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PARP (poly (ADP)-ribose polymerase) Inhibitors – Application of Synthetic Lethality Concepts in Cancer Treatments

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Abstract:- The different types and the overwhelming number of cancer cases across the globe have prompted scholars to pursue more effective therapies than traditional treatments. One approach that has demonstrated considerable progress is related to the use of PARP inhibitors. Essentially, PARP inhibitors such as Talazoparib, Olaparib and Rucaparib use a concept of synthetic lethality to kill tumour cells. According to Sebastian (2011) synthetic lethality occurs when a deficiency in one gene expression does not cause cell death while a collection of two or more deficiencies in gene expression leads to cell death. PARP inhibitors exploit this concept to eradicate tumour cells.

Keywords:- *PARP Inhibitors, Talazoparib, Olaparib, Rucaparib.*

I. INTRODUCTION

In detail, normal and cancer cells undergo constant DNA damage due to environmental hazards and other molecular toxics. Normal cells repair DNA damage through two pathways; (1)PARP which is primed for repairing single strands and ; (2) BRCA1/2 that repairs double strands (Sebastian, 2011; Litton, et al., 2018). By contrast, a cancer cell with deficiencies in BRCA1 and BRCA2 gene expression only has the PARP pathway to repair DNA damage (Sebastian, 2011). Therefore, introducing PARP inhibitors such Talazoparib, Olaparib and Rucaparib make it impossible to repair DNA damage in tumour cells thus, leading to further damage ending in cell death (Sebastian, 2011; Litton, et al., 2018). PARP inhibitors do not kill normal cells as they still have the BRCA1/2 pathways to repair DNA (Litton, et al., 2018).

II. RESULTS AND DISCUSSION

➢ *Talazoparib*

One of the most common cancer therapies based on PARP inhibitors is Talazoparib which is used to treat breast cancer (Exman, et al., 2019; Litton, et al., 2018). From the EMBRACA clinical trials, Talazoparib is a more potent treatment than conventional cancer therapy based on platinum (Litton, et al., 2018). Notably, Talazoparib, Olaparib and Rucaparib work solely in patients with mutations in BRCA1/2 which impedes homologous recombination (Exman, et al., 2019). Even though Talazoparib is considered more effective than standard cancer treatment, researchers observed a lower response rate in patients who had previous exposure with conventional therapy based on platinum (Litton, et al., 2018). Patients from the EMBRACA clinical trials indicate higher QoL, PFS and OS after the intervention in comparison to those receiving standard platinum therapy (Shen, et al., 2013).Specifically, interim analysis from the EMRACA clinical trials recorded an Overall Survival of 22.3 months in comparison to 19.5 months from standard chemotherapy (Exman, et al., 2019). The Overall Survival Rate is yet to be determined from ongoing research since Talazoparib is a relatively novel drug only approved in 16th October, 2018 (Exman, et al., 2019). Side effects of Talazoparib include nausea, fatigue and anaemia (Litton, et al., 2018).

➢ *Olaparib*

Olaparib has been studied in different types of cancer. Well known clinical trials generating knowledge on the drug are the NRG Oncology trial and the PAOLA-1 trials (Oza, et al., 2015). The drug is effective at treating refractory ovarian cancer, breast cancer and Oviduct cancer (Institute of Cancer Research, 2019). In contrast to Talazoparib, Olaparib can be used efficiently in conjunction with other cancer therapies (Washington, et al., 2019). Research indicates that Olaparib is effective at eliminating targeted tumour cells; however, cancer may relapse after a while usually less than three years (Institute of Cancer Research, 2019). Olaparib has had successful outcomes as a maintenance drug for patients suffering from Ovarian cancer. As of 2016 and with 79% maturity data, Olaparib recorded an Overall Survival Rate of 75% (European Society For Medical Oncology, 2018). Even so Olaparib is relatively ineffective in other scenarios for instance, Robson, et al.(2019) observed that there was no improvement in the Overall Survival rate for patients with metastatic breast cancer. Patients who undergo treatment with Olaparib experience side effects such as nausea, fatigue, heartburn and constipation (European Society For Medical Oncology, 2018).

➢ *Rucaparib*

Rucaparib is a PARP inhibitor used to treat advanced ovarian cancer and endometrial cancer (Shirley, 2019). In the ARIEL-2 trial, researchers emphasized the role of Rucaparib as maintenance therapy (Yvette Drew, et al., 2019). Specifically, Rucaparib is an approved therapy for women with ovarian cancer who have undergone more than two chemotherapies (Molin, et al., 2018). From studies, the

drug has different degrees of outcomes depending on the presence of LOH (loss of heterozygosity) which is the subsequent loss of a gene and the chromosomal region surrounding the gene or the existence BRCA gene mutations (Molin, et al., 2018). Data on the efficacy of Rucaparib is still being collected and is not mature to be used in the calculation of the overall survival rate (Molin, et al., 2018).Nevertheless, the overall rate of response (ORR) of Rucaparib in ARIEL 3 patients with BRCA1/2 mutations is 38% which is significantly higher than placebo at 9%. Notably, clinical trials indicate that the Rucaparib may display "off-target effects" when interacting with PARP1 and PARP2 (Molin, et al., 2018) The most common side-effects after treatment with the drug are fatigue (69%), nausea (75%), constipation and vomiting (Molin, et al., 2018; Yvette Drew, et al., 2019).

III. CONCLUSION

PARP inhibitors are generally effective in treating cancers, nonetheless, more clinical trials and research have to be conducted in order to increase its overall efficacy, improve the overall survival rate of cancer patients, and reduce the associated side effects. Furthermore, it is worth considering that PARP inhibitors should be combined with other medications to create stronger drug cocktails capable of delivering more efficacious results accompanied by lesser adverse outcomes. Overall, PARP inhibitors demonstrate high potential in cancer treatments, and might become an ideal drug, not only restricted to cancer treatments, but also in other domains of medicine and biomedical science, such as metabolic pathway disorders and genetic defects, in time to come.

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