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Significance of Thrombocytopenia in Myelodysplastic Syndromes: Associations and Prognostic Implications

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Abstract

Purpose—To analyze the incidence and significance of thrombocytopenia in patients with myelodysplastic syndrome (MDS).

Patients and Methods—A total of 2517 patients with MDS referred to our institution since 1993 were analyzed, with a specific focus on the incidence and associations of thrombocytopenia.

Results—The median age of the study group was 66 years. The median survival was 13 months. Platelet counts $<100 \times 10^9$/L were noted in 65%, and platelets counts $<30 \times 10^9$/L in 26%. Each platelets count drop below the range of 200×10^9/L has shown a larger magnitude change in terms of worsening effect on survival. Therefore, smaller ranges of platelet counts of $<200 \times 10^9$/L were studied. Platelet cutoffs of 30, 50, and 200×10^9/L thus were identified to have significant associations with differences in survival. Significant thrombocytopenia was associated with poor performance, other cytopenias, adverse karyotype, and advanced MDS phases. Thrombocytopenia was associated with worse prognosis; it also was predicted for worse outcome within each of the International Prognostic Scoring System risk groups.

Conclusion—Prognosis in MDS is directly associated with the severity of thrombocytopenia.

Keywords

Thrombocytopenia; Myelodysplastic syndrome; outcome

Introduction

The myelodysplastic syndromes (MDS) are heterogeneous hematopoietic stem cell disorders characterized by cytopenias, cellular marrows with ineffective hematopoiesis, frequent presence of cytogenetic abnormalities, dysplastic changes in one or more lineages reflective of increased apoptosis, risk of transformation to acute myeloid leukemia (AML) or death from complications of cytopenias, and a generally poor prognosis. Several risk models have

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categorized patients with MDS into different risk categories, with median survivals that range from <1 to 6 years, and risk of an AML transformation that ranges from 10% to 90%.[1–5]

Thrombocytopenia is a significant but so far downplayed manifestation of MDS at diagnosis and during the course of the disease. Thrombocytopenia with platelet counts of $<100 \times 10^9$/L is featured as one of the cytopenias of the International Prognostic Scoring System (IPSS).[3] However, 2 or more cytopenias translate into a score of 0.5, which does not reflect the significance of thrombocytopenia, or of severe thrombocytopenia, at diagnosis or during the course of MDS.[4] A prognostic MDS risk model developed and validated at the MD Anderson Cancer Center suggested severe thrombocytopenia (platelet counts $<50 \times 10^9$/L) to be one of the most important independent poor prognostic factors at diagnosis or at any time during the course of MDS.[4] Neukirchen et al[6] reviewed 2900 patients from the Duesseldorf MDS Registry and identified thrombocytopenia (platelets $<100 \times 10^9$/L) to be associated, by multivariate analysis, with significantly shorter survival and with significant increased risk of AML transformation and bleeding. In several studies, thrombocytopenia was reported to be a significant cause of death in 10% to 30% of patients.[7–9] The aims of the present analysis are to define the incidence, associations, and prognostic implications of thrombocytopenia in MDS.

Study Groups and Methods

Patients with a diagnosis of MDS referred to the MD Anderson Cancer Center since 1993 were included in the analysis. Inclusion criteria were the following: age 16 years or older, diagnosis of MDS with <30% blasts, and informed consent in compliance with institutional guidelines. All the patients were analyzed regardless of performance status, organ dysfunctions, or previous therapy. Patients with secondary MDS and proliferative chronic myelomonocytic leukemia also were included.

The patient characteristics were recorded. These included the patient age, sex, performance status, hemoglobin levels, white blood cell and platelet counts, percentage of marrow and peripheral blood blasts, creatinine and bilirubin levels, duration of MDS, previous cancers and their treatment, morphology (MDS or CMML), number and intensity of cytopenias, IPSS score, cytogenetic abnormalities, and previous therapy.

Statistical Considerations

The significance of individual factors was analyzed by standard univariate analysis.[10] Survival was calculated from the date of referral to our institution; the probability was estimated by Kaplan-Meier Method.

Results

Study Group

A total of 2517 patients were analyzed (Table 1). Their median age was 66 years (range, 16–94 years); 35% of patients were 70 years or older; 33% were women. The median hemoglobin level was 9.6 g/dL (range, 3.2–16.4 g/dL). The median platelet count was 63 ×

10^9/L (range, 1–1195 × 10^9/L). The median granulocyte count was 1.58 × 10^9/L (range, 0–74.7 × 10^9/L). The median marrow blast percentage was 7% (range, 0%–29%). The median survival of the study group was 13 months; the 2-year survival rate was 32% (Figure 1).

Significance of Thrombocytopenia

A total of 1646 (65%) patients had platelet counts <100 × 10^9/L, 1045 (42%) had platelet counts <50 × 10^9/L, and 645 (26%) had platelet counts <30 × 10^9/L. Each platelet count drop below the range of 200 × 10^9/L has shown a greater magnitude change in terms of worsening effect on survival. Therefore, smaller ranges of platelet counts of <200 × 10^9/L were studied. Platelet cutoffs of 30, 50, and 200 × 10^9/L thus were identified to have significant associations with differences in survival. Survival by these platelet cutoffs is shown in Figure 2.

The incidence of thrombocytopenia by patient and disease characteristics is shown in Table 2. Significant thrombocytopenia was associated with poor performance status, other cytopenias, increased blasts percentages, adverse karyotypes, and advanced MDS phases. Previous univariate and multivariate analyses showed the following to be independent adverse prognostic factors associated with survival (all with *P* values <.01): older age, anemia, leukocytosis, increased marrow blasts, poor performed ≥2 (ECOG [Eastern Cooperative Oncology Group]), and thrombocytopenia. The details of these analyses and proposed risk models have been published.[4] Common sites of bleeding were in the central nervous system, lungs, gastrointestinal tract, and multiple organs. As reported, platelet counts of <30, 30–49, and 50–199 × 10^9/L were important independent adverse factors for survival, their prognostic significance increasing with the increased severity of thrombocytopenia.[4] At a second time, the same analysis restricted to patients with marrow blasts <20% was performed. Thrombocytopenia remains an independent prognostic factor for survival.

The IPSS is a widely used and recognized risk model. To emphasize the independent prognostic significance of severe thrombocytopenia, we analyzed the survival of patients with low-, intermediate-1-, intermediate-2-, and high-risk IPSS by levels of platelet counts (<30, 30–49, 50–199, and ≥200 × 10^9/L). As shown in Figure 3A–D and across all the IPSS risk categories, patients with thrombocytopenia had a worse survival.

Complications of Thrombocytopenia

The main cause of death among patients who expired while still in the MDS phase, coded as known cause of death, was available in 771 (39%) patients. Among the causes of death, bleeding is recorded as the primary cause of death in 94 (12%) of 771 patients and as a contributory cause of death in 56 (7%) patients (Table 3). Common sites of bleeding were the central nervous system, lungs, and gastrointestinal tract.

Discussion

In this analysis, we confirmed the significant incidence of thrombocytopenia in patients with MDS. Sixty-five percent of patients presented to our institution with platelet counts <100 × 10^9/L, a well-accepted parameter in defining thrombocytopenia. We also confirmed that

prognosis in MDS is directly associated with the severity of thrombocytopenia. This prognostic effect is independent of other well-known prognostic factors and may suggest that thrombocytopenia is either a general measure of an independent adverse pathophysiologic factor or in itself a significant cause of mortality from bleeding complications. The latter explanation raises the possibility that the use of the new-generation thrombomimetic agents may reduce the incidence and severity of thrombocytopenia as well as the consequences of bleeding and mortality.

The purpose of this analysis was to assess the real affect of thrombocytopenia and its severity as an independent prognostic factor on survival of patients with MDS. We did not set a cutoff point at a certain time, because it was previously published.

Thrombocytopenia, so far, was downplayed as a manifestation of MDS at diagnosis and during the course of the disease.[3] Thrombocytopenia with platelet counts of $<100 \times 10^9$/L was featured as one of the cytopenias of the IPSS. However, 2 or more cytopenias translated into a score of only 0.5, which does not reflect the significance of thrombocytopenia, or of severe thrombocytopenia, at diagnosis or during the course of MDS. In our study, any degree of thrombocytopenia was associated with a poor outcome across all the stages of the IPSS.

In line with what was recently published, our current study highlighted the fact that the majority of MDS-related mortalities was caused by infections.[11] Our previous publication also provides evidence for changing trends in the cause of death in patients with MDS, with the proportion of infections declining over the past 3 decades, mainly because of the advances in the supportive care, whereas hematologic causes have been steadily rising, among them thrombocytopenia and bleeding.

Results of recent studies have shown several new-generation thrombomimetic agents to be highly effective in reducing thrombocytopenia and bleeding events in patients with immune-mediated thrombocytopenic purpura, which result in the approval by the US Food and Drug Administration of such agents (romiplostim, eltrombopag). The use of romiplostim in patients with low-risk MDS and thrombocytopenia demonstrated significant and durable improvements of platelet counts in 40% to 50%, with evidence of reductions in the need of platelet transfusions and of bleeding events.[12] Results of studies that combined romiplostim with hypomethylating agents also have shown promising results.[13] Large-scale randomized trials of romiplostim vs. placebo in patients with low-risk MDS and thrombocytopenia are ongoing. It is hoped that such thrombomimetic agents, used alone or in combination with chemotherapy, may improve on thrombocytopenia and its complications in MDS and, therefore, improve survival.

References

1. Bennett JM, Brunning RD, Vardiman JW. Myelodysplastic syndromes: from French-American-British to World Health Organization: a commentary. Blood. 2002; 99:3074–5. [PubMed: 11949634]
2. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009; 114:937–51. [PubMed: 19357394]

3. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997; 89:2079–88. [PubMed: 9058730]
4. Kantarjian H, O'Brien S, Ravandi F, et al. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. Cancer. 2008; 113:1351–61. [PubMed: 18618511]
5. Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. Blood. 2000; 96:3671–4. [PubMed: 11090046]
6. Neukirchen J, Blum S, Kuendgen A, et al. Platelet counts and haemorrhagic diathesis in patients with myelodysplastic syndromes. Eur J Haematol. 2009; 83:477–82. [PubMed: 19548919]
7. Kantarjian H, Giles F, List A, et al. The incidence and impact of thrombocytopenia in myelodysplastic syndromes. Cancer. 2007; 109:1705–14. [PubMed: 17366593]
8. Germing U, Platzbecker U, Giagounidis A, Aul C. Platelet morphology, platelet mass, platelet count and prognosis in patients with myelodysplastic syndromes. Br J Haematol. 2007; 138:399–400. [PubMed: 17555472]
9. Bowles KM, Warner BA, Baglin TP. Platelet mass has prognostic value in patients with myelodysplastic syndromes. Br J Haematol. 2006; 135:198–200. [PubMed: 16939490]
10. Cox, DR. The Analysis of Binary Data. London: Methuen; 1970.
11. Dayyani F, Conley AP, Strom SS, et al. Cause of death in patients with lower-risk myelodysplastic syndrome. Cancer. 2010; 116:2174–9. [PubMed: 20162709]
12. Kantarjian H, Fenaux P, Sekeres MA, et al. Safety and efficacy of romiplostim in patients with lower-risk myelodysplastic syndrome and thrombocytopenia. J Clin Oncol. 28:437–44. XXX. [FS1]. [PubMed: 20008626]
13. Kantarjian H, Giles F, et al. Effect of romiplostim in patients (pts) with low or intermediate risk myelodysplastic syndrome (MDS) receiving azacytidine. ASH Annual Meeting Abstracts. 2008; 112(11):224. [FS2].

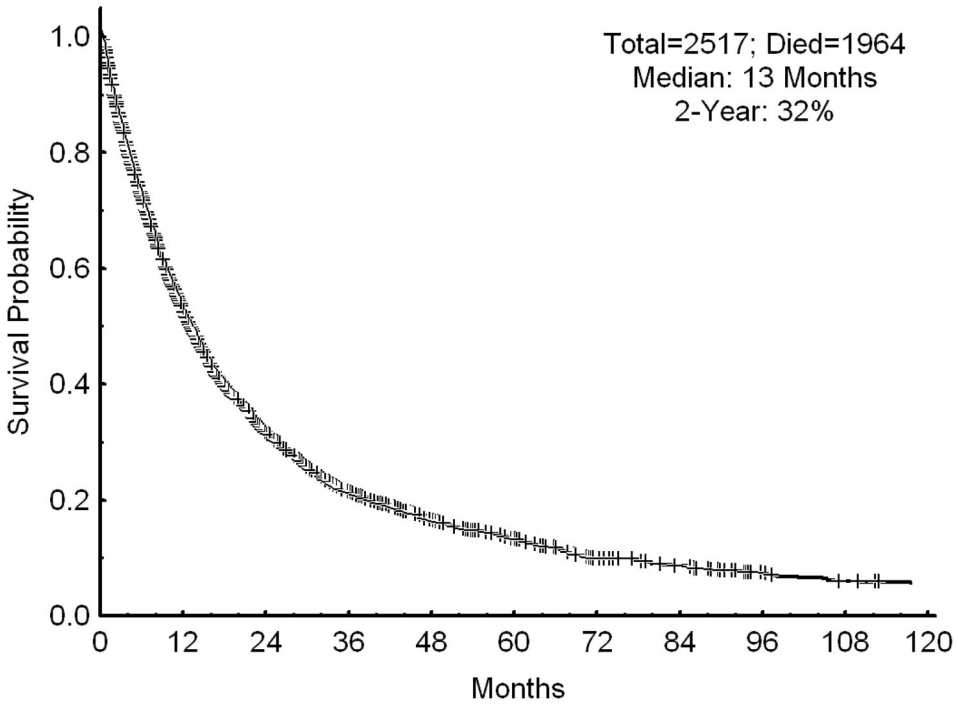

Figure 1.
Survival of the Study Group

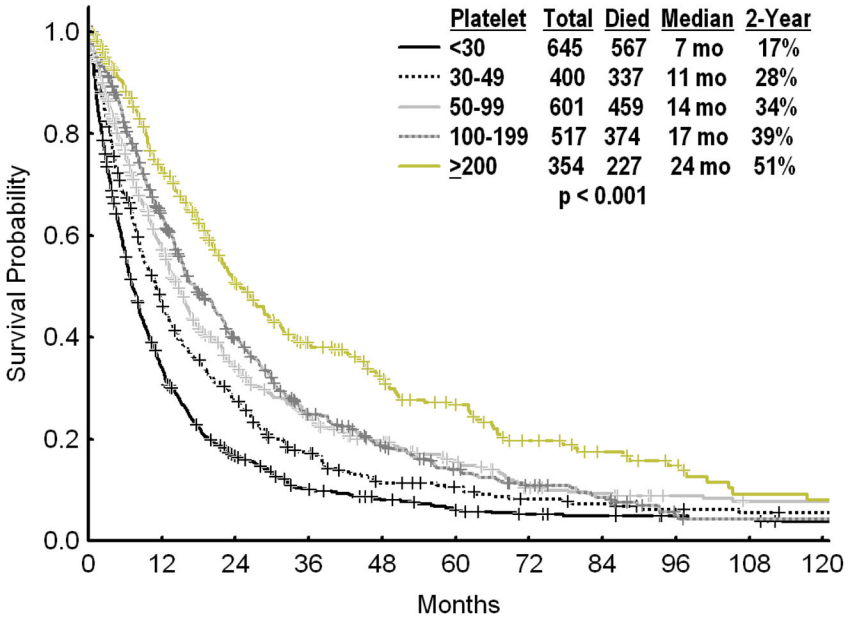

Figure 2.
Survival by Platelet Counts

Figure 3A

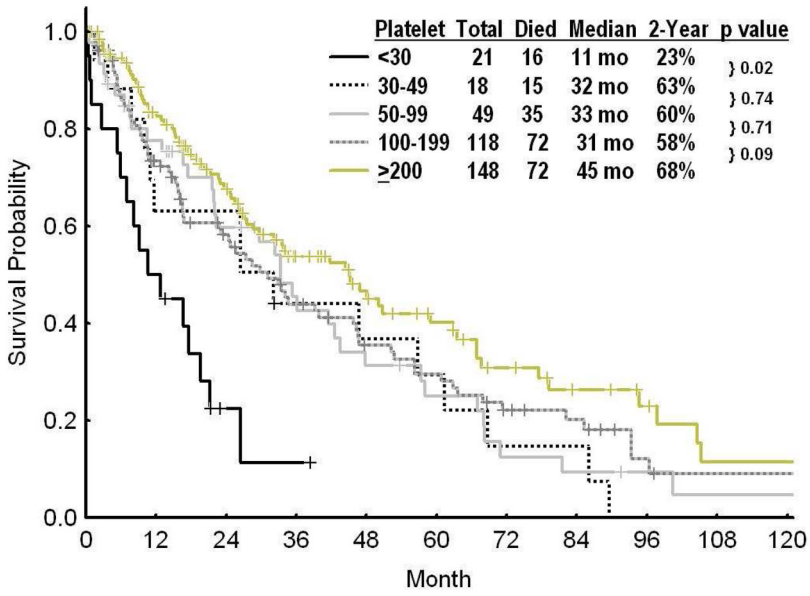

Figure 3B

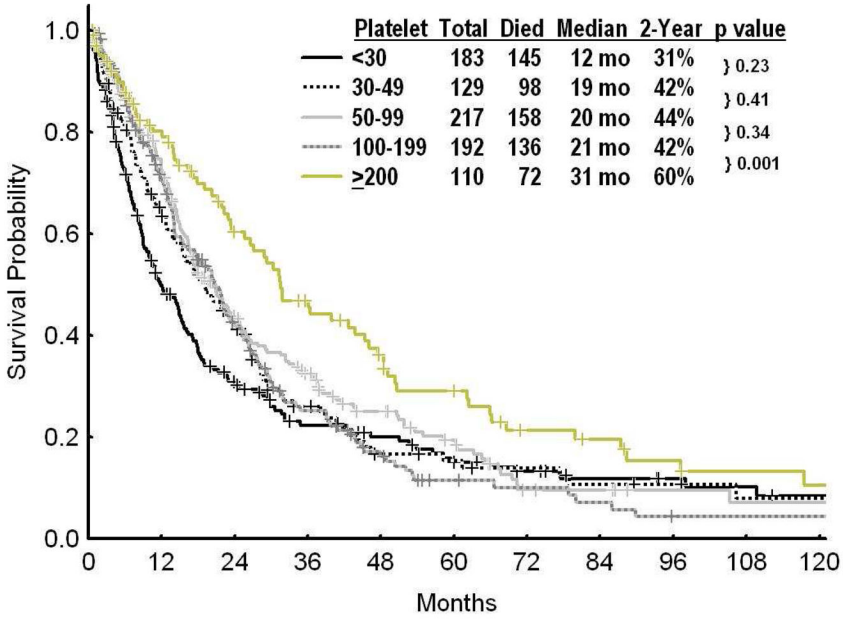

Figure 3C

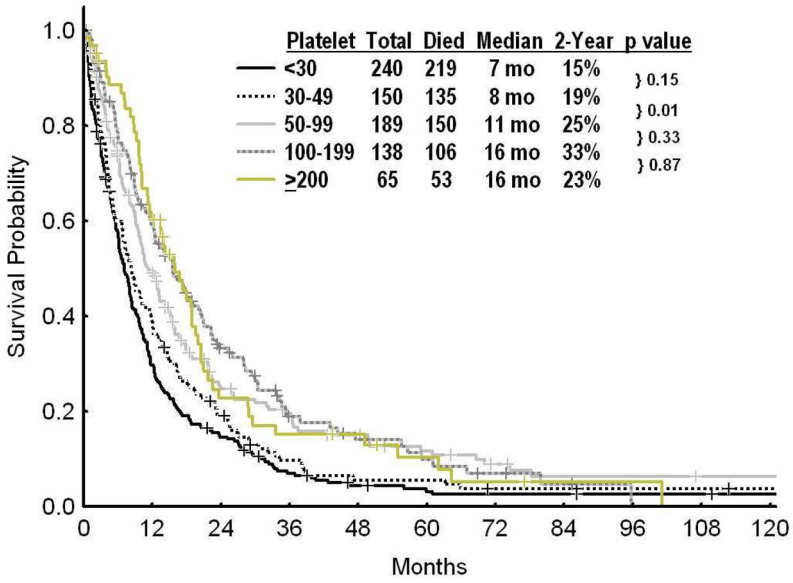

Figure 3D

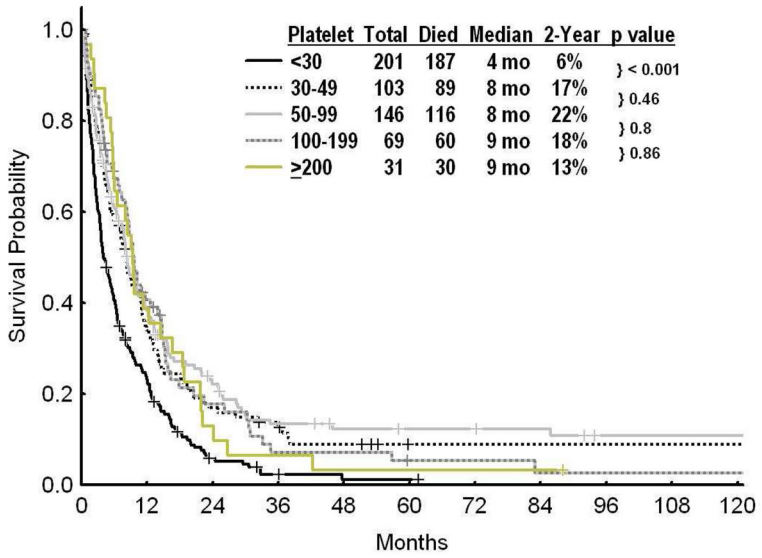

Figure 3.

Figure 3A Survival by Platelet Counts within International Prognostic Scoring System (IPSS)-low

Figure 3B Survival by Platelet Counts Within IPSS-intermediate-1

Figure 3C Survival by Platelet Counts Within IPSS-intermediate-2

Figure 3D Survival by Platelet Counts Within IPSS-high

Table 1

Characteristics of the Study Group (n = 2517)

Characteristic	Category	n (%)
Age (years)	>65	1367 (54)
Sex	Women	842 (33)
Performance Status	≥2	334 (13)
Secondary MDS	Yes	711 (28)
Hemoglobin (g/dL)	<12	2238 (89)
Platelets ($\times 10^9$/L)	<30	646 (26)
	30–49	400 (16)
	50–99	601 (24)
	100–199	517 (21)
	≥200	354 (14)
Granulocytes ($\times 10^9$/L)	<1.5	1215 (48)
Bone Marrow Blasts (%)	<5	956 (38)
	5–10	677 (27)
	11–20	599 (24)
	21–29	285 (11)
Karyotype	Deletion 5q + 1 other	93 (4)
	Deletion 20q + 1 other	46 (2)
	Normal	1194 (47)
	Chromosome 5 or 7 abn	500 (20)
	Complex karyotype	338 (13)
	Other	346 (14)
Previous Therapy for MDS	Yes	318 (13)
Disease Category	MDS	2140 (85)
	CMML	377 (15)

Abbreviations: abn = ; CMML = ; MDS = myelodysplastic syndrome

Table 2

Associations of Thrombocypenia and Patient and Disease Characteristic

Characteristic		No. (%) of Category by Platelet Count (× 10^9/L)					*P*
	Category		<30	30–49	50–199	≥200	
Sex	Women	842	204 (24)	125 (15)	381 (45)	132 (16)	.224
	Men	1675	441 (26)	275 (16)	737 (44)	222 (13)	
Performance Status	0–1	2183	514 (24)	356 (16)	993 (45)	320 (15)	<.001
	≥2	334	131 (39)	44 (13)	125 (37)	34 (10)	
Hemoglobin (g/dL)	<12	2238	612 (27)	372 (17)	939 (42)	315 (14)	<.001
		279	33 (12)	28 (10)	179 (64)	39 (14)	
Granulocytes (× 10^9/L)	<1.5	1215	364 (30)	194 (16)	555 (46)	102 (8)	<.001
		1302	281 (22)	206 (16)	563 (43)	252 (19)	
Bone Marrow Blasts (%)	<5	956	193 (20)	115 (12)	437 (46)	211 (22)	<.001
	5–10	677	177 (26)	132 (19)	306 (45)	62 (9)	
	11–20	599	185 (31)	99 (17)	253 (42)	62 (10)	
	21–29	285	90 (32)	54 (19)	122 (43)	19 (7)	
Karyotype	Deletion 5q + 1 other	93	8 (9)	4 (4)	44 (47)	37 (40)	<.001
	Deletion 20q + 1 other	46	15 (33)	8 (17)	17 (37)	6 (13)	
	Normal	1194	239 (20)	177 (15)	568 (48)	210 (18)	
	Chromosome 5 or 7 abnormalities	500	169 (34)	100 (20)	213 (43)	18 (4)	
	Complex kary.(3bn)	338	126 (37)	64 (19)	121(16)	27 (8)	
	Others	346	88 (25)	47 (14)	155 (45)	56 (16)	
Previous Rx for	Yes	318	79 (25)	54 (17)	136 (43)	49 (15)	.791
MDS	No	2199	566 (26)	346 (16)	982 (45)	305 (14)	
Disease category	MDS	2140	577 (27)	343 (16)	921 (43)	299 (14)	.001
	CMML	377	68 (18)	57 (15)	197 (52)	55915)	
IPSS Risk	Low	354	21 (6)	18 (5)	167 (47)	148 (42)	<
	Intermediate-1	831	183 (22)	129 (16)	409 (49)	110 (13)	.001
	Intermediate-2	782	240 (31)	150 (19)	327 (42)	65 (8)	
	High	550	201 (37)	103 (19)	215 (39)	3196)	

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Characteristic		No. (%) of Category by Platelet Count (× 10^9/L)					*P*
	Category		**<30**	**30–49**	**50–199**	**≥200**	
FAB Categories	RA	539	117 (22)	66 (12)	244 (45)	112 (21)	<
	RA-RS	181	32 (18)	13 (7)	71 (39)	65 (35)	.001
	RAEB	775	209 (27)	134 (17)	358 (46)	74 (10)	
	RAEBt	645	219 (34)	130 (20)	248 (38)	48 (7)	
	CMML	377	68 (18)	57 (15)	197 (52)	55 (15)	

Abbreviations: CMML = ; FAB = ; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndrome; RA = ; RAEB = ; RAEBt = ; RS = ; Rx =.

Table 3

Causes of Death in MDS (n = 1189)

Cause of Death	No. (%)
Death in MDS	771 (65)
Bleeding	94 (12)
Infections	373 (48)
Organ failures	42 (5)
Bleeding and Others	56 (7)
Other Causes	206 (27)
Progression and Death in AML	418 (35)

Abbreviations: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome.