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Poly(ADP-ribose) polymerase (PARP) inhibitors and ovarian cancer

There is still a big gap from the basic research (bench) to the clinical use (bed) in precise and personal therapy for patients with epithelial ovarian cancer (EOC) [1]. Because of slow progress in improving the outcome of EOC with chemotherapy over the past three decades, enthusiasm swelled for one of the targeted therapy, such as poly(ADP-ribose) polymerase (PARP) inhibitors which might be a part of the current treatment strategy when the positive results from the randomized, placebo-controlled, phase 3 trial (ENGOT-OV16/NOVA) conducted by the European Network for Gynecological Oncological Trial groups was obtained and published in *The New England Journal of Medicine* [2]. Maintenance therapy with the PARP inhibitor niraparib (Tesaro) produced a significantly prolonged progression-free survival (PFS) in patients with recurrent platinum-sensitive EOC with complete or partial post platinum-based chemotherapy compared with placebo. The principle investigator – Dr. Mirza and other investigators in the United States, Canada, and Hungary, enrolled 553 patients and separated them into two cohorts, including 203 patients with germline *BRCA 1/2* mutation, and the other 350 patients without germline *BRCA 1/2* mutation [2]. Although the benefit was greatest in patients with germline *BRCA 1/2* mutations with the statistically significant increase of median PFS by 15.5 months (21.0 vs. 5.5 months in the germline *BRCA 1/2* mutation cohort with and without PARP inhibitor, respectively; hazard ratio [HR] 0.27; 95% confidence interval [CI] 0.17–0.41), followed by homologous recombination deficiency (HRD)-positive tumors by increasing median PFS by 9.1 months (12.9 months vs. 3.8 months, HR 0.38, 95% CI 0.24–0.59) [2], the possible benefits of PRAP inhibitor treatment were seen in all cohorts, regardless of the presence or absence (9.3 months vs. 3.9 months, HR 0.45, 95% CI 0.34–0.61) of germline *BRCA 1/2* mutations, or of presence or absence (6.9 months vs. 3.8 months, HR 0.58, 95% CI 0.36–0.92) of HRD [3]. This result is promising, since the similar treatment strategy might be applicable for Taiwanese women with EOC. EOC is still a highly lethal disease and presents a therapeutic challenge in Taiwan [4–6]. Pathologic and genetic *BRCA 1/2* mutations in Taiwanese patients with EOC might be more common than those we supposed before [7,8]. PARP inhibitors represent a stop change in the management of ovarian cancer and *BRCA 1/2* mutations are the first genotypic predictive markers in ovarian cancer and can be used for patients who might be most likely beneficial from PARP inhibitors treatment [9,10]. In fact, our previous publication entitled "Outstanding female cancer research paper awards of the 2016 Taiwan Association of Obstetrics and Gynecology and Hsu Chien-Tien Cancer Foundation" have already echoed the potential role of pre-treatment genetic tests in patients with EOC by using wide whole gene screening [11].

To further increase our understanding how the PARP inhibitors work, DNA damage repair mechanism operational in mammalian cells should be recalled, since DNA repair processes are critical for accurate cell replication and maintenance of genomic stability [12]. Cells are always and continually faced by an outbreak of DNA damage, which occurs either through normal cellular functions, including metabolic processes resulting in the generation of reactive oxygen radicals and through replication errors, or through a result of exogenous damage such as UV light, ambient and therapeutic radiation, exposure to chemicals, heavy metals, including those in diets [12–14]. There are at least five major steps, including base excision repair, nucleotide excision repair, and mismatch repair, which are the primary mechanisms to resolve single-stranded breaks [14]. Homologous recombination, a high fidelity repair system relying on a homologous sequence of chromosomes adjacent to the site of breakage as a template to ensure accurate restoration of the DNA sequence and nonhomologous end joining, an error prone pathway with lower fidelity, which dissects the DNA damage and joins unrelated DNA strands, causing altered nucleotide sequences and gene rearrangements, are the two pathways responsible for repairing double-stranded breaks [14].

PARPs, a family of 17 proteins, including the most abundant form-PARP-1, and together with PARP-2 found in the nucleus, acting as a "molecular nick sensor" to signal DNA single-strand breaks and assist in their repair (base excision repair pathway for DNA single-strand breaks), are highly conserved enzymes, which, when activated, catalyze the formation of ADP-ribose polymers using nicotinamide adenine dinucleotide (NAD) as a substrate [15]. PARP consists of three major domains, including (1) the DNA-binding domain, which includes two zinc-finger motifs that bind DNA break; (2) a centrally located 16 kDa automodification domain; and (3) the 55 kDa catalytic domain of human PARP, located in the COOH-terminal region of the enzyme, which is the region of highest conservation between species called "PARP signature" [12]. In fact, many drugs discovery programmes have focused on the PARP signature sites [12]. PARP inhibitors cause an increase in single-strand breaks in DN that, if left unrepaired, will lead to double strand breaks when encountered by replication forks [15]. In the laboratory, HRD cells are unable to maintain genomic integrity in the presence of a large number of DNA double-strand breaks and are exquisitely sensitive to PARP inhibition [15].

Finally, PARP inhibitors represent a step change in the management of EOC, because of slow progress in improving the outcome of EOC with chemotherapy over the past three decades. PARP inhibitors, including olaparib (AZD2281, lynparza®, AstraZeneca; clinical trials of SOLO-1, SOLO-2, ENGOT oOV25, NRG-GY004, NRG-GY005, and ICON 9), rucaparib (AGO14699; CO338, and PF01367338, Clovis Oncology; clinical trials of ARIEL2 and ARIEL3), niraparib (MK4827, Tesaro; clinical trial of NOV, and ENGOT OV24), talazoparib (MDV3800, BMN 673, BioMarin Pharmaceutical Inc) and veliparib (ABT-888, AbbVie; clinical trial of GOG 3005) [9] have shown the

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greatest benefits to-date in the maintenance setting, prolonging the PFS of high-grade serous EOC, especially for those with *BRCA 1/2* mutations or HRD. A potent PARP inhibitor should have a good cell based activity, selectivity for cancer over normal cells, and oral bioavailability [12].

Conflicts of interest

All authors declare no conflict of interest.

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