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Revolutions in cancer treatment:
how can they be integrated?

From genetics to epigenetics: targeting DNA repair defects (PARP inhibitors and homologous recombination deficiency in ovarian cancer)

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Abstract

Agents targeting DNA repair defects are a major therapeutic advance in oncology. Ovarian cancer has become the model for analysis of homologous recombination deficiency (HRD) since identification of harmful constitutional or somatic mutations of BRCA or other mutations enhanced our understanding of the HRD phenotype. Poly-ADP ribose polymerase inhibitors (PARP) inhibitors have proven to be effective in the treatment of ovarian cancer with BRCA mutations. The composite phenotypic signature with HRD identifies a population of patients with intermediate sensitivity to these agents who still receive significant clinical benefit. The significance of the benefits of PARP inhibitors in ovarian cancers without HRD is still hotly debated. Only modest clinical results have been achieved by targeting HRD deficiency through epigenetic modulation, though there is a scientific rationale to support this strategy and preclinical results have been encouraging. There is also a strong rationale for synergy between PARP inhibitors and immune checkpoint inhibitors (ICIs) with the aim of restoring tumour immunogenicity. Ovarian cancer has a very low sensitivity to anti-PD-1/PD-L1s as monotherapy, but initial results using combinations of ICIs and PARP inhibitors in patients with this form of cancer justify continued exploration of such synergies.

Agents targeting DNA repair defects are a major therapeutic advance in oncology,[1] particularly ovarian cancer, which is the model for analysis of homologous recombination deficiency (HRD). Primitive Müllerian duct adenocarcinoma, whether ovarian or peritoneal, is divided into five histological subtypes with distinct pathophysiologies.[2] A deficiency in DNA repair by homologous recombination mostly occurs in high-grade serous adenocarcinoma, which is also the most common subtype comprising 70% of ovarian cancers. This subtype also includes a range of molecular subtypes characterised by mutations of *BRCA1* and 2, *TP53*, *NF1* etc.[3]

Most patients with ovarian cancer (80%) present with advanced FIGO (International Federation of Gynecology and Obstetrics) stage 3 or 4 disease, but the prognosis varies depending on i) the quality of cytoreductive surgery, ii), the index of peritoneal carcinosis, evaluated radiologically and surgically, and iii) the CA125 level, which is a marker of shrinkage kinetics. The KELIM index of CA125 kinetics is a secondary prognostic factor that, in the neoadjuvant setting, predicts the completeness of interval debulking surgery for patients with initially non-resectable disease. Finally, the nutritional status, immune status and BRCA mutation status of patients are also major prognostic factors.

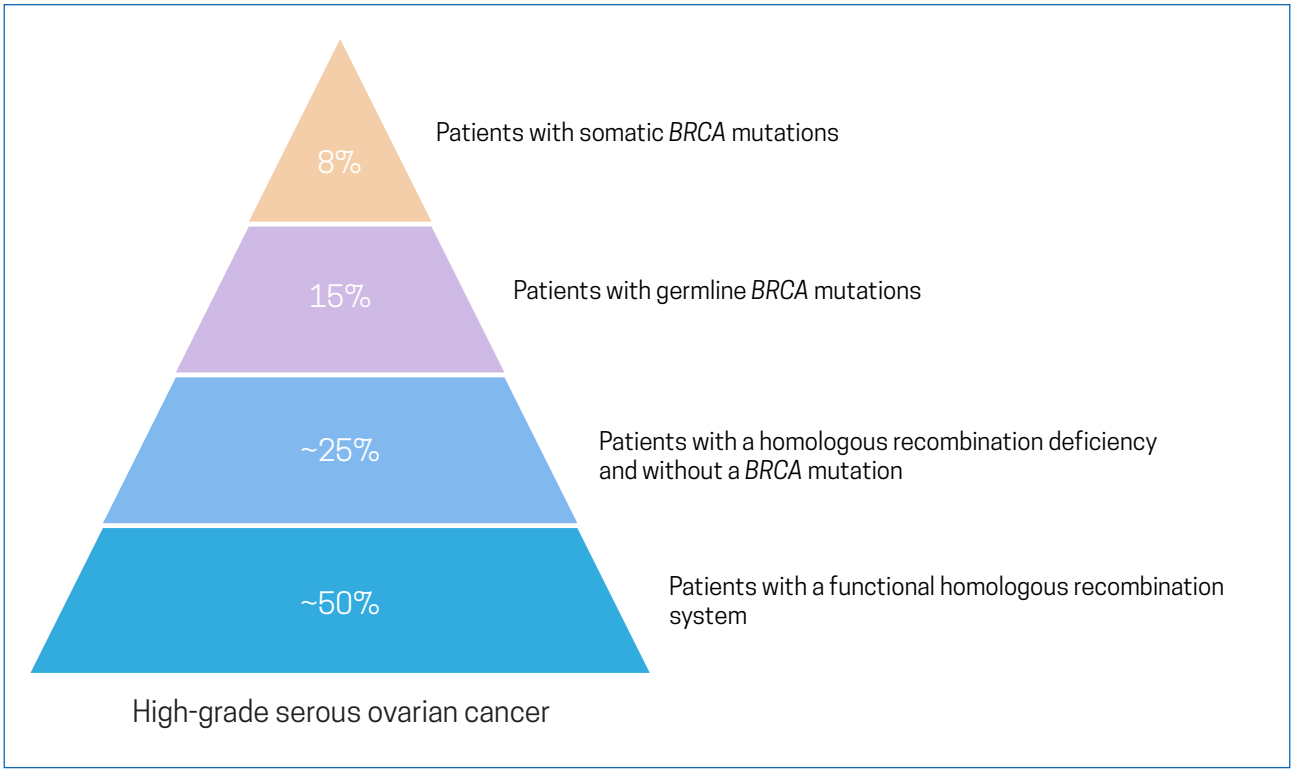
FIGO stage 3 or 4 ovarian cancer is marked by recurrence in a high proportion of patients (about 80% within 5 years). More than half of relapsing patients have platinum-sensitive disease and a minority, who have a very unfavourable prognosis, present with a resumption of tumour growth that is platinum-resistant from the outset. Very good responses have, however, been achieved for patients sensitive to the first line of treatment, particularly with poly-ADP ribose polymerase (PARP) inhibitors. The therapeutic challenge in this population of patients, who are at high risk of relapse, is to choose the optimal first line of treatment with new therapies (PARP inhibitors, immunotherapies), and identify potential therapeutic synergies before the patient develops resistance or novel mutations.

GENETICS OF OVARIAN CANCER

The discovery of the predisposing genes *BRCA1* and *BRCA2* has had a major impact on screening and prophylactic surgery for ovarian cancer, and these genes are now defining a major targeted treatment approach using PARP inhibitors.

Analysis of the *Cancer Genome Atlas* in 2011 confirmed the importance of HRD in the pathophysiology of high-grade serous ovarian adenocarcinoma.[4] The system of repair by means of homologous recombination is an important factor in tumours with *BRCA1* and *BRCA2* mutations, but methylations of *BRCA* do not cover the whole spectrum of HRD, which also involve less common mutations, including RAD51. Patients with high-grade serous ovarian cancer can be classified into different subgroups based on tumour mutations: those with sporadic constitutional or somatic *BRCA* mutations; patients with HRD but without a *BRCA* mutation, and those with other alterations. The HRD+ Myriad test makes it possible to stratify ovarian cancers based on their HRD phenotypic status; this test is valuable in predicting the response to PARP inhibitors, but it does not cover all the abnormalities in the homologous recombination system. Finally, half the patients with high-grade serous ovarian cancers have a functional homologous recombination system (**Figure 1**).

Figure 1. Genetics of high-grade serous ovarian adenocarcinoma



PARP INHIBITORS AND OVARIAN CANCER

PARP inhibitors do not act by targeting the abnormality directly – as molecular therapies that target the classical oncogenic drivers (EGFR, BRAF, PI3K, ALK, HER2) do – but rather by synthetic lethality, i.e. exacerbating the deficit by targeting a different DNA repair mechanism and increasing the genetic instability of the deficient cells, resulting in cell death. This approach carries a small risk of causing collateral genetic instability, and consequently myelodysplastic syndrome and/or secondary leukaemias, but the incidence of these haematological events is below 1%. However, this risk has limited the use of PARP inhibitors, which may otherwise have been considered for primary prevention in women with *BRCA* mutations.

PARP inhibitors are one of the recent treatment revolutions in ovarian cancer. The pivotal SOLO-1 trial showed a median improvement in progression-free survival (PFS) of more than 3 years for patients with a constitutional or somatic *BRCA* mutation treated with olaparib as first-line maintenance therapy.[5] Patients with *BRCA* mutations represent only a quarter of those with ovarian cancer (about 1000 patients per year in France), but PARP inhibitors nevertheless are a major therapeutic improvement for these patients, in whom early diagnosis is important.

The NOVA study tested niraparib as second-line maintenance therapy in in patients with platinum-sensitive disease after a recurrence, regardless of their BRCA status.[6, 7] Not only was there a significant benefit for patients with a BRCA mutation, but also for patients with HRD and no BRCA mutation. For patients without HRD, however, who make up half of the women with ovarian cancers, the benefit was marginal. The PFS improvement of 3 months may not be clinically relevant and is less than the improvement with bevacizumab. A marketing authorisation for niraparib that includes all patients would therefore expose a significant population of women to a treatment that does have some toxicity, particularly haematologically, to achieve only minimal gains.

Two trials have confirmed the benefit of maintenance with PARP inhibitors as first-line treatment in patients with BRCA mutations and those without a BRCA mutation but who do have HRD. The PAOLA trial evaluated the combination of bevacizumab and olaparib as maintenance for patients, with and without HRD, who had responded to first-line treatment with platinum and surgical management (the patients with the worst prognosis were excluded).

The addition of olaparib to bevacizumab resulted in significant benefits for patients without a BRCA mutation and with HRD, with a median increase in PFS of about 1 year.[8] The addition of olaparib, however, did not offer a greater benefit than bevacizumab monotherapy for patients without HRD. The PAOLA study did not include a treatment arm in which patients did not receive bevacizumab, so it was not possible to draw any conclusions about the synergy between olaparib/bevacizumab. The combination seemed to be useful for patients with no *BRCA* mutation who did have HRD, but the benefits were about three-fold lower in this group than in those with *BRCA* mutations. These results suggest that further research is needed to identify patients who derive a benefit from treatment with PARP inhibitors and to define treatment synergies to optimise outcomes.

There has also been extensive debate on the design of the PRIMA trial, which included patients at high risk of recurrence and excluded the standard treatment which is bevacizumab. The results of this trial were positive for the patients with HRD (median PFS of 21.9 months in the group receiving niraparib versus 10.4 months in the placebo group) but for patients without HRD, the improvement in PFS of less than three months (8.1 months with niraparib versus 5.4 months with placebo) was still inferior to the benefit achieved with bevacizumab (4 months).[9]

EPIGENETIC REGULATION

Epigenetics, the complex mechanisms controlling gene expression, are a very promising area to explore in search of treatments. One epigenetic mechanism is methylation of DNA by DNA methyltransferases (DNMTs), which either repress expression if methylation affects cytosine-phosphate-guanine dinucleotide islands, or induce it in the case of intragenic methylation. Most cancers show hypomethylation overall, but with targeted hypermethylations of tumour DNA. Other mechanisms, such as methylation of histones by histone methyltransferases, acetylation or demethylation of DNA, or regulation by miRNA, are undergoing further study. Two DNA methylation inhibitors, the cytidine analogues azacitadine (Vidaza®) and decitabine (Dacogen®), are now being used in onco-haematology. While these agents offer rather limited benefits, they have provided proof of concept for this approach.

One interesting approach involves using inhibitors of disruptor of telomeric silencing 1-like (DOT1L). DOT1L is a histone methyltransferase involved in methylating lysine 79 on histone 3 and has a role in maintaining the homologous recombination system. A DOTL1 inhibitor (pinometostat) has been evaluated in haematology and has proven the validity of the concept with modest efficacy and good tolerability.[10] Preclinical data have shown that DOT1L inhibition increases sensitivity to chemotherapy agents and PARP inhibitors (veliparib);[11] this seems to be a promising approach for patients with HRD. The potential synergy of these histone methylation inhibitors with PARP inhibitors, and the initial results, suggest that efforts should be made to look for similar therapeutic synergies and how to identify the patients who will derive the most benefit from these combinations.

IMMUNITY AND OVARIAN CANCER

The immune system has a major prognostic impact in ovarian cancer. The presence of tumour-infiltrating lymphocytes (TILs) is well established as a prognostic marker in ovarian cancers,[12] with a few cases of patients with very advanced disease who have gone into full remission. In ovarian cancer, the immune checkpoint inhibitors (ICIs) – agents targeting programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1), or cytotoxic T-lymphocyte antigen-4 (CTLA-4) – have very limited benefit when administered as monotherapy, with a response rate of <10%. This modest effect needs to be weighed against the immune-related adverse events and possible hyper-progression of the disease.[13, 14] However, these low response rates have been obtained in studies in patients with very advanced disease. It is possible that using immunomodulatory intervention early in the course of the disease could limit the adverse impact of acquired resistance as well as the adverse changes in immunity associated with multiple chemotherapies. These treatments are therefore being studied in the neoadjuvant or adjuvant settings in a number of trials such as Duo-O[15] or INeOV (Immunotherapy With Neo-adjuvant Chemotherapy for OVarian Cancer, NCT03249142).

Since PARP inhibitors can increase the mutation load and possibly create new tumour antigens, synergistic actions between these agents and ICIs have been investigated in patients with recurrent ovarian cancers in two trials, MEDIOLA (with a combination of olaparib + durvalumab)[16] and TOPACIO (niraparib + pembrolizumab)[17] which have produced some encouraging results. Other trials currently underway, such as ATALANTE (NCT02891824), EORTC1508 (NCT02659384) or FIRST (NCT03602859), are testing different combinations of ICI + PARP inhibitors and/or an anti-angiogenic.

CONCLUSION

Ovarian cancer is a complex disease for which there are no easy right or wrong treatment decisions. The 30% of high-grade non-serous ovarian cancers (endometrioid, low-grade serous, clear cell, carcinosarcoma, mucinous) have their own pathophysiological specificities, and are often underrepresented in clinical trials, and the small number of ovarian cancers that are chemo-refractory from the outset (5% to 10%) still represent a therapeutic impasse.

Ovarian cancer is the model for analysis of HRD. Understanding of the harmful constitutional or sporadic somatic mutations of BRCA and investigation of other harmful mutations have enhanced our understanding of the HRD phenotype; a composite phenotypic HRD signature has good predictive value, but it limits more detailed analysis of the mechanisms involved.

Enthusiasm for treatment with PARP inhibitors is justified in patients with ovarian cancer and BRCA mutations, but should be measured when it comes to the impact of these agents in patients with HRD and no BRCA mutation. In this setting, a more detailed analysis of the mechanisms of resistance is required. There may be considerable reticence about exposing patients without HRD and without a BRCA mutation to these treatments, based on the marginal benefit in patients without HRD.

There are high expectations for the numerous treatment combinations that are being studied in clinical trials, such as PARP inhibitors plus ICIs, PARP inhibitors plus kinases involved in the DNA repair process (Ataxia telangiectasia mutated, Ataxia telangiectasia and Rad3-related, Wee1), and also the synergy between PARP inhibitors and epigenetic modulators.

REFERENCES (Underlined references link to PubMed abstracts)

[1] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74.
[2] Malpica A, Deavers MT, Lu K, Bodurka DC, Atkinson EN, Gershenson DM et al. Grading ovarian serous carcinoma using a two-tier system. Am J Surg Pathol 2004;28:496-504.
[3] Banerjee S, Kaye SB. New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential. Clin Cancer Genome Atlas Research Network 2013;19:961-8.
[4] Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609-15.
[5] Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018;379:2495-505.
[6] Del Campo JM, Matulonis UA, Malander S, Provencher D, Mahner S, Follana P et al. Niraparib maintenance therapy in patients with recurrent ovarian cancer after a partial response to the last platinum-based chemotherapy in the ENGOT-OV16/NOVA trial. J Clin Oncol 2019;37:2968-73.
[7] Moore KN, Mirza MR, Matulonis UA. The poly (ADP ribose) polymerase inhibitor niraparib: management of toxicities. Gynecol Oncol 2018;149:214-20.
[8] Ray-Coquard I, Pautier P, Pignata S, Perol D, Gonzalez-Martin A, Berger R et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med 2019;381:2416-28.
[9] Gonzalez-Martin A, Pothuri B, Vergote I, DePont CR, Graybill W, Mirza MR et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2019;381:2391-402.

[10] Stein EM, Garcia-Manero G, Rizzieri DA, Tibes R, Berdeja JG, Savona MR et al. The DOT1L inhibitor pinometostat reduces H3K79 methylation and has modest clinical activity in adult acute leukemia. Blood 2018;131:2661-9.

[11] Kari V, Raul SK, Henck JM, Kitz J, Kramer F, Kosinsky RL et al. The histone methyltransferase DOT1L is required for proper DNA damage response, DNA repair, and modulates chemotherapy responsiveness. Clin Epigenetics 2019;11:4.

[12] Maine CJ, Aziz NH, Chatterjee J, Hayford C, Brewig N, Whilding L et al. Programmed death ligand-1 over-expression correlates with malignancy and contributes to immune regulation in ovarian cancer. Cancer Immunol Immunother 2014;63:215-24.

[13] Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, Murayama T et al. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. J Clin Oncol 2015;33:4015-22.

[14] Inayama Y, Hamanishi J, Matsumura N, Murakami R, Abiko K, Yamaguchi K et al. Antitumor effect of nivolumab on subsequent chemotherapy for platinum-resistant ovarian cancer. Oncologist 2018;23:1382-4.

[15] Harter P, BidziÅski M, Colombo N, Floquet A, Rubio PÃrez MJ, Kim JW et al. DUO-O: A randomized phase III trial of durvalumab (durva) in combination with chemotherapy and bevacizumab (bev), followed by maintenance durva, bev and olaparib (olap), in newly diagnosed advanced ovarian cancer patients. J Clin Oncol 2019;37:TPS5598.

[16] Penson RT, Drew Y, de Jonge MJA, Hong SH, Park YH, Wolfer A et al. MEDIOLA: A phase I/II trial of olaparib (PARP inhibitor) in combination with durvalumab (anti-PD-L1 antibody) in pts with advanced solid tumours - new ovarian cancer cohorts. Ann Oncol 2018;29 Suppl 8:viii147.

[17] Konstantinopoulos PA, Waggoner S, Vidal GA, Mita M, Moroney JW, Holloway R et al. Single-arm phases 1 and 2 trial of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant ovarian carcinoma. JAMA Oncol 2019;5:1141-9.