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EDITORIAL

Recurrent ovarian cancer in the era of poly-ADP ribose polymerase inhibitors: time to re-assess established clinical practices

As oncologists reflecting on the past 20 years of medical oncology, we recognize many therapeutic advances that have changed our practice and, above all, saved patients' lives. For epithelial ovarian cancer (EOC), the introduction of poly-ADP ribose polymerase inhibitors (PARPi) is one such historic achievement, comparable with the implementation of anti-human epidermal growth factor receptor 2 (HER2) antibodies for the treatment of HER2-positive breast cancer.

The PARPi revolution started in the setting of recurrent EOC, when three molecules—olaparib, niraparib and rucaparib administered as maintenance therapy—demonstrated remarkable effectiveness in prolonging time to progression in platinum-responsive patients.[1-4] Carriers of *BRCA1* or *BRCA2* mutations benefitted the most from PARPi. In particular, olaparib provided a clinically meaningful gain in survival over placebo in patients with recurrent EOC and a somatic or germline mutation in *BRCA* genes.[5] In these studies, a response to platinum-based chemotherapy was the main requisite to receive PARPi maintenance therapy.

Given their effectiveness as second and further lines of therapy, PARPi were tested up front after response to platinum therapy. Olaparib was the first PARPi to demonstrate a clear benefit by prolonging time to recurrence in *BRCA1/2*-mutated EOC patients, according to the SOLO1 trial.[6] Moreover, olaparib showed effectiveness in association with bevacizumab for the first-line treatment of EOC with a homologous recombination deficiency (HRD), defined as a tumor harboring a *BRCA* mutation or an HRD score of 42 or higher on the myChoice HRD Plus assay (Myriad Genetic Laboratories, Salt Lake City, UT).[7] Finally, niraparib has been approved by both the US Food and Drug Administration and the Europen Medicines Agency for newly diagnosed EOC irrespective of *BRCA* mutation status, broadening the spectrum of patients who can receive a PARPi after diagnosis.[8,9]

In the upcoming months, as we scrutinize the data from the reported trials, we will discuss the impact of first-line PARPi maintenance therapy on overall survival. Meanwhile, in daily practice we are facing an increasing number of EOC patients in progression after PARPi. Management of these patients is currently at the focus of attention, for both clinicians and researchers, since they seem to benefit less than expected from platinum-based therapy, with first preliminary evidences from second-line studies supporting a possible cross-resistance between PARPi and platinum agents.

Ovarian cancer is considered highly chemosensitive, in particular to platinum salts. In fact, the period between the last platinum dose and the evidence of relapsing disease, the so-called platinum-free interval (PFI), has been widely used as a surrogate of platinum sensitivity to guide successive treatment choices. For patients with a PFI $\geq$6 months (i.e. disease recurrence 6 or more months after the last platinum dose), platinum-based chemotherapy is used to be rechallenged again. Despite the fact that the clinical utility of PFI has been previously questioned and integrated within the concept of treatment-free interval since the introduction of maintenance strategies,[10] we should recognize that its use in clinics has never been abandoned. One explanation for the continued use of PFI is its ability to predict benefit from a rechallenge with platinum, even in patients undergoing maintenance therapy with bevacizumab. This evidence comes from the MITO 16b trial of second-line platinum therapy plus bevacizumab beyond progression that has been recently published in the *Lancet Oncology*.[11] The study found that the effectiveness of platinum chemotherapy, with or without bevacizumab, seems to not have been affected by the previous anti-angiogenic therapy. Moreover, the benefit of bevacizumab on progression-free survival was similar to that reported in the OCEANS trial, which excluded patients who had previously been treated with bevacizumab.[12]

Our own clinical experience and initial observations reported in the literature suggest that *BRCA*-mutated tumors progressing during PARPi may have cross-resistance to platinum. For this reason, we question the usefulness of the PFI in this clinical setting. Recently, at the 2020 annual meeting of the European Society for Medical Oncology, a secondary analysis of post-progression outcomes of patients in the SOLO2 trial was presented. With major limitations due to the unbalance between the two treatment's arms at olaparib/placebo progression, patients in the placebo arm seemed to benefit the most from a rechallenge with platinum, while those who received olaparib did worse, with median times to second progression of about 14 months versus 7 months, respectively.[13] These findings are in accordance with our MITO retrospective study of 234 patients with *BRCA1/2*-mutated recurrent EOC receiving olaparib as for clinical practice.[14] The study found a lower than expected response rate to subsequent platinum therapy that, in patients with a PFI >12 months at the time of recurrence to olaparib, was only about 22%. A similar finding has been presented by Baert et al.[15] in a mixed population of patients treated with olaparib and niraparib

who showed a low response to subsequent platinum when compared with matched PARPi naive controls.

From a biological point of view, the molecular drivers of resistance to PARPi are not fully known, but are thought to involve the restoration of homologous recombination proficiency through reverse mutations in *BRCA1*, *RAD51C* or *RAD51D*, demethylation of the *BRCA1* promoter and overexpression of *ABCB1*, which encodes a transmembrane drug exporter.[16] Moreover, PARPi and platinum agents share several mechanisms of resistance that can explain the cross-resistance to the two drugs.

Given the emerging evidence that PFI is unable to predict benefit from additional platinum therapy, at least in patients with *BRCA*-mutated recurrent EOC progressing during PARPi, future studies aimed to test new agents that could be able to overcome cross-resistance mechanisms are needed, especially in the recurrent setting where patients receive PARPi until disease progression developing a possible 'primary resistance'.

By contrast, in patients receiving PARPi after first-line platinum therapy, disease recurrence can be detected after the completion of the 24 or 36 months of PARPi adjuvant therapy and they could continue to benefit from platinum and PARPi in a sort of 'secondary resistance'; this issue is currently under investigation in the OReO trial (NCT03106987).

Waiting for the results of new investigational drugs, the treatment options yet available should be reassessed in the recurrent setting in order to define the best treatment sequence. It appears useful to re-test if the addition of bevacizumab can enhance the platinum performance, as previously demonstrated in PARPi-naive patients.[12,17,18] New studies should also analyze whether non-platinum-based chemotherapy, such as trabectedin combined with the pegylated liposomal doxorubicin, performs better than platinum-based chemotherapy, a possibility considering their different mechanisms of action on tumor cells.[19] Finally, a secondary tumor debulking could theoretically reduce the amount of drug-resistant tumor cells, improving the effectiveness of subsequent treatments. Thus, the importance of secondary cytoreductive surgery that should be considered a standard of care in platinum-sensitive recurrent EOC after the DESKTOP III and the SOC-1 trials[20,21] could be further reinforced in the post-PARPi scenario, in particular for those patients receiving PARPi in a first-line setting and who experience a recurrence after the end of therapy. Although reasonable, this hypothesis needs a prospective validation.

In conclusion, we believe that many of the groundbreaking achievements in the treatment of EOC that we considered established, in particular the use of PFI, the options of platinum and non-platinum therapy for recurrent disease, and the addition of bevacizumab to improve the activity of platinum-based chemotherapy, need to be reassessed for patients previously treated with PARPi.

Further secondary analyses of post-progression outcomes from the pivotal PARPi trials could identify new predictive factors of platinum benefit other than PFI; these analyses should be encouraged as they are hypotheses generating for future trials. Furthermore, more data on post-progression outcomes for *BRCA* wild-type patients in progression to PARPi are needed, since these patients are considered less chemosensitive compared with the *BRCA*-mutated counterpart and thus the benefit of post-progression therapies could be even worse.

Hopefully, novel treatment combinations that could overcome resistance to PARPi and platinum salts are under investigation and they could fulfill the unmet clinical need in this setting. In particular, small molecules targeting checkpoint proteins activated in response to replication stress, like ATR, CHK1 and WEE1, can have a synergistic activity with PARPi, as they could overcome key mechanisms of PARPi resistance while PARP inhibition sensitizes to ATR/CHK1/WEE1 inhibition.[22] Even the combination of PARPi with PI3K inhibitors has shown a synergistic activity in patients with *de novo* or acquired HR proficient EOC, and the association of olaparib plus alpelisib, a selective α-specific PI3K inhibitor, is under evaluation in a randomized phase III trial (NCT04729387).

Preclinical studies will also play a crucial role in our understanding of the mechanisms of PARPi resistance, and the inclusion of translational research in future clinical trials will be decisive.

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