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Characterization of neuroendocrine breast carcinomas for biomarkers of therapeutic options

Zoran Gatalica MD, DSc[1], Rebecca Feldman PhD[1], David Arguello MD[1], Anatole Ghazalpour PhD[1], Semir Vranic MD, PhD[2]

[1]Caris Life Sciences, Phoenix, AZ; [2] Department of Pathology, University of Sarajevo Clinical Center and School of Medicine, Sarajevo, Bosnia and Herzegovina

ABSTRACT

Introduction: Neuroendocrine breast carcinoma (NBC) is an extremely rare type of cancer, constituting less than 0.1% of all breast tumors, without specific treatment options. We investigated a biomarker database for frequency of molecular markers that may guide personalized treatment choices for these patients.

Materials and Methods: Molecular profiles of 40 breast carcinomas with neuroendocrine features [ER/PR+ (n=20), HER2+ (n=1) and TNBC (n=14)] were assessed (all female patients, mean age: 60.3 years, range: 39-83 years). Gene expression (Illumina DASL microarray platform), protein expression (IHC), gene amplification (ISH) and next-generation sequencing (NGS; TruSeq Illumina platform) were performed.

Results: 57% of NBCs were positive for hormone receptors (ER/PR), 40% were triple negative TNBC and 3% HER2+ subtypes. Therapeutic biomarkers (IHC) that may guide chemotherapies (and used in other primary sites neuroendocrine tumors) included: high TOP2A (85%) for etoposide or doxorubicin, low TS (57%) for 5-fluorouracil and low ERCC1 (45%) for cisplatin. Additional biomarkers for chemotherapy included: high TOPO1 (60%) for irinotecan, low RRM1 (48%) for gemcitabine and low MGMT (57%) for temozolomide. Biomarkers associated with available targeted therapies included: PTEN loss (39%), positive ALK (33%), cKit (30%), EGFR (29%), AR (26%) and PDGFRA (17%). No gene amplifications were detected in *cMET, EGFR,* or *TOP2A*. Targeted sequencing analysis of 47 genes detected variants in *TP53, PIK3CA, ERBB4* and *APC* genes. Gene expression data (included somatostatin receptor gene family- SSTR1/2/3/4/5) was available for 5 patients, for which 3/5 patients exhibited overexpression of at least one SSTR gene.

Conclusions: Molecular profiling by a multiplatform approach reveals potential personalized therapy options for this very rare breast cancer subtype. With recent success of somatostatin analogs for other neuroendocrine tumors, the overexpression of SSTR gene family in NBC is worthy of further investigation.

OBJECTIVES

Neuroendocrine breast carcinoma (NBC) is an extremely rare type of cancer, constituting less than 0.1% of all breast tumors, without specific treatment options (1). Several studies confirmed its poor prognosis (2,3).

In the present study, we investigated a biomarker database for frequency of molecular markers that may guide personalized treatment choices for these patients.

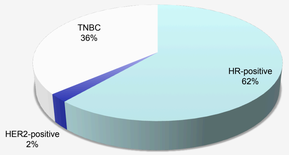
METHODS

Molecular profiles on 44 specimens were available (all female patients, mean age: 60.4 years, range: 39-83 years).

Gene expression (Illumina DASL microarray platform), protein expression (IHC), **gene amplification** (ISH) and **next-generation sequencing** (NGS; TruSeq Illumina platform) were performed.

RESULTS (UPDATED)

BC Subtypes in Cohort (n=44)



NGS genes	Mutation frequency
APC	7% (1/14)
ERBB4	7% (1/14)
NOTCH1	7% (1/14)
PIK3CA	**27% (4/15)**
TP53	**50% (7/14)**

Non-amplified ISH◆ in NBC

ALK (0/1), *EGFR* (0/14), *MET* (0/8), *MYC* (0/3), *TOP2A* (0/19)

Biomarkers	Platforms	% Overexpression or amplification
ER	IHC◆	61% (27/44)
PR	IHC◆	59% (26/44)
Her-2/neu	IHC◆	2% (1/44)
HER2 (ERBB2)	ISH◆	0% (0/20)

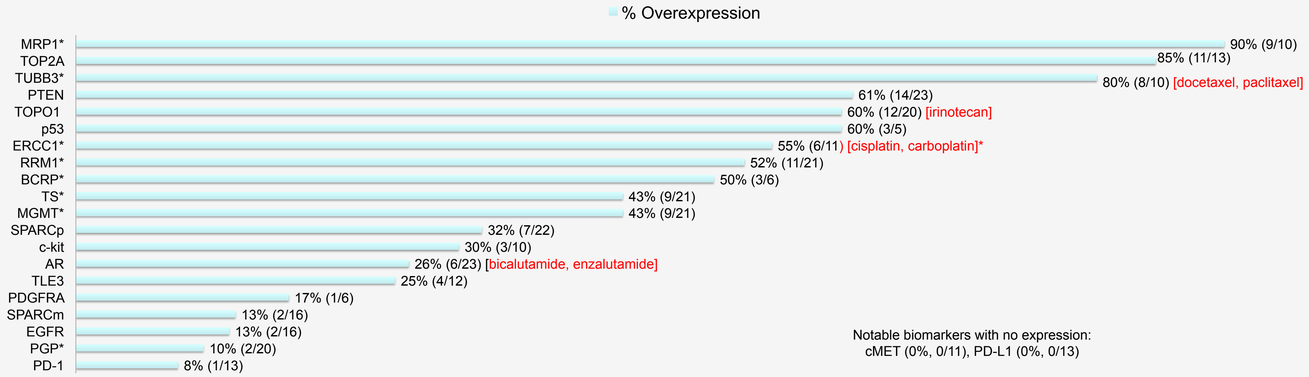
◆IHC = immunohistochemistry; ISH – in-situ hybridization

SSTR* **mRNA expression (results)**
***SSTR1-5* (1.1-3.1x)**
SSTR1,3,5 (0.8-1.3x)
***SSTR2,4,5* (0.2-12.2x)**
SSTR5 (0.4x)
***SSTR1,2,4* (0.9-2.0x)**

In all, 60% (3/5) NBC exhibited gene overexpression in at least one SSTR (1-5) gene.

*** SSTR = Somatostatin receptor**

Predictive and prognostic biomarkers in NBC outside of ER/PR/HER2



*** Biomarkers where no expression may predict a potential benefit.**

Agents mentioned in red have favorable biomarker evidence in breast carcinoma.

CONCLUSIONS

- Molecular profiling by a multiplatform approach reveals potential personalized therapy options for this very rare breast cancer subtype.
- Gene overexpression of the SSTR family in NBC is worthy of further investigation given the recent success of **somatostatin** analogs in other neuroendocrine tumors.
- The presence of ***PIK3CA*** mutations and/or loss of **PTEN** along with **androgen receptor** overexpression in a subset of NBCs indicates a potential use for targeted therapy (e.g. mTOR inhibitors, anti-androgen therapy) in patients with advanced and/or metastatic disease. In addition, we also identified biomarkers (**TOPO1, TOPO2A, RRM1, ERCC1, MGMT, TS**) that may predict response to conventional chemotherapy options.
- Prospective clinical trials are urgently needed in this disease.

REFERENCES

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