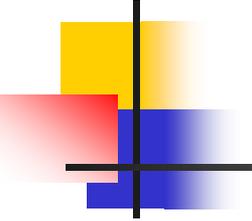


MYELOYDYSPLASIA

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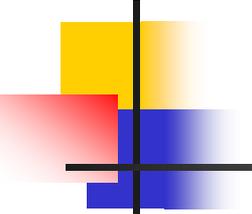
Myelodysplastic Syndromes (MDS)

Group of blood disorders that affect the production of normal blood cells in the bone marrow leading to abnormal cellular maturation and low blood counts.

Incidence of **Primary MDS: 2-4 pts/100,000~10,000 population.
~10,000 new cases/year in US**

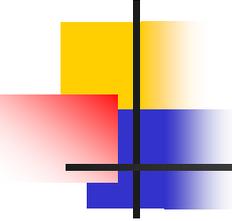
Therapy related MDS. Post chemotherapy or radiation

Risk of progression to an Acute Leukemia (“preleukemia”)



Myelodysplastic Syndromes (MDS)

- **Abnormal bone marrow stem cells (*blast* cells) do not grow properly and often die prematurely.**
- **Bone Marrow is Dysplastic (delayed and distorted maturation and development of the blood cells)**
- **Results in lower numbers of mature blood cells produced (Anemia, Thrombocytopenia, Leukopenia)**
- **The blood cells that do survive are often of poor quality (*dysplastic*) and unable to function properly.**
- **The release of these abnormal cells from the bone marrow into the blood stream is also defective.**
- **Bone marrow may look very active but have a low number of circulating blood cells.**
- **Present with symptoms related to cytopenias (weakness, fatigue, infections, bleeding)**



MDS

- There are different types of MDS and the disease can vary in its severity and the degree to which normal blood cell production is affected. People with mild disease are often found to simply be anemic, or they might have a lower than normal white blood cell or platelet count, but in many cases they have few, if any, troubling symptoms from their disease. In more severe cases, the lack of circulating blood cells is more pronounced, causing more symptoms

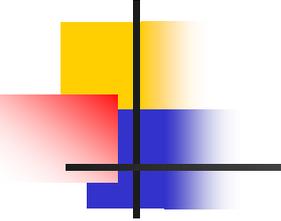
World Health Organization MDS classification system

Disease	Marrow blasts	Clinical presentation	Cytogenetic abnormalities
Refractory anemia (RA)	<5 percent	Anemia	25 percent
RA with ring sideroblasts (RARS)	<5 percent	Anemia, ≥ 15 percent ringed sideroblasts in erythroid precursors	5 to 20 percent
MDS with isolated del (5q) (5q-syndrome)	<5 percent	Anemia, normal platelets	100 percent
Refractory cytopenia with multilineage dysplasia (RCMD)	<5 percent	Bicytopenia or pancytopenia ± 15 ring sideroblasts	50 percent
Refractory anemia with excess blasts-1	5 to 9 percent	Cytopenias +/- peripheral blood blasts (<5 percent)	30 to 50 percent
Refractory anemia with excess blasts-2	10 to 19 percent	Cytopenias, peripheral blood blasts present	50 to 70 percent
Myelodysplastic syndrome, unclassified	<5 percent	Neutropenia or thrombocytopenia	50 percent

MDS: myelodysplastic syndrome.

Source: Vardiman, JW, Brunning, RD, Arber, DA, et al. Introduction and overview of the classification of myeloid neoplasms. In: WHO classification of tumors of hematopoietic and lymphoid tissues, Swerdlow, SH, Campo, E, Harris, NL, et al. (Eds), WHO Press, 2008, p.18.

IPSS for MDS: Survival and AML Evolution



Variable	Score				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	<5	5-10	-	11-20	21-30
Karyotype*	Good	Intermediate	Poor	-	-
Cytopenias•	0/1	2/3	-	-	-

SCORES FOR RISK GROUPS:

Low = 0; INT-1 = 0.5-1.0; INT-2 = 1.5- 2.0; and High \geq 2.5

* KARYOTYPE:

Good = normal, -Y, isolated del (5q), Del (20q)

Poor = complex (> 3 abnormalities) or chromosome 7 abnormalities

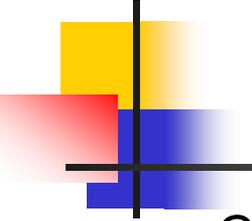
Intermediate = other abnormalities.

• CYTOPENIAS DEFINITIONS:

Red blood cells: Hemoglobin <10 g/dL (100 g/L)

White blood cells: Absolute neutrophil count <1800/ μ L

Platelets: Platelet count <100,000/ μ L



CHROMOSOMES IN MDS

Clonal chromosomal abnormalities can be detected in 40-70% of cases with **Primary MDS**:

Complex karyotype (18%)

Del (5q) (6%)

Trisomy 8 (4%)

del (20q) (3%)

Trisomy 11 (0.3%)

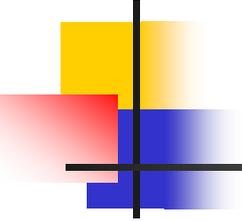
Chromosome changes can be predictive of outcome:

Good = normal, -Y, isolated del (5q) or Del (20q)

**Poor = complex (> 3 abnormalities) or chromosome 7 abnormalities
(also trisomy 11)**

Intermediate = other abnormalities

Aberrant DNA methylation has been demonstrated in a multitude of genes in patients with MDS (?proapoptotic)



MDS TREATMENTS

(Consider symptoms, age, IPSS, clinical status of pt)

Transfusions (Iron chelation if freq RBC tx)
Growth factors (Epo, GCSF, thrombopoietins)
Antibiotics for infections

Lenalidomide (best for 5Q-, and low IPSS scores)
Azacytadine, Decitabine (Hypomethylating agents)

Pyridoxine (Vit B6) for RARS
Hypocellular MDS : ATG, Cyclosporine

CMML: Hydrea, Decitabine, other chemotherapy
(Imatinib if have t(5;12) or PDGFRB fusion gene abnormalities)

Intensive chemotherapy (AML regimens) if transforming to AML

Allogeneic Hematopoietic Stem Cell Transplantation (only curative rx)

REFRACTORY ANEMIA 5Q MINUS (5Q-) SYNDROME

**A DISTINCTIVE TYPE OF PRIMARY MDS THAT PRIMARILY OCCURS
IN OLDER WOMEN**

ISOLATED 5Q MINUS CYTOGENETIC ABNORMALITY

MEDIAN AGE AT DIAGNOSIS IS 65-70 YEARS

FEMALE PREDOMINANCE OF 7:3

(INCONTRAST TO MALE PREDOMINANCE ON OTHER FORMS OF MDS)

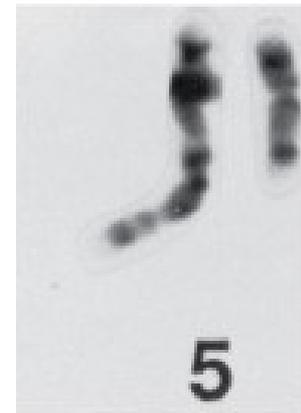
TYPICALLY PRESENT WITH:

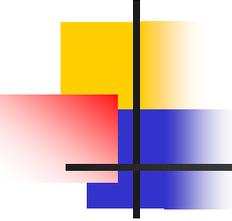
**REFRACTORY MACROCYTIC ANEMIA,
NORMAL OR INCREASED PLATELET COUNTS AND
NO SIGNIFICANT NEUTROPENIA**

GOOD RESPONSE RATE (~80%) WITH LENALIDOMIDE

**Haploinsufficiency of a ribosomal protein (RPS14) leads to a ribosomal processing defect
(analogous to the functional ribosomal defect in Diamond Blackfan)**

MicroRNAs and other genes on 5q also being implicated.

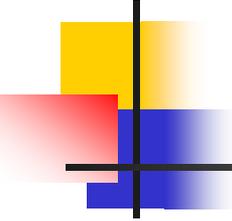




HYPOMETHYLATING AGENTS

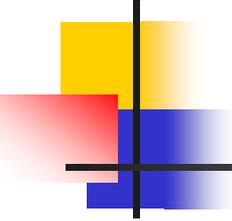
(AZACYTIDINE, DEOXYCYTIDINE)

- **METHYLATION OF GENES IS IMPORTANT FOR THEIR ACTION.**
- **IN MDS THE METHYLATION PATTERN IS ABNORMAL**
- **METHYLATION STATUS MAY CONTRIBUTE TO THE ALTERED GROWTH AND DIFFERENTIATION OF MDS CELLS**
- **SEVERAL GENES THAT REGULATE METHYLATION ARE ABNORMAL IN MDS**
- **DRUGS THAT INTERFERE WITH METHYLATION (AZACYTIDINE, DEOXYCYTIDINE) CAN BE EFFECTIVE IN MDS**



UPDATE ON HYPOMETHYLATING AGENTS

- **Lower dose Decitabine:** Non-cytotoxic doses of Demethylating agents can relieve repression of some differentiation genes in the lab
Reported on the first 15 patients. Median time to nadir was 40 days. Complete hematologic and cytogenetic remission with persistent dysplasia occurred in 2 subjects. Hematologic improvement in 4 subjects. (ORR 40%) And stable disease in 7 pts. No or minimal side effects.
- **Compared Azacitadine and Decitabine:**
Both were effective (~60%), and low side effects, but some minor differences:
Decitabine better in IPSS low/intermediate, duration <1 yr, or excellent performance status.
Azacitidine better in MDS duration >1 yr.
- **Aza for therapy related MDS.** Azacitidine is active in t-MDS; response rates are comparable to de novo MDS patients. Overall survival for t-MDS treated with azacitidine is slightly inferior to de novo MDS treated on AZA-001 study in general but similar to those with poor karyotype on the same study.
- **Aza for 5q- after Lenolidomide failure.** Response rates are similar to those reported in non-del(5q) patients providing azacitidine as an effective option for salvage treatment.
In another group: 40% of the patients with lower risk MDS and del 5q who progressed under LEN could be salvaged by AZA



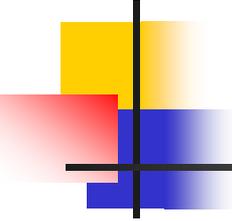
Newer agents in early trials

■ **Panobinostat (LBH589):**

Panobinostat is a pan-deacetylase inhibitor (pan-DACi) (Histone Deacetylase inhibitors can effect cell turnover and differentiation):

Preclinical studies suggest a combination of AZA and a pan-DACi may have synergistic Effects on gene reactivation and apoptosis induction

- To investigate the safety, tolerability and preliminary efficacy of combining the oral pan-DACi panobinostat (LBH589) with azacitidine in previously untreated MDS or AML, not fit for standard induction therapy. (Tan et al, multi-international trial)
In previously untreated MDS/AML Panobinostat and Azacitidine is well tolerated and preliminary assessments demonstrate clinical activity. Further evaluation of this combination with panobinostat 30mg dose is ongoing in the dose-expansion phase of the study.
- Determination of a Phase II Dose of Panobinostat in Combination with 5-Azacitidine in Patients with MDS, CMML, AML (Ottmann et al, multinational trial).
31 patients. Showed that oral panobinostat at 30 mg/day on days 1, 3, 5, 8, 10, and 12 of a 28-day cycle can be safely combined with AZA (75 mg/m² sc) on days 1-7. Additional studies will further characterize the safety profile and activity at the 30-mg dose level. Preliminary efficacy shows that CR/CRi was achieved in 4 pts, SD was achieved in 6 pts, and hematologic improvement was observed in 4 pts.

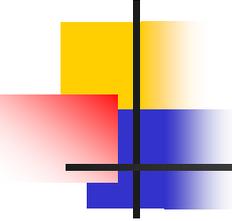


Newer agents in early trials

Ezatiostat is a glutathione analog. Has been shown to stimulate the multilineage differentiation of hematopoietic progenitors in vitro and overcomes the block in myeloblast differentiation (ineffectivemyelopoiesis) in leukemia cell line

- **Phase 1 Dose-Ranging Study of Oral Ezatiostat Hydrochloride (Telintra®, TLK199) in Combination with Lenalidomide (Revlimid®) in Patients with Non-Deletion(5q) Low to Intermediate-1 Risk MDS.** (Raza et al, multicenter trial) Based on the novel mechanism of action, response rates, non-overlapping toxicities, and tolerability observed in a single agent ezatiostat Phase 2 study in MDS, a study of the combination of ezatiostat and lenalidomide was conducted to determine the safety and efficacy of ezatiostat with lenalidomide in **non-del(5q) Low to Int-1 risk MDS.**

18 Patients. Saw some reductions in RBC and platelet transfusions, including RBC and platelet transfusion independence. reductions in RBC and platelet transfusions, including RBC and platelet transfusion independence. Since ezatiostat is non-myelosuppressive, it is a good candidate for combination with lenalidomide and in this study, the combination was well tolerated. Ezatiostat may also have the potential to enhance lenalidomide's efficacy. They found the recommended doses of this combination regimen for future studies is the ezatiostat/lenalidomide 2000/10 mg.



Newer agents in early trials

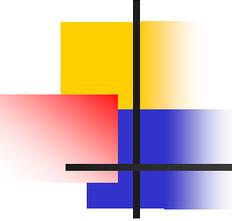
Rigosertib (ON 01910.Na) is a multi-kinase inhibitor that selectively induces mitotic arrest leading to apoptosis in cancer cells and myeloblasts, while being relatively non-toxic to normal cells.

- **Final Phase I/II Results of Rigosertib (ON 01910.Na) Hematological Effects in Patients with Myelodysplastic Syndrome and Correlation with Overall Survival (Raza et al, multicenter trial).**

60 patients. Rigosertib infusions were well tolerated without evidence of bone marrow myelotoxicity. Hematologic improvement was seen in some patients. These results have led to the initiation of a randomized Phase III trial of rigosertib 3-day CIV infusions vs best supportive care in RAEB - 1, -2 and -t pts who failed or progressed after receiving hypomethylating agents.

- **Oral Formulation of Rigosertib (ON 01910.Na) in Patients with Myelodysplastic Syndrome (MDS) – Phase I Study Results (Komrokji, et al. Multicenter trial)**

33 MDS patients were enrolled in this phase I dose escalating study of a novel oral formulation of rigosertib. Encouraging signs of activity were observed, including two marrow CR responses at the 140 and 560 mg dose levels; erythroid response (reduction of at least 4 units of RBC transfusions over 56 days) in four Low/Int-1 risk transfusion dependent MDS patients (3 at 560mg and 1 at 700 mg dose levels). Oral rigosertib is bioavailable and well tolerated. The recommended phase II dose will be: 560 mg bid for 2 weeks of a 3 week course. Early encouraging responses are being confirmed in the expansion phase of the study.



THROMBOCYTOPENIA IN MDS

Romiplostim is a Thrombopoietin (TPO)-Receptor Agonist that can increase platelet production

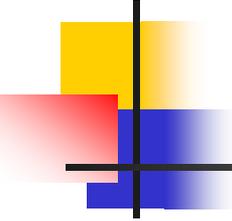
- **Romiplostim in Thrombocytopenic Patients (Pts) with Low or Intermediate-1 (Int-1) Risk Myelodysplastic Syndrome (MDS): Placebo controlled.**
(Giagounidis, et al Multinational study)

250 Patients. Improvement in platelet counts was seen in 37% of the patients receiving the romiplostim. More platelet transfusions were required and a trend for more clinically significant bleeding events in the placebo group.

Increases in peripheral blasts >10% occurred more frequently with romiplostim (although generally resolved after romiplostim discontinuation) but concern caused closure of study. Awaiting longer followup to see if any difference in the leukemia transformation.
- **Update of an Open Label Extension Study Evaluating the Long-Term Safety and Efficacy of Romiplostim in Thrombocytopenic Patients with MDS.**
(Fenaux et al. Multinational trial)

72 patients. Had been on prior studies. Median treatment duration during this extension study was 28 weeks (range: 2-181 weeks); for those patients who received romiplostim in prior studies, there was additional exposure for a median of 52 weeks (range: 7-74 weeks).

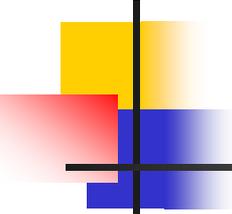
Long-term treatment of MDS patients with romiplostim for up to 3.5 years (5 years with prior studies) was well tolerated and resulted in platelet responses in 83% of patients. Among patients in this extension study, AML progression occurred at expected rates.



SMOKING & MDS

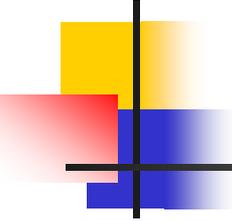
(Moffitt Cancer Center)

- Several epidemiologic studies suggest a linkage between smoking history and risk of myelodysplastic syndromes (MDS). They investigated the effect of smoking on disease outcome. The adverse effect of smoking was greatest in low and intermediate-1 IPSS risk groups where median OS was 69 months (95%CI= 42-96) in never smokers compared to 48 months (95%CI= 41-55) in smokers ($p=0.006$). The median OS was 69 mo (95%CI =42-96), 50 mo (95%CI= 43-57), and 38 mo (95%CI= 23-53) respectively in never-smoker, former-smoker, and current smoker groups in lower risk MDS ($p=0.01$). No difference was observed in int-2 and high risk IPSS groups with a median OS of 22 months (95%CI =11.75-32.2) in never smokers and 18 months (95%CI =14.3-21.7) in the ever smoker group. ($p=0.89$). An adverse impact of smoking was observed in good and intermediate risk karyotypes but not in poor risk karyotypes. Among low/int-1 risk IPSS, the rate of AML transformation was 18.2% in ever smokers compared to 9.5% in non-smokers ($p=0.04$) while no difference in rate of AML transformation was observed in int-2/high risk IPSS MDS between the 2 groups.
- The study confirms a negative impact of tobacco use on disease natural history and OS in a large cohort of MDS patients.



MECHANISMS IN MDS

- MULTIGENE HAPLOINSUFFICIENCY DELETION OF PART OR ALL OF A CHROMOSOME RESULT IN INSUFFICIENCY OF SOME GENES (tumor suppressor genes or loss of normal differentiating genes).
- ALTERATIONS IN DNA METHYLATION
- MUTATIONS AFFECTING HISTONE FUNCTION (deregulation of cell turnover and survival)
- T-LYMPHOCYTE–MEDIATED inhibition of hematopoiesis occurs in some MDS patients (usually hypoplastic MDS) and contributes to cytopenias.



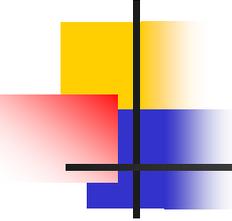
MECHANISMS IN MDS (2)

- **Possible new animal model and new targets:**

Role of inflammation in the abnormal hematopoiesis.

Patients with MDS have expansion of inflammation-related hematopoietic suppressive cells called immature myeloid-derived suppressor cells (MDSC) that can directly kill and suppress hematopoietic progenitor cells (HPCs). MDSC activation, expansion and development is driven by overexpression of inflammatory-related signaling molecules (especially MRP14). They generated S100A9 transgenic mice (S100A9Tg) overexpressing MRP14 and investigated the role of this protein in bone marrow failure. They saw many changes similar to human MDS, indicating that the microenvironment can be playing a role in the development of MDS.

S100A9Tg transgenic mice provide a novel animal model of human MDS for target discovery and testing of novel therapeutics.



MECHANISMS IN MDS (3)

- MDS patients exhibit downregulation of miR-146a, a miRNA that negatively regulates the innate immune pathway by targeting IRAK1 and TRAF6. Mice lacking miR-146a show elevated IRAK1 protein expression, and develop AML and MDS-like features resembling the human diseases.

They demonstrated IRAK1 overexpression in MDS patients by gene expression profiles.

They observed that Bortezomib, (but not Lenalidomide), inhibits IRAK1 mRNA and protein expression in MDS/AML cells and is cytotoxic. The cytotoxic effect of Bortezomib can be partly rescued by increasing IRAK1 in these cells. These findings are the first to implicate IRAK1 in the maintenance of myeloid malignancies and describe the effectiveness of an IRAK1 inhibitor on suppressing MDS and AML viability, suggesting possible treatment options and new targets.