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PARP inhibition: opening up new horizons?

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"The primary lesson learned from these results is the undoubted need of incorporating translational studies into the clinical trials in order to identify predictive markers of PARP-inhibition sensitivity."

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Over the last almost 50 years, poly(ADP-ribosyl)ation polymerase (PARP) has sailed the calm seas of clearly arranged basic research and steady gathering of evidence, its relevance remaining elusive for substantial parts of the biomedical community. Although it is widely appreciated that PARP is involved in different steps of DNA repair, research did not pick up pace until two landmark papers were published in 2005 and, subsequently, clinical PARP science gathered momentum. These papers described the mechanism of 'synthetic lethality' in *BRCA1*- and *BRCA2*-mutant cell lines after their exposure to PARP inhibitors. According to this concept, cells carrying BRCA mutations are "profoundly sensitized, to the inhibition of PARP-enzymatic activity" [1,2] owing to their reduced capability of homologues recombination. Since PARP is an integral component of the single-strand break-repair complex, inhibition of PARP results in accumulation of unrepaired single-strand breaks, leading to double-strand breaks during DNA transcription, which normally is 'repaired' sufficiently in cells with functioning homologous recombination. Therefore, *BRCA*-mutant cells that do not harbor this feature sufficiently are prone to chromosomal instability, cell cycle arrest and subsequent apoptosis.

The aforementioned sudden acceleration of PARP research was rendered possible by the development of potent hydrophile and nontoxic PARP inhibitors, the 'freshening wind' in this narrative. PARP inhibitors became available as early as the 1970s, but one of the crucial developments of second-generation PARP inhibitors was the bi- and tri-cyclic shape of the molecules that increased the potency of PARP inhibition early in the third millennium [3].

The way was led by the promising preclinical results, thus clinical trials in *BRCA*-mutation carriers were launched in breast and ovarian cancer patients. Those studies also showed encouraging results, and apparitional land was suspected at the horizon of the seascape of cancer treatment. One of the first PARP inhibitors in the clinical setting was olaparib and it has been shown to be active as a single agent in BRCA-mutation carriers with recurrent high-grade serous ovarian cancer [4] and metastatic breast cancer [5]. However, cancers due to *BRCA* mutations only account for approximately 5% of breast and 5–10% of ovarian cancer cases [6], and thus the apparitional land at the horizon was rather suspected to be islands rather than continents by most, but not all.

Enthusiastic reports described a phenomenon called 'BRCAness', indicating that cancers even with a nonmutated *BRCA1* gene might exhibit a loss of functioning homologues recombination. Several causative mechanisms for BRCAness were proposed, for example aberrant methylation of cytosine residues in CpG dinucleotids of the BRCA1 promoter or the fanconia anaemia gene, both active in homologues recombination [7].

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In ovarian cancer it is most likely that the concept of BRCAness is appropriate [8], and it was hypothesized that up to 31% of patients with high-grade serous ovarian cancer would apply to the concept of BRCAness and dysfunctional BRCA.

The triple-negative breast cancer phenotype, characterized by non-expression of estrogen, progesterone and HER2 receptors has been associated with shortened disease-free and overall survival, and chemotherapy is presently the only therapeutic option [9]. Up to 19.5% of these patients show BRCA mutations [10] and 'although the concept of BRCAness is not proved in triple-negative breast cancer' [11], it shares typical pathological features with tumors of BRCA-mutation carriers [7]. Owing to this observation, a randomized Phase II trial using another PARP inhibitor (iniparib) in combination with carboplatin and gemcitabine was conducted and encouraging results were recently published [12].

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However, the approach towards the newly discovered land is difficult, since some questions remain open and concerns about the quality of BRCAness in triple-negative breast cancer were raised in another Phase II trial. Patients with recurrent ovarian cancer and metastatic triple-negative breast cancer were treated with a monotherapy olaparib [13]. In this trial, patients with BRCA-associated ovarian cancer and spontaneously occurred ovarian cancer showed an overall response rate of 41 and 26% (evaluated by Response Evaluation Criteria In Solid Tumors [RECIST]), respectively, but none of the patients with triple-negative (non-*BRCA* mutated) breast cancer demonstrated a convincing response [13]. These results indicate that BRCAness might not be a characteristic property of triple-negative breast cancer and/or that different cancers are more or less sensitive to different PARP inhibitors. However, the latter Phase II trial was rather small, including only some 20 triple-negative breast cancer patients, and thus no final statement was warranted.

In a January 2011 alert, Sanofi-Aventis announced that the randomized Phase III trial evaluating iniparib in combination with carboplatin and gemcitabine in patients with metastatic triple-negative breast cancer did not meet the primary end points of overall survival and progression-free survival, and thus further vigilance is necessary in this field [101].

The primary lesson learned from these results is the undoubted need of incorporating translational studies into the clinical trials in order to identify predictive markers of PARP-inhibition sensitivity. The practical determination of this BRCAness as a prerequisite for PARP-inhibitor treatment is one of the most urgent scientific challenge in this field. Two interesting approaches to this challenge have been published recently. In one study, core biopsies from breast cancer patients were obtained and subjected to x-irradiation. Samples were incubated and then frozen for analysis. It was shown that three out of seven irradiated tumor-tissue specimens had an increased percentage of cell nuclei containing RAD51 foci – the biological detectable correlate for homologues recombination – when compared with the non-irradiated controls [14]. In another study, harvested malignant ascites from patients with ovarian cancer, were seeded and exposed to a PARP inhibitor. The status of homologues recombination was again determined by the assessment of RAD51 foci formation. Cytotoxic effects caused by treatment with a PARP inhibitor were demonstrated in all 25 primary cultures, and nine out of 25 samples demonstrated elevated RAD51 levels, and were thus deemed to be competent in homologues recombination. Moreover, all samples competent in homologues recombination remained viable in cell survival assays, but in 15 out of 16 samples, which were supposed to be incompetent in homologues recombination, a reduction in cell survival was observed [15].

These studies suggest that DNA-repair foci could be used to detect functionally relevant BRCA defects in sporadic breast and ovarian cancers. Nevertheless, although these techniques look quite sophisticated, no correlations were reported with respect to the clinical course of the patients, and the concept of cytotoxic assays has not been successfully evaluated in prospective randomized trials yet.

Another wide field for further research is the expansion of PARP-inhibition therapeutic use beyond the treatment of breast and ovarian cancer. Phase I trials have included patients with other solid malignancies such as prostate and non-small-cell lung cancer as well as patients with hemato-oncologic malignancies [16]. In a Phase I trial of the PARP inhibitor, MK-4827, it was demonstrated that patients with metastatic non-small-cell lung cancer had stable disease for more than 4 months [102], and in another Phase I trial, the combination of olaparib and dacarbazine resulted in partial responses in melanoma patients [17]. Results of a large randomized Phase II trial of ABT-888 and temozolomide with over 300 patients will provide more insight into the potential for PARP inhibition in melanoma [103].

Further potential indications for PARP inhibition are conceivable in entities treated with chemotherapeutic agents inducing DNA single-strand breaks and radiation. The underlying mechanism of action would not be the concept of 'synthetic lethality', but a sensitizing of tumor cells for other cytotoxic agents, for example platinum or radiation. One way to identify further tumor entities that might be susceptible to treatment with PARP inhibitors is the conventional approach, that is, Phase I and II trials. In the case of clinical development of the agent ABT-888, another approach was chosen. Patients with advanced solid tumors were included in a Phase 0 trial and subjected to sequential biopsies after application of the PARP inhibitor. One of the goals of this study was to determine activity of PARP in the tumor specimen dependent on the ABT-888 dose, and it was demonstrated that PARP activity was reduced significantly with single doses of the drug [18]. In continuation of the latter approach, it seems to be feasible to conduct screening studies in other entities with known effective dosages of a PARP inhibitor. After a tumor biopsy and baseline assessment of PARP activity, a PARP inhibitor is administered, and further activity of PARP and consecutive homologues recombination would be assessed in sequential biopsies. If PARP activity would be reduced in these specimens and homologues recombination is elevated, the treated entity would likely be a further candidate for PARP inhibition.

Finally, it has to be stated that PARP inhibition is an elegant way to target weaknesses of cancer cells, and *BRCA*-mutation carriers with breast cancer and ovarian cancer are most likely to respond to this treatment. Conflicting results with respect to a possible expansion of the indication of cancers thought to exhibit features of BRCAness, such as triple-negative breast cancer, have been reported, and further research will focus on predictors of successfull PARP-inhibition treatment.

The question of whether this narrative will eventually end with the discovery of new land is currently still open, and even more so, the question of whether it will be an island or a continent. The appropriation of a new island – the introduction of PARP inhibitors in the routine treatment of patients with *BRCA*-germline mutations – will depend on the results of the currently recruiting Phase III trials. However, the discovery of opportunities to broaden the spectrum of indications – indeed a possible new 'continent' – requires far more basic research, in particular, in terms of the selection of patients with a potential benefit.

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