Editorials

Chemotherapy-free treatments: are we ready for prime time?

Epithelial ovarian cancer (EOC) is most frequently diagnosed at an advanced stage and, despite high response rates to initial taxane-platinum-based chemotherapy, more than 70% of patients will develop recurrent disease and will receive several chemotherapy treatments. At present, the 5-year overall survival (OS) for women diagnosed with stage III–IV disease is ∼46% and patients with genetic impairments of DNA repair pathways [BRCA mutations and in general homologous recombination deficiency (HRD)] live longer and possibly will receive even more lines of chemotherapy [1].

The cumulative toxicity of chemotherapy, particularly if platinum-based, in terms of neurotoxicity, nephrotoxicity and myelotoxicity, is a limiting factor in patients scheduled to receive multiple lines of treatment. Moreover, allergic reactions to platinum, whose frequency increases with multiple treatment lines, is a great challenge, particularly in long-surviving patients. Finally, the risk of secondary tumors, particularly in HRD patients, seems to be related to the number of previous chemotherapy lines—and platinum in particular—thus introducing important concerns on the long-term safety of patients [2].

Based on these issues, the development of active and well-tolerated chemotherapy-free regimens may provide an attractive alternative for patients who will receive multiple lines of therapy.

The initial discovery that poly-adenosine diphosphate [ADP]-ribose polymerase (PARP) inhibitor enhance anticancer activity *in vitro* in BRCA mutated (BRCAmut) cancers led to the initial testing of PARP inhibitors as single agents and as maintenance treatment in BRCAmut cancers, platinum-sensitive and platinum-responsive, and their subsequent regulatory approval in these settings [3]. More recently, this strategy has been broadened to also include all patients in the platinum-sensitive setting regardless of the HRD signature.

PARP inhibitors work based on the concept of synthetic lethality, which refers to the presence in the cell of an inherent vulnerability (HRD) that is by itself not lethal, but when combined with another genetic event may become lethal. Some conditions, such as hypoxia, may artificially create or enhance a condition of genomic instability. Tumor cells exposed to chronic hypoxia following anti-angiogenic treatment [4] have been shown to acquire defects in homologous recombination (HR) DNA repair, through downregulation of HR repair proteins such as BRCA1 and RAD51, resulting in an increased sensitivity to PARP inhibition [5].

Cediranib, a potent antiangiogenic tyrosine kinase inhibitor of VEGFR-1/2/3 has demonstrated significant antitumor activity and delayed tumor progression when given as maintenance therapy in women with recurrent ovarian cancer [6]. The primary analysis of a randomized phase II trial in 90 recurrent platinum-sensitive ovarian cancer patients suggested that the combination of cediranib and olaparib, a PARP inhibitor [1], was synergistic with a 6-month increase in progression-free survival (PFS) compared with olaparib alone [7].

In a retrospective analysis of the BRCAmut and BRCAwt subgroups, the difference in PFS was greatest in BRCAwt women (HR 0.32 compared with HR 0.55 in BRCAmut). Grade 3 or higher adverse events were observed in 70% of patients treated with the initial dose of cediranib 30 mg in the combination, the most frequent being diarrhea, fatigue and hypertension. However, compliance with treatment was very high (97%) due to dose reduction of cediranib in 77% of patients [7].

In the update analysis at a median follow-up of 46 months published in this issue, Liu et al. [8] confirmed a significantly longer median PFS with cediranib/olaparib compared with olaparib alone of 16.5 versus 8.2 months (HR 0.50; $P = 0.007$). Subset analyses in BRCAwt/unknown patients demonstrated a statistically significant improvement in PFS (23.7 versus 5.7 months, $P = 0.002$) and OS (37.8 versus 23.0 months, $P = 0.047$), without OS differences in the overall study population (44.2 versus 33.3 months, HR 0.64; $P = 0.11$).

This study reported that a chemotherapy-free treatment in a population of platinum-sensitive recurrent EOC can produce the same oncologic outcomes interms of PFS and OS of the most commonly used chemotherapy treatments [9], thus representing a potentially new strategy. Based on the same assumptions of other chemotherapy-free combinations, the ENGOT-OV24/AVANOVA study is testing the combination of bevacizumab and niraparib in the platinum-sensitive setting (NCT02354131).

Immune checkpoint inhibitors have led to important clinical advances in the treatment of some solid tumors, but unfortunately have reported limited single-agent activity in ovarian cancer leading to the opportunity to test combination strategies [10]. The possibility of combining PARP inhibitors and anticheckpoint blockade appears very promising; preclinical studies showed DNA damage promotes neoantigen expression [11] and it is possible that increased DNA damage by PARPi would yield greater mutational burden and expand neoantigen expression, leading to greater immune recognition of the tumor.

The TOPACIO trial [12] has tested the combination of niraparib and pembrolizumab in a population of triple-negative breast cancer and recurrent platinum-resistant EOC (NCT02657889). Among the 60 evaluable EOC patients, an overall response rate (ORR) of 25% and a disease control rate of 68% were reported. Moreover, responses were not dependent on biomarker status; ORR was 26% in BRCAwt patients and 29% in patients with HRD-positive tumors. The combination was well-tolerated with an incidence of grade 3/4 thrombocytopenia (9%), anemia (19%) and neutropenia (6%).

With the same strategy, the combination of durvalumab and olaparib registered a disappointing 15% ORR in a population of 34 recurrent, mainly platinum-resistant, heavily pretreated EOC patients [13] while an outstanding 71% RR was reported with the same combination in a population of recurrent, platinum-sensitive BRCAmt EOC patients. This suggests that appropriate selection of the setting of disease and patient population is important [14].

At present, chemotherapy-free treatments are a clinical reality: olaparib has been approved by FDA as a single agent for the treatment of BRCAmut-EOC treated with at least three previous chemotherapy lines. Rucaparib, another PARP inhibitor, has been approved by FDA and EMA in the same setting in a less pretreated BRCAmut population (at least two previous chemotherapy lines) based on the results of two phase II studies reporting ORR in line with that achieved with standard chemotherapy and a completely different toxicity profile [15].

Nevertheless, what clinicians and patients should be conscious of is that chemotherapy-free treatments still present some tricky and sometimes life-threatening toxicities that may significantly impact patients quality of life, which could greatly reduce their compliance to treatment (particularly in the case of orally administered drugs) with potential consequences on efficacy.

Toxicity still remains a concern with respect to these new oncologic treatments: after definitively abandoning the initial idea they lacked toxicity; the scientific community has learned in the last years to manage different, but not less impactful, toxicities of PARP inhibitors, antiangiogenic agents and immunocheckpoint inhibitors. There is sometimes the clear sense that phase I trials fail to identify the appropriate dosage, and that often these drugs have been developed according to the old criterium of the maximum tolerated dosage, rather than minimum effective dose, which avoids any further consideration of flat dose immunotherapy, which appear sometimes senseless in addition to being highly costly [16].

Finally, the appropriate setting of disease and patients selection remains mandatory even for chemotherapy-free strategies: it is very difficult to imagine in the future that carboplatin-paclitaxel will be deleted from first-line treatment of ovarian cancer, while it appears much more convincing that the combination of a checkpoint inhibitor and a PARP inhibitor or an anti-VEGF and a PARP inhibitors may be substitutes for chemotherapy in the treatment of recurrent disease, especially in later lines.

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