UNIVERSITÄTSMEDIZIN HALLE

Medizinische Fakultät der Martin-Luther-Universität Halle-Wittenberg

UKH Universitätsklinikum Halle (Saale)

FPN: 297P
Abstract #4237

Prognostic and predictive impact of NOTCH1 in early breast cancer

[1]J. Engel, [1] V. Wieder, [2]T. Lantzsch, [3]V. Hanf [4] C. Uleer, [5]S. Peschel, [6]J. John, [7]M. Poehler, [8]J. Buchmann, [9]E. Weigert, [10] K. Buerrig, [1,11] E. - J. Kantelhardt, [1]C. Thomssen, [1]M. Vetter

[1]Dept. of Gynaecology Martin Luther University Halle-Wittenberg, Halle (Saale); [2]Germany; Dept. of Gynaecology Hospital St. Elisabeth & St. Barbara, Halle (Saale); [3]Dept. of Gynaecology, Nathanstift, Klinikum Fürth; [4]Gynaecological Practice, Hildesheim; [5]Dept. of Gynaecology St. Bernward Hospital, Hildesheim; [6]Dept. of Gynaecology Klinikum Hildesheim, Hildesheim; [7]Dept. of Gynaecology Hospital Goslar, [8]Institute of Pathology Hospital Martha-Maria, Halle (Saale); [9]Institute of Pathology Klinikum Fürth, Fürth; [10]Institute of Pathology Klinikum Hildesheim, Hildesheim; [11]Institute of Epidemiology, Biometry and Informatics Martin Luther University Halle-Wittenberg, all in Germany, in behalf of the PiA-study group

Universitätsklinikum Brustzentrum Halle

Background

Systemic therapy plays a major part in the cure of patients with early breast cancer. However, more individualized treatment concepts are required with increasing success to avoid potentially harmful overtreatment. Therefore, biomarkers are needed and the Notch-signalling pathway is considered to be suitable as a prognostic or predictive marker in breast cancer as it is involved in proliferation, invasiveness and chemotherapy resistance[1].

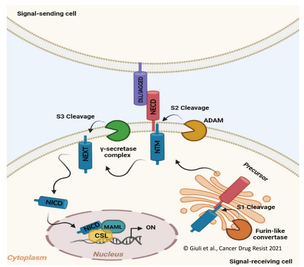

Figure 1: Notch signalling pathway[2]

Patients and Methods

- Prospective, multicenter cohort (**P**rognostic Assessment **i**n Routine **A**pplication **(PiA)**, 2009-2011, NCT01592825) of 1,270 breast cancer patients, median follow-up of 60 months
- Determination of relative *NOTCH1*-mRNA expression in tumour tissue (n=414) by quantitative RT-PCR
- **Primary objective:** Evaluation of *NOTCH1*-mRNA expression and its association with patients and tumours characteristics
- **Secondary objectives:** Association of *NOTCH1*-mRNA expression with recurrence-free interval (RFI), overall survival (OS), and the predictive value of *NOTCH1*-mRNA expression with regard to adjuvant chemotherapy

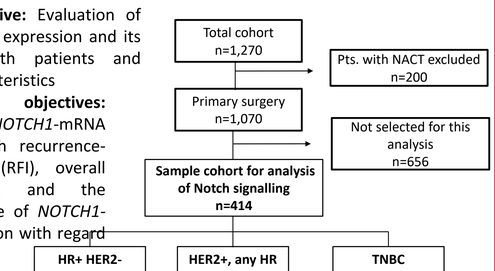

Figure 2: Consort diagram. Patients of the PiA-cohort (n = 1,270) and groups used for multivariate *NOTCH1-m*RNA expression analysis (n = 414).

Table 1: Distribution of low and high *NOTCH1*-mRNA expression in selected groups.

	Notch-cohort n=414 (100%)	*NOTCH1-mRNA* low n=287 (69.3%)	*NOTCH1-mRNA* high n=127 (30.7%)
Age			
< 50 yrs	104 (25.1%)	77 (26.8%)	27 (21.3%)
≥ 50 yrs	310 (73.2%)	210 (73.2%)	100 (78.7%)
Nodal status			
Negative	251 (60.6%)	175 (61.0%)	76 (59.8%)
Positive	163 (39.4%)	112 (39.0%)	51 (40.2%)
Tumour histology			
Ductal (NST)	329 (79.5%)	220 (76.7%)	109 (85.8%)
Lobular	67 (16.2%)	52 (18.1%)	15 (11.8%)
Others	18 (4.4%)	15 (5.2%)	3 (2.4%)
Tumour size			
≤ 2cm	198 (47.8%)	130 (45.3%)	68 (53.5%)
> 2cm	216 (52.2%)	157 (54.7%)	59 (46.5%)
Grading			
G1	39 (9.4%)	27 (9.4%)	12 (9.5%)
G2	267 (64.5%)	189 (65.9%)	78 (61.4%)
G3	108 (26.1%)	71 (24.74%)	37 (29.1%)
Hormone receptor status			
Positive (ER and/or PgR ≥ 1%)	357 (86.2%)	256 (89.2%)	**101 (79.5%)**
Negative (ER and PgR < 1%)	57 (13.8%)	31 (10.8%)	**26 (20.5%)**
HER2 status			
Positive (DAKO 2 if ISH positive, DAKO 3)	65 (15.7%)	30 (10.5%)	**35 (27.6%)**
Negative (DAKO 0, 1 or 2 if ISH negative)	349 (84.3%)	257 (89.5%)	**92 (72.4%)**
uPA/PAI-1 status			
Low: uPA and PAI-1 low	155 (37.4%)	120 (41.8%)	**35 (27.6%)**
High: uPA and/or PAI-1 high	259 (62.6%)	167 (58.2%)	**92 (72.4%)**

Abbreviations: estrogen receptor (ER), progesteron receptor (PgR), hormone receptor (HR), human epidermal growth factor receptor 2 (HER2), urokinase-type plasminogen activator (uPA), cut off ≥3 ng/mg total protein, plasminogen activator inhibitor type 1 (PAI-1) cut off ≥14 ng/mg total protein, bold: p-value (Pearson χ2 test) < 0.05

Results I

- High *NOTCH1*-mRNA expression was detected in one-third of the tumours
- Significant prognostic impact of high *NOTCH1*-mRNA expression with regard to RFI (adjusted hazard ratio 2.1, 95% CI 1.077–4.118)
- Combination of *NOTCH1*-mRNA expression and uPA/PAI-1: highest risk of recurrences and poorest overall survival for the patient group with high *NOTCH1*-mRNA expression combined with high uPA/PAI-1.

Results II

- Patients with high *NOTCH1*-mRNA expression and chemotherapy (n = 86) had a worse clinical outcome (adjusted hazard ratio of 3.1 for disease-related events, 95% CI 1.321–7.245, p = 0.009)

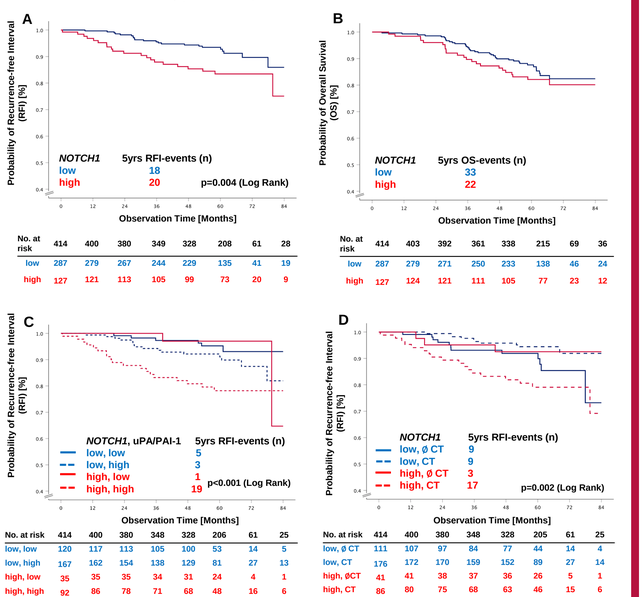

Figure 3: Survival estimates for *NOTCH1*-mRNA expression with regard to RFI (A) and OS (B); considering *NOTCH1*-mRNA expression and uPA/PAI-1 status with regard to RFI (C); considering *NOTCH1*-mRNA expression and receiving chemotherapy with regard to RFI (D), the tables present the effective sample size for each interval (No. at risk). Abbreviation: Chemotherapy (CT)

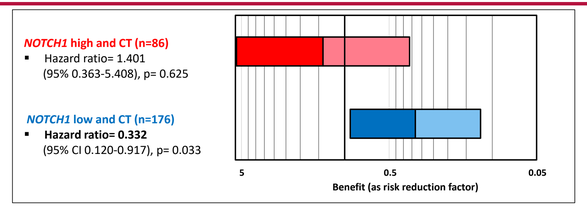

Figure 4: Benefit of chemotherapy visualised in a stacked bar graph in terms of hazard ratios for CT by low and high *NOTCH1*-mRNA expression. Abbreviations: chemotherapy (CT), confidence interval (CI)

Table 2: Multivariate analysis of *NOTCH1*-mRNA expression (n = 414).

Parameters	sample size	Multivariate analysis RFI		
	n = 414	events	Hazard Ratio	95% CI
ALL[a]				
NOTCH1 low	287	18	1	
NOTCH1 high	127	20	**2.10**	1.077-4.118
ALL with regard to NOTCH1 and uPA/PAI-1[b]				
NOTCH1 low, uPA/PAI-1 low	120	5	1	
NOTCH1 high, uPA/PAI-1 high	92	19	**3.68**	1.452-9.334
ALL with regard to CT[c]				
NOTCH1 low, no CT	111	9	**2.85**	1.103-7.388
NOTCH1 low, CT	176	9	1	
NOTCH1 high, no CT	41	3	2.33	0.617-8.828
NOTCH1 high, CT	86	17	**3.09**	1.321-7.245

[a] adjusted *NOTCH1*-mRNA expression to: nodal status and histopathological groups, [b] adjusted *NOTCH1*-mRNA expression to: uPA/PAI-1, nodal status and grading, [c] adjusted *NOTCH1*-mRNA expression to: nodal status, HR status and HER2 status

Conclusion

In summary, in our cohort for NOTCH1 we showed a prognostic and, particularly, a significant predictive impact of *NOCTH1*-mRNA expression. We observed that tumours with high *NOTCH1*-mRNA expression seem to be less sensitive to cytotoxic treatment. Therefore, we postulate, that downregulation of the Notch-signalling pathway, e.g. with γ-secretase inhibitors, may improve the efficacy of breast cancer therapy by restoring chemosensitivity.

ESMO congress MADRID SPAIN 20-24 OCTOBER 2023

References

[1]Chimento A, D'Amico M, Pezzi V et al. (2022) Notch Signaling in Breast Tumor Microenvironment as Mediator of Drug Resistance. International journal of molecular sciences 23(11). doi: 10.3390/ijms23116296

[2]Giuli MV, Mancusi A, Giuliani E, Screpanti I, Checquolo S. Notch signaling in female cancers: a multifaceted node to overcome drug resistance. Cancer Drug Resist. 2021 Aug 5;4(4):805-836. doi: 10.20517/cdr.2021.53

Contact

Contact for permission to reprint and/or distribute: julia.engel@student.uni-halle.de, www.umh.de