A Review on Newly Approved PARP Inhibitors: Talazoparib and Olaparib

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A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

It is hereby declared that

1. The project submitted is my/our own original work while completing a degree at BRAC University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled “A Review on Newly Approved PARP Inhibitors: Talazoparib and Olaparib” submitted by Azrin Karim ID:20146077 of Summer 2023 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

No human or animal tests are involved in this study.

Abstract

This review delves into the intricate landscape of Poly ADP-ribose polymerase (PARP) inhibitors, specifically focusing on two notable contenders in cancer therapy – Talazoparib and Olaparib. By targeting the DNA Damage Repair (DDR) signaling system crucial for cancer growth, these inhibitors disrupt essential mechanisms like homologous recombination, base excision repair, and mismatch repair.

Talazoparib, a PARP inhibitor, has demonstrated its potential as a breakthrough in metastatic breast cancer with BRCA1/2 mutations, surpassing traditional chemotherapy in efficacy. Through PARP trapping and catalytic inhibition, Talazoparib disrupts repair processes, earning approval for BRCA-mutated breast cancer and homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer.Similarly, Olaparib, another PARP inhibitor, is approved for treating pancreatic, ovarian, breast, and prostate cancers. Its impact on synthetic lethality in cancer cells with BRCA mutations is evident, blocking PARP-mediated repair of single-strand breaks. Clinical trials affirm Olaparib's manageable safety profile and efficacy in treating HER2-negative metastatic breast cancer, prostate cancer, and ovarian cancer.

The study concludes that Olaparib and Talazoparib stand as effective therapeutic options across various cancer types and genetic abnormalities. It aims to enlighten medical professionals about the potential of precision medicine in advancing cancer therapy, emphasizing the need for personalized approaches in clinical practice.

Key word

PARP inhibitors,Talazoparib,Olaparib,DNA damage repair,DDR signaling pathway,BRCA mutations,Metastatic breast cancer,Homologous recombination repair (HRR),Prostate cancer,Ovarian cancer,Clinical trials,Efficacy-Safety profile,Adverse events

Dedications

Dedicated to my beloved grandmother, whose knowledge and kindness inspire me even in her absence and to my parents, whose constant affection and sacrifices have made it possible for me to be here today.

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List of Acronyms

PARP	Poly (ADP-ribose) polymerases
BRCA	Breast Cancer gene
DNA	Deoxyribonucleic acid
BRCAm	Breast Cancer Gene Mutation
DDR	DNA Damage Repair
HR	Homologous recombination
SSBs	Single Strand Breaks
BER	Base Excision Repair
DSB	Double Strand Break
HER2	Human Epidermal Growth Factor receptor 2
gBRCAm	Germline Breast Cancer Gene mutation
HRR	Homologous Recombination Repair
mCRPC	Metastatic Castration Resistant prostate cancer
NAD	Nicotinamide Adenine Dinucleotide
PARylation	Poly ADP-ribosylation
PFS	Progression Free Survival
ORR	Objective Reaction Rate
OS	Overall Survival
MDS	Myelodysplastic Syndrome
AML	Acute Myeloid Agency
EMA	European Medicine Agency
FDA	Food and Drug Administration
HRD	Homologous Recombination Deficiency
AEs	Adverse Events
GI	Gastrointestinal

Chapter One

Chapter One

Introduction

Worldwide, cancer is a major threat to public health. According to the World Health Organization, millions of new instances of cancer are identified yearly across a wide range of demographics and areas, making it one of the top causes of morbidity and mortality worldwide. Preventive, early diagnosis, and enhanced treatment efforts are still vital in treating the complicated and extensive range of cancers that affect people all over the world. A potential therapeutic approach for specifically targeting cancer cells is to target the PARP (Poly ADP-ribose polymerase) enzymes as one of the cancer treatment methods (Chan, Tan, & Cornelissen, 2021). PARP inhibitors (PARP) have recently been used to treat BRCA-mutated tumors and have shown promise as effective treatments for a variety of cancer types. There are some newly approved drugs that are known as PARPi, which are used to treat cancer including Talazoparib and Olaparib. They specifically target an enzyme that helps to repair damaged DNA in cells, especially cancer cells that lack the capacity to repair DNA through alternative pathways, such as those resulting from BRCA1 and BRCA2 gene mutations.

Talazoparib, a poly(adenosine diphosphate–ribose) polymerase PARPi, proved to be significantly superior to conventional chemotherapy for patients with advanced breast cancer with a hereditary BRCA1/2 mutation. Based on observations, talazoparib yielded better outcomes. Preclinical results for talazoparib as a PARP inhibitor show strong catalytic inhibition and the ability to trap PARPs (Litton et al., 2018). Again, Olaparib, another PARPi, is approved for use in the maintenance the context for patients with BRCA1/2 mutation (BRCAm)-negative platinum-sensitive relapsed ovarian cancer, breast cancer, fallopian tube cancer, peritoneal cancer, pancreatic cancer, and prostate cancer (Friedlander et al., 2018).

1.1 PARP inhibitors and how it responds to cancer

The field of cancer treatment that targets DNA Damage Repair (DDR) signaling is rapidly developing.DNA damage-induced genomic instability makes DDR necessary for cell survival. The transcription of the relevant repair protein is started by DDR signaling, and this leads to the expression of the repair protein and the activation of DNA repair mechanisms. PARP, a DNA repair protein, is widely distributed and vital. Numerous DDR mechanisms, including mismatch repair, base excision repair, homologous recombination (HR), nucleotide excision repair, conventional and alternative non-homologous end joining, microhomology-mediated end joining, and replication fork stability, are regulated by it. Furthermore, ovarian, breast, and other cancers have been discovered to express excessive PARP in contrast to the usual surrounding healthy tissues (Chan, Tan, & Cornelissen, 2021). This suggests that inhibiting PARP activity is a promising strategy for cancer therapeutics, as it disrupts PARP functions and impairs the DDR pathways of cancer cells (Lord & Ashworth,2017).

One class of targeted cancer medication is PARP inhibitor. It is now well proven to use PARP inhibition to treat ovarian or breast cancers with BRCA1/2 mutations, or deficits in the HR. Using a PARP inhibitor (PARPi), one may hinder the repair of Single-Strand Breaks (SSBs) and turn them into double-strand breaks by slowing down replication or increasing fork elongation, which calls for HR repair during the S phase (Chan, Tan, & Cornelissen, 2021).

Additionally, they are being studied as a cancer treatment for many types of cancer. Olaparib, niraparib, and rucaparib are examples of PARP inhibitors. Endogenous Single-Strand Breaks (SSB) are frequent in proliferating cells and are mostly repaired by the PARP-dependent Base Excision Repair (BER) pathway. An efficient SSB repair mechanism is required for cell survival. By inhibiting PARP, inhibitors of PARP stop BER from fixing SSB. Homologous Recombination (HR) is the main process by which unrepaired SSB are mended during cell replication. Double-Strand Breaks (DSB) that are not fixed can become hazardous DSB. HR-proficient cells can repair DSB arising from SSB to preserve genomic integrity and cell viability, while HR-deficient cells that are unable to repair such DSB undergo apoptosis and death as a result. (Zheng et al., 2020).

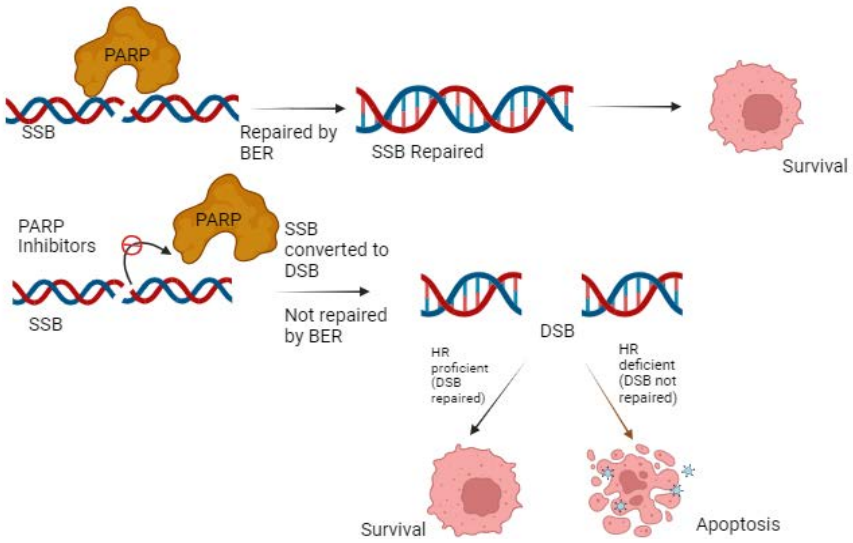


Figure 1.1: Adapted from Zheng et al., 2020 *mechanism of action of PARP inhibitors*

1.2 Talazoparib

A PARPi called talazoparib is used to treat metastatic castration-resistant prostate cancer in combination with another cancer therapy and Human Epidermal Growth Factor 2(HER2)-mutant BRCA-affected locally progressed or metastatic breast cancer. It inhibits the enzymes known as mammalian polyadenosine 5'-diphosphoribose polymerases (PARPs), which are in charge of controlling vital biological processes including DNA transcription and DNA repair (DrugBank,2024).

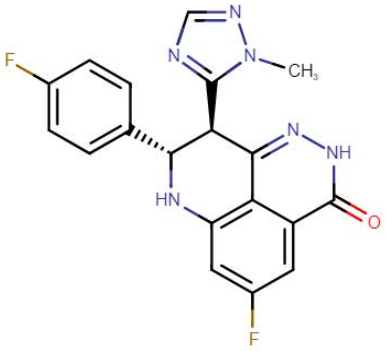


Figure 1.2:Adapted from Drugbank,2024, Structure of Talazoparib

1.2.1 Indication

1.2.1.1 gBRCAm, or BRCA-mutant HER2-negative Breast Cancer: Locally Advanced or Metastatic

Treatment with talazoparib alone is recommended for adult patients with human epidermal growth factor receptor 2 (HER2)-negative, locally progressed or metastatic breast cancer who have a gBRCAm mutation in their germline breast cancer susceptibility gene (BRCA) or who suspect a gBRCAm mutation (FDA & CDER, 2018).

1.2.1.2 HRR Gene-mutated mCRPC

In addition to enzalutamide, adult patients with metastatic castration-resistant prostate cancer (mCRPC) caused by a mutation in the Homologous Recombination Repair (HRR) gene should get Talazoparib (FDA & CDER, 2018).

1.2.1.3 Prostate Cancer

Combining talazoparib and enzalutamide is approved as a treatment for prostate cancer patients whose cancer has changed a particular set of genes involved in DNA damage repair. When combined with mutated DNA repair genes, talazoparib inhibits the DNA repair functions of a protein called PARP, hence impairing the ability of cancer cells to proliferate. Enzalutamide functions by preventing hormones from promoting the development of cancer cells (National Cancer Institute, 2023).

1.2.2 Mechanism of Action

After attaching to DNA damage sites, PARP1 and PARP2 become enzymatically active and attach lengthy chains of poly-(ADP-ribose) to themselves and other nuclear proteins using Nicotinamide Adenine Dinucleotide (NAD+). At the location of DNA damage, a process known as poly(ADP)-ribosylation or PARylation attracts PAR-binding domains harboring DNA repair factors. By two different methods, Talazoparib inhibits the base-excision repair pathway's ability to repair DNA SSBs. First, Talazoparib binds to the PARP1/2 catalytic domain and suppresses PARylation by structurally resembling NAD+. In a second, more harmful mechanism called PARP entrapment, Talazoparib stops PARP-DNA complexes from dissociating, which is necessary for PARP-mediated DNA SSB repair.However, as a result of PARP inhibition, DNA replication forks stop or collapse upon encountering the persistent DNA SSBs. But if DNA SSBs are transformed into DNA DSBs and effectively fixed by the error-free HR repair pathway, replication fork function can be saved. Hence, alternative error-prone DSB repair methods are used by cancers with BRCA1/2 mutations and compromised HR repair pathway, which leads to chromatid instability, cell cycle arrest, and ultimately death. This artificially fatal model depends on the homologous recombination deficiency of tumor tissue in carriers of the BRCA1/2 mutation, which offers a therapeutic window for treating these cancers specifically (Hobbs, Litton, & Yap, 2021).

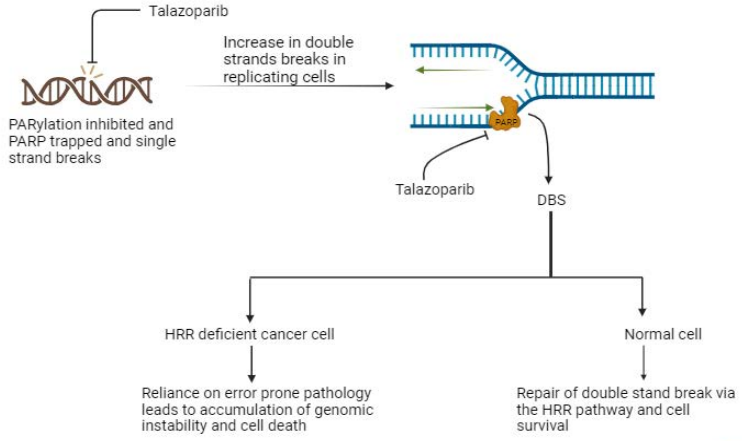


Figure 1.2.2: Adapted from Hobbs, Litton, & Yap, 2021, *Mechanism of action of Talazoparib*

1.2.3 Efficacy status

Talazoparib is a viable treatment option that has strong effectiveness evidence to back it up. Its efficacy in postponing disease progression and eliciting tumor responses is demonstrated by its superiority in Progression Free Survival(PFS), uniform benefits across subgroups, and a significant rise in Objective Response Rate (ORR). The tendency towards better survival, even if the Overall Survival (OS) analysis did not reach statistical significance, raises the possibility that Talazoparib might provide a survival benefit. The drug's attractiveness is increased by the prolonged Duration of Response, which suggests persistent efficacy. Taken together, our results establish Talazoparib as an effective and adaptable therapy option for patients with HER2-negative, germline BRCA-mutated breast cancer, providing significant response rates as well as possible survival advantages (Pfizer,2023).

1.2.4 Safety status

Serious adverse effects of Talazoparib include Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML).

Some cancer patients who had previously had chemotherapy or treatment with specific other medications acquired MDS or AML during or following their Talazoparib treatment. AML or MDS can be fatal. The following adverse effects may also be seen when using talazoparib:weakness, loss of weight, fever, recurrent infections, blood in the urine or feces, breathing difficulties extreme fatigue, and a greater tendency to bruises or bleeding (*Taking TALZENNA® (Talazoparib) | Safety Info*, 2023).

1.2.5 Regulatory status

Regulatory bodies including the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA) in Europe have approved Talazoparib, which is sold under the trade name Talazenna. It can be used to treat locally advanced or metastatic germline cancer in some countries. HER2-negative, BRCA-mutant breast cancer (FDA & CDER, 2018;European Medicines Agency,2023)

1.3 Olaparib

Olaparib is a PARP inhibitor that is used to treat prostate, pancreatic, ovarian, and breast cancers. Poly (ADP-ribose) polymerase (PARP) enzymes, PARP1 and PARP2, are selectively and potently inhibited by olaparib. A novel class of anti-cancer medication called PARP inhibitors kills cancer cells by taking advantage of a weakness in DNA repair in cancer cells with BRCA mutations. Prostate, pancreatic, ovarian, and breast cancers are among the BRCA-associated cancers that Olaparib is used to treat. Health Canada approved it in April 2016 after it was first approved by the FDA and EU in December 2014 (Drugbank,2024).

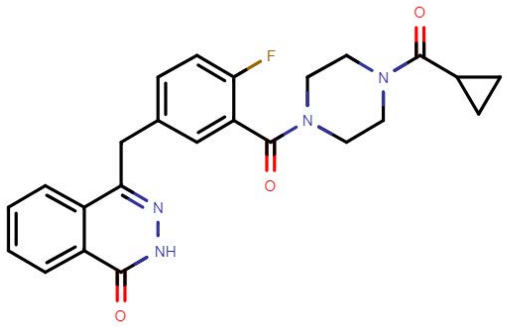


Figure 1.3:Adapted from Drugbank,2024, Structure of Olaparib

1.3.1 Indication

According to European Medicines Agency,2023,Olaparib is used for the continuation of treating high-grade (rapidly growing) cancers of the ovaries, fallopian tubes (which connect the ovaries to the womb), and membrane (abdominal membrane) beyond the initial course of treatment. It is administered to patients whose cancer returned following previous treatment and whose cancer had been reduced in size or completely eradicated by platinum-based chemotherapy.

Olaparib is used to treat women with newly diagnosed advanced cancer who have mutations in one or both of their BRCA1 or BRCA2 genes. If the cancer has not spread to other body parts following chemotherapy given either before or after surgery (early breast cancer), or if the tumor has shrunk or been cleared by bevacizumab and platinum-based chemotherapy, then this particular medication can be used to treat HER2-negative breast cancer in patients with BRCA1 or BRCA2 mutations. For patients undergoing treatment for metastatic pancreatic cancer with BRCA1 or BRCA2 gene mutations if the disease has not progressed after at least four months of platinum-based chemotherapy and has spread to other regions of the body. Women with advanced cancer who are homologous recombination deficiency (HRD)-positive, where one of the mechanisms to repair damaged DNA does not work, which can be due to a defect in certain genes such as BRCA1 and BRCA2. Olaparib can be used in prostate cancer medications to treat men with BRCA1 or BRCA2 gene mutations whose cancer has progressed after receiving treatment for metastatic prostate cancer. This includes cancer that has spread beyond the original site after treatment with specific breast cancer medications that have stopped working or were inappropriate (European Medicines Agency,2023).

1.3.2 Mechanism of action

Under normal conditions, an error-free PARP-mediated process repairs SSBs in DNA. DSBs can happen during DNA replication if SSBs are present. The BRCA 1/2-mediated homologous recombination is thought to be an error-free repair process that preferentially repairs these, however there have been reports of mutagenesis effects recently. Olaparib prevents the PARP-mediated error-free repair of SSB, which causes synthetic lethality in cancer cells linked with BRCA because additional error-prone repair mechanisms, such as non-homologous end joining and single-strand annealing, are used to repair DNA. When there is significant DNA damage, such as following treatment with genotoxic chemicals, these alternate repair systems are overpowered. This leads to the accumulation of DSBs, incorrect DNA, and eventually, cell death (Goulooze, Cohen, & Rissmann, 2016).

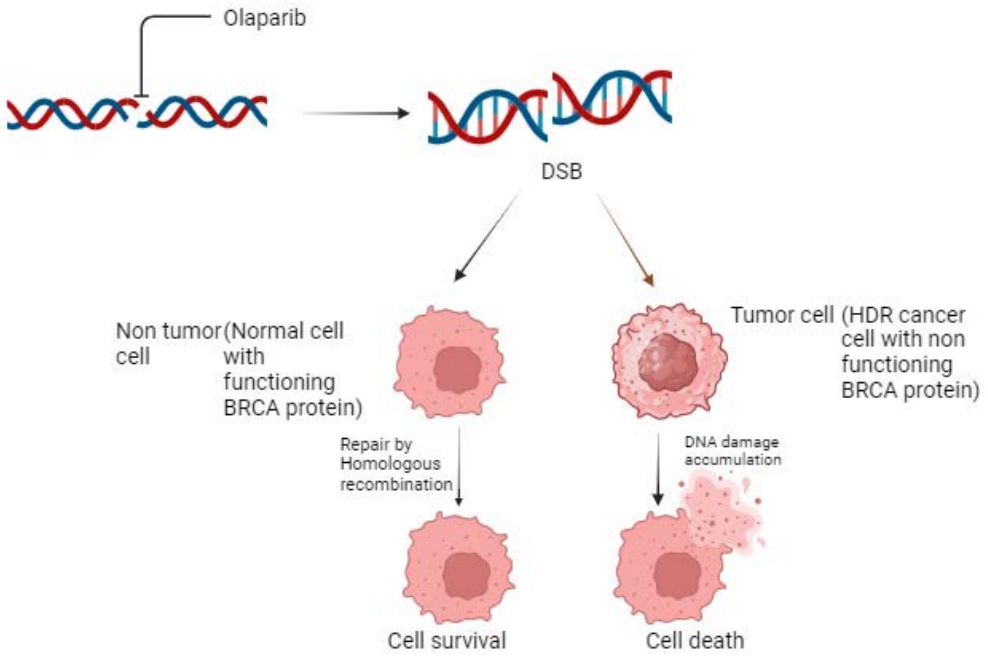


Figure 1.3.2: Adapted from Goulooze, Cohen, & Rissmann, 2016,*Mechanism of action of Olaparib*

1.3.3 Efficacy status

Olaparib demonstrated consistent and substantial efficacy in gBRCAm, HER2-negative mBC across various subgroups, reaffirming its role as a valuable treatment option. These findings not only support the use of olaparib monotherapy in metastatic breast cancer but also underscore its potential as an effective therapy for high-risk gBRCAm, HER2-negative early breast cancer, as demonstrated in the OlympiA trial. The study reinforces the importance of identifying gBRCAm early in breast cancer patients, paving the way for targeted and effective treatment with PARP inhibitors like olaparib (Senkus et al.,2023).

1.3.4 Safety status

Treatment response,PFS, and OS are all significantly improved by olaparib across a range of cancer types. However, while making treatment options,there are potential hematologic toxicities, especially in cases of severe anemia, and need to take the patient's unique circumstances into account.Severe fatigue and gastrointestinal (GI) toxicity were comparatively less common adverse events. Instances of severe fatigue were reported, along with occurrences of severe GI problems, particularly nausea.Even though olaparib therapies show great clinical promise, there are still issues to be resolved, such as resistance mechanisms and possible long-term toxicities such MDS,AML.Monitoring for resistance mechanisms and long-term effects is critical for the safe and successful use of olaparib in cancer treatment (Guo et al., 2018).

1.3.5 Regulatory status

Olaparib, which is sold under the Lynparza brand, has been approved for a number of uses.

With the U.S. Food and Drug Administration's (FDA) accelerated approval of Lynparza(olaparib) capsules on December 19, 2014, AstraZeneca accomplished a major oncology milestone. This was the first time that a monotherapy for advanced ovarian cancer patients with deleterious or suspected deleterious germline BRCA mutations had been approved (AstraZeneca,2014).

1.4 Difference Between Indication of Talazoparib and Olaparib

The newly permitted indications for PARP inhibitors, Talazoparib and Olaparib differ, especially with regard to the specific cancer that each is intended to treat. However, the precise application of medications such as Olaparib or Talazoparib in a certain cancer typically depends on a number of variables, including the drug's safety profile, effectiveness, regulatory approvals, and results from clinical trials. Talazoparib may not be utilized in the same way as Olaparib in cases of pancreatic or ovarian cancer or prostate cancer for the following reasons:

1.4.1 Combination therapy and monotherapy in prostate cancer

Combining talazoparib and enzalutamide is authorized as a treatment for prostate cancer patients whose cancer has changed a particular set of genes involved in DNA damage repair(National Cancer Institute, 2023). On the other hand, eOlaparib monotherapy is effective, and the data indicate that it resulted in a much longer imaging-based progression-free survival when compared to the treatment plan that the doctor had recommended, which involved taking either abiraterone or enzalutamide. Consequently, for the designated patient group in this trial, olaparib was administered as a stand-alone medication rather than combined with other medicines (Tosh, 2022).

1.4.2 Comparable Adverse Events

Generally, no significant difference in the effectiveness of talazoparib and olaparib, according to the indirect treatment comparison (ITC). Nonetheless, variations in safety profiles were noted. Specific adverse effects (AEs) differed, although overall AEs were comparable. Individuals on olaparib were more likely to have nausea and vomiting, whereas patients on talazoparib were more likely to experience neutropenia, thrombocytopenia, alopecia, and anemia.It was shown that talazoparib did not show increased effectiveness in treating metastatic breast cancer, while showing more potent PARP trapping and stronger antiproliferative activity in vitro when compared to olaparib. The two PARP inhibitors' median overall survival (OS) and the doctor's recommended course of treatment did not differ much from one another. In all trials, hematological toxicities—a frequent class impact of PARP inhibitors—were effectively controlled, and the rate of treatment termination because of adverse events was minimal (McCrea et al., 2021).

1.4.3 Regulatory Approval

Talazoparib was granted approval in 2018 by FDA- The extension of Talazoparib's indications to encompass additional cancer types demands independent clinical studies and regulatory permission, which may not have been adequately studied in the case of pancreatic or ovarian cancer. Talazoparib has been approved by regulatory bodies, such as the U.S. Food and Drug Administration (FDA), for use in combination treatment to treat prostate cancer and germline BRCA-mutated, HER2-negative breast cancer (FDA & CDER, 2018).

In addition, Olaparib received FDA approval in 2014 and is now authorized for a number of indications, including ovarian, breast, and prostate cancer. It has been permitted for use in the treatment of select patients with metastatic castration-resistant prostate cancer (mCRPC) who have certain genetic abnormalities, such as ATM or BRCA1/2 (FDA & CDER, 2014).

1.4.4 Treatment Landscape and Physician Preference

Due to its approvals, availability, and proven efficacy, Olaparib may have become the treatment of choice or standard for pancreatic,prostate and ovarian cancer, resulting in its more widespread usage than Talazoparib in these cancer types

1.7 Aim and Objective of the study

The aim of the work is to thoroughly assess and examine the pharmacological activities, clinical effectiveness, safety profiles, and potential applications of the recently licensed PARP inhibitors- Talazoparib and Olaparib and emphasizing their importance in the treatment of cancer.
This study attempts to answer following research question-

- ❖ How do Olaparib and Talazoparib compare in terms of safety profiles, tolerability, and efficacy for different types of cancer?How do Olaparib and Talazoparib react differently to different patient populations regarding factors like age, gender, ethnicity, underlying medical disorders, etc. ?
- ❖ How do genetic mutations affect the way the body reacts to Olaparib and Talazoparib?
- ❖ What are the specific side effects of Olaparib and Talazoparib, and how should they be managed?

Thus the objectives of the project work are as follow-

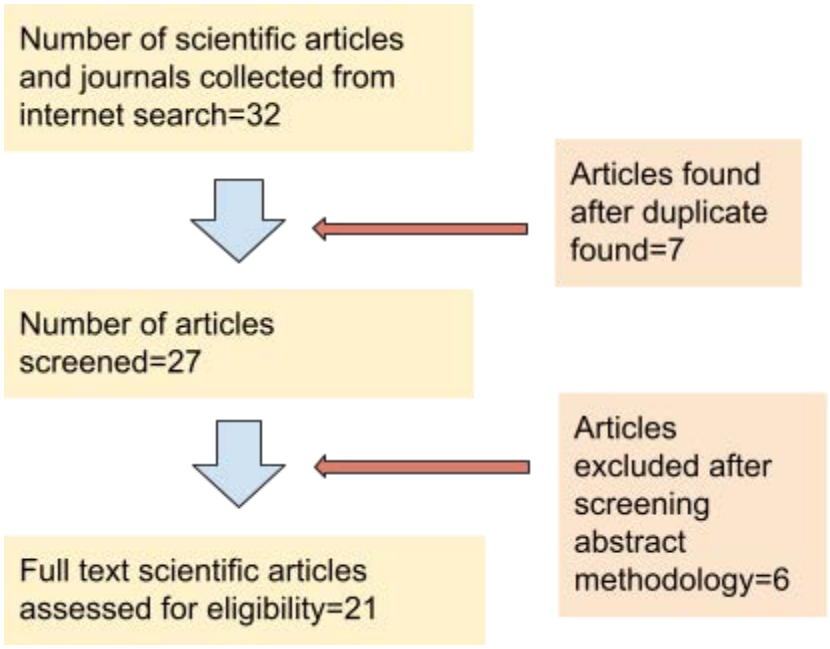
- Evaluation of pharmacological activities of the drugs: Talazoparib and Olaparib
- Clinical efficacy assessment
- Analysis of safety profiles
- Prospective consequences and dire

Chapter Two

Methodology

The stated review “A review on newly approved PARP inhibitors: Talazoparib and Olaparib " started with a comprehensive assessment of academic publications sourced from reliable sources that indicate topics of interest from internet search. This review's essential data was gathered from reliable internet search engines and journals from Pubmed, Google Scholar, Sciencedirect, Elsevier and websites like Drugbank. Also, websites of regulatory bodies from different countries and continents like U.S Food and Drug Administration (FDA),European Medicine Agency(EMA)websites were also consulted in order to get knowledge relevant to the subject. An outline was created once all the necessary and essential information had been determined. In order to occur this, it was necessary to first identify all of the recently developed medications used as PARP inhibitors. In addition, an additional search of the literature was done to determine the chosen drugs (Talazoparib,Olaparib) mechanism of action, benefits, and limitations. The use of accurate and appropriate information was prioritized first. Additionally, proper citation of applicable literation for the review was ensured.

Table 2.1: Selection of scientific articles



Chapter Three

Result

3.1 Tabular representation of the safety,efficacy and adverse events from several studies

Following two tables from all the relevant papers with relevant information has been organized into a table considering study design, sample size, efficacy,safety/ADEs(Adverse events)after using Talazoparib and Olaparib observed adverse effects.

Table 3.1: Studies that outlining the efficacy and safety of Talazoparib

Number of entity	Title	Sample size and description	Study design	Efficacy	Safety/ADEs(Adverse events)
1	***Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation*** (Litton et al., 2018)	Talazoparib Patient=219 Standard-Therapy Patient=114 Age=at least 18 years Individuals with germline BRCA1/2 mutation-expressing advanced breast cancer are diagnosed.	Phase 3 Clinical Trial, comparing Talazoparib with Chemotherapy.	Progression-Free Survival (PFS): Comparing the talazoparib group and standard-therapy group, the Talazoparib group had a 46% decreased chance of fatality or disease progression. Overall Response Rate (ORR): The response rate was twice as high in the talazoparib group (62.6%) as it was in the standard group (27.2%).	-Hematologic evaluation abnormalities were the cause of three to four adverse consequences -Hematologic toxic effects did not result on drug discontinuation -Notable overall improvements were observed. -Changes in patient-reported results suggested that the side-effect profile of Talazoparib was favorable.

2	***Talazoparib in Advanced Breast Cancer: A Comprehensive Review*** (Hobbs et al.,2022)	<u>Patients=58</u> Individuals with genetic BRCA1/2 mutations and advanced breast cancer.	The phase 3 EMBRACA trial- The study employed talazoparib monotherapy and compared it with standard chemotherapy, assessing various efficacy and safety parameters.	<u>Progression-Free Survival (PFS):</u> Talazoparib showed a 46% decreased risk of disease progression or death compared to the standard group. <u>Objective Response Rate (ORR):</u> The overall response rate increased by double to 62.6% from the standard group 27.2% <u>Overall Survival (OS):</u> The OS benefit is still under evaluation. According to patient reports, Talazoparib significantly improved both overall health and quality of life.	-Grade 2 fatigue was more common with talazoparib (24%) than standard therapy (16%). -First 3–4 months hematological toxicities were the main adverse events (AE) -Non-hematologic toxicities included fatigue, nausea/vomiting, and alopecia. AEs associated with death occurred in 2.1% of talazoparib treated and 3.2% of standard therapy-treated patients. <u>-Management:</u> Dose modifications and adjustment.

3	***A phase II study of talazoparib monotherapy in patients with wild-type BRCA1 and BRCA2 with a mutation in other homologous recombination genes*** *(Gruber et al., 2022).*	Female patients=15 Male patient=5 Age range=49–80 In a phase II trial of talazoparib monotherapy, patients with mutations in additional homologous recombination genes but wild-type BRCA1 and BRCA2 were included.	Monotherapy, phase II study	<u>Objective Response Rate (ORR):</u> The objective of the study was to evaluate whether single-agent talazoparib could result in a 30% or greater rate of objective response. <u>PFS(progression free survival):</u> The median PFS was 5.6 months among the individual with breast cancer and 2.6 months among the individual with non-breast cancer and 5.5 months in the combined cohort.	-According to the study's findings, talazoparib monotherapy is a potential therapeutic choice for patients since it is well-tolerated and has acceptable toxicity. -The low rate of serious adverse events and the lack of permanent medication withdrawal as a result of toxicity indicate talazoparib's potential therapeutic relevance in the patient group under study.

Table 3.2: Studies that outlining the efficacy and safety of Olaparib

Number of entity	Title	Sample size and description	Study Design	Efficacy	Safety/ADEs(Adverse events)
1	***Long-term Efficacy, Tolerability, and Overall Survival in Patients with Platinum-Sensitive, Recurrent Ovarian Cancer Treated with Olaparib: Study 19***(Friedlander et al., 2018).	Patients with high-grade serous ovarian cancer that is platinum-sensitive and recurrent, received at least two courses of platinum-based chemotherapy and were responding fully or partially to their most recent treatment. With tolerable toxicity, Olaparib maintenance monotherapy was continued until the disease progressed.	Phase II, randomized, double-blind, placebo-controlled investigation. -Progression-free survival (PFS) was the main goal of the study -Details on randomization, therapy, and assessment are included in the previously published PROfound research design, eligibility requirements, and patient disposition. -Olympiad,an open-label, multicenter, randomized investigation, was carried out in phase III.	Olaparib maintenance monotherapy significantly prolonged progression-free survival compared to placebo. -The trial reported that 32 patients (24%) received maintenance olaparib for over 2 years, with 15 patients (11%) continuing treatment for over 6 years.	-Adverse events were of a low quality. -With prolonged therapy, no new tolerability signs were seen. -Adverse event-related discontinuations were uncommon (6%). **<u>Management</u>** -Decreased dosage -Through recording of events, physical examinations, vital sign monitoring, and laboratory results, the study kept an eye on adverse occurrences.

2	***Olaparib tolerability and common adverse-event management in patients with metastatic castration resistant prostate cancer: Further analyses from the PROfound study*** (Roubaud et al., 2022)	Patients=256, with metastatic castration-resistant prostate cancer who had disease progression on a prior next-generation hormonal agent (e.g., enzalutamide or abiraterone). -Patients were randomized 2:1 to receive olaparib tablets or a control group with enzalutamide or abiraterone.	The PROfound study enrolled patients with metastatic castration-resistant prostate cancer (mCRPC) who had disease progression on a prior next-generation hormonal agent. They were randomized 2:1 to receive olaparib tablets or a control of physician's choice (enzalutamide or abiraterone), with specific genetic criteria for inclusion in different cohorts.	Progression-free survival (PFS), objective response rate (ORR), or overall survival (OS).	-Anaemia, nausea, fatigue/asthenia, and decreased appetite were the four most frequent adverse events (AEs) -After a 30-day follow-up period, one patient in the olaparib group developed an MDS/AML incident. **<u>Management</u>** AEs were usually controllable with dosage decreases or pauses, avoiding therapy cessation.

3	**Olaparib: A Novel Therapy for Metastatic Breast Cancer in Patients With a BRCA1/2 Mutation** (Caulfield et al., 2019)	Patients=302, with metastatic HER2-negative breast cancer, predominantly in the adjuvant or neoadjuvant settings.	The article discusses the efficacy of olaparib in metastatic breast cancer, focusing on the results of the phase III OlympiAD trial.	**PFS:**Olaparib demonstrated a significantly longer PFS compared to standard chemotherapy (7.0 months vs. 4.2 months). **OS:** Overall survival did not show a significant difference between the olaparib and standard therapy groups (19.3 months vs. 19.6 months). **ORR:** The objective response rate was higher in the olaparib group (59.9% vs. 28.8%).	Olaparib exhibited a manageable safety profile. Adverse events (AEs) were reported in 97% of olaparib-treated patients, with the majority being grade 1/2. Common AEs (>20%) included anemia, neutropenia, nausea, vomiting, diarrhea, and fatigue. Grade 3/4 AEs occurred less frequently in the olaparib group compared to standard therapy (37% vs. 51%). **Management** Dose reductions and interruptions were implemented for AEs, with careful monitoring of hematologic toxicity. Discontinuation occurred in 5% of patients due to various AEs, including anemia, thrombocytopenia, and abdominal pain

4	**PROFOUND trial –a new era in targeted therapeutics for prostate carcinoma** (Tosh, 2022)	Patient Number=387 Age range= Older than 18 Olaparib PARPi was tested for safety and effectiveness in men with metastatic castrate-resistant prostate cancer (mCRPC) who experienced treatment-related progression while receiving enzalutamide or abiraterone, as part of the PROfound study.	The PROfound study was a prospective, randomized, open-label, phase 3 trial.	**Progression-free survival(PFS):** showed that Olaparib lasted 7.4 months as opposed to 3.6 months for the control group. **Overall Survival (OS):** The median OS for the olaparib group was 19.3 months, whereas the conventional treatment group's was 19.6 months. Despite this, the study did not reveal a statistically significant difference in OS. **Objective Response Rate (ORR):** Olaparib's ORR was doubled. In the group receiving olaparib, the ORR was 59.9%, while in the group receiving standard care, it was 28.8%.	Anemia (46 % vs. 15%), nausea, and exhaustion were the most frequent adverse events of any grade in the olaparib group, while fatigue or exhaustion (42% vs. 41%) occurred more often in the control group. The main outcome measure was radiological progression-free survival (PFS), which is the amount of time that passes between randomization and either soft-tissue progression, bone lesion progression, or death. The Olaparib group experienced more adverse effects than the control group, with anemia being the most common.

Chapter Four

Discussion

Targeting DNA damage repair (DDR) signaling is the main focus of the review; the discovery of PARP (poly ADP-ribose polymerase) inhibitors represents a major advance in the treatment of cancer. The DDR pathway network is complicated and comprises the essential enzyme PARP, which regulates homologous recombination (HR), base excision repair, and mismatch repair. The expression of PARP is a potential target for cancer therapy because it has been connected to ovarian, breast, and prostate cancers among other cancer types (Chan, Tan, & Cornelissen, 2021). For the treatment of certain cancers, two well-known newly approved PARPi Talazoparib and Olaparib have been discussed. Potent PARP inhibitor talazoparib has proven to be more effective than traditional chemotherapy for treating metastatic breast cancer with a genetic BRCA1/2 mutation (Litton et al., 2018). Through catalytic inhibition and PARP entrapment, it disrupts repair processes and produces better results. The medication is authorized for the treatment of homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer and BRCA-mutated breast cancer (FDA & CDER, 2018). Another PARP inhibitor, Olaparib, has been approved for use in the treatment of ovarian, breast, pancreatic, and prostate cancers, among other conditions (European Medicines Agency, 2023). The medication causes synthetic mortality in cancer cells with BRCA mutations by blocking PARP-mediated repair of single-strand breaks (SBs). When compared to conventional chemotherapy, olaparib has consistently demonstrated effectiveness in treating gBRCAm, HER2-negative metastatic breast cancer, as evidenced by a significant improvement in PFS (Senkus et al., 2023). Despite being linked to typical side effects including nausea and anemia, the drug's safety profile has proven tolerable, enabling extended therapy (Roubaud et al., 2022).

There are variations in the indications, modes of action, and regulatory approvals between Olaparib and Talazoparib. Particular types of breast and prostate cancers are authorized for talazoparib, highlighting the drug's use in combination therapy. Olaparib is preferred as a conventional treatment due to its monotherapy effect in prostate cancer than Talazoparib. The choice between Olaparib and Talazoparib may be impacted by variables including patient characteristics, physician preferences, and the regulatory environment.

From table 3.1,Talazoparib had positive results in a Phase 3 Clinical Trial comprising 219 patients with metastatic breast cancer who expressed genetic BRCA1/2 mutations headed by Talazoparib and conventional chemotherapy were compared in the trial. Progression-Free Survival (PFS) was improved with Talazoparib, as evidenced by a 46% decreased chance of disease progression or death in the group treated with it. Furthermore, the Talazoparib group's Overall Response Rate (ORR) was double that of the group receiving conventional therapy, demonstrating the drug's ability to elicit favorable treatment outcomes. The safety profile showed significant increases in patient-reported outcomes along with controllable hematologic toxic effects (Litton et al.,2018).Again,a following trial from table 3.1,which focused on a cohort of 58 patients with advanced breast cancer and genetic BRCA1/2 mutations, Talazoparib was explored as monotherapy in a Phase II context. Progression-Free Survival (PFS) and Objective Response Rate (ORR) were the study's main objectives. Talazoparib had a good safety profile with low incidence of major adverse events, and the data showed a median PFS of 5.6 months. This shows that talazoparib is a potentially effective monotherapy that is well-tolerated (Hobbs et al.,2022). Finally, Talazoparib monotherapy was investigated in individuals with wild-type BRCA1 and BRCA2 but mutations in additional homologous recombination genes in a phase II research conducted a median age of 53.9 years (range: 49–80), the study's sample consisted of 15 females and 5 men. The objective response rate (ORR) was to be evaluated in this phase II experiment with a focus on attaining a response rate of 30% or above. The main goal was met by the encouraging outcomes. When used alone, talazoparib produced an ORR of at least 30%. The examination of progression-free survival (PFS) showed that the combined cohort had a median PFS of 5.5 months, non-breast cancer participants had a median PFS of 2.6 months, and breast cancer patients had a median PFS of 5.6 months. The median PFS for patients with a gPALB2 mutation was 6.9 months (Gruber et al.,2022).

From table 3.2,Regarding Olaparib, investigated its effectiveness in a Phase II trial comprising 265 patients with recurrent high-grade serous ovarian cancer that was platinum-sensitive. Progression-free survival was markedly extended by olaparib maintenance monotherapy, and overall survival improved. Adverse events were mainly low grade, and long-term safety study demonstrated low discontinuation rates, confirming Olaparib's effectiveness and tolerability in the context of ovarian cancer (Friedlander et al.,2018). In addition, Olaparib's effect on metastatic castration-resistant prostate cancer was the subject of a research by which included 256 patients. Significant improvements in progression-free survival and controllable side effects, including anemia, nausea, fatigue/asthenia, and reduced appetite, were shown in the randomized study. This demonstrates Olaparib's promise in treating prostate cancer with a favorable safety profile (Roubaud et al.,2022).Likewise,In a 2019 research directed by Caulfield et al., 302 patients with metastatic HER2-negative breast cancer participated in a randomized Phase III trial to examine olaparib. A statistically significant change in overall survival was not seen, despite a considerable improvement in progression-free survival. 97% of patients receiving olaparib reported experiencing adverse events, most of which were grade 1/2, suggesting tolerable toxicity.Moreover, a research encompassing 387 patients with metastatic castrate-resistant prostate cancer, indicated Olaparib's considerable impact on progression-free survival and a higher Confirmed Objective Response Rate (ORR). Anemia, nausea, and fatigue were among the adverse events that were more common in the Olaparib group than in the control group (Tosh,2022).

Chapter Five

Conclusion

Olaparib and Talazoparib equally work in terms of response rates and progression-free survival in many cancer types. Hematologic toxic effects are common but well-tolerated side effects, according to the safety profiles of both drugs. The research highlights the significance of outcomes reported by patients as well as the necessity of closely observing and managing adverse events.Olaparib and Talazoparib show potential in terms of response rates and progression-free survival across a range of cancer types. Their safety profiles show that hematologic toxic effects are frequent but well-tolerated adverse events that may be managed. Notably, Adverse events, particularly anemia, were more prevalent in the olaparib group compared to the control group (Tosh,2022). The research emphasizes how important it is to closely monitor and handle side effects in order to guarantee that these medications provide the best possible therapeutic results. All things considered, the data point to talazoparib and olaparib as reasonable treatment choices that can be extremely beneficial for individuals with particular genetic alterations and cancer types.

Physicians and healthcare professionals should be informed about these findings to make informed decisions tailored to individual patient profiles. A greater knowledge of the uses of olaparib and talazoparib as well as improved treatment plans for individuals with relevant mutations may result from increased use of these medications. In the end, raising awareness among medical professionals and oncologists is essential to the ongoing progress of precision medicine in the field of cancer..

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