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617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Assessment of *SIRT1-SIRT7* and *TP53* Genes Expression in Patients with Acute Myeloid Leukemia

Piotr Strzalka, MD[1], Kinga Krawiec[1], Dariusz Jarych, PhD[2], Aneta Wiśnik, MSc[3], Michał Soin, MSc[2], Magdalena Góralska, MSc[3], Damian Mikulski[4], Magdalena Czemerska, MD PhD[1], Izabela Zawlik, PhD[5], Agnieszka Pluta, MD PhD[6], Agnieszka Wierzbowska, MD, PhD[7]

[1] Department of Hematology and Transplantology, Copernicus Memorial Hospital in Lodz, Department of Hematology, Medical University of Lodz, Łódź, Poland
[2] Department of Hematology, Medical University of Lodz, Łódź, Poland
[3] Copernicus Memorial Hospital in Lodz, Łódź, Poland
[4] Department of Hematooncology, Copernicus Memorial Hospital in Lodz, Department of Biostatistics and Translational Medicine, Medical University of Lodz, Łódź, Poland
[5] Laboratory of Molecular Biology, Centre for Innovative Research in Medical and Natural Sciences, College of Medical Sciences, University of Rzeszow, Rzeszów, Poland
[6] Department of Hematology and Transplantology, Copernicus Memorial Hospital in Lodz, Department of Hematology, Medical University of Lodz, Lodz, Poland
[7] Department of Hematology and Transplantology, Multidisciplinary Provincial Centre of Traumatology and Oncology Nicolas Copernicus in Lodz, Lodz, Poland

BACKGROUND

Sirtuins (*SIRTs*) are a family of histone deacetylases with 7 representatives (*SIRT1-7*), which affect cell survival and metabolism. They influence gene expression by interacting with histones and transcription factors, or directly modulate pathways associated with cell survival, for instance by downregulating p53, thus potentially contributing to cancerogenesis. On the other hand, SIRTs may function as tumor suppressors depending on cellular context. While the role of *SIRTs* expression is widely discussed in solid neoplasms, they have not been comprehensively evaluated in acute myeloid leukemia (AML) yet.

AIMS

To investigate the prognostic importance of initial *SIRTs* expression in AML patients (pts) and its relationship with the expression of *TP53*.

METHODS

The study included 40 newly diagnosed AML pts (19 women, 21 men), with a mean age of 62 years (range: 26-87). Low-, intermediate- or high-risk AML according to European LeukemiaNet (ELN) 2022 stratification was diagnosed in 6 (15%), 13 (32.5%), and 21 (52.5%) of pts respectively. The expression of *SIRT1-7* and *TP53* was examined by real-time PCR using the TaqMan chemistry and the QuantStudio7 thermal cycler (Applied Biosystems-Thermo Fisher Scientific). The reference genes were selected using GeNorm and NormFinder. The mRNA levels were normalized by the formula $\Delta Ct = Ct(reference) - Ct(particular\ mRNA)$. Group comparisons were performed using Welch's t-test. Pearson correlation evaluated the relationship between individual gene expression. Overall survival (OS) was assessed by the Kaplan-Meier method with the log-rank test. Cox proportional hazard regression of clinical factors and genes expression for predicting OS was performed.

RESULTS

FLT3 ITDor TKD mutations were present in 10 (25%) of pts, *NPM1* in 9 (23%), and *IDH1 or IDH2* in 6 (15%). 14 (35%) of the study group were diagnosed with AML with myelodysplasia-related cytogenetic abnormalities, AML progressed from myelodysplastic syndrome, or therapy-related AML (secondary AML, sAML). Standard induction chemotherapy was given in 42.5% of pts, 25% were treated with azacitidine+venetoclax (Aza+Ven), and other non-intensive therapies were administered to 32.5%. *SIRT4* expression was detected in 92.5% of pts, while expression of the other genes studied was found in all pts. There were no differences in *SIRT 1-7* expression in terms of ELN2022 risk stratification. However, *TP53* was downregulated in the high-risk group (fold change - FC=0.6, $p=0.004$). In pts with *FLT3* mutation, *SIRT7* was downregulated (FC=0.8, $p=0.07$), while in both *NPM1* and *IDH1/2* mutated groups, we showed upregulation of *TP53* (FC=1.5, $p=0.03$, and FC=1.5, $p=0.001$, respectively).

Moreover, in older pts (>60 years old) *TP53* was downregulated (FC=0.7, *p*=0.02). In sAML group *SIRT3* and *TP53* were downregulated (FC=0.7, *p*=0.08, and FC=0.7, *p*=0.05, respectively).

Significant positive correlations were shown between the expression of individual *SIRT*s, and it was most strongly expressed between *SIRT2* and *SIRT6* (r=0.85, *p*=0.00), *SIRT2* and *SIRT7* (r=0.81, *p*=0.00), and *SIRT6* and *SIRT7* (r=0.76, *p*=0.00).

The median follow-up was 6.7 months (95% CI: 4.5-9.1). The median OS in the study cohort was not reached. There were no significant differences in treatment response or OS considering each *SIRT* expression level. However, pts with higher *TP53* expression (> median) presented longer OS (median OS not reached vs 5.8 months (95% CI:1.3-5.8, *p*=0.05) [Figure 1].

In the multivariate Cox proportional hazard model for OS, upregulation of *TP53* (HR 0.25, 95%CI: 0.08-0.60, *p*=0.01), age (HR 1.06, 95%CI: 1.01-1.12, *p*=0.03), as well as initial albumins (HR 0.01, 95%CI: 0.00-0.07, *p*=0.01), and LDH levels (HR 1.00, 95%CI: 1.00-1.01, *p*=0.01) were factors influencing the outcome [Table 1].

CONCLUSIONS

The expression of *SIRT*s in AML presented no evident impact on treatment outcome. However, our study revealed that higher *TP53* expression was associated with longer OS. Moreover, *TP53* upregulation was found in pts with certain mutational profiles, while downregulation in the elderly and those with sAML. The analysis indicates that *SIRT*s expression may also vary markedly depending on the clinical and molecular context. The expression of individual *SIRT*s is closely correlated with each other, but these preliminary results did not show their direct relationship with *TP53* expression. Further studies on *SIRT*s are needed to assess their impact on AML.

Figure 1. Kaplan–Meier analysis of overall survival (OS) according to expression of *TP53* in AML patients.
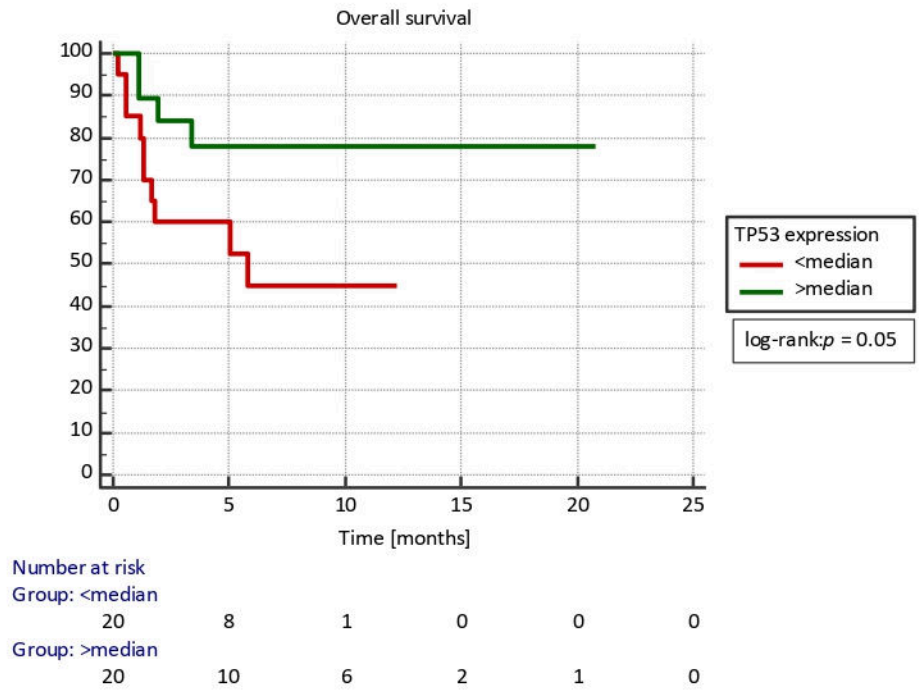

Table 1. Multivariate Cox regression model for overall survival (OS).

Variable	Coefficient	*p* value	Hazard ratio (HR)	95% CI lower	95% CI higher
Age	0.10	0.03	1.06	1.01	1.12
LDH	0.01	0.01	1.00	1.00	1.01
Albumins	-5.54	0.01	0.01	0.00	0.07
TP53 expression	-1.37	0.01	0.25	0.08	0.60

Figure 1

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