THERAPEUTIC TARGETING OF DNA REPAIR DEFICIENCIES IN GYNECOLOGIC CANCERS

DNA Repair Deficiencies Are Common in Gynecologic Cancers and Can Be Targeted by Therapies to Kill Cancer Cells

Deficient mismatch repair (dMMR) causes mutations and **microsatellite instability (MSI)**

DNA DAMAGE

Alterations in ***BRCA1/2, RAD51C/D, BRIP1, ATM,*** or genes in the Fanconi anemia pathway can cause **homologous recombination deficiency (HRD)**

Damaged bases or single-strand breaks are repaired by:

- Base excision repair
- Nucleotide excision repair
- **Mismatch repair**

Double-strand breaks are repaired by:

- **Homologous recombination**
- Nonhomologous end joining

~33% of **endometrial cancers** have **dMMR/MSI**

~50% of **ovarian cancers** have **HRD**

dMMR/MSI Is a Biomarker for Response to Checkpoint Inhibitors

dMMR/MSI tumors:

- Have high mutation rates
- Accumulate neoantigens
- Are immunogenic

dMMR/MSI can be identified by immunohistochemistry or polymerase chain reaction analysis

HRD May Predict Magnitude of Sensitivity to PARPi

BRCA1/2 mutation is an important cause of HRD, although HRD can also result from many other causes

Platinum sensitivity is a biomarker for PARPi sensitivity in some settings

Current genetic tests (eg, BRCA mutation analysis, HRD testing) cannot identify all patients who may benefit from PARPi therapy

DNA repair deficiencies can render cancer cells sensitive to chemotherapy and some targeted therapies

Patients with ovarian or endometrial cancer should undergo genetic testing

Genetic counseling is required for patients with germline mutations

Combinations with therapies targeting DNA repair deficiencies are under active investigation

For additional content on this topic, please visit www.GemstoneOncology.com

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BRCA, breast cancer susceptibility gene; dMMR, deficient mismatch repair; HRD, homologous recombination deficiency; MSI, microsatellite instability; PARP, poly ADP ribose polymerase; PARPi, PARP inhibitor.

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