Therapy-related Myeloid Neoplasms Following PARP Inhibitors—Letter

Felipe Batalini[1], Lida A. Mina[1], and Alain Mina[2]

Marmouset and colleagues describe an association between certain clinical and laboratory parameters and previous exposure to PARP inhibitors (PARPi; ref. 1). There are however important confounders, perhaps inappropriately correlating therapy-related myeloid neoplasms (t-MN) to PARPi, that are important to highlight.

The authors report a cumulative incidence of t-MN of 3.5% and a 66% increase in t-MN but it was not reported whether the number of patients seen for ovarian cancer have remained the same. Also, patients with ovarian cancer are exposed to platinum agents and taxanes, thus the attribution of t-MN to PARPi is unclear. Because chemotherapies are also associated with secondary malignancies, the evaluation of prior agents is critical for the correct attribution of t-MN to PARPi.

The authors compare features of PARPi-exposed patients with t-MN referred to hematology consultation for cytopenia with those who did not develop t-MN. Patients with t-MN had a longer exposure to PARPi, lower platelet levels, and more cytopenias. While the discussion includes the fact that the longer time observed can explain the higher event rate, it can be artificial that thrombocytopenia and cytopenias were associated with t-MN, because these are laboratory manifestations of the disease itself. From a prospective perspective, all cytopenias should be monitored and evaluated, particularly those that are more prolonged.

Associations between clinical outcomes and baseline demographic and molecular characteristics need to take into account the historical context of clinical practice. Twenty-four PARPi-naïve patients with t-MN after ovarian cancer diagnosis were identified and compared with 13 patients with post-PARPi t-MN, and the most significant difference was enrichment of *BRCA1/2* carriers among those who received PARPi, which likely reflects the fact that initial studies with PARPi were restricted to *BRCA1/2* carriers (2). From 69 patients with post-PARPi t-MN were identified from a national database, those treated with olaparib had a more complex karyotypes and worse overall survival compared with other PARPi. All these are confounded by the fact that olaparib's initial approval included heavily pretreated *BRCA1/2* carriers while newer agents are used in earlier lines and include *BRCA1/2* wild-type patients (3, 4).

The OlympiA trial analyzed 1,836 patients with g*BRCA1*/2m and high-risk early breast cancer. After 3.5 years of median follow-up, the rate of myelodysplastic syndrome/acute myeloid leukemia was 0.3% with placebo and 0.2% with olaparib (5). Longer follow-up will be necessary to establish or disprove the strength of the link between PARPi and t-MN. Ongoing efforts will be critical to identify clinical, laboratory, and molecular characteristics associated with the risk of t-MN, and to distinguish the effects of PARPi from chemotherapy on hematopoietic stem cells.

[1]Mayo Clinic, Phoenix, Arizona. [2]NIH, Bethesda, Maryland.

Corresponding Author: Felipe Batalini, Mayo Clinic, Phoenix, AZ 85054. E-mail: Batalini.Felipe@mayo.edu

Clin Cancer Res 2023;29:1157

doi: 10.1158/1078-0432.CCR-22-3510

Authors' Disclosures

F. Batalini reports personal fees from Curio Science, Novartis, Grail, and Daiichi Sankyo outside the submitted work. No disclosures were reported by the other authors.

Received November 11, 2022; revised December 21, 2022; accepted January 25, 2023; published first March 14, 2023.

References

1. Marmouset V, Decroocq J, Garciaz S, Etienne G, Belhabri A, Bertoli S, et al. Therapy related myeloid neoplasms following PARP inhibitors: real-life experience. Clin Cancer Res 2022;28:5211–20.
2. Moore K, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018;379:2495–505.
3. González-Martín A, Pothuri B, Vergote I, Christensen RD, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2019;381:2391–402.
4. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med 2019;381:2403–15.
5. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. N Engl J Med 2021;384:2394–405.