The role of transcriptomic SMARCA4 expression in ovarian cancer biology

Leitner K[1], Wieser V[1], Tsibulak I[1], Degasper C[1], Welponer H[1], Reimer D[1], Wiedemair A[1], Marth C[1], Fiegl H[1]*, Zeimet AG[1]*

[1] Department of Obstetrics and Gynecology, Medical University of Innsbruck, Innsbruck, Austria

Frauenheilkunde Innsbruck

Introduction

The SWI/SNF complex – a chromatin remodelling complex – is recurrently mutated and inactivated in ~20% of human cancers. Mutations of the SMARCA4 gene, which encodes the ATPase of the SWI/SNF complex, can be found in the majority of small cell carcinomas of the ovary, hypercalcaemic type (SCCOHT).

EZH2 is the catalytic subunit of the PCR2-complex, which is an opponent of the SWI/SNF complex. EZH2 inhibitors could play a potential role in the therapy of SCCOHT. The aim of this study was to explore the role of SMARCA4 mRNA-expression in the various histological ovarian cancer subtypes.

Methods

SMARCA4 mRNA-expression was investigated in 20 non-neoplastic fallopian tubes and 276 ovarian carcinomas (OC) (including 144 high grade serous ovarian carcinomas, HGSOC) in relation to their clinical characteristics, p53- and BRCA1/2-mutational status, BRCA1/2 mRNA-expression and EZH2 mRNA-expression.

Results

The SMARCA4 mRNA-expression in OCs was significantly higher compared to the control group (P<0,001). There were no significant differences in SMARCA4 mRNA-expression between the various histological subtypes.

A subgroup-analysis of HGSOC showed higher SMARCA4 mRNA-expression in patients younger than 65 years (P=0,021), in patients without residual disease after surgical debulking (P=0,008) and patients with early FIGO stages I-II (P=0,004).

High SMARCA4-expression was associated with better progression-free survival (PFS) (P=0,05) and overall survival (OS) (P=0,002). Patients with p53-mutations showed higher SMARCA4-expression (P=0,004). There was a significant correlation between the expressions of SMARCA4 and EZH2 (P=0,000; r=0,377).

Multivariate Cox-regression model revealed independency of the prognostic value of SMARCA4 mRNA-expression for OS in patients under the age of 65 years (P=0,015).

Conclusion

High SMARCA4-expression in patients with HGSOC is associated with younger age at onset of disease, p53 mutated cancers and with absence of residual disease after primary debulking. In patients younger than 65 years, high SMARCA4-expression is independently associated with better overall survival.

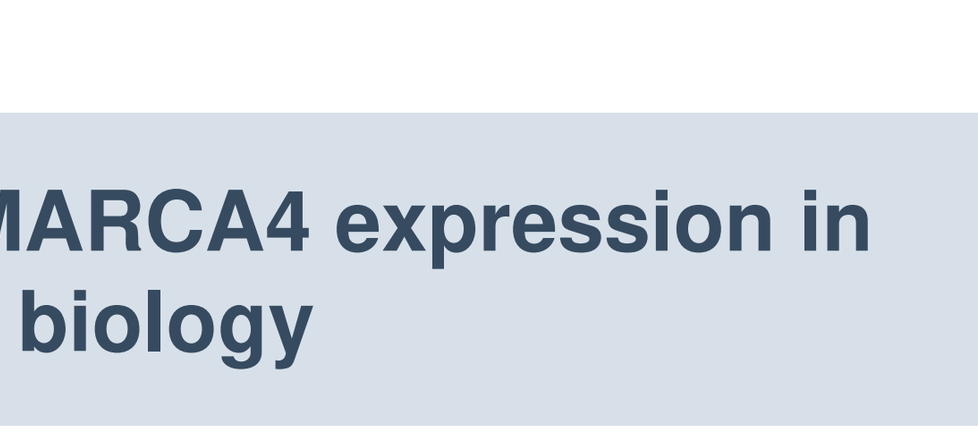

Fig. 1: SMARCA4 mRNA-expression in OCs was significantly higher compared to the control group (P<0,001).

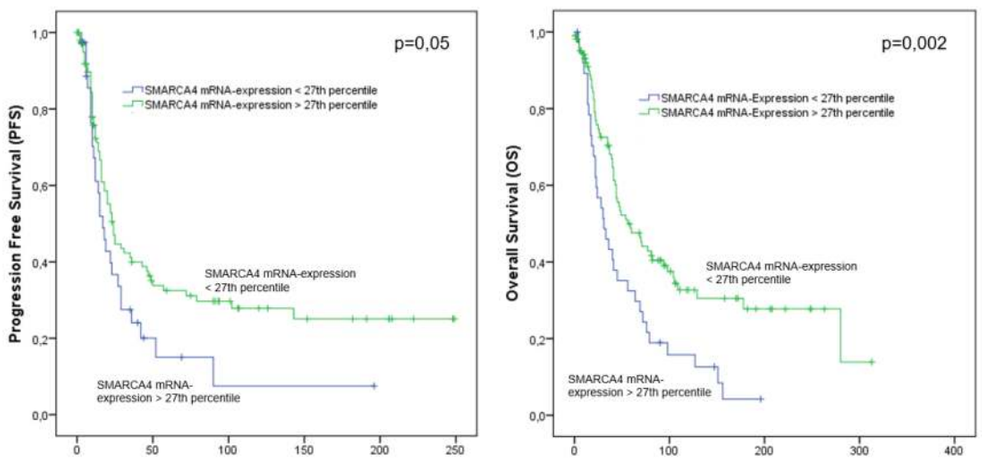

Fig. 2: High SMARCA4-expression is associated with better PFS (P=0,05) and OS (P=0,002).

	Number (%)	SMARCA4 mRNA-expression Median (IQR)	P value
Univariate Analysis			
Ovarian carcinomas	276	2,08 (1,32)	**<0,001**
Non-neoplastic fallopian tubes	20	1,23 (0,36)	
Histology			
High grade serous ovarian carcinomas	144 (52,2 %)	2,25 (1,35)	0,235
Low grade serous ovarian carcinomas	12 (4,3 %)	1,88 (0,95)	
Endometrioid ovarian carcinomas	44 (15,9 %)	2,10 (1,44)	
Clear cell ovarian carcinomas	11 (4,0 %)	2,22 (2,20)	
Mucinous ovarian carcinomas	27 (9,8 %)	2,12 (1,64)	
Borderline tumors	38 (13,8 %)	1,86 (0,73)	
Subgroup analysis HGSOC			
Age			
< 65 years	86 (59,7 %)	2,42 (1,72)	**0,021**
> 65 years	58 (40,3 %)	2,00 (1,52)	
FIGO stage			
I-II	26 (18,1 %)	2,84 (1,94)	**0,004**
III-IV	118 (81,9 %)	2,08 (1,25)	
Tumor grade			
2	73 (51,4 %)	2,23 (1,45)	0,586
3	69 (48,6 %)	2,30 (1,28)	
Residual disease			
Macroscopically tumor-free	53 (39,3 %)	2,54 (1,82)	**0,008**
Any tumor residual	82 (60,7 %)	2,05 (1,15)	
p53-Status			
p53 non mutated	40 (32,0 %)	2,01 (1,06)	**0,004**
p53 mutated	85 (68,0 %)	2,45 (1,71)	
BRCA1-Status			
wild type	101 (80,2 %)	2,27 (1,32)	0,618
C4- und C5-Mutation	25 (19,8 %)	2,44 (1,75)	
BRCA2-Status			
wild type	118 (93,7 %)	2,29 (1,32)	0,984
C4- und C5-Mutation	8 (6,3 %)	2,10 (1,80)	

Multivariate analysis (patients under 65 years)		Progression Free Survival		Overall Survival	
		Hazard Ratio (95 % CI)	P value	Hazard Ratio (95 % CI)	P value
FIGO stage	I-II vs. III-IV	0,73 (0,22-2,40)	0,605	0,54 (0,17-)1,72	0,295
Tumor grade	II vs. III	1,28 (0,69-2,37)	0,426	1,27 (0,68-2,39)	0,461
Residual disease	yes vs. no	4,63 (1,71-12,52)	**0,003**	6,75 (2,31-19,73)	**<0,001**
p53 mutation	yes vs. no	2,37 (1,10-5,10)	**0,027**	3,26 (1,74-7,22)	**0,004**
BRCA1 mutation	yes vs. no	0,86 (0,44-1,67)	0,649	0,89 (0,44-1,80)	0,750
BRCA2 mutation	yes vs. no	0,64 (0,22-1,86)	0,422	1,11 (0,41-3,02)	0,832
SMARCA4 mRNA expression	high vs. low	0,50 (0,22-1,13)	0,096	0,39 (0,18-0,83)	**0,015**

Tab. 1: Univariate and multivariate analysis of SMARCA4 mRNA-expression