PARP inhibitor era: current status and future directions

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Received 13 March 2023
Accepted 13 March 2023
Published Online First 23 March 2023

Caruso and colleagues nicely detail the clinical narrative for ovarian cancer treatment in the era of anti-angiogenesis and poly (ADP-ribose) polymerase inhibitor (PARPi) therapy.[1] The authors outline a clinical decision algorithm based on results from recent trials, molecular annotation, and emerging science, describing probabilistic models of innate and acquired drug resistance. As is clearly presented, the next wave of clinical trials will be prospectively addressing important hypotheses raised from these initial observations in an attempt to better define treatment strategies that optimize care.

One interesting concept raised by the authors is treatment de-escalation. They focus on clinical trials attempting to restructure primary chemotherapy in patients with molecularly annotated tumors. A key variable enabling this opportunity is the functionality of homologous recombination deficiency (HRD) as a predictive biomarker for PARPi therapy. Paralleling early clinical development of all three available PARPis in the recurrent disease setting, it is expected that induction therapy will induce an objective response. The degree to which this observation will change primary therapy remains to be seen. However, another de-escalation opportunity exists in the maintenance phase for similarly selected patients completing primary therapy. In each of the three single-agent phase III trials (SOLO1, PRIMA, ATHENA-mono), disease progression event rates in the control and experimental groups achieved unity several months before the completion of the prescribed therapy. In addition, 5–20% of HRD test-positive patients progressed within 6 months of initiating therapy.[2 3] Both scenarios highlight the critical need for functional assays of homologous recombination compliancy, where treatment de-escalation could be executed to limit unnecessary treatment or perhaps enable alternative therapy addressing resistance before objective progression.

Throughout the paper the authors also provide an insight into treatment strategies in various clinical scenarios, balanced by regulatory approvals and constraints that variably exist around the world. For instance, re-use of bevacizumab in second or later lines of therapy following initial treatment is not universally approved, despite level 1 evidence of efficacy. This puts the clinician at odds with available clinical data and can impact decision-making in anticipation of need for later use. This is unfortunate since the best chance for lasting treatment success or 'cure' is in the primary disease setting. One situation, also raised by the authors, is the indication for bevacizumab in the primary setting. Current dose and duration of therapy for this agent is based on GOG-0218, a placebo-controlled three-arm phase III trial that demonstrated in a population of patients with optimal (except complete gross resection) and sub-optimally debulked stage III/IV ovarian cancer.[4] Both this trial and another (ICON7) demonstrated significant improvement in progression-free survival; however, only a 'high-risk' cohort in the latter trial (not confirmed in GOG-0218) suggested a benefit in overall survival.[5] This sub-group, while pre-defined (and adjusted), was non-analytical and should have been considered only hypothesis-generating. To bolster the risk of over-interpretation, a sub-group analysis of patients in GOG-0218 showed that the stratification variable of stage III, less than 1 cm residual disease had the lowest hazard ratio for bevacizumab treatment effect. Further, in a sub-group analysis of PAOLA1 using ICON7 'high-risk' definitions, the greatest impact for the olaparib/bevacizumab combination was in the low-risk cohort. Interpretation of clinical trials should follow valid statistical principles and optimized therapy should be leveraged as early as possible.

Nevertheless, further expansion of our understanding of key driving factors in the tumor microenvironment along with macro-enviroment tumor surveillance will drive future clinical trials, providing the opportunity to dynamically customize care for our patients, leveraging new assets as they are discovered and rigorously interrogated.

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Funding The author has not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Linked

► http://dx.doi.org/10.1136/ijgc-2022-004149

To cite: Coleman RL. *Int J Gynecol Cancer* 2023;**33**:444–445.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

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