Germline and somatic NGS-based analysis on BRCA-related tumors

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Our group is long evaluating epidemiological and genetic features of breast-ovarian cancers and other BRCA-related tumor in North Sardinia, Italy. Individuals carrying a predisposing mutation in one or both of the BRCA (BRCA1 or BRCA2) genes have a significantly increased risk of developing breast/ovarian cancer (BOC) and other BRCA-related tumors such as pancreatic and prostate cancer. Epidemiological data on incidence and distribution of such cancers are obtained from the local tumor registry; 411 genetic testing for BRCA gene mutations have been performed.

Germline NGS-based analysis were performed in all young breast cancer patients or all women (over 50 years) with a strong family history of BOC (total of 384 cases), males with sporadic breast cancer (6 cases) and one with prostate cancer, and lately patients with pancreatic cancer (20 cases). Genetic testing for breast and ovarian cancer has clinical importance for identification of potentially affected families and for cancer prevention. Approximately, 5-10% of breast and ovarian cancer are familiar while about 90% are sporadic tumor cases. BRCA germline mutations account for approximately 10–15% of BOC cancers.

Confirming previous results from our group, a higher prevalence of the BRCA2 mutation was observed in North Sardinia as compared to the general population and highlight the presence of specific germline mutation associated with the “founder effect” in distinct genetic subgroups reflecting genetic drift. Conversely, BRCA1 mutations are much more strongly associated at higher rates of BOC cancer in South Sardinia.

Heterozygous BRCA mutations determine loss of function of the remaining wild-type allele, resulting in deficient homologous recombination DNA repair, which causes genetic aberrations that drive carcinogenesis. PARP inhibition in mutated tumor cells with deficient homologous-recombination repair generates unrepaired DNA single-strand breaks that are likely to cause the accumulation of DNA double-strand breaks and collapsed replication forks. Currently, analysis performed on somatic tissue allows to identify a greater number of mutations in BRCA-related tumor (additional 5-7% of cases as compared to germline testing). As consequence, the current mutational analysis is based on the use of multi-genic NGS customized “Oncomine Cancer panels” that allow to analyze additional genes involved in the onset of cancer (SMAD4, ATM, CHEK2, APC, NF, KRAS, CDKN2A) as well as in maintaining the genome integrity (POLE, PALB2, PTEN, TP53, PIK3CA). Notably, detection of three PIK3CA hot spot mutations - E545K, E542K, H1047R (detected in about 40% cases) - is a new targeted therapy with PIK3CA inhibitors and represent a new strategy to overcome resistance in mutated advanced breast cancer.

Analogously, combination of PARP and AR (androgen receptor) inhibitors was demonstrated to exert a benefit into the treatment of prostate cancer. The androgen receptor promotes DNA damage repair and upregulates PARP-mediated repair pathways, thus increasing the effectiveness of the PARP inhibitor. Finally, in pancreatic adenocarcinoma, the presence of mutations in cancer susceptibility genes and the involvement of external factors (such as those underlying local inflammation) play a role in pathogenesis along with the occurrence of somatic mutation in KRAS and other “driver”genes (SMAD4 and CDKN2A), leading to the use of new targeted therapies.

Keywords: BRCA1-2 genes, NGS, PARP-AR inhibitors