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A guide to poly ADP-ribose polymerase inhibitor (PARPi) toxicity management

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Ovarian cancer is the fifth most common cause of cancer-related death in women and is the leading cause of gynecologic-related deaths in the United States.[1 2] Only ~40% of patients with ovarian cancer achieve a cure and the 5-year overall survival is ~47%.[1] The majority of ovarian neoplasms are categorized as high-grade serous epithelial cancer and have initial chemosensitivity, but then become resistant to chemotherapy as recurrence occurs. Surgery in combination with chemotherapy is the standard treatment, but, due to increased resistance, oncologists will often consider maintenance therapy.[2]

For years, maintenance bevacizumab was the only option: however, in 2014, the Food and Drug Administration approved the first poly ADP-ribose polymerase inhibitor (PARPi). PARPi's cause single-strand breaks which causes accumulation of double-strand breaks during DNA replication.[2] Mutations in the BRCA1 and BRCA2 genes cause interruption in the repair of double-strand breaks, which adds to the efficacy of these medications in those that have these alterations. The BRCA gene plays a role in repairing DNA via homologous recombination (HR), and mutations of this gene leads to HR deficiency.[3]

Due to their mechanism of action and some off-target activity, the PARPi can cause both class-wide and unique adverse events. Management of these adverse events has become an area of interest as they are becoming more prominent in the treatment of ovarian cancer.[3] In the current issue of this journal, Dr Madariaga and colleagues provide management strategies for the most commonly seen adverse events.[4] The frequency of the adverse events reported in this article come from findings reported in the landmark trials that led to PARPi approval.

Authors of the article divide the adverse events into those that occur as class effects, those that are specific to the individual agents, and those that are rare in presentation. Dr Madariaga and colleagues provide a table for the reader's reference that outlines all the adverse events, the patient population the adverse events were seen in, and the frequency at which these events occurred, making the article a great resource for new oncologists using PARPi.[4]

Though it is difficult to directly compare the activity of different PARPis since head-to-head studies are lacking, similarly designed clinical trials evaluating different PARPis have shown similar results. After years in development, several PARPis have achieved indications for ovarian cancer including the treatment of recurrent disease or maintenance therapy after response to platinum-based chemotherapy.[2] Though they are sometimes mistaken for well-tolerated oral chemotherapy, they do warrant knowledge of their toxicities and guidance on toxicity management.

Although many other agents are used in the treatment of recurrent ovarian cancer, efficacy decreases with each subsequent line of therapy. Therefore, new strategies of combining PARPis with other agents that target different pathways or have complementary mechanisms, such as immune checkpoint inhibitors and DNA-damaging chemotherapy are currently being studied.[2 3] By providing a reference for the management of PARPi-related toxicities, Dr Madariaga and colleagues have made it easier to identify and manage toxicities, whether these agents are being used as monotherapy or combination therapy.

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