Gynecologic Oncology Reports 35 (2021) 100710

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

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Taking the next step in PARP-inhibitor clinical trials in older women with ovarian cancer – Staging the aging

Dear Editor,

We read the recently published *post hoc* exploratory analysis of the ARIEL3 study (Colombo et al., 2020) conducted by Colombo and colleagues with great interest and would like to congratulate the authors for their important contribution to the field of older patients with ovarian cancer. The authors focused on the effect of age on efficacy, safety, and patient-centered outcomes in women with ovarian cancer receiving rucaparib maintenance treatment. On the experimental arm, 365 patients were included in total; 237 patients aged <65, 113 aged 65–74, and 25 women ≥75 years. All patients had Eastern Cooperative Oncology Group (ECOG) performance status 0–1. The median progression-free survival (mPFS) benefit was 5.7 months in the younger age group (11.1 vs 5.4 months; hazard ratio [HR]: 0.33 [95% confidence interval (95% CI): 0.25–0.43]; $p < 0.0001$) and 3 months in the older 8.3 vs 5.3 months; HR 0.43, 95% CI: 0.29–0.63; $p < 0.0001$); the oldest age group experienced no significant benefit (9.2 vs 5.5 months; HR 0.47, 95% CI: 0.16–1.35; $p = 0.1593$). All patients experienced toxicities at any grade. Grade 3 ≤ toxicities occurred in 54% in the younger age group and 69.9% in the older age group. Dose reduction was registered in 46.8% of younger and 70.8% of older patients. Treatment discontinuation occurred in 11.9% of younger and 21.2% in older age groups. The safety of rucaparib was similar across the age groups according to the authors. Patient-centered outcomes were reported as similar between the age groups. However, it seems that older patients tend to derive shorter mPFS benefit and experience more toxicity than younger women. In the oldest subgroup aged 75 ≤ no conclusion can be drawn because of the low number of the patients.

Currently, oncologists are treating older or/and vulnerable patients with PARP-inhibitors based on data extrapolated from young and healthy cohorts of patients (Colombo et al., 2020; Liposits et al., 2020; Liposits et al., 2018). However, older patients tend to experience more toxicity (Wildiers and de Glas, 2020) and derive shorter mPFS benefit from PARP-inhibitor treatment (Colombo et al., 2020; Liposits et al., 2020; Liposits et al., 2018). Many of them are dealing with pre-existing comorbidities, and polypharmacy, thus, the increased pill burden and potential drug interactions may increase the harms of the PARP-inhibitor treatment and leads to lower therapeutic index. Furthermore, given the cost of PARP-inhibitors, the economic burden on healthcare system, and financial toxicity, patients may experience important issues. Therefore, the efficacy of PARP-inhibitors should be extensively investigated in "real-world" older women with ovarian cancer.

The appropriate way to do that is the implementation of the "staging the aging" concept; the comprehensive assessment of older patients, termed geriatric assessment (GA). GA can identify deficits and abnormalities not found by past medical history or routine physical examination (Jolly et al., 2015), can help to stratify older patients according their fitness, and may guide cancer treatment (Mohile et al., 2018). Furthermore, GA can estimate survival, avoid overtreatment, assist decision making, predict treatment-related complications and toxicities, and contribute to physical and mental well-being in older patients with cancer (Mohile et al., 2018).

Unquestionably, the authors of ARIEL3-trial have made an important contribution to the field of older patients with ovarian cancer and their efforts are highly appreciated by the geriatric oncology community. The next step forward should be designing randomized controlled trials dedicated to older and vulnerable patients with ovarian cancer incorporating the principles of geriatric assessment and patient-centered outcomes.

Incorporating geriatric assessment in clinical trials is feasible and the benefits of this approach are undeniable (Soto-Perez-de-Celis et al., 2020). Furthermore, geriatric assessment has shown not to be time-consuming (Hamaker et al., 2017), and the implementation of a novel, pragmatic study design is reasonable and cost-effective (Nipp et al., 2016). We would like to encourage the authors to continue their important contribution in older patients with ovarian cancer, by taking this next step.

Author contribution: GL, SLM

Funding

GL received no funding for this work. SML is supported by the NCI Cancer Center Support Grant (P30CA008748).

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

https://doi.org/10.1016/j.gore.2021.100710

Received 9 December 2020; Received in revised form 21 December 2020; Accepted 12 January 2021

Available online 24 January 2021

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