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Prognosis and outcome in *CDH1*-mutant lobular breast cancer

G. Corso[1,#], **P. Veronesi**[1,2], **V. Sacchini**[1,2], **V. Galimberti**[3]

[1.] European Institute of Oncology, Division of Breast Cancer Surgery - Via G. Ripamonti 435, Milan, Italy.

[2.] School of Medicine, University of Milano, Milano, Italy.

[3.] European Institute of Oncology, Unit of Molecular Senology - Via G. Ripamonti 435, Milan, Italy.

Human *CDH1* germline mutation encodes for the E-cadherin protein and is responsible for the so-called Hereditary Diffuse Gastric Cancer (HDGC) syndrome (Caldas *et al.*, 1999). Lobular Breast Cancer (LBC) is a component of this inherited disorder as sporadic or familial setting (Corso *et al.*, 2016). Apart from the well-documented association between LBC and HDGC syndrome, novel E-cadherin germline mutations have recently been detected in women affected by LBCs without history for DGC. About 3% of these LBCs carrying *CDH1* germline mutations are defined as “hereditary breast tumor” without any manifestation of gastric carcinoma; some studies suspected that this group could be represent an independent cancer syndrome (Benusiglio *et al.*, 2013; Petridis *et al.*, 2014; Corso *et al.*, 2014).

Clinical studies have verified that GC patients with *CDH1* germline mutations have shorter survival times (van der Post *et al.*, 2015). Similarly, a worse prognosis is also demonstrated in *CDH1* somatic alteration carriers (Corso *et al.*, 2013).

Regarding LBC presenting any *CDH1* germline pathogenic alteration, no information is available in the literature about prognosis and overall survival; mutation frequencies are insufficient to perform a complete analysis.

However, patients with hereditary syndrome carrying *BRCA1/2* germline mutations have a worse breast cancer-specific survival than to *BRCA*-negative/sporadic cases (Baretta *et al.*, 2016).

Similar observations are reported in HDGC syndrome, despite the fact that genetic, clinical disease and tumorigenesis are vastly different (van der Post *et al.*, 2015). It seems that patients with hereditary cancer carrying a documented germline mutation show a worse prognosis in comparison to those patients with the wild-type sporadic subset.

In a recent study, Ping et al. (2016) demonstrated that the *CDH1* somatic mutation did not impact the prognosis of LBC patients who had an invasive histology; however, the presence

[#]Corresponding Author.

Conflict of interest

The Authors have no conflict of interests to declare.

of *CDH1* plus *ERBB2* mutations leads to a worse prognosis. The synergic effect of the *CDH1-ERBB2* complex is not well documented; Suriano et al. described *EGFR* over-expression as being well documented in the presence of *CDH1* extracellular domain mutations (Suriano *et al.*, 2003). *ERBB2* probably could play a part in this circuit, belonging to the *EGFR* family.

In this study, *ERBB2* mutations were identified in six of the 100 (6%) *CDH1*-altered LBC and in 6/169 (3.5%) of all screened LBC cases (Ping *et al.*, 2016). It is interesting to observe that germline *CDH1* mutations affect about 3% of LBC cases submitted for genetic screening (Corso *et al.*, 2016). There is some clinical and molecular information leading us to suspect that LBC patients described by Ping et al. (2016) could be affected by an inherited syndrome (such as HDGC or sporadic early onset), carrying *CDH1* germline mutations. It could be interesting to explore the family history of this sub-group to assess the eligibility of *CDH1* genetic screening. Additional further genetic studies will clarify if the presences of *CDH1* germline mutation exert a negative prognostic factor in LBC outcome, as hereditary cancer syndrome.

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