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Chapter 5

Myelodysplastic Disorders, Monosomy 7

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/64549

Abstract

Myelodysplastic syndromes (MDSs) are heterogeneous hematopoietic disorders associated with various degrees of myelosuppression and transformation into acute leukemia. Chromosome 7 abnormalities occur at any age, have several disease associations, and are generally associated with poor outcome. Treatment of the associated disease conditions may have a positive impact on the outcome of certain types of MDSs. For patients eligible for hematopoietic stem cell transplantation (HSCT), allografts are the standard of care, while supportive measures and the use of hypomethylating agents, such as 5-azacytidine and decitabine, constitute the mainstay of management in individuals who are not fit for allogeneic HSCT. However, the use of hypomethylating agents in conjunction with allogeneic HSCT using nonmyeloablative conditioning therapies may be an appealing therapeutic option for older patients with comorbid medical conditions.

Keywords: myelodysplastic syndrome, monosomy 7, 5-azacytidine, decitabine, hematopoietic stem cell transplantation

1. Introduction

MDSs are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, dysplastic changes in the peripheral blood and bone marrow (BM), and a variable risk of progression into acute myeloid leukemia (AML) [1–4]. Primary MDS has a bimodal age incidence. It is usually a disease of old age as more than 50% of patients are ≥70 years of age [5]. Primary MDS is less common in the pediatric population and it includes specific pediatric syndromes such as juvenile chronic myeloid leukemia (JCML) and infantile monosomy 7 syndrome [5].

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The clinical, pathologic, and cytogenetic features of primary MDS in younger patients appear to be different from those in elderly individuals suggesting that this may represent a biologically different disease [5]. In patients with MDS, with or without abnormal chromosomal karyotype, the type and the quantity of the abnormal karyotype have clinical values in predicting transformation to acute leukemia [6]. The use of granulocyte-monocyte colony stimulating factor (GM-CSF) in congenital BM failure syndromes may induce or accelerate the onset of leukemic transformation [7].

2. Pathogenetic mechanisms in MDSs

Several mechanisms are involved in the pathogenesis of MDSs and these include: (1) enhancement of a self-renewal of a hematopoietic stem cell or acquisition of self-renewal in a progenitor cell, (2) enhancement of proliferative capacity in the disease-sustaining clone and/or in its more differentiated progeny, (3) impairment or blockade of differentiation, (4) genetic or epigenetic instability, (5) antiapoptotic mechanisms in the disease-sustaining cells, (6) evasion of the immune system, and (7) suppression of normal hematopoiesis leading ultimately to BM failure [8].

3. Epigenetics in MDSs

Epigenetics is the heritable alteration in gene expression without DNA sequence change. The primary epigenetic modifiers are DNA methylation and histone modifications, both of which are potentially reversible [9]. DNA methylation plays a major role in tissue- and stage-specific gene regulation and it increases with age. Aberrant methylation of certain promoter regions can occur in diseases particularly cancers and correlates with gene silencing [9]. Epigenetic changes in the form of modification of the transcriptional capacity of the cell via processes such as DNA methylation and histone deacetylation can also alter gene expression impacting disease biology [10].

Advances in the science of epigenetics have led to better understanding of the specific pathogenetic mechanisms underlying MDSs. DNA methylation provides a major epigenetic code of lineage and development-specific genes that control expression of normal cells [8]. The most relevant molecular mediators of the epigenetic state in MDS are gene expression patterns maintained by methylation of cytosine residues in DNA and covalent modification of histones. TET2 status may be a genetic predictor of response to azacytidine, independently of karyotype and holds promise as one of the tools available to help in better selection of patients for treatment [8].

Cancer is characterized by global DNA hypomethylation and regional promoter hypermethylation of genes [9, 10]. Promoter methylation of CDKN2B [encoding $p15^{INK4b}$] has been shown to be restricted to the malignant hematological disorders [9, 10]. Several tumor suppressor genes (TSGs) are inactivated by promoter hypermethylation. Potentially reversible

silencing of genes, such as CDKN2B, by promoter methylation has been shown to occur in MDS and it increases with disease progression [9, 10].

1. Unknown etiology.		
2. Old age; more than 50 years		
3. Obesity		
4. Alcohol intake		
5. Tobacco use		
6. Sweet's syndrome		
7. Vitamin deficiency: B_{12} and folate		
8. Infections:	- Human immunodeficiency virus	- Epstein-barr virus
	- Tuberculosis	- Brucellosis
9. Autoimmune disorders:		
	- Behcet syndrome	
	- Fibrosing alveolitis	
	- Systemic lupus erythromatosis	
10. Exposure to:	- Solvents	- Lead
	- Benzene	- Arsenic
	- Herbicides	- Hair dyes
	- Pesticides	- Agricultural chemicals
11. Cytotoxic chemotherapy:	- Alkylating agents	- Topoisomerase Π inhibitors
12. Radiotherapy		
13. Bone marrow failure syndromes:	- Aplastic anemia	- Fanconi anemia
	- Dyskeratosis congenita	- Diamond Blackfan syndrome
	- Paroxysmal nocturnal hemoglobinuria	
	- Congenital neutropenia (Kostmann's syndrome)	
14. Genetic, familial and hereditary disorders:	- Ataxia telangiectasia	- Trisomy 8 mosaicism
	- Xeroderma pigmentosa	- Down syndrome
	- Bloom's syndrome	- Neurofibromatosis
15. Miscellaneous:		
	- Polycythemia rubra vera	
	- Familial myelodysplastic syndromes; monosomy 7	
	- Germ cell tumors (embryonal dysgenesis)	
	- Mutagen detoxification [$GSTq_1$ - null]	
	- Family history of hematopoietic cancer	

Table 1. .Etiology, risk factors and epidemiological associations of myelodysplastic syndromes.

4. Etiology and associations of MDSs

MDSs have several etiologies, risk factors, and epidemiological associations as shown in **Table 1** [11–43]. Also, several hereditary diseases predispose to familial forms of MDS/AML as shown in **Table 2** [11, 16, 18, 23, 25, 27, 44–48].

4.1. Familial MDSs

Familial MDSs are rare diseases. The most common form of familial MDSs is familial platelet disorder, caused by heterozygous germline RUNX1 mutations, which has the propensity to evolve into myeloid malignancy. Many patients lack history of bleeding or thrombocytopenia [44, 46, 47]. Several cases of T-acute lymphoblastic leukemia (ALL) have been reported in patients with inherited RUNX1 mutations [44]. Novel causative mechanisms such as RUNX1 deficiency result in constitutional microdeletions of 21q22 and myelodysplasia associated with telomerase deficiency [44]. Treatment of familial MDS is allogeneic hematopoietic stem cell transplantation (HSCT) but donors have to be screened for deficiency of RUNX1 and deficiency of telomerase [44].

The following genetic mutations have been described in familial MDS/AML: TERC, TERT, CEBPA, GATA2, and RUNX1 [16, 44, 46–48].

4.2. MonoMac syndrome

MonoMac syndrome is a familial disorder associated with GATA2 deficiency, inherited as autosomal dominant and causes early onset of MDS/AML [47, 48]. Additional acquisitions include: monosomy 7 and ASXL1 mutations. Genetic mutations are detected in dendritic cells, monocytes, natural killer (NK) cells and B-lymphocytes. Many carriers are asymptomatic. The syndrome is associated with severe infectious complications and familial predisposition to cancer. Aggressive therapeutic strategies are needed as the disease has poor outcome [47, 48]. GATA2 mutations have also been described in familial MDS/AML and Emberger syndrome [46–48].

5. Cytogenetic abnormalities in MDSs

Chromosomal abnormalities are detectable in 40–60% of patients with *de novo* MDS and approximately 90% of patients with secondary therapy-related MDSs (t-MDSs) [1]. The most frequent cytogenetic abnormalities are del(5q), monosomy 7, del(7q), trisomy 8, complex karyotype, and -Y [1]. Chromosome 5 and 7 abnormalities are considered to be the most frequent recurrent genetic abnormalities in myeloid malignancies (MDS and AML) as they occur in 10–20% of myeloid neoplasms [49].

http://dx.doi.org/10.5772/64549

Pure familial MDS	Familial MDS/AML
1. Familial monosomy 7	- Bone marrow failure syndromes:
2. Chromosome 21q22 deletions	1. Diamond-Blackfan syndrome
3. Telomere deficiency-associated familial MDS [occult dyskeratosis congenita]	2. Severe congenital neutropenia
	3. Congenital amegakaryocytic thrombocytopenia
4. Familial platelet disorder with propensity to myeloid malignancy	4. Dyskeratosis congenita
	5. Schwachman-Diamond syndrome
	- DNA repair deficiency syndrome:
	1. Fanconi anemia
	2. Bloom syndrome
	3. Li-Fraumeni syndrome
	- Signal transductions:
	1. Noonan syndrome
	2. Neuorofibromatosis-1
	- Numerical chromosomal abnormalities:
	1. Trisomy 21

Abbreviations: MDS, myelodysplastic syndrome; AML, acute myeloid leukemia.

Table 2. Familial MDS/AML.

6. Chromosome 7 abnormalities

Abnormalities involving chromosome 7 occur in approximately 20% of patients with MDS having clonal cytogenetic abnormalities. Abnormalities of chromosome 7 include: (1) total loss of chromosome 7 [monosomy 7], (2) deletion of a segment of the long arm of chromosome 7 [del(7q)], and (3) translocations involving chromosome 7 [2]. However, these cytogenetic anomalies have different prognostic significance [1, 2, 50, 51]. MDS with monosomy 7 has poor prognosis, while isolated del (7q) has a better outcome compared to isolated monosomy 7 [2]. Del(7q) which has distinct clinical and pathological characteristics should no longer be considered in the same prognostic category as monosomy 7 [2]. Also, the prognostic impact of der(7) t(1,7) (q10 or p10) is less adverse once compared to monosomy 7 or del (7q) [1]. In a series of 246 patients with myeloid disorders: monosomy 7 or -7 was the most frequent chromosomal abnormality as it was reported in 51% of patients with secondary myeloid disorders, del(7q) was found in 7% of cases, and partial monosomy was found in 8% of secondary myeloid diseases, while in *de novo* myeloid disorders, monosomy 7 and del(7q) were reported in only 10% of patients [52].

6.1. Disease associations

Chromosome 7 abnormalities are associated with: (1) de novo and t-MDS, (2) de novo and therapy related AML (t-AML), (3) JCML, (4) juvenile myelomonocytic leukemia [JMML], (5) familial monosomy 7, (6) primary myelofibrosis, (7) Down's syndrome, (8) Fanconi anemia,

and (9) lymphoma [50, 51, 53]. Monosomy 7 is the commonest chromosomal abnormality in all of the above conditions except in primary myelofibrosis, where del(7q) is the commonest chromosome 7 anomaly [53]. In adults, chromosome 7 abnormalities are associated with: (1) advanced age, (2) antecedent MDS, and (3) resistance to current therapies [54]. In patients with MDS and AML, chromosome 7 abnormalities usually carry poor prognosis [54].

6.2. Genes on chromosome 7 and their detection

Genes that have been reported to have microdeletions involving chromosome 7q21.2-q21.3 include: SAMD9, SAMD9L, and HEPACAM2 [55]. The following acquired somatic deletions have also been reported at chromosome 7q36.1: EZH2, CUL1, and TET2 [56, 57]. Examples of additional genetic mutations that have been reported in monosomy 7 and del(7q) include: ASXL1, RUNX1, CBL, ETV6, FAM40B, FAM115A, SEMA3A, LUC7L2, SSPO, NRCAM, GRM8, HYAL4, RABL5, TRIM24, FISI, and CUX1 [51, 57, 58]. Chromosome 7 abnormalities can be detected by conventional cytogenetics or interphase fluorescence *in situ* hybridization (FISH) [59]. Interphase FISH is a very useful method in detecting -7/7q- in patients with MDS. Also, it is more sensitive in detecting chromosome 7 abnormalities than conventional cytogenetics [59]. Refined chromosomal analysis has emerged as a tool that has considerable impact on decision making and development of treatment protocols in patients with MDS and AML [60].

6.3. The commonly deleted segments (CDSs)

Several studies on MDS and AML specimens with interstitial deletions on chromosome 7 have implicated three putative CDSs at the following chromosome bands: 7q22, 7q34, and 7q35-36. However, 7q22 is the most frequently deleted band in patients with MDS/AML having del(7q) [3]. The following genes in monosomy 7/del(7q) MDS/AML have been reported to be inactivated or to harbor recurrent genetic mutations such as EZH2, LUC7L2, and CUX1 [3].

The CDS on the long arm of chromosome 7 between 7q22 and 7q36 has been identified to harbor a number of haploinsufficient myeloid TSGs [49, 50, 54]. Loss of function of at least one TSG contributes to disease progression and leukemogenesis or leukemic transformation [50, 54]. It is feasible to somatically delete a large chromosomal segment that is implicated in tumor suppression in hematopoietic cell population *in vitro* [54]. The CDSs that occur at chromosomal bands7q22, 7q34, and 7q35-q36 contain the following genes: TRIM24, SVOPL, ATP6V0A4, TMEM213, KIAA1549, LUC7L2, KLRG2, CLEK2L, HIPK2, TBXAS1, ZC34AV1L, ZC3HAV1, TTC26, UBN2, C7orf55, TPK1, CNTNAP2, MIR548F3, C7orf33, CUL1, and EZH2 [49].

Loss of TP53 is more frequently associated with del5q rather than del7q, while loss of ETV6 is particularly associated with concurrent del(5q) and del(7q) [49]. CUX1, a gene encoding a homeodomain-containing transcription factor, has been identified within the CDS on chromosome 7 (7q22.1) [61]. CUX1 is expressed at haploinsufficient levels in leukemias with chromosome 7 abnormalities. Haploinsufficiency of CUX1 gave human hematopoietic cells a significant engraftment advantage on transplantation in immunodeficient mice [61].

Monosomy 7 and del(7q) are highly recurrent chromosomal abnormalities in myeloid malignancies including: AML, *de novo* MDS, and t-MDS/AML [51, 54, 61]. Also, monosomy 7 and

http://dx.doi.org/10.5772/64549

del(7q) are common findings in children and adults who develop MDS as a second malignant neoplasm [27]. In t-MDS/AML with chromosome 7 abnormalities, the peak incidence is between 3 and 7 years after cessation of cytotoxic chemotherapy such as alkylating agents [27]. Under such circumstances, monosomy 7 and del(7q) are not equivalent in prognosis and spectrum of disease phenotype [51].

Monosomy 7 and del(7q) are highly prevalent in acquired cytogenetic abnormalities in *de novo* MDS/AML and t-MDS/AML [3]. The proportion of -7/del (7q) cells is markedly increased in hematopoietic stem cell (HSC) and progenitor cell compartments of MDS patients relative to T and B lymphocytes [3]. Recent studies demonstrating quantitative changes in the frequencies of phenotypic primitive long-term HSCs, common myeloid progenitors, and granulocyte-monocyte progenitors in MDS patients with -7/del(7q) further support the diverse effects on hematopoiesis [3].

After many attempts, mice with 5A3 deletions in the CDS of chromosome band 7q22 have been successfully generated [54]. The 5A3 deleted mice have shown normal hematologic parameters but have not developed myeloid malignancies spontaneously [54]. Animal studies have also shown that heterozygous 5A3 deletion does not accelerate the evolution of leukemia or modulate the responsiveness to antileukemic drugs, while homozygous 5A3 deletions are embryonically lethal [54].

The following 7q genes have been implicated in contributing to leukemogenesis by haploinsufficiency or epigenetic transcriptional repression: SAMD9L, RASA4, dedicator of cytokinesis 4 (DOCK4), and MLL3 [3]. Animal studies have shown that the long-term HSC compartment is expanded in $5A3^{+/del}$ mice and that the 5A3 deletion partially rescues defective repopulation in GATA2 mutant mice [3]. Studies have also shown that 7q22 deletions are implicated in playing a strong haploinsufficiency role in leukemogenesis [3]. Mutations in DOCK4 gene which is a putative 7q gene have been identified in prostate and ovarian cancers and studies have demonstrated that DOCK4 gene acts as a tumor suppressor [62]. Depletion of DOCK4 levels in MDS stem and progenitor cells leads to erythroid dysplasia by disrupting the action of cytoskeleton in developing red blood cells (RBCs) ultimately leading to dysplastic morphology of erythroid cells both *in vivo* and *in vitro* [62].

7. Monosomy 7 MDS

Monosomy 7 is characterized by (1) lower median age of affected patients than that of 5q-syndrome, (2) severe refractory cytopenias, (3) rapid disease progression, (4) resistance to therapy, and (5) increased susceptibility to infectious complications [52, 63]. Infections encountered in monosomy 7 may be life-threatening and they include (1) bacterial infections: these are the most common types of infections and may be complicated by sepsis, and (2) invasive aspergillosis [63, 64]. Infectious complications in monosomy 7 are caused by neutropenia, dysfunctional neutrophils, and chemotherapy or targeted therapy given to control the disease [64].

In patients having monosomy 7, isolated monosomy 7 occurs in 36% of the cases, monosomy 7 and one additional chromosomal abnormality are encountered in 14% of patients, and monosomy 7 associated with complex cytogenetics in seen in approximately 50% of the cases [63]. Monosomy 7 can be associated with the following chromosomal abnormalities: trisomy 8, chromosome 5 abnormalities, and t(1,7) [63]. Chromosomal microarray analysis is a clinically useful tool in the diagnosis and follow-up of MDS patients with monosomy 7 [65]. In monosomy 7, there is an association between DNA loss and functional impairment or defect of granulocytes [66]. Monosomy 7 is not rare in acute lymphoblastic leukemia as it has been reported in 3–6% of the cases of ALL and in 16% of Philadelphia chromosome positive ALL as it occurs as a secondary anomaly to t(9,22) [52]. Monosomy 7 carries poor prognosis as studies have shown that (1) relapse rate of monosomy 7 at 1 year to be 81%, and (2) event-free survival at 7 years to be 6% [52]. Monosomy 7 does not usually affect lymphoid subpopulations but it is restricted to committed progenitor cells with the capacity to differentiate into mature myeloid cells [67].

Analysis of expression profiles in CD34+ cells from MDS patients with monosomy 7 has shown a malignant phenotype with highly proliferative potential expressing HOX9A, PRAME, BMI-1, PLAB, and BRCA2 (DNA repair gene) [63]. Gene therapy for chronic granulomatous disease has been reported to cause activation of ectopic viral integration site 1 (EVI1) which in turn induces development of genomic instability that ultimately results in clonal progression toward myelodysplasia and monosomy 7 [68].

Conventional chemotherapy in monosomy 7 carries a high risk of early death and poor response. Even if complete remissions are obtained, they are usually short-lived [63]. Targeted therapies such as 5-azacytidine and lenalidomide are more effective than cytotoxic chemotherapy in patients with monosomy 7 MDS. However, lenalidomide is more effective in patients having monosomy 7 and 5q- syndrome. Complete hematological and even cytogenetic responses have been documented in patients with monosomy 7 MDS treated with lenalidomide [63].

In transplant-eligible patients, allogeneic HSCT is the treatment of choice in patients with monosomy 7 [25, 63, 69]. Following allogeneic HSCT, presence of monosomy 7 is a predictor of unfavorable outcome [52].

Masked monosomy 7 refers to monosomy 7 that is detected by FISH but not by conventional cytogenetics. It has been reported in varying frequencies in patients with MDS [70]. Masked monosomy 7 is less common than has been thought and does not seem to carry the same prognostic weight as monosomy 7 diagnosed by metaphase cytogenetics [70].

7.1. Monosomy 7 in children

MDS is uncommon in children as it accounts for less than 5% of all hematopoietic neoplasms [33, 71]. Viral infections including Epstein-Barr virus (EBV) may contribute to the pathogenesis of MDS by stimulating a preexisting clone and may induce certain genetic mutations [33]. Chromosome 7 abnormalities, monosomy 7 and del (7q), are common cytogenetic abnormalities in MDS and they are found in 31% of children with myeloid neoplasms [22, 71]. They are

http://dx.doi.org/10.5772/64549

characterized by ineffective erythropoiesis, BM dysplasia, and increased risk of leukemic transformation [22]. Monosomy 7 is the most common chromosomal abnormality in children with MDS [33, 71]. In children, monosomy 7 implies poor prognosis because it is associated with high risk of transformation into acute leukemia including ALL [33, 71].

Treatment of children with MDS/AML associated with monosomy 7 with allogeneic HSCT, using a variety of donor types such as sibling donor, unrelated donor, and umbilical cord blood, as well as different sources such as BM and peripheral blood, is an effective therapeutic modality [69]. In patients with more advanced disease, optimization of conditioning therapies may further improve disease-free survival [69]. Graft versus leukemia effect appears to play a major role in leukemia control for some patients and quality of life (QOL) in patients surviving allogeneic HSCT is usually very good [69].

7.2. Familial monosomy 7 syndrome

Familial monosomy 7 syndrome is a rare familial disorder [44, 45]. It is inherited as autosomal dominant with incomplete penetrance [45]. Familial monosomy 7 can be partial or complete monosomy and it is associated with the following chromosomal abnormalities: trisomy 8, 5q-, and t(1;7) [45]. It has even sex distribution and often presents before the age of 18 years and the median age at diagnosis in 8 years [45]. Allogeneic HSCT in this category of MDS is problematic due to familial predisposition to cancer, hence the prognosis is usually poor [44, 45]. Familial monosomy 7 has several associations including: (1) inherited BM failure syndromes, (2) secondary MDS/AML, (3) occupational exposure to chemical toxins, (4) exposure to cytotoxic chemotherapy, particularly alkylating agents, (5) Noonan syndrome, (6) Fanconi anemia, and (7) cerebellar ataxia [44, 45]. The cell origin or phenotype is multipotential progenitor cell [45]. The clinical manifestations of familial monosomy 7 syndrome include complications of cytopenias, dysplasia, and acute leukemic transformation in addition to features of the associated disease conditions [44, 45].

7.3. JMML

JMML is a rare clonal MDS/myeloproliferative neoplasm (MPN) of young children [44, 45, 72, 73]. It has also been described as juvenile CML and was formerly grouped in the French-American-British (FAB) classification of MDS [74]. Without treatment, the 10-year overall survival (OS) of patients with JMML is 6% [74]. Allogeneic HSCT is the only curative therapy for children with JMML [72, 74]. Studies have also shown that event-free survival is 52% at 5 years post-HSCT [72]. Also, relapse is expected to occur in 50% of transplanted patients [72, 73]. Treatment options of relapsed JMML after the first HSCT include: (1) withdrawal of immunosuppressive therapy and/or donor lymphocyte infusion, and (2) second allogeneic HSCT, which may be the treatment of choice in such situations [72]. The major causes of HSCT failure in patients with JMML are treatment-related mortality and relapse [74].

8. Anemia in MDS

Severe anemia should be considered a major criterion for deciding not only the type but also the timing of therapeutic interventions in patients with MDS [75]. Once anemia is symptomatic, transfusion of packed RBCs is the mainstay of therapy in MDS [76]. The redistribution of transfusion iron from reticuloendothelial cells to parenchymal cells is modulated by hepcidin. Ineffective erythropoiesis has a suppressive effect on hepcidin production and hence increases iron redistribution [76].

9. Iron overload in high-risk MDS

Transfusion history should be considered in transplantation decision making in patients with MDS because pre-HSCT transfusion history and serum ferritin levels have been shown to have significant prognostic value in patients with MDS undergoing allogeneic HSCT [77]. Elevated serum ferritin and elevated liver iron content in patients with MDS and acute leukemia prior to HSCT are associated with inferior post-HSCT survival [78]. Studies have shown that transfusion dependency is independently associated with (1) reduced overall survival, (2) increased nonrelapse mortality (NRM), and (3) increased risk of acute graft versus host disease (GVHD) in patients with MDS undergoing allogeneic HSCT [77].

In patients with high-risk MDS, iron overload has adverse consequences on the outcome of HSCT as it has been associated with (1) increased transfusion-related mortality, (2) infectious complications, and (3) AML progression [79]. Iron chelation therapy in patients with higher risk MDS should be considered to possibly (1) reduce infectious complications, (2) delay leukemic transformation, and (3) improve the outcome of HSCT [80].

Nuclear factor-kappaB (NF-kB) is key regulator of many cellular processes and its impaired activity has been described in different myeloid malignancies including MDS [81]. NF-kB inhibition by deferasirox could prove to be an important therapeutic option in higher risk MDS patients by targeting blast cells in which increased NF-kB activity has been extensively demonstrated thus acting as a possible enhancer of chemosensitivity of the malignant clone [81].

10. Management of MDS

The following therapeutic modalities are available for patients with MDS: (1) supportive measures: packed RBCs and platelet (PLT) transfusions, antimicrobial therapy, and hematopoietic growth factors, (2) drug therapies including novel agents such as lenalidomide, azacytidine, and decitabine, and (3) various forms of HSCT [82].

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10.1. Epigenetic therapies of MDS

Epigenetic therapies cause potentially reversible epigenetic changes that can alter gene expression patterns [83]. Epigenetic therapies in MDS include (1) histone deacetylase inhibitors, and (2) hypomethylating agents, such as azacytidine and decitabine, that inhibit the DNA methyltransferase enzymes (DNMT) [83].

Epigenetic silencing is a universal mechanism of gene inactivation in malignant cells, probably exceeding mutational events. Recent therapeutic approaches targeting the aberrant epigenome of cancer has been developed [84]. The hypomethylating agents, azacytidine and decitabine, have shown remarkable activity in older individuals with higher risk MDSs including patients with poor-risk cytogenetic profiles. Translational studies performed on BM biopsies obtained from MDS patients with both azanucleoside demethylating agents have indicated that both azanucleosides can revert the aberrant hypermethylation state *in vivo* [84].

10.2. Hypomethylating agents

The azanucleosides, 5-azacytidine and decitabine, were originally synthesized more than 50 years ago in order to be used as classical cytotoxic agents [85–88]. Azacytidine was first described by Sorm in 1964 as a cancerostatic agent [89]. Both hypomethylating agents, 5-azacytidine and decitabine, had demonstrated activity against lymphoid leukemic cells as well as hemopoietic tissues in experimental leukemia mice models [90–93].

10.2.1. 5-Azacytidine

Azacytidine is a pyrimidine nucleoside analog that differs from cytosine by the presence of nitrogen, rather than ring carbon, at position 5 [8, 9]. It was first manufactured in Europe in the 1960s [8, 9]. Azacytidine is a DNA methyltransferase inhibitor (DMTI) that has *in vitro* and *in vivo* demethylating effects [9]. The hypomethylating effects of azacytidine appear to primarily depend on the structural alternations at position 5 [8]. Azacytidine was the first hypomethylating agent to be approved by the Food and Drug Administration (FDA) in United States of America for the treatment of all subtypes of MDS in May 2009 [8, 10, 94]. In patients with high-risk MDS, the benefits of azacytidine therapy on survival compared to conventional chemotherapy have not been established outside clinical trials [95, 96]. Despite the wide spread use of azacytidine in the treatment of high-risk MDSs, there is lack of improvement in long-term survival. Therefore, identification of predicting factors of response and survival is mandatory [95, 96].

Hypomethylating agents or azanucleosides are becoming the standard therapy for patients with higher-risk MDSs [97]. Patients with high-risk MDSs treated with azanucleosides have a median overall survival of 11–16 months, so they should be strongly considered for upfront allogeneic HSCT or experimental therapies [97]. In patients with high-risk MDSs planned for allogeneic HSCT, azacytidine treatment may be valuable in stabilizing the disease and preventing relapse [98]. Additionally, pretransplant administration of azacytidine does not adversely affect transplant outcome [98]. Preemptive azacytidine therapy has an acceptable

safety profile and can substantially prevent or at least delay relapse in patients with MDS or AML with minimal residual disease after allogeneic HSCT [99].

Name of trial	CALG-B/8421 trial	CALG-B/8921 trial
Phase	Phase I	Phase II
Azacytidine therapy	IV administration Initial dose: 75 mg/m^2 continuous IV infusion over 7 days every 28 daysdose escalated to 150 mg/m^2	SC administration 100 mg/m^2
Number of patients evaluated	43	68
Complete response	5 patients (12%)	8 patients (12%)
Partial response	11 patients (25%)	10 patients (15%)
Improvement	5 patients (12%)	18 patients (27%)
Total response	21 Patients (49%)	36 patients (53%)

Abbreviations: MDS, myelodysplastic syndrome; IV, intravenous; CALG-B, cancer and leukemia group B; SC, subcutaneous.

Table 3. Phase I and phase II CALG-B clinical trials on azacytidine in MDS.

The outcome of patients with high-risk MDSs after failure of azacytidine treatment is generally poor [100]. After failure of azacytidine treatment, the options are rather limited to (1) best supportive care in patients unfit for allogeneic HSCT, and (2) allogeneic HSCT and investigational agents in patients who are eligible for such therapies [100]. Mechanisms of action of 5-azacytidine are multifactorial and they include (1) demethylation of several key genes, that is, reduction of DNA methylation by inhibition of methyltransferase enzymes, (2) cytotoxic action by inhibition of protein translation, and (3) enhancement of apoptosis [8–10]. In patients with MDSs, 5-azacytodine is indicated in (1) high-risk MDSs, and (2) intermediate 2 risk MDSs [8, 10, 95, 97, 100–102]. The side effects of azacytidine therapy include myelosuppression (leucopenia, anemia, and thrombocytopenia); gastrointestinal (GIT) upset (nausea, vomiting, diarrhea, and constipation); injection site reactions and erythema; serum sickness-like illness; abnormal liver function tests; fatigue; weakness; lethargy; anorexia; headache; arthralgias; febrile neutropenia; cytomegalovirus infection; and pneumonia [9, 10, 99, 101, 103].

The effects of azacytidine in patients with MDSs include (1) prolongation of survival, (2) improvement in QOL, and (3) delayed leukemic transformation [8, 10, 95, 101, 102]. Responses to azacytidine according to karyotypes are as follows: (1) excellent responses are expected in patients with normal cytogenetics, (2) durable remission and 80% response rate are expected in patients having chromosome 7 abnormalities as the sole karyotypic abnormalities, and (3) good early responses but early relapses in patients with trisomy 8 [9]. Predictors of positive responses to DMTIs is include (1) doubling of PLT count, (2) mutated TET2, (3) mutated EZH2, (4) Phosphoinositide-phospholipase C beta hypomethylation, and (5) low serum level of micro-RNA-21 [96, 104, 105]. Predictors of poor response to DMTIs include (1) BM blasts >15%,

(2) previous therapy, (3) transfusion dependency, (4) grade 3 marrow fibrosis, (5) mutated p53, (6) abnormal karyotype of complex cytogenetics, (7) high serum level of micro-RNA-21, and (8) increased cytidine deaminase expression of activity in males [96, 104, 106].

Trial	**AZA-001 trial**			**CALG-B 9221 trial**		
Phase	Phase III randomized controlled multicenter international study			Phase III randomized controlled study		
Study design	Azacytidine	Conventional care	*P*-value	Azacytidine	Best supportive care	*P*-value
Number of patients	179	179	–	99	92	–
IPSS class intermediate 2 and high risk	158 patients (89%)	155 patients (87%)	–	20%	26%	–
Median survival (months)	24.5 months	15 months	≤0.0001	18 months	11 months	0.03
2 year overall survival	50.8%	26.2%	<0.0001	–	–	–
Transformation to AML				15%	38%	0.001
Median time to AML transformation	17.8 months	11.5 months	≤0.0001	21 months	13 months	0.007
Complete response	30 patients (17%)	14 patients (4%)	0.015	7%	0%	0.01
Partial response	21 patients (12%)	7 patients (4%)	0.0094	16%	0%	<0.0001
Improvement	Stable disease 75 patients (42%)	Stable disease 65 patients (36%)	0.33	37%	5%	<0.0001
Overall response	HI in 87 patients (49%)	HI in 51 patients (29%)		60%	5%	-

Abbreviations: MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; IPSS, International Prognostic Scoring System; CALG-B, cancer and leukemia group B; AZA, azacytidine HI: hematological improvement.

Table 4. Phase III randomized controlled clinical trials on azacytidine.

In patients with high-risk MDSs and AML, the combination of 5-azacytidine, valproic acid, and all-trans retinoic acid (ATRA) are safe and they are active and associated with induction of global DNA hypomethylation and histone acetylation [107, 108]. Lessons learned from clinical experience with hypomethylating agents include (1) in the majority of treated patients, the beneficial effects are only noted after approximately four cycles of therapy, (2) the achievement of hematological improvement is sufficient to ensure prolonged OS, (3) in

almost all patients, interruption of treatment induces relapse, (4) patients who relapse after treatment or who are refractory to therapy have extremely limited survival, and (5) patients with complex karyotype involving monosomy 7 or monosomy 5 have negligible survival advantage from hypomethylating agents despite achievement of response [96]. Clinical phase I, II, and III trials on the use of azacytidine in patients with MDSs are shown in **Tables 3** and **4** [9, 10, 101, 103, 109]. Investigational agents that can be used in the treatment of MDSs in case of failure of hypomethylating agents include (1) rigosertib, (2) sapacitabine, (3) clofarabine, and (4) BCL2 inhibitors (proapoptotic drug therapy) including ABT-737 and ABT-199 [96, 110].

Conclusion that can be drawn from phase III trials on azacytidine include: (1) in CALG-B 9221 trial: compared to best supportive care (BSC), azacytidine therapy resulted in (a) significantly higher response rates, (b) improved QOL, (c) improved survival, and (d) reduced risk of leukemic transformation; and (2) in AZA-001 trial: compared to conventional therapy, that Included BSC, low dose cytarabine ± intensive chemotherapy, azacytidine increased OS in patients with high-risk MDS [101, 109]. In patients with chromosome 7 abnormalities [monosomy 7 and del(7q)], the median survival was 13.1 months in patients treated with azacytidine compared to 4.6 months in patients who received conventional therapies [101].

10.2.2. Decitabine

Decitabine (5-aza-2-deoxycytidine) inhibits DNMT. It was approved by the FDA in the United States for the treatment of MDS in the year 2006 [83, 111, 112]. It is postulated that initially the drug and the DNMT enzymes become attached, then the outcome will be: (1) enzyme degradation resulting in low DNMT levels, and (2) ultimately achievement of hypomethylation [83]. Although decitabine antitumor activity is not fully understood, there are several possible mechanisms of action that include (1) induction of hypomethylation or reversal of cancer-associated hypermethylation effects, (2) reactivation of genes responsible for cellular differentiation, (3) stimulation or induction of immune responses, (4) induction of DNA damage pathways or apoptotic response pathways, that is, induction of changes in the rates of apoptosis, and (5) augmentation of stem cell renewal [83, 105]. Various doses, schedules, and even routes of administration have been used: 10, 15, or 20 mg/m^2 intravenously (IV) or subcutaneously (SC) for 3–5 days, each cycle for at least four cycles that are given at 4- to 6-week intervals [83, 111, 112].

Although it has been used in the treatment of all FAB subtypes of MDS, the specific indications are as follows: (1) intermediate 1, intermediate 2, and high-risk MDS, (2) *de novo* and secondary MDS, including t-MDS, (3) MDS transforming into AML, in individuals unfit for intensive cytotoxic chemotherapy, as upfront therapy, (4) treatment of MDS refractory to lenalidomide, (5) debulking treatment prior to HSCT in high-risk patients, and (6) patients with chronic myelomonocytic leukemia (CMML) [83, 105, 111]. The adverse effects of decitabine therapy include (1) myelosuppression leading to febrile neutropenia, sepsis, pneumonia, and fungal infections, (2) gastrointestinal effects including nausea, vomiting, diarrhea, and mucositis, (3) hair loss, skin rashes, fatigue, and bleeding, (4) renal failure, (5) cardiovascular complications are uncommon, and (6) pleural effusions and acute lung injury [83, 112, 113]. Encountering

myelosuppression that requires decitabine dose modification may truly indicate response to therapy [112].

Despite the efficacy of dectiabine therapy, there are no known definitive predictors of response. However, in patients with high-risk MDS treated with decitabine, high expression of human equilibrative nucleoside transporter-1 (hENT-1) gene appears to predict a good response to decitabine therapy and is associated with prolonged survival [114]. Patients with chromosome 7 abnormalities usually respond more favorably to continuous IV infusion of low-dose decitabine than to conventional chemotherapy with low-dose cytarabine [115]. Results of clinical trials on decitabine are shown in **Table 5** [83, 84, 111, 113]. Unfortunately, there is no head-to-head comparison with 5-azacytidine. Also, decitabine has not shown a statistically significant evidence of prolonged survival benefit in prospective studies. In addition, the role of decitabine after HSCT needs further evaluation [83].

10.2.3. Rigosertib (ON01910.Na)

Rigosertib is a multikinase inhibitor that inhibits both the phosphoinositide 3 kinase and the polo-like kinase pathways [116–120]. It inhibits the cell-cycle progression by selectively inducing a mitotic arrest and apoptosis in cancer cells [116, 118–120]. Recently, it has been highlighted as a novel anticancer agent for the treatment of MDS. Rigosertib has shown activity in the following malignancies: (1) mantle cell lymphoma, (2) chronic lymphocytic leukemia, and (3) MDS [118]. In MDS, rigosertib has several mechanisms of action that include: (a) upregulation of genes related to microtubule kinetics, (b) downregulation of the mRNA degradation system, that is, suppression of nonsense mRNA decay (NMD) gene, (c) suppression of cyclin-D1 in BM CD34+ cells in MDS patients with trisomy 8 and monosomy 7, and (d) induction of cell death by inhibition of PI3kinase/Akt pathway and DNA damage-induced G2/M arrest, that is, induction of mitotic arrest and apoptosis in myeloblasts while sparing normal cells [118–120].

Rigosetib has shown efficacy in all morphologic, prognostic risk and cytogenetic subgroups of MDS and has produced complete responses in some patients [121]. It has shown activity in high-risk MDS patients and in those having monosomy 7 and trisomy 8. It has produced the following beneficial effects: (1) decrease in BM blasts, (2) improvement in hematopoiesis, (3) inhibition of cyclin D1 accumulation, and (4) decrease in trisomy 8 and monosomy 7 aneuploidy [116, 119, 121]. However, a randomized controlled, phase 3, clinical trial that had been performed in 74 institutions in Europe and the United States on the use of rigosertib in patients with high-risk MDS after failure of hypomethylating agents did not show significant OS compared to best supportive care [117]. The drug is available in oral and injectable formulations [120, 121]. Although rigosertib has exhibited a favorable safety profile, the following adverse effects have been reported: syncope, fatigue, nausea, vomiting, abdominal pain, hypotension, anemia, thrombocytopenia, neutropenia, febrile neuropenia, pneumonia, dysuria, and hematuria [116, 117, 120].

Trial	Number of patients	Phase and design of trial	Study focus	Results	Total dose per course/ interval between cycles	Median number of courses	Time to AML progress	Median survival
Kantarjian et al. Cancer 2006	170	Phase II randomized multicenter	Decitabine vs. BSC	OR: 17% CR: 9% PR: 8% HI: 13%	135 mg/m² 6 weekly	3	12.1 months vs. 7.8 months	14 months vs. 14.9 months
Ruter et al. Cancer 2006	22	Phase II pooled analysis of 3 trials	Low dose decitabine as salvage therapy at relapse	OR: 45% CR: 4.5% PR: 9.1% HI: 31.8%	135 mg/m² 6 weekly	3	-	37.5 months
Kantarjian et al. Cancer 2007	115	Phase II 1 single center	Prognostic factors associated with outcome	OR: 70% CR: 35% PR: 2% HI: 10–23%	100 mg/m² 4 weekly	≥7	Not reached	22 months
Kantarjian et al. Blood 2007	95	Phase II randomized single center	Optimal dosage of decitabine	OR: 73% CR: 34–39% PR: 1% HI: 14–24%	100 mg/m² -	≥6	27% over 18 months	19 months
Kantarjian et al. Cancer 2007	491	Phase II historical comparison of 2 groups of patients at single center	Decitabine vs. AML type of intensive chemotherapy	CR: decit: 43% vs. intensive chemotherapy: 34%	100 mg/m² –	–	–	22 months vs. 12 months
Borthakur et al. Leuk Lymphoma 2008	14	Phase II early results	Efficacy of decitabine after failure of vidaza	OR: 28% CR: 21% HI: 7%	100 mg/m² 4 weekly	3	4 months	6 months
Steensma et al. JCO 2009	99	Phase II multicenter non randomized	Efficacy & safety of decitabine as outpatient regimen	OR: 32% CR: 17% HI: 18%	100 mg/m² 4 weekly	5	–	19.4 months
Lubbert et al. JCO 2011	233	Phase III- 2 arms multicenter	Decitabine vs. BSC	CR: 13% PR: 6% HI: 15%	95 mg/m² 6 weekly	4	8.8 months vs. 6.1 months	PFS: 6.6 months vs. 3 months

Trial	Number of patients	Phase and design of trial	Study focus	Results	Total dose per course/ interval between cycles	Median number of courses	Time to AML progress	Median survival
Jabbour et al. Clin Lymphoma Myeloma Leuk 2013	183	Phase III pooled analysis of 2 multicenter trials	Decitabine vs. BSC in *de novo* MDS vs. 2^0 MDS	OR: 28% *de novo* MDS vs. 15.4% in 2^0 MDS	135 mg/m^2 4–6 weekly	3 and 5 courses	33 months for 2° MDS not reached for *de novo* MDS	OS: 16.6 months vs. 9 months

Abbreviations: MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; OR, overall response; CR, complete response; PR, partial response; HI, hematological improvement; BSC, best supportive care; vs., versus; 2^0, secondary; OS, overall survival.

Table 5. Decitabine trials in MDS patients.

11. The role of HSCT in high-risk MDSs including monosomy 7

11.1. HSCT in adults with MDSs

Allogeneic HSCT is the only potentially curative therapy for MDS patients [4, 82, 122–124]. Recently, HSCT is being used with increasing frequency in patients with MDS, partly due to the development of novel conditioning therapies, such as nonmyeloablative conditioning, that allow HSCT to be offered to older patients [4, 122]. Also, the use of immunomodulatory drugs and hypomethylating agents prior to HSCT has shown efficacy in (1) controlling disease, that is, a bridging approach to HSCT, and (2) tumor debulking before HSCT [4, 122]. The indications of allogeneic HSCT in adults with MDS are shown in **Table 6** [4, 82, 122–125].

MDS patients with monosomy 7 or complex cytogenetics and preserved BM are considered indications for immediate rather than delayed HSCT. Secondary MDS is another special indication for HSCT [82, 125]. Currently, patients with therapy-related MDS (t-MDS) are being treated using the same paradigm as in *de novo* MDS [82]. Despite its curative potential, the role of allogeneic HSCT in the treatment of elderly patients with MDS is less well defined than in younger individuals [4]. The following issues related to HSCT remain an area of intense investigations: (1) pretransplant disease burden, (2) optimal conditioning therapies, (3) optimal donor selection, (4) optimal stem cell source, (5) GVHD prophylaxis, and (6) post-transplant relapse [122]. The following complications of allogeneic HSCT: GVHD, infections, and non-relapse mortality may offset the benefits of allogeneic HSCT over medical therapies [82]. Despite the remarkable improvement in both efficacy and safety of HSCT over the past

two decades, therapy-related morbidity and mortality as well as disease relapse still pose significant risks to transplanted patients [82, 122, 123]. Methods employed to prevent and treat relapse of MDS following HSCT include (1) donor lymphocyte infusion (DLI), (2) hypomethylating agents, (3) novel cellular therapies including vaccination, and (4) use of alloreactive natural killer cells [4, 122].

In children	In adults
1- Refractory anemia with excess of blasts (RAEB)	(A) Definite indications:
2- Refractory anemia with excess of blasts in transformation (RAEB-t)	1- Intermediate 2 IPSS
3- Chemotherapy or radiotherapy related MDS (t-MDS)	2- High-risk IPSS
4- Juvenile myelomonocytic leukemia	(B) Probable indications:
5- Refractory cytopenias associated with:	1- t-MDS or secondary MDS
a- transfusion dependence	2- Packed Red blood cell transfusions refractory to:
b- cytogenetic abnormalities	- Hematopoietic growth factors
	- Immunomodulatory drugs
	- Hypomethylating agents
	3- Severe neutropenia or thrombocytopenia
	4- At least one line of cytopenia with multilineage dysplasia
	5- High risk chromosomal abnormalities: monosomy 7 and complex cytogenetics
	6- High percentage of blasts [≥10%]

Abbreviations: MDS, myelodysplastic syndrome; t-MDS, therapy-related myelodysplastic syndrome; RAEB, refractory anemia with excess of blasts; RAEB-t, refractory anemia with excess of blasts in transformation; SCT, hematopoietic stem cell transplantation.

Table 6. Indications for allogeneic HSCT in patients with MDS.

Predictors of outcome of allogeneic HSCT in MDS patients include: (1) disease stage including blast count, (2) transfusion dependence, and (3) karyotype, cytogenetic abnormalities and molecular aberrations or genetic mutations such as: monosomal karyotype, complex cytogenetic and TP53 mutation [82, 122, 125].

11.2. HSCT in children with MDSs

Allogeneic HSCT is the only potentially curative therapy for children with MDSs, particularly those having JMML [73, 126]. The indications of allogeneic HSCT in children with MDSs are shown in **Table 6** [73, 126–128]. Relapse rate following allogeneic HSCT performed for JMML may reach 50% or more [73]. Children with MDS and JMML should be referred for allogeneic HSCT soon after making the diagnosis in order to prevent disease progression as pretransplant chemotherapy does not appear to improve outcome [127, 128]. Predictors of poor outcome of allogeneic HSCT in children with MDS include (1) monosomy 7, (2) age more than 4 years at transplant, (3) relapse after HSCT, (4) female gender, and (5) human leukocyte antigen (HLA)-mismatched allografts [73].

http://dx.doi.org/10.5772/64549

11.3. HSCT in higher risk MDS patients

Patients with higher risk MDS who have an HLA-matched donor should be transplanted early before progression of their disease or acquisition of a nonhematological contraindication to HSCT [129]. In patients with intermediate-2 or high-risk MDS, aged 60–79 years, subjected to reduced intensity conditioning allogeneic HSCT, life expectancy is about 36 months compared to 28 months in patients not subjected to HSCT, that is, HSCT in this group of patients has a survival advantage [130]. Patients with higher risk MDS should be treated with either hypomethylating agents or HSCT [131]. It is justified to offer patients with higher risk MDS who have an HLA identical donor an allograft [129]. Retrospective studies have concluded that patients with higher risk MDS have a survival advantage over demethylating agents if they can be offered an early allogeneic HSCT [129]. Transplant-related mortality remains high in HSCT, it ranges between 10% and 40% particularly after myeloablative conditioning therapy in elderly individuals [129]. Long-term survival ranges between 30% and 60% depending on patient characteristics, disease risk, type of donor, source of stem cells, and complications that evolve following HSCT [129].

12. Conclusions and future directions

In children and adults, high-risk MDSs including monosomy 7 are often complicated by various degrees of BM suppression, infectious complications, severe iron overload, and transformation into AML. Management of these disorders includes (1) supportive care that comprises transfusion of blood products, antimicrobials, and iron chelation therapy, (2) epigenetic therapies including histone deacetylase inhibitors and hypomethylating agents such as azacytidine and decitabine, and (3) various types of allogeneic HSCT. Recently, the role of allogeneic HSCT in high-risk MDSs is increasing due to the introduction of the new conditioning therapies that have allowed the application of this curative modality of therapy not only to older patients, but also to individuals with medical comorbidities. However, in patients with familial causes of their MDSs of BM failure planned for allogeneic HSCT using a sibling donor, great caution should be exercised and enough investigations should be performed before clearing the sibling for donation. The role of certain growth factors in the management of patients with high-risk MDS is controversial as G-CSF has been reported to accelerate the progression into acute leukemia.

The recent developments in the diagnostics of MDSs and the recently introduced therapeutic agents such as rigosertib, clofarabine, sapacitabine, and BCL2 inhibitors as well as the evolving modalities of HSCT are likely to improve the outcome of patients with higher risk MDSs significantly.

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