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Review Article

# Targeted Therapy in Myelodysplastic Syndrome

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## Abstract

Myelodysplastic syndrome is a heterogeneous category of hematologic disorders that has been recognized primarily by abnormal morphology and number of blood cells originating from hematopoietic stem cells in the bone marrow based on the genetic as well as epigenetic changes in the hematopoietic stem cells. Its frequency is increased by aging, emphasizing the role genetic and epigenetic factors in its occurrence and most of the cases have been diagnosed at the age of 65 and higher. Marked genetic abnormalities as the cause of the syndrome and the old age of the patients make it a difficult category of hematologic disorders from therapeutic point of view. However, the disease is not limited to the elder adults and pediatric patients with Myelodysplastic disorders have been diagnosed with the median age of 6 years with a significantly less frequency. Chemotherapy has been applied as the only therapeutic option in these patients with variable response rate and duration of response. However, further basic investigation addressing the molecular aspects and the pathogenesis of MDS categories has clarified its association with certain genetic mutations and signaling pathways; hence opening new opportunities in MDS treatment. . In this paper, we will discuss the current concept and trends of targeted therapies for Myelodysplastic syndrome.

***Keywords:*** *Myelodysplastic syndrome; Immunotherapy; Refractory anemia; Targeted therapy*

## Introduction/Epidemiology

Myelodysplastic syndrome (MDS) is a heterogeneous group of hematologic disorders that is characterized by refractory anemia accompanied with a spectrum of different cytogenetic abnormalities. According to the National Cancer Institute in 2014, it was estimated that there were more than 10,000 new cases diagnosed. Compared to the rest of the world, western countries have the highest incidence rate of this disease. [1] Myelodysplastic syndrome represents an age-standardized rate incidence of 4.1 per 100,000. [2].

Myelodysplastic syndrome includes different types of histopathological and genetic characteristics. There is a predominance of male over female (2:1), with higher incidence observed in a median age of 71. [3] The etiological factors, which may increase the risk of Myelodysplastic syndrome, are congenital syndromes like Down's syndrome, Fanconianemia, dyskeratosiscongentia, Schwachman-Diamond syndrome, and neurofibromatosis [3].

Exposure to benzene and other industrial solvents may lead to the development of MDS. [3] Some therapies such as radiation treatment, alkylating agents including chlorambucil, cyclophosphamide, melphalan and other chemotherapy agents, may increase the risk of MDS. [3] Population studies done in the US have found that the annual incidence rate increases from 1 per 100,000 people younger than 50 years to 44.5 per 100,000 people older than 80 years [4].

**Pathophysiology/Molecular basis**

MDS has been categorized in at least six distinct categories. The following classification is by for the last classification that has been proposed by WHO:

a. Refractory cytopenia with unilineage dysplasia (that has been previously referred as refractory anemia, refractory neutropenia, or refractory thrombocytopenia) and has been diagnosed in less than 5 percent of the patients' population,
b. Refractory anemia with ring sideroblasts that is another rather uncommon subtype with the frequency of less than 5 percent,
c. Refractory cytopenia with multiline age dysplasia as the most common subtype that is reported in around 70 percent of the cases,
d. Refractory anemia with excess blasts that is somehow difficult to be distinguished from primary acute leukemia and is the second most frequent subtype, reported in 25 percent,
e. MDS with isolated del(5q), a distinct category mostly diagnosed in female patients unlike other subtypes of MDS and is found in 5 percent,
f. MDS, unclassified that is reported in less than 5 percent of the cases and cannot be categorized in any of the mentioned groups.

Childhood MDS is considered a distinct entity in the WHO classification system. The main category of the pediatric MDS is "Refractory cytopenia of childhood" that accounts for approximately half of childhood MDS and is the most common subtype in this setting.

Both genetic and epigenetic alterations are considered as the basic molecular pathogenesis of the disease, affecting the proliferation, maturation, and apoptosis of the hematopoietic cells originating from bone marrow stem cells. MDS is a clonal disease resulting from multiple genetic mutations as well as global DNA hypomethylation and concomitant hypermethylation of gene-promoter regions compared to the normal hematopoietic cells throughout the genome. Among the genetic mutations, ASXL1, TP53, DNMT3A, RUNX1, and genes that are components of the 3' RNA splicing machinery (eg, SF3B1, U2AF1, SRSF2, ZRSR2, and U2AF35) are the most commonly affected genes. Somatic mutations in the SF3B1 gene that encodes components of the RNA splicing machinery occurs in 60 to 80 percent of the MDS subtype refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis (RARS-T) [5].

Chemotherapy is also another etiologic factor for genetic abnormalities and is considered as a potential etiology causing MDS. Alkylating agents as well as topoisomerase II inhibitors are the main chemotherapeutic drug categories with known etiologic correlation with MDS. In this secondary chemotherapy associated MDS (therapy related MDS, t-MDS), chromosomal translocation t(5;12) (q33;p13) is found as a common chromosomal abnormality. Translocation of 11q23 is present in t (11;19) (q23;p13.1) and t (11;16) (q23;p13), which generate MLL/MEN (ELL) and MLL/CBP chimeric genes, respectively. However, these mutations are detected in both primary and therapy-related MDS. Another chromosomal abnormality in t-MDS is the t (3;21) (q26;q22) [5]. These treatment associated subtypes of the MDS are considered poor prognosis and rarely respond to the available therapeutic modalities.

There are three main epigenetic events, which regulate tumor-associated genes: [6]

a. The aberrant hypermethylation of tumor suppressor genes.
b. Post-translational modifications of histones.
c. Post-transcriptional modifications by regulatory miRNA.

**Prognosis in MDS**

Based on the cytogenetic aspects of the disease and the severity of bone marrow involvement, several prognostic scoring systems has been introduced. The importance of these prognostic scoring systems is not only to have the estimation of the duration of survival, but to have a guideline for choosing therapeutic decisions based on the extent of the disease and the impact of the genetic abnormality on the natural history of the disease. The International Prognostic Scoring System (IPSS) has been classically applied in MDS patients; however, the latest by far most accurate scoring system is the revised IPSS that has been suggested and applied. The IPSS-R is summarized in the following table:

**Targeted therapy in MDS**

Based on the molecular pathogenesis of the MDS several lines of targeted therapies have been proposed and validated in the setting of clinical trials. Most of these targeted therapies have been focused on the genetic alteration, epigenetic hypermethyltion of the gene promoting regions and activating cell mediated cytotoxicity immune response against abnormal, genetic altered clone of proliferating MDS cells. Some of these drugs have gained FDA approval and many of them are in early phase clinical studies and their safety and efficacy is under further clinical evaluation. The targeted therapeutic options of the MDS are classified in the following categories;

**A. Immunomodulators**

**1. Lenalidomide**

Lenalidomide is a thalidomide analogue, indicated for the treatment of patients with transfusion-dependent anemia due to low or intermediate-1-riskMDS.It is also approved for the treatment of MDS patients with isolated Del (5q), a distinct subtype of MDS [7].

There are several mechanisms of action that has been suggested for the therapeutic effect of lenalidomide in MDS. It has anti-inflammatory, anti-angiogenesis and immune modulatory role. Lenalidomide is involved in the activation of T cells, natural killer (NK) cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes, thereby, possessing immunomodulatory properties for MDS. Moreover, its anti-angiogenesis role has been mostly related to its therapeutic effect in myelodysplasia. It has been observed that vascular endothelial growth factor (VEGF) directly stimulates leukemia cell self-renewal and leukemia cells in turn, may excrete VEGF and express VEGF-receptors. In Del (5q) Myelodysplastic syndromes, the levels of VEGF and its receptor were significantly reduced in all complete responders to lenalidomide, and vascularization normalized. This observation and similar studies proves the role of VEGF as a prognostic factor for remission induction and remission maintenance and emphasize the anti-angiogenesis role of lenalidomide in the specific subtypes of MDS, respectively.

Warnings include embryo-fetal toxicity, hematologic toxicity, and venous and arterial thromboembolism. Most common adverse reactions are thrombocytopenia, neutropenia, diarrhea, pruritus, rash, fatigue, constipation, nausea, nasopharyngitis, arthralgia, pyrexia, back pain, peripheral edema, cough, dizziness, headache, muscle cramp, dyspnea, pharyngitis, and epistaxis.

Despite the fact that lenalidomide has been approved for del 5q subtype of MDS, European Medicines Agency raised concern over a potential risk of AML progression caused by lenalidomide in some lower-risk MDS with del 5q and has requested further analyses. However, the 3 available retrospective analyses comparing the long-term outcome of lower-risk MDS with Del 5q treated with and without lenalidomide have found no excess risk of AML with its administration.

**The Immunomodulators that are under clinical trials in Phase I–III are mentioned in Table 1 below**

**1. Thalidomide**

Thalidomide acts primarily by inhibiting both the production of tumor necrosis factor alpha (TNF-alpha) in stimulated peripheral monocytes and the activities of interleukins and interferons. This agent also inhibits polymorphonuclear chemotaxis and monocyte phagocytosis. In addition, thalidomide inhibits pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), thereby inhibiting angiogenesis.

**2. Pomalidomide**

Pomalidomide is an immunomodulatory agent with antineoplastic activity. It enhances the immune response, which kill cancer cells. It is shown to inhibit proliferation and induce apoptosis of various tumor cells.

**B. Monoclonal Antibodies**

There are other MABs that are not currently approved by FDA for MDS. However, many MABs are under clinical trials in phase I, II, and III as in Table 2 below. Most of these monoclonal antibodies target the inflammatory cytokines while others directly aim the specific myeloid cells by targeting myeloid specific surface antigens such as CD45 and CD56. Conjugating chemotherapeutic agents or

radioisotope with these monoclonal antibodies theoretically potentiates their efficacy through a synergic effect either by facilitating the entrance of the chemotherapeutic agents within abnormal cells or through exposing these targeted cells to the radioisotopes.

| Drug | Clinical Trial Identifier Number | Phase | Study Design | Target |
|---|---|---|---|---|
| Thalidomide | NCT00015990 | Phase II | Safety/Efficacy study, Open label | TNF-alpha |
| Pomalidomide | NCT02029950 | Phase I | Safety Study, Open Label | Protein Cereblon |

***Table 1:*** *Non-FDA approved immunomodulators [8, 9].*

**1. Siltuximab**

This is a monoclonal antibody with anti-neoplastic, anti-inflammatory and anti-tumor activity. It binds to and targets to IL-6 and inhibits the IL-6/IL-6R-mediated signal transduction pathway [10].

**2. Infliximab**

Infliximab is a monoclonal antibody with anti-neoplastic activity that targets TNF-alpha [11].

**3. Iodine I 131 Monoclonal Antibody BC8**

This is a radio-immunoconjugate consisting of BC8, a murine IgG1 anti-CD45 monoclonal antibody labelled with iodine 131 (I-131), with radio-immunotherapeutic properties. Using the monoclonal antibody, BC8, as a carrier for I-131 results in the targeted destruction of cells expressing CD45. CD45 is tyrosine phosphatase expressed on virtually all leukocytes including myeloid and lymphoid precursors in bone marrow and mature lymphocytes in lymph nodes. It is also expressed on most myeloid and lymphoid leukemic cells but not on mature erythrocytes or platelets [12].

**4. Ipilimumab**

Ipilimumab is a monoclonal antibody directed against cytotoxic, T-lymphocyte-associated antigen-4 (CTLA4), which is an antigen that is expressed on activated T-cells and exhibits affinity for B7 co-stimulatory molecules. By binding CTLA4, ipilimumab enhances T-cell activation and blocks B7-1 and B7-2 T-cell co-stimulatory pathways [13].

**5. Basiliximab**

This acts as an IL-2 receptor antagonist. It binds and blocks the activity of IL-2R alpha that is expressed on the surface of activated T-lymphocytes. As a result of this, it prevents interleukin-2-binding and inhibits the interleukin-2-mediated activation of lymphocytes [14].

**6. CDX-1401**

This is a fusion protein consisting of a fully human monoclonal antibody directed against the endocytic dendritic cell (DC) receptor, DEC-205, linked to the tumor-associated antigen (TAA) NY-ESO-1 with potential immune stimulating and antineoplastic activities. The monoclonal antibody moiety of DEC-205/NY-ESO-1 fusion protein CDX-1401 binds to the endocytic DC receptor, which may result in DC endocytic internalization of this agent, specifically delivering the NY-ESO-1 moiety. DC processing of NY-ESO-1 may boost the immune system to mount a cytotoxic T-lymphocyte response (CTL) against cancer cells expressing NY-ESO-1. NY-ESO-1, a cell surface protein expressed in normal fetal and adult testes, is upregulated in a variety of tumor cell types [15].

**7. KB004**

Study of the Anti-EphA3 Monoclonal Antibody KB004 in Subjects with Hematologic Malignancies (Myelodysplastic Syndrome, MDS, Myelofibrosis, and MF) is in phase II trial [16].

**8. Lorvotuzumab Mertansine**

[17] A study in patients with CD56 expressing hematological malignancies including, but not limited to AML, high-risk MDS, natural-killer leukemia, acute lymphoblastic leukemia, accelerated and blast-phase CML who have failed prior therapy or for which no standard therapy exist.

| Drug | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| Siltuximab | NCT01513317 | Phase II | Randomized, Double blind, Efficacy Study | IL-6 |
| Infliximab | NCT00074074 | Phase II | Randomized, Open label | TNF-alpha |
| Iodine I 131 Monoclonal Antibody BC8 | NCT00589316 | Phase II | Safety/Efficacy Study, Open Label | CD45 |
| Ipilimumab | NCT01822509 | Phase I | Safety Study, Open label | CTLA-4 |
| Basiliximab | NCT01842139 | Phase I | Efficacy Study, Open Label | IL-2R alpha |
| DEC-205/NY-ESO-1 fusion protein CDX-1401 | NCT01834248 | Phase I | SafetyStudy, Open Label | Endocytic DC-receptor |
| KB004 | NCT01211691 | Phase I | SafetyStudy, Open Label | EphA3 |
| Lorvotuzumab Mertansine | NCT02420873 | Phase II | Treatment, Open Label | CD56 |

***Table 2:*** *MAB drugs [10–17].*

**C. Kinase Inhibitors**

There are no kinase inhibitors that are currently approved by FDA for MDS. However, few kinase inhibitors are under clinical trials in phases I- III as shown in Table 3 below.

**1. Sorafenib**

Sorafenib blocks the enzyme RAF kinase, a critical component of the RAF/MEK/ERK signaling pathway that controls cell division and proliferation; in addition, sorafenib inhibits the VEGFR-2/PDGFR-beta signaling cascade, thereby blocking tumor angiogenesis [18].

**2. Vatalanib**

It is a kinase inhibitor with anti-neoplastic activity, which binds to and targets VEGFR-1 and VEGFR-2. It also inhibits RTK as well as PDGF receptor, c-Fms, and cKit [19].

**3. Sunitinib**

This is anindolinone-based tyrosine kinase inhibitor with potential antineoplastic activity. Sunitinib blocks the tyrosine kinase activities of vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor b (PDGFRb), and c-kit, thereby inhibiting angiogenesis and cell proliferation. This agent also inhibits the phosphorylation of Fms-related tyrosine kinase 3 (FLT3), another RTK expressed by some leukemic cells [20].

**4. Dasatinib**

Dasatinib is a small molecule-inhibitor of the SRC-family protein-tyrosine kinases. Dasatinib binds to and inhibits the growth-promoting activities of these kinases. Apparently, because of its less stringent binding affinity for the Bcr-Abl kinase, dasatinib has been shown to overcome the resistance to imatinib of chronic myeloid leukemia (CML) cells harboring Bcr-Abl kinase domain point mutations. SRC-family protein-tyrosine kinases interact with a variety of cell-surface receptors and participate in intracellular signal transduction pathways; tumorigenic forms can occur through altered regulation or expression of the endogenous protein and by way of virally-encoded kinase genes [21].

**5. WEE1 Inhibitor MK-1775**

This is a small molecule inhibitor of the tyrosine kinase WEE1 with potential antineoplastic sensitizing activity. MK-1775 selectively targets and inhibits WEE1, a tyrosine kinase that phosphorylates cyclin-dependent kinase 1 (CDK1, CDC2) to inactivate the CDC2/cyclin B complex. Inhibition of WEE1 activity prevents the phosphorylation of CDC2 and impairs the G2 DNA damage checkpoint. This may lead to apoptosis upon treatment with DNA damaging chemotherapeutic agents. Unlike normal cells, most p53-deficient or mutated human cancers lack the G1 checkpoint as p53 is the key regulator of the G1 checkpoint and these cells rely on the G2 checkpoint for DNA repair to damaged cells. Annulment of the G2 checkpoint may therefore make p53-deficient tumor cells more vulnerable to antineoplastic agents and enhance their cytotoxic effect [22].

**6. Binimetinib**

Binimetinib is a potent and selective inhibitor of MEK1/2, and has been studied in Treating Patients with Relapsed, Refractory, or Poor Prognosis Acute Myeloid Leukemia, Myelodysplastic Syndrome, or Acute Lymphoblastic Leukemia is in phase I/II [23].

**7. Rigosertib**

Rigosertib is a small molecule that inhibits cellular signaling in cancer cells by acting as a Ras mimetic. This is believed to be mediated by the binding of rigosertib to the Ras-binding domain (RBD) found in many Ras effector proteins, including the Raf (see video) and PI3K kinases. A Phase 2 Study of Oral Rigosertib in Combination with Azacitidine for MDS and AML Patients is under trial [24].

| Drug | Clinical trial identifier number | Phase | Study design | Target |
|---|---|---|---|---|
| Sorafenib | NCT00510289 | Phase II | Open label, Efficacy Study | VEGFR-2/PDGFR-beta signalling |
| Vatalanib | NCT00072475 | Phase II | Non-Randomized, Open label, Safety/Efficacy Study | VEGFR-1/2 |
| Sunitinib Malate | NCT00451048 | Phase II | Open label, Safety/Efficacy Study | VEGFR2, PDGFRb, FLT3, c-kit |
| Dasatinib | NCT01643603 | Phase I/II | Safety/Efficacy Study Open label | BCR-ABL,SRC |
| WEE1 inhibitor MK-1775 | NCT02381548 | Phase I | Safety Study, Open Label | cyclin-dependent kinase 1 (CDC2) |
| Binimetinib | NCT02089230 | Phase I/II | Treatment | MEK inhibitor |
| Rigosertib | NCT01926587 | Phase I/II | Biomarker/Laboratory analysis, Treatment | Ras-binding domain (RBD) |

***Table 3:*** *Kinase inhibitor drugs [18–24].*

**D. Proteasome inhibitor**

**1. Bortezomib**

Bortezomib reversibly inhibits the 26S proteasome, a large protease complex that degrades ubiquinated proteins. By blocking the targeted proteolysis, normally performed by the proteasome, Bortezomib disrupts various cell signaling pathways, leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis. Specifically, the agent inhibits nuclear factor (NF)-kappa B, a protein that is constitutively activated in some cancers, thereby interfering with NF-kappa B-mediated cell survival, tumor growth, and angiogenesis. This drug is in phase I trial as in Table 4 below [25].

**E. Hypomethylating agents**

Considering the hypermethylation of the gene promoter as one of the main molecular pathogeneses of the MDS, epigenetic therapeutic approach with hypomethylating agents has been suggested as an attractive treatment modality. Azacitidine and Decitabine are

hypomethylating agents that have already been approved for the treatment of low risk MDS patients. These two medications belong to the category of DNA methyltransferase inhibitors and has been administered both in oral and injection form in low risk MDS patients. Clinical trials combining these medications with other lines of treatment such as histone deacetylase inhibitors and lenalidomide are also ongoing to validate the safety and efficacy of these combination therapies in selected MDS patients [26].

| Drug | Clinical trial identifier no. | Phase | Study Design | Target |
|---|---|---|---|---|
| Bortezomib + Thalidomide | NCT00271804 | Phase I | Non-Randomized, Safety/ Efficacy Study, Open Label | 26S proteasome |

***Table 4:*** *Proteasome inhibitor [25].*

**F. Histone Deacetylase Inhibitors**

Similar to azacitidine and decitabine, this category of MDS treatment also targets gene activation/deactivation via epigenetic structures. It has been observed that histone acetylation patterns lead to altered folding of the nucleosomal fiber and making these chromosomal domains more accessible. Hence the transcription machinery may be able to access promoters followed by initiating transcription. Histone deacetylation may in turn reverse these changes, leaving the chromatin in a n dense less accessible position. Several anti-cancer mechanisms have been suggested and observed in histone deacetylase inhibitors. They might cause accumulation of acetylated forms of the protein substrates involved in regulation of gene expression, cell proliferation and cell death within cells. Furthermore, they are able to induce growth arrest, activation of the extrinsic and/or intrinsic apoptotic pathways and finally led to cell death. There are no Histone Deacetylase Inhibitors that are currently approved by FDA for MDS. However, few drugs of this class are under clinical trials in phases I-III as in Table 5 below.

| Drug | Clinical trial identifier no. | Phase | Study Design | Target |
|---|---|---|---|---|
| Entinostat | NCT00462605 | Phase II | Efficacy Study, Open Label | Histone deacetylase |
| Phenyl butyrate | NCT00006019 | Phase II | Open Label | Myelodysplastic cells |
| Valproic acid | NCT02124174 | Phase II | Efficacy Study, Open Label | Histone deacetylase |
| Romidepsin | NCT00042822 | Phase II | Treatment | Histone deacetylase |
| Vorinostat | NCT00875745 | Phase I | Safety Study, Open Label | Histone deacetylases |
| Belinostat | NCT02381548 | Phase I | Safety Study, Open Label | HDAC enzymes |

***Table 5:*** *Histone Deacetylase Inhibitors [26–31].*

**G. Other suggested therapies**

Various other therapies that are not approved by FDA for MDSand under clinical trial in phases I- III are listed in Table 6 below.

**1. Arsenic Trioxide:** This agent causes damage to or degradation of the promyelocytic leukemia protein/retinoic acid receptor-alpha (PML/RARa) fusion protein, induces apoptosis in Acute Promyelocytic Leukemia (APL) cells and in many other tumor cell types, promotes cell differentiation and suppresses cell proliferation in many different tumor cell types, and is pro-angiogenic [32].

**2. Erismodegib:** This is an orally, bioavailable, small-molecule Smoothened (Smo) antagonist with potential antineoplastic activity. Erismodegib selectively binds to the Hedgehog (Hh)-ligand cell surface receptor Smo, which may result in the suppression of the Hh signaling pathway, and the inhibition of tumor cells in which this pathway is abnormally activated. The Hh signaling pathway plays an important role in cellular growth, differentiation and repair. Inappropriate activation of Hh pathway signaling and uncontrolled cellular proliferation, as is observed in a variety of cancers, may be associated with mutations in the Hh-ligand cell surface receptor Smo [33].

**3. Everolimus:** Everolimus binds to the immunophilin FK Binding Protein-12 (FKBP-12) to generate an immunosuppressive complex that binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), a key regulatory kinase. Inhibition of mTOR activation results in the inhibition of T lymphocyte activation and proliferation associated with antigen and cytokine (IL-2, IL-4, and IL-15) stimulation and the inhibition of antibody production [34].

**4. Sargramostim:** Sargramostimisa recombinant therapeutic agent, which is chemically identical to or similar to endogenous human GM-CSF. Binding to specific cell surface receptors, sargramostim modulates the proliferation and differentiation of a variety of hematopoietic progenitor cells with some specificity towards stimulation of leukocyte production and may reverse treatment-induced neutropenia. This agent also promotes antigen presentation, up-regulates antibody-dependent cellular cytotoxicity (ADCC), and increases interleukin-2-mediated lymphokine-activated killer cell function; it may also augment host antitumoral immunity [35].

**5. Cytokines**

They directly stimulate immune effector cells and stromal cells at the tumor site and enhance tumor cell recognition by cytotoxic effector cells. Considering the cytopenia as the main clinical finding causing symptoms in MDS patients, growth factors stimulating the proliferation and differentiation of certain hematopoietic subtypes, such as platelet producing megakaryocytes, granulocyte producing colonies and erythroid precursors inducing red blood cells has been suggested as therapeutic options to reduce the need of the patients for blood and component transfusion. However, these treatment modalities might be administered in selected low risk patients. [36] The duration of response as well as the impact of these treatment modalities in overall survival is also different among different groups of MDS patients.

| rug | Clinical trial identifier no. | Phase | Study Design | Target |
|---|---|---|---|---|
| Arsenic trioxide | NCT00671697 | Phase I | Non-Randomized, Safety/ Efficacy Study, Open Label | Myelodysplastic cells |
| Erismodegib | NCT02129101 | Phase I | Safety/Efficacy Study | Hedgehog (Hh)-ligand cell surface receptor Smo |
| Everolimus | NCT00809185 | Phase II | Safety/Efficacy Study | Immunophilin FK Binding Protein-12 (FKBP-12) |
| Sargramostim | NCT01700673 | Phase II | Efficacy Study, Open Label | Granulocyte-macrophage colony-stimulating factor |
| Cytokine-Immunotherapy | NCT00520468 | Phase II | Non-Randomized, | |
| Safety/Efficacy Study, Open Label | Myelodysplastic cells | | | |

***Table 6:*** *Non FDA approved other drugs.*

**1. Hematopoietic stem cell transplantation**

Allogeneic stem cell transplantation is considered as the only potentially curative therapeutic option in patients with Myelodysplastic syndrome, especially in the high risk patients with poor prognostic cytogenetic features. However, most of the cases are elderly patients with co-morbidities that put them among the clinically unfit candidates for allogeneic stem cell transplantation. Advances in HSCT such as availability of cord blood or haploidentical donors as well as novel reduced-intensity conditioning allogeneic stem cell transplantation (mini- transplant) approaches in older patients and those with comorbidities, and graft manipulation with post-HSCT azacitidine or with specific immunotherapies all may increase the rate of HSCT use. However, many questions need to be addressed about optimal approaches to MDS treatment before transplant, donor selection, conditioning regimen, and post-transplant therapy to prevent relapse and increase overall and disease free survival while minimizing the transplant associated morbidities and mortalities in MDS patients.

**Conclusion: please elaborate more**

Myelodysplastic syndrome is a heterogeneous classification of the hematologic disorder that is mainly recognized by the presence of refractory anemia combined with any cytopenia reported in other marrow derived hematopoietic cells such as platelets and white blood cells. The disease mainly affects old age adults but cases among pediatric patients have been reported. The main pathogenesis of the disease in the cytogenetic abnormalities and epigenetic changes that has led to abnormal proliferation and differentiation of hematopoietic derived blood cells. Anemia, thrombocytopenia and inadequate neutrophils are the general MDS associated symptoms and abnormal cytogenetic change in the MDS clone eventually lead to malignant transformation into overt leukemia. However, the median transformation time is different among categories of the MDS based on the prognostic features classified as revised international prognostic scoring system (r-IPSS) hence; the therapeutic approach to these patients varies based on the IPSS as well as the age and the co-morbidities from supportive transfusion of blood and hematopoietic cells to the curative allogeneic stem cell transplantation approach. Immune mechanisms have been suggested to have an impact on the disease promotion and immune therapies such as immune suppressive ATG and Alemtuzumab has been tried in low risk MDS cases with survival benefit. Moreover, the recent advances in molecular pathogenesis of MDS and its categories have suggested multiple potential targeted therapeutic approaches that need to be further validated through clinical studies. Additionally, combining these therapeutic modalities may result in the higher response rates and longer duration of survival while minimizing the treatment associated adverse events. Proper preclinical and clinical designs are the important pillars in understanding the future of targeted therapies in treating MDS patients.

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