Prognostic Implications of Cytogenetic Features in Myelodysplastic Syndromes

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Abstract

Myelodysplastic Syndromes (MDS) are a heterogeneous group of hematologic diseases characterized by refractory cytopenia(s) and variable risk of leukemic progression. Cytogenetic analysis is important in day-to-day clinical practice helping to define subgroups of MDS patients who share similarities in the course of the disease. There are recurring aberrations affecting chromosomes 5, 7, 8, and 20. While all of them do not suggest a therapeutic approach, their presence has been considered as a risk indicator since the original international prognostic scoring system (IPSS) was published. The most recent cytogenetic stratifications tried to find the prognostic significance of less frequent alterations which have been longer included in the intermediate group. Moreover, monitoring of karyotype changes is suggested to evaluate cytogenetic response to treatments and the acquisition of new aberrations associated to an unfavorable outcome. This review focuses on different cytogenetic risk stratifications that have been published during the past 20 years and the molecular background of the most relevant chromosomal findings.

Myelodysplastic Syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell diseases characterized by morphologic changes in the bone marrow, peripheral cytopenia(s), and susceptibility to bone marrow failure with or without progression to Acute Myeloid Leukemia (AML). Although there is an inherited predisposition to develop MDS/AML in patients with congenital bone marrow failure syndromes, most of MDS are idiopathic and develop de novo MDS without any pre-existing hematologic abnormalities. In secondary MDS, cytotoxic chemotherapy and radiation exposure are major factors in the induction of marrow failure and subsequent malignant transformation.[1-5]

Cytogenetic analyses have proven an extremely valuable diagnostic tools in MDS, involving the whole genome, supporting the cytomorphologic diagnosis, confirming disease clonality, providing prognostic information, and, in some cases, helping with selection of treatment. The frequency of clonal chromosomal abnormalities in de novo MDS varies between 14–65 % (see Table 1) increasing to nearly 80 % in secondary MDS.[6-31] Cytogenetic findings are not specific for the disease because they can be observed in other oncohematologic disorders and none of them is specifically associated with any morphologic subtype (except for the isolated del(5q) in the presence of blast count less than 5 %, which is considered as distinct entity by the World Health Organization [WHO] classification). However, the proportion of normal karyotypes decreases according to worsening prognosis from 54–59 % in refractory anemia (RA) and RA with ringed sideroblasts (RS) to 41–34 % in RA with excess of blasts (RAEB) and RAEB in transformation (RAEBt) patients (see Table 2).[7,8,10,11,16,21-22,24,27,32-34] The wide range of percentage of observed cytogenetic alterations in published MDS series may be related to difficulties in assessing and discriminating between regional variations, differences in classification, sizes of the population based-studies and the inclusion/exclusion of therapy-related MDS or AML cases (see Table 1).[6-31]

MDS are not associated with any specific chromosomal alteration and can vary from simple to complex.[6,9,11-12,34-35] Although all chromosomes may be involved in a variety of cytogenetic aberrations, chromosomes 5, 7, 11, 17, 20 and Y are the most commonly affected, mainly by partial or total loss; followed by trisomies of chromosomes 8 and 21, and rare translocations or other structural alterations predominantly implicating chromosomes 1, 2, 3 and 11.[34] Deletions are more often interstitials and display variable sizes; however, 'common deleted regions' have been described for most

Table 1: Cytogenetic Alterations in Different Published Myelodysplastic Syndromes Series

Series	Country	Normal (%)	5q- (%)	7/7q- (%)	+ 8 (%)	20q- (%)	-Y (%)	Others (%)	Complex Karyotypes (%)	Total
Morel et al., 1993[6] $	France	259 (63)	19 (5)	11 (3)	12 (3)	9 (3)	8 (2)	23 (6)	67 (16)	408
Paquette et al., 1993[7]	USA	124 (60)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	208
Parlier et al., 1994[8] $	Switzerland	48 (44)	9 (8)	5 (4)	4 (4)	5 (5)	5 (4)	17 (16)	16 (15)	109
Greenberg et al., 1997[9] $	International	489 (60)	48 (6)	10 (1)	38 (5)	16 (2)	17 (2)	117 (14)	81 (10)	816
de Souza Fernandez, et al., 2000[10] $	Brazil	76 (61)	9 (7)	6 (5)	3 (2)	2 (2)	3 (2)	25 (20)	1 (1)	125
Solé et al., 2000[11] $	Spain	313 (49)	32 (5)	24 (4)	31 (5)	8 (1)	8 (1)	136 (21)	88 (14)	640
Belli et al., 2002[12] $	Argentine	116 (59)	5 (3)	9 (5)	6 (3)	4 (2)	1 (1)	35 (17)	22 (11)	198
Lee et al., 2003[13] $	Korea	67 (56)	2 (2)	2 (2)	7 (6)	0 (0)	3 (3)	20 (17)	18 (15)	119
Lau et al., 2004[14] $	Singapore	21 (53)	0 (0)	n.s	n.s	n.s	n.s	n.s.	8 (20)	40
Lorand-Metze et al., 2004[15] &	Brazil	74 (86)	1 (1)	1 (1)	1 (1)	0 (0)	2 (2)	0 (0)	7 (8)	86
Solé et al., 2005[16] $	Spain	514 (53)	55 (6)	43 (4)	56 (6)	13(1)	17(2)	163 (17)	107 (11)	968
Malcovati et al., 2005[17] &	Italy	222 (58)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	386
Müller-Berndorff et al., 2006[18] $	Germany	46 (58)	5 (6)	3 (4)	n.s.	n.s.	1 (1)	13 (16)	11 (14)	79
Irons et al., 2006[19] &	China	121 (74)	0 (0)	n.s.	n.s.	n.s.	n.s.	n.s.	8 (5)	164
Sakuma et al., 2006[20] &#	Japan	43 (43)	0 (0)	1 (1)	6 (6)	5 (5)	6 (6)	12 (12)	27 (27)	100
Bernasconi et al., 2007[21] $	Italy	197 (40)	43 (9)	33 (7)	22 (4)	15 (3)	5 (1)	135 (27)	41 (8)	491
Haase et al., 2007, 2008[22-23] $ # *	Germany–Austria	988 (48)	146 (7)	86 (4)	81 (4)	36 (2)	41 (2)	395 (19)	299 (14)	2072
Gmidene et al., 2008[24] $	Tunisia	110 (49)	30 (13)	17 (8)	7 (3)	7 (3)	1 (1)	34 (15)	18 (8)	224
Poznyakova et al., 2008[25] &	USA	571 (55)	61 (6)	17 (2)	38 (4)	28 (3)	22 (2)	111 (11)	181 (18)	1029
Kantarjian et al., 2008[26] $ *	USA	440 (46)	27 (3)	n.s	n.s.	21 (2)	14 (1)	123 (13)	n.s.	958
Vundinti et al., 2009[27] $ @ *	India	66 (45) £	5 (3)	11 (8)	4 (3)	1 (1)	0 (0)	58 (40)	0 (0)	145
Schanz 2011[28] $	Germany-Austria-USA	1156 (49)	146 (6)	99 (4)	132 (6)	52 (2)	42 (2)	266 (11)	458 (20)	2351
Qu et al., 2012[29] &	China	186 (35)	8 (2)	n.s.	67 (13)	n.s.	n.s.	n.s.	85 (16)	532
Belli et al., 2012[30] $	Argentine	296 (57)	19 (4)	15 (3)	26 (5)	14 (3)	14 (3)	93 (18)	41 (8)	518
Schanz et al., 2012[31] $	International	1543 (55)	180 (6)	59 (2)	133 (5)	48 (2)	63 (2)	519 (19)	256 (9)	2801
Mean (Range)		52 (35–86)%	6 (0–13)%	3 (1–8)%	5 (1–13)%	2 (0–5)%	2 (1–6)%	16 (0–40)%	12 (0–27)%	

$ = FAB classified population, # = including patients with AML, * = including patients with seccondary MDS & WHO classified population, @ = including pediatric cases, £ = including FISH results; ns = non specified, ¥ = excluding patients with Chronic Myelomonocitic Leukemia.

of these.[36,37] The predominance of partial or total chromosomal losses suggests involvement of tumor suppressor genes. One of both alleles is deleted and the remaining may also be deleted, mutated, or silenced by aberrant hypermethylation. However, other relevant mechanisms have been recently added to this list: segments of acquired uniparental disomy (injury resulting in loss of heterozygosity that does not alter the number of copies) that probably represent an attempt to repair chromosomal deletions using the remaining chromosome copy as template[38] and haploinsufficiency (when the protein produced by a normal gene copy is not sufficient to fulfill its function).[39]

Table 2: Normal Karyotype According to Each French-American-British Subgroup

Series	Country	FAB Categories				
		RA (%)	RARS (%)	RAEB (%)	RAEBt (%)	CMML (%)
Paquette et al., 1993[7]	USA	53/71 (75)	30/43 (70)	23/ 54(43)	4/21 (19)	14/19 (74)
Parlier et al., 1994[8]	Switzerland	10/21 (48)	13/26 (50)	7/16 (44)	3/10 (30)	14/25 (56)
de Souza Fernandez, et al., 2000[10]	Brazil	59/74 (80)	8/9 (89)	6/21 (29)	0/14 (0)	3/7 (43)
Solé et al., 2000[11]	Spain	104/184 (57)	51/76 (67)	80/208 (39)	24/79 (30)	54/93 (58)
Nösslinger et al., 2001[32]	Austria	(45)	(55)	(48)	(38)	(52)
Matsuda et al, 2005[33]	Japan	72/102 (71)				
	Germany	94/199 (47)				
Solé et al., 2005[16]	Spain	151/264 (57)	106/160 (66)	109/ 269 (41)	31/ 105 (30)	117/170 (69)
Bernasconi et al., 2007[21]	Italy	99/209 (47)	45/79 (57)	44/152 (29)	9/51 (18)	Not included
Haase et al., 2007[22]	Germany-Austria	267/573 (47)	147/252 (58)	179/415 (43)	132/305 (43)	170/272 (63)
Gmidene et al., 2008[24]	Tunisia	36/78 (46)	10/21 (48)	29/ 57 (51)	6/16 (38)	20/25 (80)
Vandinti et al., 2009[27]	India	29/55 (53)	7/9 (78)	17/41 (41)	6/30 (20)	7/10 (70)
Belli et al., 2011[34]	Argentine	133/208 (64)	22/36 (61)	51/103 (50)	9/25 (36)	30/49 (61)
Mean % (Range)		54 (45–80)	59 (48–89)	41 (29–51)	34 (0–43)	64 (43–80)

RA = Refractory Anemia, RARS = RA with ringed sideroblast, RAEB = RA with excess of blasts, RAEBt = RAEB in transformation, CMML = Chronic Myelomonocytic Leukemia

Risk Stratification of Cytogenetic Findings in Myelodysplastic Syndromes

Clinical course of MDS is highly variable, ranging from stable disease over 10 or more years to death within a few months due to cytopenias or transformation to AML. Since the development of the Bournemouth index in 1985,[40] various scoring systems have been designed, based on clinical characteristics at presentation, in order to define prognostic subgroups.

The karyotype was recognized as an independent prognostic factor in 1993, and its inclusion among different prognostic systems has contributed to improve the assessment of prognosis.[6] Morel et al. confirmed that the presence of complex karyotypes (≥ 3 altered chromosomes) was associated with short survival and leukemic evolution,[6] while Lausanne-Bournemouth index included the presence of two aberrations among the worst prognostic karyotypes[35] (see *Table 3*).

In 1997, the International Prognostic Scoring System (IPSS)[9] established that the most frequent cytogenetic findings were associated with specific prognosis and clearly differentiated three cytogenetic risk categories: good, intermediate, and poor with median survivals of 46, 29 and 10 months, respectively. This modality was later adopted by the WHO classification-based Prognostic Scoring System (WPSS) in 2005.[41] Complex karyotypes (≥3 cytogenetic alterations) and -7/del(7q) were associated with worse prognosis and unfavorable outcome after allogeneic bone marrow transplant.[42] Schanz et al. showed that the independent prognostic impact of poor risk cytogenetics on the overall survival was equivalent to the impact of high blast counts and its predictive power was unaffected by type of therapy given.[28] Normal karyotype, Y chromosome loss, isolated del(5q), or del(20q) constituted good prognostic findings that were associated with longer survival and reduced risk of progression. However, the intermediate group, including trisomy 8 and other miscellaneous, less frequent single and double chromosome defects,

showed considerable heterogeneity.[9] Recent evidence suggests that some of these less common abnormalities may play a significant role in the MDS clinical outcome when larger patient series are examined (see *Table 3*).[6,9,11,16,21-23,25,30-31,34-35,43-46]

The 'prognostic index cytogenetics' (pi score),[44] published in 1999, differentiated four risk groups according to cytogenetic aberrations (see *Table 3*). Pfeilstöcker et al. found that patients with isolated del(5q), del(20q), Y chromosome loss or other single miscellaneous findings show an intermediate-I outcome compared with normal karyotype. In addition, they described no statistically differences between patients that present -7/del(7q) or +8.[44]

In 2005, the Spanish Cytogenetic Working Group (GCECGH) defined four cytogenetic prognostic subgroups based on 968 patients. They included isolated del(11q) and del(12p) into the good prognosis group; rearrangements of 3q21q26, +8, +19, t(11q) and del(17p) into the intermediate-I; a new intermediate-II group of miscellaneous single or double cytogenetic abnormalities and the i(17q) into the worst prognostic group. These risk groups showed median survivals of 4.3, 2.7, 1.0 and 0.7 years, respectively.[16]

Bernasconi et al., 2007[21], redefined the IPSS cytogenetic categories. In terms of survival, they included del(11q) and del(12p) within the good risk, del(7q) within the intermediate risk and rearrangements of 3q within the high-risk category. Patients classified accordingly showed 2-years overall survival of 90, 69 and 26 %, respectively. In terms of the risk of AML progression, the isolated del(11q) and del(12p) were associated with good outcome, del(20q) with intermediate risk; whereas, +8 with higher risk to develop AML.[21]

In 2007 and 2008, the German–Austrian MDS Group analyzed a series of 1,202 MDS patients treated only with supportive care and defined

Table 3: Cytogenetic Risk Groups According to Different Prognostic Scoring Systems

Prognostic Systems	Cytogenetic Groups of Risk					
	Very Good	Good	Intermediate		Poor	Very Poor
			Intermediate I	Intermediate II		
Lille (Morel et al.,1993)[6]		Normal Karyotype 1 or 2 altered chromosomes			≥ 3 altered chromosomes	
Lausanne-Bournemouth (Parlier et al., 1995)[35]		Normal Karyotype 1 cytogenetic alteration			≥ 2 alterations	
IPSS (Greemberg et al., 1997)[9]		Normal Karyotype -Y, del(5q), del(20q)	+8, 1 or 2 cytogenetic alterations (others)		≥ 3 alterations -7/del(7q)	
Cytogenetic Prognostic Index (Pi) (Pfeilstöcker et al., 1999) $[44]		Normal Karyotype	1 point	2 o 3 points	≥ 4 points	
GCECGH (Solé et al., 2005)[16]		Normal Karyotype, -Y, del(5q), del(20q), del(11q), del(12p)	+8, Rearr. 3(q21q26), +9, +18, +19, t(11q), del(17p)	cytogenetic alterations (others)	≥ 3 alterations; -7/del(7q), i(17q)	
WPSS (Malcovati et al., 2005)[17]		Normal Karyotype -Y, del(5q), del(20q)	+8, 1 or 2 cytogenetic alterations (others)		≥ 3 alterations -7/del(7q)	
(Bernasconi et al., 2007)[21] SV		Normal Karyotype, -Y, del(5q), del(20q), del(11q), del(12p)	+8, del(7q), 1 or 2 cytogenetic alterations (others)		Rearr. 3(q21q26), -7, ≥ 3 alterations	
PFI		Normal Karyotype, -Y, del(5q), del(11q), del(12p)	Rearr. 3(q21q26), del(20q), 1 or 2 cytogenetic alterations (others)		-7/del(7q), +8, ≥ 3 alterations	
German- Austrian Group (Haase et al., 2007, 2008)[22-23] IPSS-R (Schanz et al., 2010)[46]		Normal Karyotype; -Y, -X, del(5q), del(20q), +1/+1q, t(1q), t(7q), del(9q), del(12p), chr. 15 abn., t(17q), +/-21	+8 del(11q)	= 3 cytogenetic alterations; -7/del(7q); 3q rearr., +19, t(11)(q23)	> 3 alterations t(5q)	
MDACC (Kantarjian et al., 2008)[26]		Normal Karyotype, 1 o 2 cytogenetic alterations (others)			≥ 3 alterations -7/del(7q)	
German- Austrian Group (Haase et al., 2009)[45]		Normal Karyotype, -Y, del(5q), del(20q), del(11q), t(11)(q23), del(12p), +21 and 2 cytogenetic alterations including chr. 5	+8, +1q, rearr. 3q, t(7q), +19, -21, 2 cytogenetic alterations excluding chr. 5 or 7	-X -7/del(7q) simplex o double = 3 alterations	> 3 alterations	
IPSS-R (Schanz et al., 2010)[46]	del(11q), -Y	Normal karyotype, der(1;7), del(5q), del(12p), del(20q), or double incl. del(5q)	-7/7q-, +8, i(17q), +19, +21, any other single, or any other double, independent clones		der(3)(q21)/der(3)(q26), double incl. -7/del(7q), complex 3 abnormalities	> 3 alterations
IPSS-MK (Belli et al., 2011,2012)[30,34]		Normal Karyotype, -Y, del(5q), del(20q), other isolated deletions	+8, 1 o 2 cytogenetic alterations (others)		≥ 3 alterations -7/del(7q), MK	
IPSS-R (Schanz et al., 2012)[31]	del(11q), -Y	Normal Karyotype, del(5q), del(12p), del(20q), 2 cytogenetic alterations including chr. 5	del(7q), +8, i(17q), +19, any other single or double, independent clones		der(3)(q21)/der(3)(q26), -7, double incl. -7/del(7q), complex 3 abnormalities	> 3 alterations

$ 1 point: alterations chr 5, non complex alterations excluding chr. 5, 7 and 8; 3 points: chr 7 or 8 alterations; 4 points: complex alterations. SV: Survival; PFI: progression free interval; MK: Monosomal Karyotype.

four different cytogenetic groups with median survival of 55, 29, 15 and 9 months, respectively. In this study, the abnormalities associated with a favorable clinical course, with median survivals longer than 32 months, were: normal karyotype, t(1q), del(5q), t(7q), del(9q), del(12p), del(15q)/t(15q), t(17q), del(20q), +21, −21, −X, and −Y. The intermediate-I alterations were isolated del(11q) and +8, with median survival of 26 and 23 months, respectively. The intermediate-II alterations were t(11q23), rearrangements of 3q, +19, -7/del(7q) and complex (= three anomalies), with median survivals ranging from 20 to 14 months. In the very poor prognostic group were complex (> 3 anomalies) and t(5q) with median survival of 9 and 4 months, respectively.[22–23] In 2009, the same group presented a new stratification for some of above described alterations[45] (see *Table 3*).

In 2010, the German–Austrian group, the International MDS risk analysis workshop (IMRAW), the GCECGH, and the International Cytogenetics Working Group of the MDS Foundation (ICWG) and the M.D. Anderson Cancer Center (MDACC), proposed five cytogenetic prognostic subgroups for the IPSS-revised (IPSS-R) stratification.[46] In 2012, after some modifications, the final published categories, based on 2801 patients, were defined as follows: very good [del(11q) or –Y], good [normal, del(5q), del(12p), del(20q), or double abnormalities including del(5q)], intermediate [del(7q), +8, i(17q), +19, any other single or double, independent clones], poor [der(3)(q21)/ der(3)(q26), -7, double incl. -7/del(7q), or complex (= 3 abnormalities)], and very poor [complex (>3 abnormalities)] with median overall survivals of 61, 49, 26, 16 and 6 months, respectively.[31]

Recently we have found that the presence of an isolated deletion, excluding del(7q), is a good prognostic finding, while the presence of a monosomal karyotype (MK) is a high risk marker (IPSS-MK). This alternative but complementary strategy to the original IPSS system showed an independent prognostic impact and a better discriminating power than not only the original IPSS categories[34] but also the initially proposed IPSS-R ones in our series.[30] MK refers to the presence of two or more distinct autosomal monosomies or a single monosomy in the presence of structural abnormalities.[47] New published data supported the adverse prognosis associated with MK in MDS.[48]

Cytogenetic Alterations
Isolated Y Chromosome Loss
Loss of Y chromosome is relatively common with a reported frequency of 2 % (range 1–6 %) for the overall MDS population (see *Table 1*). Y chromosome loss is dependent on age, diagnosis, and appears to be neutral or favorable for survival or therapy with no consistent relationship between changes in the percentage and disease progression or remission.[49] Although the United Kingdom Cancer Cytogenetics Group study sustain that Y loss should not be interpreted as a marker of the malignant clone in elderly,[50] Wiktor et al. found that if the clone is present in >75 % of metaphase cells, it probably represents a disease-associated clonal population. In addition, Y chromosome loss appeared to be more frequent in AML and MDS when compared to a control group or to those with Myeloproliferative Disorders or B-cell diseases.[49]

Long Arm of Chromosome 5 Isolated Deletion
The isolated del(5q) is observed with a reported frequency of 6 % (range 0–13 %) in different published series (see *Table 1*). The 5q-

syndrome is characterized by the presence of a del(5q) as the sole karyotypic abnormality, female preponderance, macrocytic anemia, normal to high platelet counts, less than 5 % of blasts in bone marrow, dismegakaryopoiesis with hypolobulated megakaryocytes, long survival with low risk of leukemic evolution[51] and good response to lenalidomide treatment.[52] The clinical outcome of del(5q) patients is not determined by the different breakpoints of the interstitial deletion, but instead by marrow blast cell percentage, being more evident for blast cell counts more than 10 %[21] and by a therapy-related etiology. In addition, the good prognosis is significantly modified by additional cytogenetic changes or mutations that can transform the clone allowing its expansion.[22–23,53–56] These adverse marrow subclones might be present in patients with early stage disease and may expand due to the acquisition of new genetic alterations or because the clones are insensitive to lenalidomide,[57] therefore monitoring of cytogenetic response is mandatory.[58] TP53 mutations were present in almost one-fifth of low-risk MDS patients with del(5q) and were associated with lower complete cytogenetic response and subsequent leukemic evolution.[56] In addition, TP53 mutations were associated with del(5q) in the context of complex karyotype and lenalidomide treatment had no effect on the majority of these patients.[59]

The deleted region varies in size: the proximal endpoints vary from 5q11 to 5q23 while the distal breaks from 5q31 to 5qter.[60] The common deleted region contains more than 24 genes.[37] A recent study implicated haploinsufficiency of multiple genes as the relevant genetic consequence of this deletion.[39] The decreased expression of these genes, including the ribosomal protein 14 gene (RPS14), miR-145, miR-146a and the tumor suppressor gene secreted protein acidic and rich in cysteine (SPARC), among others, may cooperate to cause several of the key features of the 5q- syndrome and may be related to lenalidomide response in these patients.[37,55-56,61-65]

Partial or Total Loss of Chromosome 7
Isolated -7/del(7q) is observed with a reported frequency of 3 % (1–8 %) (see *Table 1*). Several studies suggest 'critical regions' with a marked heterogeneity in the breakpoints involving 7q22, 7q32-34 and 7q35-36 bands.[66-69] These distinct critical loci may contribute alone or in combination to the evolution of MDS and AML.[70] A correlation between survival and deletion limits in del(7q) myeloid neoplasms suggests that the size of the del(7q) clone, presence of complex aberrations, refractoriness to therapy, survival and clinical progression depend on the deleted region on the del(7q) marker.[71] The MLL5 is a MLL family member located within the human chromosome band 7q22 and seems to play an essential role in regulating proliferation and functional integrity of hematopoietic stem/ progenitor cells.[72]

The number of apoptotic and Fas-expressing CD34 cells was decreased in MDS patients with monosomy 7 (-7)[73], and the gene expression pattern in their progenitor cells was consistent with functional characteristics of high proliferation and malignant potential.[74] In addition, monosomy 7 CD34 cells showed increased expression of the Granulocyte Colony Stimulating Factor receptor (GCSFR) class IV mRNA isoform which is defective in signaling cell maturation and differentiation.[75]

The presence of an isolated -7/del(7q) was considered as an unfavorable finding by the ICWG[76] and also by the IPSS[9], the GCEGCH[16], WPSS,

MDACC[26] and the IPSS-MK[30,34] systems, among others. However, other risk stratifications assigned an intermediate-I or-II risk to -7/del(7q).[22-23,44,46] Despite the different risk categorization assigned to these alterations median survivals show good consistency, which vary from 14 to 16 months, when both alterations are plotted together.[16,23,29-30] However, when these alterations were separately analyzed, del(7q) was more favorable compared with the loss of the whole chromosome 7 with regard to overall survival, with median survivals ranging from 16–26 and 9–16 months, respectively[16,21,23,25,31], as well as risk of AML transformation.[31]

Trisomy 8

The trisomy 8 (+8) is a unique cytogenetic abnormality in 5 % (1–13 %) of MDS patients (see *Table 1*). Upregulated genes in patients with trisomy 8 were primarily involved in immune and inflammatory responses.[74,77] All patients had significant CD8+ T-cell expansions of one or more T-cell receptor Vß subfamilies. These findings are consistent with an immune response where activated T cells, in proximity to trisomy 8 cells which would express neoantigen, would release cytokines up-regulating Fas expression on the surface of hematopoietic cells.[73] MDS patients with +8 respond to immunosuppressive therapies with durable reversal of cytopenias and restoration of transfusion independence.[78]

Deletion (20q)

The isolated del(20q) is observed in 2 % (range 0–5 %) of MDS patients (see *Table 1*). These patients present with higher reticulocyte, lower platelet, and marrow blast counts.[79] The deletion is interstitial with heterogeneity of both centromeric and telomeric breakpoints including a commonly deleted region corresponding to the 20q11.2-q12 bands where several genes are located.[36] The most attractive candidate is the human homologue of a Drosophila tumor suppressor gene (L3MBTL1) which regulates chromatin structure during mitosis.[80]

Complex Karyotypes

Multiple chromosome rearrangements (≥ 3 cytogenetic alterations) are found in 12 % (range 0-27 %) (see *Table 1*) and 50 % of patients with *de novo* and secondary MDS, respectively. They often result in chromosome loss of 5q (50 %) (as interstitial deletion or as a result of unbalanced translocations), del(7q) (40 %) and del(17p) [frequently accompanied by del(5q)], gain of chromosome 8 and rare specific translocations.[16,54,81-82] Characteristics associated with complex karyotypes include old age, short survival time[82], and its prognostic value has been shown to be independent of blast cell percentage.[43] The median survival seems to depend on the number of observed aberrations, and ranges from 16–17 and 9–6 months for patients with 3 and >3 abnormalities, respectively.[22-23,31] Among complex karyotypes, around 80 % fulfilled the monosomal karyotype (MK) criteria associated with significant inferior survival.[48]

Less-frequent Cytogenetic Alterations

Different series include a wide range of less frequent (<1 %) alteration, for example: rearrangements (3q), +9/del(9q), +11/del(11q), del(12p)/t(12p), -13/del(13q), del(17p)/i(17q)/ t(17p) idic(Xq) and several balanced translocations such as t(6;9)(p23;q34), resulting in a fusion of DEK and CAN/NUP214; t(11;16)(q23;p13), leading to a chimeric MLL/CREBBP gene; t(2;11)(p21;q23), which leads to a strong up-regulation of microRNA miR-125b-1, among others.[9-10,16,11,21,46]

Major abnormalities of 3q, including t(1;3)(p36;q21), inv(3)(q21q26), t(3;3) (q21;q26), t(3;5)(q25;q34) or t(3;21)(q26;q22), are observed in 0.5–2 % of MDS and AML patients, and 30-50% of them are therapy related. Patients with rearrangements of 3q26 usually present with excess of blast, abnormal multilineage hematopoiesis, frequent dismegakaryopoiesis, normal or elevated platelet counts and inappropriate expression of the zinc finger transcription factor oncogene EVI1 located at 3q26. The patients show a particularly aggressive course of disease and unfavorable treatment outcome characterized by short median survival and high risk of disease progression to AML.[83-85]

Deletions of chromosome 11q [del(11q)] as part of a non-complex karyotype are present predominately in *de novo* MDS with an overall 0.6% frequency. Wang et al. described 32 MDS cases that were characterized by lack of cryptic MLL rearrangements, transfusion-dependent anemia (65 %), frequent ring sideroblasts (59 %), bone marrow hypocellularity (22 %) and less severe thrombocytopenia, with an overall survival of 35 months, and 38 % cases progressed to AML.[86] However, a study of 20 (0.7 %) *de novo* MDS patients, found an overall median survival of 141 months. As a result, the IPSS-R classified del(11q) as a very good prognostic finding.[31]

Trisomy 11 (+11) is observed rarely in MDS and its presence correlates with clinical aggressiveness, significantly inferior survival to patients in the IPSS intermediate-risk cytogenetic group and would be best considered a high-risk cytogenetic abnormality in MDS prognosis. Moreover, MLL partial tandem duplication is observed in 50 % of MDS patients.[87]

Cytogenetic abnormalities of 12p in hematologic malignancies result in different molecular changes: deletions, amplifications and structural rearrangements. FISH analysis of patients with del(12p) demonstrated that the deletions are interstitial,[88] and overlapped deleted region might be localized between CDKN1B (KlP7, p27) and ETV6 (TEL) genes.[89] Recently, in a study, by single nucleotide polymorphism microarray analysis, of seven patients with del(12p) encompassing only the region centromeric of ETV6 it was observed that the minimally deleted region displays a size of 815 kb and nine genes are localized, including CDKN1B.[90] The clinical outcome of del(12p) patients seems to be determined by the different breakpoints of the interstitial deletion and the presence of the small deletion del(12)(p11.2p13) has been associated with a mild clinical course.[91] Latest reports are in agreement regarding the good outcome of MDS patients with del(12p) who show a median overall survival longer than 59 months.[16,22-23,25,31,34]

Alterations resulting in 17p deletion include -17, del(17p), i(17q) and unbalanced translocations that mainly involve chromosome five. They are observed in 3 % to 5 % of AML and MDS cases (most of them are therapy-related), usually as a part of complex karyotypes where del(5q) is frequently accompanying.[54,81] The 17p- syndrome has been described as a morphologic-cytogenetic-molecular entity based on a strong correlation between cytogenetic rearrangements leading to 17p loss, a typical form of dysgranulopoiesis combining pseudo-Pelger-Huët hypolobulation, small vacuoles in neutrophils, loss of one copy of TP53 (17p13) and mutation of the remaining TP53 allele.[81]

Patients with i(17q) are characterized by male predominance, severe anemia, prominent pseudo-Pelger-Huët neutrophils, granulocytic hyperplasia,

increased micromegakaryocytes and poor clinical prognosis.[92] An association between these patients and wild-type TP53 allele was first described by Fioretos in 1999[93], and recently confirmed.[94] The selective advantage may be conferred by gene dosage imbalances resulting from loss of 17p and gain of 17q material.

Most recent cytogenetic stratifications tried to find the prognostic significance of rare alterations [(i.e. der(1;7), rearrangements of 3q, del(11q), del(12p), i(17q), +19 and +21, among others]. The frequencies of these alterations ranged among 0.2–0.7 %, and the respective percentages represent a low number of patients which may be reflected in differences in the assessed prognostic implications. However seems to be an apparent coincidence regarding the good prognostic associated with del(12p) and del(11q).[16,21-23,25,31,34,45-46] Large study groups are important to obtain the minimum of 10 cases required to properly evaluate rare alterations in order to fulfill the ICWG criteria.[76,95]

Discussion and Conclusion

Cytogenetic information, in addition to the development of new technologies, has contributed an additional level of biologic understanding related to MDS clone. And far from becoming less relevant following the introduction of molecular, immunophenotypic, and histochemical staining techniques, the standard cytogenetic analysis is currently recommended for all MDS patients, retaining and increasing its importance in day-to-day clinical practice strategies.

Although MDS are still heterogeneous, cytogenetic findings help to define subgroups of patients who share similarities in the course of the disease. There are recurring, non random cytogenetic alterations specially affecting chromosomes 5, 7, 8 and 20. While they do not suggest a therapeutic approach, except for the isolated del(5q), these aberrations have been considered as risk indicators from the time the original IPSS was published.[9]

Most recent cytogenetic stratifications tried to find the prognostic significance of less frequent alterations which has been longer included in the intermediate group.[16,21-23,25,30-31,34,45-46] Moreover, monitoring of karyotype changes is suggested, not only to evaluate cytogenetic response to treatment but also to evaluate the acquisition of new cytogenetic alterations that are related to an unfavorable clinical outcome.[96-97]

The next step will be to search for unifying molecular abnormalities across the syndromes which would further refine classification, risk stratification, and, at the same time, provide potential and novel therapeutic targets. The use of approved therapeutic agents (lenalidomide, decitabine, and azacitidine) in MDS patients during the past decade has provided more information as well as more questions regarding this heterogeneous pathology because only a subgroup of patients will respond. Further insights into the biology of responding versus nonresponding patients are required to develop new adapted scoring systems based on large available information. ■

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