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INVESTIGATION OF CIRCULATING TUMOR DNA (CTDNA) IN PATIENTS WITH NON-METASTATIC TRIPLE-NEGATIVE BREAST CANCER (TNBC) SUBMITTED TO NEOADJUVANT CHEMOTHERAPY

Rafael Canfield Brianese[1], Giovana Tardin Torrezan[1], Marina de Brot Andrade[2], Vladmir Claudio Cordeiro de Lima[3], Solange Moraes Sanches[3], Maria Nirvana da Cruz Formiga[4], Fabiana Baroni Alves Makdissi[5], Dirce Maria Carraro[1]

[1]A.C. Camargo Cancer Center, Laboratory of Clinical and Functional Genomics – São Paulo (SP), Brazil.
[2]A.C. Camargo Cancer Center, Pathology Department – São Paulo (SP), Brazil.
[3]A.C. Camargo Cancer Center, Clinical Oncology Department – São Paulo (SP), Brazil.
[4]A.C. Camargo Cancer Center, Oncogenetics and Clinical Oncology Department – São Paulo (SP), Brazil.
[5]A.C. Camargo Cancer Center, Breast Surgery Department – São Paulo (SP), Brazil.

Objective: Loss-of-function germline mutation in BRCA1 increases breast cancer risk, especially in the triple-negative breast cancer (TNBC) subtype. BRCA1 impairment may confer benefit from the treatment with DNA damage-inducing drugs and PARP1 inhibitors. Patients who respond to neoadjuvant chemotherapy tend to have good outcomes. The aim of this study was to characterize the resistance to chemotherapy in patients with germline-characterized TNBC by investigating somatic mutations in ctDNA. **Methods:** Germline genetic testing was done using cancer-predisposing gene panels (26–126 genes) to classify TNBC as hereditary or sporadic. Somatic mutation identification in tumor (409 cancer-related gene panel) and screening of ctDNA in plasma samples during treatment were performed. **Results:** We enrolled 96 TNBC patients of which 88 were tested for germline variants: 23% (20/88) of cases were hereditary – BRCA1 (16%), BRCA2 (4%), PALB2 (1%), RAD51D (1%), and TP53 (1%). Tumor mutation burden (TMB) analysis (43 cases) showed that 11.6% had high and 89.4% had low TMB, not associated with hereditary status. We found, on average, 3 somatic variants per tumor (range 1–7) and used them as tumor marks for screening ctDNA in plasma. Somatic mutations in TP53 were identified in most tumors (71%). In ctDNA before treatment, detection of at least one tumor mutation was observed in 24 out of 30 patients (80%), and no association was observed between hereditary status and TMB score. Although ctDNA was not associated with the residual cancer burden score, ctDNA-positive patients were associated with clinical progression, either at baseline or during monitoring (post-neoadjuvant chemo), and ctDNA identification anticipated progression detected by imaging. **Conclusion:** Hereditary tumors, markedly due to germline variants in BRCA1, are frequent in TNBC. Tumor-mark identification using gene panels and ctDNA screening in plasma samples provide valuable information regarding the clinical progression of patients treated with preoperative chemotherapy.

Keywords: Hereditary. Triple-negative breast cancer. Circulating tumor DNA. Liquid biopsy.