Review Article

De Novo and Therapy-Related Myelodysplastic Syndromes: Analogies and Differences

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Abstract. The aim of our review has been to give an appropriate idea of analogies and differences between primitive MDS (p-MDS) and t-MDS throughout an accurate reviewing of English peer-reviewed literature focusing on clinical, cytogenetic, epigenetic, and somatic mutation features of these two groups of diseases.

Therapy-related MDS (t-MDS) are classified by WHO together with therapy-related acute myeloid leukemia (t-AML) in the same group, named therapy-related myeloid neoplasm.

However, in clinical practice, the diagnosis of t-MDS is made with the same criteria as for primitive MDS (p-MDS), and the only difference is a previous non-myeloid neoplasm. The prognosis and the consequent therapy can be established following the same criteria as for p-MDS, and the therapy is generally decided using the same criteria. We stress the possible difference in cytogenetics, mutations, and epigenetics to distinguish the two forms. Actually, there is no marker specific for t-MDS either in cytogenetics, epigenetics, or mutations; however, some alterations are also frequent in t-MDS and, in general, they induce a poorer prognosis. So, the high-risk forms in t-MDS are prevalent. The present literature data suggest classifying the t-MDS as a subgroup of MDS and introducing some parameters to evaluate the probability of previous therapy in inducing MDS. An important issue remains the patient's fitness, which strongly influences the outcome.

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Introduction. The myelodysplastic syndromes (MDS) are a group of clonal bone marrow (BM) neoplasms characterized by ineffective hematopoiesis, manifested by morphologic dysplasia in hematopoietic cells and by peripheral cytopenia(s).[1]

In the last WHO classification,[1] like in the former, MDS include various subgroups, but not therapy-related MDS (t-MDS), which are classified together with therapy-related acute myeloid leukemias (t-AML) and constitute the group of therapy-related myeloid neoplasms (t-MNs). This remains a distinct category of patients who develop a myeloid neoplasm following cytotoxic therapy (chemo-radio) for a non-myeloid neoplasm. By no means is the exposure history alone enough to prove causation, considering that not all anti-cancer drugs are leukemogenic. However, the adjunctive characteristics, like time of onset and type of drug distinguishing therapy-related from primitive (p-MDS) neoplasms, are vague and not specific, considering that diagnosis is made with the same criteria as for p-MDS.[2]

This review highlights the analogies and differences between the de novo and therapy-related MDS to

establish some criteria that should inform the clinician in determining the prognosis and therapy of t-MDS, which are all considered unfavorable in the present WHO classification tout court.

References are based on the English literature reported by PUBMED, Web of Science, and SCOPUS having as keywords, Myelodysplastic Syndromes de novo and therapy-related, Radiation and Myelodysplastic Syndromes, Drug-related Myeloid Neoplasm.

MDS Diagnosis and Risk Classification. Myelodysplastic syndrome diagnosis is based on peripheral blood (PB) counts, on the presence of dysplastic changes, and blasts in PB and bone marrow.[3] Diagnosis of both de novo and therapy-related MDS follow the same criteria. Since a single biological or reliable genetic diagnostic marker has not yet been discovered for MDS, quantitative and qualitative dysplastic alterations of bone marrow precursors and peripheral blood cells are still fundamental for diagnostic classifications.[3] The minimal diagnostic criteria for MDS include the presence of bone marrow-specific alterations, i.e., one or more of the following characteristics: dysplasia in at least 10% of at least one of the major hematopoietic lineages, at least 15% or 5% ring sideroblasts (without or with SF3B1 mutation, respectively), or 5-19% myeloblasts in bone marrow smears.[3] In the presence of a refractory cytopenia but no morphological evidence of dysplasia, specific chromosomal abnormalities detected by conventional karyotyping or FISH are considered presumptive evidence for MDS.[3] Since morphology alone is often insufficient to reach a final diagnosis, it should be integrated but not replaced, by other investigations such as flow cytometry, cytogenetics, and molecular studies, in vitro culture of hematopoietic progenitors.[1,3,4] However, if multilineage dysplasia, chromosomal aberrations, and proof of clonality are absent, the diagnosis may be difficult.[3] Flow cytometry can also help to assess the diagnosis of MDS.[4] Apart from the history of previous chemotherapy and radiotherapy, there are not, at present, laboratory features clearly distinguishing therapy-related (t-MDS) from primitive (de novo) MDS (p-MDS).

Our first aim is to investigate if there are diagnostic features derived from morphology, cytogenetics, epigenetics, and molecular studies in the present literature, favoring the diagnosis of de novo or therapy-related MDS. If this possibility does not exist, it is logical to conclude that t-MDS should be considered a special subgroup of MDS.

Considering the importance of the morphology in MDS diagnostics, the first question could be if the morphology and the subtypes of MDS are different in de novo versus therapy-related MDS. Therapy-related myelodysplastic syndrome is generally classified according to morphologic schemes used for de novo MDS.[5] Different studies agree that there are no substantial differences in morphology between de novo and therapy-related MDS.[5,6] However, the morphologic subclassification of t-MDS, based on the percentage of blasts, may not be clinically relevant.[7] A study of the Chicago group found no differences in 81 patients with therapy-related MDS concerning median survival times among patients classified into the different WHO subgroups of MDS or taking into account their bone marrow blast percentage; these results indicate a uniformly poor outcome in t-MDS regardless of morphologic classification.[7] The cytogenetic stratification by the International Prognostic Scoring System (IPSS) guidelines or karyotypic complexity was prognostically significant, independently from the bone marrow blast number. This datum was fundamental to classifying t-AML and t-MDS in the same group of therapy-related myeloid neoplasm.[1] However, it was not confirmed by a more recent study derived from a database of MD Anderson Cancer Center and Massachusetts General Hospital, including 660 patients who met the strict WHO criteria for t-MN after excluding 137 patients with >30% blast in the bone marrow. In this group, a blast percentage >5 was an independent risk factor of a bad prognosis.[8]

The group of therapy-related neoplasm includes MDS and AML post-chemotherapy, post-radiotherapy, and possibly post-benzene. According to some reports, the behavior of these last neoplasms could be like de novo ones. The drugs more frequently associated with the insurgence of MDS are reported in **table 1**.

Nardi et al.,[5] studying three groups of MDS patients, primitive, radiotherapy related (XRT), and chemotherapy-related (C/CMT), showed that the distribution of MDS types according to the WHO Classification for non–therapy-related (primary) MDS and the blood counts at presentation were similar among the three groups. Only 27% of the XRT patients had intermediate-2 or high IPSS scores, compared with 60% of the C/CMT patients. Patients in the XRT group had IPSS scores significantly lower than the C/CMT patients p<.001) but similar to the de novo (p-MDS) MDS/CMML patients. These authors conclude that patients with t-MN after XRT alone had a superior overall survival (p < .006) and a lower incidence of high-risk karyotypes (p <.01 for AML and < .001 for MDS) compared with patients in the C/CMT group. (**Table 2**)

In contrast, there were no significant differences in survival or frequency of high-risk karyotypes between the XRT and de novo groups. AML and MDS diagnosed in the past decade in patients after receiving XRT alone differ from t-MN occurring after C/CMT and share genetic features and clinical behavior with de novo AML/MDS. These results suggest that post-XRT

MDS/AML may not represent a direct consequence of radiation toxicity and warrant a therapeutic approach similar to de novo disease. Similarly, the MDS secondary to benzene (Bz) also seems to have

Table 1.

	Alkylisting agent class	Topoisomerase II inhibitor class
Cytogenetics	det(5q)-7/del(7q)	t(11q23.3), t(21q22.1)
Frequency	70% of t-MN patients	30% of t-MN patients
Latency	5-7 years	2-3 years
Presentation	MDS	AML
Implicated drugs	• Atkylating agents: benclamustine, busulfan, carmustine, chlorambucil, cyclophosphamide, dacarbazine, lornustine, melphalan, mitomycin C, nitrogen mustard, procarbazine, thiotepa • Platinum-based agents: cisplatin, carboplatin • Antimetabolite agents: azathioprine, fludarabine	• Anthracyclins: dauronobicini, epirubicin, doxorubicin • Other topoisomerase II inhibitors: etoposide, ten iposide, amsacrine, mitoxantfone

*Loss of the short arm of chrornosome 17 containing the TP5 3 gene due to del(17p) unbalanced rearrangement or —17 k 'observed in association with del(5q) in 40% of cases. AML. acute myeloid leukaemia: MDS, myeloid neoplasm. myelodysplastic syndrome: t-MNI. therapy-related.
By McNerney et Al.[23] Nat Rev Cancer. 2017.

Table 2. Cytogenetic abnormalities in 306 patients with t-MDS/t-AML (t-MDS 224, t-AML 82). Balanced chromosomal translocations are very rare in t-MDS where abnormalities of chromosomes 5 or/and 7 are prevalent. From Smith et Al.[20] Blood. 2003

Presentation	N° patients	Abnormality 5 (%)	Abnormality 7 (%)	Abnormalities 5 and 7 (%)	Balanced rearrangement (%)
I-MDS-unknown	54	10 (19)	20 (37)	9 (17)	2 (4)
I-MDS only	72	19 (26)	16 (22)	17 (24)	0
I-MDS-+--M-AML	98	19 (19)	32 (33)	28 (29)	6 (6)
I-AML only	82	14 (17)	16 (20)	12 (15)	23 (28)
Totals	306	62 (20)	84 (27)	66 (22)	31 (10)

Karyiotype	N° (%)
Normal karyotype	24(8)
Clonal abnormalities	282 (92)
Clonal abnormalities of chromosome 5, 7, or both	
(± other abnormalities)	214 (70)
Abnormal chromosome 5*	63 (21)
Abnormal chromosome 7*	85 (28)
Abnormal chromosomes 5 and 7	66 (22)
Recurring balanced rearrangements	31 (10)
t(11q23)	10 (3.3)
t(21q22)*	8 (2.6)
t(15:17)	6 (2.0)
inv(16)*	6(2.0)
t(8:16)	1 (0.3)
Other clonal abnormalities	39 (13)†

characteristics not similar or identical to t-MDS/AML, as supposed in the past.[11,12]

Irons et al.[12] recently studied the prevalence of hematopoietic and lymphoid diseases for 2,923 consecutive patients prospectively diagnosed in their laboratory in Shanghai utilizing World Health Organization (WHO) criteria. The Shanghai series of 722 cases of AML includes the most extensive published series with documented Bz exposure and 644 unexposed de novo-AML cases. They also reported the clinical,

phenotypic, and molecular characteristics of MDS developing in 649 patients, of whom 80 were determined to have some Bz exposure. In as much as t-MDS and t-AML are considered to be overlapping entities, they initially were surprised to discover that MDS presenting in individuals with chronic exposure to Bz at high concentrations (67–100 mg/m^3) did not exhibit a pattern of cytogenetic and phenotypic abnormalities typically observed in t-MDS. In fact, in their MDS series, cases associated with exposure to the highest concentrations of Bz (n 5 29) were found to have a lower prevalence of clonal cytogenetic abnormalities (24%) when compared with unexposed, that is, p-MDS cases (30%) (n 5 569). Further, they did not observe an increase in clonal deletions involving all or part of chromosomes 5 or 7 in Bz-exposed MDS relative to unexposed MDS cases and in no instance involving 5/5q- as the sole abnormality. The conclusion was that benzene exposed MDS-Leukemia patients more closely resemble de-novo than therapy-related MDS leukemia.

It is also very significant to notice that the prognosis of both MDS de novo and therapy-related can be evaluated by the same scoring systems.[8,14-17] Of the different methods of stratifying t-MDS, the best seems to be the IPSS-R (International Prognostic Scoring System, Revised), which considers, in descending order, five major variables for evaluating clinical outcomes, including cytogenetic risk groups, marrow blast

percentage, and depth of cytopenias (hemoglobin, platelet, and ANC levels, respectively), therefore, to affirm that all t-MDS patients have an unfavorable prognosis is not valid. In general, in the t-MDS series, the proportion of high-risk patients is higher.[8,14-17] Furthermore, in general, the survival of every category was lower for t-MDS; however, patients with IPSS and MPSS had a very low survival, not significantly different in both patients with t-MDS and with p-MDS.[15] In the study of Zeidan, patients with t-MDS had significantly inferior survival than p-MDS (median, 19 vs. 46 months, respectively, P=0.005), and patients with t-MDS had a higher prevalence of adverse prognostic factors such as poor risk cytogenetics and higher blast percentages. Although a less favorable clinical outcome occurred in each t-MDS subset compared with p-MDS subgroups, FAB and WHO-classification, IPSS-R, and WPSS-R (WHO-based Prognostic Scoring System-revised) effectively separated t-MDS patients into different risk groups, indicating that all established risk factors for p-MDS maintained relevance in t-MDS, with cytogenetic features having enhanced predictive power. Thus there is significant heterogeneity in clinical outcomes in t-MDS with a small subset of patients having a more indolent disease course, who might not necessarily benefit from aggressive therapeutic interventions.[15,16] All this was confirmed in a large and multicenter study[17] where the predictive power of IPSS-R was almost comparable top-MDS in patients with a solid tumor as primary disease as well as in patients after radiotherapy only. However, the predictive power was lower in patients with a history of hematologic disease treated with chemotherapy. It is important to highlight that this extensive work demonstrated an unexpectedly high percentage of good-risk and normal cytogenetics, concordantly with other more recently published data.[8,15,16] (**Figure 1, 2**)

Cytogenetics. Cytogenetics has a fundamental role in determining the prognosis of de novo MDS. However, its importance in t-MDS has been taken into consideration only recently.

Recurrent chromosomal abnormalities are present in 40%–70% of patients with *de novo* MDS at diagnosis (**Figure 3**). However, they are present in 90-95% of patients with t-MDS, frequently in the context of complex karyotypes. Frequent chromosomal abnormalities in patients with t-MDS post-alkylating agents include −5/del(5q), −7/del(7q), and/or +8, whereas translocations involving 11q23 or 21q22, as well as t(15;17); Inv 16; t(17;19)(q22;12), have been frequently reported in patients with prior exposure to topoisomerase II inhibitors.[18-23] (**Table 2, Table 3**)

In t-MDS and p-MDS, the same cytogenetics abnormalities are present. Are they indeed similar, and do they have similar significance and prognosis? Some chromosomal abnormalities are more frequent in t-MDS than in p-MDS; however, there are no specific t-MDS karyotypes. (**Figure 3, 4**). Most chromosomal abnormalities present in t-MDS have in the past been considered to have a poor prognosis, but this is not always true. (**Table 3**)

Abnormalities of chromosome 5. A typical example is a deletion of chromosome 5, which is considered favorable in p-MDS but unfavorable in t-MDS.[24-26] To justify this discrepancy, Le Beau showed among others that there are two minimally deleted regions (MDRs) on chromosome 5q: 5q31.2 in patients with t-MN, *de novo* AML, and high-risk MDS; and 5q32 in those with 5q– syndrome, now classified as MDS with isolated del(5q), which has a good prognosis.[22,24] It is essential to distinguish the simple deletion of chromosome 5 from the syndrome of 5q-;[24] furthermore, it should be mentioned that the deletion of chromosome 5 is frequently associated with another chromosome abnormality in the MDS therapy-related, as -7/del 7, and this worsens the prognosis.[22,24] However, some authoritative papers report no differences between isolate del(5q) in t-MDS and p-MDS. Lessard et Al.[27] report that the breakpoints for 5q vary,[18] mainly from
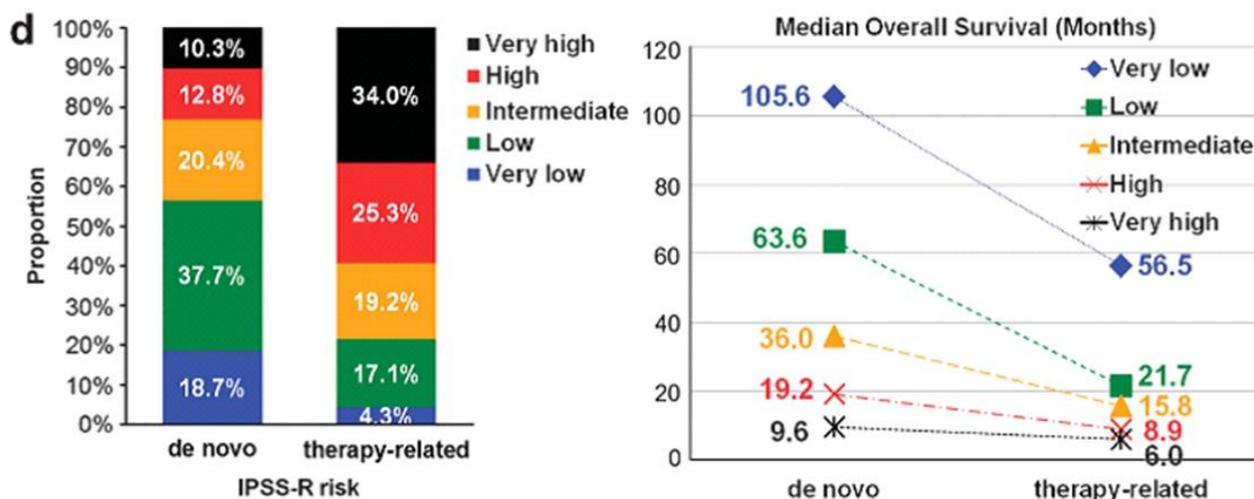
Figure 1. Differences between p-MDS and t-MDS concerning the proportion of various risk groups and the respective survivals. Ok et al.[8] Leukemia, 2014.
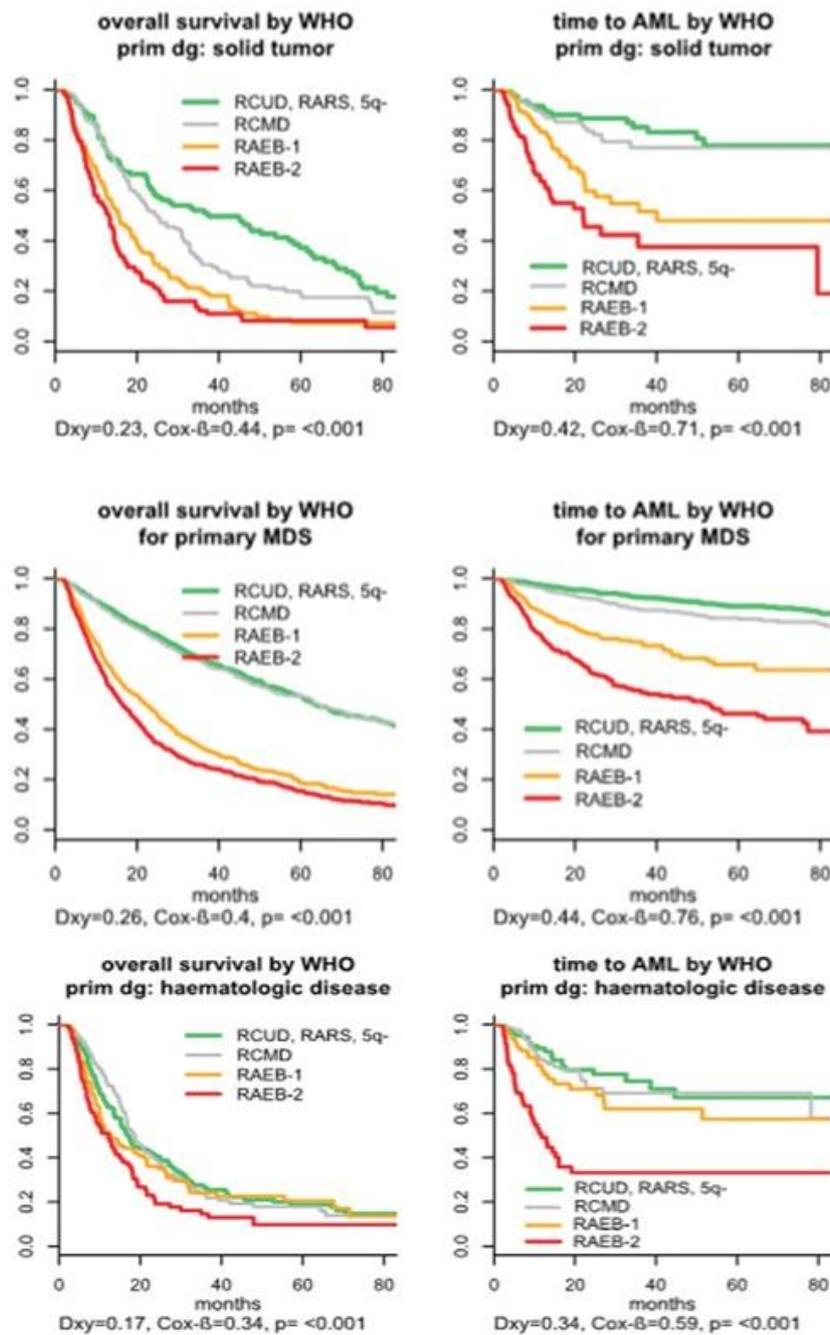

Figure 2. Comparison of Overall Survival and time to AML of the same risk groups between p-MDS and t-MDS same risk groups. Kuendgen et al.[17] Leukemia 2021.

Table 3. t-MDS p-MDS. Zeidan et al.[14] 2017: Proportions of the different karyotypes and risk groups of t-MDS versus p-MDS.

Karyotype			
Poor risk	177 (49%)	272 (18%)	<0.005
Complex (>3 abnormalities)	101 (28%)	162 (11%)	
Del 5/ - 5	106 (30%)	214 (14%)	
Del 7/-7 -	106 (30%)	142 (9%)	
IPSS-R			
Very low	30 (9%)	215 (14%)	<0.005
Low	87 (25%)	509 (34%)	
Intermediate	71 (20%)	337 (22%)	

High	71 (20%)	236 (16%)
Very high	94 (26%)	217 (14%)
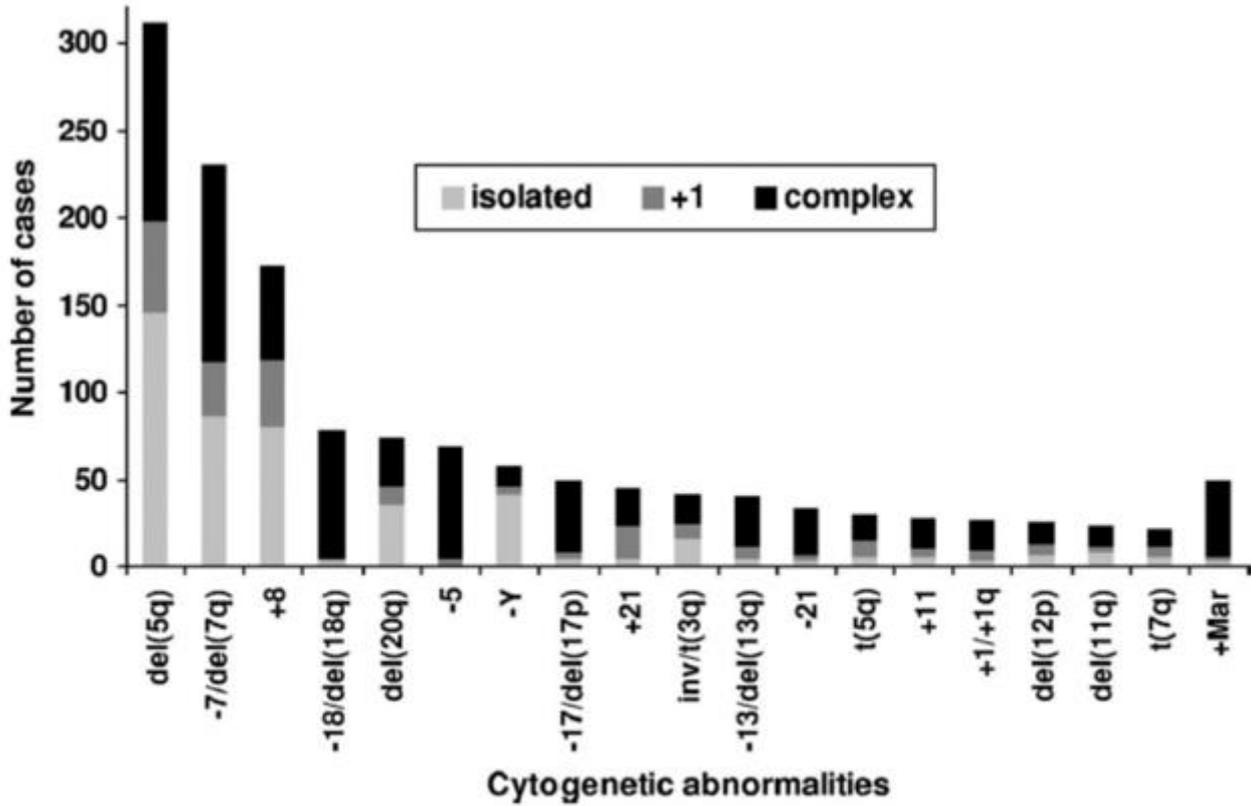
Figure 3. Frequency of common cytogenetic abnomrmalities in p-MDS, subdivided into isolated, with 1 additional anomaly, and complex anomalies (From Haase et al.[21])
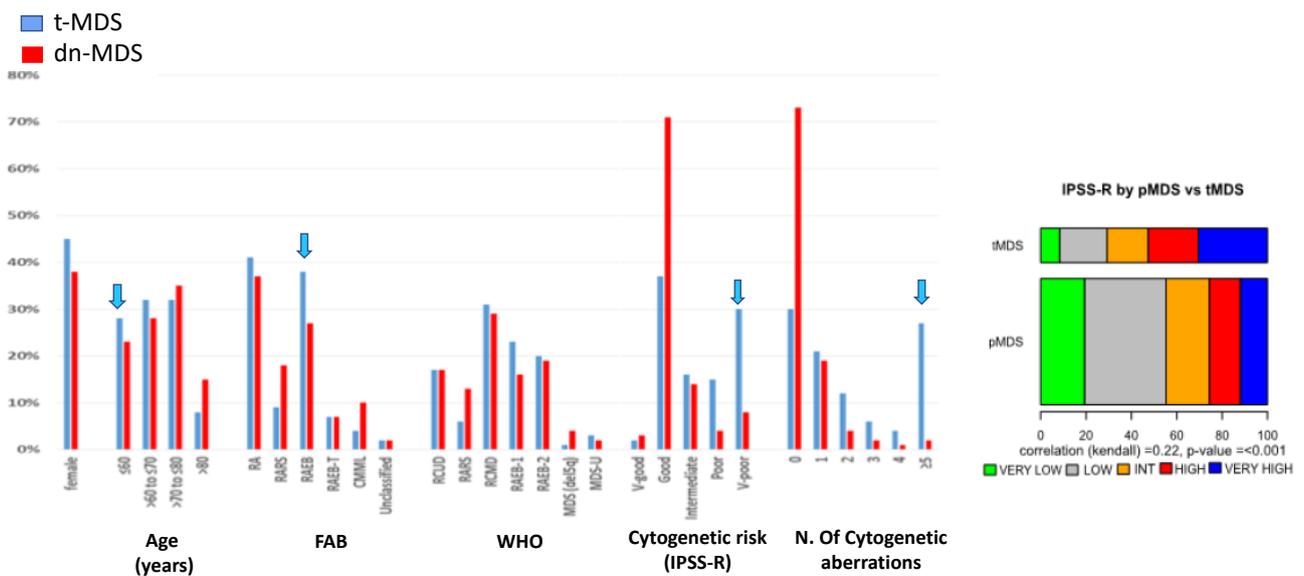

Figure 4. Patient characteristics in de novo vs therapy-related MDS (data from Kuendgen et al.[17] Leukemia 2021).

5q11 to 5q35, so the deletion size may be small (mainly 5q31), medium (size equivalent to half of the long arm, whatever bands are involved), or large (almost all the long arm). Thus, they distinguished 19 cases with small (17%), 27 cases with medium (25%), and 64 cases with large (58%) deleted segments. They found no difference in the distribution of these deletions in 28 therapy-related cases, with 6 small (21%), 5 medium (18%), and 17 large deleted segments (61%). Similarly, Holtan and Al.,[28] in their series of 130 patients with 5q deletion, of which 32 were therapy-related, found that the breakpoints defined by G-banded karyotyping poorly correlate with particular disease features. Surprisingly, the survival of patients with treatment-related MDS was equivalent to those with de novo MDS and del(5q). Morphologic features associated with del(5q) are diverse. Most patients with del(5q) MDS do not meet the criteria for WHO-defined 5q-syndrome, and the presence of del(5q) does not appear to modify the clinical phenotype. Consequently, in the IPSS-R applied to t-MDS, as for p-MDS, the 5q- appears to be a favorable factor.[15-17] However, the effects of 5 deletion is influenced by additional mutations, including *SF3B1* and *T*P53.[29]

Chromosome 7 abnormalities. Isolated monosomy 7 (−7), and/or partial loss of the long arm of chromosome 7 (del 7q) and −7/del(7q) with additional cytogenetic aberration(s) are the second most frequent chromosomal abnormalities in p-MDS and are associated with poor OS and high AML transformation rate. In t-MDS, it plays a similar unfavorable prognostic role; they represent the most frequent cytogenetic abnormalities and are frequently associated with additional cytogenetic aberration, as 5q- deletions.[17,19,20]

Recently Crisà[30] et al. reported a large series of myelodysplastic syndrome patients collected from some European centers with partial or total loss of chromosome 7. Of this series (280 patients), 32 had a t-MDS, and the outcome did not differ from that with p-MDS. The median number of mutations per patient was 2 (range 0–8). Patients harboring ≥2 mutations had a worse outcome than patients with <2 or no mutations (leukemic transformation at 24 months, 38%, and 20%, respectively, p=0.044). Untreated patients with del(7q) had better overall survival (OS) compared with those with −7 (median OS, 34 vs. 17 months, p=0.034). In multivariable analysis, blast count, TP53 mutations, and number of mutations were independent predictors of OS, whereas the cytogenetic subgroups did not retain prognostic relevance.[30]

However, del(7q) detection in patients following cytotoxic therapies is not always related to an emerging therapy-related myeloid neoplasm. Goswami et Al.[31] described 39 patients who acquired del(7q) as sole abnormality following cytotoxic therapies for malignant neoplasms. The median interval from cytotoxic therapies to del(7q) detection was 40 months (range, 4-190 months). Twenty-eight patients showed an interstitial, and 11 a terminal 7q deletion. Fifteen patients (38%) had del(7q) as a large clone and 24 (62%) as a small clone. With a median follow-up of 21 months (range, 1-135 months), 18 (46%) patients developed a therapy-related myeloid neoplasm, including all 15 patients with a large del(7q) clone and 3/24 (12.5%) with a small clone. Of the remaining 21 patients with a small del(7q) clone, 16 showed no evidence of t-MN, and 5 had an inconclusive pathological diagnosis. The authors conclude that isolated del(7q) emerging in patients after cytotoxic therapy may not be associated with t-MN in about half of patients. The clone size of del(7q) is critical; a large clone is almost always associated with therapy-related myeloid neoplasms, whereas a small clone can be a clinically indolent or transient finding.[31]

Chromosome 17 abnormalities. Chromosome 17 (chr17) abnormalities are found in about 2% of patients with de novo myelodysplastic syndrome and about 4.5 % of t-MN.[32,33] In a Spanish study,[32] chromosome 17 abnormalities were classified into three groups: isolated 17 (20.5%), with one additional abnormality (8; 9.1%), and two or more additional abnormalities (complex karyotype) (70.4%). Overall survival and transformation to AML were the same in the first two groups, while there was a significant difference with the patients with complex karyotype.

The Fenaux group,[33] between 1982 and 1996, performed a cytogenetic analysis in 755 cases of MDS and 754 cases of AML, classified according to FAB criteria. Sixty-nine of them (4.6%) had cytogenetic rearrangements leading to 17p deletion, with 25 (36%) occurring after a primary neoplasm treated with chemotherapy and/or radiotherapy; 21 were classified, according to FAB, as MDS, and only 4 as AML. Eighteen patients had unbalanced translocation between chromosome 17 and another chromosome, including chromosome 5 in 8 cases, 7 in three cases, and 1 in one.

Most frequent primary neoplasms were hematologic, with a high prevalence of Philadelphia-negative myeloproliferative neoplasms-, treated with alkylating agents, hydroxyurea or radioactive phosphorus:[33] About half of the patients, in addition, were typical in that they occurred mainly after lymphoid malignancies treated with alkylating agents, and also had monosomy 7 or del 7q. However, the remaining half unexpectedly occurred in ET or PV treated mainly by hydroxyurea, 32P, or pipobroman and rarely presented chromosome 7 abnormalities. p53 mutations and/or abnormal p53 expression were found in 16 of the 19 evaluable cases.

Isolated isochromosome (17q) has also been reported in patients with primary or therapy-related MDS/MPN and AML by the MD Anderson Cancer Center.[34] Myeloid neoplasms with isolated isochromosome 17q

represent a distinct clinicopathologic entity with myelodysplastic and myeloproliferative features, high risk of leukemic transformation, and wild-type TP53.[34] The Hellenic 5-azacytidine registry[35] of 548 adult patients with MDS treated with 5-azacytidine reports 32 patients with a chromosome 17 abnormality (6 with i[17q], 15 with -17, 3 with add[17p] and the rest with other rarer abnormalities, mostly translocations). The presence of a chromosome 17 abnormality was associated with poor prognostic features (high IPSS, IPSS-R, and WPSS scores) and a low overall survival rate (15.7 vs. 36.4 months for patients without chromosome 17 abnormalities. The Brit et Al.[36] study reported the long-term outcomes of 98 patients with AML or MDS with chromosome 17 abnormalities, 55 had de novo MDS/AML, and 43 had secondary MDS/AML. There were no differences between the two groups regarding the presence of monosomal karyotype (69.1 % versus 67.4 %; p = 0.51). Similarly, there was no significant difference in the prevalence of complex karyotype (98.1 % versus 95.3 %; p = 0.41), or of ch17 abnormalities at diagnosis between the two groups (87.3 % versus 83.7 %; p = 0.41).

Chromosome 20. 20q deletion is common in MDS, represents about 5% of all cases of p-MDS, and is considered associated with a good prognosis. Braun et al.[37] have reported for the Groupe Francophone des Myélodysplasies (GFM) over almost 20 years, 62 cases of isolated chromosome 20 deletion and 36 patients with del 20q and other cytogenetic abnormalities, and 1335 MDS patients without del20q. Characteristics of these patients were: lower platelet, a low proportion of marrow blast, and high reticulocyte counts. Median survival was 54 months in patients with isolated del 20q, not reached, and 12 months for del 20q with one or several additional abnormalities, respectively (p = 0.035), confirming the favorable prognosis of del20q without complex abnormalities. Kanagal-Shamanna et al.[38] from MD Anderson Cancer Center identified five cases of t-MN and 26 cases of de novo MDS with isolated del(20q) over ten years.[38] All cases had a long latency interval from the treatment of the primary malignancy to the onset of t-MN, and all were associated with frequent bone marrow dysplasia. del(20q) was the sole abnormality detected at the time of diagnosis of t-MN in three cases, six years before diagnosis in one case, and at the time of relapse of AML in one case. Three patients with t-MDS had a relatively indolent clinical course, whereas two presented with AML or developed AML shortly after t-MDS. The patients with de novo MDS and isolated del(20q) frequently presented with anemia and thrombocytopenia associated with bone marrow dysplasia. The median overall survival was 64 months.[38] Frequently, these patients had minimal signs of dysplasia and an indolent course.[39]

Yin, Peng, Shamanna et Al.[40] identified 92 patients who acquired isolated del(20q) following cytotoxic therapies for malignant neoplasms. Seventy-six patients showed interstitial, and sixteen patients showed terminal 20q deletion. The median interval from prior cytotoxic therapies to del(20q) detection was 58 months (range, 5-213 months). With a median follow-up of 23 months (range, 1-183 months), 21 (23%) patients developed a t-MN, and 71 (77%) patients did not. In patients who developed a t-MN, del(20q) was present in a higher percentage of metaphases (60 vs. 25%, P<0.0001); persisted for a longer period (24 vs. 10 months, P=0.0487); and was more often a terminal deletion (33 vs. 13%, P=0.0006) compared with patients who did not develop t-MN. Clonal evolution was only detected in t-MN (4 patients, 19%).

These data show that del(20q) emerging after cytotoxic therapy represents an innocuous finding in more than two-thirds of patients. However, in patients who develop a t-MN, del(20q) often involves a higher percentage of metaphases, persists longer, and more frequently is a terminal rather than an interstitial deletion.

Cameron Yin et al.[41] reported 64 patients with chronic lymphocytic leukemia (CLL) and del(20q) as the sole abnormality in 40, a stemline abnormality in 21, and a secondary abnormality in 3 cases. Fluorescence in situ hybridization (FISH) analysis revealed an additional high-risk abnormality, del(11q) or del(17p), in 25/64 (39%) cases. In most cases, the leukemic cells showed atypical cytologic features, unmutated IGHV (immunoglobulin heavy-chain variable region) genes, and ZAP70 positivity. The del(20q) was detected only after chemotherapy in all 27 cases with initial karyotype information available. With a median follow-up of 90 months, 30 patients (47%) died, most due to CLL. Eight patients developed a t-MN, seven with a complex karyotype. In 12 cases without morphologic evidence of a myeloid neoplasm, combining morphologic and FISH analysis, localized the del(20q) to the CLL in 5 (42%) cases and to myeloid/erythroid cells in 7 (58%) cases. The del(20q) was detected in myeloid cells in all 4 cases of MDS. Together, these data indicate that CLL with del(20q) acquired after therapy is heterogeneous. In the cases with morphologic evidence of dysplasia, the del(20q) likely resides in the myeloid lineage. However, in cases without morphologic evidence of dysplasia, the del(20q) may represent clonal evolution and disease progression. Combining morphologic analysis with FISH for del(20q) or performing FISH on immunomagnetically selected sub-populations to localize the cell population with this abnormality may help guide patient management.

Nilsson et al.,[42] analyzed chromosome abnormalities in MM/MGUS, including 122 MM and 26 MGUS/smoldering MM (SMM) cases. Sixty-six (54%) MMs and 8 (31%) MGUS/SMMs were karyotypically

abnormal. Of these, 6 (9%) MMs and 3 (38%) MGUS/SMMs displayed myeloid abnormalities, that is, +8 (1 case) and 20q- (8 cases) as the only anomalies, without any evidence of MDS/AML. One patient developed AML, whereas no MDS/AML occurred in the remaining eight patients. In one MGUS, FISH analyses revealed del(20q) in CD34+CD38- (hematopoietic stem cells), CD34+CD38+ (progenitors), CD19+ (B cells), and CD15+ (myeloid cells). These data indicate that 20q- occurs in 10% of karyotypically abnormal MM/MGUS cases and might arise at a multipotent progenitor/stem cell level. Patients with sole del(20q) chromosomal abnormality and without morphologic features of a MN display variable clinical outcomes. To explore the potential risk stratification markers in this group of patients, Ravindran et Al. evaluated the mutational landscape by a 35-gene MN-focused next-generation sequencing (NGS) panel and examined the association of mutations to MN progression.[43] Fifty-five patients with isolated del(20q) were studied over ten years, of whom 23 (41.1%) harbored at least one mutation, and 16.1% of them progressed into MNs during follow-up. Thus, all patients who progressed harbored one or more pathogenic mutations at the time of isolated del(20q) diagnosis, and the presence of mutations was a statistically significant risk factor for MN progression. Additionally, among the 23 patients harboring mutations, DTA epigenetic modifier mutations (DTA: *DNMT3A, TET2,* and *ASXL1*) did not influence progression, whereas mutations occurring in the non-DTA genes were differentially distributed in patients with and without progression. The mutations involving non-DTA genes include IDH1, IDH2, and BCOR, kinases CBL, PTPN11, JAK2, tumor suppressors TP53 and PHF6, and transcription factor RUNX1.

In conclusion, several studies show that chromosome 20 deletion in both de novo and t-MDS has a favorable prognostic significance when isolated, and its presence does not necessarily bring about a t-MN.

Somatic Mutations. Since traditional morphology, cytogenetics, and flow cytometry failed to identify clinical features differentiating t-MDS from p-MDS, several authors are trying to define a molecular landscape able to distinguish these two subgroups of MDS according to the presence of somatic mutations in genes known to be involved in myeloid neoplasm pathogenesis. Accordingly, 78 to 90% of MDS patients have one or more oncogenic mutations. Furthermore, de novo MDS show a mutational profile prevalently characterized by a high frequency of somatic mutations in genes involved in spliceosome machinery[44,45] (prevalently, SF3B1, SRSF2, U2AF1, and ZRSR2), DNA methylation regulators (DNMT3A, TET2, IDH1and IDH2), histone modifiers (ASXL1 and EZH2), transcription factors (RUNX1, TP53, and others) and signal transduction

genes (JAK2, KRAS, CBL).[45,46]

Mutations in the spliceosome machinery gene SF3B1 (Splicing Factor 3b Subunit 1) were closely associated with specific MDS subgroups with ring sideroblast (RS).[45,47] The recently published data extrapolated from the dataset of the IWG-PM (International Working Group for the Prognosis of MDS) strongly confirm the enrichment of these mutations in refractory anemia with RS (RARS) and refractory cytopenia multilineage dysplasia with RS (RCMD-RS) in 82% and 75% of cases, respectively.[48] Due to the tight association of SF3B1 mutations with the disease phenotype of RS,[49,50] according to "The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia", a diagnosis of MDS-RS can be made if ring sideroblasts are >5% of nucleated red cells, and a somatic mutation of SF3B1 is present, instead of 15% of RS without mutation.[1]

Several reports suggest that SF3B1 mutations have a good prognostic value on overall survival (OS) and risk of disease progression, and these findings were recently confirmed in very low and low-risk IPSS-R categories by the analysis of IWG data set.[46-50]

Although t-MN and p-MDS patients with very low or low IPSS-R show similar biological and clinical characteristics, the RS phenotype in t-MN is not associated with improved survival, even if mutations in spliceosome machinery genes have been identified at higher frequency in p-MDS compared to t-MN (56.5% vs. 25.6%, respectively)[51] and among genes belonging to this pathway, SF3B1 and U2AF1 are more frequently mutated in p-MDS (25.9% vs. 6.2% and 7.4% vs. 1.6%, respectively). In contrast, mutations in SRSF2 and ZRSR2 genes seem equally distributed. Singhal et al. showed a similar frequency of RS in their p-MDS and t-MN cohorts (29.6% vs. 24.8%), but RSs were 15% of erythroid cells in 21.3% of p-MDS and in only 14.7% of t-MN.[51] Remarkably, mutations in spliceosome pathway were identified in all patients with p-MDS and 15% of RS (SF3B1, 96%), but only in 37% of t-MN with 15% of RS (SF3B1, 32%), showing a less significant association of these mutations with the RS phenotype. Moreover, the authors identified TP53 mutations in 29.5% of the entire cohort of t-MN patients and, unexpectedly, in 92% of those with 15% RS and no SF3B1 mutations, highlighting a new potential role of TP53 mutations in the context of t-MN with RS. In this line, the median OS of t-MN with 15% RS (12 months) was significantly lower than that of p-MDS with 15% RS (38 months), pointing out the poor prognostic role of TP53 mutations also in t-MN patients with RS and the weak association with SF3B1 mutations.[51] The group of MD Anderson Cancer Center reported similar data:[52] Commonly mutated genes were TP53 (56.5%), TET2 (39.1%), SF3B1 (35.7%), ASXL1 (30.4%), DNMT3A (17.4%), RUNX1 (17.4%) and SRSF2 (14.3%). Compared with d-

MDS-RS, TP53 mutation was more common, but SF3B1 mutation was less common in t-MDS-RS (p < 0.05). In t-MDS-RS, Mutations in 4 genes (SF3B1, U2AF1, SRSF2, and ZRSR2) involving RNA splicing were found in about 50% of patients compared to ˜90% in d-MDS-RS. Overall survival was by far worse in t-MDS-RS compared to d-MDS-RS (median overall survival: 10.9 months and 111.9 months in t-MDS-RS and p-MDS-RS, respectively, p < 0.05). Progression to AML was more common in t-MDS-RS (18.4% vs. 7.4% in t-MDS-RS and d-MDS-RS, respectively, p < 0.05). Unlike de novo MDS, t-MDS-RS did not have a different outcome than t-MDS without RS (median OS: 10.9 months vs. 14.3 months, respectively, p=0.2341). Mutation profiles suggest that RS in t-MDS might be a secondary event in at least 50% of the cases or not related to mutations in RNA splicing machinery, unlike p-MDS, where they occur early and are associated with ineffective erythropoiesis. Although in the last decade, the mutational profiles of p-MDS and t-MN have been extensively analyzed, identifying 79% to 95% of patients mutated in at least one gene, without significant differences in cohorts, and none of the studied genes exclusively mutated in one of them, the prevalence of cases mutated in specific genes seem to be different[52,53,54]

Today, mutations in the TP53 gene are considered the most frequent molecular alterations identified in t-MDS/t-MN patients, with a frequency from 30 to 47%, according to both specific characteristics of the study cohort and depth of sequencing technologies.[51-56] In these series of patients, authors also identified a tight association of TP53 mutations with the presence of complex karyotype, defined as three chromosomal abnormalities, in about 80% of cases, and a poor prognosis compared to TP53 wild-type t-MN patients. In 2017, Lindsley et al., screening through t-NGS technology the mutational profile of a large cohort of 1514 MDS patients undergoing Hematopoietic Stem Cell Transplantation (HSCT), found interesting differences in the frequency of TP53 mutations stratifying patients according to p-MDS and t-MDS (311 patients) subgroups.[53] They found a higher prevalence of TP53 mutations in t-MDS than p-MDS (38% vs. 14%, respectively) and significantly shorter survival. Of note, in t-MDS, the authors also identified a higher frequency of mutations in the TP53 regulator PPM1D compared to p-MDS (15% vs. 3%, respectively), reaching the quote of 46% of mutations in TP53 or PPM1D.

Furthermore, the co-occurrence of TP53 and PPM1D mutations was higher in t-MDS than stochastically expected in patients with PPM1D mutations alone (51%), when compared with PPM1D and TP53 double wild-type patients, had a similar frequency as those with TP53 mutations alone (39%) or double mutated PPM1D and TP53 (54%).[53] Although PPM1D gene encodes a serine-threonine protein phosphatase, involved in the cellular response to environmental stress and therefore to exposure to leukemogenic therapies, through the inhibition of TP53 activity, PPM1D mutated t-MDS patients without TP53 mutations did not show any association with the presence of complex karyotypes and adverse prognosis. Even if more frequent than p-MDS,
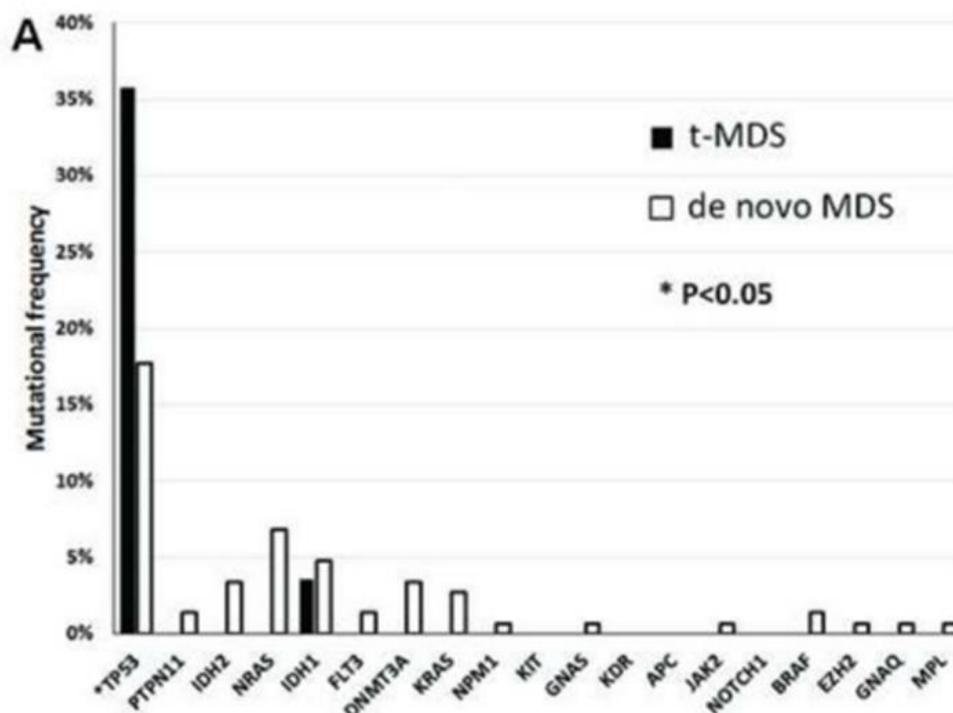

Figure 5. Mutational profiles in myeloid neoplasms. Mutational profile of therapy-related myelodysplastic syndromes (t-MDS) versus de novo

MDS. Asterisk denotes genes with a significant difference between t-MDS versus p-MDS.
Ok et al.[56] Leukemia Res., 2015.

TP53 mutation characteristics in t-MDS and t-AML are similar to de novo diseases.[55] Consistent with the tumor-suppressive role of TP53, patients may harbor both mono- and biallelic mutations. The International Working Group for Prognosis in MDS[56] assembled a cohort of 3,324 with MDS and studied the effect of TP53 allelic state on genome stability, clinical presentation, outcome, and response to therapy.[56] Outcomes of monoallelic cases significantly differed with the number of co-occurring driver mutations; for example, the 5-year survival rate of monoallelic patients with no other identifiable mutations was 81%, while it was 36% for patients with one or two other mutations, 26% for patients with three or four other mutations, and 8% for patients with more than five other mutations.

Other than prognostic predictors of outcome, acquired somatic mutations may also play a pivotal role in the context of MDS susceptibility. In 2014 a real earthquake shocked the world of hematologists redefining the borders between hematology and onco-hematology by discovering acquired somatic mutations in the same genes previously known to be involved in myeloid neoplasms in older people without traces of hematologic disorders. In independent works, screening by whole-exome sequencing (WES) in large cohorts of non-hematological patients, Genovese and Jaiswal, identified a close association between hematopoietic stem cell aging and the accumulation of somatic mutations in patients without hematological malignancies.[57,58] These mutations, now known as DTA (DNMT3A, TET2, and ASXL1), have been found enriched in a linear relationship with age, with about 20% of mutations in people 80 years old. Although DTA genes were the most enriched, other genes such as JAK2, SF3B1, PPM1D, and TP53 were found enriched in a linear relationship with age, while others such as FLT3, NPM1, IDH1, and IDH2 were rarely found mutated in these subjects.[59] These scenarios of clonal hematopoiesis, now defined as ARCH (Age-related clonal hematopoiesis) or CHIP (Clonal hematopoiesis of indeterminate potential) according to the VAF of identified mutations (without a specific cut-off or 2%, respectively),[59] have been linked to an overall increased risk of transformation to hematological malignancy, with a risk of progression of about 0.5–1% per year vs. <0.1% in non-CHIP carriers, and may represent a pre-malignant state in p-MDS and t-MN, whose development can be triggered by exposure to cytotoxic damage.[57,58,60] In this line, several authors were able to identify pre-existing somatic mutations, at very low VAF, in patients who developed a t-MN after a chemo/radiotherapeutic treatment for a primary tumor or an autoimmune disease, demonstrating the expansion of CHIP mutations and their role as a predisposing factor for MN development.[61-66] Very recently, Zeventer et al., using high-throughput t-NGS technology (gene panel of 27 driver genes at a VAF of 1%), redefined the prevalence of clonal hematopoiesis (CH) in a cohort of 621 individuals aged 80 years extrapolated from the LifeLines cohort (Netherlands database of 167,729 participants).[67] Clonal hematopoiesis was identified in the peripheral blood of 61.5% of individuals, without differences across gender. DNMT3A was mutated in 219 of 621 individuals (35%), 27% with multiple mutations. Similar results were reported for TET2 (166 of 621 individuals (27%), with multiple mutations in 24% of cases, while ASXL1, spliceosome machinery, and TP53 variants were identified at lower frequencies (6%, 4%, and 3%, respectively). Although CH was not associated with a higher risk of death in the complex, individuals carriers of mutations in genes other than DNMT3A and TET2 were at higher risk than wild-type controls (HR, 1.48; CI, 1.06-2.08). In the same line, the authors did not identify any association between elevated risk of exposure to DNA damaging toxicities (job-related exposure to pesticides, exposure to cytotoxic and/or radiation therapy for primary cancer, and smoking status), and both the prevalence of CH and the number of somatic variants.

In contrast, mutations in selected driver genes, such as spliceosome machinery and ASXL1, were identified at higher frequencies in exposed individuals (6% vs. 1% and 7% vs. 2%, respectively).[67] In this line, our group recently showed that patients CLL who developed a t-MN following treatment with chemoimmunotherapy presented prior to treatment start mutations in CHIP-related genes at a significantly higher prevalence than a large cohort of control CLL. These data show that CHIP increases susceptibility to t-MN also in the CLL context.

In the last few years, a rare mutation in MDS, the Nucleophosmin (NPM1) mutation common in AML and associated with high remission rates and prolonged survival with intensive chemotherapy, has assumed a particular significance.[69] NPM1 mutations are rare in syndromes p-MDS (MDS/MPN), representing about 2% of all MDS.[70,71] The different outcomes of these patients, if treated with intensive chemotherapy or demethylating agent, induce to combine them in a subgroup. The NPM1 mutations have been found even more rarely in t-MDS and more frequently in t-AML.[71,72] Andersen et al. observed NPM1 mutations in 7 of 51 patients presenting as overt t-AML, as compared to only 3 of 89 patients presenting as t-MDS (P<0.037); only 1 of 10 patients with NPM1 mutations presented chromosome aberrations characteristic of the therapy-related disease, and 7q-/-7, and 5q-/-5 the most frequent abnormalities of t-MDS/t-AML, were not observed (P<0.002). This raised the question of whether some of the cases presenting NPM1 mutations were, in fact, cases of de novo leukemia or de novo MDS.[72] This same issue is relevant

in p-MDS, where the presence of NPM1 mutations is associated with an increased rate of AML transformation, raising the question of whether these MDS indeed represent AML at an early stage.

All these data highlight the potential role of acquired mutations and/or cytogenetic abnormalities in the definition of de novo and therapy-related MDS, which will have to be taken into account in the next editions of the WHO classification.

Epigenetic Regulation. Changes in gene expression not directly linked to changes in DNA sequence constitute the fundamental concept of epigenetic regulation. Aberrant differentiation in MDS can often be traced to an abnormal epigenetic process represented by both gains and losses of DNA methylation genome-wide and at specific loci, as well as mutations in genes that regulate epigenetic programs, such as TET2 and DNMT3a, involved in DNA methylation control, and EZH2 and ASXL1, involved in histone methylation control.[72]

Epigenetic changes include various covalent modifications of nucleic acids and histones, which finely coordinate the gene expression of single cells, defining their role and phenotype. These regulatory mechanisms mainly include DNA methylation, histone modifications, and chromatin remodeling. Alterations in epigenetic regulation have been tightly associated with cancer development and progression.[74] Moreover, since all these mechanisms are reversible, the involved genes are considered important epigenetic targets for drug development and patient treatment. Of note, many genes involved in epigenetic regulation, such as DNA methylation regulators (DNMT3A, TET2, IDH1, and IDH2) and histone modifiers (ASXL1 and EZH2), have been identified as being frequently mutated in MDS.[44-46]

Epigenetic regulation through DNA methylation is mainly driven by DNA methyltransferase enzymes (DNMTs) by the addition of a methyl group (CH_3) to a cytosine residue (5-methylcytosine) within a CpG dinucleotide.[75] Regions enriched in CpG dinucleotides (CpG islands) have been found in the promoter region of about 50% of human genes, but a methylation enrichment was also found in enhancers and transcription factor binding sites.[76]

The nucleoside analog azacytidine (AZA, Vidaza®, Celgene) and its deoxy derivative decitabine (DAC, Dacogen®, Janssen)are able to stimulate gene expression through DNA hypomethylation, following irreversible DNMTs sequestration.[77] However, this action is reversible since inhibitors do not influence *de novo* DNMTs synthesis. In this line, *de novo* DNMTs synthesis could explain the rapid relapse after treatment interruption and the requirement for maintenance treatment as long as the response persists.[78,79]

Several authors tried to identify specific DNA sequences or methylation profiles useful as a marker of response to hypomethylating agents that may help to support the decision to continue or stop hypomethylating treatment.

Although gene-specific hypermethylation has been identified as a negative prognostic factor in hematological malignancies, there is no complete agreement on the role of specific candidate genes.

Among these, genes belonging to lineage commitment, apoptosis, cell cycle, immune response, signal transduction, and cytoskeletal remodeling are hypermethylated in MDS patients, and their expression could be modulated by hypomethylating treatment.[80-85]

In addition, the hypermethylation of some promoter genes, like DAPK1, E-cadherin, and thrombospondin-1, has been reported by several groups, including ours, as more frequent in t-MDS than p-MDS.[86]

Recently, Reilly et al. characterized the methylation profile of 114 bone marrow DNA samples from MDS patients using the bisulfite padlock probe (BSPP) sequencing method to highlight differentially methylated regions of genes belonging to different cellular pathways.[87]

Their results showed five unique methylation clusters, resulting from the bioinformatics analysis "OncoGenic Positioning System Onco-GPS", useful to sub-classify MDS patients according to their methylation profile. In particular, each methylation cluster was enriched for specific genetic variants and cytogenetic alterations, although different mutational profiles may share the same methylation state. Interestingly, their data showed that the variants in splicing factor genes were mutually exclusive and enriched in specific methylation subgroups.[87] These authors did not observe statistically significant associations between specific methylation clusters and clinical laboratory parameters such as cytopenia or bone marrow blasts percentage. On the other hand, the overall survival curves showed differences in patients belonging to specific methylation sub-groups, identifying two major patterns, demonstrating that, although genetic variants alone are insufficient for determining the methylation profile of MDS patients, the latter could be supplemental information for the prognostic stratification.

Finally, they observed enrichment of cluster-specific methylated regions not only in CpG islands belonging to promoter regions but also in distal regulatory regions of the epigenome. Indeed, results showed an equal or greater number of differentially methylated regions outside promoters.

More recently, Cabezón et al. performed a supervised global methylation analysis of 75 high-risk MDS and secondary AML patients included in CETLAM SMD-09 protocol and treated with HMA or intensive treatment according to age, comorbidities, and cytogenetics. They were able to identify a methylation signature defined by

200 probes, useful to distinguish responder from non-responder patients under AZA treatment.[88]

The same authors also identified a methylation pathway that differentiated patients according to their survival. In contrast, the methylation signature detected at the time of diagnosis was not useful for distinguishing patients who would relapse or progress.[88]

In this study, high-risk MDS and sAML showed a more heterogeneous pathway of methylation than age-matched healthy controls, and this heterogeneity precluded the separation of the patients into distinct subgroups.

While many studies have explored the epigenome of *de novo* MDS, little is known about the epigenetics of t-MN and, in particular, t-MDS.

Treatment. The therapy for MDS depends on the stage of the disease, age, comorbidities, and infections.[89-91] The stage has been historically risk-stratified using the International Prognostic Scoring System (IPSS) for MDS,[91] updated with the revised-IPSS (IPSS-R), in more recently by the molecular IPSS-M and the Euro MDS scores.[13,92] The disease stage is risk-based on cytogenetic abnormalities, the degree of cytopenias, and the percentage of bone marrow blasts. The IPSS-R subdivides patients into five groups (very low-, low-, intermediate-, high-, very high-risk) that differ in survival and risk of leukemic transformation. This classification is clinically relevant as the treatment approach differs between higher-risk and lower-risk patient subgroups.[89] However, it has been well recognized that some patients with lower-risk (LR)-MDS using IPSS or IPSS-R do not fare well. Mutations are not considered in the risk stratifications of IPSS and are particularly important in worsening the prognosis in patients with normal cytogenetics.[92,93,94] Therefore, inherent limitations of the current prognostic tools should be recognized in making clinical decisions for individual patients. Integrating molecular assessment in risk stratification tools in the Euro-MDS and IPSS-M scores will likely increase their precision and utility in clinical practice.[92-94] Therapy-related MDS have been classified together with the t-AML in the group of t-MN and considered to have the same poor prognosis, independently of the number of blasts found in the marrow.[1,7] However, in the last few years, it appeared more and more evident that the prognosis of the t-MDS is well evaluated utilizing the same parameter employed for p-MDS.[8,14,16] At variance with p-MDS,[21] most patients with t-MDS belong to high or very high risk categories, independently of the origin.[14,16] (**Figure 1, 2**; **Table 3**). The treatment goals of p-MDS and t-MDS are the same: to alter the natural history of the disease, decrease the risk of leukemic progression, and improve survival. However, the only cure of either p-MDS and t-MDS remains the allogeneic hematopoietic cell transplant (HSCT), recommended option in such patients if they are candidates for the procedure, following p-MDS established criteria.[95,96] An unanswered question is whether the transplant should be performed after the high-dose chemotherapy or immediately; a third hypothesis could be after the azacytidine bridge.[97] In any case, like all treatments, HSCT is deeply influenced by cytogenetics and mutations.[53,56] In particular, the mutations *P53*, frequently associated with complex karyotypes, are strong negative prognostic factors in younger patients.[53,56]

Nevertheless, most patients are not candidates to transplant, so patients with p-MDS or t-MDS are most often treated with the hypomethylating agents, azacytidine or decitabine.[98-108] The hypomethylating agents are both approved for MDS therapy by FDA and EMA and are similarly effective in p-MDS and t-MDS in strict relationship with cytogenetics and mutations found in the patient. Klimek et al.[100] report results in 42 patients with therapy-related MDS treated with either 5-azacitidine (AC) or 21-deoxy-5-azacitidine (DAC). Patients were 25–85 (median 70) years of age and covered the entire spectrum of MDS disease stages. As expected, 69% of patients had poor-risk cytogenetics by IPSS criteria.[8,14] The overall response rate was 38%, and complete remissions occurred in six patients (14%). The median overall survival from the start of therapy was 9.2 months. Thus, these results are very similar, if not identical, to what has been reported with AC for all-comers, most of whom have been patients with de novo MDS.

The demonstrated efficacy of demethylating agents has induced researchers to improve their efficacy by adding other drugs; the anti-PD-1 antibodies seem to be the most promising.[108-109] Furthermore, a series of targeted therapies are under investigation for HR-MDS patients, such as the IDH1 and IDH2 inhibitors evaluated in clinical trials with ivosidenib and enasidenib, respectively.[110,11] Furthermore, there is a promising pipeline of novel agents under active investigation in HR-MDS. For patients with LR-MDS, the treatment goals are to improve their quality of life by managing the underlying cytopenias and side effects. The majority of patients are anemic at presentation, representing a major clinical challenge.[3] Treatment options in this group of patients include active surveillance, red blood cell (RBC) transfusions, erythropoiesis-stimulating agents (ESAs), lenalidomide in patients with del (5q), hypomethylating agents also as oral therapy (HMAs), luspatercept in patients with ring sideroblasts, and immunosuppressive agents in a select group of patients.[110,111]

However, there is no experience of these new drugs in t-MDS, which constitutes about 10% of all MDS.[108] In addition, therapy-related MDS patients are often excluded from therapeutic clinical trials, so a comparison between de novo and therapy-related MDS outcomes

with the same stage and therapies is difficult to find in the literature.

Borate et al.[113] in their initial search, examined 1148 therapeutic clinical trials on MDS; however, excluding the trial, which did not mention t-MDS (831), and trials that excluded specifically t-MDS, they found only 18 studies (5.7%) that accrued 231 t-MDS patients in total, representing 3.2% of the total accrued MDS trial patient population. In addition, fewer t-MDS patients were accrued in therapeutic trials sponsored by pharmaceutical sponsors vs. nonpharmaceutical sponsors (2.8% vs. 4.0%; *P* 5 .0073). This pattern of exclusion continues in actively enrolling trials; only 5 (10%) of 49 studies specifically mention the inclusion of t-MDS patients in their eligibility criteria. These results indicate that therapeutic MDS trials seem to exclude t-MDS patients, rendering study results less applicable to this subset of MDS patients, who often have poor outcomes.[17,102,106] Another problem is that in the trials, t-MDS are frequently included together with t-AML as t-MN as reported by the WHO classification of myeloid neoplasm.[1-114]

Conclusions. The characterization of t-MDS and t-AML[8,14,17] has been recently improved with the use of advanced molecular techniques, and although sharing some overlapping features, these diseases exhibit substantial differences in molecular and cytogenetic characteristics and clinical presentation. A future updated classification should consider these issues, and the proposal to separate t-MDS from t-AML should be discussed. In this line, therapy-related MDS could become a subgroup of MDS. Indeed, since there is no specific marker for therapy-related MN, the diagnosis is made on an anamnestic base only, and this does not exclude that some cases of p-MDS may present after cytotoxic therapy and be defined t-MDS but still display genetic characteristics of p-MDS.

The same path has been taken in t-AML with recurrent translocations, characterized by t(15;17), t(8;21), or inv(16), which, following recent guidelines, should be treated according to patients' fitness, and not to a previous history of cytotoxic treatment, since the outcome of these AMLs in similar in de novo and therapy-related forms.

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