REVIEW ARTICLE

Cytogenetic features in myelodysplastic syndromes

Detlef Haase

Abstract Myelodysplastic syndromes (MDS) comprise a group of bone marrow diseases characterized by profound heterogeneity in morphologic presentation, clinical course, and cytogenetic features. Roughly 50% of patients display clonal chromosome abnormalities. In several multicentric studies, the karyotype turned out to be one of the most important prognostic parameters and was incorporated into statistical models aiming for a better prediction of the individual prognosis like the International Prognostic Scoring System. However, due to the profound cytogenetic heterogeneity, the impact of many rare abnormalities as well as combinations of anomalies occurring in a substantial portion of patients with MDS is still unknown and can only be delineated on the basis of large international multicentric cooperations. Recently, the German–Austrian MDS Study Group presented cytogenetic findings in 2,072 patients with MDS, which serve as a basis for the characterization of the cytogenetic subgroups discussed in this article. The availability of new therapeutic options for low- and high-risk MDS targeted against distinct entities characterized by specific chromosome abnormalities, like 5q-deletions, monosomy 7, and complex abnormalities underlines the important role of cytogenetics for the clinical management of MDS. This article thus focuses on the clinical and prognostic relevance, the molecular background, and therapeutic perspectives in these three cytogenetic subgroups.

Keywords MDS · cytogenetics · karyotype · prognosis · 5q− · monosomy 7 · Complex abnormalities

D. Haase (✉)
Department of Hematology and Oncology,
Georg-August-University,
Robert-Koch-Str. 40,
37075 Göttingen, Germany
e-mail: haase.onkologie@med.uni-goettingen.de

Introduction

The profound heterogenetity of myelodysplastic syndromes (MDS) is well-known from morphological and clinical studies, which finally lead to the establishment of classification, and prognostic scoring systems. It is becoming increasingly obvious that this heterogeneity also manifests itself against the background of genetic heterogeneity of MDS. In sharp contrast to the situation in chronic myeloid leukemia (CML) where one single cytogenetic abnormality, the translocation t(9;22)(q34;q11), is the genetic hallmark of the disease, there is an enormous variability of cytogenetic abnormalities in MDS hampering not only the prognostic classification but also the delineation of the molecular background of cytogenetic aberrations in MDS. As an example in our recent multicentric cytogenetic analysis of patients with MDS, we observed 684 different types of chromosome abnormalities in a cohort of 1,080 patients with MDS and an abnormal karyotype [1].

The cytogenetic profile of MDS

In general, MDS show a characteristic genetic profile with an overweighing of unbalanced abnormalities. Most frequently, a loss of genetic material in the form of deletions and monosomies can be observed. A gain of genetic material with the appearance of total or partial trisomies is less frequent. Loss or gain of genetic material can also be the result of unbalanced translocations, which are frequently observed in MDS with multiple abnormalities. Taken together, it is thus obvious to assume that a prime molecular mechanism in MDS is the loss or inactivation of tumor suppressor genes, while the activation of oncogenes seems to be less relevant in myelodysplasia.

In contrast to AML, balanced structural abnormalities like translocations and inversions are rare in MDS. Due to the profound genetic heterogeneity, the knowledge about distinct cytogenetic alterations was mainly restricted to the most frequent abnormalities (−5/5q−, −7/7q−, +8, 20q−, and −Y), although, in MDS, rare chromosome abnormalities are present in a substantial portion of patients. In a recent analysis of the German–Austrian MDS Study Group, 59% of all 2,370 abnormalities observed in 1,080 patients with MDS where rare; that is, they occurred with a frequency of less than 2% [1]. In this situation, prognostic knowledge can only be deepened by large-scale multicentric studies with a high enough number of abnormal cases with follow-up data. This development was initiated by the International MDS Risk Assessment Working Group (IMRAW) ending up with the establishment of the International Prognostic Scoring System (IPSS), which was based upon the analysis of 816 patients with de novo MDS of whom 327 had abnormal karyotypes [2]. A next step forward was the study of the Spanish cooperative group with 500 abnormal cases [3] followed by our German–Austrian dataset with 1,080 patients with chromosome abnormalities [1]. The situation is furthermore complicated by the fact that chromosome abnormalities in principle can occur in three different conditions: as isolated abnormality, together with one additional change, and as part of complex abnormalities with at least two additional cytogenetic alterations. Table 1 shows the incidence of the 21 most frequent abnormalities according to the number of accompanying alterations occurring in our German–Austrian patient cohort.

Cytogenetic prognosis

The first large-scale cytogenetic studies in patients with MDS encompassing more than 100 patients where published more than 20 years ago [4–7]. In the following years, the patients cohorts increased step by step from nearly 250 patients [8] to some 400 patients [9, 10]. In 1997, Greenberg published a collaborative multicentric international data set of more than 800 patients with de novo MDS, which was the basis for the establishment of the IPSS [2]. This database was further surmounted by the analyses of the Spanish cooperative group with 968 patients examined (Table 2), which represented the largest number of patients with MDS karyotyped so far [3]. Recently, the German–Austrian Study Group published their multicentric analyses of more than 2,100 patients with MDS [1].

What has changed and what has been achieved during these last 25 years of cytogenetic analyses in MDS? If the aberration rate is considered, there is a gradual increase in the portion of abnormal cases from under 40% in the most earlier studies to 50% in the more recent analyses of Toyama, Solé, and Haase [1, 3, 10]. Although the composition of the patient cohorts may play a role for the portion of clonal abnormalities in a given collective, other factors like the improvement of culture conditions possibly due to the use of recombinant myeloid growth factors [11] might have contributed to the increase in the aberration rate in cytogenetic studies. To date, an aberration rate of 50% can be regarded as an international standard.

Table 1 Incidence of chromosome abnormalities in MDS related to 2,072 patients examined successfully

Anomaly	total, n (% of all cases)	Isolated, n (%[a])	With one additional abnormality, n (%[a])	As part of complex abnormalities, n (%[a])
5q−	312 (15.1)	146 (47)	52 (17)	114 (36)
−7/7q−	230 (11.1)	86 (37.5)	31 (13.5)	113 (49)
+8	173 (8.4)	81 (46.8)	37 (21.4)	55 (31.8)
−18/18q−	78 (3.8)	3 (3.8)	2 (2.6)	73 (93.6)
20q−	74 (3.6)	36 (48.6)	10 (13.5)	28 (37.8)
−5	69 (3.3)	1 (1.4)	4 (5.8)	64 (92.8)
−Y	58 (2.8)	41 (70.7)	5 (8.6)	12 (20.7)
+21	45 (2.2)	5 (11.1)	18 (40)	22 (48.9)
−17/17p−	42 (2.0)	1 (2.4)	1 (2.4)	40 (95.2)
inv/t(3q)	41 (2.0)	16 (39)	8 (19.5)	17 (41.5)
−13/13q−	40 (1.9)	5 (12.5)	6 (15)	29 (72.5)
+1/+1q	37 (1.8)	3 (8.1)	6 (16.2)	28 (75.7)
−21	33 (1.6)	3 (9.1)	4 (12.1)	26 (78.8)
+11	28 (1.4)	6 (21.4)	4 (14.3)	18 (64.3)
−12	26 (1.3)	0	2 (7.7)	24 (92.3)
12p−	25 (1.2)	7 (28)	6 (24)	12 (48)
t(5q)	24 (1.2)	6 (25)	3 (12.5)	15 (62.5)
11q−	23 (1.1)	8 (34.8)	4 (17.4)	11 (47.8)
9q−	23 (1.1)	8 (34.8)	3 (13)	12 (52.2)
t(7q)	22 (1.1)	6 (27.3)	6 (27.3)	10 (45.5)
−20	22 (1.1)	0	0	22 (100)

[a] Of cases with the respective abnormality

Prognostic relevance of chromosome abnormalities

The prognostication of patients with MDS has become an important means for the development of therapeutic strategies based on more individualized risk assessment. Even in the most recent prognostic scoring system, the World Health Organization classification-based Prognostic Scoring System, cytogenetics play a decisive role [12]. In general, three to four prognostic cytogenetic categories can be distinguished. In several multicentric investigations, cytogenetics have been proven to be highly relevant independent prognostic parameters ([2, 3, 13], see also Table 2).

Good prognosis

Even in the earliest study considered here, Knapp et al. [4] described the prognostic relevance of cytogenetic findings with a normal karyotype as favorable and complex abnormalities as being associated with bad prognosis. The good prognosis of a normal karyotype was confirmed by nearly all other groups. Thus, in contrary to the situation in AML where patients with a normal karyotype have an intermediate outcome and prognosis is significantly influenced by additional molecular alterations, in MDS, a normal karyotype is undisputedly associated with good prognosis. Further, well-established abnormalities defining good-risk subgroups are deletions of 5q and 20q as well as loss of the Y-chromosome, although the question whether this latter abnormality is age related, or a real clonal marker is unsolved as yet. The Spanish group identified further new cytogenetic abnormalities with a good prognosis (12p− and 11q−) [3].

In the German–Austrian multicentric study, the following abnormalities were associated with a favorable clinical course with a median survival between more than 9 years and 32 months: normal karyotype, t(1q), 5q−, t(7q), 9p−, 12q−, t(15q), t(17q), 20q−, +21, −21, −X, −Y. However, prognosis was only favorable when not more than one additional abnormality was present [1].

Intermediate prognosis

In most studies, patients with trisomy 8 displayed an intermediate clinical course. Until the Spanish group published their results on more than 980 patients, the knowledge of cytogenetic findings with an intermediate prognosis was very limited. In the IPSS, all abnormalities neither belonging to the good-risk group (isolated 5q−, 20q−, and loss of Y-chromosome) nor to the bad risk cohort (complex [greater than or equal to three abnormalities] or any chromosome 7 abnormality) were designated to be of intermediate prognosis not by availability of survival data but by definition [2]. In their large Spanish dataset, Solé et al. delineated new abnormalities associated with an intermediate clinical course (3q abnormalities, trisomy 9, 11q translocations, and 17p deletions) [3]. The results of White et al. [14] and Toyama et al. [10] who identified −7/7q− and 12p− and trisomy 21, respectively, as abnormalities with an intermediate prognosis were not confirmed by other groups. Recently, the multicentric database of the German–Austrian MDS Study Group revealed several infrequent abnormalities with an intermediate prognosis. A median survival time of 23–26 months was observed in

Table 2 Cytogenetic prognostic findings in publications with greater than 100 patients examined

Author, year	Number of patients	Abnormal (%)	Favorable	Intermediate	Unfavorable
Knapp 1985	174	66 (38)	Normal (NN)		Complex
Nowell 1986–1989	144	63 (44)	5q−, 20q−	+8	−7/7q−
Billström 1988	169	74 (44)	NN, 5q−	+8	−7/7q−
Pierre 1989	247	106 (43)	NN		Complex
Morel 1993	408	151 (37)	NN, 5q−, −Y, −7/7q−, 20q−	+8	Complex
Toyama 1993	401	200 (50)	+8	−7/7q−	Complex
White 1994	198	75 (38)	NN, 5q−	12p−, +21	Complex, +8, 20q−
Greenberg 1997	816	327 (40)	NN, 5q−, 20q−, −Y	All others	Complex, abnormal #7
Solé 2005	968	500 (51)	NN, 5q−, 20q−, −Y, 11q−, 12p−	rea 3q, + 8, +9, t11q, 17p−	Complex, −7/7q−, i17q
Haase 2007	2,072	1,080 (51)	NN, +1/+1q, t(1q), 5q−, t(7q), 9p−, 12p−, abnormal #15, t(17q), 20q−, −21, + 21, −X, −Y	rea 3q, −7, 7q−, +8, 11q−, t(11q23), +19, complex (=3)	Complex (>3), t(5q)

rea Rearranged

patients with trisomy 8 and 11q− (called Intermediate-I). A more worse prognosis with a median survival time between 20 and 14 months was found for 11q23 translocations, chromosome 3q aberrations, trisomy 19, 7q deletions, and complex abnormalities with three different chromosomal alterations and monosomy 7 (called Intermediate-II) [15].

Poor prognosis

There is a great consensus in all publications on cytogenetic prognosis in MDS that complex abnormalities characterize a MDS subgroup with bad prognosis and a median survival time significantly below 1 year, although the threshold at which the number of abnormalities confers bad prognosis is a matter of debate. While in most publications, the term "complex" is used for three or more abnormalities, in the Medical Research Council AML trials, bad prognosis was assigned to cases with five or more abnormalities [16]. Recently, we clearly could show that, in patients with MDS, median survival is significantly reduced only when more than three abnormalities are present, reducing the median survival from 17 months in cases with three abnormalities to less than 9 months in cases with four or more anomalies [1]. Besides complex changes, partial and total monosomy 7 was ranked to the cytogenetic findings with an unfavorable clinical course [3, 5–7]. Within the IPSS, any chromosome 7 abnormality was counted to the bad prognostic findings [2]. As mentioned above, in the German–Austrian dataset, −7/7q− showed a significant better prognosis (14 and 19 months median survival time, respectively) as compared to the complex abnormality group defined by four or more chromosomal changes (8.7 months) and was thus attributed to the intermediate-II group [15]. The findings of Toyama et al. [10] who observed an unfavorable course in patients with trisomy 8 or 20q deletions was not confirmed by any other group. Solé et al. described a median survival of under 12 months in ten patients with an isochromosome of 17q [3]. Since, in the German–Austrian dataset, this abnormality was too infrequent for a statistically meaningful analysis, the Spanish findings are convincing but still need further confirmation.

Prognostic scoring

In the IPSS, three different cytogenetic subgroups were established and weighted against bone marrow blast counts and cytopenias by multivariate analysis [2]. Applying the cytogenetic part of the IPSS to our German–Austrian dataset, 59% of the patients had a good risk karyotype (normal, isolated 5q−, 20q−, or loss of Y-chromosome) with a median survival of 54 months, 19% of the collective

had an intermediate prognosis (neither good risk nor bad risk cytogenetics) with a median survival of 31 months, and 22% displayed a dismal prognosis (any chromosome 7 anomaly, complex [≥3] changes) with a median survival of 11 months [1].

The application of the new cytogenetic findings derived from the German–Austrian dataset allows the definition of four different cytogenetic prognostic subgroups (Table 3 and Fig. 1). The low-risk group covers 73% of patients with 14 cytogenetic categories and a median survival of 55 months, the intermediate groups I and II (15.5% of patients) with eight cytogenetic categories and a median survival of 29 (intermediate-I) and 15 months (intermediate-II), and the high-risk group (11.5% of patients) with a median survival of 8 months [15]. In comparison to the IPSS, our new cytogenetic prognostication splits the intermediate group into two distinctly separate subgroups with significantly different median survival. The bad-risk group is more strictly defined with a lower median survival time (8 vs. 11 months). While the IPSS assigned an intermediate risk by exclusion and not by knowledge, our intermediate cytogenetic subgroup was based exclusively on available survival data of patients treated with supportive care only thus reflecting the natural course of the disease. Taking into account only those patients with a known prognosis (in IPSS only good- and bad-risk patients), 81% of our patients could be categorized by the IPSS in comparison to 93% by the German–Austrian prognostic system.

A further element of the IPSS, the weighting of cytogenetics in comparison to other relevant parameters like the bone marrow blast counts, has become questionable. According to the IPSS, 0 scoring points are attributed to good-risk cytogenetics and blasts less than 5%, intermediate cytogenetics as well as 5–10% blasts get 0.5 scoring points, and bad-risk cytogenetic findings are scored with 1.0. Eleven to 20% blasts are scored with 1.5 and 21–30% blasts with 2.0 points. Thus, bad-risk cytogenetics with a median survival of 11 months get less scoring points than patients with 11–20% blasts and a median survival in our cohort of 16.5 months. According to our observations, only patients with 21–30% blasts (11.7 months median survival) had a prognosis comparable to patients with bad-risk cytogenetics. Thus in a revision of the IPSS the weight of bad-risk cytogenetics has to be readjusted [17].

Delineation of the most relevant cytogenetic subgroups 5q−, monosomy 7, and complex abnormalities

5q deletions

Deletions within the long arm of chromosome 5 are the most frequent cytogenetic changes in MDS accounting for

Table 3 New cytogenetic prognostic subgroups of the German–Austrian MDS Study Group in 1,202 patients treated with supportive care only

Cytogenetic risk	Cytogenetic finding	Number (%)	Median survival (months)
Good	12p−	7 (0.6)	n.r.
	9q−	6 (0.5)	n.r.
	t(15q)	6 (0.5)	n.r.
	15q−	5 (0.4)	n.r.
	+21	13 (1.1)	100.8
	5q−	132 (11)	77.2
	20q−	24 (2)	71.0
	−X	6 (0.5)	56.4
	normal karyotype	622 (51.7)	53.4
	−Y	33 (2.8)	39.4
	t(1q)	7 (0.6)	34.7
	t(7q)	7 (0.6)	34.7
	t(17q)	6 (0.5)	32.1
	−21	6 (0.5)	32.0
Intermediate-I	11q−	11 (0.9)	26.1
	+8	64 (5.3)	23.0
Intermediate-II	t(11q23)	6 (0.5)	20.0
	Any 3q abnormality	16 (1.3)	19.9
	+19	5 (0.4)	19.8
	7q−	11 (0.9)	19.0
	Complex (=3 anomalies)	32 (2.7)	17.0
	−7	42 (3.5)	14.0
Poor	Complex (>3 anomalies)	134 (11.1)	8.7
	t(5q)	7 (0.6)	4.4

n.r. Median survival not reached

roughly 30% of abnormal cases [1, 2, 3]. The deletions can have variable size; however, the common deleted region always spans the chromosome band 5q31. Due to intensive research during the last decade, our knowledge of the molecular background of these abnormalities is increasing. It is generally accepted that not the illegitimate fusion of deoxyribonucleic acid (DNA) sequences at the variable breakpoints of the deletions but loss of genetic information

Fig. 1 Kaplan–Meier survival curves according to the cytogenetic prognostic classification of the German–Austrian MDS Study Group. Log-rank test: $p <$ 0.0001 (3 degrees of freedom) [15]
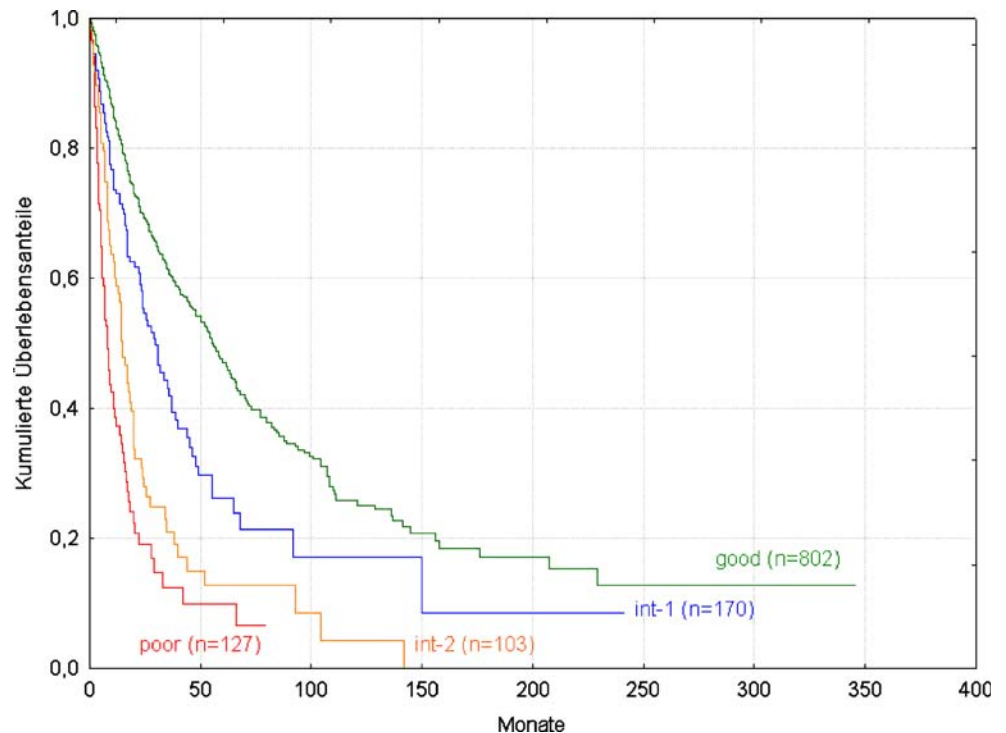
represents the relevant pathomechanism. There could be two different deleted regions in 5q31. One that is located more centromeric is possibly associated with bad prognosis, complex abnormalities, and high-risk, as well as therapy-related, MDS. A second area is located more telomeric in the vicinity of band 5q32 and is supposed to be related to the good-risk 5q− syndrome [18–21]. Recently, it has been convincingly shown by the means of sophisticated systematic knockout experiments on 41 candidate genes in the critical 5q− region that the gene for a ribosomal subunit protein, RPS41, seems to be a relevant gene in patients with 5q− syndrome on the basis of haploinsufficiency [22]. The 5q− syndrome has been first described by Van den Berghe in 1974 [23]. It is cytogenetically characterized by an isolated deletion of chromosome 5q. A female preponderance is well documented. The clinical appearance is characterized by a refractory macrocytic anemia, normal or elevated platelets, and mild leukocytopenia. The clinical course is mild and long lasting with a very low risk for leukemic transformation. The bone marrow smears reveal less than 5% blasts, while dysplasia of the erythroid and granulocytic lineages usually are discrete or even absent. Megakaryopoesis shows profound and characteristic dysplasias with either separated multiple nuclei, hypolobulation, microkaryocytes, and most characteristically monolobulated megakaryocytes with a round nucleus.

The prognosis of 5q deletions in MDS is generally favorable if they are not part of complex abnormalities; however, it is significantly modified by single additional cytogenetic changes [1, 24]. Figure 2 shows the Kaplan–Meier survival curves for patients treated with supportive care only with isolated 5q−, 5q− plus one additional abnormality, and 5q− as part of complex abnormalities derived from the German–Austrian database [1].

It is evident that additional abnormalities negatively influence survival in patients with 5q deletions. However, due to cytogenetic heterogeneity, the additive prognostic impact of distinct single additional abnormalities remains obscure as yet (Table 4).

Over a long period, the therapeutic standard in patients with noncomplex 5q deletions was supportive care only. In clinical trials, retinoic acid turned out to be inefficient, and low-dose cytarabine was more effective but led to a pronounced increase in severe neutropenic infections [25]. A preferential response to other modern therapeutic strategies like immunosuppression and suppression of DNA methyltransferase or histone deacetylase was not reported as yet. However, recently, List et al. reported a remarkably high response rate to the immunomodulating agent lenalidomide, which was especially pronounced in MDS patients with 5q deletions. Nine out of 12 patients with a 5q deletion displayed complete cytogenetic remissions, and 10 out of 12 experienced an erythroid response

[26]. Thus, a new promising agent may target cell clones in MDS bearing 5q deletions. These results could recently be confirmed on the basis of a large muliticentric trial [27].

Monosomy 7

Monosomy 7 is the second most frequent distinct chromosome abnormality in MDS occurring in some 25% of abnormal cases. It can present as total or partial monosomy. In the latter case, variable deletions of parts of the long arm lead to loss of genetic material of different size. As yet, no significant differences concerning the prognostic relevance have been observed between total and partial monosomy 7. In the German–Austrian dataset, 36% of monosomy 7 were isolated ones, 14% displayed one additional abnormality, and 50% occurred as part of complex abnormalities [1]. Comparable to the situation in 5q, also in 7q, at least two and maybe more distinct regions of common deletions have been identified: the band 7q22 and the more telomeric regions 7q31–32 and 7q36. It is interesting to note that interstitial as well as terminal deletions might be due to cryptic unbalanced translocations. In single individuals, more than one different deletion has been found in one and the same patient, either within the same copy of chromosome 7 with retention of sequences between the deleted regions or within different cell clones [28, 29]. These observations clearly underline the regional genetic instability of the long arm of chromosome 7, which makes this region especially prone to deletions of different size and localization as well as to structural abnormalities. On the other hand, it can be assumed that there must be a cluster of genes with tumor-suppressive features distributed over several chromosome bands in 7q with the same or very similar consequences when being inactivated by chromosomal abnormalities.

However, in contrast to some presumptions in the 5q deletions, as yet, no prognostic differences have been elaborated between different regions of deletions (reviewed in [20]). Investigations of the molecular background of monosomy 7 MDS are on the way. An association of this cytogentic subgroup with RAS mutations, mutations of AML1, and hypermethylation of p15INK4B have been reported [30, 31]. In an analysis of gene expression profiles in CD34+ cells from MDS patients with monosomy 7, a malignant phenotype with highly proliferative potential was found with an overexpression of HOX9A, PRAME, BMI-1, PLAB, and the DNA repair gene BRCA2. Parallelly, downregulation of the tumor suppressor gene p21, GATA2, and MAP was observed [32]. Clinically, monosomy 7 is characterized by a lower median age of the affected patients as compared to 5q deletions, severe refractory cytopenias, and a proneness to life-threatening infections. Predisposing
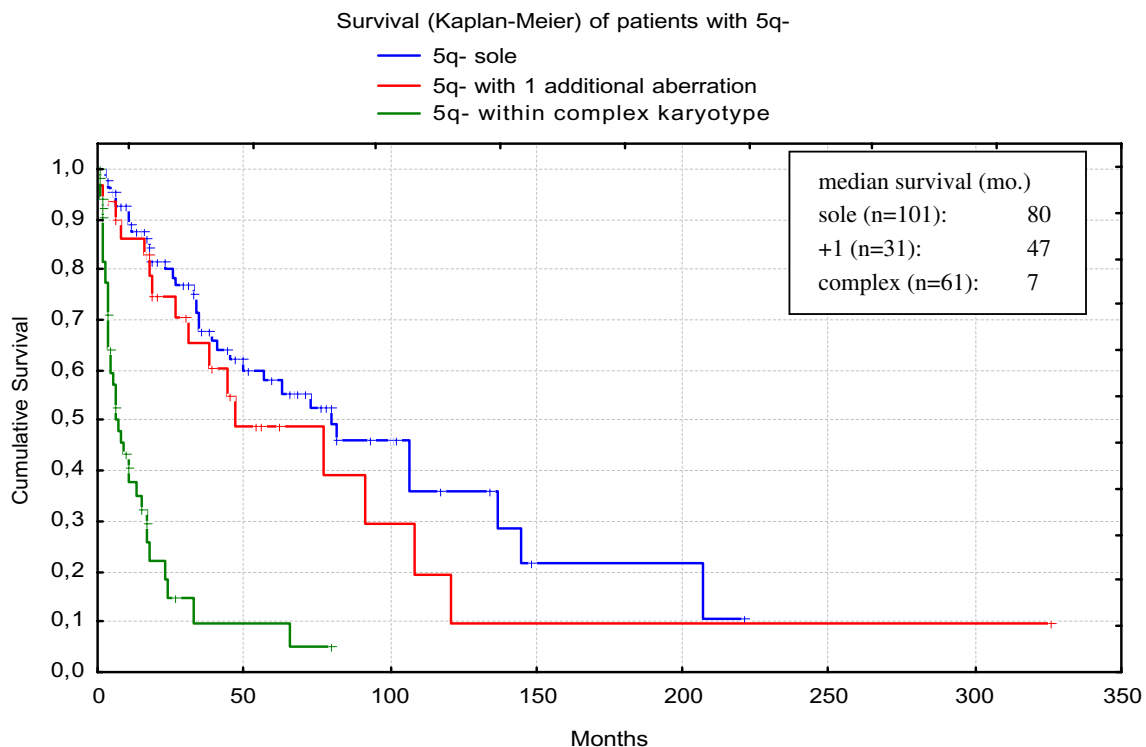
Survival (Kaplan-Meier) of patients with 5q-

Fig. 2 Median survival according to accompanying abnormalities in patients with 5q deletions. Log-rank test: $p \leq 0.0001$ (2 degrees of freedom), $p = 0.30$ (isolated vs. +1), $p \leq 0.0001$ (isolated vs. complex), $p = 0.0001$ (+1 vs. complex)

conditions recurrently observed in cases with monosomy 7 are antecedent aplastic anemia, Fanconi's anemia, neurofibromatosis type I, cyclic neutropenia, and long-term treatment with granulocyte colony-stimulating factor (G-CSF), as well as Schwachman's syndrome. It is of special interest that myeloid cells harboring monosomy 7 seem to be preferentially responsive to a stimulation by myeloid growth factors like G-CSF and granulocyte–macrophage CSF in vitro [33, 34] as well as in vivo [35]. Although being obvious, this phenomenon never was exploited

therapeutically for a targeted priming strategy for patients with monosomy 7.

In extremely rare cases, for the so-called monosomy 7 syndromes, the abnormality has a familiar background. In a substantial portion of patients, a mutagen exposition (benzene, solvents, irradiation, or radio- and/or chemotherapy) was documented.

In contrast to the situation in 5q deletions, in monosomy 7, additional abnormalities do not have such a profound impact on outcome as seen in 5q deletions, since

Table 4 Frequencies (in percent of all cases with the respective primary abnormality) of accompanying abnormalities

5q– (n=59)		−7/7q– (n=38)		trisomy 8 (n=44)	
Additional anomaly	Percent	Additional anomaly	Percent	Additional anomaly	Percent
+8	17	+21	10	5q–	23
+21	13	5q–	10	+21	11
−20/20q–	8	+8	10	der(3q21/q26)	7
−7	7	inv(3q)	5	+11	7
der/del(12p)	7	del(12p)	5	−7	5
der/del(3p)	5	t(11q23)	5	del(12p)	5
der/t(21q)	5	iso(17)(q10)	5	+13	5
t(11q23)	3	Others	50	+14	5
Others	35			+8*	5
				del(1p)	5
				Others	22

monosomy 7 even as an isolated abnormality confers a significantly bad prognosis. In our Austrian–German data-set, median survival times were 14 months for the isolated abnormality, 11 months for cases with one additional change, and 8 months for monosomy 7 as part of complex abnormalities (Fig. 3) [1].

Therapeutic options in the monosomy 7 subgroup are unsatisfying as yet. If age and clinical condition are adequate, patients should be treated with allogeneic stem cell transplantation whenever possible. Conventional intensive chemotherapy bears a high risk of early death and nonresponse. Even if a complete remission can be achieved, this frequently is of only short duration with a high risk of early relapse. In a recent report on 34 patients with MDS or AML treated with 5-azacytidine, the group of Mufti observed a preferentially good response of MDS patients with monosomy 7 to the demethylating agent 5-azacytidine. In this trial, five of the seven (71%) complete responders had isolated chromosome 7 abnormalities and achieved a continuous complete remission (10 months follow-up) in contrast to patients with other karyotype abnormalities like trisomy 8 who relapsed within the first 6 months [36]. Supporting results have been recently published for the use of decitabine by Lübbert et al. [37]. Future multicentric therapy trials are needed to verify this observation in a higher number of patients.

Complex abnormalities

According to the International System for Human Cytogenic Nomenclature criteria, complex chromomosome abnormalities are defined by the simultaneous occurrence of at least three independent abnormalities within one cell clone [38]. This cytogenetic subtype is present in some 15% of all patients with MDS (roughly 30% of all abnormal cases) and thus occurs in a frequency comparable to 5q deletions [1–3]. Complex abnormalities may be the result of a multistep process with sequential accumulation of abnormalities, called karyotype evolution. In some cases, karyotype evolution can be observed if repeated cytogenetic analyses are performed, unraveling the stepwise accumulation of secondary abnormalities with the starting point of a primary abnormality. In a few patients, cytogenetic analysis detects cell clones with primary and others with primary and secondary and possibly further abnormalities at one and the same time point. However, frequently, this process cannot be proven in the individual patient who presents with multiple chromosomal changes at first diagnosis. In most of these cases, complexity is profound with aberration numbers exceeding the threshold of three by far. Frequently, in these cases, cell-to-cell variations occur, and the chromosomal complement presents with a chaotic, mutator-like shape resembling cytogenetics of solid
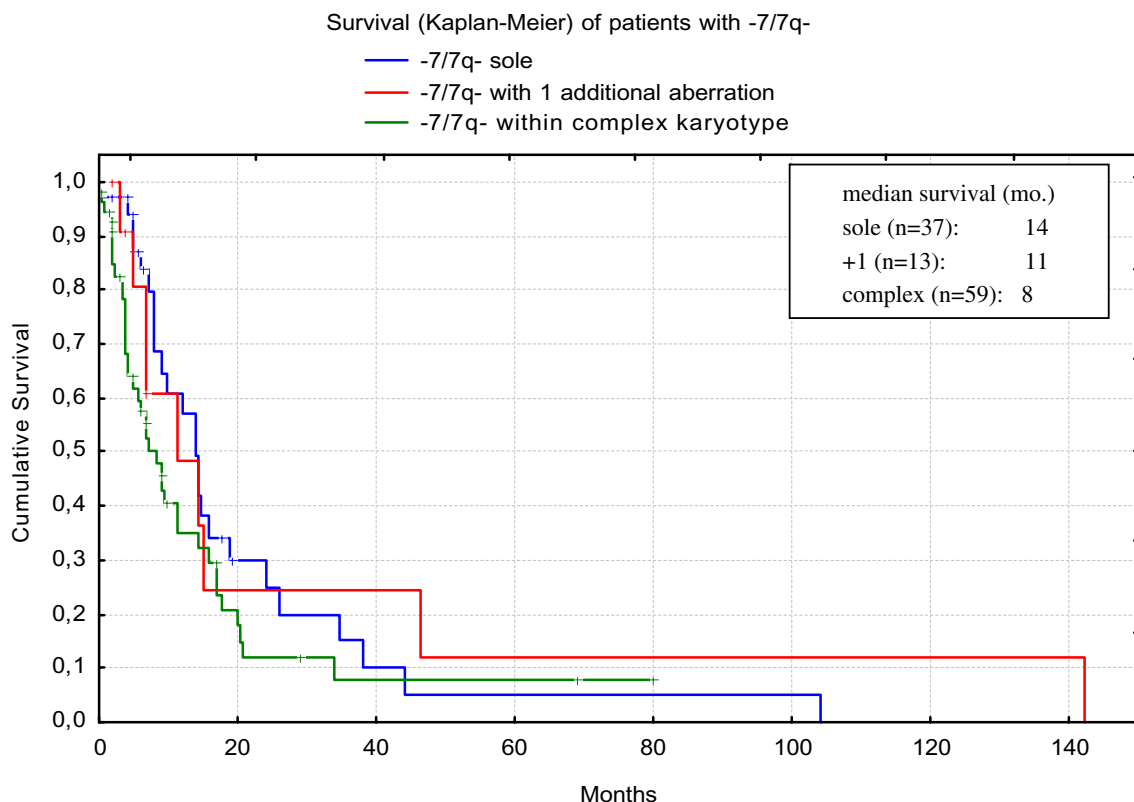

Fig. 3 Median survival according to accompanying abnormalities in patients with −7/7q−. Log-rank test: $p=0.03$ (2 degrees of freedom), $p=0.94$ (isolated vs. +1), $p=0.07$ (isolated vs. complex), $p=0.43$ (+1 vs. complex)

tumors and malignancies in chromosomal breakage syndromes. Thus, it is conceivable that, in these cases, the process leading to complex abnormalities and genetic instability must proceed rapidly on the one hand and must involve mechanisms like DNA repair and cell cycle control comparable to the situation in DNA repair deficiency syndromes. Recent results of gene expression analyses in patients with MDS and complex chromosome abnormalities support these assumptions and are considered below in more detail [39]. In a substantial portion of patients with complex abnormalities, an exposition to therapeutically applied mutagens, like anthracyclines, topoisomerase II inhibitors, alkylating agents, and/or irradiation, can be traced in the medical history [40]. Within the subgroup of patients with complex changes, a broad range of the number of abnormalities with the majority of patients displaying greater than or equal to five chromosomal changes can be observed [39].

There is a strong association with unbalanced structural abnormalities affecting most frequently chromosomes 5q and 7q. Chromosomes less frequently involved in loss of genetic material were chromosomes 3 (p- and q-arms), 12p, 13q, 16q, 17p, 18q, and 20q. Genomic gains were observed for chromosome 8/8q, 11q, and 21q [41]. Mutations of p53 have been observed in up to 90% of patients with AML and complex abnormalities [39]. Matrix comparative genomic hybridization (CGH) analyses in patients with complex abnormalities revealed an association of complex karyotype changes with amplifications in the chromosomal regions 8q24, 9p24,,11q23, 12p13, 13q12, 20q11, and 2q1q22 [42].

Recently, characteristic profiles of complex abnormalities in AML were delineated by gene expression analyses. In this respect, a significant overexpression of RAD21, a double-strand-break DNA repair enzyme, as well as overexpression of other genes related to DNA-repair, apoptotic mechanisms, and cell-cycle control (RAD1, RAD 9A, RAD23B, RAD51AP1, NBS1, MSH6, SUMO1, and PARP2) was observed [39].

Taken together, these data might help to understand complex abnormalities as a maximum manifestation of genetic instability by allowing cells with significant DNA damages to circumvent physiologically protective apoptosis and to escape cytotoxicity of chemotherapy by intensified DNA repair. This model is also compatible with the high extent of chemo-resistance of hematopoietic cells with complex chromosome abnormalities, which is a well-known and severe problem in the clinical management of high-risk MDS. Further clinical associations are the high median age of patients within this cytogenetic subgroup [43] and, related to conventional intensive chemotherapy, short remission durations and a high risk for early relapse [44]. Allogeneic stem cell transplantation, the only curative option for these patients, will only be feasible for a minority

of individuals with complex chromosomal changes due to age-related multimorbidity and organ dysfunctions. New therapeutic strategies targeting hypermethylation, deacetylation, and immunomodulation, which have proven their tolerability also in aged patient populations, are now available for the treatment of patients with high-risk MDS. In this respect, two studies have to be mentioned. Cytogenetic responses in a substantial portion of patients with high-risk MDS have been observed in a multicentric study of decitabine, a potent demethylating agent. Major cytogenetic responses (MajCR) were observed in 38% of 50 patients. Remarkably, 10 out of 26 patients (38%) with high-risk cytogenetics displayed a MajCR; five of them had complex chromosome abnormalities. In the patients' group with MajCR, median survival time was 24 months as compared to the significantly shorter median survival time of 11 months in patients with persisting cytogenetic aberrations [45]. These observations are further supported by observations of our group. Within a cohort of 14 patients with high-risk MDS, we recently observed hematologic and cytogenetic responses to 5-azacytidine according to the modified International Working Group criteria [46] in three out of four patients with complex abnormalities [47].

Another new therapeutic mechanism, immunomodulation, might be effective in cases with complex karyotypic changes too. In this connection, a complete cytogenetic response to the immunomodulatory drug lenalidomide has been reported in patients with high-risk MDS with complex chromosome abnormalities harboring 5q deletions [48]. Further multicentric clinical trials are needed to confirm these observations.

Conclusions

In contrast to CML where the bcr–abl fusion forms the homogenous genetic basis of the disease [49], MDS show a profound heterogeneity, not only on the morphologic and clinical level but also on the genetic presentation. Three cytogenetic subgroups with prognostic relevance have been identified and were incorporated into prognostic scoring by the IPSS. However, in the great majority of cytogenetic changes, the prognostic relevance is still obscure. Genetic heterogeneity in MDS leads to the paradox situation that rare abnormalities can be observed frequently [1] with the consequence that, for a relevant portion of abnormalities, their prognostic impact is still unknown. The only chance to overcome these shortcomings is to establish multicentric cooperations, which are the goals of the German–Austrian MDS Study Group, which is now cooperating with the MD Anderson Cancer Centre as well as the IMRAW group [50–52]. New

therapeutic strategies targeting immunomodulation and epigenetic changes proved to be of outstanding effectiveness and tolerability in comparison to established therapies not only for the low-risk 5q syndrome but also for high-risk MDS with as yet deleterious cytogenetic alterations like monosomy 7 and complex abnormalities.

However, what about the subgroup of nearly 50% of patients presenting with a normal karyotype? New techniques will help to further delineate the genetic background in these cases. Thus, very recently, two groups published their results of single nucleotide polymorphism analyses in MDS [53, 54]. The group of Mufti performed high-resolution single-nucleotide polymorphism (SNP) array analyses in 119 low-risk MDS patients of whom 32% displayed clonal chromosome abnormalities to search for cryptic chromosomal aberrations not detectable by chromosomal banding analyses. They found uniparental disomy (UPD), a copy number neutral loss of heterozygosity, in 46% of patients, small deletions in 10%, and amplifications in 8% of the cohort. The changes of copy numbers were acquired while UPDs were constitutional. The former aberrations were associated with a worsened outcome of the patients. The authors speculated that the high frequency of UPD may be indicative for a constitutional genomic instability in these patients [53]. This could be a predisposing factor for MDS. Maciejewski et al. applied 250 K SNP arrays to 94 patients with MDS and observed SNP aberrations in 75% of patients as compared to 59% clonal chromosomal abnormalities detected by metaphase analyses. Previously unknown lesions were found in patients with a normal—as well as in others with an abnormal—karyotype. In this study, UPD occurred in 20% of the MDS patients [54].

New analytical tools like matrix CGH, microarray gene expression analyses, proteomics, and methylation profiling will add substantially to the understanding of pathogenesis, delineation of therapeutic targets, and individualization of therapy in MDS.

Taken together cytogenetics is still the gold standard of genetic diagnosis in MDS providing "labels" like 5q−, monosomy 7, or complex abnormalities for disease entities with a common biological behavior and clinical as well as prognostic impact. In the future, scientific progress will depend on the ability to combine established and newly developed methods to gain a comprehensive understanding of MDS, which will translate into an individualized and highly effective and well-tolerable treatment for all patients with MDS.

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