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Review

'BRCAness' and Its Implications for Platinum Action in Gynecologic Cancer*

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Abstract. *Gynecological carcinomas are major therapeutic targets of platinum-containing regimens. They may be particularly susceptible to these agents if their origins are related to hereditary breast cancer (BRCA) mutations; this implicates defective DNA repair secondary to inherited alterations in BRCA function. The concept of 'BRCAness' was introduced by Ashworth and colleagues in order to identify phenotypic changes in sporadic cancer that would lead to analogous treatment susceptibility. In fact, recent analyses of genetic alterations in ovarian cancer have led to further extending this concept to all women with high-grade serous cancer, the predominant form of ovarian cancer arising in association with hereditary mutations in BRCA genes. Presumably, most serous types of cancer of gynecological origin share BRCA dysfunction to some extent. This renders these types of cancer susceptible to platinum and to other DNA-damaging agents, justifying the general inclusion of this histology in trials of new drugs and therapeutic strategies that have shown activity against hereditary cancer. More recently, however, differences in outcome between BRCA mutation carriers vis-à-vis those with no mutations or those with epigenetic or acquired forms of BRCA genes (somatic mutations) in their respective tumors have been identified. These findings raise additional questions on modifiers of 'BRCAness' and other pathways that appear to contribute to the effects of platinum and other DNA-damaging agents in ovarian cancer. The Cancer Genome Atlas analyses delineate the complexity of genomic alterations in ovarian cancer and other malignancies of Mullerian epithelial origin promising further refinements of the 'BRCAness' concept.*

Platinum drugs play an essential role in gynecological cancer treatment. Cisplatin or carboplatin (1-3) are coupled to surgery as part of the initial treatment in more than 90% of patients with epithelial ovarian cancer. Upon recurrence, all patients except those whose disease is labeled as platinum-resistant usually receive multiple courses of carboplatin (4). Platinum-based chemotherapy has also emerged in the last decade as the prevailing strategy (over radiation) for adjuvant treatment of endometrial cancer following identification of some high-risk features at hysterectomy, and forms part of the systemic treatment of patients with metastatic disease beyond rare cases of well-differentiated tumors that metastasize (5-13). Finally, in cancer of the uterine cervix, the use of either cisplatin or carboplatin in combination with other drugs or use of cisplatin as a radiosensitizer have yielded improvements in outcome for patients with locally advanced or metastatic presentations (14-18).

The Cancer Genome Atlas (TCGA) provides some insight into the efficacy of platinum compounds whether alone or in combination with other drugs in the treatment of ovarian and endometrial cancer (19). Specifically, TCGA has shown some common abnormalities among high-grade ovarian cancer with poorly-differentiated endometrioid, high-grade serous cancer of the endometrium, and basal-like carcinomas of breast origin (also updated on line at cancergenome.nih.gov). All of these are characterized by high genomic instability and BRCA mutation/silencing through epigenetic changes. Such genomic changes have not readily provided identifiable driver mutations that may be targeted; however, they have re-inforced the concept of 'BRCAness' introduced by Ashworth and colleagues to identify phenotypic changes in sporadic cancer that would imply similar treatment susceptibility to DNA-damaging agents (20). We elaborate on the evolving clinical implications behind this concept in the main portion of this article.

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BRCA Function and DNA Repair

The past decade has witnessed impressive advances in our understanding over various cellular components required for maintenance of the genome under the on-slaught of DNA damage. Among these, the sensors of DNA damage, ataxia telangiectasia and Rad3-related protein (ATR) and ataxia telangiectasia mutated (ATM) are central to turning on DNA repair machinery (21-30). In recent years, major roles have also been assigned to BRCA1 and BRCA2 functions in leading high-fidelity repair by homologous recombination (HR) (31-41). Cellular systems have served to probe and identify defects in such repair functions by verifying the formation of foci when BRCA-mediated repair is intact. Lack of foci formation implies defects in the HR pathway, among others. *BRCA2* and a number of other Fanconi-related genes also have additional key functions in non-HR repair (20, 42-56). Selective forms of DNA damage, such as nucleotide excision repair (NER) or base excision repair (BER), rely on other repair pathways, in which polyadenosyldiphosphate ribose polymerase (PARP) plays a major role, particularly in the absence of HR.

Interest in tumor repair pathways has led to the recognition of their importance in determining cellular sensitivity to chemotherapeutic agents. Attention was naturally drawn to epithelial ovarian cancer and its known sensitivity to the classical DNA-damaging drugs, alkylating agents (from 1950-1980), and subsequently the more effective platinum agents. In particular, the clinical and analog development of cisplatin was greatly stimulated by its remarkable activity in the common advanced presentations of ovarian cancer.

Clinical trials by the Gynecologic Oncology Group (GOG) and others eventually identified a consistent pattern of greater sensitivity of high-grade serous carcinomas to cisplatin, and relative resistance of other epithelial types such as mucinous, clear cell, and low-grade serous carcinomas to this agent (57-68). Additional studies in patients after platinum-based treatment suggested the loss of mismatch repair function and increasing tolerance of platinum–DNA adducts as a mechanism of resistance. The incidental finding of invasive and *in situ* high-grade serous carcinomas in Fallopian tube fimbriae of *BRCA* mutation carriers subjected to risk-reducing surgeries spurred focus on BRCA function as a determinant of the known platinum sensitivity of this histological type. In addition, as more reports accumulated (69), it became evident that ovarian adenocarcinomas, arising in *BRCA1* and *BRCA2* mutation carriers, had better overall outcomes and greater response rates to platinum compounds, as well as to other drugs in common use for ovarian cancer recurrence (*e.g.* pegylated liposomal doxorubicin, gemcitabine, topotecan) (70). Such results have strengthened the association between lack of BRCA function and platinum sensitivity, as well as a similar association with sensitivity to other DNA-damaging agents that were known to be active in ovarian cancer.

PARP Inhibitors and Synthetic Lethality

Research groups in Newcastle and the Institute for Cancer Research (led by Curtin and Ashworth, respectively) independently reported the remarkable *in vitro* findings in 2005 of 'synthetic lethality' in $BRCA^{-/-}$ cells, *i.e.* enhanced lethality of DNA-damaging agents (including radiation) and PARP, respectively in knock-out *versus* wild-type cells, that is, when HR- and PARP-related repair were either defective or blocked. These finding have rekindled the clinical development of PARP inhibitors that had begun at Newcastle under the leadership of A. Hilary Calvert and culminated in a trial of AGO14699 (now known as rucaparib) in a trial mostly consisting of patients with melanoma conducted by Ruth Plummer (summarized in references 71-74).

The subsequent clinical development of PARP inhibitors has not been without challenges. Although these agents are well-tolerated by themselves, when administered in combination with other drugs, their doses generally had to be reduced. Although iniparib was an exception to this, this agent was subsequently proven as unlikely to function as a PARP1 inhibitor. Disappointingly, the initial lead identified in phase I showing single-agent efficacy of olaparib against ovarian cancer in mutation carriers was also not pursued as vigorously as many gynecological oncologists would have wished for their patients. Nevertheless, veliparib (GOG270, unpublished data) and niratinib (J. DeBono, June 1st, poster presentation at ASCO 2013) have also shown single-agent activity in *BRCA* mutation carriers with ovarian cancer. Furthermore, retrospective analyses have also suggested that these patients do particularly well when maintained with oliparib after platinum-induced complete responses, a finding that is less obvious when epigenetic BRCA function is silenced, or if an unidentifiable mutation is present (3, 34, 36, 71-78) (and further documented in the oral presentation by J Ledermann, ASCO June 2nd, 2013).

Prospective studies of PARP inhibitors have utilized the concept of 'BRCAness' to enrich the population under study beyond those with known hereditary cancer that were shown to benefit during the phase I study of olaparib as documented through imaging as far back as April 2006 by Fong *et al.* (76). Several studies have shown that olaparib also presented certain clinical benefit in patients with ovarian cancer who are not *BRCA* mutation carriers, and thus this PARP inhibitor may be used to treat a larger subset of patients with epithelial ovarian cancer but not patients with low-grade tumors, mucinous, or clear-cell adenocarcinomas. Some patients with high-grade endometrioid adenocarcinomas do share sensitivity to platinum and point to the risk of over-relying on a histological diagnosis alone to identify those tumors that may be extremely sensitive to platinum and PARP inhibitors (79-80).

Refining the Definition of 'BRCAness'

As noted above, when 'BRCAness' was introduced in 2004, it was hoped that the hallmarks of susceptibility to breast and ovarian cancer through the known inherited *BRCA1* and *BRCA2* mutations would be identified in otherwise sporadic cancer. Specifically, the postulate was that "the existence of a significant proportion of sporadic breast, ovarian, and other cancers with BRCA-like functional abnormalities raises the possibility of a wider application of treatment regimens designed for familial BRCA tumors" (20). Moreover, the authors pointed out the need to seek phenotypic changes that would allow such assignment of 'BRCAness'. Subsequent articles (now 30 in number under PubMed) have been published separately in the breast and ovarian cancer literature–not unreasonable, since the phenotypic expression of *BRCA1* mutations in breast cancer relates primarily to triple-negative breast cancer with basal cell features, whereas *BRCA2* mutations have more variable phenotypic features. Some of the literature on breast cancer has sought correlations beyond the anticipated enhanced benefit from DNA-damaging drugs, including lack of responsiveness to taxanes (81, 82).

The terminology itself, although widely used, is potentially open to ambiguous interpretation. For example, it has been pointed out that 'BRCAness' actually refers to '*BRCAless*ness' because it is the deficiency of BRCA function that defines this phenotype (83). Tan *et al*. (84) upon comparing chemoresponsiveness in BRCA mutation carriers to that of patients with 'non-hereditary' cancer characterized the 'BRCAness' syndrome in ovarian cancer by the following: i) high response rates to first-line platinum-based treatment; ii) high response rates to subsequent therapies including platinum agents; iii) long treatment-free intervals beyond relapse, iv) improved overall survival; and v) tumors that are usually, but not exclusively, of serous histology. Thus, this study refers to hereditary *BRCA* mutation carriers, albeit in the less studied non-Ashkenazi Jewish population, under the term 'BRCAness'. Notwithstanding potential ambiguities, the term has caught on, and although "there is no standardized method to detect 'BRCAness'" (83), the original intent of Turner *et al*. (20) to provide more robust indications of extending the therapeutic implications beyond *BRCA* mutations remains valid and awaits further development.

Konstantinopoulos *et al*. developed a "gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer" (85). Their "optimal classifier" was a 60-gene diagonal linear discriminant predictor and was then applied to 35 clinical samples that were sequenced to ensure that *BRCA1* and *BRCA2* were wild-type for classification as BRCA-like to non-BRCA-like, and this 'optimal classifier' was similarly applied to another 35 clinical samples that were non-sequenced. This 'BRCAness' profile was shown to correlate with responsiveness to platinum and to PARP inhibitors and had an independent prognostic value on multivariate analysis. The 70 patients had stage III (80%), grade 3 (86%) disease with mostly serous histology (93%). This study supports the notion that genes other than *BRCA1* or *BRCA2* are responsible for 'BRCAness' in sporadic disease; one cannot exclude, however, that sporadic mutations or epigenetic alterations in the *BRCA* genes themselves account for their BRCA-like classifier. An editorial by Bast and Mills stressed platinum sensitivity as a reliable predictor of 'BRCAness' (86): the gene expression profile signature of 'BRCAness' correctly identified 8 out of 10 *BRCA* mutation carriers as responders to platinum agents; the two exceptions had *BRCA2* mutations, suggesting that the signature is better at detecting *BRCA1* than *BRCA2* dysfunction. The authors go on to emphasize that "identifying genomic signatures associated with BRCA dysfunction may directly impact the extent of platinum sensitivity and could have substantial impact on clinical outcomes". In fact, Lesnock and Krivak's group and our retrospective experience within phase II studies of intra-peritoneal platinum agents (87) suggest that *BRCA* status (by immunohistochemistry in the GOG172 study or by known *BRCA* mutation carrier state) predicts an especially favorable outcome after intra-peritoneal therapy. Bast and Mills further suggest that reverse-phase protein arrays have the potential to add a new dimension to predictive assays of sensitivity to treatment beyond *BRCA* status (86).

'BRCAness' in Ovarian Cancer: Implications for Platinum Agents and Other Drugs

As noted in the preceding section, a decade after its introduction, refining our definition of 'BRCAness' has become a central theme in the treatment of epithelial ovarian cancer. The most dramatic demonstration of its impact may be in the benefit conferred by cisplatin when given by the intraperitoneal route. Whether this impressive gain in sensitivity carries over to outcomes from PARP inhibitors and other drugs is not known. However, our studies suggest that *BRCA* mutation carrier status also confers greater sensitivity to pegylated liposomal doxorubicin (69), and to drugs such as gemcitabine; not enough experience is available for topotecan (70). Since TGCA did not identify driver mutations, and the predominant theme remains sensitivity to platinum agents, future studies into 'BRCAness' and correlations with outcome remain a high priority for study. Additionally, manipulations to enhance platinum sensitivity such as by increasing uptake, for example through the use of bortezomib and carboplatin given by intraperitoneal administration, have high interest. Another area that needs further research is identification of genes that affect BRCA function, such as *EMSY* amplification and overexpression capable of inhibiting *BRCA2* transcriptional activity (20, 88, 89). Factors resulting in re-gaining (*e.g*. reversing) activity of BRCA even in the presence

Table I. *Genetic and other characteristics associated with 'BRCAness' in ovarian cancer*.*

Abnormal features and genetic abnormalities	% In ovarian cancer	Reference
*BRCA*1/2 germline mutation	10-15	90
*BRCA*1/2 somatic mutation	5-10	91
BRCA promoter methylation	5-30	92
EMSY amplification	20	93
Fanconi anemia complex defects	21	42
PTEN focal deletion/mutation	7	94
RAD51 hypermethylation	3	95
ATM/*ATR* mutation	2	96
Serous, pseudo-endometrioid, transitional cell-like, ↑TIL	majority	97

*Modified from reference 33. ATM, Ataxia telangiectasia mutated, ATR, ataxia telangiectasia and Rad3-related protein, BRCA, breast cancer, PTEM, phosphatase and tensin homolog, TIL, tumor infiltrating lymphocytes.

of deleterious mutations need to be identified, including the suggestion that prior exposure to anticancer agents for breast cancer enhances the likelihood of such reversing activity. Table I lists 'BRCAness'-related genetic and epigenetic alterations.

In conclusion, the concept of ' BRCAness', as originally introduced, has proven useful in emphasizing the central role of the BRCA genes both in breast and in ovarian cancer biology and treatment. Therapeutic implications emanating from this concept appear to differ in ovarian cancer compared with breast cancer, further reinforcing the importance of the context in which *BRCA* and related genes function in these malignancies. The remarkable effects of the platinum compounds may hopefully be extended further by studying to what extent the population with 'BRCAness' attains similar outcomes to those with germline *BRCA* mutations.

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