the majority of cases. However, recurrent genetic mutations involving RNA splicing machinery have been identified; (3) haploinsufficiency of ribosomal proteins particularly ribosomal protein (RPS) 14 in del (5q); (4) telomere dysfunction and aberrant or absent expression of micro-RNA species; (5) epigenetic changes: MDS genomes are characterized by global DNA hypomethylation with concomitant hypermethylation of gene-promoter regions relative to normal controls; (6) factors extrinsic to hematopoietic cells such as stromal abnormalities and T-cell dysregulation that may occur causally or secondary to the primary genetic defects; (7) accelerated apoptosis and ineffective erythropoiesis; (8) altered immune responses such as polyclonal expansion of helper T cells (CD4+) and oligoclonal expansion of cytotoxic T cells (CD8+) in the peripheral blood and BM; (10) leukemic transformation in MDS; the estimated risk of leukemic transformation is more than 50% and is more frequent in patients with high-risk MDS such as refractory anemia with excess of blasts (RAEB) II, monosomy 7, deletion of short arm of chromosome 17, deletion of long arm of chromosome 7, and trisomy 8 [5, 12].

3. Chromosome 5 abnormalities in MDS

Approximately, 15% of patients with MDS have abnormalities of chromosome 5 that include insertional deletion of a segment of the long arm of the chromosome [del (5q) or 5q-syndrome], monosomy 5, and unbalanced translocations [13].

3.1. Del (5q) type of MDS

The insertional deletion of the long arm of chromosome 5, del (5q), is the one of the most common cytogenetic abnormality encountered in patients with MDSs as it has been reported in 10–30% of patients with MDS [14–17]. The long arm of chromosome 5 has two distinct commonly deleted regions (CDRs). The more distal CDR lies in 5q33.1 and contains 40 protein coding genes and genes that code for microRNAs (miR-143 and miR-145) [13]. Many genes related to hematopoiesis are located on the long arm of chromosome 5 [18]. In del (5q), one allele is deleted and this accounts for the genetic haploinsufficiency [13]. The gene cluster at 5q31 includes interleukins (ILs) 3, 4, 5, 9, 13, and 17β in addition to granulocyte monocyte-colony-stimulating factor (CSF). Several cytokine receptor genes are also located on the long arm of chromosome 5 including: CSF-1 receptor and platelet-derived growth factor-β [18].

The world health organization (WHO) recognizes del (5q), which was first described by Van den Berghe et al. in the year 1974, as a distinct form of MDS [15, 18–20]. The 5q-syndrome is the most distinct type of all MDSs as it has clear genotype/phenotype relationship [18, 21]. If

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del (5q) occurs as the only cytogenetic abnormality, it is associated with favorable prognosis but once it is encountered in association with other single or multiple chromosomal abnormalities, particularly in the setting of complex cytogenetics, the clinical outcome is rendered poor [14, 16, 20, 22, 23].

Patients with del (5q) have specific clinical and pathological features [15, 18, 20]. The 5 q-syndrome is usually characterized by the following: (1) female predominance, (2) refractory macrocytic anemia that is often severe, (3) normal or elevated platelet count, (4) BM findings of erythroid hypoplasia, less than 5% blasts as well as abnormal, dysplastic or hypolobulated megakaryocytes, (5) del (5q) chromosomal abnormality as the sole karyotypic abnormality, and (6) a rather benign clinical course with approximately 10% of patients ultimately progressing to AML [13, 14, 18–20].

Despite the remarkable progress that has been achieved recently, certain unclear issues related to the pathogenesis of del (5q) need further evaluation [18, 20]. Del (5q) MDS is considered a disorder of the hematopoietic stem cells with lympho-myeloid potential. Also, involvement of B cells, rather than T cells, was documented by combining immunophenotyping and fluorescence *in situ* hybridization (FISH) analysis [18]. Cytogenetic and FISH analysis in BM progenitor cells have revealed that, in del (5q) MDS, the deletion was generally present in the pluripotent hematopoietic stem cells (CD34+ and CD38+) with the persistence of the normal progenitor cells in the BM [20]. Genomic stability in 5q-syndrome is related to the infrequency of additional cytogenetic abnormalities [18]. The lack of mutations in the genes mapping the CDR suggests that haploisufficiency is the basis of 5q-syndrome [13, 18, 20]. Candidate genes that show haploinsufficiency in del (5q) include SPARC (secreted protein acidic and cysteine rich), a tumor suppressor gene, and RPS14, which is a component of the 40s ribosomal subunit [13]. Only in advanced forms of the disease, rare mutations involving p53, JAK2, and MPL genes have been described [13, 18, 20].

The erythroid defect or failure in del (5q) appears to be multifactorial as it has been reported to involve in the following: (1) the decreased expression or haploinsufficiency of the ribosomal protein S14 [RPS14] gene, (2) the upregulation of the p53 pathway induced by ribosomal stress, and (3) enhancement of the endogenous erythropoietin production that ultimately leads to red cell transfusion dependence in most patients [13, 15, 18, 21]. On the other hand, loss of the microRNA genes miR-145 and miR-146a has been associated with the thrombocytosis observed in 5q-syndrome patients [21]. Also, the increased expression of Friend leukemia virus integration 1(FLI1), which is one of the target genes of miR-145, maintains effective megakaryopoiesis in del (5q) MDS resulting in normal or elevated platelet (PLT) counts [13].

Isolated del (5q) has been reported in in higher grade MDSs such as RAEB and RAEB-thrombocytosis (RAEB-T), thus contributing to the heterogeneity of the disease [20, 22]. MDS with del (5q) occurs not only in myelodysplastic disorders, but also in AML and it contributes to the pathogenesis of both myeloid diseases by deleting one or more of the tumor suppressor genes [22]. Once associated with additional cytogenetic abnormalities and once new genetic mutations are acquired, such as TP53 mutation, MDS with del (5q) becomes an aggressive disease with rapid evolution into AML [20, 22]. Therefore, isolated del (5q) MDS should be differentiated from other forms of myelodysplasia having del (5q) associated with other

cytogenetic abnormalities and an excess of BM blasts [20]. Other specific aspects of 5q- syndrome will be discussed separately in the subsequent sections of the review manuscript.

3.2. Monosomy 5 type of MDS

Loss of the whole chromosome 5 has been described in about 3–8% MDS cases. Recent studies have shown that many suspected monosomies 5 are in fact cryptic translocations or insertions, undetectable by conventional G-banding [24]. The mechanism responsible for the fragmentation of deleted chromosome 5 remains unclear. One of the possible explanations might be the phenomenon called chromothripsis, whereby one or more chromosomes or chromosomal regions shatter into pieces in a single catastrophic event. MDS patients with deleted chromosome 5 involved in complex rearrangements should be considered as a unique entity with extremely poor prognosis [24].

Monosomy 5 does exist but is rarely encountered and the presence of this chromosomal abnormality is usually associated with complex karyotypes, conferring poor prognosis [25]. Studies have shown that, compared to 5q- syndrome, monosomy 5 is more frequently associated with: advanced or higher risk MDS, other chromosomal abnormalities including chromosome 7 abnormalities and inferior overall survival [26]. Monosomy 5 has been reported in therapy-related MDS (t-MDS) with complex cytogenetics and rapid progression to death [27].

4. Clinical manifestations and complications of MDS

MDS has nonspecific signs and symptoms at presentation. However, many patients are asymptomatic at presentation. The main manifestations of MDS are those related to cytopenia. Anemic manifestations include fatigue, weakness, dizziness, exercise intolerance, angina, cognitive impairment, and altered sense of well-being [12, 28]. Patients having thrombocytopenia present with bleeding from various sites such as skin and mucous membranes. Easy bruising, epistaxis, petechiae, ecchymoses, and gum bleeding are the main manifestations [12, 28]. Patients with neutropenia may develop fever and infections may be due to viruses, bacteria, fungi, and mycobacteria [12, 28, 29]. Physical examination in patients with MDS usually reveals: pallor, petechiae or ecchymoses, hepatosplenomegaly, and lymphadenopathy uncommonly, weight loss in advanced cases and skin manifestations in case of associated Sweet's syndrome [12, 28].

Autoimmune abnormalities may be present in MDS patients and they include cutaneous vasculitis, monoarticular arthritis, pericarditis, pleural effusions, edema formation, skin ulcerations, iritis, myositis, peripheral neuropathy, fever, and pulmonary infiltrates [12]. Other abnormalities that may be encountered in patients with MDS include pure red cell aplasia, acquired HbH disease, myeloid sarcomas, Sweet's syndrome, myocardial ischemia, and thrombocytosis in patients with del (5q) and RARS-T [12, 28].

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5. Diagnosis and subtypes of MDS

Minimal morphological diagnostic criteria in MDS include the following: (1) BM findings: ≥ 10% dysplastic cells in ≥ 1 myeloid lineages, (2) highly suggestive features: (a) granulocytic series: agranular neutrophils and Pelger–Huet neutrophils, (b) megakaryocytes, small binucleated megakaryocytes and small round separated nuclei in megakaryocytes, and (c) erythroid series: multinuclear or asymmetrical nuclei, nuclear bridging, and ring sideroblasts [6, 30, 31].

The minimal diagnostic criteria in MDS include the following: (1) prerequisite criteria that include (a) constant cytopenia in ≥ 1 of the following lineages: erythroid: Hb < 11 g/dL, neutrophilic; absolute neutrophil count (ANC) < 1.5 × 10^9/L or megakaryocytic, PLTs < 100 × 10^9/L. (b) exclusion of all other hematopoietic and nonhematopoietic disorders as primary reasons for cytopenia or dysplasia; (2) MDS-related or decisive criteria: (a) dysplasia in at least 10% of all cells in one of the following lineages in the BM smear; erythroid, neutrophilic or megakaryocytic or > 15% ring sideroblasts on iron staining, (b) 5–19% blasts on BM smears, and (c) typical chromosomal abnormality by FISH or conventional karyotype. (3) cocriteria for patients fulfilling (1) but not (2): (a) abnormal phenotype of BM cells clearly indicative of a monoclonal population of erythroid and/ or myeloid cells determined by flow cytometry, (b) clear molecular signs of a monoclonal cell population in human androgen receptor (HUMARA) assay, gene chip profiling or point mutation analysis such as RAS mutation, (c) markedly or persistently reduced colony formation of BM and/or circulating progenitor cells by colony-forming unit assay [6, 30, 31]. The subtypes of MDS according to the WHO classification are illustrated in **Table 1** [6, 30, 31].

Subtype of MDS	Proportion of MDS patients	Peripheral blood findings	Bone marrow findings
RAEB I [refractory anemia with excess of blasts I]	–	Cytopenia (s) <5% blasts No Auer rods Monocytes: <1G/L or <1 × 10^9/L	Unilineage or multilineage dysplasia No Auer rods 5–10% blasts
RAEB II [refractory anemia with excess of blasts II]	40%	Cytopenia(s) 5–19% blasts Possible Auer rods Monocytes: <1 G/L or <1 × 10^9/L	Unilineage or multilineage dysplasia 5–19% blasts Possible Auer rods
RCUD [refractory anemia with unilineage dysplasia, uni	**Refractory:** Anemia: 10–20% Neutropenia: < 1%	Anemia Neutropenia Thrombocytopenia	Only one cytopenia with dysplasia in >10% of cells. > 5% blasts< 15% ring

Subtype of MDS	Proportion of MDS patients	Peripheral blood findings	Bone marrow findings
or bicytopenia]	↓ PLT: < 1%	No or < 1% blasts	sideroblasts
RARS [refractory anemia ring sideroblasts]	3–11%	Anemia No blasts	Unilineage erythroid dysplasia < 5% blasts ≥ 15% ring siderblasts
RCMD [refractory anemia with multi lineage dysplasia with or without ring sideroblasts]	30%	Cytopenia(s) < 1% blasts No Auer rods Monocytes < 1 G/L	Dysplasia in ≥ 10% of cells belonging to at least 2 cell lines < 5% blasts without Auer rods ± 15% ring sideroblasts
MDS with isolated del (5q)	Uncommon	Anemia Normal or high PLT count < 1% blasts	5% blasts without Auer rods Megakaryocytes: normal or ↑; hypolobulated
MDS-U [unclassified MDS]	Unknown percentage	Cytopenia ≤ 1% blasts	Dysplasia in < 10% cells but cytogenetic abnormalities are considered presumptive for MDS < 5% blasts

MDS: myelodysplastic syndrome; PLT: platelet; ↑: increased.

Table 1. WHO classification of MDS.

5.1. Cytogenetics in MDS

Several cytogenetic abnormalities can be encountered in patients with MDSs, some of these are balanced, while others are unbalanced as illustrated in **Table 2** [6]. Cytogenetic abnormalities are major determinants in the pathogenesis of MDS. They are becoming increasingly recognized as the basis of selecting drugs in individual patients with MDS and they play a significant role in monitoring response to treatment [32]. Chromosomal abnormalities are detected in approximately 50% of patients with *de novo* MDS and 80% of patients with t-MDS [32]. Recently, our ability to define the prognosis of the individual patient with MDS has improved significantly [6]. Cytogenetic abnormalities are becoming essential in determining the prognosis of MDS because they constitute the basis of the new cytogenetic scoring system as shown in **Table 3** [31, 33, 34]. The values of the new prognostic systems will certainly become higher as new genetic-based therapy move through trials and into clinical practice [6].

http://dx.doi.org/10.5772/64202

Balanced chromosomal abnormalities		Unbalanced chromosomal abnormalities	
Abnormality	Frequency	Abnormality	Frequency
t (11,16) (q23;p13.3)	–	+8	10%
t (3,21) (q26. 2; q22.1)	–	−7 or del (7q)	10%
t (1,3) (p36.3; q21.2)	–	−5 or del (5q)	5–8%
t(2,11) (p21; q23)	1%	Del (20q)	5%
inv (3) (q21; q26.2)	1%	−Y	3–5%
t (6,9) (p23; q34)	1%	I (17q) or t (17p)	3%
		−13 or del (13q)	3%
		Del (11q)	10%
		Del (12p) or t (12p)	3%
		Del (9q)	1–2%
		Idic (x) (q13)	1–2%

*MDS: myelodysplastic syndrome.

Table 2. Chromosomal abnormalities in MDS.

Prognostic class	Proportion of patients	Karyotype or cytogenetic abnormalities	Median survival in years	Time to 25% AML transformation
Very good	4%	−Y del (11q)	5.4	Not reached
Good	72%	Normal del (5q) del (20q) del (12q) Double including del (5q)	4.8	9.4
Intermediate	13%	del (72) +8 +19 isochromosome (17q) Any other single or double independent clones	2.7	2.5
Poor	4%	−7 inv (3); *t*(3q); del (3q) Double including -7/del (7q) Complex: 3 cytogenetic abnormalities	1.5	1.7
Very poor	4%	Complex > 3 cytogenetic abnormalities	0.7	0.7

MDS: myelodysplastic syndrome; AML: acute myeloid leukemia.

Table 3. New cytogenetic scoring system for MDS.

5.2. Impact of monosomal karyotype on the prognosis of MDS

A monosomal karyotype (MK) is defined by the presence of ≥ 2 distinct autosomal chromosome monosomies or a single autosomal monosomy associated with ≥ 1 structural abnormality [1]. In AML, MK has been associated with a worse prognosis than an otherwise complex karyotype, regardless the specific type of autosome involved [1].

Studies have shown that MK in MDS identifies a prognostically worse subgroup of patients than a complex karyotype regardless of whether monosomy 7 or 5 is part of the MK component [1]. Chromosomal abnormalities are present in 20–70% of patients with MDS, but complex cytogenetics are universally considered unfavorable as they are associated with poor overall survival (OS) and high rates of leukemic transformation [1, 32, 34].

5.3. Genetic mutations described in MDSs and 5q-syndrome

Several classes of genetic mutations have been described in patients with MDS as shown in **Tables 4–6** [34–40]. These mutations are essential in not only determining the prognosis but also constituting a platform for the current and future novel and targeted therapies for various types of myelodysplasia (**Tables 4** and **6**) [34–39].

Class	Mutation	Chromosomal location	Frequency	Prognostic significance	– Associations: phenotypes and MDS types – Application to treatment
(1) RNA- splicing machinery (50%)	**SF3B1** [Splicing factor 3b, subunit 1]	2q33.1	15–60%	Good	**– Phenotype:** ring sideroblasts **– MDS types:** – RARS – RCMD – RS – RARS – T
	SRSF2 [Serine/arginine-rich splicing factor-2]	17q22.3	6–20%	Poor	**– MDS types:** – RCMD – RAEB – CMML
	U2AF1 [U_2 small nuclear RNA auxiliary factor-1]	21q22.3	5–12%	Unclear/poor	**– MDS types:** – RCMD – RAEB – CMML
	ZRSR2 [Zinc finger RNA-binding mofit and serine/arginine rich 2]	Xp22.1	3–10%	Unknown	**– MDS types:** – RCMD – RAEB – CMML

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Class	Mutation	Chromosomal location	Frequency	Prognostic significance	– Associations: phenotypes and MDS types – Application to treatment
	ZRSF2	17q25.1	6–12%	Poor	–
	PRPF8	17p13.3	3.3%	Unclear	–
(2) Epigenetic pathways: DNA methylation and chromatin modification (45%)	**DNMT3A** [DNA methyltransferase 3 alpha]	2 p23	8–12%	Adverse/ negative – Decreased survival – Increased risk of sAML	– All MDS types
	TET 2 [tetmethylcytosine deoxygenase-2]	4q 24	15–30% 2%	Unclear / possibly positive – Improved response to azacitidine – Inconsistent impact on survival	**– Phenotype:** myeloid dominancy **– MDS types:** dominancy – all MDS types – Normal karyotype – CMML
	IDH1 [isocitrate dehydrogenase-1] (soluble)	2q 33.3	2%	Unclear – Advanced MDS – AML progression	**– MDS types:** – RCMD – RAEB – CMML
	IDH2 [isocitrate dehydrogenase-2] (mitochondrial)	15q 26.1	2%	Poor prognosis – Decreased survival	**– MDS types:** – RCMD – RAEB – CMML
	EZH2 [enhancer of zeste homolog 2]	−7/7q- 7q35–q36	2–6%	Poor prognosis – Decreased survival	**– MDS types:** – RCMD – RAEB – CMML
	ASXL1 [additional sex combs like 1]	20q 11	10–21%	Poor prognosis – Decreased survival	**– MDS types:** – RCMD – RAEB – CMML
(3) Signal transduction	**NRAS** [neuroblastoma	1 p13.2	10%	Unclear/ adverse	**– MDS types:** – All MDS types

Class	Mutation	Chromosomal location	Frequency	Prognostic significance	– Associations: phenotypes and MDS types – Application to treatment
(kinase signaling)	RAS viral oncogene homolog]			– Increased risk of progression to AML	– CMML – JMML
	KRAS	12 p12.1	2–6%	Unclear/ adverse – Increased risk of progression to AML	– **MDS types**: – All MDS types – CMML – JMML
	CBL [cbl proto-oncogene E3 ubiquitin protein ligase]	11q 23.3	1–5%	Unknown	– **MDS types:** – All MDS types – CMML – JMML
	JAK 2 [Janus kinase 2]	9p24	6.2–8.3%	Unknown – Does not appear to alter prognosis	– **Phenotype:** – Megakaryocytosis – **MDS types:** – all types/RARS-T/RA – JAK2 Inhibitors
	NF1	–	<5%	Poor	– **MDS types:** – all MDS types – JMML
	FLT3 [Fms-related tyrosine -kinase 3]	13 q12	<5%	– Poor prognosis – Progression to AML	– **MDS types:** – All MDS types – FLT 3 Inhibitors
(4) Cohesin family-complex pathway	**RAD 21**	8 p24	2%	– Adverse prognosis	–
	STAG 2	X q25	5–10%	– Adverse prognosis	– **MDS types:** – RCMD – CMML – RAEB
	SMC1 A	Xp 11.22-P11.121	<1%	– Adverse prognosis	–
	SMC 3	10q25	2%	– Adverse prognosis	–

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Class	Mutation	Chromosomal location	Frequency	Prognostic significance	– Associations: phenotypes and MDS types – Application to treatment
(5) Transcriptional factors and corepressors	**TP 53** [tumor protein P53]	17q13.1	5–10%	– Very poor – Adverse outcome	– **Phenotype:** – Complex karyotype – Poor prognosis – Rapid progression to AML – **MDS types:** – RAEB – Isolated del (5q) – Therapy related MDS
	RUNX1 [runt-related transcription factor 1]	21q22.3	9–20%	– Adverse outcome – Very poor – Associated with -7/del (7q) – *High risk of progression to AML	– **Phenotype:** thrombocytopenia – **MDS types:** – RCMD – RAEB – CMML
	BCOR1/BCORL1	Xp 11.4/X q25-q26.1	6–9.1%	– Adverse outcome	– **MDS types:** – RCMD – RAEB
	CEBPA [CCAAT/enhancer-binding protein, alpha]	19q13.1	<5%	– Poor prognosis	– **MDS types:** – RCMD – RAEB
	ETV6 Ets variant-6	12 p13	<5%	– Poor outcome	– **MDS types:** – RCMD – RAEB
	SETBP1 SET-binding protein$_1$	18q21.1	2–5%	– Negative/ adverse outcome	–
	KMT2A Lysine -K-specific methyltransferase-2A	11q21.1	Approximately 4%	– Negative/ adverse outcome	–
	NPM1 nucleophosmin	5q35.1	Approximately 2%	Unknown	–
	KIT	4q11-q12	Approximately 1%	Unclear	–

Class	Mutation	Chromosomal location	Frequency	Prognostic significance	– Associations: phenotypes and MDS types – Application to treatment
	[V-KitHardy-Zuckerman 4 Feline sarcoma viral oncogene homolog]				
(6) Other genetic mutations	**GNAS** [GNAS complex 10ms]	20q 13.3	Approximately 1%	Unknown	
	PTPN11 Protein tyrosine phosphatase non-receptor type11	12q 24	Approximately 1%	Unknown	
	PTEN	10q 23	<1%	–	
	CDKN2A	9q (12)	<1%	–	
	BRAF	7q 34	<1%	–	
	CSF1R	–	–	– Poor prognosis – Advanced MDS – Progression to AML	– Normal karyotype predominantly
	ATRX	–	Rare		Associated with acquired α-thalassemia, often with severe anemia
	MPL	–	–	– Poor prognosis – Advanced MDS – Progression to AML	5% of RARS – T

MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia; JMML: juvenile myelomonocytic leukemia; AML: acute myeloid leukemia; RCMD: refractory cytopenia with multilineage dysplasia; RA: refractory anemia; RAEB: refractory anemia with excess of blasts; RARS: refractory anemia with ring sideroblasts; RARS-T: refractory anemia with ring sideroblasts thrombocytosis.

Table 4. Genetic mutations in MDS.

TP53 encodes a cytoplasmic protein p53 that regulates cell growth and death. TP53 mutations have been found mainly in intermediate to high-risk MDS patients [41]. Patients having TP53

mutations often present with severe thrombocytopenia, complex cytogenetic abnormalities, an increased risk of leukemic transformation, and a shorter survival [41, 42]. Patients with mutant p53, compared to patients carrying wild-type p53, have the following features: older age, anemia, and leucopenia at the time of diagnosis and shorter median survival. Molecular identification of mutant p53 contributes to the risk stratification of patients with lower-risk MDS that may alter the treatment approach [41]. TP53 mutations develop at an early disease stage in almost 20% of patients with lower-risk MDS having del (5q) [42].

Biological process	**Genetic mutation**	
Transcriptional regulators	– SF3 B1 nm	– SRSF2 nm
	– UZ AF1	– CUX1
	– SETBP1	
Epigenetic regulators	– ASXL1	– TET2 nm
	– DNMT3 A	– EZH2
Cell cycle regulators	– TP53	
	– NPM1	
Apoptosis	– BCL2	
Translation	– RPS14 nm	–RPL 23
	– RPS 4x	– RPS 25
	– RPA 19	
Signaling or differentiation	– RUNX1	– N-RAS
	– ETV 6	– FMS
	– FLT 3	– SET BP1

*MDS: myelodysplastic syndrome;

* nm: non-mutated

Table 5. Genetic mutations associated with poor prognosis in MDS.

Mouse models of the 5q-syndrome have indicated that a p53-dependent mechanism underlies the pathophysiology of this disorder. Importantly, activation of p53 has been demonstrated in the human 5q-syndrome [43]. Recurrent TP53 mutations have been associated with an increased risk of AML disease evolution and with decreased response to lenalidomide therapy in del (5q) MDS patients [43].

TP53 mutations are usually present years before disease progression. They are associated with p53 overexpression but are not associated with specific clinical manifestations [42]. The presence of TP53 mutations in low-risk MDS with del (5q) contributes to the heterogeneous disease and may significantly affect clinical decision making [42].

Pathway	Examples of genetic mutations	Frequency in MDS (%)	Application to treatment
DNA splicing machinery	– SF3B1, – UZAF1 – SRSF1, – PRPF8 – SRSR2/SRSF2, – UTx	60–70%	None
DNA methylation	– DNMT3A – TET2 – IDH1/IDH2	40–50%	– DNA methyl transferase inhibitors – IDH1/IDH2 inhibitors
Chromatin modification	– ASXL1 – EZH2	20–30%	– Deacetylyase inhibitors
Signal transduction	– NRAS/KRAS – CBL – JAK2 – NF1 – FLT3	20–30%	– Kinase inhibitors – JAK inhibitors – FLT3 inhibitors
Cohesion complex/family pathway	– STAG2 – RAD21 – SMC1A – SMC3	10%	None
Transcription factors and corepressors	– TP53 – RUNX1 – BCOR1/BCORL1 – CEBPA – ETV6	20–40%	None

MDS: myelodysplastic syndrome.

Table 6. Point mutations in MDS.

In patients with 5q-syndrome, TP53 mutations are present in a small fraction of patients and they cause p53 overexpression subsequently. These aberrant subclones remain quiescent during treatment with lenalidomide and they expand at transformation into acute leukemia [44]. Studies have confirmed that in patient with low-risk MDS having 5q-syndrome, TP53 mutations are associated with strong p53 expression and that p53 positivity is the strongest independent predictor of transformation into AML [45]. Patients with MDS having del (5q) may have mutations other than TP53 such as FOXP1, TP63, JAK2, and MPL mutations [19, 46]. FOXP1 and TP63 mutations may be involved not only in the pathogenesis of the disease, but also they may play a role in the progression into AML [46]. JAK2 and MPL mutations may be found in a small proportion of patients, but their presence does not seem to affect phenotype or progression [19].

Potential new therapeutic agents for del (5q) MDS include the translation enhancer L-leucine, as it may have some efficacy in ribosomopathies. L-leucine has shown increased hemoglobi-

nization and red cell numbers and reduced developmental defects both in humans and in mouse models [43].

6. Prognostic systems in MDSs

In MDS, there are several prognostic scoring systems and these include the following: (1) the international prognostic scoring index (IPSS), (2) the revised IPSS (R-IPSS) (**Table 7**), (3) the WHO prognostic scoring system (WPSS), (4) MD Anderson Cancer Center (MDACC) MDS model that includes the global and the lower-risk scoring systems, and (5) the French prognostic scoring system (FPSS) [30, 31, 33, 47, 48]. The components of the prognostic stratification systems of MDS are as follows: BM blast cells, age, comorbid medical conditions, serum lactic dehydrogenase (LDH), cytogenetics, number of cytopenia, severity of anemia, and high white blood cell (WBC) count [4].

Prognostic variable	**Points**						
	0	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetics	Very good	–	Good	–	Intermediate	Poor	Very poor
Bone marrow blasts %	≤2	–	>2–5%	–	5–10%	>10%	–
Hb (g/dL)	≥10	–	8– < 10	<8	–	–	–
PLT count $\times 10^9$/L	≥100	50–100	<50	–	–	–	–
ANC $\times 10^9$/L	≥0.8	<0.8	–	–	–	–	–

MDS: myelodysplastic syndrome; Hb: hemoglobin; ANC: absolute neutrophil count – indicates not applicable; PLT: platelet.

Table 7. (R-IPSS) Revised international prognostic scoring system for MDS.

The IPSS is composed of: blast percentage, karyotype or cytogenetics and the number of cytopenia. The IPSS is classified into low, intemediate-1, intemediate-2, and high-risk score [6, 49]. The R-IPSS model incorporates: BM blasts, cytogenetics, hemoglobin (Hb) level, PLTs, and ANC. The R-IPSS is divided into five risk categories: very low, low, intermediate, high, and very high risks (**Table 7**) [30, 31, 33, 47]. The R-IPSS is an excellent predictor of MDS in the era of disease modifying therapies. The early recognition of patients at high risk of progression to aggressive disease may optimize the timing of treatment before worsening of comorbidities [50]. The precise definition of a prognostic score, such as the R-IPSS, and the probability of leukemia evolution are particularly important in patients with lower-risk MDS in which new approaches including allogeneic HSCT may be addressed in younger patients in a refined manner [50].

The WPSS incorporates the following variables: WHO classification of MDS, cytogenetics, and the need for RBC transfusions [6, 47]. The MD Anderson prognostic model depends on the following factors: age, performance status, prior blood transfusion, WBC and PLT counts, Hb level, BM blasts, and karyotype [47, 49]. The scoring system is divided into four risk categories: low, intermediate-1, intermediate-2, and high [47, 49]. The FPSS includes the following items: the Eastern Cooperative Oncology Group (ECOG) performance status, IPSS cytogenetic risk, the presence of circulating blasts, and packed red blood cell (RBC) transfusion dependency [48]. The prognostic models of MDS are important, as they are used as tools in determining the severity of the illness, the prognosis of MDS, and the best line of management to be considered, that is, supportive care, hypomethylating agents, immunomodulatory drugs or HSCT [49]. The proliferation index (PI) of specific compartments of BM cells is a dynamic parameter that reflects the ongoing rate of production of hematopoietic cells in MDS. It is directly related to the maturation-associated alteration of distinct subgroups of hematopoietic cells in individual patients [4]. Assessment of the PI of nucleated RBCS and other components of BM precursors, such as myeloid CD34+ hematopoietic progenitor cells, could significantly contribute to a better management of MDS. The PI of nucleated RBCS is emerging as an independent prognostic factor for both OS and progression-free survival (PFS) in MDS [4].

7. Anemia and iron overload in MDSs and 5q-syndrome

Anemia is a very common finding in MDS patients [51, 52]. Packed RBC transfusions are the only therapeutic option in 40% of MDS patients [51, 52]. RBC transfusions are considered in MDS patients when Hb level falls below 8 g/dL and may provide temporary relief of anemic symptoms [51, 52]. Anemia contributes to cardiac dysfunction predominantly in elderly individuals [51]. In MDS patients, anemia can be corrected by the following: (1) RBC transfusions, (2) administration of hematopoietic growth factors such as erythropoietin, (3) administration of certain drugs such as lenalidomide, cyclosporine-A, and antithymocyte globulin (ATG), and (4) allogeneic HSCT that is the only curative therapeutic approach [51, 52].

Anemia and blood transfusions have significant impact on the quality of life (QOL) of MDS patients [51]. Transfusion dependency is associated with shortened overall and leukemia-free survival in MDS patients [51]. In these patients, transfusion dependency and iron overload have been retrospectively associated with: (1) inferior survival, (2) worse clinical outcome including cardiac, hepatic, and endocrine dysfunction and in some studies, (3) leukemic transformation, and infectious complications [52].

The most serious side effects of regular blood transfusion are elevation of iron blood levels and iron overload, that is, deposition of iron in body tissues [51–54]. Magnetic resonance imaging (MRI) of the heart and liver is an excellent noninvasive diagnostic tool for (1) the assessment of iron overload and (2) monitoring the response to iron chelation therapy [51, 55, 56]. MRI of the heart and liver is superior to the surrogate markers of iron overload such as serum ferritin, liver iron, ventricular ejection fraction, and tissue-related parameter [51]. The diagnostic parameters used for the evaluation of iron overload in MDS are shown in **Table 8**

[55]. Serum erythropoietin is a predictive factor for response to therapy with subcutaneous erythropoietin [57]. MDS patients with higher values of erythropoietin have poorer response to the administration of erythropoietin therapy even at higher doses [57].

Method	Normal level	Mild to moderate iron overload	Severe iron overload
Serum ferritin (ng/mL)	<400	1000–2500	>2500
Transferrin saturation (%)	20–40	50–70	>70
Labile plasma iron (MM)	<0.4	>0.4	>0.4
Liver T2-MRI (ms)	<6.3	<6.3	<1.4
Cardiac T2-MRI (ms)	>20	8–20	<8

* MDS: myelodysplastic syndrome. * MRI: magnetic resonance imaging.

Table 8. Diagnostic parameters used for evaluation of iron overload in MDS.

7.1. Iron overload in low-risk MDS

In patients with low-risk MDS, packed RBC transfusion are required to correct anemia. Ultimately, these patients become transfusion dependent [55, 58, 59]. Also, more aggressive disease is usually associated with a high transfusion rate and thus significant transfusion dependency becomes a surrogate marker of aggressive disease [59]. On the long-term, transfusion dependence leads to the development of iron overload, which becomes an important clinical problem, that is associated with an increase in morbidity and mortality [59]. However, in some transfusion-independent low-risk MDS patients, an increased erythropoietic activity results in the suppression of hepcidin and contributes to iron loading [55].

In patients with low-risk MDS who are chronically transfused, transfusion-related morbidity is an emerging challenge [58]. Blood transfusion therapy may lead to organ toxicity due to the formation of nontransferrin bound iron and resulting in oxidative stress. Therefore, in low-risk MDS patients with longer life expectancy, preventing organ damage due to iron overload is an important concern [59].

Recently, high serum ferritin level has been identified as a prognostic factor for short time to progression to acute leukemia [59]. Transfusion-dependent patients with an isolated erythroid dysplasia and a low risk of leukemic transformation are more likely to develop parenchymal iron overload and its toxicity and hence benefit from iron chelation therapy [56]. In low-risk MDS patients with relatively lower RBC transfusion requirements, T2-MRI is indicated every 10–20 units of packed RBCS in order to evaluate the need to: (1) initiate iron chelation therapy, (2) assess the effectiveness of treatment, and (3) determine the need for dose adjustment [55].

Currently, the initiation of iron chelation therapy is based on: (1) the total number of RBC transfusions and (2) increased serum ferritin in transfusion-dependent patients [55]. Iron chelation therapy is generally recommended for selected patients with low-risk MDS [52–54]. It is reasonable to offer iron chelation therapy to low-risk MDS patients who are at high risk of developing iron overload [55, 59]. Data from multiple retrospective studies have demonstrated that iron chelation therapy results in marked survival benefit in patients with low-risk MDS [52, 55].

8. Management of MDSs and 5q-syndrome

Most patients with MDS are treated with supportive measures due to their old age and comorbid medical conditions [3]. However, there are various therapeutic options for patients with low or intermediate-1 risk MDS and these include the following: (1) blood product transfusions: packed RBCS and PLTs, (2) iron chelation therapy with: deferasirox, deferoxamine, and deferiprone, (3) erythropoietin with or without granulocyte-CSF, (4) ATG and cyclosporine-A, (5) danazol, (6) pyridoxine, (7) valproic acid, (8) lenalidomide, (9) 5-azacitidine, (10) decitabine, and (11) low-dose cytarabine [60].

8.1. Iron chelation therapy

The role of iron chelation therapy in MDS patients with transfusion dependency and iron overload remains a very controversial issue in the management of MDS, mainly due to lack of solid prospective clinical trials [52, 59, 61]. However, case–control studies, retrospective analyses, and phase-II clinical trials have indicated that iron chelation therapy reduces iron overload as measured by serum ferritin and may even prolong overall survival [54].

Iron chelation therapy is indicated in the following categories of patients: (1) patients with frank iron overload; stable or increasing serum ferritin > 1000 ng/mL without signs of active inflammation or liver disease; who are transfusion-dependent at any frequency and have a life expectancy of >1 year, (2) transfusion-dependent patient who receive > 2 units of packed RBCs per month, at any serum ferritin level, and have a life expectancy of > 2 years, except for patients with frank iron deficiency such as chronic gastrointestinal (GIT) bleeding, and (3) in selected patients, iron chelation therapy is considered when life expectancy < 2 years. Examples include: planned curative treatment such as HSCT, massive iron overload with consecutive organ dysfunction or massive iron overload that is judged to significantly reduce QOL [51, 58]. Additional parameters that may influence decision to treat with iron-chelating agents in selected MDS patients include the following: (1) old age, (2) social and mental circumstances, (3) comorbidity and organ dysfunction, and (4) genetic status such as HFE gene mutations [51, 58]. The guidelines of the National Comprehensive Cancer Network **(**NCCN**)** and those of the MDS Foundation for the treatment of iron overload in MDS are illustrated in **Table 9** [52, 55]. The proposed response criteria for iron chelation therapy in MDS are shown in **Table 10** [58].

Source	Transfusion status	Serum ferritin level ng/mL or mg/L	MDS risk category	Patient profile
NCCN	– Received >20 RBC units	>2500 Mg/L	IPSS: low or intermediate	Candidate for allogeneic HSCT
MDS foundation	– Continuing transfusion	>1000 mg/L	– IPSS: low or intermediate – WHO: RA/RARS/5q-	– Candidate for allogeneic HSCT – No erythroid response to primary therapy

MDS: myelodysplastic syndrome; HSCT: hematopoietic stem cell transplantation; IPSS: international prognostic scoring index; WHO: world health organization; RA: refractory anemia; RARS: refractory anemia with ring sideroblasts.

Table 9. Guidelines for the treatment of iron overload in MDS.

Complete response (CR)	Minor response (MR)	Stable iron load	No response
Decrease in serum ferritin to <200 ng/mL or Decrease in serum ferritin by 500 ng/mL	Decrease in serum ferritin to < 200 ng/mL or Decrease in serum ferritin by less than 500 ng/mL	Constantly elevated serum ferritin but <4000 ng/mL	Further increase in serum ferritin by at least 500 ng/mL or serum ferritin level constantly above 400 ng/mL

MDS: myelodysplastic syndrome.

Table 10. Proposed response criteria for iron chelation therapy in MDS.

There are three forms of iron-chelating agents, namely (1) oral deferasirox (exjade), (2) oral deferiprone (feriprox), and (3) parenteral deferoxamine (desferal) [54, 58]. The availability of two effective oral chelating agents, deferasirox and deferiprone, has renewed interest in the evaluation of iron chelation therapy in MDS [52].

The beneficial effects of iron chelation therapy in MDS patients having iron overload include significant reduction of: labile plasma iron, nontransferrin-bound iron and reactive oxygen species (ROS) that mediate tissue damage observed in iron overload [52]. Adverse effects of iron chelation therapy include cost and toxicity. Therefore, MDS patients should be initiated on iron chelation therapy after weighing potential risks and benefits for each patient until more definitive data are available [53]. Application of recent advances in the treatment of MDS can reduce or eliminate the need for blood product transfusions thus minimizing the risk of iron overload [54]. Careful attention to iron parameters with early initiation of iron chelation therapy in patients with evidence of transfusion-related iron overload is an important component of high-quality MDS care [61].

8.2. Lenalidomide

There are 40 genes in the CDR on the long arm of chromosome 5 in MDS with del (5q). Examples of the CDR genes and the effects of lenalidomide on the haplodeficient genes are shown in **Table 11** [13, 62, 63].

Gene	Effect of deletion	phenotype	Effect of lenalidomide	Functional effect of lenalidomide
SPARC	Increased cell adhesion	– Anemia – Thrombocytopenia	Increased expression in MDS CD34+ cells ex vivo	– Inhibition of proliferation and adhesion
RPS 14	Defective ribosomal processing	– Macrocytic anemia	Increased expression in patients with del (5q)	Erythroid response
EGR1	Decrease in tumor suppressors	– Leukocytosis – Anemia – Thrombocytopenia	Increased expression in an MDS-related del (5q) cell line	Reduced proliferation
miR145 miR-146a	Elevated innate immune signaling	– Thrombocytosis – Neutropenia – Megakaryocytic dysplasia	Increased expression in patients with del (5q)	Possible anti-inflammatory
CDC 25C1 PP2A	Defective G2 – M phase regulation	G1 and G2 M arrest and apoptosis	– Direct inhibition of: CDC 25 C – Indirect inhibition of: PP_2 A	G1 and G2 M arrest and apoptosis Restoration of erythropoiesis
DIAPH	Defective cytoskeleton tumor suppression	Clonal dominance	Unknown; to be determined	Unknown Immunomodulatory Antiproliferative

MDS: myelodysplastic syndrome.

Table 11. Genes in the commonly deleted region and effects of lenalidomide on the haplodeficient genes.

Lenalidomide is a novel thalidomide analog that has enhanced immunomodulatory and antiangiogenic effects and diminished thalidomide-related adverse events [60]. The approved indications of lenalidomide treatment in MDS include the following: (1) patients with del (5q) who have symptomatic transfusion-dependent anemia, (2) lower risk, according to IPSS, MDS patients having 5q- syndrome, and (3) other low-risk and intermediate 1 risk types of MDSs [60, 62].

The important clinical trials of lenalidomide in patients with MDS are shown in **Table 12** [60, 62–66]. Lenalidomide has several mechanisms of action that include the following: (1) promotion of erythropoiesis by inhibition of CD45 protein tyrosine phosphatase and activation of EPO-R/STAT5-signaling pathway, (2) the stimulation of production of certain ILs such as

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IL-2, IL-10, and interferon (IFN) -δ, (3) inhibition of pro-inflammatory cytokines and chemokines such as tumor necrosis factor (TNF)-α, IL-12, IL-1*B*, IL-6, monocyte chemotactic protein-1, and macrophage anti-inflammatory protein-1α, (4) anti-angiogenic effects of lenalidomide-mediated through endothelial cell migration inhibition, that is, inhibition of bFGF-, VEGF-, and TNF-α-induced endothelial cell migration, (5) immunomodulatory effects, (6) anti-inflammatory properties, (7) direct antineoplastic activity by the inhibition of malignant clone and upregulation of SPARC gene, (8) direct cytotoxic effect on abnormal del (5q) clones by targeting haploinsufficient genes and their pathways, (9) T-cell activation or stimulation of T-cell proliferation including natural killer (NK) cells number and function and production of multiple cytokines, and (10) inhibition of haplodeficient phosphatases and release of progenitors from p53 arrest [14, 21, 60, 62, 63, 67]. The adverse effects of lenalidomide include the following: (1) myelosuppression: neutropenia, anemia and thrombocytopenia, (2) venous thromboembolism such as deep venous thrombosis in 3.4% of treated patients, (3) infectious complications such as pneumonia, fever and febrile neutropenia, (4) skin rashes, pruritis, and urticaria, (5) GIT upset including nausea and diarrhea, (6) fatigue, muscle cramps, and bone pains, (7) bleeding diathesis, (8) hypokalemia, (9) autoimmune hemolytic anemia, (10) edema formation, and (11) rarely, hypothyroidism and hypogonadism [15, 17, 60, 62, 64, 68]. The mechanisms of resistance to lenalidomide include the following: (1) over expression of PP2A and (2) restoration of p53 expression leading to accumulation of p53 [62].

Cereblon, an E3 ligase protein, was first described to be the molecular target of lenalidomide in a seminal paper, published in the year 2010, that linked its role to the teratogenic effects of thalidomide in zebrafish and chicks [69, 70]. In 2011, cereblon was found to play a key role in mediating the antiproliferative and immunomodulatory activities of lenalidomide and pomalidomide in multiple myeloma (MM) and T cells, respectively [69, 70]. Thalidomide has been shown to bind and inhibit cereblon and cereblon loss had been found to cause birth defects [71]. Studies on MM cell lines have shown lack of correlation between cereblon expression and sensitivity to lenalidomide. However, in MM cell lines, made resistant to lenalidomide and pomalidomide, cereblon protein was greatly reduced [69–71].

The central role of cereblon as a target of lenalidomide and pomalidomide suggests its potential utility as a predictive biomarker of response or resistance to immunomodulatory drug therapy [69]. The currently available commercial assays that are used in measuring cereblon levels have their own limitations. Therefore, standardization and validation of the techniques used are needed to accurately assess the role of cerebron as a predictive biomarker of the response to immunomodulatory drugs [69].

The serine-thionine kinase, casein kinase 1α (CK1α), is encoded by casein kinase 1 A1 (CSNK1A1) gene [72, 73]. CK1α has been implicated in the biology of del (5q) MDS and has been shown to be a therapeutic target in myeloid malignancies and is therefore an attractive candidate for mediating the effects of lenalidomide in del (5q) MDS [73]. CSNK1A1 gene is a putative tumor suppressor gene located in the CDR at 5q 32 for del (5q) MDS and is expressed at haploinsufficiency levels in MDS with del(5q) [72–74]. Haploinsufficiency of CSNK1A1 leads to hematopoietic stem-cell expansion in mice and may play a role in the initial clonal expansion in patients with 5q-syndrome [43]. CSNK1A1 gene plays a central role in the biology

or pathogenesis of del (5q) MDS and is a promising therapeutic target [74]. Lenalidomide induces the ubiquitination of CSNK1A1 by the E_3 ubiquitin ligase [CRL4 ^{CRBN}] resulting in CSNK1A1 degradation. Lenalidomide significantly alters the protein abundance of three out of five differentiated ubiquitinated proteins [73].

The development of CK1α inhibitors may provide a new therapeutic opportunity in MDS patients with del (5q) and CSNK1A1 mutations [72]. In MDS patients with del (5q), CSNK1A1 mutations have been found in 7.2% of patients and are associated with older age [72]. CSNK1A1 mutations may coexist with ASKL1 but not with p53 mutations. They are usually responsive to lenalidomide and have no independent prognostic impact on overall survival [72].

In del (5q) MDS, lenalidomide-induced degradation of CSNK1A1 below the haploinsufficiency levels induces p53 activity, that is, CSNK1A1 is a negative regulator of p53 [73]. The deletion of genes on chromosome 5q, such as RPS-14, may further sensitize del (5q) cells to p53 activation. This mechanism of activity is consistent with the acquisition of TP53 mutations in del (5q) MDS patients who develop resistance to lenalidomide [73].

Lenalidomide is a potent therapy for low-risk MDS with del (5q) that causes transfusion independency in 67% of patients and complete cytogenetic remission in 45% of patients [44]. However, 50% of patients responding to lenalidomide relapse within 2 years, and 15% of patients achieving cytogenetic response, and 67% of patients not achieving cytogenetic response are at risk of leukemic transformation within 10 years [44].

8.3. The role of HSCT in MDSs

Allogeneic HSCT is the only known curative therapeutic option for MDS [2, 3, 75–84]. Not only the rates of allogeneic HSCT to treat MDS are continuously increasing, but also survival rates are steadily improving [76, 85]. In patients with MDS, the indications of HSCT are as follows: (1) higher-risk MDS, (2) intermediate-2 MDS, (3) MDS in blast cell crisis, (4) younger patients with MDS having good performance status, and (5) patients with low-risk MDS with poor prognostic features such as: old age, refractory cytopenias and transfusion-dependence [3, 75, 76, 81, 82]. Both blast percentage and percentage of cytogenetically abnormal cells reflect MDS disease burden and predict the outcome of HSCT [86]. Therefore, accurate assessment of MDS disease burden and MDS disease biology based on cytogenetic and molecular profiles is critical to determine the optimal HSCT timing and improve the outcome of HSCT [86]. Incorporation of novel diagnostic techniques such as flow cytometry, molecular cytogenetics and microarray gene expression profiling in the diagnostic algorithms and risk stratification may further optimize therapeutic decisions including the timing of allogeneic HSCT [85].

In patients with MDS undergoing HSCT, predictors of the outcome of HSCT include the following: (1) age, (2) performance status, (3) transfusion dependence, (4) serum erythropoietin level, (5) HSCT-comorbidity index, (6) MK, (7) MDS risk score such as R-IPSS category, and (8) severity of cytopenias [75, 76, 79, 82]. Novel classification schemes for MDS allow for more accurate prognostication and consequently recommendations for HSCT or non-HSCT

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therapies [78]. MDS disease classification by IPSS, R-IPSS, and WPSS as well as patient characteristics as assessed by HSCT-comorbidity index provide guidance for optimal patient management [81].

Trial	MDS-001 Open label-single center-phase II	MDS - 003 Single arm-multi center-phase II	MDS - 004 Phase III - randomized - double blind - placebo controlled study
Number of patients	43	148	139
Median Age (years)	72	71	69
IPSS risk category	- Low: 51% - Intermediate I : 27% - Intermediate II : 9% - High : 2%	- Low: 37% - Intermediate I: 44% - Intermediate II: 2-5% - Unclassified: 14%	- Low: 49% - Intermediate I : 51%
FAB subtype	- RA : 47% - RAEB-T 2% - RARS : 30% - CMML : 2% - RAEB : 19%	- RA: 52% - RARS: 12% - RAEB: 20% - CMML: 2%	- RA : 68% - RARS : 15% - RAEB : 10.8% - CMML : 2%
Karyotype	- Del (5q) : 28% - Normal : 53% - Other : 9%	- Isolated del (5q): 74% - Del (5q) + others: 25%	- Isolated Del (5q) : 76% - Del (5q) + others : 24%
Response	**Hematological** **Cytogenetic** - Del(5q): 83% - Del(5q): 75% - Normal cytogenetics 57% - others: 3% - Others: 9%	- Erythroid response: 76% - Transfusion independence: 67% - Cytogenetic response: 73% - Complete response: 45%	- Packed RBC transfusion independence: 49% after 4 cycles (4 weeks)
Time to response	- Median time to response: 9-11.5 weeks - Median duration of response: not reached	- Median time to response: 4.6 weeks - Median duration of response: 115 weeks	- Median duration of response: not reached with either 5mg or 10mg / day of lenalidomide
Adverse effects of lenalidomide encountered	- Neutropenia : 65% - Thrombocytopenia: 53% - Pneumonia: 7% - Fatigue: 5% - Diarrhea: 2%	- Neutropenia: 55% - Thrombocytopenia: 44% - Rash: 6% - Pruritis: 3% - Fatigue: 3% - Nausea: 3% - DVT: 3% - Pneumonia: 3% - Hemorrhage: - Diarrhea: 3%	**5 mg dose** **10 mg dose** - ↓ N1: 74% - ↓ N1: 75% - ↓ PLTS: 33% - ↓ PLT: 41% - ↓ Hb: 5.8% - ↓ Hb: 2.9% - ↓ WBC: 13% - ↓ WBC: 8.7% - DVT: 1.4% - DVT: 5.8%

Trial	Ades et al Phase II trial	Reza et al Phase II trial
Number of patients	47	214
Median age (in years)	69	72
IPSS-risk category	- Intermediate 2 : 60% - High risk : 40%	- Low risk: 43% - Intermediate 1: 36% - Intermediate 2: 4% - Unclassified: 18%
FAB subtype	-	- Normal karyotype: 75% - Clonal (non-5q) cytogenetic abnormalities: 22%
Karyotype	- Isolated del (5q): 9% - Del (5q) + additional abnormalities: 23% - Del (5q) + ≥ 2 additional abnormalities: 58%	- Hematological overall response: 43% - Transfusion independence: 26%
Response	- Over all response: 27% - Complete hematological response: 15% - Transfusion independence: 25%	- Median time to transfusion independence: 4.8 weeks - Median duration of transfusion independence: 41 weeks - Cytogenetic overall response: 19%
Time to response	- Median duration of complete hematological response: 11 months - Median overall response: 9 months	-
Adverse effects encountered	Grade 3/4 cytopenias: 76%	- Neutropenia: 28% - Thrombocytopenia: 26%

- MDS: myelodysplastic syndrome
- CMML: chronic myelomonocytic leukemia
- IPSS: international prognostic scoring index
- FAB: French-American-British
- RBC: red blood cell
- PLT: platelet
- RAEB: refractory anemia with excess of blasts
- RARS: refractory anemia with ring sideroblasts
- RARS-T: refractory anemia with ring sideroblasts thrombocytosis
- RA: refractory anemia
- WBC: white blood cell
- DVT: deep venous thrombosis

Table 12. Clinical trials on lenalidomide in MDS.

The age of MDS patients undergoing HSCT has increased significantly over the last 30 years. While HSCT is being carried out in older patients with MDS, this enthusiasm has been over shadowed by the impact of the procedure and its complications, namely graft versus host disease (GVHD) on the QOL and socioeconomic status [78]. Comorbid medical conditions are the major patient characteristics impacting transplantation success. Validation of comorbidity scoring systems has provided the basis for risk assignment to a given patient [78]. HSCT comorbidity index allows estimation of the probability of non-relapse mortality after HSCT [81].

Pre-HSCT serum ferritin > 100 mg/L has been shown to have an adverse impact on OS following HSCT [75]. Adverse consequences of iron overload on the outcome of HSCT include increased risk of septicemia, invasive fungal infections, and sinusoidal obstruction syndrome [75]. BM blast percentage < 5% at the time of HSCT is the major predictor of improved disease-free survival (DFS) and disease relapse [80]. Prior treatment to decrease blast percentage < 5% prior to allogeneic HSCT is recommended as it has been shown to improve DFS particularly in patients undergoing nonmyeloablative (NMA)-conditioning therapy [80].

The major factors that have a negative effect on relapse-free survival in MDS patients subjected to HSCT are pretransplant karyotype and pre-HSCT BM blast count [76, 81]. Patients with very poor cytogenetics, including MK, have a 10% or less probability of long-term survival [81]. Studies have also shown that a patient with MDS having MK has lower survival rates, higher relapse rates, and higher overall mortality following allogeneic HSCT [76]. The presence of p53, DNMT3A, and TET_2 genetic mutations in the pre-HSCT period decreases the probability of post-transplant survival by a factor of 3–4 [76, 81]. On the other hand, $SF3B_1$ mutations are associated with superior leukemia-free survival and OS in MDS patients subjected to allogeneic HSCT [81].

In MDS patients receiving allogeneic HSCT, the stem cell sources are the following: peripheral blood, BM, and umbilical cord blood (UCB) have yielded similar outcomes [80, 83]. Peripheral blood progenitor cells are currently the preferred source of stem cells due to faster engraftment and higher risk of GVHD giving rise to more potent graft versus tumor (GVT) effect [81, 83]. Cord blood cells are typically associated with slow engraftment and hence higher risk of infections and bleeding complications [81]. UCB-derived hematopoietic grafts provide the advantage of transplanting rather immature cells that allows successful HSCT in some patients even in the presence of HLA mismatches [87]. The following forms of allografts are available for MDS patients who are eligible for transplantation: HLA-matched sibling grafts, matched unrelated donor (MUD) allografts, UCB grafts, and HLA-haploidentical donor allografts [78, 83]. The availability of: HLA matched related and unrelated donors, HLA-haploidentical relatives and UCB helps to identify donors for the vast majority of MDS patients [81]. Traditionally, transplantation of HLA-haploidentical cells carries an increased risk of graft rejection and an increased risk of GVHD. However, the recently introduced conditioning regimens have reduced the risk of graft rejection and the administration of cyclophosphamide in the early post-transplant period has minimized the risk of GVHD to similar or even lower rates than observed following HLA-matched donor cell [81].

An increased use of unrelated donors and the establishment of protocols for cord blood HSCT and HLA-haploidentical HSCT have made HSCT available for a rapidly growing number of patients [78]. Haploidentical HSCT performed using T-cell replete allografts and post-transplant cyclophosphamide can achieve outcomes equivalent to those of conventional HSCT using HLA-matched related or unrelated donors [87]. The preferred donor for MDS patients undergoing allogeneic HSCT is an HLA-matched sibling or alternatively a fully matched unrelated donor as both have comparable survival rates. However, MUD form of HSCT is associated with higher treatment-related mortality (TRM) [82].

Development of a broad range of conditioning regimens has allowed clinicians to offer HSCT taking into consideration: stage of the disease and patient characteristics [78]. Conventional myeloablative conditioning (MAC) protocols include the following: total body irradiation (TBI), cyclophosphamide, busulfan, and fludarabine, while reduced intensity conditioning (RIC) regimens incorporate low-dose TBI, fludarabine, cyclophosphamide, ATG, and alemtuzumab in various doses and schedules [75]. MAC therapy is associated with lower relapse rate particularly in patients in complete remission or with < 5% blasts. MAC therapy is also associated with increased toxicity and nonrelapse mortality [78, 80]. Long-term survival results in remission following allogeneic HSCT from HLA-matched related or unrelated donor and high-intensity conditioning treatment are as follows: lower-risk MDS: 75%, intermediate-1 MDS: 60%, intermediate-2 MDS: 45% and high-risk MDS: 30% [81]. NMA or RIC conditioning regimens may be considered for MDS patients who are not candidates for MAC regimens due to comorbidities or old age, but such regimens should ideally be used within the context of a clinical trial [82]. Since approximately 75% of MDS patients are > 60 years of age at diagnosis, MAC-allogeneic HSCT can only be offered to a subset of individuals [82]. In patients unfit for MAC therapy, NMA conditioning yields equivalent: TRM, DFS, and OS [80]. For patients with *de novo* MDS aged 60–70 years, the favored therapy varies according to the IPSS risk for patients with low risk and intermediate-1 IPSS risk, nontransplantation approaches are preferred and for patients with intermediate-2 and high-IPSS risk, RIC-allogeneic HSCT offers overall and quality-adjusted survival benefit [88]. In patients with MDS, emphasis should be shifted from high-dose chemotherapy aimed at maximum tumor-cell kill to RIC allogeneic HSCT relying on the donor cell-mediated GVT effect that is most prominent in patients having chronic GVHD in particular in order to eradicate the disease [81]. RIC regimens for allogeneic HSCT have the capacity to result in long-term remissions in MDS patients who are ineligible for conventional allogeneic HSCT [89]. The role of RIC-allogeneic HSCT in MDS patients is to induce chronic GVHD which in turn reduces relapse rate and improves DFS and OS [82, 89].

Autologous HSCT is applicable only to a minority of younger patients with MDS because of difficulty in harvesting adequate numbers of CD34+ cells even in low-risk MDS patients and lack of graft versus leukemia or GVT effect thus resulting in high risk of MDS relapse [3].

8.4. HSCT in lower risk MDS patients

In patients with low- or intermediate-1-risk MDS, aged 60–79 years, life expectancy following RIC-allogeneic HSCT is about 38 months compared to 77 months in patients not subjected to HSCT, that is, there is no survival benefit of HSCT in this category of patients [81]. Patients

with low or very low-risk MDS should ideally be treated with supportive measures and low intensity therapies, such as lenalidomide, erythropoiesis stimulating agents, hypomethylating agents or immunosuppressive therapies rather than allogeneic HSCT [81, 84].

8.5. Road blocks and other unresolved issues related to HSCT in MDSs

The major road blocks to a universally successful HSCT are relapse of MDS and NRM, often related to GVHD [75, 78, 83]. Allogeneic HSCT in MDS patients can lead to considerable mortality and morbidity mostly as a consequence of toxicity to organs, infectious complications and GVHD [87]. Acute and chronic GVHD are frequent causes of morbidity after HSCT in MDS patients [78]. Additional research is required to prevent GVHD while maintaining the GVT effect [81]. The graft versus dysplasia resulting from allogeneic HSCT and the infusion of donor leukocytes has led to a great understanding of the immunological mechanisms that govern the outcome of HSCT in MDS patients [3]. Post-transplant relapse is a major hurdle to greater success, particularly in patients with high-risk cytogenetics [78]. Pretransplant cytogenetics and BM blasts are the strongest risk factors for post-HSCT relapse [81]. The time interval from allogeneic HSCT until relapse represents a crucial factor to predict response to salvage therapy and survival in patients with high-risk MDS relapsing after allogeneic HSCT [90]. Strategies to reduce relapse and TRM and improve outcome of HSCT include the following: (1) modification of the intensity of conditioning therapy taking into consideration: age, organ function and comorbid medical conditions, (2) pretransplantation strategies that include (A) improvement of remission: (a) hypomethylating agents and/or histone deacetylase inhibitors (HDACs), (b) induction therapy followed by RIC (FLAMSA), and (c) clofarabine and/or cytosine arabinoside. (B) induction of cytogenetic remission by lenalidomide for 5q-syndrome and hypomethylating agents for monosomy 7, and (3) post-transplantation strategies that include (a) boosting GVL effect by immune enhancers such as lenalidomide, CTLA4 (cytotoxic T-lymphocyte-associated protein 4), anti-PDL1 (programmed death-ligand 1) and adoptive transfer of tumor-reactive T cells and natural killer cells, (b) maintenance with HDACs and/or donor lymphocyte infusion (DLI), and (c) maintenance with lenalidomide and/or DLI [83, 91].

The following represent the unresolved issues related to HSCT in MDS: (1) timing of the transplant; standard conditioning for younger patients and RIC for older patient with comorbidities, (2) disease status at transplant, (3) pre-HSCT therapy or pretransplant tumor debulking with traditional chemotherapeutic agents or the novel DNA hypomethylating drugs, (4) the intensity of the conditioning therapies, (5) stem cell source and alternative donors, (6) optimal therapy for intermediate-risk MDS, and (7) the combination of HSCT with novel therapies such as hypomethylating agents and immunomodulatory drugs [3, 79, 80, 84, 92]. As MDS patients are usually on the old side, QOL is a top priority for most patients, so discussion regarding transplantation in older patients must include not only the acute effects of transplantation but also the delayed effects [81]. Incorporation or integration of novel non-HSCT therapeutic modalities in the overall management of MDS patients undergoing allogeneic HSCT is needed [78].

9. Prognosis in low-risk MDS

There are several poor prognostic factors in patients with MDS. The poor prognostic factors in MDS in general are listed in **Table 13** [47]. However, in low-risk disease, the following factors have been found to correlate with poor prognosis: (1) severe anemia, (2) transfusion dependence, (3) poor performance status, (4) older age, (5) number and severity of medical comorbidities, (6) leukocytosis, and (7) elevated level of serum LDH [4].

1. Old age
2. Poor performance status
3. Presence of comorbid medical conditions
4. WBC count > 20×10^9/L
5. Severe anemia
6. Severe or refractory thrombocytopenia; PLTs <30×10^9/L
7. Eosinophilia: > 350/microliter (μL) and basophilia: > 250/μL
8. Absolute lymphocytic count < 1200/mL
9. Reduced platelet mass
10. Transfusion dependence
11. Presence of bone marrow fibrosis
12. CD34 positivity of nucleated BM cells
13. RBC-MCV (mean corpuscular volume) < 100 FL
14. Increased expression of WT_1 (Wilm's tumor gene)
15. Monsomy 5 or del (5q) associated with other chromosomal abnormalities
16. Specific genetic mutations: TP53/TET2/DNMT3A/FLT3/EZH2/ETV6/BCOR
17. Reduced circulating endothelial cells
18. Increased levels of: TNF-α, single-nucleotide polymorphism in TNF gene
19. Increased serum B2 microglobulin concentration
20. Downregulation of granulopoiesis regulator lymphoid enhancer-binding factor 1 (LEF1)
21. Abnormal localization of immature precursors (ALIP)
22. Increased DNA methylation
23. Failure of decitabine therapy

Table 13. Adverse prognostic factors in MDS.

In patients with del (5q), the following factors have been found to be independent predictors of shortened survival: age, transfusion need at diagnosis and dysgranulopoiesis [18, 19].

10. Conclusions and future perspectives

MDSs including 5q-syndrome are often complicated by BM suppression reflected by cytopenias, infectious complications, iron overload and transformation into AML. Management of these disorders includes the following: (1) supportive care that comprises transfusion of blood products, antimicrobials, growth factors, and iron chelation therapy; (2) targeted therapies, such as lenalidomide, and (3) various forms of HSCT. The role of allogeneic HSCT in MDSs is surging as the recently introduced conditioning therapies have allowed application of this curative therapy to older patients and those with comorbid medical conditions. The recent developments in the science of MDSs will allow more advanced targeted therapies to be integrated into the therapeutic algorithms of these disorders.

The role of cereblon as a molecular target for lenalidomide and pomalidomide and that of CK1α in mediating the effects of lenalidomide will ultimately translate into more refined targeted therapies for patients with del (5q) MDS. Also, early incorporation of more pinpointed targeting of clones harboring TP53 mutations and utilization of the translation enhancer, L-leucine, will further improve not only the management but also the outcome of patients with 5q-syndrome.

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