Homologous recombination deficiency in ovarian cancer and beyond

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Abstract
It has been well established that failure in the homologous recombination repair (HRR) mechanism for DNA double strand repair causes genomic instability and increases the risk for cell transformation. Mutations in *BRCA1* and *BRCA2* are currently known to be the most frequent responsible for homologous recombination deficiency (HRD) but HRD can occur through other processes including mutations and epigenetic aberration of HRD-related genes and the indirect interaction of BRCA proteins with other proteins involved in the DNA repair. Current efforts in this field are concentrating in identifying an HRD molecular signature able to predict response to chemotherapy and PARP inhibitors, thus allowing to extend novel targeted treatments beyond germline BRCA mutated ovarian cancer patients. The aim of this brief review is to summarize the current evidence regarding HRD beyond germline BRCA mutations and therapeutic approaches.

Key words: BRCA genes, HRD, ovarian cancer, PARP inhibitors

Defining the homologous recombination deficiency phenomenon in ovarian cancer

Despite recent advances in molecular oncology and personalized medicine, ovarian cancer still remains the most lethal gynaecological malignancy [1] and there have been no major improvements in survival over the last 20 years. Radical surgery followed by platinum-based chemotherapy remains the cornerstone of initial ovarian cancer treatment. The majority of patients with advanced ovarian cancer eventually develops progressive disease, which is usually treated with a variety of chemotherapy agents. Over the last few years, the anti-angiogenic agent, bevacizumab, has also become an option for women with ovarian cancer.

The recognition that ovarian cancer comprises several genomically and phenotypically distinct subgroups of tumors with heterogeneous clinical behaviours is changing the approach to ovarian cancer therapies [2]. Several molecular subtypes of ovarian cancer have been described and this is leading to the development of novel targeted therapies and clinical trials evaluating new tailored treatments for patients with ovarian cancer [3].

The introduction of poly ADP ribose polymerase (PARP) inhibitors into clinical practice for patients with BRCA mutations represents a milestone for ovarian cancer. It is recognised that PARP inhibitors are likely to have multiple mechanisms of action. Of these, the base excision repair inhibition model is most widely described [4]. To summarise, DNA single strand breaks (SSBs), normally repaired by base excision repair, persist in the presence of PARP inhibitors. This leads to the accumulation of double strand breaks (DSBs) which are repaired by homologous recombination (HR) in a normal cell. However, in an HR-deficient cell (eg. BRCA mutated) these remain unrepaired and lead to cell death. This phenomenon is termed "synthetic lethality" [5]. In order to keep its genomic integrity, cells activate a complex system of molecular pathways to repair DNA lesions (including single base modifications, DSBs, SSBs and intra-strand and inter-strand cross-links [6]). HR is one mechanism of DNA repair involved in the repair of DSBs. The HR pathway acts mostly in the S and G2 phases of the cell cycle and requires the interactions of many proteins including BRCA1 and BRCA2, proteins of the MNR complex (MRE11/RAD50/ NBS1), CtIP, MRE11, RAD51, ATM, H2AX, PALB2, RPA, RAD52 and proteins of the Fanconi anaemia pathway [7]. Cells with defect(s) in the function of these genes may have a compromised HR pathway. This can lead to activation of non-homologous end joining (NHEJ) as an alternative pathway for DNA DSB repair, which can cause chromo-

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somal instability and substantially increases the risk of oncogenesis [6, 8].

The most well characterized key elements of the HR pathway are the BRCA1/2 genes. Mutations in tumor suppressor genes *BRCA1* and *BRCA2*, encountered in up to 20% of ovarian cancer cases [9-11], are currently known to be the most frequent causes of HR deficiency (HRD) and are an important genetic risk factor for both breast and ovarian cancer [12]. However, alteration of BRCA gene function can occur through several biologically distinct phenomena, including genetic mutation (germline or somatic), epigenetic aberration of the BRCA promoter region [13, 14] and the indirect interaction of BRCA proteins with other proteins involved in the DNA repair.

The epigenetic phenomenon occurs through the methylation of CpG islands in the gene promoter [15]. For BRCA genes, this process prevents BRCA gene transcription and determines their resulting inactivation, thus increasing the risk of DNA damage and cell transformation. Other genes involved in HRD may have epigenetic changes: hypermethylation of Rad51C, a protein that traces DNA repair machinery to the damaged strand; mutation/deletion in ATM, ATR, and PTEN, which is involved in the transcription regulation of Rad51 [16], mutations in CHEK2, FANCA/FANCI, BRIP1 and PALB2 [11, 17].

Approximtely 50% of women with high-grade serous ovarian cancer (HGSOC) have loss of genes involved in the DNA HR repair pathways and, as a consequence, these tumors behave like BRCA1/2 mutated cancers [11]. This phenomenon is called "*BRCAness*" [18] and its clinical implications are progressively changing the therapeutic approaches to ovarian cancer, with PARP inhibitor use extended beyond germline BRCA-mutated tumors.

Somatic BRCA mutations in ovarian cancer

In 2011, the Cancer Genome Atlas Research Network carried out the most comprehensive analysis of whole exome sequence in 316 FIGO stage II–IV HGSOCs, and matched the results with normal DNA samples [11]. BRCA1 and BRCA2 germline mutations were found in 9% and 8% of the cases, respectively, but a further 3% also showed somatic mutations of the BRCA genes.

Hennessy et al. [19] studied 235 unselected ovarian cancer samples for BRCA gene mutations. They detected 44 BRCA mutated cases (19%; 13% BRCA1 mutated and 6% BRCA2 mutated) and these were found to be somatic mutations in a large proportion of cases. Furthermore, BRCA mutations were more frequently encountered among HGSOC specimens.

Pennington et al. [20] analyzed 390 ovarian cancer tissue samples for germline and somatic mutations in 30 genes, including BRCA 1/2 genes. They found germline and somatic mutations on at least one of 13 studied HR genes (BRCA1, BRCA2, ATM, BARD1, BRIP1, CHEK1, CHEK2, FAM175A, MRE11A, NBN, PALB2, RAD51C and RAD51D) in 24% and 9% of cases, respectively. In particular, for somatic mutations, BRCA1 and BRCA2 genes were the most frequently involved in the vast majority of cases (BRCA1 54%, BRCA2 17%), followed by BRIP1 (6%), CHEK2 (9%) and RAD51C (3%) genes. Overall, somatic BRCA genes mutations occur in approximately 5-7% of ovarian cancer cases.

The clinical impact of somatic rather than germline BRCA mutations in ovarian cancer patients is not fully understood but available data show that patients with somatic BRCA mutations appear to behave clinically in a way more similar to germline BRCA mutation carriers than those without a mutation. Hennessy et al. [19] observed that somatic BRCA-mutated ovarian cancer patients had longer progression-free survival (PFS), but similar overall survival (OS), compared with BRCA wild type patients. Similarly, Pennington et al. [20] found that patients with somatic BRCA mutations were more likely to be platinum-sensitive compared to patients with no mutations.

The role of BRCA mutations as predictive biomarkers of PARP inhibitor treatment efficacy was investigated in the pivotal trial, Study 19, a randomized, placebo-controlled phase II clinical trial testing olaparib monotherapy 400 mg bid as maintenance treatment in platinum-sensitive relapsed HGSOC patients [21, 22]; 51% of patients had either germline or somatic BRCA mutations. In the BRCA-mutated group there was a significant improvement in PFS in the olaparib group *versus* placebo (11.2 *vs* 4.3 months; hazard ratio [HR] 0.18, 95% confidence interval [CI] 0.10-0.31; $p<0.0001$). Of note, BRCA-wild type patients also derived significant benefit from olaparib, although the magnitude of effect was smaller (HR 0.54, 95%CI 0.34-0.85; $p=0.0075$) [22]. This supports the notion that patients without BRCA mutations can also have HRD and thus benefit from PARP inhibition. Eighteen (14%) of the 136 patients with a BRCA mutation harboured a somatic mutation (in absence of a germline BRCA mutation). Fewer patients with somatic BRCA mutations had disease progression in the olaparib arm (3/8, 38%) than the placebo group (6/10, 60%). Although the number of cases is small, this observation provides support for olaparib in somatic BRCA mutated patients. The results of larger studies such as SOLO-2 (NCT01874353), NOVA (NCT01847274), ARIEL-3 (NCT01968213) will help to establish the impact of PARP inhibitors for patients with somatic BRCA-mu-

tated ovarian cancer compared to those with a germline BRCA mutation and also for HR-deficient patients beyond BRCA.

Olaparib has European approval as maintenance treatment in platinum-sensitive recurrent ovarian cancer patients for both germline and somatic BRCA-mutated ovarian cancer.

BRCA genes epigenetic aberrations in ovarian cancer

HRD can be the result of epigenetic aberrations occurring in HR genes. Promoter hypermethylation of BRCA1 gene leading to reduced BRCA1 expression has been reported up to 30% of ovarian cancer cases [11, 21, 23, 24]. In The Cancer Genome Atlas Research Network's analyses [11], BRCA1 promoter hypermethylation was found in 11% of HGSOC cases, with no survival differences compared with BRCA1/2 wild type patients. In another study, 38/257 (15%) sporadic epithelial ovarian cancers (EOCs) were found to have BRCA1 promoter hypermethylation [24]. The same frequency of BRCA1 promother hypermethylation was observed in a smaller series [23]. In this study, BRCA1 promoter hypermethylation did not correlate with family history of breast and ovarian cancer, and this epigenetic aberration was detected in both primary and recurrent tumors derived from the same patients, thus suggesting the stability of epigenetic-mediated BRCA1 gene silencing.

The influence of epigenetic BRCA aberrations on survival is not clear; available data are limited and the results conflicting. In a 2006 study [25], BRCA1 promoter hypermethylation was associated with worse prognosis (OS, 35.6 months) compared with both germline BRCA1 mutated (63.3 months) and BRCA1 wild type patients (78.6 months), suggesting more aggressive disease related to BRCA1 hypermethylated tumors. More recently, preliminary results of a pooled analysis of 1,278 EOC patients from five studies showed no difference in median PFS (18.7 *vs* 19.1 months; p=0.42) or OS (44.3 *vs* 46 months; p=0.62) between the BRCA1-methylated and non-BRCA1-methylated patients, suggesting that the BRCA1 methylation phenomenon had no effect on prognosis [26]. Prospective studies will help clarify the predictive and prognostic value of BRCA methylation.

Role of other genes in HRD phenomenon for ovarian cancer

In The Cancer Genome Atlas Research Network's analyses [11], multiple alterations in HR genes other than BRCA1 or BRCA2 were detected. For example, EMSY mutation (8%), focal deletion or mutation of PTEN (7%), hypermethylation of RAD51C (3%), ATM or ATR mutations (2%) and mutations of Fanconi anaemia genes (5%) were noted. Researchers worldwide are currently trying to develop the optimal HR assay able to detect the complete HRD signature, which can be possibly considered predictive of platinum and PARP inhibitor response.

Up to now, tecniques such as gene-expression profiling, proteomics [27] and RNA analyses [28] have been applied to define the "BRCAness" signatures in ovarian cancer [11, 29]. In this setting, it is well established that absence of RAD51 is considered a biomarker for HRD and a predictive factor for unresponsiveness to chemotherapy and PARP inhibitor treatment [30, 31]. A single nucleotide polymorphism array has been performed to define the "genomic instability signature". This score includes telomeric allelic imbalance, large-scale transition and loss of heterozygosity (LOH) and may represent a biomarker of HRD and PARP inhibitor efficacy [32].

Using this approach, the ARIEL-2 study tested a new Next-Generation Sequencing-based HRD assay together with an algorithm which predicted sensitivity to the PARP inhibitor rucaparib in platinum-sensitive recurrent HGSOC or endometrioid ovarian cancer patients [33]. This is the first prospective study showing that an HRD signature can identify ovarian cancer patients without a BRCA mutation who may benefit from a PARP inhibitor. Patients were classified into three different genomic subgroups: tBRCAmut (germline and somatic BRCA mutations), tBRCA-like (high genomic LOH) and biomarker-negative (low genomic LOH). The response rate to rucaparib treatment was 85% in the tBRCAmut group, with no significant differences between germline- and somatic-mutated BRCA patients. Furthermore, a higher PFS was seen in tBRCA-like patients compared with the biomarker-negative group (36% *vs* 16%) [34].

HRD in other solid tumors

In addition to ovarian cancer, there is increasing evidence of a role for HRD in other tumor types and evidence for the clinical impact of PARP inhibitors in the management of these malignancies is emerging [35].

Up to approximately 10% of breast cancer cases is due to a hereditary cancer syndrome and many are BRCA-related [36], less frequently involved in other cancer types. The HRD phenomenon has been reported in up to 5% of melanoma and gastric cancer cases and in up to 19% of familial pancreatic cancers [37]. Furthermore, germline BRCA mutations appear to be responsible for 1% of prostate cancer cases [38] and 2.7% of non-small cell lung cancers (NSCLCs) [39]. PARP inhibitors are currently

being tested in these solid tumor patients in several phase I/II clinical trials.

In breast cancer setting, PARP inhibitor monotherapy administered in metastatic disease showed promising results in terms of both response rates and toxicity profile. In a study of 298 breast cancer patients [40] (62 with BRCA1/2 mutated tumors), the objective response rate to olaparib monotherapy was 12.9%, and 47% of patients had stable disease for >8 weeks. More recently, an HRD score has been developed in breast cancer based on three different measurements of genomic instability in terms of LOH, telomeric allelic imbalance (TAI), and large-scale state transitions (LST) [41]. An HRD score ≥42 has been associated to HR deficiency. This score has been applied to pre-treated triple negative breast cancer (TNBC) tumors in three different trials of platinum-based neoadjuvant chemotherapy. The HRD positive score was found to identify tumors more likely responsive to platinum-based therapy.

Germline BRCA2 mutation was shown to increase the risk of prostate cancer by up to 8.6-fold [38]. Moreover, BRCA-related prostate cancer has been correlated with higher rates of lymph nodal tumor spread, distant metastasis and worse survival [42]. Single-agent olaparib has shown clinical efficacy in patients with germline BRCA-mutated castration-resistant prostate cancer (CRPC). In a phase I study, a patient with germline BRCA2 mutation treated with olaparib monotherapy obtained a complete response lasting over 2 years [16]. A phase II study [43] of unselected metastatic CRPC treated with olaparib monotherapy showed an objective response rate of 33% (16/49). Tumor specimens from all enrolled patients were subjected to Next-Generation Sequencing and tested for DNA-repair genes defects. HRD phenomenon was indentified in 33% of cases (16 patients; 4 with somatic BRCA2 mutation, 3 with BRCA2 germline mutation and 4 with ATM aberrations); of these, 14 patients showed response to olaparib. This is the first study demonstrating olaparib efficacy in HRD-deficient prostate cancer.

In NSCLC, it has been observed that BRCA1 silencing increased susceptibility to olaparib in NSCLC cell lines [44] and has led to clinical trials in this subset of lung cancer patients. Furthermore, up to 9% of NSCLC showed somatic mutation in PTEN. Olaparib has shown synergistic activity with cisplatin in homozygous deleted PTEN-deficient NSCLC cells and xenograft models [45]. Currently, the SWOG 1206 trial, a phase I/II study, is investigating the efficacy of veliparib with or without radiotherapy and carboplatin/paclitaxel in patients with stage III NSCLC not amenable to surgical treatment.

Current unmet needs and future directions

The are several unmet needs in the field of HRD in oncology. The first is to identify HRD biomarkers which can lead to a more accurate selection of cancer patients who may benefit from treatment with PARP inhibitors. Until validated HRD tests are available, the largest benefit of these new targeted agents will not be fully achieved, and BRCA mutation status will remain the only genetic signature available to discriminate patients suitable for PARP inhibitor therapy. A recent press release reported encouraging results of a phase III trial of the PARP inhibitor, niraparib, as maintenance therapy in ovarian cancer patients and utilises an HRD assay to predict benefit [46]. Robust testing for HRD requires some important technical issues to be optimised, including DNA extraction methods for archival formalin-fixed paraffin-embedded (FFPE) specimens. Another important issue is the interpretation of sequencing data. Up to now, there has not been a unanimous interpretation of missense genes mutations and many of them are currently classified as VUS (variants of uncertain significance). Data sharing among laboratories working on HRD will be pivotal for clarifyng the clinical role of these variants in ovarian cancer occurrence and prognosis. The stability of BRCA1 and BRCA2 somatic mutations over time, despite multiple treatment lines, is a further issue that needs careful clarification. A recent tumor biopsy may be needed to confirm the presence of somatic BRCA mutations at the time of initiating therapy.

PARP inhibitor combinations to further improve efficacy and overcome resistance are under clinical evaluation. These include PARP inhibitors in combination with antiangiogenic therapy (e.g. cediranib) and immunotherapy. Such a combination is being currently tested in a phase I study, the preliminary results of which were presented at ASCO 2016 [47]. Treatment with the immune checkpoint inhibitor anti-PD-L1 durvalumab in combination with olaparib or cediranib in a subset of advanced or recurrent ovarian, triple negative breast, lung, prostate and colorectal cancers (NCT02484404) was associated with a 67% disease control rate in the subgroup of patients with ovarian cancer and breast cancer treated with olaparib+durvalumab (1 partial response and 5 stable disease). Interestingly, all responders were BRCA wild type. Grade 3/4 adverse events included lymphopenia (2/12) and anemia (1/12). Phase III trials initiated in 2015 are now underway, testing olaparib combined with cediranib *versus* standard chemotherapy in platinum-sensitive (NCT02446600) and recurrent platinum resistant/refractory ovarian cancer (COCOS trial, NCT02502266).

Finally, PARP inhibitors for maintenance therapy of HRD-related tumors were recently deemed to be not cost-effective due to the high estimated monthly cost per month ($US 13,440) [48]. A global strategy for the sustainability of these drugs should be performed to facilitate increased availability to all cancer patients who may derive significant clinical benefit from PARP inhibitor treatment.

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Conflicts of Interest

I. Ruscito declares no conflict of interest. S. Banerjee is member of advisory board of Clovis and AstraZeneca. No personal financial remuneration.

Table 1. Clinical trials testing HRD in ovarian cancer (OC).

Trial name	Trial number	Study phase	Patients population	HRD subgroups	Interventions	Status	Estimated primary completion date
ARIEL-2	NCT01891344	Phase II	Platinum-sensitive, recurrent, high-grade serous or endometrioid OC	Tumor $BRCA^{mut}$, $BRCA^{wt}/LOH^{high}$ (BRCA-like) and $BRCA^{wt}/LOH^{low}$	600 mg bid rucaparib	Ongoing. Patients recruitment closed	March 2017
ARIEL-3	NCT01968213	Phase III	Platinum-sensitive, recurrent, high-grade serous or endometrioid OC	Tumor $BRCA^{mut}$, $BRCA^{wt}/LOH^{high}$ (BRCA-like) and $BRCA^{wt}/LOH^{low}$	600 mg bid rucaparib *vs* placebo	Ongoing. Patients recruitment closed	March 2017
PRIMA	NCT02655016	Phase III	Advanced OC after response on front-line platinum-based chemotherapy	BRCA Diagnostic test ± HRD Diagnostic test ±*	Maintenance niraparib once daily *vs* placebo	Ongoing. Recruiting participants	March 2018

*Myriad®; LOH: loss of heterozygosity; mut: mutated; wt: wild type

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