Myelodysplastic syndrome from theoretical review to clinical application view

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Abstract

Myelodysplastic syndromes (MDS), called ineffective hematopoiesis is indicated by bone marrow failure and tendency to acute myeloid leukemia transformation. Since the disease is more common in elderly with non- hematology co-morbidities, the research for less toxic and curative novel agents is essential. More than 12 years without new Food and Drug Administration approved drugs in MDS management through the whole course, only 5 drugs. We summarized the basic data in diagnosis, treatment guidelines and future direction.

Introduction

Myelodysplastic syndromes (MDS) usually designated as bone marrow (BM) failure are a heterogeneous group of myeloid clonal disorders caused by a failure of blood cells maturation. The co-morbidities result from a variable degree of cytopenia and clonal instability with a tendency to progression mainly into acute myeloid leukemia (AML) but very rare into acute lymphoblastic leukemia.[1] MDS is rare below 40 years old, according to Surveillance, Epidemiology & End Reports (SEER), the estimated incidence increases with age with fivefold difference in risk between age 60 and ≥80 years. The incidence rate is about 4.9 per 100,000 persons/year in the general population. At all ages, it predominantly affects males more than in females.[2]

The management of MDS is considered one of the challenging issues facing the hemato-oncologists as the results of many obstacles such as the advanced age which is usually associated with non-hematological co-morbidities make them relatively intolerance to therapy. Moreover, the cases progressed named secondary AML usually experience a lower response to standard of care therapy than the de novo cases. We aimed in this review to summarize the basic concept in MDS management and focus on the availability of the Food and Drug Administration (FDA)-approved agents with some hints on future direction.

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Pathophysiology and etiology

The early stages of MDS, excessive programmed cell death (apoptosis) is the predominant event with subsequent cytopenia with its variable degree and extent. Furthermore, with disease progression, gene mutation, and leukemic transformation, causing smashing of BM via the leukemic cells. Clonal mutation is the trigger for MDS development leading to normal stem cell suppression. This mutation may result from genetic susceptibility or damage of hematopoietic stem cells.

Most patients with MDS have no apparent cause (approximately 80%) and named as idiopathic or primary. Secondary MDS according to The World Health Organization (WHO) develops years after exposure to known agents causing chromosomal damage such as chemotherapy (alkylating agents, topoisomerase II inhibitors), radiotherapy, heavy metals (mercury, lead), viral infection, toxic chemicals (benzene, fungicide), and some autoimmune conditions. Chemotherapy-related MDS represented the most obvious causal factor. We have 2 types of therapy; alkylating agents ± radiotherapy and topoisomerase II inhibitors. The developed MDS had special featured depending on the offending risk factor. Post alkylating agents such as Nitrogen mustards, characterized by late onset about 5-7 years after exposure with specific karyotyping (-5, del(5q), -7, del(q) and complex). While in case of post topoisomerase II inhibitors such as anthracycline /etoposide, characterized by early onset 1-3 years with chromosomal abnormalities (*MLL* gene 11q23).[3] Although genetic predisposition is rare, familial incidences are reported. Familial platelet disorder is the best example characterized by a mutation in RUNX1 and GATA2 predisposing to MDS. Familial AML with mutated CEBPA and telomere biology disorders are another forms of familial MDS may be detected during family members screening for BM transplantation.[4] Two-hit model of progression from chronic MDS into AML may help in understanding the basic of leukemic transformation. It may include molecular and cytogenetic aberrations either in first or second hit class mutations during the disease progression. Actually, the mechanisms of leukemic transformation are not clearly understood.[5]

Classifications and prognostic stratifications

MDS is a heterogeneous disease, some cases have an indolent course and others develop profound cytopenias. Bleeding and

infections represented most of the mortality/morbidity related to MDS. The other scenario is following more aggressive behavior and evolution into AML. Based on the WHO, the French-American-British (FAB) Cooperative Group, and the MDS Risk Analysis Workshop risk stratification systems had been developed in patients with MDS. Historically, MDS was classified into 5 subgroups, based on The FAB system.[5]

The WHO classification proposed for MDS firstly was in 1999 and updated 3 times; in 2001, 2008, and 2016. The updated WHO classification of MDS had evolved 2 changes; firstly, the subdivision of MDS- ring sideroblasts (RS) into single lineage dysplasia (SLD) and multilineage dysplasia (MLD) based on the presence of single or multiple lineage dysplasia respectively. Secondly; MDS-RS had expanded to include patients with SF3B1 mutations but without excess blasts or isolated 5q- an abnormality. The 5q− entity is recognized by isolated del (5q) as the only karyotype abnormality, blast cell <5% ± one other abnormality except for -7/7q-, which is linked to poor prognosis. Another change in the update is the need for 1% blasts in the peripheral blood to diagnose MDS-U on 2 separate occasions.[6,7] Table 1 summarizes the updated classification of MDS.

The cut off between AML and MDS is a continuous field of debate. According to FAB classification, MDS included 29% blast cells, however, the figure is reduced to 19% according to WHO classification in 2001. Therefore, these patients were reclassified as AML with myelodysplasia- related changes. It was noted those patients may have less aggressive course, better response to treatment, and improved outcome in comparison to patients with ≥30% blasts.[8] Due to this heterogeneity of the disease, The National Comprehensive Cancer Network (NCCN) panel recognized that MDS course depended not only on blasts count but also on other biological features, and hence they recommended that patients with 20%-29% blast cells with stable disease course for at least 2 months to be diagnosed either AML or MDS. Patients with mutations in FLT3 and NPM1 are less likely to have MDS.[9] Generally, 5q- entity has a relatively favorable outcome with good response to lenalidomide therapy.[10] With a relative degree, the MDS- RS-SLD and MDS-RS have a better survival outcome in comparison to MDS-EB and MDS-EB-T with a median survival of approximately 5-12 months and 3-6 months, respectively. Moreover, with increasing the risk stratification, the incidence of leukemic transformation increased; ranges from 5%-15 % in low-risk MDS-RS-SLD to 30%-40% in MDS-EB.[11] Recently, evidence suggested that splicing factor (SF) mutation comprised special clinical phenotypic features differed from theses without the mutation. In a study done by Taskesen *et al.* on 47 (RAEB) patients, 29 AML cases with low BM blasts count, and 325 other AML patients to evaluate the mutational status of SF. The results revealed that SF-mutant AML and SF-mutant RAEB are molecular, cytologically, and clinically highly similar.[12]

Prognostic scoring system

International prognostic scoring system and revised (IPSS/IPSS-R)

Owing to the variability in outcome of MDS subtypes and to help in treatment selection, the International MDS Risk Analysis Workshop (IMRWS) developed a scoring system named International Prognostic Scoring System (IPSS). Firstly, published in 1997 and then revised in 2012 (IPSS-R)[13,14] (Tables 2 and 3).

Table 1. WHO classification of MDS (2016).

Subtype	Blood	Bone marrow
MDS-SLD	Single or bi-cytopenia	Dysplasia ≥10% of on cell line, <5% blasts
MDS-RS	Anemia, no blasts	≥15% of erythroid precursors with RS or ≥5% RS if SF3B1 mutation is present.
MDS-MLD	Cytopenias <1×10^9/L monocytes	Dysplasia ≥10% of cells in ≥2 hematopoietic lineages, <15% RS or <5% RS if SF3B1 mutation present) <5% blasts
MDS-EB-1	Cytopenias ≤2%-4% blasts, <1 ×109/L monocytes	SLD or MLD, 5%-9% blasts, no auer Rods
MDS-EB-2	Cytopenias, ≤5%-19% blasts, <1 ×109/L monocytes	SLD or MLD, 10%-19% blasts, ± auer Rods
MDS-U	Cytopenias, ±1% blasts on at least 2 occcasions	SLD or no dysplasia but characteristic MDS cytogenetics, <5% blasts
MDS with isolated del(5q)	Anemia, platelets normal or increased	Unil-lineage erythroid dysplasia, isolated del(5q), <5% blasts ± one other abnormality except -7/del(7q)
Refractory cytopenia of childhood	Cytopenias <2% blasts	Dysplasia 1-3 lineages, <5% blasts

MDS-SLD, MDS with single lineage dysplasia; MDS-RS, MDS with ring sideroblasts; MDS-MLD, MDS with multilineage dysplasia; MDS-EB-1, MDS with excess blasts-1; MDS-EB-2, MDS with excess blasts-2; MDS-U, unclassifiable MDS. Lineage dysplasia includes Refractory anemia, Refractory neutropenia, and Refractory thrombocytopenia depending on number of cell lines involved (uni-lineage, bi-lineage or multi-lineage). Adapted from NCCN guidelines version 1 (2019).[20]

Table 2. Survival and AML evaluation based on International Prognostic Scoring System (IPSS).

	International Prognostic Scoring System (IPSS)				
Prognostic variable	0.0	0.5	1.0	1.5	2.0
Blasts in BM	<5	5-10	-	11-20	21-30
Karyotype	Good	Intermediate	Poor	-	-
Cytopenia	0/1	2/3	-	-	-
Risk category	**Total score**	**Median survival (y) without treatment**		**25%AML progression (y) without treatment**	
Low	0	5.7		9.4	
Intermeadiate-1	0.5-1.0	3.5		3.3	
Intermeadiate-2	1.5-2	1.1		1.1	
High	≥2.5	0.4		0.2	

Cytogenetics: good; normal, -Y alone, del(5q) alone, del(20q) alone; poor: complex (≥abnormalities) or chromosome 7 abnormality; intermediate: other abnormalities. Presence of karyotype t (8:21), t (15,17), and inversion 16, denote AML rather than MDS. Cytopenia; neutrophil <1800/mcl, platelet <100,000/mcl, hemoglobin <10 gm/dL. Adapted from NCCN guidelines version 1 (2019).[20]

WHO classification-based prognostic scoring system and revised (WPSS&WPSS-R)

Its rationale depended on incorporation the IPSS cytogenetics, WHO morphologic, and degree of RBC transfusion. In that system, the frequency of transfusion and depth of anemia are considered poor prognostic markers[15,16] (Table 4).

Lower risk prognostic scoring system (LR-PSS)

It aimed to help in determination patients with low or intermediate-1 (low risk) who may be associated with poor outcome and need earlier interference. It included clinical and laboratory data from patients with low IPSS. The score involved the following independent predictor factors: age ≥60 years, platelet count ≤200×10^9/L, Hb<10 gm/dL, unfavourable cytogenetics, and BM blasts ≥4%. The sum of the scoring system is ranging from 0-7, resulting 3-risk categories: category-1 (0-2 points), category-2 (3/4 points), category-3 (5-7 points). By this scoring system, the median survival was: 80.3 months, 26.6 months, and 14.2 months for category 1, 2, and 3, respectively.[17]

Diagnosis

There is no specific history regarding MDS diagnosis except which related to BM failure in form of ecchymoses, petechiae, and bleeding from nose and gum are the general manifestations of thrombocytopenia. Fever, recurrent infection, and up to shock may be a manifestation of neutropenia. Malaise, fatigue, and aggravating cardiac disease may result from anemia. An International Consensus Working Group recommended at least 2 criteria to diagnose MDS: stable cytopenia for 6 months or 2 months only when was associated with specific cytogenetic or bi-lineage dysplasia, in addition, the other causes of dysplasia and cytopenia should be excluded. Moreover, the diagnosis needs at least one of the following items: firstly, dysplasia ≥10% in one or more of three BM lineage; secondly, blasts count from 5%-19%; thirdly, MDS-related karyotyping (5q-, 20q-, +8, -7/7q-). There are more co-criteria can help in the diagnosis include abnormal BM histology, aberrant immunophenotyping, and the presence of molecular markers as abnormal CD34.[18]

Table 3. Survival and AML evaluation based on the Revised International Prognostic Scoring System (IPSS-R).

Revised International Prognostic Scoring System (IPSS-R)							
Prognostic variable	0	0.5	1.0	1.5	2	3	4
Cytogenetic	Very good		Good		Intermediate	Poor	Very poor
Blasts in BM	≤2	-	>2-<5		5-10	>10	
Hemoglobin	≥10		8-<10	<8			
Platelet	≥100	50-<100	<50				
ANC	≥0.8	<0.8					
Risk category	**Total score**	**Median survival (y) without treatment**			**25%AML progression (y) without treatment**		
Very low	≤1.5	8.8			Not reached		
Low	>1.5-≤3	5.3			10.8		
Intermeadiate	>3-≤4.5	3.0			3.2		
High	>4.5-≤6	1.5			1.4		
Very high	>6.0	0.8			0.7		

Cytogenetics: very good; del(11q), -Y alone; Good; normal, del(12p), double including del(5q), del(20q); poor: -7, inv(3)/t(3q)/ del (3q), double inducing -7/ del(7q), complex = abnormalities: very poor> 3 abnormalities; intermediate: del(7q), +8, +19, (i17p), and any other single or double independent clones. Presence of karyotype t (8:21), t (15,17), and inversion 16, denote AML rather than MDS. Adapted from NCCN guidelines version 1 (2019).[20]

Table 4. Survival and AML evaluation based on WHO based prognostic scoring system (WPSS).

WHO based prognostic scoring system (WPSS)				
Prognostic variable	0	1	2	3
WHO category	RCUD, RARS, MDS with isolated 5q-	RCMD	RAEB-1	RAEB-2
Karyotype	Good	Intermediate	Poor	-
Severe anemia	Absent	Present	-	-
Risk category	**Total score**	**Median survival (y) without treatment**	**25%AML progression (y) without treatment**	
Very low	0	11.6	Not reached	
Low	1	9.3	14.7	
Intermediate	2	5.7	7.8	
High	3-4	1.8	1.8	
Very high	5-6	1.1	1.0	

Cytogenetics: good; normal, -Y alone, del(5q) alone, del(20q) alone; poor: complex (≥ abnormalities) or chromosome 7 abnormality; intermediate: other abnormalities. Hemoglobin <9 in males and <8 in females. Adapted from NCCN guidelines version 1 (2019).[20]

Cytogenetic studies

The cytogenetics role is gaining a great importance owing to the nonspecific histopathological changes. Some investigators claimed up to79% rate of chromosomal abnormalities in primary MDS. Patients with MDS fall into three categories: complex karyotypes (>3 abnormalities), normal karyotype, and balanced chromosomal abnormality. The chromosomal abnormalities may be multiple and indicate poor prognosis and may be single and usually indicates good prognosis except those with chromosome 7. The most common chromosomal abnormalities are monosomy 7 (-7) or 7q-, 5q-, trisomy 8 (+8). Presence of karyotype t (8:21), t (15,17), and inversion 16 denote AML rather than MDS.[19]

Approach considerations

Initial evaluation in patients with suspected MDS includes CBC with differential, blood smear, BM examination, and cytogenetic studies. Additional genetic and molecular tests may be required in special conditions such as hereditary hematologic malignancy. NCCN recommends also some additional studies when MDS is suspected: serum erythropoietin (prior to RBCs transfusion), RBC folate and serum vitamin B-12, Serum ferritin, iron, and total iron-binding capacity (TIBC), Thyroid-stimulating hormone (TSH), Lactate dehydrogenase (LDH), and HIV testing if clinically indicated.[20]

In the early stage, single cytopenia (anemia, thrombocytopenia, or neutropenia) while with disease progression bicytopenia or pancytopenia may be encountered. Hypercellularity and trilineage dysplastic changes are the most common finding in BM examination, however, in a small number of patients' BM may be hypocellular which may be confused with aplastic anemia and paroxysmal nocturnal hemoglobinuria (PNH), which may need to evaluate CD55 and CD59 level.[21]

Differential diagnosis

All causes of secondary BM failure should be put in the list of differential diagnosis and included PNH, aplastic anemia, infections as viral hepatitis, HIV, parvovirus, brucellosis, tuberculosis, leishmaniasis, B12 deficiency, autoimmune disorders as systemic lupus erythematosus, and effect due to various toxins and drugs

.

Treatment

Co-morbidities indices

As MDS is a disease of the elderly carrying the possibility of poor treatment tolerance. Many studies reported up to 50% of new diagnosed MDS presented with ≥1 co-morbidity such as cardiac and or diabetic diseases.[22,23] Charlson Co-Morbidity Index (CCI) and Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) are the most commonly used indices to evaluate the co-morbidities and provided a significant prognostic information for patients stratified in high or intermediate risk but not in low risk as categorized by IPSS. Until now, there is no superiority of one co-morbidity index over the other, however, the presence and extent of co-morbidity are representing very important factors in the treatment decision.

IPSS/IPSS-R is mainly used for treatment selection, while WPSS gives a dynamic estimation of disease prognosis during the course of the disease. The therapeutic options included 2 main categories: best supportive care (BSC) and disease-directed therapy which subsequently divided into low intensity and high intensity therapy. Most of the studies used the standardized International Working Group (IWG) response criteria which included 4 items based on treatment aims: altering the natural history of the disease, cytogenetic response, hematologic improvement (HI), and quality of life (QOL).[24]

Irrespective to risk stratifications, all patients should receive some sort of supportive care. The patients should be categorized as low risk (IPSS low, int-1; IPSS-R very low, intermediate; WPSS very low, low, intermediate); and high risk: (IPSS high, int-2; IPSS-R intermediate, high, very high; WPSS high, very high). According to IWG response criteria, the therapeutic goal for MDS low risk group would be HI, while for high risk group, altering the natural history of the disease is exhibited as essential. Moreover, QOL and cytogenetic response are significant parameters to evaluate.

Supportive care

Nowadays, the backbone of MDS management is supportive care with the items including clinical follow up and QOL domains such as functional, physical, emotional, social and spiritual, all may have an adverse effect on patients' lives.

Treatment of anemia

Erythropoiesis-stimulating agents (ESAs) are drugs which stimulate the BM to produce RBCs. Long acting darbepoetin and human recombinant Epo are ESAs with or without G-CSF were evaluated in patients with symptomatic anemia without effect on leukemic transformation. Evidence from clinical trials demonstrated that there is no clear superiority of one ESA over the other.[25] In addition, the analysis of data from previous trials showed up to 39% haematological response when Epo and G-CSF given simultaneous and followed by maintenance in responders without increasing in AML transformation. The benefit was more in low risk MDS with low serum level of erythropoietin, low blast cell count, and less frequent RBC transfusion (less than 2 units/month).[26,27]

Iron overload

Although the ESAs ±G-CSF may decrease the need and the frequency of PRBCs transfusion, still a considerable number of patients did not respond and mandated transfusion with a subsequent high risk of siderosis, which may be another causative factor for morbidity/mortality in early stage MDS. The diagnosis through measuring the serum ferritin level and the goal of therapy is to keep the level below 1000 mcg/L. Recently, hepatic iron overload can be evaluated by T2* MRI and Superconducting quantum interference device (SQUID). Reversible of some sequences of iron overload had been demonstrated in cases of transfusion independent (TI), and therefore change the risk of morbidity/mortality.[28]

We have 3 approved chelating agents for the treatment of iron overload. Deferoxamine, deferasirox, and deferiprone. Due to poor absorption of the oral route and ineffective intramuscular injection, of deferoxamine, continuous infusion or subcutaneous infusion is the preferred line, and more effective when the transfusion <4 packed RBC/ month.[29]

Deferasirox, orally given chelating agent with significant

adverse effect on liver and kidney, in addition to increasing the risk of gastrointestinal bleeding in a subgroup of patients including high risk MDS, therefore, it is contraindicated in those patients. Deferoxamine and deferasirox are contraindicated when creatinine clearance <40 mL/min.[30] Deferiprone (given orally), usually used after failure of other chelating agents. Agranulocytosis and fatal neutropenia are represented the most critical side effects. Although it is FDA approved in 2011, its use still a matter of challenge.[31]

Treatment of thrombocytopenia

The standard management is platelet transfusion. Many studies demonstrated that among the MDS patients, the thrombopoietin (TPO) endogenous level is high and the TPO receptor level was decreased in comparison to healthy persons Although this observation, there were promising results by use of romiplostim (TPO receptor agonist) in form of decrease the rate of platelet transfusion and the frequencies of bleeding. Sekeres et al. proposed a model to predict the response to romiplostim included; TPO levels <500 pg/mL, history of limited platelet transfusion, in low risk MDS.[32]

Early data from the use of eltrombopag, (another TPO receptor agonist) in low risk MDS reported improving in platelet number.[33] In a phase II trial evaluating the addition of eltrombopag to hypomethylating agents after their failure. The preliminary results are promising; however large prospective trials are needed.[34] The leukemic evolution after TPO agonist is an area of controversy, and it must be known that their use currently is not approved in MDS management.

Treatment of neutropenia

Despite some patients may need granulocyte transfusions, it is not preferable due to the high risk of refractoriness and alloimmunization. In certain circumstances, the prophylactic antibiotics may be considered.

Individual medications

Low intensity therapy

This type of therapy is usually used in low risk MDS and high risk unfit for high intensity therapy and include; lenalidomide, hypomethylating agents, anti-thymocyte globulin (ATG) and cyclosporine.

Lenalidomide

It is a thalidomide analogue, more potent and less teratogenic effect, FDA approved for treatment of transfusion dependent (TD) anemia MDS with low risk or int-1 according to (IPSS). Despite it is the standard of care for 5q- syndrome specially 5q31, it may be used in other chromosomal abnormalities but it is not allowed to be given in case of p53 mutation.

In a study done by List et al, lenalidomide showed 67% of patients no longer required transfusion, 45% had a complete cytogenetic response (CR), and more than one third of the patients achieved normal BM histology.[35]

In another trial evaluating lenalidomide *vs* BSC in MDS patients with low risk/int-1 IPSS (TD) with 5q- syndrome to evaluate the incidence of AML transformation and survival outcome. In a univariate and multivariate analysis, lenalidomide was not a determinant factor in AML progression. Regarding the survival analysis, the 2 years and 5 years OS probabilities were 90%, 74% and 54%, 40.5% for lenalidomide and BSC, respectively.[36]

An international trial resembles to the previous trial in design included 239 MDS patients but without 5q- abnormalities, patients in lenalidomide arm experienced higher RBCs TI (26.9% *vs* 2.5%; P<0.001). Despite the incidence of myelosuppression in lenalidomide was more, the therapy- related mortality was the same in both arms.[37]

The combination of lenalidomide with Epo vs lenalidomide alone in non del 5q abnormality, ESAs refractory, low risk MDS, failed to show statistical significance in RBCs TI, however in subanalysis group the benefits were seen after exclusion of heavily transfused patients, suggesting that the lenalidomide may restore the sensitivity of erythroid precursors to Epo.[38]

Hypomethylating agents

The rationale for their use is depending on reversing the DNA methylation effect (methylation leads to inhibition of tumor suppressor genes and subsequently increased the risk of AML transformation).

Azacitidine and decitabine are DNA methyltransferase inhibitors (DMTI), hypomethylating agents are currently approved in the treatment of all subtypes of MDS except 5q-syndrome. Despite both drugs are identical, azacytidine (Aza C) has RNA and DNA activity compared with decitabine. In a phase III trial included all risk groups of MDS to compare Aza C to BSC. The results showed prolonged time to AML progression (21 *vs* 13 months: P=0.007) and 60% hematological response in form of 7% CR, 16% PR and 37% HI in Aza C arm compared to 5 % HI in BSC arm without response.[39]

The analysis of 3 major trials for use Aza C either SC or IV in high risk MDS revealed CR in approximately 17% and HI in 36% belong to Aza C arm.[40] The investigators concluded that Aza C is a good option in high risk MDS regarding the clinical benefits and OS. Moreover, data evidence indicates the possibility of their use as a bridge till the availability of allogeneic HCT with both reduced-intensity conditioning (RIC) and myeloablative type.[41]

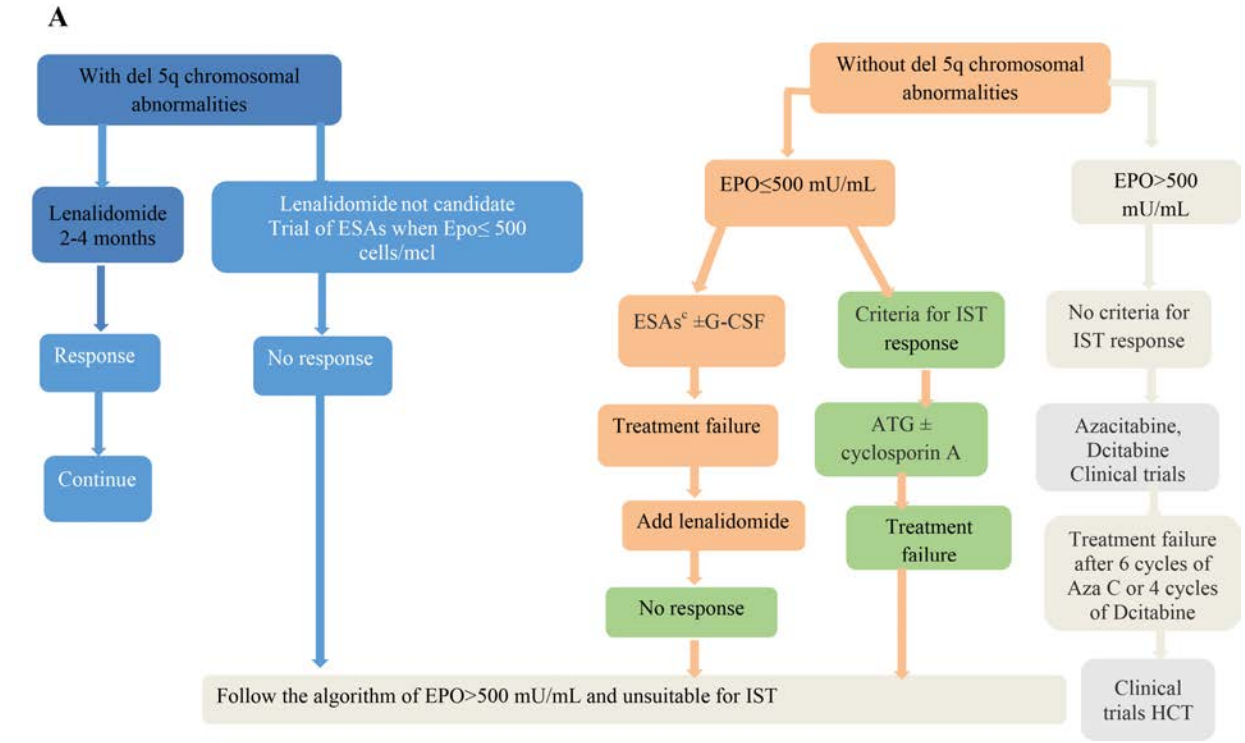
Decitabine is another hypomethylating agent given restrict IV mandated the hospitalization produce similar therapeutic results to seen with Aza C.

Failure of hypomethylating agents are indicative by lack of response (CR or PR), HI or AML progression after a minimum 4 cycles of decitabine or 8 cycles of Aza C. For how long hypomethylating agents could be used? Till now there is no clear answer and still a matter of debate. The NCCN Panel advised continuing the therapy as long as there are a response and no toxicity. Dose modifications only when toxicity encountered.

Although the Aza C and decitabine have the same response, the survival benefit is reported with Aza C. Till now there was no head to head trial comparing both drugs.

Anti-thymocyte globulin (ATG) and cyclosporine

They are immunomodulatory agents acting through inhibition or depletion of T-lymphocytes were evaluated in the management of MDS. In a trial included 129 patients with MDS were treated with immunosuppressive treatment (IST); cyclosporine combined with equine ATG, or alone. The analysis of the study provided the predictive factors to those agents and involved; HLA-DR15 histocompatibility type, low risk, normal cytogenetics, hypocellular BM, and PNH clone.[42] Only limited data about the use of rabbit ATG in MDS, the equine type is the standard, unlike the treatment



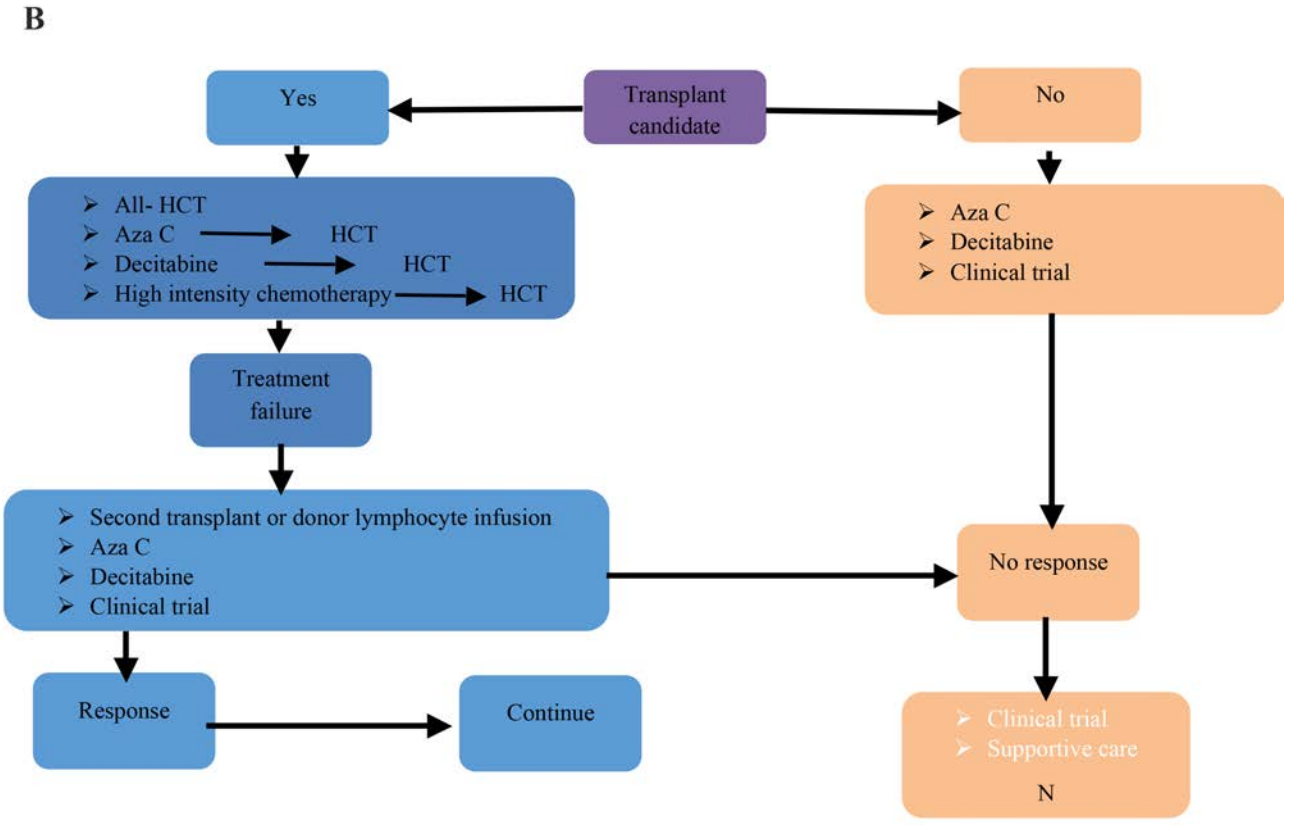


Figure 1. A) Proposed algorithm for low risk (IPSS low, intermediate; IPSS-R or WPSS, very low, low or intermediate) management. Chromosomal abnormality and with symptomatic anemia follow the same algorithm (except chromosome 7). a) The lenalidomide standard dose is 10 mg/day for 3 weeks and 1 week of (3/4), however, in the presence of significant neutropenia (platelet count <25000 cell/mcl) ± neutrophil count <500 cell/mcl), the dose may be modified or withdrawal; b) ESAs included darbepoetin alfa (150-300 mcg SC every other week) and human recombinant Epo (40,000 to 60,000 SC units twice/week); c) Ring sideroblasts ≥15% in BM and EPO≤500 mU/Ml are predictive markers for better response. 1-2mcg/kg twice/week in the standard dose of G-CSF; d) Treatment failure is defined as loss of the response after 3 months. We must exclude iron deficiency. Response evaluation according to IWG; e) Criteria for IST are HLA-DR15 histocompatibility type, low risk, normal cytogenetics, hypocellular BM, and PNH clone. B) Proposed algorithm for high risk MDS (IPSS int-2, high; IPSS-R intermediate, high, very high; WPSS high, very high) management. IST: immunosuppressive treatment, HCT: Hematopoietic stem cell transplantation.

of aplastic anemia (AA), in which both equine and rabbit ATG are therapeutically equal.[43,44]

Recent data showed up to 5% of MDS had STAT3 mutant CTLC (cytotoxic T-lymphocyte clone) associated with hypo cellular BM, neutropenia, and HLA-DR 15 +ve. Although there were no survival benefits between mutant and non-mutant groups, STAT3-mutant may assist in persistently dysregulated autoimmune activation, responsible for BM failure in a subgroup of MDS patients.[45]

High intensity therapy

It includes chemotherapy and Hematopoietic stem cell transplantation (HCT). Owing to the high risk of therapy-related morbidity/mortality, the investigators still considering them in the state of trials. Numerous comparative studies and reviews failed to get standard of care chemotherapy, no one is superior over the other.[46]

Intensive chemotherapy

The eligibility criteria included; high count BM blasts to decrease the tumor burden, good PS with competent organs but with no available donor.[47]

Lack or absence of response to chemotherapy may be related to the high degree of multidrug resistance (MDR) in BM precursor cells in case of advanced MDS. So more efforts are needed to discover new therapeutic agents to overcome MDR in the field of hemato-oncology.

Hematopoietic stem cell transplantation

The results of HLA matched sibling and unrelated donors are comparable. With the growing use of hypo identical related donor and cord blood donor, HCT became a reasonable election for many patients. While the RIC is accepted option for frail elderly patients, the high dose is the standard for fit and young.[48]

Many studies reported the age is not the only element to determine the treatment eligibility.[49,50] A prospective study done on high risk MDS patients showed there was no association between the age and PFS, OS, and non-treatment failure mortality.[51]

Based on data from previous studies, RIC is better to be used in age between 55-65 years and blasts count in BM is less than 10%.[52]

Regarding the best time for transplantation, through Markov analysis and based on IMRAW database, the investigators concluded the longest life expectancy with HCT when applied to patients with IPSS int-2 and high risk with age ≤60 years. Whereas in low risk, the best outcome when delayed till disease progression.[53]

Using of hypomethylating therapy is accepted option as bridge therapy as discussed before, but it should not a cause to delay BMT.

In case of relapse after prolonged remission post HCT, we have 2 options either to repeat it or consider donor lymphocyte infusion. The timing of transplantation is still a matter of debate, either after induction with chemotherapeutic agents or without, waiting for comparative studies to solve these issues.[54]

Nonintensive therapy

In high-risk MDS patients with lack of donor or not candidate for intensive therapy, the hypomethylating agents/clinical trials are suitable options. Data from comparative trials evaluation Aza C and decitabine vs best supportive care, reported improvement in platelet and neutrophil count, AML transformation, and PFS in the treated arm.[55]

Summary of recommended approaches

MDS is a heterogeneous disease, the blasts count is not the only determining factor in treatment selection. Based on scoring systems, we should put the patient in a low or high-risk group category. Low risk includes IPSS low, intermediate; IPSS-R or WPSS, very low, low or intermediate. High risk includes IPSS intermediate-2, high; IPSS-R intermediate, high, very high; WPSS high, very high.

FDA approved drugs in that field include; lenalidomide mainly in 5q-syndrome, hypomethylating agents (Aza C and decitabine) for high risk MDS patients with lack of donor or not a candidate for intensive therapy. In addition to iron chelating agents (deferoxamine and deferasirox. Supportive care is the hallmark in disease management irrespective the risk stratification.

Figure 1 illustrates the proposed algorithm for management of MDS both low and high-risk category.

Future direction

Luspatercept (ACE-536) is a fusion protein acts through modification of Act RII (activin II receptor) leading to change in TGF (transforming growth factor signals) with subsequent improving the erythropoiesis.[56] In a phase III trials comparing luspatercept vs placebo (ClinicalTrials.gov.NCT02631070) for the treatment of anemia in low risk MDS. This trial completed accrual in 2017 and waiting for the results.

Many drugs are under evaluation in a lot of trials aiming to increase the field of options to improve the outcome in patients with MDS. These include rigosertib, luspatercept, venetoclax, imetelstat and immune checkpoint inhibitors. Moreover, there are 3 novel hypomethylating agents currently under investigation in clinical trials in MDS management. Guadecitabine, antimetabolite of decitabine with anti-tumor activity (previously named SGI-110), CC486 is an oral form of azacitidine, and cedazurine (previously named ASTX727), is a combination of a cytidine deaminase inhibitor and decitabine, orally administered in fixed-dose.[57] APR-246, a TP53 modulator is currently under research to restore its activity (ClinicalTrials.gov NCT03072043).

Due to the lack of effective treatment in a considerable subset of MDS patients, clinical trials still a reasonable option in many situations. New therapeutic agents and more advances are needed to improve the outcome.

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