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TP53 mutation defines a unique subgroup within complex karyotype de novo and therapy-related MDS/AML

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Key Points

- Among patients with MDS and AML, the presence of *TP53* mutation in the context of CK identifies a homogeneously aggressive disease.
- *TP53* mutation (in particular multihit) identifies an aggressive disease, irrespective of the blast count or therapy-relatedness.

A subset of myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) show complex karyotype (CK), and these cases include a relatively high proportion of cases of therapy-related myeloid neoplasms and *TP53* mutations. We aimed to evaluate the clinicopathologic features of outcome of 299 AML and MDS patients with CK collected from multiple academic institutions. Mutations were present in 287 patients (96%), and the most common mutation detected was in *TP53* gene (247, 83%). A higher frequency of *TP53* mutations was present in therapy-related cases ($P = .008$), with a trend for worse overall survival (OS) in therapy-related patients as compared with de novo disease ($P = .08$) and within the therapy-related group; the presence of *TP53* mutation strongly predicted for worse outcome ($P = .0017$). However, there was no difference in survival between CK patients based on categorization of AML vs MDS ($P = .96$) or presence of absence of circulating blasts ≥1% ($P = .52$). *TP53*-mutated patients presented with older age ($P = .06$) and lower hemoglobin levels ($P = .004$) and marrow blast counts ($P = .02$) compared with those with CK lacking *TP53* mutation. Multivariable analysis identified presence of multihit *TP53* mutation as strongest predictor of worse outcome, whereas neither a diagnosis of AML vs MDS nor therapy-relatedness independently influenced OS. Our findings suggest that among patients with MDS and AML, the presence of *TP53* mutation (in particular multihit *TP53* mutation) in the context of CK identifies a homogeneously aggressive disease, irrespective of the blast count at presentation or therapy-relatedness. The current classification of these cases into different disease categories artificially separates a single biologic disease entity.

Introduction

The presence of a complex karyotype (CK), defined as ≥3 chromosomal abnormalities, comprises 10% to 12% of all acute myeloid leukemia (AML) patients and constitutes the second largest cytogenetic subset of AML patients (after those with normal karyotype). Complex karyotype is also present in 10% to 30% of myelodysplastic syndrome (MDS) patients.[1-3] In MDS and oligoblastic AML (with 20% to 29% blasts), the Revised International Prognostic Scoring System (IPSS-R) assigns a substantial risk to

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The full-text version of this article contains a data supplement.

patients with complex karyotype: patients with 3 abnormalities have poor cytogenetic risk, whereas those with 4 or more have a very poor cytogenetic risk, with a score that exceeds the score contributed by a blast count of >10%.[4-8]

Complex karyotype in both AML and MDS is associated with *TP53* mutations. Although the overall incidence of *TP53* mutations in de novo AML is relatively low (5% to 20%), its incidence increases with age and in therapy-related disease. Indeed, *TP53* mutations are regarded as a molecular hallmark of patients with CK AML and occur in 70% to 80% of such patients,[9] being particularly frequent in AML with monosomal karyotype (MK).[10,11] *TP53* mutations are also present in 55% of MDS patients with complex karyotypes and are associated with relatively few cooperating somatic mutations in other MDS-associated genes.[5] Bernard et al analyzed 3324 patients with MDS for *TP53* mutations and allelic imbalances and found that one-third have monoallelic mutations, whereas two-thirds have multiple hits or losses of the *TP53* gene, consistent with biallelic targeting. Interestingly, only multihit *TP53,* but not monoallelic *TP53* mutation, was associated with complex karyotype and poorer outcome.[12]

Both AML and MDS with complex karyotypes are enriched in therapy-related cases (t-AML and t-MDS), and in the current World Health Organization (WHO) classification, they are regarded together in a single group of therapy-related myeloid neoplasms (t-MN) independent of their morphologic features or designation as MDS or AML based on blast count.[13-17] The grouping of t-MDS with t-AML in the WHO classification was largely based on a study by Sing et al, which compared 155 t-MDS and t-AML patients and showed no significance difference in survival, with a uniformly poor outcome regardless of blast count.[18] Of note, complex karyotype was present in nearly half of the cases in this study.[18] Currently, patients presenting with either MDS or AML with complex karyotypes are classified together as t-MN if the disease occurs after cytotoxic chemotherapy or radiotherapy and are classified as MDS (with subcategorization depending on the morphology and blast count) or AML with myelodysplasia-related changes (AML-MRC) if there is no history of prior therapy. We questioned whether these distinct diagnostic categories of MDS/AML patients had clinical relevance in the setting of a CK or if *TP53* mutation status could identify a more biologically homogeneous group within CK MDS and AML.

Methods

We reviewed cases from the pathology archives at Massachusetts General Hospital, Yale, University of Texas Southwestern, Weill Cornell, and Stanford Medical Center between 2012 and 2020. Medical records were thoroughly reviewed to confirm a diagnosis of MDS or AML in which at least 3 independent cytogenetic abnormalities were present and in which targeted next-generation sequencing (NGS) panels were performed as part of the clinical workup. In all cases, the bone marrow (BM) blast percentage was based on manual count of the BM aspirate smear. Cases with inv(16), t(8;21), *PML-RARA* rearrangement, or *KMT2A* rearrangement in the context of a complex karyotype were excluded. The NGS was performed on specimens taken either at the time of initial diagnosis or after the initial diagnosis in patients who had not been treated by any disease-modifying therapies. Patient and disease clinical characteristics, including treatments administered, patient follow-up, and outcome measures, were collected using the electronic health records. This study was approved by the institutional review boards of all participating institutions and was performed in accordance with the Declaration of Helsinki.

Targeted NGS

Targeted NGS was performed to detect gene mutations commonly found in hematologic malignancies at each participating institution as described previously.[19] The NGS panels were variable at each institution and across time periods, interrogating commonly mutated genes in hematopoietic neoplasms and sequencing across >90% of the gene coding regions; 51 genes were common to all 3 panels and were tested in all patients. Variants were classified as pathogenic/likely pathogenic, of uncertain significance, and likely benign/benign according to the American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology (AMP) recommendations; only pathogenic or likely pathogenic mutations were included in the analysis.[20] The variant allele frequency (VAF) cutoffs of pathogenic mutations were based on cutoffs established in each laboratory; for the *TP53* gene, the minimum VAF cutoff was 2%. *TP53* mutations were considered to be multihit if either 2 different *TP53* mutations, a single *TP53* mutation with VAF > 60%, or a single *TP53* mutation with 17p loss on karyotype were present. Deidentified patient sequencing data are presented in supplemental Table 1.

Cytogenetics

Conventional karyotype was performed on G-banded metaphase cells prepared from unstimulated BM aspirate cultures using standard techniques. Twenty metaphases were analyzed, and the results were reported using the International System for Human Cytogenetic Nomenclature. Complex karyotype was defined as previously described.[21] MK was identified as previously defined by the presence of a chromosomal aberration pattern characterized by the presence of at least 2 autosomal monosomies or of 1 monosomy plus 1 or more structural aberrations (not including loss of a chromosome).[6]

Statistical analyses

Overall survival (OS) was calculated from the date of diagnosis to the date of death or the last date of follow-up. Survival probability was determined using the Kaplan-Meier method, with differences compared by the log-rank test. Multivariable analyses (MA) were performed for OS on any variables significant to the level of $P < .20$ on univariate analysis, with stepwise elimination of nonsignificant variables. Comparison among categorical variables and numerical variables was carried out by using the Fisher's exact test and Mann-Whitney *U* test, respectively. Statistical analysis was performed using GraphPad Prism (GraphPad software, San Diego, CA) and Xlstat, with significance set at a *P* value <.05 (2-sided).

Results

Patient cohort

The total cohort included 299 patients (144 AML and 155 MDS) with a median age of 69.7 years (range, 1-91). Of these, 118 patients (45 AML and 73 MDS) were considered to have therapy-related disease. Median blast percentage by AML and MDS is shown in supplemental Figure 1A. Prior therapy included 20

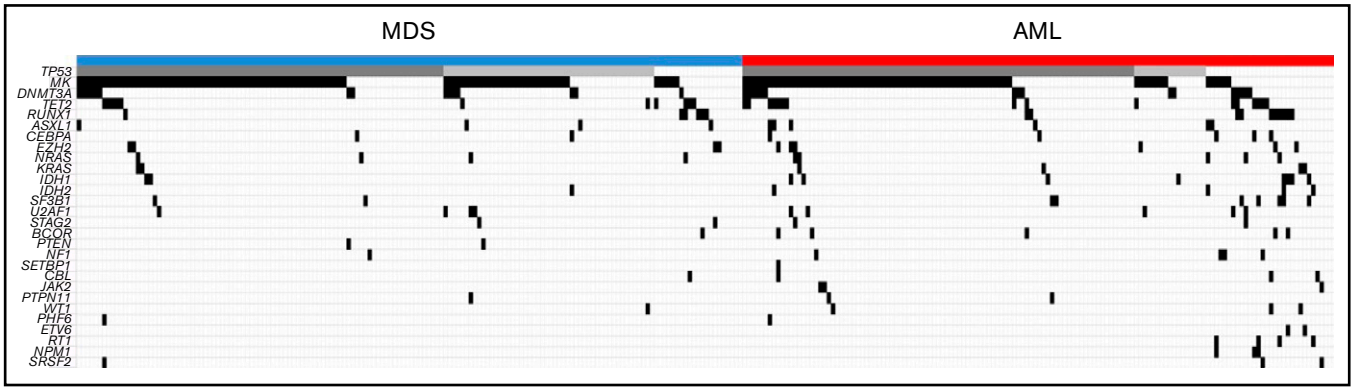

Figure 1. Heatmap of most frequent mutations divided by AML (red) and MDS status (blue). *TP53* allelic status is indicated by dark gray (multihit) and light gray (monoallelic), and white is absence of TP53. All other mutations are indicated by black (present) and white (absent). MK is also indicated by black (present) and white (absent).

patients who received only radiation, 54 who received only chemotherapy, and 23 who received both chemotherapy and radiation; therapy type was unknown for 23 patients. Cytogenetic analysis showed complex karyotype in all patients and MK in 181 patients (supplemental Table 1). The interval between initial diagnosis and time of NGS ranged from 0 to 12.0 months (median, 0 months; mean, 0.3 months). Seventy-eight patients received allogeneic stem cell transplant (SCT).

Mutations

Mutations were present in 287 patients (96%), and the most common mutation detected was in *TP53* gene (247, 83%), with a median VAF of 44% among the 176 *TP53*-mutated cases with available VAF information (supplemental Figure 1B). Of these, 180 (63%) patients had multihit *TP53* mutation. The most frequent comutations (in decreasing order) were *DNMT3A* (31, 10%), *TET2* (28, 9%), *RUNX1* (17, 6%), *EZH2* (11, 4%), *NRAS* (10, 4%), *IDH1* (10, 3%), *ASXL1* (10, 3%), and *U2AF1* (9, 3%) (Figure 1). Eleven patients did not have any detectable mutations. Mutations involved a single gene in 130 patients and >1 gene in 158, with a median of 2 mutations (range, 0-8) in each case.

Comparison of therapy-related cases with de novo cases

Compared with the 118 therapy-related patients, the de novo MDS/AML patients showed no difference in gender distribution or age at presentation (Table 1). Therapy-related patients had lower peripheral and BM blast counts ($P = .002$ and $P = .0003$) but a trend toward higher BM cellularity ($P = .06$). A higher proportion of MK and *TP53* mutations was seen in therapy-related cases ($P = .07$ and $P = .008$) compared with de novo cases. There was a trend for worse OS in therapy-related patients (median OS, 10.2 months) as compared with de novo disease (median OS, 12.2 months) ($P = .08$) (Figure 2A). Within therapy-related group, the presence of *TP53* mutation strongly predicted for worse outcome ($P = .0017$), whereas ≥5% blasts in the BM ($P = .065$) trended toward worse outcome. Considering the entire patient cohort, there was no significant effect of MK ($P = .16$), AML vs MDS diagnosis ($P = .96$), any blasts in peripheral blood (≥1%, $P = .52$) or BM blasts (0% to 4%, vs 5% to 9% vs 10% to 19% vs >20%, $P = .52$) on OS (Figure 2B and C).

TP53-mutated cases

Patients harboring *TP53* mutations (n = 247) presented with older age ($P = .06$) and lower hemoglobin ($P = .004$) and BM blast counts ($P = .02$) compared with patients with complex karyotype and wild-type *TP53* (Table 2). Compared with patients lacking *TP53* mutations, those with *TP53* mutation were enriched in abnormalities of chromosome 5 (212/247 vs 22/51, $P < .0001$), chromosome 7 (147/247 vs 22/51 vs $P = .028$), and chromosome 17p (105/247 vs 8/51 $P = .0001$). CK-*TP53*–mutated patients had a median of 8 chromosomal abnormalities, whereas CK-*TP53*–wild-type patients had a median of 4 chromosomal abnormalities ($P < .0001$). Of the 244 *TP53*-mutated patients with treatment information, 27 (11%) received supportive care only, 134 (55%) low-intensity therapies (128 hypomethylating agents [HMA], 6 other low-intensity agents), 35 (14%) HMA/venetoclax combination, and 48 (20%) intensive induction therapy. Of the 52 *TP53*–wild-type patients with treatment information, 2 (4%) received supportive care only, 25 (48%) low-intensity therapies (22 HMA, 3 other agents), 7 (13%) HMA/venetoclax combination, and 18 (35%) intensive induction therapy. These treatment data are shown in supplemental Table 2, and treatments administered based on *TP53* monoallelic vs *TP53* multihit status are shown in supplemental Table 3. Considering only *TP53*-mutated patients, there was no significant difference between therapy-related (median OS, 8.5 months) vs de novo (median OS, 10.7 months) disease ($P = .19$) (supplemental Figure 2). There was no difference in OS between AML and all MDS ($P = .36$) or between MDS-SLD/MLD (13.2 months) vs MDS-EB (10.7 months) vs AML (8.3 months) ($P = .16$) groups, although there was borderline significance when comparing OS of AML patients to MDS-SLD/MLD patients ($P = .08$). There was no significant effect of MK on OS (median, 11.8 months without MK and 9.6 months with), $P = .24$. There was no significant difference in OS comparing isolated *TP53* mutations vs *TP53* occurring with other mutations (median OS, 9.2 vs 10.7 months, $P = .23$) or with the presence of ≥3 mutations vs <3 mutations (including the *TP53*), $P = .94$ (median OS, 9.4 months with <3 mutations, 13.6 months with ≥3 mutations). Comparing OS of all patients based on *TP53* mutation status showed that no *TP53* mutation (median, 33.9 months) vs *TP53* monoallelic (median, 12.5 months) vs *TP53* multihit (median, 9.4 months) was significant ($P < .0001$) (Figure 2D), whereas comparison of TP53 monoallelic vs multihit showed a trend toward worse outcome ($P = .05$). There

Table 1. Comparison of AML vs MDS and therapy-related vs de novo complex karyotype cases

	AML (n = 144)	MDS (n = 155)	*P*	Therapy-related (n = 118)	De novo (n = 81)	*P*
Age (median, y)	69 (1-91)	70 (22-91)	.7	71 (37-91)	70 (1-88)	.06
Gender, M:F	181:76	43:18		65:61	25:10	
WHO subtype						
AML	144 (100%)	–		45 (38%)	99 (55%)	.006
MDS-SLD	–	1 (1%)		0 (0%)	1 (1%)	
MDS-MLD	–	38 (25%)		28 (24%)	10 (6%)	
MDS–RS-SLD	–	0 (0%)		0 (0%)	0 (0%)	
MDS–RS-MLD	–	11 (7%)		5 (4%)	6 (3%)	
MDS-U	–	1 (1%)		0 (0%)	1 (1%)	
MDS-EB1	–	41 (26%)		17 (14%)	24 (13%)	
MDS-EB2	–	63 (41%)		23 (19%)	40 (22%)	
Monosomal karyotype	81 (56%)	100 (65%)	.15	79 (67%)	102 (56%)	.07
Any *TP53* mutation	113 (78%)	134 (86%)	0.09	106 (90%)	141 (78%)	.008
Multihit *TP53* mutation	94 (65%)	86 (55%)	0.1	73 (62%)	107 (59%)	.72
Blood counts						
ANC	0.7 (0-58.7)	1.2 (0.02-10.1)	.0004	1.11 (0-58.7)	0.83 (0-25.4)	.49
HGB	8.3 (4-13.5)	8.8 (3.8-13.7)	.001	8.6 (4-13.7)	8.6 (3.8-13.7)	.91
WBC	2.8 (0.1-281)	3.1 (0.6-36.8)	.85	2.8 (0.6-88)	3.2 (0.1-281)	.16
Platelets	47 (5-464)	55 (3-308)	.05	55 (3-308)	49 (5-464)	.37
PB blasts, %	8 (0-97)	0 (0-16)	<.0001	0 (0-79)	2 (0-97)	.002
BM features						
Cellularity, %	77.5 (20-100)	65 (10-100)	.0007	72.5 (10-100)	70 (10-100)	.06
Blast, %	50 (14-95)	7 (0-18)	<.0001	12 (0-94)	22 (0-95)	.0003

ANC, Absolute neutrophil count; HGB, Hemoglobin; MDS-EB1, Myelodysplastic syndrome with excess blasts-1; MDS-EB2, Myelodysplastic syndrome with excess blasts-2; MDS–RS-MLD, Myelodysplastic syndrome with ring sideroblasts and multilineage dysplasia; MDS–RS-SLD, Myelodysplastic syndrome with ring sideroblasts and single lineage dysplasia; MDS-U, Myelodysplastic syndrome, unclassifiable; PB, Peripheral blood; WBC, White blood cell count.

was no significant influence of *TP53* VAF as a continuous variable or using VAF cutoffs of 20%, 40%, 60%, or 80% on OS (data not shown). Comparison of MDS patients based on *TP53* mutation status showed that no mutation (median, 36.5 months) vs *TP53* monoallelic (median, 15.4 months) vs *TP53* multihit (median, 10.2 months) was also significant ($P < .0001$ for all 3 groups and $P = .02$ for monoallelic vs multihit) (Figure 2E). Similar comparison of AML patients based on *TP53* mutation status showed no mutation (median, 23.2 months) vs TP53 monoallelic (median, 5.2 months) vs TP53 multihit (median, 9.0 months) had different outcomes ($P = .003$), although there was no significant difference between *TP53* monoallelic vs multihit ($P = .68$) (Figure 2F).

Treatment with SCT was strongly associated with longer OS (median, 18.3 months vs 7.7 months, $P < .0001$).

MA. Performing MA (including all variables significant to a level of $P < .20$ in univariate analysis with sequential elimination) showed that TP53 mutation status, SCT, and treatment (low intensity/hypomethylating agents, with or without venetoclax, compared with supportive care) retained independent impact on prognosis (Table 3). Platelet count had borderline significance ($P = .13$), whereas the AML vs MDS distinction had no independent impact on prognosis (Table 3); there was also no independent significance of therapy-relatedness on OS. Similar results were seen when censoring patients at the time of SCT or considering platelets using a cutoff value of $< 50 \times 10^9$/L (data not shown).

Discussion

Therapy-related MNs have been considered to result from a consequence of DNA damage induced by cytotoxic therapy, but there is currently active debate in the field of cancer biology regarding relative contribution of inherent risk factors and environment exposure.[22] Over the last few years, it has been proposed that higher rate of *TP53* mutations in t-AML may be associated with the cytotoxic effect of chemotherapy and radiation on the BM microenvironment, leading to expansion of previously mutated hematopoietic clones; Wong et al reported that standard chemotherapy did not directly produce *TP53* mutations but instead fostered the outgrowth of preexisting *TP53*-mutated clones.[23] The high incidence of *TP53* mutations in CK AML is well known, and in our cohort of CK MDS and AML patients, *TP53* mutations were present in 84% and predicted for significantly shorter OS ($P < .0001$). Within the therapy-related group, the presence of a *TP53* mutation also strongly predicted for worse outcome ($P = .0017$). Conversely, among *TP53*-mutated patients, we found no significant difference between therapy-related vs de novo disease (median OS, 8.5 months vs 10.7 months, respectively, $P = .19$). Our findings underscore the importance of *TP53* mutations rather than

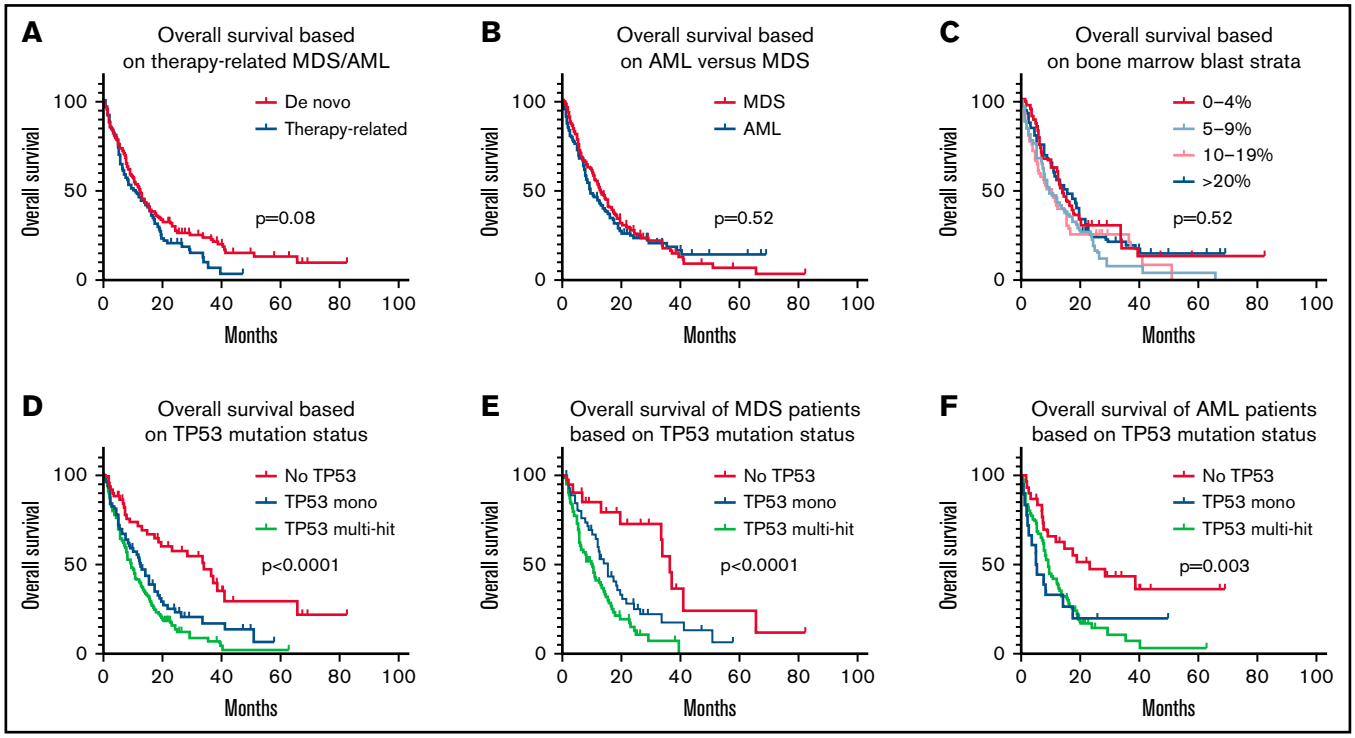

Figure 2. Overall survival (OS) of patients based on therapy related status, AML vs. MDS, bone marrow blast percentage strata, and TP53 status in all patients and in the MDS and AML subsets. (A) OS of all patients based on therapy-related (median, 10.2 months) vs de novo status (median, 12.2 months), $P = .08$. (B) OS of all patients based on MDS (median OS, 13.0 months) vs AML (median, 9.4 months, $P = .52$). (C) OS of all patients based on BM blasts 0% to 4% (median, 14 months) vs 5% to 9% blasts (median, 15.5 months) vs 10% to 19% blasts (median, 10.5 months) vs >20% blasts (median, 9.5 months) ($P = .52$). (D) OS of all patients based on TP53 mutation status; no mutation (median, 33.9 months) vs TP53 monoallelic (median, 12.5 months) vs TP53 multihit (median, 9.4 months), $P < .0001$. For TP53 monoallelic vs multihit, $P = .05$. (E) OS of MDS patients based on TP53 mutation status; no mutation (median, 36.5 months) vs TP53 monoallelic (median, 15.4 months) vs TP53 multihit (median, 10.2 months), $P < .0001$. For TP53 monoallelic vs multihit, $P = .02$. (F) OS of AML patients based on TP53 mutation status; no mutation (median, 23.2 months) vs TP53 monoallelic (median, 5.2 months) vs TP53 multihit (median, 9.0 months), $P = .003$. For TP53 monoallelic vs multihit, $P = .68$.

disease ontogeny in determining outcome of MDS and AML patients with CK. MK was present in 58% of all patients (55% in AML and 66% in MDS) and was associated with shorter survival ($P = .02$), as has been previously shown.[7] However, among *TP53*-mutated patients, there was no significant impact of MK on outcome. Our study was limited in assessing allelic imbalances of the *TP53* locus as most NGS platforms used in clinical practice do not assess for loss of heterozygosity required to definitively determine the *TP53* allelic state, and a subset of our cases lacked *TP53* VAF information. Nevertheless, using a definition of multihit *TP53* approximated by the presence of >1 *TP53* mutation, >60% VAF for 1 *TP53* mutation, or 1 *TP53* mutation with loss of the 17p locus on karyotype, we found an independent effect of multihit *TP53* compared with single-hit *TP53* mutation on OS in our cohort. *TP53*–wild-type patients more often received induction chemotherapy and less often received supportive care only compared with *TP53*-mutated patients, and *TP53* multihit patients more often received induction or HMA/venetoclax compared with *TP53* monoallelic patients, which likely reflects different proportions of AML vs MDS patients in these subgroups (Tables 1 and 2). However, in MA (Table 3), both monoallelic and multihit *TP53* mutation retained independent prognostic impact on OS; thus, the effect of *TP53* mutations on outcome did not appear to be due to differences in therapeutic approach. Although patients who received SCT had a significantly longer OS in our cohort, other studies have shown adverse prognostic effect of *TP53* mutation on MDS patients treated with SCT, whether patients received reduced-intensity conditioning regimens or myeloablative conditioning regimens.[24]

Within myeloid malignancies, the BM blast cutoff point of 20% distinguishes MDS from AML, although this remains a subject of debate.[19] The importance of this cutoff point in relationship to other factors, including patient age and measures of proliferative disease, such as *FLT3* mutations or tempo of blast increase, is ill defined.[25] Moreover, the genetic signature of MDS cases with 10% to 19% blasts (MDS-EB2) resemble those of AML following a preceding MDS (AML-MRC).[26] In our study of CK cases, we found that the AML vs MDS distinction was not significant in univariate or MA for OS, in either the whole cohort or in the *TP53*-mutated subset (data not shown). To our knowledge, this is the first study to analyze unselected complex karyotype MDS and AML cases across the entire blast spectrum (range, 0% to 94% blasts) while taking into account comprehensive mutational profiling. Our data suggest that CK, *TP53*-mutated MN represents a unique entity with very poor prognosis, irrespective of whether the blast percentage indicates MDS or AML or whether the disease is therapy-related or de novo in its ontogeny. The current assignment of these cases into MDS, AML-MRC, or t-MN appears to inappropriately divide a biologically similar disease into different diagnostic groups. Identifying TP53-mutated complex karyotype MNs as a unique, highly

Table 2. Comparison of *TP53*-mutated to *TP53* wild-type and multihit to monoallelic *TP53*-mutated cases

	TP53-mutated (n = 247)	TP53 wild-type (n = 52)	*P*	TP53 biallelic (n = 180)	TP53 monoallelic (n = 67)	*P*
Age	70 (21-91)	68 (1-87)	.06	70 (30-91)	70 (22-87)	.93
Gender, M:F	124:114	26:26		98:82	35:32	.0009
WHO subtypes						
AML	113 (46%)	31 (59%)		94 (52%)	19 (28%)	
MDS-SLD	0 (0%)	1 (2%)		0 (0%)	0 (0%)	
MDS-MLD	32 (13%)	6 (12%)		19 (11%)	13 (19%)	
MDS–RS-SLD	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
MDS–RS-MLD	10 (4%)	1 (2%)		10 (6%)	0 (0%)	
MDS-U	1 (0%)	0 (0%)		1 (1%)	0 (0%)	
MDS-EB1	37 (15%)	4 (8%)		21 (12%)	16 (24%)	
MDS-EB2	54 (22%)	9 (17%)		35 (19%)	19 (28%)	
Monosomal karyotype	168 (69%)	13 (25%)	<.0001	130 (72%)	38 (59%)	.06
Blood counts (median, range)						
ANC	1.0 (0-58.7)	0.9 (0-25.4)	.55	1.0 (0-13)	1.0 (0.01-6.7)	.47
HGB	8.5 (3.8-12.9)	9.0 (4.9-13.7)	.004	8.4 (3.8-12.9)	9 (4.0-12.5)	.12
WBC	3.0 (0.6-88.2)	3.2 (0.1-281.0)	.28	3.2(0.6-88)	2.6 (0.6-88)	.035
Platelets	50 (3-464)	54 (5-347)	.44	49 (3-464)	52 (13-225)	.5
PB blasts	1 (0-90)	4 (0-97)	.17	1 (0-90)	1 (0-45)	.024
BM features						
Cellularity	70 (25-100)	60 (20-100)	.14	70 (10-100)	65 (10-100)	.036
Blast %	15 (0-95)	35 (1-95)	.02	19 (0-95)	12 (0-95)	.015

ANC, Absolute neutrophil count; HGB, Hemoglobin; MDS-EB1, Myelodysplastic syndrome with excess blasts-1; MDS-EB2, Myelodysplastic syndrome with excess blasts-2; MDS–RS-MLD, Myelodysplastic syndrome with ring sideroblasts and multilineage dysplasia; MDS–RS-SLD, Myelodysplastic syndrome with ring sideroblasts and single lineage dysplasia; MDS-U, Myelodysplastic syndrome, unclassifiable; PB, Peripheral blood; WBC, White blood cell count.

Table 3. Multivariable model for OS

Variable	*P*	Hazard ratio	Hazard ratio lower bound (95%)	Hazard ratio upper bound (95%)
Platelets ($\times 10^9$/L)	.136	0.999	0.997	1.000
TP53 monoallelic	.003	2.081	1.286	3.369
TP53 multihit	<.0001	2.952	1.917	4.545
Stem cell transplant	<.0001	0.344	0.000	0.505
Therapy administered				
Low-intensity therapies*	.005	0.529	0.000	0.827
HMA/venetoclax*	.010	0.496	0.000	0.845
Induction therapy*	.236	0.732	0.437	1.226

*Compared with supportive care.

aggressive disease entity will help in developing new therapeutic approaches and avoid the current division between trials and approved therapies that are limited to either AML or MDS or to primary vs secondary/therapy-related disease. Our data also confirm the importance of multihit status of the *TP53* mutation in driving prognosis in this combined AML and MDS cohort. Future studies to validate this observation in cohorts that incorporate *TP53* loss-of-heterozygosity status as well as prospective studies on *TP53* CK patients are warranted to better understand the biology underlying their highly aggressive behavior.

Authorship

Contribution: O.K.W. and R.H.P. designed the project, collected data, analyzed the results, and wrote the paper; A.S., J.H.K., M.M.O., D.N., and P.D.C. collected data and assisted with the manuscript; and Y.F.M., J.G., and D.A.A. analyzed the results and assisted with manuscript.

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