

Rucaparib: a PARP inhibitor for the treatment of advanced ovarian cancer

Merin Babu^{1*}, Josini C. J.²

¹Department of Pharmacology,
²Department of Pharmaceutics,
The Dale View College of
Pharmacy and Research Centre,
Punalal P.O, Poovachal,
Thiruvananthapuram 695575,
Kerala, India

Received: 31 January 2017

Accepted: 28 February 2017

***Correspondence to:**

Ms. Merin Babu,

Email:

merinbabu78@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Ovarian cancers arise from the uncontrolled growth and replication of epithelial cells of the surface of ovary which constitutes 90% of cases. PARP (poly ADP-ribose polymerase) inhibitors are a novel type of therapy that prevents cancer cells from repairing their DNA which have been damaged by other chemotherapeutic agents. Rucaparib is a novel drug that was approved by the US FDA in 2016 for the treatment of patients with deleterious BRCA mutation associated advanced ovarian cancer. Inhibition of the PARP enzymes leads to the increased formation of PARP-DNA complexes which results in DNA damage, apoptosis and cell death. Nausea, fatigue including asthenia, vomiting, anemia, abdominal pain, constipation, decreased appetite, diarrhea, thrombocytopenia and dyspnea were the common adverse effects seen among rucaparib users. Even though, the drug may cause myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) it remains as novel therapeutic target for the treatment of advanced ovarian cancer involving BRCA mutation.

Keywords: PARP inhibitor, Ovarian cancer, Rucaparib

INTRODUCTION

Cancers of ovary has emerged the sixth common cancer and seventh most common cause of death in women which affects throughout the abdomen.¹ Ovarian cancers arise from the uncontrolled growth and replication of epithelial cells of the surface of ovary. Epithelial carcinoma (90% of cases), germ cell carcinoma (originates from cells which turn to form eggs within the ovaries) and stromal cell carcinoma (cancer of hormone releasing cells) are the three types of ovarian cancers.

A number of risk factors including genetics, family history, age, child birth and menopause, lifestyle changes, previous gynecological problems lead to ovarian cancer.² PARP (poly ADP-ribose polymerase) inhibitors are a

novel type of therapy that prevents cancer cells from repairing their DNA which have been damaged by other chemotherapeutic agents.¹ The first oral PARP inhibitor, olaparib for BRCA-mutated high-grade serous ovarian cancer which targets tumours with defective DNA repair mechanism such as aberrant homologous recombination repair due to loss of BRCA1 and 2 gene function.³

Rucaparib is a novel drug that was approved by the US FDA in 2016 for the treatment of patients with deleterious BRCA mutation associated advanced ovarian cancer.⁴ We have attempted a brief review on the mechanism of action, efficacy, safety, pharmacokinetics of rucaparib in the treatment of advanced ovarian cancer.

MECHANISM OF ACTION

The poly (ADP-ribose) polymerase (PARP) is the major DNA repair enzyme. Inhibition of the PARP enzymes which include PARP-1, PARP-2 and PARP-3 leads to the increased formation of PARP-DNA complexes which results in DNA damage, apoptosis and cell death.⁴

EFFICACY

The efficacy of the rucaparib drug has been evaluated by three pivotal, multinational; phase 3 studies [ARIEL2, ARIEL3 and ARIEL4]. The ARIEL2 (Assessment of Rucaparib in ovarian CancEr Trial) was a Phase 2 trial for women with relapsed, high-grade serous or endometrioid ovarian, fallopian tube or primary peritoneal cancer.⁵ The ARIEL3 was a double-blinded study to evaluate the effect of rucaparib as maintenance therapy following platinum-based therapy in women with platinum-sensitive, relapsed, high grade serous or endometrial cancer.⁶ ARIEL4 study compared the effects of the investigational drug rucaparib versus chemotherapy standard of care.

SAFETY

Nausea ($\geq 20\%$), fatigue including asthenia, vomiting, anemia, abdominal pain, constipation, decreased appetite, diarrhea, thrombocytopenia and dyspnea were common adverse events seen among rucaparib users. There were instances of worsening serum creatinine in a small proportion of patients with rucaparib and that resolved before completion of study without dosage adjustment. Major adverse Myelodysplastic syndrome/ Acute Myeloid Leukemia (MDS/AML), discontinue the drug immediately.⁴

PHARMACOKINETICS

The drug has a mean bioavailability of 36% and reaches a C_{max} within 1.9hrs. Volume of distribution is 113 L (single intravenous dose 12mg given). Mean half-life is approximately 17 to 19 hrs and total clearance is 15.3 to 79.2 L/hr. The drug is primarily metabolized by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4 enzyme.⁴

CURRENT STATUS OF DRUG

The US Food and Drug Administration (FDA) have approved rucaparib (Rubraca, Clovis Oncology) 600 mg

orally twice daily with or without food to treat patients with deleterious BRCA mutation associated advanced ovarian cancer who have been treated with two or more chemotherapies. The drug is to be avoided in lactating mothers.⁴

CONCLUSION

The approval of rucaparib is certainly good news for physicians to treat women suffering the advanced stages of ovarian cancer. The results of phase 3 trials have given sufficient ground for the drug's approval by the regulatory bodies. The long term safety of this drug molecule can be estimated only through the post-marketing surveillance of the drug.

Funding: No funding sources

Conflict of interest: No

Ethical approval: Not Required

REFERENCES

1. Wiggins AJ, Cass GKS, Bryanth A, Lawrie TA, Morrison J. Poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer (Review). Conch Database of systemic reviews. 2015;5:1-51.
2. Clovis Oncology. Assessment of Rucaparib in ovarian cancer: phase 3 trials, 2016. Available at: <http://arielstudy.com/about-ovarian-cancer>. Assessed on: 31st January, 2017.
3. Cibula D, Balmana J. PARP inhibitors in ovarian cancer. Bri J Can. 2015;113:S1-2.
4. RUBRACA rucaparib tablets for oral use.pdf Cited: December 2016. Available from: <http://www.accessdata.fda.gov/drugsatfda-docs/label/209115s000lbl.pdf>
5. Clovis Oncology. Assessment of Rucaparib in ovarian cancer: phase 3 trials, 2016. Available at: <http://arielstudy.com/ariel-2-clinical-trial>. Assessed on: 31st January, 2017.
6. Clovis Oncology. Announces FDA Accelerated Approval of RUBRACA for the monotherapy treatment of advanced ovarian cancer in women with deleterious germline or Somatic BRCA mutations treated with two or more chemotherapies. Assessed on: 31st January 2017.

Cite this article as: Babu M, Josini CJ. Rucaparib: a PARP inhibitor for the treatment of advanced ovarian cancer. Int J Basic Clin Pharmacol 2017;6:1018-9.