Single institution assessment of pathogenic BRCA1 mutation in Triple Negative Breast Cancer and its association with clinical features and treatment response

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BACKGROUND: Triple-negative breast cancer (TNBC) accounts for 15-20% of all breast cancer cases and is a subtype characterized by the lack of hormonal receptors for estrogen and progesterone (ER and PR) and also absence of super-expression/amplification of the Human Epidermal Growth Factor Receptor 2 (HER2). Therefore, this subtype does not respond to conventional hormonal and immunotherapy that are effective in other subtypes and the treatment is based on systemic chemotherapy. Moreover, TNBC displays higher aggressiveness and distinct metastatic pattern compared to other breast tumors, resulting in worse prognosis and survival for TNBC patients. Our group and others have reported high prevalence of germline pathogenic mutations in the *BRCA1* gene among young women diagnosed with TNBC. This gene acts as a tumor suppressor gene and germline mutation that leads to loss of function of its respective protein may favor cancer development. However, it is not well established the proportion of pathogenic mutation in *BRCA1* in TNBC patients unselected for age at diagnosis and for family history in Brazil nor the mutation origin, whether somatic or germline. Thereby, it is important to evaluate the prevalence of these mutations in TNBC patients in different age at diagnosis; to characterize the somatic or germline origin of the mutation and to establish an association between the mutation presence and clinic and demographic features of TNBC patients.

HYPOTHESIS: TNBC displays high *BRCA1*-mutation rate.

METHODS: Samples from 131 TNBC patients unselected for age or family history and attending A.C.Camargo Cancer Center were screened for pathogenic mutation in *BRCA1* entire CDS and exon-intron boundaries using next generation sequencing (Ion PGM Torrent). Sanger sequencing were performed to validate findings and to determine mutation origin. Multiplex Ligation-dependent Probe Amplification (MLPA) was used to investigate *BRCA1* large rearrangements in a subset of 97 of these samples. Clinical features and treatment response were associated to mutation status.

RESULTS: Tumor samples from 131 TNBC were analyzed: sixteen (12,21% - 16/131) harbored *BRCA1* pathogenic mutations; four (3,05% - 4/131) showed a Variant of Uncertain Significance (VUS) and 111 (84,73% - 111/131) were classified as wild type. One of the *BRCA1*-mutated tumors harbored a germline large rearrangement identified by MLPA. Germline mutations accounted for 92,8% of the pathogenic mutations detected. *BRCA1*-mutated tumors were statistically more prone to be developed by patients with family history of breast cancer and in younger women than *BRCA1*-wild type tumors. Other clinopathological variables slightly varied with no statistical significance. There was a trend to better overall and disease-free survival in TNBC *BRCA1*-mutated patients although not statistically significant. Most of patients were treated with chemotherapy in an anthracyclines-based regimen combined or not with taxanes.

CONCLUSION: Lastly, our findings showed that loss of function mutations in *BRCA1* gene is a recurrent event in TNBC that affects young Brazilian women and confirm that women diagnosed with TNBC at early age are in risk of carrying *BRCA1* germline pathogenic mutation and thus should be referred to genetic testing