PARP inhibitors in BRCA1-/BRCA2-associated and triple-negative breast cancers

“PARP inhibitors induce the generation of unrepaired DNA single-strand breaks, which appear to cause the accumulation of double-strand breaks...”

Justin Stebbing[†], Paul Ellis & Andrew Tutt

[†]Author for correspondence: Imperial College Healthcare NHS Trust, The Hammersmith Hospitals, Department of Oncology & Surgery, Du Cane Road, London, W12 0NN, UK ■ Tel.: +44 203 311 8295 ■ Fax: +44 208 846 1433 ■ j.stebbing@imperial.ac.uk

Damage to DNA has emerged as a major culprit in cancer. The stability of the genome is supported by an intricate machinery of repair, damage tolerance and checkpoint pathways that counteracts such damage. In addition, DNA damage and other stresses can trigger a highly conserved anticancer survival response that suppresses metabolism and growth, and enhances defenses that maintain the integrity of the cell. Although DNA is the carrier of genetic information, it has limited chemical stability, and specific DNA repair processes counteract mutagenesis [1]. Unable to remanufacture itself, DNA remains the only biologic molecule that relies solely on the repair of existing molecules.

One of the most topical mechanisms of repair now concerns the structurally diverse poly(ADP-ribose) polymerases (PARPs); especially PARP1, enzymes that repair single-strand breaks or ‘nicks’ via base excision. PARP inhibition fosters the accumulation of DNA single-strand breaks, which can lead to DNA double-strand breaks at replication forks. Normally, these breaks are repaired by means of the error-free homologous-recombination dsDNA repair pathway [2], key components of which are the tumor-suppressor proteins BRCA1 and BRCA2 [3].

Carcinogenesis in cells with loss-of-function BRCA mutations is driven by their defective homologous-recombination repair. PARP inhibitors induce the generation of unrepaired DNA single-strand breaks, which appear to cause the accumulation of double-strand breaks, remarkable findings as shown by back-to-back reports in *Nature* [4,5]. This represents so-called ‘synthetic lethality’: two genes are said to be in

a synthetic lethal relationship if a mutation in either gene alone is not lethal but mutations in both cause the death of the cell.

One of the first Phase I studies using this genetically defined targeted approach was published in the *New England Journal of Medicine* [6]: Fong *et al.* demonstrated stabilization or regression of BRCA1- or BRCA2-defective breast, ovarian and prostate cancers in response to an oral PARP inhibitor; no activity was seen outside BRCA1- or BRCA2-defective tumors. As the products of oncogenes that are overexpressed in cancer cells are usually identical to, or very similar to, their normal counterparts, the selective killing of these cancer cells is of particular significance.

“...stabilization or regression of BRCA1- or BRCA2-defective breast, ovarian and prostate cancers in response to an oral PARP inhibitor (was demonstrated)...”

In a subsequent single-arm, proof-of-concept Phase II study using PARP inhibitors in patients with BRCA1/BRCA2 mutations and recurrent, measurable, chemotherapy-refractory breast cancer, the overall response rate measured 38%, with the main grade 3 toxicities being fatigue, nausea and vomiting [7]. In a randomized Phase II study using an intravenous version of a PARP inhibitor, the 60 patients with metastatic triple-negative breast cancer who received the new therapy in addition to standard of care had statistically significant improvements in progression-free (hazard ratio: 0.3; 95% CI: 0.15–0.59) and overall survival (hazard ratio: 0.24; 95% CI: 0.09–0.61) [8], even after

Keywords

- breast cancer ■ BRCA
- PARP inhibitor
- triple negative

future medicine part of fsg

crossover from the gemcitabine–carboplatin control arm. Similar data were obtained for BRCA-deficient advanced ovarian cancer [9].

Tumors are genetically complex, and the story is far from perfect. For example, BRCA2 reversion, for example in pancreatic cell lines, causes resistance to both cisplatin and PARP inhibition [10], and similar observations have occurred with BRCA1 reversion in ovarian lines [11]. In a simple experiment, resistance to PARP inhibition, once again in pancreatic cancer lines, can be acquired by deletion of a frameshift mutation in BRCA2 [12]. As mechanisms of resistance appear to be shared by PARP inhibitors and platinum salts, it remains to be seen whether individual mutations may be predictive of therapeutic response and ultimately prognostic for overall survival. If genetic reversion events are stochastic, this implies that resistance is statistically more likely to occur in advanced disease, where the challenge is to sterilize a large mass of cancer cells compared with the adjuvant setting, where few micrometastases may be present, which can in turn provide the raw material for resistance to develop [13,14].

In oncology, we have often been unable to replicate the successes observed at Phase II in the later stages of drug development, but a number of features here (i.e., rational mechanism based on synthetic lethality and consistency of data, including consistency across pharmaceutical companies) suggest that the end points of the large registration-quality randomized studies will be achieved. The frequent derailment of DNA damage-response systems in tumors presents a likely route by which new treatments can act selectively on cancer cells. As well as leading to a new therapeutic area, such endeavors have implications for understanding drug resistance in BRCA mutation carriers and in tumor cells in general.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1. Lindahl T: Instability and decay of the primary structure of DNA. *Nature* 362(6422), 709–715 (1993).
2. McCabe N, Turner NC, Lord CJ *et al.*: Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. *Cancer Res.* 66(16), 8109–8115 (2006).
3. Gudmundsdottir K, Ashworth A: The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability. *Oncogene* 25(43), 5864–5874 (2006).
4. Farmer H, McCabe N, Lord CJ *et al.*: Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 434(7035), 917–921 (2005).
5. Bryant HE, Schultz N, Thomas HD *et al.*: Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 434(7035), 913–917 (2005).
6. Fong PC, Boss DS, Yap TA *et al.*: Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N. Engl. J. Med.* 361(2), 123–134 (2009).
7. Tutt A, Robson M, Garber JE, Domchek S: Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer. *J. Clin. Oncol.* 27(Suppl. Abstract CRA501), S18 (2009).
8. O'Shaughnessy JO, Osborne C, Pippen J, Yoffe M: Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): results of a randomized Phase II trial. *J. Clin. Oncol.* 27(Suppl. Abstract 3), S18 (2009).
9. Audeh MW, Penson RT, Friedlander M, Powell B: Phase II trial of the oral PARP inhibitor olaparib (AZD2281) in BRCA-deficient advanced ovarian cancer. *J. Clin. Oncol.* 27(Suppl. Abstract 5500), S15 (2009).
10. Sakai W, Swisher EM, Karlan BY *et al.*: Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. *Nature* 451(7182), 1116–1120 (2008).
11. Swisher EM, Sakai W, Karlan BY, Wurz K, Urban N, Taniguchi T: Secondary BRCA1 mutations in BRCA1-mutated ovarian carcinomas with platinum resistance. *Cancer Res.* 68(8), 2581–2586 (2008).
12. Edwards SL, Brough R, Lord CJ *et al.*: Resistance to therapy caused by intragenic deletion in BRCA2. *Nature* 451(7182), 1111–1115 (2008).
13. Ashworth A: Drug resistance caused by reversion mutation. *Cancer Res.* 68(24), 10021–10023 (2008).
14. Ashworth A: A synthetic lethal therapeutic approach: poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. *J. Clin. Oncol.* 26(22), 3785–3790 (2008).

Affiliations

- Paul Ellis
Department of Oncology,
Guy's & St Thomas' NHS Trust, & Kings
College Hospital, London, UK
paul@ellis-uk.org
- Justin Stebbing, MA, MRCP,
FRCPath, PhD
Consultant Medical Oncologist/ Senior
Lecturer, Imperial College Healthcare
NHS Trust, The Hammersmith Hospitals,
Department of Oncology & Surgery,
Du Cane Road, London, W12 0NN, UK
Tel.: +44 203 311 8295
Fax: +44 208 846 1433
j.stebbing@imperial.ac.uk
- Andrew Tutt, PhD, MRCP, FRCR
Consultant Clinical Oncologist/Director,
Breakthrough Breast Cancer Research
Unit, Guy's Hospital, King's Health
Partners AHSC, London, UK
andrew.tutt@kcl.ac.uk