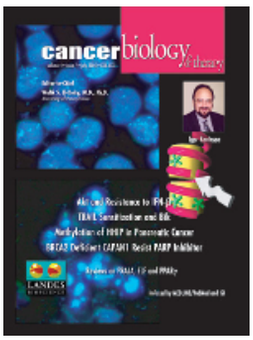

Cancer Biology & Therapy

ISSN: 1538-4047 (Print) 1555-8576 (Online) Journal homepage: https://www.tandfonline.com/loi/kcbt20

Targeted therapy for BRCA2 deficient tumors

Matthew Goetz & Fergus J Couch

To cite this article: Matthew Goetz & Fergus J Couch (2005) Targeted therapy for BRCA2 deficient tumors, Cancer Biology & Therapy, 4:7, 707-708, DOI: 10.4161/cbt.4.7.1998

To link to this article: https://doi.org/10.4161/cbt.4.7.1998

Published online: 25 May 2005.

[Cancer Biology & Therapy 4:7, 707-708, July 2005]; ©2005 Landes Bioscience

Commentary

Targeted Therapy for BRCA2 Deficient Tumors

Matthew Goetz

Fergus J. Couch*

Departments of Oncology and Laboratory Medicine and Pathology; Mayo Clinic School of Medicine; Rochester, Minnesota USA

*Correspondence to: Fergus J. Couch; 200 First Street SW; Mayo Clinic; Rochester Minnesota 55905 USA; Tel.: 507.284.3623; Fax 507.266.0824; Email: couch.fergus@mayo.edu

Received 07/19/05; Accepted 07/20/05

Previously published online as a *Cancer Biology & Therapy* E-publication: http://www.landesbioscience.com/journals/cbt/abstract.php?id=1998

KEY WORDS

BRCA1, BRCA2, PARP, chemotherapy, tissue specificty

Commentary to:

Absence of Specific Cell Killing of the BRCA2-Deficient Human Cancer Cell Line CAPAN1 by Poly(ADP-Ribose) Polymerase Inhibition

Eike Gallmeier and Scott E. Kern

A growing understanding of the molecular, genetic and biochemical changes that occur during the process of carcinogenesis, progression and metastasis has shifted the focus of drug development away from empirical therapy towards therapeutics that act on specific molecular targets responsible for the malignant phenotype. A prime example of this is trastuzumab, a monoclonal antibody that targets the extracellular domain of Her2 and reduces disease recurrence and improves survival for surgically resected Her2 overexpressing breast cancer patients (NSAPB B31 and NCCTG N9831 joint analysis, and HERA trial, ASCO 2005).

Similar efforts are now underway to develop targeted therapies for breast tumors arising in *BRCA1* and *BRCA2* mutation carriers. The genetic changes in the *BRCA1* and *BRCA2* tumor suppressor genes that predispose to carcinogenesis have been well characterized and have been shown to result in unique patterns of chromosomal rearrangements[1] and gene expression.[2] Indeed, mutations in *BRCA1* are strongly associated with the so-called basal-type or myoepithelial-like breast tumors that are commonly estrogen receptor negative, progesterone receptor negative and Her2 negative and often EGFR positive. Based on these observations preclinical studies of the influence of targeted therapies such as EGFR inhibitors on *BRCA1* deficient cells are underway. In contrast, *BRCA2* deficient tumors do not display such an obvious genotype-phenotype correlation. However, disruption of BRCA2 in cells, similarly to BRCA1, results in a significant deficiency in homologous recombination.[3,4] Importantly, this phenotype is evident in all evaluated BRCA2 deficient cell types including embryonic stem cells (ES), mouse embryonic fibroblasts (MEFs), chinese hamster lung fibroblasts (V-C8), the CAPAN1 human pancreatic cancer cell line, FANCD1 BRCA2 deficient cells and BRCA2 RNAi treated cancer cell lines, suggesting that this phenotype could be targeted for therapeutic purposes.

Recent studies demonstrating enhanced sensitivity to cross-linking agents such as cis- or carboplatinum or mitomycin C in BRCA2 deficient cells supports the promise of this approach.[5-7] These agents promote intra- and interstrand crosslinks which are repaired predominately by homologous recombination and secondarily by single strand annealing (SSA) and/or non-homologous end joining (NHEJ). In the absence of BRCA2 these induced crosslinks result in either unrepaired DNA breaks and chromosomal instability and/or error prone repair and subsequent cell death. To evaluate the clinical efficacy of these agents in BRCA2 deficient tumors two clinical trials have proposed. One randomizes patients with metastatic *BRCA1* or *BRCA2* breast cancers to carboplatin and docetaxel chemotherapy,[8] while the other randomizes patients with *BRCA2* pancreatic cancers to gemcitabine and mitomycin C.[9]

However, because of the partial redundancy in cellular DNA repair it may be necessary to promote the formation of double strand breaks in BRCA2 deficient cells in order to induce lethality. Recently, two separate groups suggested that the use of Poly(ADP-ribose)polymerase (PARP) enzyme inhibitors in BRCA1 and BRCA2 mutant cell lines may lead to the development of replication dependent double strand breaks which persist in the absence of BRCA1 or BRCA2 dependent homologous recombination and cause enhanced cell death.[10,11]These groups demonstrated that PARP inhibition led to selective toxicity in BRCA2 deficient ES cells, V-C8 cells and BRCA2 RNAi treated cancer cells, and proposed that PARP inhibition may prove useful as a highly specific and non-toxic treatment for patients with BRCA deficiency. Importantly, Gallmeier and colleagues have shown in the accompanying article[12] that the use of a PARP inhibitor in the cancer cell line CAPAN1, a pancreatic cancer cell line harboring the common inactivating *BRCA2* 6174delT mutation, did not result in cell killing. The authors cautioned that PARP inhibition alone may not be sufficient for BRCA2 deficient cell killing.[12]

How must these differing results be interpreted? In the report by Gallmeier et al.[12] it is unclear whether the level of PARP enzyme inhibition was adequate for cell killing, a finding which could be analyzed by examining PARP protein levels or by means of introducing

PARP siRNA into the CAPAN1 cell line. This is important, as BRCA deficient cancer cells may have increased levels of PARP as a means of cell survival. However, the most glaring difference between these reports is in the cells that were used for evaluation of PARP inhibition. Farmer et al.[10] utilized BRCA2 deficient ES cells for cell survival and xenograft studies of specific PARP inhibitors, while Bryant et al.[11] were limited to BRCA2 deficient V-C8 hamster cells and human breast cancer cell lines engineered for BRCA2 deficiency using RNAi approaches. In contrast, Gallmeier and colleagues used a pancreatic cancer cell line deficient in BRCA2 repair secondary to an inactivating mutation.[12] Given the range of cells used in these studies it is not possible to reconcile the results. Clearly, tissue specific differences in DNA repair capacity and in active DNA repair pathways may contribute to the different outcomes. Should pancreatic epithelial cells exhibit more active single and double strand repair activity in the absence of BRCA2 than breast epithelial cells, even in the form of error-prone repair, then the toxicity induced by PARP inhibition might be expected to be greatly reduced. In addition, when considering the value of the presented data one must question how the influence of PARP inhibition on mouse ES cells and hamster lung fibroblasts translates to either breast or pancreatic epithelial tumor cells. Likewise, it is important to consider how genetic events secondary to BRCA2 deficiency that have accumulated in these models may also influence the response to PARP inhibition. Overall, there is no perfect preclinical model for evaluation of the influence of PARP inhibitors on BRCA2 deficient tumors, although the application of PARP inhibitors to orthotopic xenografts of human BRCA2 deficient tumors or to tumors developing in brca2 deficient conditional mouse models would represent the most rigorous approach. One additional variable in these studies that should not be overlooked is the form of PARP inhibitor utilized. It is certainly plausible that the different agents used to inhibit PARP may have differing secondary effects on other proteins and/or pathways in cells in a manner that contributes to the discrepancy in the results.

Overall, these studies raise the interesting prospect that targeted therapeutics for BRCA2 and BRCA1 deficient tumors may be available in the near future. However, in the context of PARP inhibition, it is clear that more work must be done to better understand the specificity and sensitivity of PARP inhibitors for BRCA2 deficient cells and tumors. We must await the outcome of additional studies to determine whether PARP inhibitors alone or in combination with crosslinking agents or inhibitors of other BRCA1 or BRCA2 specific signaling pathways may prove useful for treatment of patients carrying *BRCA1* and/or *BRCA2* mutations. In addition, these studies further illustrate the limited availability of reagents for study of BRCA deficiency and treatment of BRCA deficient tumors and suggests the continued need for development of appropriate cancer models for these purposes.

References

1. Tirkkonen M, Johannsson O, Agnarsson BA, Olsson H, Ingvarsson S, Karhu R, Tanner M, Isola J, Barkardottir RB, Borg A, Kallioniemi OP. Distinct somatic genetic changes associated with tumor progression in carriers of BRCA1 and BRCA2 germ-line mutations. Cancer Res 1997; 57:1222-7.
2. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge Ø, Pergamenschikov A, Williams C, Zhus SX, Lonning PE, Borresen-Dale A, Brown PO, Botstein D. Molecular portraits of human breast tumours. Nature 2000; 406:747-52.
3. Moynahan ME, Chiu JW, Koller BH, Jasin M. Brca1 controls homology-directed DNA repair. Mol Cell 1999; 4:511-8.
4. Moynahan ME, Pierce AJ, Jasin M. BRCA2 is required for homology-directed repair of chromosomal breaks. Mol Cell 2001; 7:263-72.
5. Howlett NG, Taniguchi T, Olson S, Cox B, Waisfisz Q, De Die-Smulders C, Persky N, Grompe M, Joenje H, Pals G, Ikeda H, Fox EA, D'Andrea AD. Biallelic inactivation of BRCA2 in Fanconi anemia. Science 2002; 297:606-9.
6. Kraakman-van der Zwet M, Overkamp WJ, van Lange RE, Essers J, van Duijn-Goedhart A, Wiggers I, Swaminathan S, van Buul PP, Errami A, Tan RT, Jaspers NG, Sharan SK, Kanaar R, Zdzienicka MZ. Brca2 (XRCC11) deficiency results in radioresistant DNA synthesis and a higher frequency of spontaneous deletions. Mol Cell Biol 2002; 22:669-79.
7. Bhattacharyya A, Ear US, Koller BH, Weichselbaum RR, Bishop DK. The breast cancer susceptibility gene BRCA1 is required for subnuclear assembly of Rad51 and survival following treatment with the DNA cross-linking agent cisplatin. J Biol Chem 2000; 275:23899-903.
8. Couzin J. Choices - and uncertainties - for women with BRCA mutations. Science 2003; 302:592.
9. van der Heijden MS, Brody JR, Gallmeier E, Cunningham SC, Dezentje DA, Shen D, Hruban RH, Kern SE. Functional defects in the fanconi anemia pathway in pancreatic cancer cells. Am J Pathol 2004; 165:651-7.
10. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005; 434:917-21.
11. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, Kyle S, Meuth M, Curtin NJ, Helleday T. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005; 434:913-7.
12. Gallmeier E and Kern SE. Absence of Specific Cell Killing of the BRCA2-Deficient Human Cancer Cell Line CAPAN1 by Poly(ADP-ribose) Polymerase Inhibition. Cancer Biol and Therapy 2005; 4:70-3.