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Management of Elderly and Frail Patients with Comorbidities and Myelodysplastic Syndromes (MDS): A Case Study

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I will describe our management of elderly and frail patients with comorbidities and MDS. Here, we will start by describing the clinical presentation and disease course of one of our patients, trying to focus some main points of the treatment algorithm with the accompanying supportive evidence. Then, after an overview of MDS diagnostic classification and prognostic assessment, I'll try to very briefly discuss the difficult topic of end-stage MDS management, supportive care, and end of life.

Mr. M. is an 82-year-old gentleman with a history of MDS associated with isolated del(5q), now progressed to refractory cytopenia with excess of blasts – type 2 (RAEB-2) after lenalidomide and azacitidine failure.

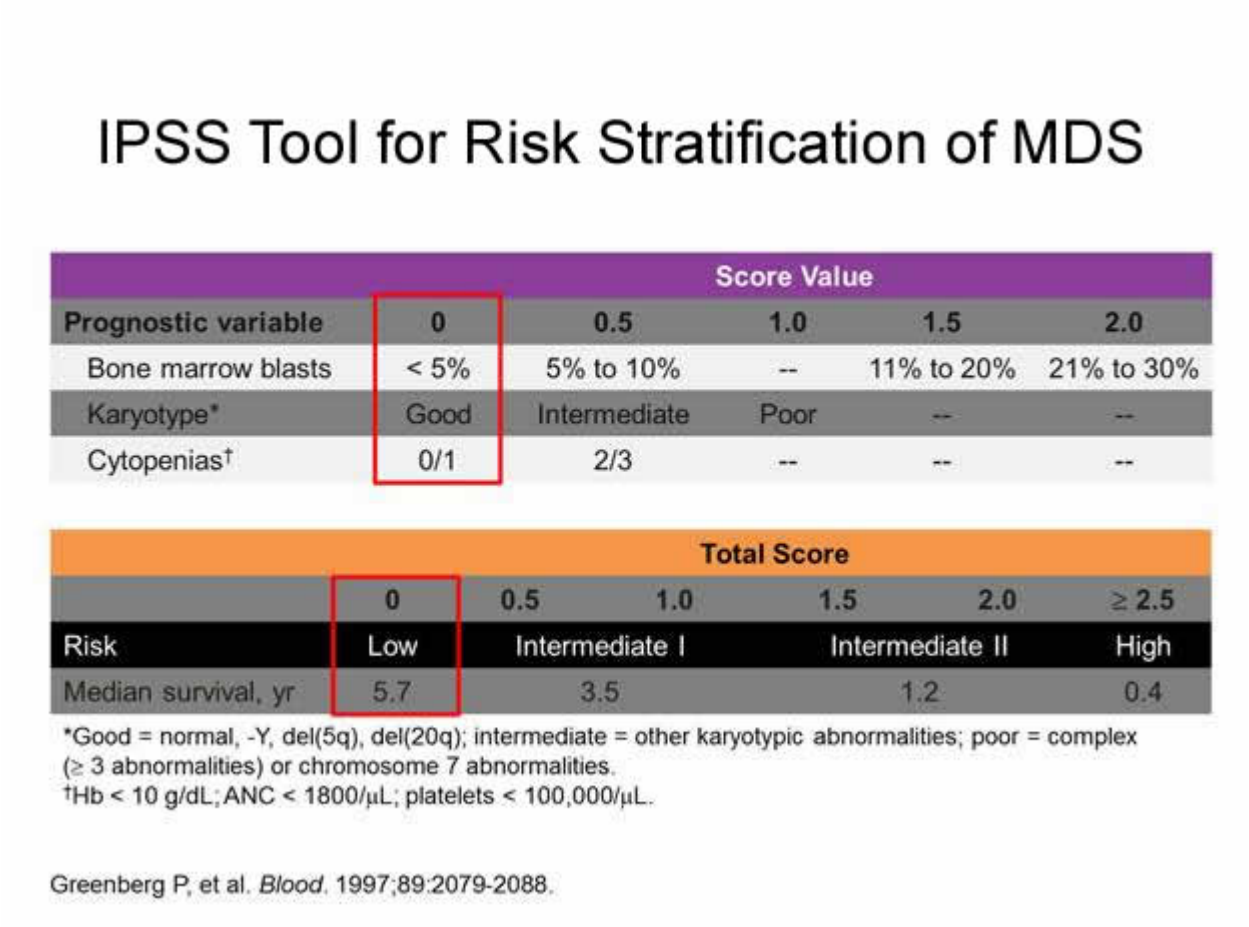
Initial Diagnosis and Staging

He presented in May 2009 with macrocytic anemia. His peripheral blood count revealed a white blood cell (WBC) count of 5,300/mm^3, absolute neutrophil count (ANC) 1,800/mm^3, hemoglobin 9.9 g/dL, hematocrit 28.7%, red blood cell volume (MCV) 106 fL, and platelet count 199,000/mm^3. No vitamin B-12, folic acid or iron deficiency was present. His past medical history was notable for hypertension, coronary artery disease (CAD) status post stent placement in 2001, history of bleeding ulcers, gastroesophageal reflux disease, glaucoma surgery, chronic renal insufficiency (moderate, glomerular filtration rate (GFR) of around 55%), and intermittent leg pain. The bone marrow biopsy and aspirate performed at that time showed a hypocellular marrow (20% of cellularity), myeloid:erythroid ratio 3:1, almost universally dysplastic megakaryocytes and no obvious dysplastic features on the other cell lines. No reticulin fibrosis was reported. Blasts by morphology on marrow aspirate were estimated at fewer than 3%. Abnormal blasts by flow cytometry represented 0.55% of the non-erythroid cells. The cytogenetics at that time were reported as normal on 20 out of 20 metaphases. Using the World Health Organization (WHO) 2008 classification[1] he was diagnosed with refractory cytopenia with unilineage dysplasia (RCUD).

Applying the International Prognostic Scoring System (IPSS) score, [2] Mr. M. scored 0 points because the blast count was lower than 5%, the karyotype was normal and only

one cytopenia was present (***Fig. 1***). This placed him in the low-risk group, with a median life expectancy of 5.7 years. I'll briefly describe this staging system next.

Figure 1. **International Prognostic Scoring System (IPSS) for MDS**



IPSS Tool for Risk Stratification of MDS

	Score Value				
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone marrow blasts	< 5%	5% to 10%	--	11% to 20%	21% to 30%
Karyotype*	Good	Intermediate	Poor	--	--
Cytopenias†	0/1	2/3	--	--	--

	Total Score					
	0	**0.5**	**1.0**	**1.5**	**2.0**	**≥ 2.5**
Risk	Low	Intermediate I		Intermediate II		High
Median survival, yr	5.7	3.5		1.2		0.4

*Good = normal, -Y, del(5q), del(20q); intermediate = other karyotypic abnormalities; poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.
†Hb < 10 g/dL; ANC < 1800/μL; platelets < 100,000/μL.

Greenberg P, et al. *Blood*. 1997;89:2079-2088.

Retrospectively applying the Revised-IPSS[3] that was developed and published in 2011, Mr. M. receives 1 point for the normal cytogenetics (***Fig. 2A and 2B***), 1 point for hemoglobin less than 10 g/dL, and 0 points for marrow blasts, platelets and ANC (***Fig. 2B***). Even with this newer scoring system, Mr. M. is considered to be in the "good" risk group, with an age-adjusted life expectancy of 5.3 years (***Fig. 2C***).

***Figure 2A*. Revised International Prognostic Scoring System (IPSS-R) for MDS – Cytogenetic Groups**

Cytogenetic Groups in the IPSS-R

Risk group	Included karyotypes (19 categories)	Median survival, months	Proportion of patients in this group
Very good	del(11q), -Y	60.8	2.9%
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	48.6	65.7%
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones	26.1	19.2%
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities	15.8	5.4%
Very poor	Complex with > 3 abnormalities	5.9	6.8%

Adapted with permission from Schanz J, et al. *J Clin Oncol*. 2012;30(11):820-829. Greenberg PL, et al. *Blood* 2012;120:2454-65.

***Figure 2B*. Revised International Prognostic Scoring System (IPSS-R) for MDS – Scoring**

Scoring for the IPSS-R

His Score = 2 by IPSS-R

Parameter	Categories and Associated Scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow blast proportion	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Abs. neutrophil count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			

Possible range of summed scores: 0-10

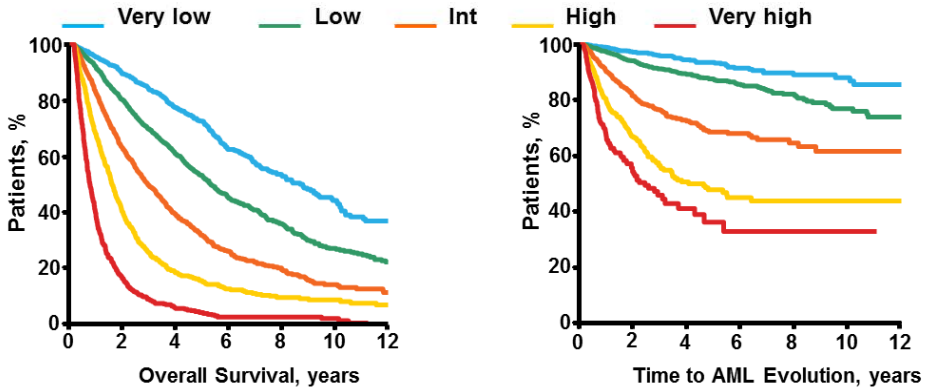
Adapted with permission from Schanz J, et al. *J Clin Oncol*. 2012;30(11):820-829. Greenberg PL, et al. *Blood* 2012;120:2454-65.

***Figure 2C*. Revised International Prognostic Scoring System (IPSS-R) for MDS – Prognosis for Different Risk Groups**

Risk Groups for the IPSS-R

His Score = 2 by IPSS-R

Risk group	Points	% of Patients	Median survival, years	Time until 25% of patients develop AML, years
Very low	≤ 1.5	19 %	8.8	Not reached
Low	> 1.5 – 3	38 %	5.3	10.8
Intermediate	> 3 – 4.5	20 %	3.0	3.2
High	> 4.5 – 6	13 %	1.6	1.4
Very High	> 6	10 %	0.8	0.73



Adapted with permission from Schanz J, et al. *J Clin Oncol*. 2012;30(11):820-829. Greenberg PL, et al. *Blood* 2012;120:2454-65.

Treatment, Monitoring and Emergence of del(5q)

He was initially followed with a watch-and-wait approach until he started to report symptoms of fatigue and exertional dyspnea. His hemoglobin was around 9.5 mg/dL; however, because of concerns regarding his previous CAD (cyclophosphamide, Adriamycin and dexamethasone), treatment with darbepoetin 3 mcg/kg on a weekly basis was added. It is unclear if a serum erythropoietin (EPO) level was determined before starting. Mr. M. experienced only a transient response to EPO treatment. Three months later, on November 2009, he received his first red blood cell (RBC) transfusion and the darbepoetin was discontinued.

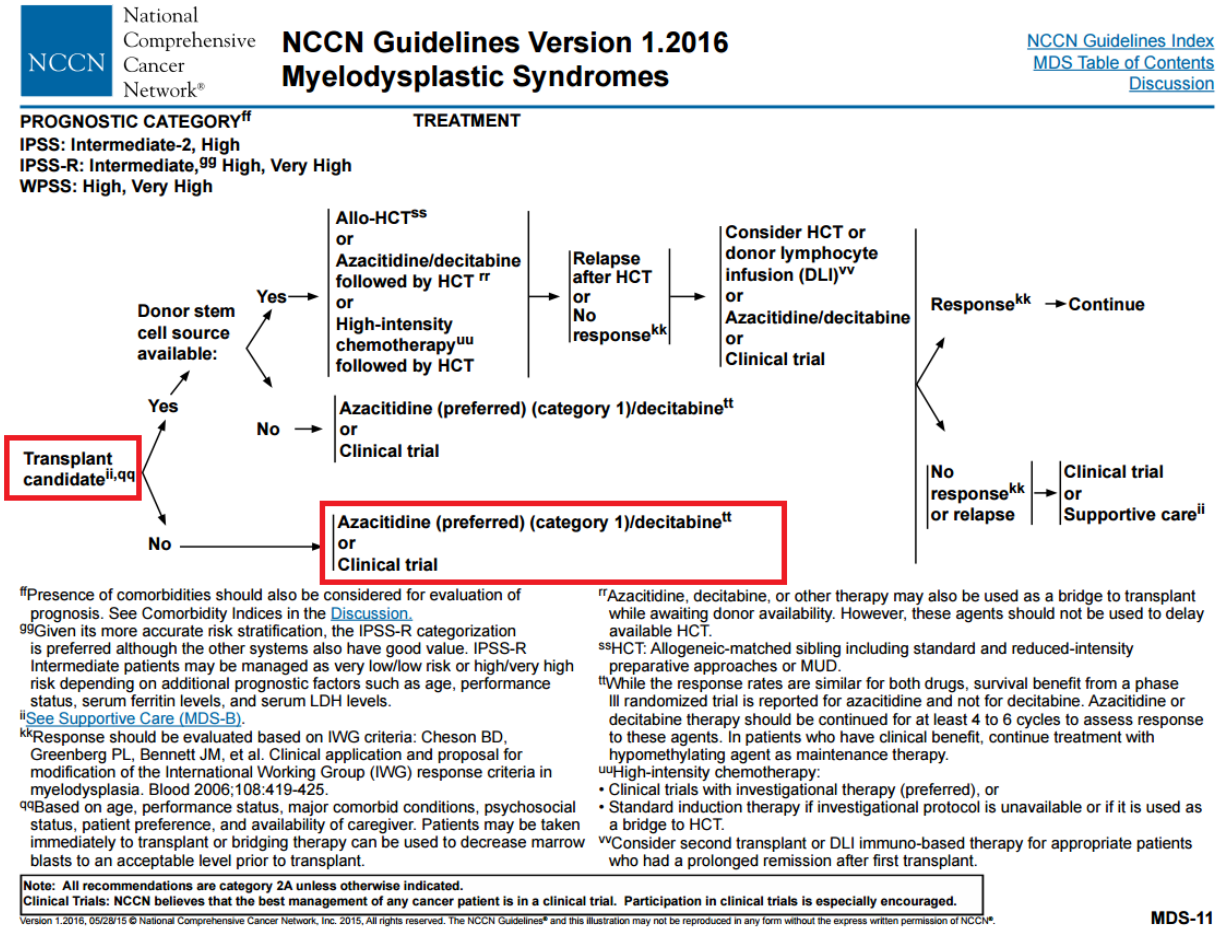
Because of concerns of disease progression, a bone marrow aspirate was repeated. The blast count was still lower than 2%, with megakaryocyte dysplasia only. Interestingly,

this time the cytogenetics showed the presence of the deletion of the long arm of chromosome 5 del(5)q in 1 out of 9 analyzed metaphases. For this reason his diagnosis was modified to MDS associated with isolated del(5)q. The patient continued to be followed with a watch-and-wait approach with a low RBC transfusion requirement (2 units every 8 weeks) until May 2010. This transfusion requirement was considered not sufficient to start an active treatment for his MDS. In July 2010, Mr. M. was diagnosed with atrial fibrillation and placed on warfarin anticoagulation. His platelet count was still normal at that point in time. Between September and October 2010, the patient transfusion requirements began to increase. A repeated marrow aspirate confirmed again the diagnosis of MDS associated with isolated del(5)q.

Treatment of del5q and Achievement of Transfusion Independence
Considering the presence of symptomatic anemia in an elderly patient with a history of CAD who failed EPO therapy, treatment with lenalidomide was initiated at the dose of 5 mg daily in November 2010, and was subsequently reduced to 5 mg every other day because of toxicity (thrombocytopenia resulting from concomitant warfarin administration). This course of action is consistent with today's National Comprehensive Cancer Network (NCCN) Guidelines™ for Myelodysplastic Syndromes, Version 2.2015 which was released on January 26, 2015. Mr. M. had a nice response to lenalidomide treatment with achievement of transfusion independence and mild thrombocytopenia (platelet count stable between 50,000 and 80,000) that lasted for more than 2 years. No further bleeding complications were observed despite the concomitant anticoagulation.

Loss of Transfusion Independence, Disease Reassessment
However, in January 2013, Mr. M. once again became transfusion dependent with low transfusion requirement. A new attempt of EPO treatment was unsuccessful. A repeated bone marrow biopsy in September 2013 showed progression to refractory anemia with excess of blasts type 1 (RAEB-1 by WHO 2008 classification). By morphology the blast count was reported as 7%, 12.3% by flow cytometry, and this time the cytogenetics did show new changes with del(7) and del(17)p in 13 metaphases, del(5)q in 2 metaphases and del(16) in 3 out of 20 metaphases. The peripheral blood count revealed a WBC of 1,670/mm^3, ANC 920/mm^3, hemoglobin 8 g/dL (transfusion requirement: 2 RBC units every 4 weeks), MCV 107 fL, and platelet count 42,000/mm^3.

***Figure 3*. NCCN Guidelines Version 1.2016 MDS; Treatment Recommendations for IPSS-R: Intermediate, High, Very High**



Azacitidine Treatment and Monitoring

In October 2013, Mr. M. received his first cycle of azacitidine at the standard dose of 75 mg/m^2 for 7 consecutive days in a 28-day cycle consistent with NCCN Guidelines (***Fig. 3***). He tolerated the treatment well, with no infective complications and no bleeding issues, and only mild nausea during the days of drug administration. The repeated marrow aspirate after the 6th cycle showed morphologic response with reduction in bone marrow blast count down to less than 5%. However, the cytogenetics continued to remain positive for the previously evidenced abnormalities.

Disease Progression on Azacitidine

After the 11th cycle of azacitidine, in September 2014, not surprisingly, the patient started again to show an increased transfusion requirement (2 units every 2 or 3 weeks)

associated with symptoms of fatigue and dyspnea. Because of concerns of disease progression, a bone marrow aspirate was repeated and showed the presence of 12% blasts by morphology, 14% by flow cytometry, and multiple cytogenetic abnormalities. The azacitidine was then discontinued.

At that point the main question was: What is the management for an elderly patient with multiple comorbidities that failed various lines of therapy, and shows progressive disease?

After a long discussion with the patient, his family, and our colleagues of the palliative care service, we concluded with the decision to follow a supportive care-based approach. Mr. M. did not have any factors associated with good response to immunosuppression (as described below). Moreover, the risk of death related to high intensity chemotherapy regimens was considered too high. Applying the treatment-related mortality (TRM) score proposed by Walter et al. in the acute myeloid leukemia (AML) setting,[4] we estimated a risk of death with induction chemotherapy of greater than 30%. Moreover, the impact on quality of life (QoL) was considered excessive.[5] See Treatment Related Mortality (TRM) Calculator provided by the Fred Hutchinson Cancer Research Center available at *https://cstaging.fhcrc-research.org/TRM/Default.aspx*. Last accessed May 19, 2015.

After 6 months from the interruption of any active treatment for MDS, the patient is alive with an ECOG performance status of 2. He did not have infection or bleeding. He requires 2 units of RBC every 2 weeks. He is not platelet transfusion dependent (platelet count of ~25,000 at the last clinical visit). Mr M. continues to report good QoL. He spends the majority of time with his family.

The latest blood counts on 4/19/2015 showed: WBC of 8,270/mm^3, ANC 1,410/mm^3, monocytes 660, blasts 2,320 (28%), hemoglobin 10.3 g/dL (after transfusion), and platelets 24,000/mm^3.

DISCUSSION

Myelodysplastic Syndromes Risk Assessment

MDS comprises a heterogeneous group of stem cell disorders, which are characterized by cytopenias and variable risk of progression into acute myeloid leukemia (AML).[6] The widely adopted classification of MDS was proposed by the WHO in 2008 and is based on myeloblast count by morphology on bone marrow aspirate, the presence of dysplasia in the various cell lines, and the presence of cytogenetic abnormalities (*Table 1*).[1]

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Table 1. **Peripheral blood and bone marrow findings in myelodysplastic syndrome (MDS) - The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia**

Disease	Blood findings	Bone marrow (BM) findings
Refractory cytopenia with unilineage dysplasia (RCUD): [refractory anemia (RA); refractory neutropenia (RN); refractory thrombocytopenia (RT)]	Unicytopenia or bicytopenia No or rare blasts (<1%)	Unilineage dysplasia: ≥10% of the cells in one myeloid lineage <5% blasts <15% of erythroid precursors are ring sideroblasts
Refractory anemia with ring sideroblasts (RARS)	Anemia No blasts	≥15% of erythroid precursors are ring sideroblasts Erythroid dysplasia only <5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (<1%) No Auer rods <1 × 10^9/L monocytes	Dysplasia in ≥10% of the cells in ≥2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) <5% blasts in marrow No Auer rods ± 15% ring sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s) < 5% blasts No Auer rods <1 × 10^9/L monocytes	Unilineage or multilineage dysplasia 5%-9% blasts[1] No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5%-19% blasts. Auer rods ± <1 × 10^9/L monocytes	Unilineage or multilineage dysplasia 10%-19% blasts[1] Auer rods ±[1]
Myelodysplastic syndrome—unclassified (MDS-U)	Cytopenias <1% blasts	Unequivocal dysplasia in <10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS <5% blasts

Disease	Blood findings	Bone marrow (BM) findings
MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (<1%)	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

Vardiman, et al. *Blood* 2009;114:937-951.

For the assessment of prognosis, two main scoring systems have been developed. The IPSS published by Greenberg, et al. in 1997 was recently updated. The Revised-IPSS[3] published in 2011 is now the most widely adopted scoring system in clinical practice. It places greater importance on the cytogenetic features of the disease rather than the blast count and presence/number of cytopenias ***(Tables 2A, B, C)***.

Table 2A. **Revised International Prognostic Scoring System (IPSS-R)**

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤2	—	>2%- <5%	—	5%-10%	>10%	—
Hemoglobin	≥10	—	8- <10	<8	—	—	—
Platelets	≥100	50-< 100	<50	—	—	—	—
ANC	≥0.8	<0.8	—	—	—	—	—

Table 2B. **Revised International Prognostic Scoring System (IPSS-R)-Cytogenetic Prognostic Subgroups and Corresponding Risk Score**

Cytogenetic prognostic subgroups	Risk score
Very good	-Y; del(11)q
Good	Normal; del(5)q; del(12)p; del(20)q; double including del(5)q
Intermediate	Del(7)q; +8; +19; i(17)q; any other single or double independent clones
Poor	-7; inv(3)/t(3)q/del(3)q; double including -7/del(7)q, Complex: 3 abnormalities
Very poor	Complex >3 abnormalities

Table 2C. **Revised International Prognostic Scoring System (IPSS-R)-Risk Category, Risk Score and Corresponding Median Survival (years)**

Risk category	Risk score	Median years of survival
Very low	≤1.5	8.8
Low	>1.5-3	5.3
Intermediate	>3-4.5	3.0
High	>4.5-6	1.6
Very high	>6	0.8

Greenberg, et al. *Blood*. 2012;120:2454-2465.

Note: The MDS Foundation has developed an IPSS-R staging calculator which can be accessed online at: *www.mds-foundation.org/ipss-r-calculator/* (last accessed May 19, 2015).

***Allogeneic Hematopoietic Cell Transplantation (AHCT*)**

The allogeneic hematopoietic cell transplantation is the only known treatment with curative potential in MDS.[7] However, transplantation is not an option for the majority of patients, considering that more than 80% of newly diagnosed patients are older than 60 years.[8] The presence of comorbidities can further reduce the proportion of patients eligible for this potentially curative approach.

Treatment Options for Elderly/Unfit Patients with MDS

The possible treatment options for elderly, unfit patients with MDS are described below. (The indications to growth factor treatment are not described here.) For additional information please visit NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Myelodysplastic Syndromes. Version 2.2015. [*www.nccn.org/professionals/physician_gls/pdf/mds.pdf*] Username and Password is required to view the NCCN Guidelines.

Lenalidomide

On December 27, 2005, the U.S. Food and Drug Administration (FDA) granted Subpart H approval (restricted distribution) to lenalidomide for use in patients with transfusion-dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.[9] The approval was based on results of the MDS-003 trial where a 67% transfusion-independence rate was observed in patients with isolated del(5)q treated with lenalidomide.[10] List and colleagues reported that patients with del(5q) MDS who achieved transfusion independence in the MDS-003 study had a median response duration that had not been reached after a median follow-up of 2 years. Neutropenia and thrombocytopenia are the most common treatment-associated adverse events ***(Table 3).***

Table 3. **Hematological adverse events at a glance (lenalidomide-001-trial, total number of patients, n = 43)[11]**

	Grade 1 or 2 (NCI)	Grade 3 or 4 (NCI)	All patients, all grades
Neutropenia	**0**	**28 (65%)**	**28 (65%)**
Thrombocytopenia	**9 (21%)**	**23 (53%)**	**32 (74%)**

The oral administration and the relatively good toxic profile increase the interest of lenalidomide in elderly and unfit populations. A phase II trial published in *Blood* in 2008[12] showed a transfusion independence rate of 26% in lower risk MDS with karyotypes other than del(5)q. In our opinion, this drug can be considered as an option for elderly and unfit patients, taking into account the adverse effect profile, especially thrombocytopenia.

Hypomethylating Agents

Azacitidine is FDA-approved for all subtypes of MDS, and a randomized study of azacitidine has been shown to improve overall survival (OS), resulting in a median overall survival of approximately 9 months in higher-risk patients.[13] In addition, hypomethylating agents such as azacitidine and decitabine have been shown to result in hematologic improvement within the erythroid lineage. Approximately 44% of patients who were transfusion dependent prior to starting azacitidine therapy became transfusion independent. In clinical trials, azacitidine is generally administered at a dose of 75 mg/m^2, every day for 7 consecutive days; every 28-days either intravenously or subcutaneously, and this regimen has been associated with improvements in transfusion dependence and OS in phase III trials.[13-15] A more recent study has compared three different dosing strategies in which MDS patients were randomly assigned to 1 of 3 regimens every 4 weeks for 6 cycles: azacitidine 5-2-2 (75 $mg/m^2/d$ subcutaneously for 5 days, followed by 2 days no treatment, then 75 $mg/m^2/d$ for 2 days); azacitidine 5-2-5 (50 $mg/m^2/d$ subcutaneously for 5 days, followed by 2 days no treatment, then 50 $mg/m^2/d$ for 5 days); or azacitidine 5 (75 $mg/m^2/d$ subcutaneously for 5 days).[16] In this study there was no difference in outcomes between the three different dosing strategies. The original phase III trial showed improvement in OS with the 7 consecutive day schedule compared to the conventional care group, as previously mentioned above; therefore, this remains our first choice.[13]

Of note, patients with renal impairment may be at increased risk for renal toxicity. Azacitidine and its metabolites are primarily excreted by the kidney, and a dose reduction or a discontinuation of the drug should be considered in patients with renal impairment. Dose reduction for the following cycles should be considered even for low neutrophils or platelets.[17]

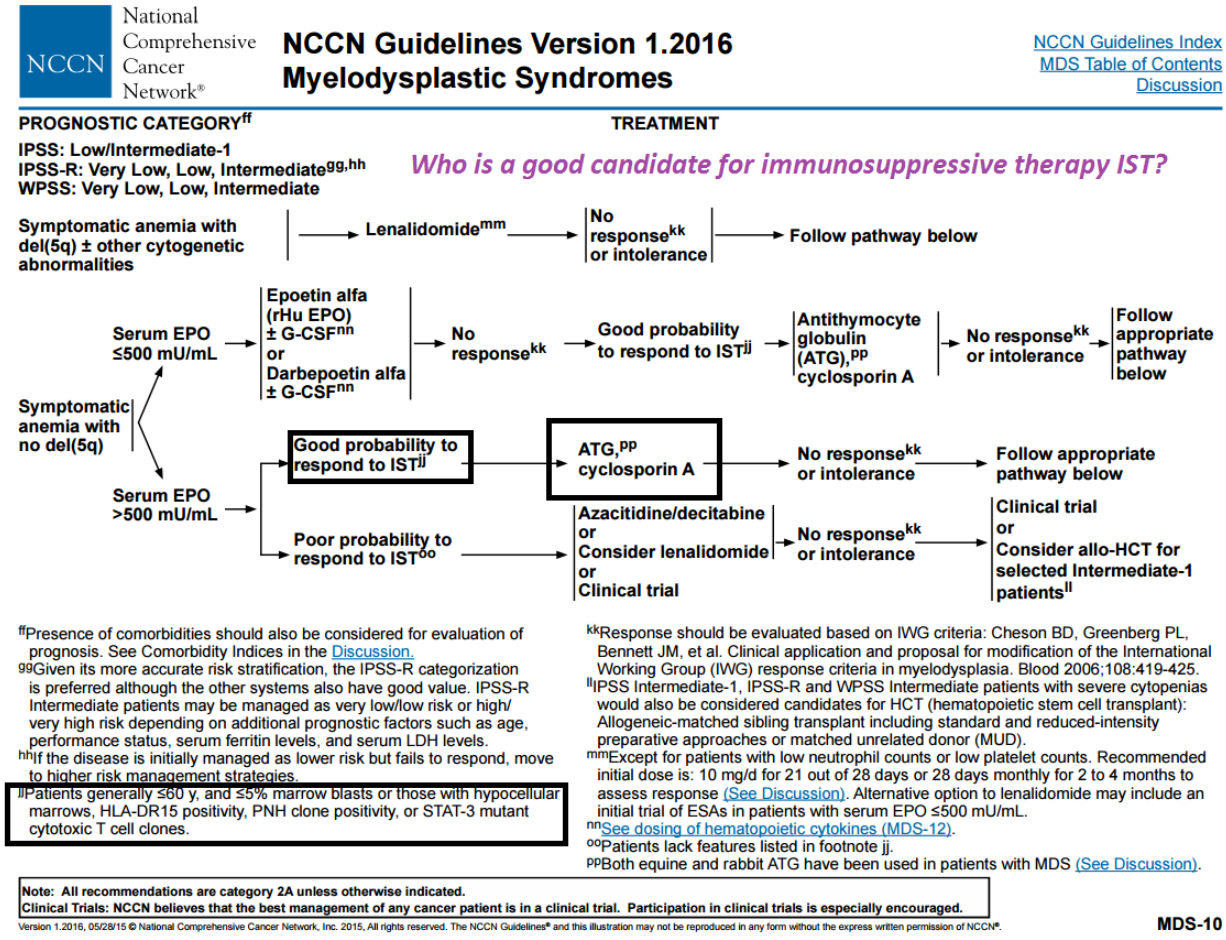
The other FDA-approved hypomethylating agent for MDS is decitabine. The drug is FDA-approved for patients who have intermediate 1, intermediate 2 or high-risk MDS (by IPSS). In a phase III randomized study, decitabine was shown to provide durable responses and improved time to AML transformation or death.[18] Additionally, a randomized study evaluating different doses of decitabine at 20 mg/m^2 given consecutively for 5 days was shown to be superior to alternative dosing regimens.[19] The results of this trial have been further documented in a multicenter study evaluating decitabine at 20 mg/m^2 for 5 consecutive days every 4 weeks.[20] In this study, there were 99 patients treated with decitabine. The overall response rate was 32%. There were 17 complete responses and 15 marrow complete remissions (CRs), and the overall improvement rate was 51% which included 18% hematologic improvement. However, as reported in the NCCN-MDS guidelines [NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Myelodysplastic Syndromes. Version 1.2016],[21] an OS advantage of decitabine in a phase III trial has not been reported yet. For this reason, this drug with an NCCN category 2A recommendation is not our first choice at the moment, but rather azacitidine with a category 1 (preferred) designation is our first choice at this time **(*Fig 3*)**.[22]

Immunosuppression

There have been several studies evaluating the use of immunosuppressive therapy (IST) in patients with MDS including antithymocyte globulins (ATG) and cyclosporine A.[23] Predictors for response to immunosuppression include younger age, shorter duration of RBC transfusion dependence, the presence of trisomy 8, and myelomonocytic surface antigen (MMSA) Ia HLA-DR2 phenotype. Other predictors of response to immunosuppressive therapy include the presence of a paroxysmal nocturnal hemoglobinuria (PNH) clone and bone marrow cellularity.[25] Additional studies have shown that if patients respond to anti-thymocyte globulin (ATG) therapy, they typically have a very good prognosis with prolonged survival.[24] In this study, the overall response rate was 34%, with 34% of the patients becoming transfusion independent. For patients who responded to ATG therapy, the survival at 80 months after treatment was 95%, whereas it was only 45% in patients who did not respond to ATG therapy. A recent analysis by Sloand, et al. has shown that immunosuppressive therapy can result in significant improvement of the pancytopenia and was associated with improved OS and progression-free survival, but especially in younger patients with lower risk disease.[26] In our opinion, an attempt with immunosuppression can be considered even in elderly and unfit patient with high transfusion requirement, especially if trisomy 8 and a PNH clone are present. The major side effects of ATG are allergic reactions during the infusion and an increased infection risk related to immunosuppression. As a result, ATG is not usually our first choice of treatment as the NCCN states that good probability to respond to IST includes patients who are generally ≤60 years of age, and ≤5% marrow blasts or those with hypocellular marrows, HLA-DR15 positivity, PNH clone positivity, or STAT-3 mutant

cytotoxic T-cell clones are present ***(Table 4)*** and this precludes many of the elderly patients we see.

Table 4. **NCCN Guidelines Version 1.2016 Myelodysplastic Syndromes – Who is a good candidate for immunosuppressive therapy (IST)?**



Best supportive care and palliative approach

New data on palliative care in cancer patients are emerging. In a subgroup of selected patients (elderly and unfit patients, or younger patients with multiple comorbidities) the palliative approach may be associated not only with a better quality of life, but also a prolonged life than could possibly be achieved with additional active therapy. An interesting paper recently published in the *Journal of Clinical Oncology* by the Leadership Developing Program (LDP) of the American Society of Clinical Oncology (ASCO) reviewed this topic.[27] They concluded with the following statement:

"As a community, we need to overcome the perception of the cure/care dichotomy and recognize that palliative care belongs throughout the continuum of care."

This is a crucial point that oncologists should keep in mind, especially managing diseases more common in the elderly population, as well as MDS. There is evidence in advanced solid tumors of improvement in QoL with a supportive care-based approach.[28] In another interesting paper published in *The New England Journal of Medicine* in 2012,[29] authors reported advantages in QoL, presence of depressive symptoms (16% vs. 38%, *P* = .01) and median OS (11.6 months vs. 8.9 months, *P* = .02) in patients assigned to early palliative care versus standard care. No data are available at the moment for hematological malignancies. However, the evidence from advanced solid tumors are, in my opinion, sufficient to support the inclusion of palliative care in the treatment options that should be discussed and integrated in the standard oncologic care.

In conclusion, there are various treatment options for unfit, elderly patients with comorbidities. Besides the FDA-approved drugs briefly described herein, various research centers have clinical trials open to enrollment. The NCCN believes that the best management of any cancer patient is in clinical trials and this is particularly important for diseases where potential curative therapy is not an option, a position most elderly MDS patient currently face. Recent analysis using next-generation sequencing has provided great advances in identifying relationships between gene mutations and clinical phenotypes of MDS and this should promote future drug developments for MDS.[30,31] Novel agents are undergoing clinical development both as monotherapies as well as in combination strategies, with multiple cellular targets such as those promoting apoptosis like histone deacetylase (HDAC) inhibitors panobinostat, vorinostat and belinostat [ClinicalTrials.gov Identifiers: NCT01463046; NCT01451268; NCT01617226; NCT02381548] and inhibition of the DNA damage checkpoint kinase WEE1 (MK-1775) [ClinicalTrials.gov Identifier: NCT02381548] or agents that target molecules in the TGF-beta superfamily such as LY-2157299 [ClinicalTrials.gov Identifier: NCT02008318], and even active immunotherapeutic strategies such as anti-CTLA-4 (ipilimumab) checkpoint inhibitor [ClinicalTrials.gov Identifier: NCT01757639] and chimeric antigen receptor engineered T-cell therapy [ClinicalTrials.gov Identifier:NCT02203825].[32] Finally, an important option that the oncologist and hematologist should address with patients and caregivers is the palliative approach, more oriented to improving or maintaining the patient's QoL, and reducing the time spent in the health care structures. Looking back, we are now completely certain that the palliative care strategy was the best possible third-line approach for the patient described in this report.

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