Changing paradigm in recurrent ovarian cancer treatment

Despite optimal surgery and appropriate first-line chemotherapy, approximately 80% of patients with epithelial ovarian cancer (OC) will develop a disease recurrence over time. The likelihood of relapse depends on many factors, including the distribution of disease at initial presentation, the success of initial surgical cytoreduction (i.e., the presence of any residual disease), the rapidity of cancer antigen (Ca-125) resolution, and treatment response after primary therapy. OC relapse can be detected biochemically (rising of Ca-125), clinically or radiologically. Subsequent sequential treatment strategies maximize quality and length of life but are not curative. Prognosis at relapse is mainly dominated by the chemosensitivity of the tumor. The choice of second-line chemotherapy depends on several factors, such as platinum-free interval (PFI), the persistence of side effects of prior treatments, the schedules and toxicity profiles of next therapies, and patient preferences.

In the last two years, the old paradigm based on PFI has been changing according to our better understanding of the biology of OC. The new paradigm considers other important patient characteristics further to PFI, including histologic subtype, BRCA1/2 mutation status, and previous first-line treatment with bevacizumab, that taken together can influence the clinician's therapeutic algorithm.

Retreatment with chemotherapy should not be routinely started in asymptomatic patients with Ca-125 progression alone. Some data in the literature have demonstrated that early initiation of chemotherapy is not associated with any survival advantage, and impacts negatively on quality of life [1]. Until now, the PFI has been considered as the main prognostic factor that guides the treatment choice at the recurrence. Therefore, time from last platinum injection to recurrence drives a treatment strategy that is based on non-platinum chemotherapy if PFI is shorter than 6 months (platinum-resistant), and on platinum-containing doublets if PFI is longer than 12 months (platinum-sensitive). When the PFI is between 6 and 12 months (partially platinum-sensitive) there is uncertainty, due to unsatisfactory results with platinum-containing doublets.

Although these definitions have been used to identify some populations of interest in some clinical trials, these categories are somewhat arbitrary, because they are related to results from retrospective assessments of literature data. The resistance to platinum-based treatment is not a categorical variable and, therefore, in real-world practice, the distinction between resistant and sensitive disease is considerably less rigid and not only linked to the PFI. However, the emergence of a maintenance approach confuses this initial definition regarding the time to progression. Therefore, the concept of PFI is no longer applicable today.

In the last consensus conference of the Gynecologic Cancer InterGroup (GCIG), held in Tokyo in 2015 (5th Ovarian Carcinoma Consensus

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CANCER BREAKING NEWS 2017;5(1):3-6
DOI: 10.19156/cbn.2017.0031

Conference) [2] the PFI paradigm was partially revisited in the light of the introduction in trials and clinical practice of new targeted agents. In particular, this arbitrary distinction collides with the increasing knowledge of the heterogeneity of the tumor histologies, but more transversely, with the different molecular abnormalities that underlie individual histologic subtypes. In proposing the best treatment for our patients, greater consideration should be given to the likelihood of response to platinum as a continuum rather than related to arbitrary time points, and probably linked to tumor biology and/or to the genomic profile at a specific time of ovarian cancer natural history. Also, resistance to treatment is often not absolute and may be partially overcome. It seems that we may consider only early and delayed relapses as a reflection of the ability of the tumor to respond to subsequent medical treatments.

Patients who have relapsed during first-line treatment (refractory) or in the few months following (resistant) represent a very heterogeneous group of various biological tumor behaviors. This condition is linked to unfavorable prognosis, so the main objective of treatment is to palliate symptoms and preserve quality of life. Monotherapy with non-platinum chemotherapy has been shown to be equally effective and less toxic compared to combination therapy. A Cochrane systematic review of trials in platinum-resistant epithelial OC found that paclitaxel, pegylated liposomal doxorubicin (PLD) and topotecan offer similar objective response rates (10-20%), a median progression-free survival (PFS) of 3-4 months, and overall survival (OS) around 12 months, with different toxicity profiles [3].

Regarding molecular targeted therapy, interesting data have been obtained in this setting with antiangiogenic compounds. In the AURELIA randomized phase III trial [4], bevacizumab in combination with standard chemotherapy (PLD, weekly paclitaxel, or topotecan) and as single agent maintenance until progression prolonged PFS (6.7 *vs* 3.4 months, hazard ratio [HR] 0.48, 95% confidence interval [CI] 0.38-0.60; $p<0.001$) but not OS, compared to standard chemotherapy. In a sub-group analysis, there was a significant OS benefit for bevacizumab in the weekly paclitaxel group (median 22 *vs* 13 months). On the basis of those results, bevacizumab was licensed in this setting [4].

Patients that relapse after 6 months are usually categorized as platinum-sensitive and partially-sensitive patients and are generally more responsive to chemotherapy. Chemosensitivity to platinum compounds is supposed to increase with a longer interval from the initial therapy. For more than 15 years, the hypothesis that a benefit could derive from the artificial extension of PFI has been largely used in clinical practice and the development of new drugs, without any prospective confirmation of its validity. While for patients with PFI >12 months the use of platinum-based combinations (carboplatin/PLD; carboplatin/paclitaxel and carboplatin/gemcitabine) is associated with a better outcome (PFS, OS) compared to non-platinum or platinum single agent treatments [5, 6]; in patients with a PFI between 6 and 12 months (partially platinum-sensitive) the efficacy of platinum doublets has been unsatisfactory. Some studies have aimed to confirm this hypothesis (MITO8, INOVATYON). MITO8, a strategy-based phase III trial that compared the sequence of platinum-based chemotherapy (PBC) followed by a non-platinum-based chemo (NPBC), recently demonstrated that the use of NPBC to artificially prolong the PFI is not beneficial for

partially sensitive relapsed OC patients [7]. This evidence confirmed that platinum-based treatment should be the first choice in this population, also because it increases the opportunity of another therapeutic option (olaparib or bevacizumab) in the case of response. In patients with platinum-sensitive recurrence that are not candidate for platinum therapy a non-platinum-containing doublet (trabectedin plus PLD) has been recently introduced in the treatment of patients with platinum-sensitive recurrent OC based on PFS (but not OS) prolongation in the OVA-301 randomized trial [8]; a subgroup analysis suggested an OS prolongation in the same population of the MITO8 trial. Interestingly, the combination of trabectedin/PLD prolonged OS in those patients that received platinum after progression. There are two established maintenance therapies for women affected by platinum-sensitive recurrent OC: bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor, and olaparib, an inhibitor of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARPi).

The activity of bevacizumab in platinum-sensitive relapsed epithelial OC was demonstrated in the OCEANS trial, which randomized 484 women with platinum-sensitive recurrent OC to carboplatin and gemcitabine plus either bevacizumab or placebo. The bevacizumab-containing combination was associated with a better objective response rate (78.5% *vs* 57.4% with the non-bevacizumab containing combination), and a longer PFS (12.4 *vs* 8.4 months), however, with no difference in OS, probably due to crossover [9]. Olaparib is the first-in-class to be licensed for the treatment of recurrent OC harboring deleterious BRCA mutations. The activity of olaparib as maintenance after response to platinum-based chemotherapy was shown in the randomized trial "Study 19" in the platinum-sensitive high grade serous relapsed ovarian, fallopian tube or peritoneal cancer. Olaparib maintenance significantly prolonged PFS, by 6.9 months (range 4.3-11.2 months, hazard ratio [HR] 0.18, 95% CI 0.10-0.31; p=0.00001), compared to placebo. A smaller but significant benefit was also seen in BRCA wild-type patients (HR 0.54, 95% CI 0.34-0.85; p=0.0075) [10]. Recently, data from another PARP inhibitor, niraparib, have been published, showing a similar positive effect in patients with BRCA mutation, but also significant activity in patients without the mutation. In the NOVA study, niraparib was effective, with statistically significant results in terms of PFS that were also seen in non-BRCA-mutated patients with a homologous recombination deficiency (HRD) profile and even in patients without HRD, although with less impressive results [11]. Thus, it is likely that treatment with PARP inhibition will be extended in clinical practice to patients that are platinum-sensitive and responsive to platinum without BRCA mutation. PARP inhibitors are undergoing clinical trials in first line, in combination with chemotherapy, and with other molecular targeted therapies. Results are expected during the next 2-5 years and will most likely extend the opportunities for the treatment of OC.

Finally, almost all clinical trials in OC grouped all histologic subtypes together. However, there are five different histologic types of OC with a different genomic landscape, natural histories and patterns of response to therapy. It is very likely that in the future different treatment strategies will be adopted for the different subtypes. In the 5th Ovarian Carcinoma

Consensus Conference, a greater clarity was "imposed" in the designing of future clinical trials, with special attention to rare histologies that have different prognoses and biological behavior [12].

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Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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