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Clinical implications of *TP53* mutations in a southeast asian cohort of acute myeloid leukaemia patients

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Abstract

Background: *TP53* gene is a tumour suppressor gene located in the short arm of chromosome 17. *TP53* plays a pivotal role in maintaining genomic stability in response to DNA damage. It is mutated in more than 50% of the human cancer. *TP53* mutation (*TP53mut)* is commonly associated with therapy-related acute myeloid leukemia (AML) and complex karyotype. The incidence of *TP53mut*n was between 5-10% in de novo AML. This study described the clinicopathologic features of *TP53mut* AML and their clinical outcome in an Asian cohort.

Method: 166 consecutively cell-banked marrow samples of AML were tested for *TP53* mutations using a next generation sequencing platform. Baseline disease characteristic and clinical outcomes were retrospectively collected with approval granted by institutional review board.

Results: 9/166 had *TP53mut* (5.4%). 6/9 of *TP53mut* AML was associated with complex karyotype (p<0.001). The remaining 3 cases were two acute promyelocytic leukemia (APML) and one with normal cytogenetics. *TP53mut* was mutually exclusive with *FLT3* mutation. Two cases had concomitant *NPM1* mutation and another two had *ASXL1* mutation. *TP53mut* AML appeared to be associated with *TET2* mutation (3/9, 33.3%) compared to 10.2% of the *TP53wt* (p=0.069). *TP53mut* AML had a lower CR rate compared to *TP53wt* (28.6% vs 84.3%, p=0.003). Only two cases achieved CR, one was an APML who remained in continuous remission after 4 years. The other case achieved CR after allogeneic transplant but, relapsed 8 months later. *TP53mut* AML was significantly associated with inferior OS compared to *TP53wt* (p=0.001). 0.8 months (95%CI: 0.159 - 1.484) and 36.8 months (95%CI: 0.000 - 92.676) respectively. It remains an independent predictor of OS in multivariate analysis that include cytogenetic risk, WBC, LDH and BM blasts (HR 43.07, 95%CI: 6.87-272.41, p<0.001).

Conclusion: Our results confirmed the extremely dismal prognosis of *TP53mut* AML. TP53 mutation testing should be included as part of the pre-chemotherapy workout since this is not a standard practice as yet. The significance of its association with TET2 mutation requires further exploration in a larger study cohort.

Introduction

Acute myeloid leukaemia (AML) is a clonal disorder, characterized by accumulation of immature myeloid progenitor cells [1,2], resulting from uncontrolled cell division and impaired differentiation. It is the most common form of acute leukemia affecting adults [2]. AML is a heterogenous group of condition, consisting chromosomal abnormalities, recurrently mutated genes and microRNA deregulations [3], and it has varied clinical outcome. Risk stratification is conventionally done based on cytogenetic profile and it divides patients into three categories: favourable, intermediate and poor [4]. However, a significant number of AML patients with normal karyotype are classified as intermediate risk despite differing clinical outcomes due to underlying molecular mutations [5]. Hence, more recently, recurrent genetic mutations have been incorporated into risk stratification to refine individual prognosis and management of AML [2].

With next-generation sequencing (NGS), the discovery of recurrent molecular mutations found in AML patients with normal cytogenetics is accelerated [1]. An overview of these recurrent mutations is now available due to the presence of NGS. Such parallel sequencing of a large number of genes reduces cost and time needed [1,6], making molecular genetic testing a viable part of a potential diagnostic measure. After much study on these recurrent gene mutations and their prognostic significance, *NPM1*, *CEPBA* and *FLT3-ITD* have been incorporated into the 2010 recommendations by European LeukemiaNet (ELN) [7].

In the recent 2017 ELN guidelines, *TP53*, the most commonly mutated gene in human tumours [8,9], has also been included. *TP53* is a tumour suppressor gene located in the short arm of chromosome 17 and it plays a pivotal role in maintaining genomic stability in response to DNA damage [10]. It activates DNA-repair programs and triggers cell-cycle arrest. Some of the common forms of inactivation of *TP53* include deletion of the short arm of chromosome 17 and missense point mutations. The incidence of *TP53* mutation has been reported to be between 5-10% in de novo AML [10]. It is also associated with therapy-related AML, complex cytogenetics, low blast counts, and an under-representation of concomitant mutations in *FLT3*, *RAS*, *NPM1*, and *RUNX1* [10]. These patients exhibit lower response rates to intensive chemotherapy and shorter complete remission (CR) durations [11,12], translating into inferior survival in both younger and older patients [13].

In this study, we aim to evaluate the prognostic significance of *TP53* mutational status in a South East Asian cohort. Singapore is a racially diverse country with the majority of its citizens being from around the

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Southeast Asian region, providing unique population demographics for this study.

Material and methods

Study population

After obtaining approval from the institutional review board, pre-treatment diagnostic bone marrow (BM) samples of 166 AML patients were obtained from the archives of the Department of Haematology-Oncology, National University Hospital, Singapore. These patients were diagnosed with AML between 2001 and 2016, in accordance with the 2001, 2008 and 2016 WHO classifications. The demographic, laboratory and clinical data were recorded retrospectively.

Next-generation sequencing mutational analysis

Genomic DNA was extracted from the consecutively cell-banked marrow samples of AML. In brief, targeted DNA sequencing was performed using the TruSeq Custom Amplicon assay for the TruSight Myeloid Sequencing Panel (Illumina) as previously described [14]. The 54 genes assessed via the TruSight Myeloid Sequencing Panel include ABL1, ASXL1, ATRX, BCOR, BCORL1, BRAF, CALR, CBL, CBLB, CBLC, CDKN2A, CEBPA, CSF3R, CUX1, DNMT3A, ETV6, EZH2, FBXW7, FLT3, GATA1,GATA2, GNAS, HRAS, IDH1, IDH2, IKZF1, JAK2, JAK3, KDM6A, KIT, KMT2A, KRAS, MPL, MYD88, NOTCH1, NPM1, NRAS, PDGFRA, PHF6, PTEN, PTPN11, RAD21, RUNX1, SETBP1, SF3B1, SMC1A, SMC3, SRSF2, STAG2, TET2, TP53, U2AF1, WT1 and ZRSR2. The TruSeq Amplicon (BaseSpace workflow, V.1.1.0.0) was used to generate the BAM and VCF files. Subsequently, the VCF files were annotated using Illumina VariantStudio (V.2.2). Only variants that met the following criteria were included: non-synonymous; only variants inside genes; quality >99 and variant allele frequency ≥ 10%. Variant-calling was done using either the Illumina MiSeq Reporter.

Statistical analysis

The association between *TP53* mutational status and patients' demography, such as age, ethnicity, gender, and baseline disease characteristics, such as percentage of bone marrow blasts, white blood cell count, haemoglobin levels and LDH Levels, were analysed using Chi Square and Fisher exact test for categorical variables, and Independent T-test for continuous variables. The clinicopathology of all the *TP53-mut* cases were described and the correlation of *TP53* mutational status with other genetic mutations, such as *NPM1*, *FLT3*, *ASXL1* and *TET2*, was also analysed using Fisher exact test.

Association of variables such as age, *TP53* mutational status and cytogenetic risk, with treatment response are also analysed using Fisher exact test. Overall survival analysis based on mutational status was done using Kaplan-Meier survival analysis. Univariate and multivariate analysis were used to predict treatment response.

All statistical analysis in this report was performed using IBM® SPSS® Statistics Version 22.

Results

Patient characteristics

The study cohort consisted of a total of 166 AML patients. The median age of the patients was 46.5 years. There are 85 male patients (51.2%) and 81 female patients (48.8%) respectively. *TP53* genetic mutations were found in 9 patients (5.4%) with a larger proportion of males (77.8%) than females (22.2%). No *TP53* mutations was found in Malay and Indian patients in this study. The various baseline clinical characteristics and molecular abnormalities were compared between the *TP53mut* and *TP53wt* groups as summarised in (Table 1). Only cytogenetic risk classification and complex cytogenetics were found to be statistically significant characteristics.

In addition, six out of the nine *TP53mut* was associated with complex karyotype (p=0.002) and was categorised to have an adverse cytogenetic risk. The frequency of *TP53* mutations in cytogenetically complex AML patients was 30% (six out of twenty patients). Of the remaining three *TP53mut* cases, two had favourable APML (t (15;17)) translocation and one had normal cytogenetics (Table 2). Both APML cases have a white cell count ≤ $10x10^9$/L and platelet count ≤ $40x10^9$/L, which are considered to be intermediate risk APML.

Types of TP53 mutations and correlation with other genetic mutations

Of the 9 TP53 mutations, 7 were missense mutations while 2 were nonsense mutations that resulted in premature truncation of the protein (Figure 1).

Overall, the most frequent gene mutation among 166 AML patients is *NPM1* (22.9%), followed by *ASXL1* (20.2%) and *RUNX* (18.1%) (Table 3). *TP53* gene mutation was found in 5.4% of patients. It appears to be mutually exclusive with *FLT3* and *IDH2* mutation. Two cases with *TP53* mutations had concomitant *NPM1* mutation, of which one (Case 5) had complex cytogenetics and did not achieve CR, eventually had progressive disease, and the other (Case 9) had normal karyotype but was complicated by induction death. Another two had *ASXL1* mutation (Case 1 and 6). *TP53* mutation AML appeared to be associated with *TET2* mutation (3/9, 33.3%) compared to 10.2% of the *TP53wt* (p=0.069, Fisher-exact test).

Treatment response and overall survival

For the subsequent analysis, 26 patients, who received palliative treatment, and 20 patients who travelled back to their home country for treatment and are therefore lost to follow-up are excluded from analysis. 11 APML (M3) patients are also excluded from analysis as APML is a subtype of AML with exceptionally good outcomes due to its responsiveness to all-*trans* retinoic acid (ATRA) therapy that is not representative of other AML subtypes. A total of 109 non-APML patients received curative treatment. The median follow-up time is 52.4 months (95% CI: 35.6 – 69.3).

Six out of seven non-APML *TP53-mut* patients underwent curative treatment. Three (Cases 7, 8 and 9) were complicated by induction deaths, two (Cases 4 and 5) did not achieve complete remission and had primary refractory disease and the remaining one (Case 3) achieved CR only after allogeneic stem cell transplantation. The patient then relapsed after a short CR of 6.8 months. Compared to *wt-TP53* patients, *mut-TP53* patients have a much lower CR rate (16.7% vs 82.7%, p<0.005, Fisher exact test) (Table 4). In addition, older age as well as adverse cytogenetics were also associated with lower CR rate.

TP53 mutation AML was significantly associated with inferior OS compared to TP53wt (p<0.001). Median overall survival (OS) was 0.8 months (95% CI: 0.159-1.484) and 36.8 months (95% CI: 0.000-92.676) respectively (Figure 2). *TP53* mutational status remains an independent predictor of OS in multivariate analysis that include cytogenetic risk, WBC, LDH and BM blasts (HR 43.1, 95%CI: 6.8 – 272.4, p<0.001) (Table 4).

Table 1. Comparison of clinical and disease characteristic according to mutational status

Baseline characteristic	Overall (n=166)	*TP53*-mutated (n=9)	*TP53*-wild type (n=157)	p Value
Age (y), mean (range)	47.36 (17 – 81)	50.00 (20 – 81)	47.20 (17 – 80)	0.608
Ethnicity, n (%)				0.735
Chinese	100 (60.2)	6 (66.7)	94 (59.9)	
Malay	18 (10.8)	0 (0.0)	18 (11.5)	
Indian	11 (6.6)	0 (0.0)	11 (7.0)	
Others	37 (22.3%)	3 (33.3)	34 (21.7)	
Gender, n (%)				0.169
Male	85 (51.2)	7 (77.8)	78 (49.7)	
Female	81 (48.8)	2 (22.2)	79 (50.3)	
Bone marrow blasts (%), mean (range)#	64.66 (1–99)	76.00 (26–98)	63.89 (1–99)	0.202
White blood cell count ($\times 10^9$/L)*, mean (range)	60.58 (0.45–435.00)	49.76 (0.45–312.70)	61.16 (0.79–435.00)	0.714
Haemoglobin levels (g/L)**, mean (range)	8.33 (2.0–14.0)	8.56 (5.1–11.1)	8.32 (2.0–14.0)	0.72
Platelet levels ($\times 10^9$/L)***, mean (range)	65.08 (1–772)	59.73 (1–178)	65.37 (5–772)	0.836
LDH levels (U/L), mean (range) ****	1285.73 (304–5720)	1601.25 (491–5720)	1266.90 (304–5033)	0.36
Cytogenetic risk stratification, n (%) *****				0.002
Favourable	29 (18.4)	2 (22.2)	27 (18.1)	
Intermediate	95 (60.1)	1 (11.1)	94 (63.1)	
Adverse	34 (21.5)	6 (66.7)	28 (18.8)	
Complex Cytogenetics, n (%)				<0.001
Complex	20 (12.0)	6 (66.7)	14 (8.9)	
Non-complex	146 (88.0)	3 (33.3)	143 (91.1)	

Table 2. Summary of the clinicopathology of all the *TP53-mut* cases

Case No.	Age (yr)	Karyotype	Other concomitant mutations	Treatment intent	Response to induction	Relapsed/ refractory	Survival status
1	81	Complex	*ASXL1, IDH1*	Palliative	NA	NA	Dead
2	48	t(15;17)	*TET2*	Curative	CR	No	Alive
3	31	Complex	Nil	Curative	No CR (achieved CR after allogeneic SCT)	Yes	Dead
4	61	Complex	Nil	Curative	No CR	Yes	Loss f/u
5	20	Complex	*NPM1*	Curative	No CR	Yes	Dead
6	29	t(15;17)	*ASXL1, RUNX1, DNMT3a, TET2*	Curative	NA	NA	Loss f/u
7	56	Complex	Nil	Curative	Induction death	NA	Dead
8	54	Complex	Nil	Curative	Induction death	NA	Dead
9	70	Normal	*NPM1, TET2*	Curative	Induction death	NA	Dead

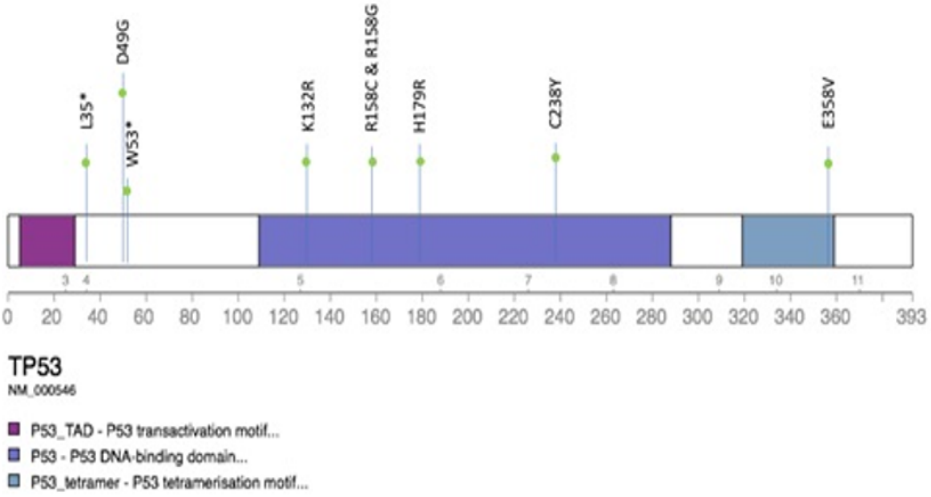

Figure 1. The type and location of TP53 mutations detected

Table 3. Correlation of TP53 mutations with other recurrent genetic mutations

Gene Mutation	Overall (n=166)	Mutated *TP53* (n=9)	Wild-type *TP53* (n=157)	p Value
NPM1, n (%)				1
Wild type	128 (77.1)	7 (77.8)	121 (77.1)	
Mutated	38 (22.9)	2 (22.2)	36 (22.9)	
FLT3, n (%)				0.592
Wild type	133 (80.1)	9 (100)	124 (79.0)	
Mutated ITD	25 (15.1)	0 (0)	25 (15.9)	
TKD	8 (4.8)	0 (0)	8 (5.1)	
ASXL1, n (%)				0.231
Wild type	149 (89.8)	7 (77.8)	142 (90.4)	
Mutated	17 (20.2)	2 (22.2)	15 (9.6)	
TET2, n (%)				0.069
Wild type	147 (88.6)	6 (66.7)	141 (89.8)	
Mutated	19 (11.4)	3 (33.3)	16 (10.2)	
RUNX, n (%)				1
Wild type	136 (81.9)	8 (88.9)	128 (81.5)	
Mutated	30 (18.1)	1 (11.1)	29 (18.5)	
IDH1, n (%)				0.5
Wild type	154 (92.8)	8 (88.9)	146 (93.0)	
Mutated	12 (7.2)	1 (11.1)	11 (7.0)	
IDH2, n(%)				0.6
Wild type	149 (89.8)	9 (100.0)	140 (89.2)	
Mutated	17 (10.2)	0 (0.0)	17 (10.8)	

Table 4. Association between individual risk factors and CR

Variables	Achieved CR	Did not achieve CR	p Value
Age, n (%)			0.001
	79 (84.0)	15 (16.0)	
≤ 60 years			
	4 (36.4)	7 (63.3)	
>60 years			
TP53, n (%)			0.001
Mutated	1 (16.7)	5 (83.3)	
Wildtype	82 (82.8)	17 (17.2)	
Cytogenetic Risk, n (%)			0.041
Favourable	11 (84.6)	2 (15.4)	
Intermediate	53 (84.1)	10 (15.9)	
Adverse	13 (59.1)	9 (40.9)	

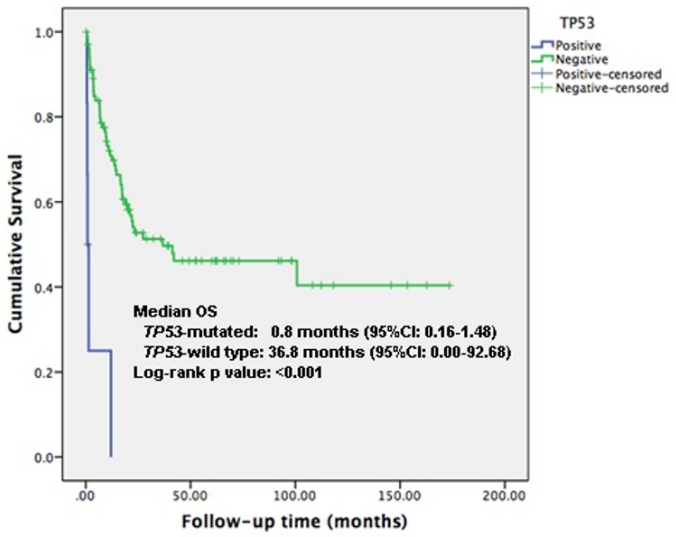

Figure 2. Overall survival according to mutational status

Discussion

Patient characteristics

In our study, we found that the incidence of *TP53* genetic mutations in a South East Asian cohort of patients to be 5.4%, which is consistent with previously reported 5 to 10% incidence in various studies in other populations [10]. There appears to be a higher incidence of *TP53* mutations in male patients.

Compared with wt-TP53 cohort, mut-TP53 patients are significantly more likely to have a complex karyotype, 66.7% as compared to 8.9% for wt-TP53 patients. Many studies have reported this association, but it remains unclear whether the TP53 genetic mutation and the resultant loss of its tumour suppressor function led to the chromosomal instability or if the TP53 genetic mutation arose secondary to the chromosomal instability. Interestingly, in our cohort of 9 patients, we found 6 cases of mut-TP53 patients with complex cytogenetics, 2 cases of APML mut-TP53 patients as well as a case with normal cytogenetics (Table 2). Further studies are required to determine the causal relationship and elucidate the underlying pathological mechanisms.

While *TP53* mutations is associated with an adverse prognosis, one interesting observation in this study is that the mutational status of *TP53* did not appear to influence the outcome for APML patients, a subset of AML with exceptionally favourable prognosis due to its sensitivity to all-trans retinoic acid (ATRA) treatment. The two *TP53-mut* APML patients are classified into the intermediate risk category with a white blood cell count < 10,000/μL and a platelet count < 40,000/μL. One of the APML patient (Case 2) underwent treatment achieved and remained in complete remission after 4 years. The other APML patient (Case 6) returned to his home country for treatment and was lost to follow up.

Types of TP53 mutations and correlation with other genetic mutations

TP53 (tumour protein 53) is a transcription factor composed of a transcription activation domain, a DNA-binding domain, a proline-rich

Table 5. Multivariate Cox Proportional Hazards Regression analysis for overall survival

Risk Factors	Adjusted HR	95% CI	p value
Mutational Status: *Mut-TP53* vs *wt-TP53*	43.07	6.81 – 272.41	<0.001
Cytogenetic Risk			
Adverse vs Favourable	1.75	0.43 – 7.19	0.437
Intermediate vs Favourable	1.35	0.37 – 4.96	0.648
White Blood Count	1	1.00 – 1.01	0.175
LDH Levels	1	1.00 – 1.00	0.364
Bone Marrow Blasts Percentage	1.02	1.00 – 1.04	0.095

domain, and a tetramerization domain [15]. Most studies have focused on mutations in the DNA-binding domain of *TP53* gene. However, recently, Terada et al. reported that *TP53* mutations outside the DNA binding domain contributes to poorer outcomes compared to *TP53* mutation in the DNA binding domain [16]. In addition, they found that all cases with gene deletion involved a monoallelic deletion with gene mutation on opposite side. The impact of various *TP53* mutations and deletion on clinical outcomes is an area that can be further expounded on future studies.

Our study also found a mutual exclusivity of *FLT3* and *TP53* mutations. Although it did not reach statistical significance, this finding has been corroborated by many studies. *FLT3* is a commonly mutated gene in AML patients (21.0% in this study) and *FLT3-ITD* mutation has been shown to be associated with poor prognosis in patients with normal karyotype and is believed to be a driver mutation in leukemogenesis [17].

In addition, there appears to be a correlation between *TET2* and *TP53* mutations, which did not reach statistical significance, likely attributable to the small sample size of the study. This is probably the first time that this association has been suggested. Previously other studies have suggested that DNA-methylation regulatory gene mutations, such as *DNMT3A* and *TET2*, appear to be founder gene mutations [18,19] and are frequently co-present with high-frequency mutations such as *FLT3-ITD* and *NPM1*. Since *TP53* mutations tend to be mutually exclusive with *FLT3-ITD* and *NPM1* [20], they are less likely to be associated with *DNMT3A* and *TET2* too.

Treatment response and overall survival

In a multivariate analysis that includes age, cytogenetic risk stratification, WBC, LDH and BM blasts, *TP53* mutational status remains an independent predictor of CR and OS. *TP53-mut* patients are more likely to be resistant to the standard induction chemotherapy and present with primary refractory disease. Hence, they may benefit from allogeneic stem cell transplantation (SCT) or earlier enrolment into clinical trials. Allogeneic SCT could improve the leukemia free survival to around 25% in patients with TP53 who were transplanted in CR1 [21]. Ohgami also reported that cases that received hematopoietic stem cell transplant in the first remission period tended to have a higher rate of OS (p=0.0606) while there was no significant positive outcome for patients that were transplanted not in the first remission [22]. For those who are unfit for allogeneic SCT, treatment with hypomethylating agent like decitabine might produce a better response compared to conventional chemotherapy [23].

There has also been an increasing interest in small molecule target drugs. Selinexor, a protein pump inhibitor, is one such candidate. It works by binding with and inhibiting the nuclear export protein XPO1 (also called CRM1), leading to the accumulation of tumor suppressor proteins such as *p53* in the cell nucleus. This reactivates and enhances tumour suppressor function. Preclinical studies have suggested that XPO1 inhibitors lead to the targeted apoptosis of cancer cells, while sparing normal cells [24]. This may be a promising candidate drug for patients with *TP53* mutations and relapsed AML patients, whereby the incidence of *TP53* mutations may be high.

There has been increasing interest in targeted therapies based on genetic mutations. As missense TP53 mutations are most common and this often results in the loss of DNA binding ability and accumulation of mutated p53 protein in the tumour cells at high concentration, the reactivation of these mutated p53 protein hence holds promising therapeutic potential [25] Various drugs/ compounds have been studied. Of note, PRIMA-1 and PRIMA-1^{MET}/APR-246 have been validated in animal models and is currently in clinical trials [26]. Successful development of drugs targeting TP53 mutations will help broaden the range of therapeutic options available for patients as well as potentially reverse the poor prognosis associated with TP53 mutations.

Conclusion

Our results in the South East Asian study cohort affirmed the extremely dismal prognosis of *TP53* mutation AML, in line with the European Leukemia Net guidelines. *TP53-mut* patients are significantly more likely to be associated with complex karyotype, lower CR rates and shorter OS. *TP53* mutation testing should be included as part of the pre-chemotherapy workout to improve risk stratification of AML. However, the role of *TP53* prognostication in APML remains to be explored as it does not appear to be affecting the prognosis. The ability to draw correlations between *TP53* and other recurrent genetic mutations is limited by the small patient cohort in this study. The significance of *TP53* mutation association with *TET2* mutation may be worth further exploration in a larger study cohort. In addition, genetic testing for *TP53* should be done at various time points in treatment to elucidate the contribution of *TP53* in the pathogenesis, clonal evolution and development of treatment resistance.

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