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Überörtliche Berufsausübungsgemeinschaft
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Laboratory information 5/2017

PARP inhibition in BRCA carriers

Medical background

Mutations in BRCA1 or BRCA2 cause hereditary breast and ovarian cancer. Moreover, mutations in these genes are associated with other cancers, e.g. pancreatic cancer and prostate cancer. BRCA mutations appear in 14% of all ovarian (up to 25% of high grade serous)[1,8] and 5-10% of breast cancers[2], respectively. It is thought that BRCA deficient tumor cells cannot repair DNA double strand damage that has been introduced into their DNA by previous chemotherapy regimens.

Due to this "synthetic lethality", women with high grade serous, platin-sensitive (progression-free interval >6 month) but recidivated ovarian cancer may be treated more successfully with addition of a poly-ADP ribose polymerase (PARP) inhibitor, e.g. Olaparib (Lynparza™) after several lines of previous chemotherapy, especially when a BRCA mutation is present. The AGO-TR1 study showed, that 21.8% of women with that special cancer type indeed carry a germline mutation in BRCA1 or 2 while *at least* additional 4.0% of patients have BRCA1 or BRCA 2 mutation(s) in their tumor only. Other studies show that 28-44% more mutations are detected analyzing tumor tissue instead of blood.[4-6] These somatic BRCA "tumor-only" mutations are not inherited, and also advantageous concerning "synthetic lethality" with PARP inhibition. As even 40% of ovarian cancer patients with a BRCA mutation may have no documented family history for breast or ovarian cancers[1,3] some disease management strategies consider BRCA1 and 2 genes to be tested in *every* woman with non-mucinous, non-borderline epithelial ovarian cancer regardless of family history.[9]

In general, women with known BRCA status may benefit from adapted treatment decisions, e.g. proven better response to platinum-based chemotherapy[13], or may undergo largely risk-reducing, preventive surgery.[14,15] Guidelines for genetic counseling vary between countries and are often a bottle neck to testing BRCA on a fast track. The picture on the right shows how testing may be accelerated where other guidelines do not apply.

PARP inhibitor therapy with olaparib is in in the future expected to be also an option in castrate resistant prostate tumors as well as in HER2-negative metastatic breast cancer harboring germline BRCA1 or BRCA2 mutations. Other key PARP inhibitors currently under clinical development[11] are rucaparib (rubraca™), veliparib, talazoparib and niraparib. Rucaparib is approved for "treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies", regardless of whether the disease is platinum-sensitive or platinum-resistant.[12]

Method

Direct sequencing of complete BRCA1 and BRCA2 genes plus deletion/duplication scanning with MLPA from blood and/or tumor tissues.

Turnaround time

Allow two weeks.

Reporting

For each medical report, we supply an individual interpretation along with further diagnostic recommendation.

Material

Ascertained tumor tissue (FFPE tissue scored as tumor by pathologist) plus EDTA whole blood (2 ml).

Contact

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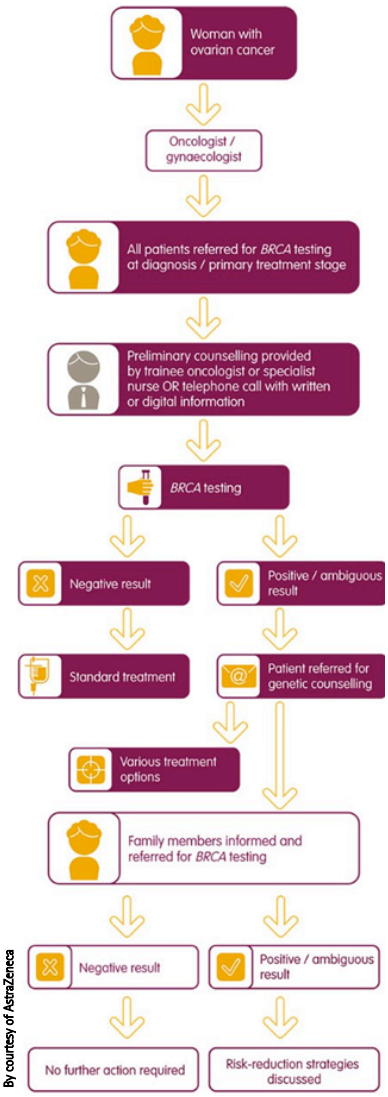

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