Abstract

Curr Treat Options Oncol. 2022 Nov;23(11):1566-1589. doi: 10.1007/s11864-022-01024-5. Epub 2022 Oct 15.

The Role of PARP Inhibitors in Patients with Primary Malignant Central Nervous System Tumors.

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Primary malignant central nervous (CNS) tumors are a devastating group of diseases with urgent need for improved treatment options. Surgery, radiation, and cytotoxic chemotherapy remain the primary standard treatment modalities, with molecularly targeted therapies having proven efficacy in only small subsets of cases. Poly(ADP-ribose) polymerase (PARP) inhibitors, which have had immense success in the treatment of extracranial cancers with homologous recombination deficiency (HRD), are emerging as a potential targeted treatment for various CNS tumors. Although few primary CNS tumors display canonical BRCA gene defects, preclinical evidence suggests that PARP inhibitors may benefit certain CNS tumors with functional HRD or elevated replication stress. In addition, other preclinical studies indicate that PARP inhibitors may synergize with standard therapies used for CNS tumors including radiation and alkylating agents and may prevent or overcome drug resistance. Thus far, initial clinical trials with early-generation PARP inhibitors, typically as monotherapy or in the absence of selective biomarkers, have shown limited efficacy. However, the scientific rationale remains promising, and many clinical trials are ongoing, including investigations of more CNS penetrant or more potent inhibitors and of combination therapy with immune checkpoint inhibitors. Early phase trials are also critically focusing on determining active drug CNS penetration and identifying biomarkers of therapy response. In this review, we will discuss the preclinical evidence supporting use of PARP inhibitors in primary CNS tumors and clinical trial results to date, highlighting ongoing trials and future directions in the field that may yield important findings and potentially impact the treatment of these devastating malignancies in the coming years.

DOI: 10.1007/s11864-022-01024-5
PMID: 36242713 [Indexed for MEDLINE]