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Ovarian cancer treatment is evolving: more choices, more chances

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Up until the last Ovarian Cancer Consensus Conference in 2015,[1] standard treatment for advanced-stage ovarian cancer was established to be intravenous 3-weekly carboplatin and paclitaxel, with the addition of maintenance bevacizumab considered as an acceptable alternative. No data about predictive biomarkers of response were available, and neither BRCA1/2 mutation was considered at that point in the decision process.

Soon afterwards, things changed considerably, and after the publication of the SOLO 1 trial, the addition of olaparib maintenance after standard carboplatin and paclitaxel has allowed BRCA1/2-mutated (mBRCA) patients to achieve a dramatic increase in progression-free survival, with data about overall survival still pending.[2] Moving further to enlarge polyadenosine diphosphate ribose polymerase inhibitors (PARP-i) maintenance to the wild-type BRCA (wtBRCA) ovarian cancer population, other randomized controlled trials have been conducted. In the PRIMA study, niraparib was investigated in all comers with ovarian cancer at primary diagnosis, and it was effective independently of BRCA status (HR for disease progression or death 0.62, 95% CI 0.50 to 0.76). However, the magnitude of benefit was higher in mBRCA patients (HR 0.40, 95% CI 0.27 to 0.62) and in homologous recombination-deficient (HRD) patients (HR 0.50, 95% CI 0.31 to 0.83).[3] These results will probably encourage the use of PARP-i in all advanced-stage ovarian cancer patients in the primary setting, regardless of BRCA mutational status.

In this context, the role of anti-angiogenetic drugs is called into question. The PAOLA1 study[4] has shown that the association of standard carboplatin and paclitaxel with olaparib and bevacizumab results in a 6-month increase in progression-free survival, compared with bevacizumab alone, in all advanced-stage ovarian cancer patients. Again, the greatest benefit was found in mBRCA women (HR 0.31, 95% CI 0.20 to 0.47), followed by the HRD population (HR 0.33, 95% CI 0.25 to 0.45). Nonetheless, different to the PRIMA trial, the HR-proficient/unknown population did not gain any benefit when both treatments were given together (HR 0.92, CI 95% 0.72–1.17).

In the light of these three studies, one of the most frequent questions raised during our clinical practice is whether to use both treatments as front line, or leave bevacizumab for recurrence. Clarifying this issue is beyond our capability, but the choice of primary treatment will certainly influence the type of subsequent treatment at recurrence. Indeed, although the concept of platinum sensitivity has been revised, due to the advance of maintenance treatment, the choice of subsequent therapy is rarely based on molecular tumor assessment, but rather on platinum-free interval and patients' characteristics.

In the pre-PARP-i era, any patient with ovarian cancer receiving standard carboplatin and paclitaxel ± bevacizumab had a 20%–25% probability of recurrence as partially platinum-sensitive (defined as a platinum-free interval of between 6 and 12 months) and a 15%–20% probability of recurrence as platinum-resistant (defined as a platinum-free interval of <6 months).[5] After the introduction of olaparib maintenance as part of the first-line treatment, mBRCA patients have a 10% risk of developing a partially platinum-sensitive relapse, and a 10% risk of developing a platinum-resistant relapse. The same outcome seems to occur when giving niraparib or olaparib plus bevacizumab in the whole ovarian cancer population. In other words, the use of PARP-i reduces the rate of patients who relapse as platinum-resistant or partially platinum-sensitive, and increases the rate of patients who experience a fully platinum-sensitive relapse. While awaiting a decision by the regulatory authorities, a platinum-based treatment followed by PARP-i maintenance (in responsive cases) is the first choice for recurrent platinum-sensitive and partially platinum-sensitive patients, especially those with mBRCA status. Indeed, any PARP-i maintenance has shown a clear improvement in median progression-free survival, with respect to any other treatment, but it also assures a lower but nonetheless significant progression-free survival benefit in both wtBRCA/HR-deficient and HR-proficient patients. The issue of whether to treat platinum-sensitive and partially platinum-sensitive cases with PARP-i after first-line PARP-i is still under investigation and is currently impossible to investigate outside a clinical trial. Collaterally, in the platinum-sensitive and partially platinum-sensitive population, the role of secondary cytoreductive surgery is nowadays

questionable, due to one randomized controlled trial (GOG213) that recently raised doubts as to its efficacy.[6] However, although it is reasonable to consider that surgery is not beneficial for all recurrent ovarian cancer patients as a whole, in the era of personalized therapy, secondary cytoreductive surgery could be suitable for some subgroups of women, such as the mBRCA ovarian cancer recurrent population.[7]

If maintenance with bevacizumab is a straightforward option in women who received front-line PARP-i maintenance, it would also seem to be a reasonable alternative in naïve wtBRCA patients. In fact, PARP-i trials included only patients with favorable profiles, such as response at the last platinum treatment, and/or limited amount of disease. In the same platinum-sensitive and partially platinum-sensitive population, the combination of trabectedin and pegylated liposomal doxorubicin could be considered, as this showed a median progression-free survival of 11 months,[8] according to the NIMES study, a non-interventional multicenter, European study that evaluated this schedule in real-life clinical practice. Interestingly, similar results were reported in the bevacizumab trials at relapse (OCEANS, 13 months; GOG213, 14 months)[9 10] in which patients' BRCA status was also unknown. Furthermore, it should be highlighted that almost 40% of the patients in the NIMES study had previously received more than three treatments.

In conclusion, treatment options for our ovarian cancer patients have increased in recent years and allow us to offer different treatment sequences that should be based on a clinically oriented and personalized algorithm. It is unclear which is the best sequence to recommend, but it is mandatory that each patient should be given the chance to receive *each and every* treatment opportunity.

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