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Olaparib an anticancer drug: A review

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Abstract

Olaparib is an anti-cancer drug which comes under N-acyl piperazines class. The action of olaparib is PRPA inhibition. Drug taken by oral route which shows action in 1 to 3 hrs. after administration. It is FDA approved drug for various cancer treatment such as ovarian cancer, breast cancer, prostatic cancer and pancreatic cancer. Olaparib also useful different mutation conditions such as BRCA1/2 mutation. Olaparib prescribes after the chemotherapy treatment either singly or in combination. In serious and advanced mutation conditions combination therapy used. In this review paper, we put a narrative information about olaparib action, treatment approaches, pharmacokinetics, dosing regimen and resistance. Here we briefly give information about resistance mechanism of olaparib, treatment approaches in ovarian cancer, breast cancer and prostate cancer.

Keywords: PRPA inhibition; BRCA mutation; Pharmacokinetic; Resistance; Dosing regimen

1. Introduction

Olaparib is an FDA approved anticancer agent which used in treat various type of cancer treatment in adults. olaparib an orally active drug which pharmacological act as PARP inhibitor which comes under targeted drug delivery system. olaparib act on PRAP enzyme to stop repairing of cancer cells and allow to die them to cause decrease in cancer infected cells which further leads to cause destruction of tumour. Majorly used in treatment of metastatic ovarian cancer. Advantages of olaparib is, it only affects cancer cells not healthy or unaffected cells. In various cancer treatment, it used as monotherapy which also effective in BRCA mutation. These BRCA mutation mainly shown by ovarian, breast and prostate cancer. These BRCA mutation further divided in two types such as BRCA 1 and BRCA 2 type mutation which can see in serious condition only so, Olaparib effectively used in serious condition without any major or serious side effects. Olaparib approved for germline BRCA (gBRCAm) ovarian advanced cancer treatment, germline BRCA (gBRCAm) HER2 metastatic breast cancer; in both treatment drug used under monotherapy. Due to their potency, effectivity and recent clinical trials or study olaparib approved for many new indication and treatment. It also available in India.

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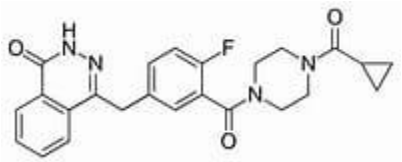
Table 1 Characteristics of olaparib

Parameters	Description
Structure	
IUPAC name	4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4,fluorophenyl)methyl]phthalazin-1(2H)-one
Molecular formula	$C_{24}H_{23}FN_4O_3$
Molecular weight	434.471 g·mol^{-1}
Solubility	Soluble in DMSO and ethanol, poorly soluble in water.
Nature	Crystalline and non-chiral.

2. Mechanism of action [3] [4]

Olaparib act on PARP enzyme which stands for "poly adenosine diphosphate-ribose polymerase". These PARAP enzyme helps in DNA repairing and some cellular processes such as transcription, translation, chromatin structure modulation genomic stability, programmed cell death etc. PARP enzyme mainly found in cell nucleus and detects the any SSB which means "Single Stranded DNA Breaks" SSB cause by any way such as during metabolism, chemical or radiation induced, during chemotherapy (mainly seen in case of alkylating agent treatment because it directly acts on DNA and break it.) These SSB repair by one pathway which is nucleotide base excision repair pathway. PRPA not only healthy cells but also helps cancer infected cells and repair their DNA which affected during chemotherapy. Due to these process, effectivity of anticancer drugs decreases because cells which undergone chemotherapy; those cells they can repair their own damaged DNA by using PRAP enzyme. PRAP enzyme categorised in three types which are PRAP1, PRAP2 and PRAP3. These all enzymes effectively inhibited by Olaparib. During inhibition; olaparib first target nucleotide base excision repair pathway and reduce their ability to repair SSB. Due to olaparib effect extension pathway action totally changed and it repairs "Double Stranded DNA" which only repair homologous and non-homologous end joining. Due to this action SSB of infected cell can't repair and death of cells occurs. olaparib reduces PRAP action but still it binds to infected cells which leads to cause formation of various PRAP-DNA complexes can also occurs death of cancer cells.

3. Pharmacokinetics [1] [5]

3.1. Absorption

It is poorly water-soluble drug taken by orally. After administration it achieves peak plasma concentration within 1 to 3 hrs. the absorption rate of Olaparib mainly affected by fatty meal. Food mainly delayed t_{max} by 2.5 hrs. and C_{max} reduced by21% but not affect on extent of absorption.

3.2. Distribution

About 80 to 82 % drug undergo distribution and binds to plasma protein. The steady state concentration of drug achieves in 3 to 4 days of daily dosing.

3.3. Metabolism

Olaparib metabolism done by liver under CYP3A4 microsomal enzyme. Here Olaparib undergone various chemical reaction such as oxidation reaction, sulfate or glucuronidation reaction. Oxidation reaction majorly involved in metabolism process. The mean maximal extent of drug in mononuclear cells is about 50 % and in tumour tissue about 70%.

3.4. Excretion

The half-life of Olaparib is 5 to 7 hrs. nearby 90% of drug excreted out from body in which drug majorly excrete out from urine. About 40 to 42% drugs excrete via faeces and 44 to 46% excrete from urine. These excreted drugs are in form of inactivated metabolites.

Table 2 Key features of olaparib

Key features	Description
Class of drug	PRPA inhibitor
Mechanism of action	Inhibit PAPA enzyme activity which useful in repairmen of DNA.
Absorption	Achieve peak plasma concentration within 1 to 3 hrs.
Distribution	About 80% drug undergo distribution
Protein binding	82% protein binding shows in “in vitro” studies.
Metabolism	Metabolised in liver under CYP3A4 isoenzyme.
Excretion	Drug excrete out via urine and faeces.
Clearance	4.6 L/h.
Half-life of drug	5 to 7 hrs.
Volume of distribution	40.3L per 100 mg/kg.
Administration	Via oral route
Dosing regimen	300 or 400 mg drug administered twice a day. In renal insufficiency, 200 mg drug used twice a day.
Dosage forms	Tablet with 300 mg content. Capsule with 400 mg content.
Molecular predicator of response	BRCA1/2 mutations.
Used for treatment of	ovarian cancer such as epithelial ovarian cancer (EOC), Advanced ovarian cancer and BRCA 1/2 mutated ovarian cancer. metastatic HER-2 negative breast cancer with BRCA 1/2 mutation. metastatic castration-resistant prostate cancer
Storage condition	`Store at 20ºC to 25ºC (68ºF to 77ºF).

4. Resistance Mechanism of Olaparib [6] [7]

Olaparib is effectively treat cancer by acting on PRAP enzyme but overdose or over use can affect the effectiveness and potency of drug which called as resistance. Due to resistance; activity of drug totally abolished. The resistance mechanism of olaparib are given below….

4.1. Alteration in PRAP enzyme

PRAP enzyme made up from 4 domain which are DNA binding domain, Caspase cleaved domain, Auto modification domain and Catalytic domain. These all domains one by one undergo mutation which leads to cause PRAP enzyme retain their own DNA repairing action. Mutants formed in domains can increase action of PRAP enzyme which means it easily detect SSB and repair it. But majorly affect on olaparib, it can’t trap PRAP enzyme and remain ineffective.

Another way of PRAP alteration is post translation modification where PRAP inhibitor binding activity reduces towards PRAP enzyme. It leads to cause increase activity of PRAP enzyme and shown resistance towards PRAP inhibitor. This type of mutation also shown by MET inhibitor (In breast cancer treatment).

4.2. Restoration of homologous recombination

4.2.1. Restoration of HR-associated protein

Restoration of homologous recombination mainly shown due to reversion mutation. These types of reversion mutation shown by HR protein which described under somatic BRCA mutation. These BRCA 1/2 shown mutations which leads to cause formation of non-functional protein structures, protein truncation, addition or deletion of protein groups also change amino acid sequences. These can easily affect drug-enzyme binding and create resistance. BRCA1 promoter alteration also participates in restoration of HR where demethylation can affect BRCA 1 and leading to cause re-expression of protein and cause desensitisation of PRAP inhibitor towards enzyme and forms resistance.

4.2.2. Restoration of end resection

End resection is crucial and important step in homologous recombination. This end resection process initiated by MRN complex which is protein complex made up from MRE 11, RAD50 and nibrin. The extension of resection done by various nucleases such as EXO-1 and DNA-2. During end resection process protein alteration can be happened which leads to cause restoration of HR capability in cancer (HR-deficient) patient. These restored HR capably repair DNA of cancer cells and develop resistance against PRAP inhibitor.

4.2.3. Promotion of repair protein recruitment

This recruitment mainly caused due EHMT 1/2 enzyme. This enzyme mainly repairs protein of damaged DNA which related to HR. protein repair recruitment of DNA further increases due to over-expression of EHMT 1/2 and further it leads to develop resistance against PRAP inhibitor.

4.2.4. Repression of alternative DNA repair pathway

Here new alternative pathway form or develop to repair DNA. That alternative pathway not block by any PRAP inhibitor because those pathway action totally different from inhibitor drugs and that can only possible due to mutation.

4.2.5. PRAP inhibitor efflux

Drug efflux cause due to overexpression of p-glycoprotein (MDR-1) transporter. This over expression can have caused due to alteration of gene which is ABCB-1. The overexpression of p-glycoprotein includes intergenic deletion, 5’ region mutation, transcript fusion etc.

Table 3 Resistance mechanisms of olaparib

Resistance mechanisms	Description
Alteration in PRAP enzyme	Mutation in enzyme domain post translation modification in PRPA enzyme
Restoration of homologous recombination	Restoration of HR-associated protein Restoration of end resection Promotion of repair protein recruitment Repression of alternative DNA repair pathway
PRAP inhibitor efflux	overexpression of p-glycoprotein (MDR-1) transporter

5. Dosage and administration [5] [8]

Olaparib are available in two dosage forms which are tablet and capsule. Both are orally administered dosage form but drug content in both are different. Tablet contains 300 mg drug and capsule contains 400 mg drug. olaparib administration regimen is twice a day.

5.1. Treatment in various cancer

5.1.1. Ovarian cancer [9] [10] [11]

Ovarian cancer means abnormal growth of cells seen on or in female ovary. This cancer risk more to those females which more ovulated in their life time. Cancer at any stage of age means risk of cancer for both younger and older females.

Olaparib used for the treatment of ovarian cancer such as epithelial ovarian cancer (EOC), Advanced ovarian cancer and BRCA 1/2 mutated ovarian cancer. Both mono and combination therapies used for treatment. In monotherapy, single olaparib drug used twice a daily which used in early stage of ovarian cancer. In combination therapy, olaparib drug combined with other cytotoxic and targeted therapeutic agent which improves effectivity of treatment regarding targeted organ. This combination therapy tried after chemotherapy. Olaparib and cederanib (ATP-competitive tyrosine kinase inhibitor of VGFR 1/2/3) combination therapy used in treatment of recurrent ovarian cancer. Advanced ovarian cancer (With/without mutation in BRCA genes) also treated under combination therapy in which olaparib combined with first line PRAP inhibitor rucaparib (Also used in third line treatment of BRCA mutated cancer). Pevacizumab and niraparibcan be used in combination with Olaparib for maintenance treatment mutated or non-mutated cancer.

5.1.2. Breast cancer [12] [13] [14]

In this disease uncontrolled growth of breast cells happened and forms tumour. Breast cancer majorly seen in lobules, ducts and connective tissue of breast. This cancer cells spread outside breast via blood vessels and lymph vessels.

Olaparib used as first line treatment in breast cancer. Olaparib mainly used to treat metastatic HER-2 negative breast cancer with BRCA 1/2 mutation. It also prescribes in gBRCAm mutant breast cancer. Here Olaparib used as monotherapy after pervious treatment of chemotherapy.

5.1.3. Prostate cancer [15] [16]

This cancer begins in gland cells which only occurs in males. This gland is walnut size shaped which produces the seminal fluid. It is most common cancer among men. Further prostate cancer spread all over body but it majorly targets bones and lymph node

And this process called as “metastasis”. Cancer majorly seen at older persons and athletes. Genetics and family history also responsible for prostate cancer.

Olaparib used for the treatment of metastatic castration-resistant prostate cancer which advanced form of prostate cancer. In this metastatic castration-resistant prostate cancer DNA damage repair/response genes are in high amount which works abnormally so, cancer infected cells use those genes for repairing of their own DNA. As per name, cancer shows metastasis means spreading of cancerous cells to other body parts.

5.2. Advantages [17]

- Potent action
- Shows targeted action on particular organ.
- Effective with less side effect.
- Best over chemotherapy.
- Treat various types of cancer such as ovarian cancer, breast cancer, prostate cancer, pancreatic cancer etc.
- Also effective in BRCA mutant cancer.
- Olaparib also prescribe in renal dysfunction condition (at low dose).

5.3. Disadvantages [17]

- Loss of taste sensation.
- Over dosing affects body strength.
- PRPA inhibition also effect on DNA of healthy cell.

5.4. Side Effects [18]

5.4.1. Common side effects

- Nausea, vomiting, weakness and dyspepsia

- Inflammation in mouth lining
- Diarrhoea and stomatitis
- Headache and dizziness
- Upper abdominal pain
- Loss of appetite
- Cough

5.4.2. Serious side effects

- Decrease haemoglobin level
- Increase mean corpuscular volume
- Decrease WBC and RBC count
- Anaemia
- Fatigue
- Edema

5.5. Toxicities [5] [18]

Olaparib also shows toxicity in various those are given below.

- Over use of olaparib can increases the risk of infection such as upper respiratory infection and pharyngitis.
- Pneumonitis risk can be increases.
- Myelosuppression also be occurred etc.
- myelodysplastic syndrome (MDS), acute myeloid leukemia (AML)

5.6. Interactions [5]

5.6.1. Food Interaction

Olaparib taken with or without food but in some cases, it shows interaction with food. Mainly grape fruit juice avoids during treatment because it boosts up metabolism of Olaparib via increasing CYP3A4 isoenzyme activity.

5.6.2. Drug interaction

Specific drugs show interaction with olaparib and affect on their activity and action those drugs are given below…

- Losartan: When losartan combines with olaparib they can be increased to risk of adverse effect.
- Polythiazide: When ploythiazide combine with olaparib they can be risk to increase to risk of thrombocytopenia
- Acetylsalicylic acid: Theolaparib and acetylsalicylic acid are combined they can be risk to increased bleeding
- Osimertinib: When osimertinib combine with olaparib they can be risk to decreased metabolism rate of olaparib
- Nifedipine: In combination nifedipine can be increase the rate of metabolism of olaparib.
- BCG Vaccine: To risk of Infection can be occur when the BCG Vaccine and olaparib are combine.
- Prazocin: When prazocin and olaparib are combine they can be risk to decrease excretion rate of olaparib.
- Clindamycin: Clindamycin combination with olaparib can be decrease the metabolism rate of olaparib.
- Parnaparin: Increase bleeding when parnaparin and olaparib are combine.

5.7. Ongoing clinical studies in Olaparib [1]

- Maintenance treatment of olaparib over ovarian cancer.
- Advanced gBRCA-mutated Ovarian Cancer Treated with 3 or More Prior Lines of Chemotherapy.
- Maintenance treatment of olaparib in resected pancreatic cancer.
- Olaparib in relapsed refractory MDS (Myelodysplastic syndrome) or AML (Acute myeloid leukemia) with IDH (Isocitrate dehydrogenase) mutations.
- Olaparib also under clinical investigation regarding combinational therapy for treatment of various mutated cancer.

6. Abbreviations

- PRPA: poly adenosine diphosphate-ribose polymerase.
- FDA: Food and drug administration
- BRCA 1: Breast cancer 1
- BRCA 2: Breast cancer 2
- SSB: Single Strand (DNA) break
- DMSO: Dimethyl sulfoxide
- CYP3A4: Cytochrome p-450 3A4
- EOC: epithelial ovarian cancer
- EHMT: Euchromatic histone-lysine N-methyltransferase 1
- MDR 1: Multi drug resistance protein 1
- ABCB gene: ATP binding cassette subfamily B member 1
- VGFR: Vascular endothelial growth factor receptor
- HER-2 breast cancer: Human epidermal growth factor receptor 2 breast cancer
- BCG vaccine: BacilleCalmette-Gaurin vaccine
- MDS: Myelodysplastic syndrome
- AML: Acute myeloid leukemia
- IDH mutation: Isocitrate dehydrogenase

7. Conclusion

Olaparib is FDA approved anticancer drug for adults in various cancer treatment which act via inhibiting PRPA enzyme. Majorly used as monotherapy for cancer treatment but in advanced cancer, used in combination treatment which are under clinical trial. Olaparib is currently under the various clinical investigations. Olaparib is rapidly developing and emerging drug due to their effectiveness and targeted action. It also effective works in different mutated cancers. Some researches regarding Olaparib are under clinical trial such as combination therapy of olaparib for advanced treatment approaches. Also, olaparib under research regarding different tumours treatment.

Compliance with ethical standards

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Disclosure of conflict of interest

On behalf of all authors, the corresponding authors states that there is no conflict of interest.

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