Introduction

Triple-negative breast cancer (TNBC) -negative for estrogen and progesterone receptors and HER2 - accounts for 15% of all breast cancer cases and presents poor outcome. Germline mutations in BRCA1 gene increase the risk of breast/ovarian cancer, especially the TNBC subtype. About 80% of BRCA1- mutation carriers who develop breast cancer have TNBC and about 10% of all TNBC cases are hereditary and BRCA1-related. A significant increase of hereditary TNBC triggered by BRCA1 germline pathogenic mutations has been reported in young women (~20%), including our group (24%), irrespective of family history for cancer. Moreover, BRCA1 somatic promoter hypermethylation is detected in 20% of all sporadic TNBC cases, also with increased rates in young women (~35%). BRCA1 inactivation, considering both germline mutations and gene promoter methylation, are present in nearly 30% of all TNBC and are accentuated (~55%) in tumors diagnosed at an early age (Brianei et al., 2017). Patients with tumors harboring germline BRCA1 mutations seem to benefit from treatment with drugs that ultimately induce DNA damage. Hence, molecularly characterizing triple-negative tumors in the context of BRCA1 inactivation is of great interest in understanding the mechanisms of resistance and response to current therapies for TNBC, both in sporadic and hereditary tumors. The detection of ctDNA has been arising as a non-invasive strategy to monitoring the tumor dynamics through time, once these DNA molecules mirror the mutations present in the tumor masses.

Goal

Investigate the tumor dynamics during preoperative chemotherapy by the analysis of ctDNA as a liquid biopsy in patients diagnosed with TNBC tumors with or without BRCA1 inactivation.

Methodology

Results

21 TNBC patients were currently accrued (mean age 47; median 42) and had leukocyte samples sequenced. Three (14% - 3/21) were carriers of BRCA1 pathogenic germline mutations (Table 1). Eighteen variants of uncertain significance were identified (Table 2) in 13 patients.

For 4 patients, tumor and plasma DNA were also sequenced for identifying somatic variants. At least one of the somatic variants identified in tumor DNA were also identified in plasma DNA for all patients (Table 3).

Blood draws for plasma DNA isolation and screening of tumor marks are in progress (Table 4).

We plan to recruit 30 TNBC patients and optimize the analysis of gene panels including strategies for increasing the sensitivity in the identification of variants of low frequency (i.e. molecular barcodes) in ctDNA in order to have insights about the tumor biology and its dynamics during treatment helping to achieve more personalized strategies for the treatment of TNBC patients.

Conclusions

BRCA1 pathogenic germline mutations are frequent events in triple-negative breast cancer and TNBC with BRCA1 deficiency seems to be more sensitivity to treatment with platinum-based chemotherapy and PARP1 inhibitors. Screening of specific tumor mutations in cell-free DNA from plasma of TNBC patients characterized by BRCA1/2 and other genes associated with homologous recombination (RH) might be useful for understanding the genetic mechanisms of treatment response and resistance.

Financial support