HHS Public Access

Author manuscript

Anticancer Res. Author manuscript; available in PMC 2015 December 17.

Published in final edited form as:

Anticancer Res. 2014 February ; 34(2): 551–556.

'BRCAness and its implications for platinum action in gynecologic cancer*

Franco Muggia[1,^] and **Tamar Safra**[2]

[1]NYU Cancer Institute, New York, NY 10016

[2] Sourasky Medical Center, Tel Aviv, Israel (Currently on sabbatical at American Cancer Hospital, Shanghai, China)

Abstract

Gynecologic cancers are major therapeutic targets of platinum-containing regimens. They may be particularly susceptible to these agents if their origins are related to hereditary 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 cancers that would lead to analogous treatment susceptibility. In fact, recent analyses of the genetic alterations in ovarian cancer have led to further extending this concept to all women with high-grade serous cancers –the predominant form of ovarian cancer arising in association with hereditary mutations in BRCA genes. Presumably, most serous cancers of gynecologic origin share to some extent BRCA dysfunction rendering these cancers susceptible to platinums and to other DNA damaging agents, and justifying general inclusion of this histology in trials of new drugs and therapeutic strategies that have shown activity against hereditary cancers. More recently, however, differences in outcome between BRCA mutation carriers vis-á-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 platinums 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.

Keywords

ovarian cancer; BRCAness; cisplatin; carboplatin; homologous recombination; PARP inhibitors

Introduction

Platinum drugs play an essential role in gynecologic cancer treatment. Cisplatin or carboplatin[1-3] are coupled with surgery as part of the initial treatment in more than 90% of

*combining individual presentations made on gynecologic cancers at ISPCC2012

^ Correspondence to: NYU Cancer Institute, New York University Langone Medical Center, 550 First Avenue, New, NY 10016.

**The full names, institutional addresses, and e-mail addresses for all authors must be included on the title page. The corresponding author should also be indicated.

epithelial ovarian cancer patients. Upon recurrence all patients except those labeled as 'platinum resistant' usually receive multiple courses of carboplatin[4]. Platinum-based chemotherapy also has 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 uterine cervix cancer, 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 effectiveness of platinum compounds either alone or in combination with other drugs in the treatment of ovarian and endometrial cancers[19]. Specifically, TCGA has shown some common abnormalities among high-grade ovarian cancers with poorly differentiated endometrioid, high grade serous 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 mutations and/or silencing through epigenetic changes. Such genomic changes did not readily provide identifiable 'driver mutations' that may be targeted; however, they have reinforced the concept of 'BRCAness' introduced by Ashworth and colleagues to identify phenotypic changes in sporadic cancers 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 manuscript.

BRCA function and DNA repair

The past decade has witnessed impressive advances in our understanding of the various cellular components required for maintenance of the genome under the onslaught 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 (NER) or base excision repair (BER) rely on other repair pathways, in which poly-adenosyldiphosphate-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 platinums. In particular, cisplatin's clinical and analog development 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 cancers to cisplatin, and relative resistance of other epithelial types such as mucinous, clear cell, and low grade serous to this agent[57-68]. Additional studies in patients after platinum-based treatment suggested losing 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 focusing on BRCA function as a determinant of the known platinum sensitivity of this histologic type. In addition, as more reports accumulated[69], it became evident that ovarian adenocarcinomas, arising in BRCA 1 and BRCA2 mutation carriers, had better overall outcomes and greater response-rates to platinum compounds as well as other drugs in common use for ovarian cancer recurrences [e.g. pegylated liposomal doxorubicin (PLD), gemcitabine, topotecan][70]. Such results have strengthened the association between absence 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 in 2005 the remarkable *in vitro* findings of 'synthetic lethality' in BRCA −/− cells, i.e. enhanced lethality of DNA damaging agents (including radiation) and PARP, respectively in knockout 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 had to be generally attenuated. Although iniparib was an exception to the above, this agent was subsequently proven as unlikely to function as a PARP1 inhibitor. Disappointingly, also the initial lead identified in phase I showing single-agent efficacy of olaparib against ovarian cancer in mutation carriers , was not pursued as vigorously as many gynecologic oncologists would have wished for their patients. Nevertheless, veliparib (GOG270, unpublished) 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 cancers 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 (reference 75). Several studies have shown that olaparib also had some clinical benefit in ovarian cancer patients that 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 the sensitivity to platinums and point to the risk of over relying on a histologic diagnosis by itself to identify those tumors that may be extremely sensitive to platinums 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 breast and ovarian cancer susceptibility to the known inherited BRCA1 and BRCA2 mutations would be identified in otherwise sporadic cancers. 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 for phenotypic changes that would allow such BRCAness assignment. Subsequent publications (now 30 in number under pubmed) have proceeded 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 with basal cell features, whereas BRCA2 mutations have more variable phenotypic features. Some of the breast cancer literature has sought correlations beyond the anticipated enhanced benefit from DNA-damaging drugs but also with lack of responsiveness to taxanes[81, 82].

The terminology itself, though widely used, is potentially open to ambiguous interpretation. For example, it has been pointed out that 'BRCAness' actually refers to 'BRCAlessness' 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 'non-hereditary' patients characterized the BRCAness syndrome in ovarian cancer by the following: 1) high response rates to first-line platinum base treatment; 2) high response rates to subsequent therapies including platinums; 3) long treatment-free intervals beyond relapse, 4) improved overall survival; and 5) 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 not standardized method to detect BRCAness' [83] the original intent of Turner et al[20] to come up with more robust indications of extending the therapeutic implications beyond BRCA mutations remains viable 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 then applied to 35 clinical samples that were sequenced to ensure that BRCA1 and BRCA2 were wild type for classification as BRCA-like (BL) to non-BRCA-like (nBL), 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 were stage III (80%), grade 3 (86%) 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 BL classifier. An accompanying 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 of 10 BRCA mutation carriers as responders to platinums –the two exceptions had BRCA2 mutations, suggesting that the signature is better at detecting BRCA1 than BRCA2 dysfunction. These 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 intraperitoneal platinums [87,88] suggest that BRCA status (by immunohistochemistry in the GOG172 study or by presence of known BRCA mutation carrier state) predicts an especially favorable outcome after intraperitoneal (IP) therapy. Bast and Mills further suggest that reverse-phase protein arrays have the potential to add a new dimension in predictive assays of sensitivity to treatment beyond BRCA status[86].

BRCAness in ovarian cancer: implications for platinums and other drugs

As noted in the preceding section, a decade after introducing ‘BRCAness’, refining our definitions 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 IP 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 PLD[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 platinums, 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, --through the use of bortezomib and carboplatin given by IP administration, as an example, --hold 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, 89, 90]. Factors resulting in the regaining (e.g., revertant) activity of BRCA even in the presence of deleterious mutations need to be identified, including the suggestion that prior exposure to anticancer agents for breast cancer enhances the likelihood of such revertant activity. Table 1 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 vis-a-vis 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.

Acknowledgments

Supported in part by NYU grants P30 CA16087 & CTSI (NIH), and the Chemotherapy Foundation

References

1. Ledermann JA. Primary chemotherapy: the future for the management of advanced ovarian cancer? Int J Gynecol Cancer. 2010; 20(11 Suppl 2):S17–S19. [PubMed: 20975354]
2. Ledermann JA, Kristeleit RS. Optimal treatment for relapsing ovarian cancer. Ann Oncol. 21(Suppl 7):vii218–vii222. [PubMed: 20943618]
3. Liu J, Matulonis UA. New advances in ovarian cancer. Oncology (Williston Park). 24(8):721–728. [PubMed: 20718251]
4. Markman M, Hoskins W. Responses to salvage chemotherapy in ovarian cancer: a critical need for precise definitions of the treated population. J Clin Oncol. 1992; 10(4):513–514. [PubMed: 1548513]
5. Tazi Y, Pautier P, Lhomme C. Systemic therapy for advanced endometrial cancer. Bull Cancer. 2012; 99(1):93–97. [PubMed: 22236886]
6. Johnson N, Bryant A, MILES T, Hogberg T, Cornes P. Adjuvant chemotherapy for endometrial cancer after hysterectomy. Cochrane Database Syst Rev. 2011; 10:CD003175. [PubMed: 21975736]
7. Hogberg T. What is the role of chemotherapy in endometrial cancer? Curr Oncol Rep. 2011; 13(6): 433–341. [PubMed: 21874283]
8. Olawaiye AB, Boruta DM 2nd. Management of women with clear cell endometrial cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol. 2009; 113(2):277–283. [PubMed: 19251307]
9. Kodama J, Seki N, Hiramatsu Y. Chemotherapy for high-risk early-stage endometrial cancer. Curr Opin Obstet Gynecol. 2007; 19(1):42–47. [PubMed: 17218851]
10. Humber CE, Tierney JF, Symonds RP, Collingwood M, Kirwan J, Williams C, Green JA. Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. Ann Oncol. 2007; 18(3):409–420. [PubMed: 17150999]
11. Obel JC, Friberg G, Fleming GF. Chemotherapy in endometrial cancer. Clin Adv Hematol Oncol. 2006; 4(6):459–468. [PubMed: 16981669]
12. Markman M. Unresolved issues in the chemotherapeutic management of gynecologic malignancies. Semin Oncol. 2006; 33(2 Suppl 6):S33–S38. [PubMed: 16716801]
13. Muggia FM. Recent updates in the clinical use of platinum compounds for the treatment of gynecologic cancers. Semin Oncol. 2004; 31(6 Suppl 14):17–124. [PubMed: 15726530]
14. Scatchard K, Forrest JL, Flubacher M, Cornes P, Williams C. Chemotherapy for metastatic and recurrent cervical cancer. Cochrane Database Syst Rev. 2012; 10:CD006469. [PubMed: 23076924]
15. Rosa DD, Medeiros LR, Edelweiss MI, Pohlmann PR, Stein AT. Adjuvant platinum-based chemotherapy for early stage cervical cancer. Cochrane Database Syst Rev. 2012; 6:CD005342. [PubMed: 22696349]
16. Klopp AH, Eifel PJ. Chemoradiotherapy for cervical cancer in 2010. Curr Oncol Rep. 2011; 13(1): 77–85. [PubMed: 21042887]
17. Al-Mansour Z, Verschraegen C. Locally advanced cervical cancer: what is the standard of care? Curr Opin Oncol. 2010; 22(5):503–512. [PubMed: 20473164]
18. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane Database Syst Rev. 2009; (1):CD008285.

19. Cancer Genome Atlas Research Network. Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, Yua C, Laird PW, Ding L, ZHang W, Mills GB, Kucherlapati R, Mardis ER, Levine DA. Integrated genomic characterization of endometrial carcinoma. Nature. 2013; 497(7447):67–73. [PubMed: 23636398]
20. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer. 4(10):814–819. [PubMed: 15510162]
21. Furgason JM, Bahassi el M. Targeting DNA repair mechanisms in cancer. Pharmacol Ther. 2013; 137(3):298–308. [PubMed: 23107892]
22. Sperka T, Wang J, Rudolph KL. Rudolph, DNA damage checkpoints in stem cells, ageing and cancer. Nat Rev Mol Cell Biol. 2012; 13(9):579–590. [PubMed: 22914294]
23. Thompson LH. Recognition, signaling, and repair of DNA double-strand breaks produced by ionizing radiation in mammalian cells: the molecular choreography. Mutat Res. 2012; 751(2):158–246. [PubMed: 22743550]
24. Roos WP, Kaina B. DNA damage-induced cell death: from specific DNA lesions to the DNA damage response and apoptosis. Cancer Lett. 2013; 332(2):237–248. [PubMed: 22261329]
25. Chen BP, Li M, Asaithamby A. New insights into the roles of ATM and DNA-PKcs in the cellular response to oxidative stress. Cancer Lett. 2012; 327(1-2):103–110. [PubMed: 22155347]
26. Langerak P, Russell P. Regulatory networks integrating cell cycle control with DNA damage checkpoints and double-strand break repair. Philos Trans R Soc Lond B Biol Sci. 2011; 366(1584):3562–3571. [PubMed: 22084383]
27. Flynn RL, Zou L. ATR: a master conductor of cellular responses to DNA replication stress. Trends Biochem Sci. 2011; 36(3):133–140. [PubMed: 20947357]
28. Lopez-Contreras AJ, Fernandez-Capetillo O. The ATR barrier to replication-born DNA damage. DNA Repair (Amst). 2010; 9(12):1249–1255. [PubMed: 21036674]
29. Poehlmann A, Roessner A. Importance of DNA damage checkpoints in the pathogenesis of human cancers. Pathol Res Pract. 2010; 206(9):591–601. [PubMed: 20674189]
30. Smith J, Tho LM, Xu N, Gillespie DA. The ATM-Chk2 and ATR-Chk1 pathways in DNA damage signaling and cancer. Adv Cancer Res. 2010; 108:73–112. [PubMed: 21034966]
31. Pennington KP, Swisher EM. Hereditary ovarian cancer: beyond the usual suspects. Gynecol Oncol. 2012; 124(2):347–353. [PubMed: 22264603]
32. Foulkes WD, Shuen AY. In brief: BRCA1 and BRCA2. J Pathol. 2013; 230(4):347–349. [PubMed: 23620175]
33. Rigakos G, Razis E. BRCAness: finding the Achilles heel in ovarian cancer. Oncologist. 2012; 17(7):956–962. [PubMed: 22673632]
34. Tinker AV, Gelmon K. The role of PARP inhibitors in the treatment of ovarian carcinomas. Curr Pharm Des. 2012; 18(25):3770–3774. [PubMed: 22591423]
35. Bast RC Jr. Molecular approaches to personalizing management of ovarian cancer. Ann Oncol. 2011; 22(Suppl 8):viii5–viii15. [PubMed: 22180401]
36. Banerjee S, Kaye S. PARP inhibitors in BRCA gene-mutated ovarian cancer and beyond. Curr Oncol Rep. 2011; 13(6):442–9. [PubMed: 21913063]
37. Kalamanathan S, Bates V, Lord R, Green JA. The mutational profile of sporadic epithelial ovarian carcinoma. Anticancer Res. 2011; 31(8):2661–2668. [PubMed: 21778320]
38. Long KC, Kauff ND. Hereditary ovarian cancer: recent molecular insights and their impact on screening strategies. Curr Opin Oncol. 2011; 23(5):526–530. [PubMed: 21734577]
39. Trainer AH, Lewis CR, Tucker K, Meiser B, Friedlander M, Ward RL. The role of BRCA mutation testing in determining breast cancer therapy. Nat Rev Clin Oncol. 2010; 7(12):708–717. [PubMed: 21060331]
40. Martin SA, Hewish M, Lord CJ, Ashworth A. Genomic instability and the selection of treatments for cancer. J Pathol. 2010; 220(2):281–289. [PubMed: 19890832]
41. Safra T. Hereditary ovarian cancer: biology, response to chemotherapy and prognosis. Womens Health (Lond Engl). 2009; 5(5):543–553. [PubMed: 19702453]
42. Garcia MJ, Benitez J. The Fanconi anaemia/BRCA pathway and cancer susceptibility. Searching for new therapeutic targets. Clin Transl Oncol. 2008; 10(2):78–84. [PubMed: 18258506]

43. Bogliolo M, Cabré O, Callén E, Castillo V, Creus A, Marcos R, Surrallés J. The Fanconi anaemia genome stability and tumour suppressor network. Mutagenesis. 2002; 17(6):529–538. [PubMed: 12435850]
44. Duker NJ. Chromosome breakage syndromes and cancer. Am J Med Genet. 2002; 115(3):125–129. [PubMed: 12407692]
45. Thompson LH, Schild D. Recombinational DNA repair and human disease. Mutat Res. 2002; 509(1-2):49–78. [PubMed: 12427531]
46. Yao CJ, Du W, Zhang Q, Zhang F, Zeng F, Chen FP. Fanconi anemia pathway--the way of DNA interstrand cross-link repair. Pharmazie. 2013; 68(1):5–11. [PubMed: 23444773]
47. Kim H, D'Andrea AD. Regulation of DNA cross-link repair by the Fanconi anemia/BRCA pathway. Genes Dev. 2012; 26(13):1393–1408. [PubMed: 22751496]
48. Stecklein SR, Jensen RA. Identifying and exploiting defects in the Fanconi anemia/BRCA pathway in oncology. Transl Res. 2012; 160(3):178–197. [PubMed: 22683426]
49. Knoch J, Kamenisch Y, Kubisch C, Berneburg M. Rare hereditary diseases with defects in DNA-repair. Eur J Dermatol. 2012; 22(4):443–455. [PubMed: 22436139]
50. Crossan GP, Patel KJ. The Fanconi anaemia pathway orchestrates incisions at sites of crosslinked DNA. J Pathol. 2012; 226(2):326–337. [PubMed: 21956823]
51. Su X, Huang J. The Fanconi anemia pathway and DNA interstrand cross-link repair. Protein Cell. 2011; 2(9):704–711. [PubMed: 21948210]
52. Symington LS, Gautier J. Double-strand break end resection and repair pathway choice. Annu Rev Genet. 2011; 45:247–271. [PubMed: 21910633]
53. Deans AJ, West SC. DNA interstrand crosslink repair and cancer. Nat Rev Cancer. 2011; 11(7): 467–480. [PubMed: 21701511]
54. Deakyne JS, Mazin AV. Fanconi anemia: at the crossroads of DNA repair. Biochemistry (Mosc). 2011; 76(1):36–48. [PubMed: 21568838]
55. Hucl T, Gallmeier E. DNA repair: exploiting the Fanconi anemia pathway as a potential therapeutic target. Physiol Res. 2011; 60(3):453–465. [PubMed: 21401292]
56. Cantor SB, Guillemette S. Hereditary breast cancer and the BRCA1-associated FANCJ/BACH1/BRIP1. Future Oncol. 2011; 7(2):253–261. [PubMed: 21345144]
57. Vargas-Hernandez VM. [Endometriosis as a risk factor for ovarian cancer]. Cir Cir. 2013; 81(2): 163–168. [PubMed: 23522320]
58. Gurung A, Hung T, Morin J, Gilks CB. Molecular abnormalities in ovarian carcinoma: clinical, morphological and therapeutic correlates. Histopathology. 2013; 62(1):59–70. [PubMed: 23240670]
59. Ahmed N, Abubaker K, Findlay J, Quinn M. Cancerous ovarian stem cells: obscure targets for therapy but relevant to chemoresistance. J Cell Biochem. 2013; 114(1):21–34. [PubMed: 22887554]
60. Romero I, Bast RC Jr. Minireview: human ovarian cancer: biology, current management, and paths to personalizing therapy. Endocrinology. 2012; 153(4):1593–1602. [PubMed: 22416079]
61. Prat J. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. Virchows Arch. 2012; 460(3):237–249. [PubMed: 22322322]
62. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. Pathology. 2011; 43(5):420–432. [PubMed: 21716157]
63. Lalwani N, Prasad SR, Vikram R, Shanbhogue AK, Huettner PC, Fasih N. Histologic, molecular, and cytogenetic features of ovarian cancers: implications for diagnosis and treatment. Radiographics. 2011; 31(3):625–646. [PubMed: 21571648]
64. Muggia F, Safra T, Dubeau L. BRCA genes: lessons learned from experimental and clinical cancer. Annals of Oncology. 2011; 22(Suppl 1):i7–i10. [PubMed: 21285156]
65. Cho KR. Ovarian cancer update: lessons from morphology, molecules, and mice. Arch Pathol Lab Med. 2009; 133(11):1775–1781. [PubMed: 19886711]
66. Muggia F. Platinum compounds 30 years after the introduction of cisplatin: implications for the treatment of ovarian cancer. Gynecol Oncol. 2009; 112(1):275–81. [PubMed: 18977023]

67. Kurman RJ, Shih IeM. Pathogenesis of ovarian cancer: lessons from morphology and molecular biology and their clinical implications. Int J Gynecol Pathol. 2008; 27(2):151–160. [PubMed: 18317228]
68. Gilks CB. Subclassification of ovarian surface epithelial tumors based on correlation of histologic and molecular pathologic data. Int J Gynecol Pathol. 2004; 23(3):200–205. [PubMed: 15213595]
69. Safra T, Borgato L, Nicoletto MO, Rolnitzky L, Pelles-Avraham S, Geva R, Donach ME, Curtin J, Novetsky A, Grenader T, Lai WC, Gabizon A, Boyd L, Muggia F. BRCA mutation status and determinant of outcome in women with recurrent epithelial ovarian cancer treated with pegylated liposomal doxorubicin. Mol Cancer Ther. 2011; 10(10):2000–2007. [PubMed: 21835933]
70. Safra T, Rogowski O, Muggia FM. Effect of germ-line BRCA mutations on response to chemotherapy and outcome of recurrent ovarian cancer. In revision, Int J Gynec Cancer. 2013
71. Bryant HE, Schulz N, Thomas HD, Curtin N. Specific killing of BRCA2 deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005; 434:913–17. [PubMed: 15829966]
72. Farmer H, McCabe N, Lord C, Ashworth A. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005; 434:917–21. [PubMed: 15829967]
73. Plummer R, Jones C, Middleton M, Calvert AH. Phase I study of the poly(ADP-ribose) polymerase inhibitor, AG14699, with temozolomide in patients with advanced solid tumors. Clin Cancer Res. 2008; 14:7917–23. [PubMed: 19047122]
74. Calvert H, Azzariti A. The clinical development of inhibitors of poly(ADP-ribose) polymerase. Ann Oncol. 2011; 22(Suppl 1):i53–i59. [PubMed: 21285153]
75. Fong PC, Boss BS, Yap TA, Gore ME, Kaye SB. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. New Eng J Med. 361:123–134. [PubMed: 19553641]
76. Westin SN, Herzog TJ, Coleman RL. Investigational agents in development for the treatment of ovarian cancer. Invest New Drugs. 2013; 31(1):213–29. [PubMed: 22661305]
77. Banerjee S, Kaye S. The role of targeted therapy in ovarian cancer. Eur J Cancer. 2011; 47(Suppl 3):S116–S130. [PubMed: 21943965]
78. Liang H, Tan AR. Iniparib, a PARP1 inhibitor for the potential treatment of cancer, including triple-negative breast cancer. IDrugs. 2010; 13(9):646–656. [PubMed: 20799148]
79. Kaye SB, Lubinski J, Matulonis U, Ang JE, Gourley C, Karlan BY, Amnon A, Bell-McGuinn KM, Chen LM, Friedlander M, Safra T, Vergote I, Wickens M, Lowe ES, Carmichael J, Kaufman B. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol. 2012; 30(4):372–379. [PubMed: 22203755]
80. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, Scott C, Meier W, Shapira-Frommer R Safra T, Matei D, Macpherson E, Watkins C, Carmichael J, Matulonis U. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012; 366(15): 1382–1392. [PubMed: 22452356]
81. Quinn JE, Carser JE, James CR, Kennedy RD, Harkin DP. BRCA1 and implications for response to chemotherapy in ovarian cancer. Gynecol Oncol. 2009; 113(1):134–142. [PubMed: 19168207]
82. Quinn JE, James CR, Stewart GE, Mulligan JM, White P, Chang GK, Mullan PB, Johnston PG, Wilson RH, Harkin DP. BRCA1 mRNA expression levels predict for overall survival in ovarian cancer after chemotherapy. Clin Cancer Res. 2007; 13(24):7413–7420. [PubMed: 18094425]
83. Chalasani P, Livingston R. Differential Chemotherapeutic Sensitivity for Breast Tumors With "BRCAness": A Review. Oncologist. 2003; 18(8):909–916. [PubMed: 23881989]
84. Tan DS, Rothermundt C, Thomas K, Bancroft E, Eeles R, Shanley S, Ardern-Jones A, Norman A, Kaye SB, Gore ME. "BRCAness" syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. J Clin Oncol. 2008; 26(34):5530–5536. [PubMed: 18955455]
85. Konstantinopoulos PA, Spentzos D, Karlan BY, Taniguchi T, Fountzilas E, Francoeur N, Levine DA, Cannistra SA. Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. J Clin Oncol. 2010; 28(22):3555–3561. [PubMed: 20547991]

86. Bast RC Jr, Mills GB. Personalizing therapy for ovarian cancer: BRCAness and beyond. J Clin Oncol. 2010; 28(22):3545–3548. [PubMed: 20547987]

87. Lesnock JL, Darcy KM, Tian C, Deloia JA, Thrall MM, Zahn C, Armstrong DK, Birrer MJ, Krivak TC. BRCA1 expression and improved survival in ovarian cancer patients treated with intraperitoneal cisplatin and paclitaxel: a Gynecologic Oncology Group Study. Br J Cancer. 2013; 108(6):1231–1237. [PubMed: 23462720]

88. Kwa M, Edwards S, Downey A, Reich E, Wallack R, Curtin J, Muggia F. Ovarian cancer in BRCA mutation carriers: improved outcome after intraperitoneal (IP) cisplatin. Ann Surg Oncol. 2013 (in press).

89. Hughes-Davies L, Huntsman D, Ruas M, Fuks F, Bye J, Chin SF, Milner J, Brown LA, Hsu F, Gilks B, Nielsen T, Schulzer M, Chia S, Ragaz J, Cahn A, Linger L, Ozdag H, Cattaneo E, Jordanova ES, Schuuring E, Yu DS, Venkitaraman A, Ponder B, Doherty A, Aparicio S, Bentley D, Theillet C, Ponting CP, Caldas C, Kouzarides T. EMSY links the BRCA2 pathway to sporadic breast and ovarian cancer. Cell. 2003; 115(5):523–535. [PubMed: 14651845]

90. Rigakos G, Razis E. BRCAness: finding the Achilles heel in ovarian cancer. Oncologist. 2012; 17(7):956–62. [PubMed: 22673632]

Table 1

Genetic and other characteristics associated with BRCAness in ovarian cancer*

Abnormal features and genetic abnormalities	% in ovarian Ca	Reference
BRCA 1 & 2 germline mutation	10-15	96
BRCA 1 & 2 somatic mutation	5-10	97
BRCA promoter methylation	5-30	98
EMSY amplification	20	99
Fanconi anemia complex defects	21	42
PTEN focal deletion/mutation	7	100
Rad 51 hypermethylation	3	101
ATM/ATR mutation	2	102
Serous, pseudo-endometrioid, transitional-cell like, ↑TIL	majority	103

* Modified from reference 90