Elucidating a risk of developing second primary malignancy during and after treatment with PARP inhibitors

Although PARP inhibitors interfere with DNA repair processes leading to warnings in terms of risk for developing second primary malignancies, findings from a systematic review and safety meta-analysis of placebo-controlled randomised studies are reassuring for patients starting PARP inhibitors in the first-line setting that there is no increased risk of developing second primary malignancies (myelodysplastic syndrome or acute myeloid leukaemia).

Overall, 51 second primary malignancies were reported in the PARP inhibitor arms (0.9%) and 24 second primary malignancies in placebo arms (0.7%). Studies included in the analysis had a median follow-up ranging from 3.8 to 78 months. The results are published by Prof. Joachim Alexandre of the Normandie University, UNICAEN, CHU de Caen Normandie in Caen, France and colleagues in August 2021 issue of the *Annals of Oncology*.

Geen verhoogd risico op het ontwikkelen van een tweede primaire tumor bij behandeling met PARP-remmers

PARP-remmers hebben een interactie met de reparatieprocessen in het DNA. Een mogelijk risico daarbij is dat zich een tweede primaire tumor ontwikkelt. Uit onderzoek is gebleken dat er geen verhoogd risico voor het ontwikkelen van een tweede maligniteit (myelodysplastisch syndroom of acute myeloïde leukemie)

Findings from a systematic review and safety meta-analysis of placebo-controlled randomised controlled studies with a median follow-up ranging up to 78 months

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Topics:

Anticancer agents & Biologic therapy; Epidemiology/Etiology/Cancer Prevention; Gynaecologic malignancies; Haematologic malignancies

Although PARP inhibitors interfere with DNA repair processes leading to warnings in terms of risk for developing second primary malignancies, findings from a systematic review and safety meta-analysis of placebo-controlled randomised controlled studies are reassuring for patients starting PARP inhibitors in the first-line setting that there is no increased risk of developing second primary malignancies. Studies included in that analysis had a median follow-up ranging from 3.8 to 78 months. The results are published by Prof. Joachim Alexandre of the Normandie University, UNICAEN, CHU de Caen Normandie in Caen, France and colleagues in August 2021 issue of the *Annals of Oncology*.

In another letter to the editors published in the same issue of the *Annals of Oncology*, a group of researchers led by Dr. Jean-Baptiste Micol of the Gustave Roussy, Université Paris-Saclay in Villejuif, France reported findings from a series of retrospectively identified 20 patients with myelodysplastic syndrome or acute myeloid leukaemia occurring during or after administration of PARP inhibitor. They wrote that their data support the hypothesis that PARP inhibitors may act by exerting a selective pressure that boosts clonal expansion, especially *TP53* and *PPM1D* mutations.

Dr. Micol and colleagues aimed to describe the prevalence and evolution of clonal haematopoiesis and therapy-related myeloid neoplasms following treatment with PARP inhibitor in patients with ovarian cancer to better understand the molecular mechanisms underlying development of haematological disease. Their analysis followed a recent safety meta-analysis of randomised controlled studies and a retrospective study of the WHO pharmacovigilance database, published earlier this year in the *Lancet Haematology*, which indicated an increased risk of therapy-related myeloid neoplasms after administration of PARP inhibitors.

In the series of 11 patients with secondary myelodysplastic syndrome and 9 patients with secondary acute myeloid leukaemia that Dr. Micol and colleagues described in the *Annals of Oncology*, median duration of previous treatment with PARP inhibitor was 17 months (range, 3 to 57). Therapy-related myeloid neoplasms occurred 2 years (range, 0.4 to 4.8) after initiation of PARP inhibitor and 1.6 months (range, 0.4 to 17.6) after discontinuation of PARP inhibitor.

All patients had unfavourable karyotypes, of which 19 of 20 (95%) had complex karyotypes and 10 of 12 (83%) harboured mutations in the DDR genes. Despite 11 patients (55%) with ovarian cancer being in complete remission, median overall survival was 4.3 months.

The study team further identified 36 patients with ovarian cancer with or without maintenance treatment with PARP inhibitor who were free of haematological disease to compare occurrence of clonal haematopoiesis. Median duration of treatment with PARP inhibitor was 11.2 months (range, 0.4 to 45.8) and median time between initiation of PARP inhibitor and next-generation sequencing was 8.5 months (range, 1.1 to 15.6). No significant differences in terms of patient characteristics were found between the two groups.

Clonal haematopoiesis was found in 14 of 18 patients (78%) who received maintenance treatment compared to 7 of 18 patients (39%) without maintenance treatment with PARP inhibitor ($p = 0.018$). Twelve patients (67%) treated with PARP inhibitor harboured mutations in the DDR pathway compared to 3 of 18 patients (16.7%) without maintenance treatment with PARP inhibitor ($p = 0.002$).

The study team sequenced 9 paired specimens before and after treatment with PARP inhibitor showing that mutations emerged or expanded during the treatment with PARP inhibitor.

Dr. Micol and colleagues commented that the clinical benefit of maintenance treatment with PARP inhibitor for ovarian cancer is not questionable, but their data

raise the question of identification and potential preventive strategies in patients who are considered at high risk of developing therapy-related myeloid neoplasms.

Prof. Alexandre and colleagues systematically reviewed placebo-controlled randomised clinical studies with PARP inhibitors administered in adult patients. They selected for the analysis 23 placebo-controlled randomised studies involving 8857 patients of whom 5492 patients (62%) were randomised to the PARP inhibitor arms and 3365 patients (38%) in the placebo arms.

Overall, 51 second primary malignancies were reported in the PARP inhibitor arms (0.9%) and 24 second primary malignancies in placebo arms (0.7%). Exposure to PARP inhibitor was not associated with an increased risk of developing second primary malignancy versus placebo, with a median follow-up ranging from 3.8 to 78 months (Peto OR 1.13, 95% confidence interval 0.70-1.83; p = 0.62) with no heterogeneity across studies.

According to the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium tool, all 23 studies included in that analysis were rated as having unclear risk of bias.

Although the study team acknowledged several limitations of their analysis, such as being conducted at study-level, non-availability of individual safety data, use of pooled data from studies with different length of follow-up, and inclusion of patients with initial and relapsed cancers, the authors concluded that their findings do not suggest a need for additional close monitoring of patients treated with PARP inhibitors in terms of risk for developing second primary malignancy.

References

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