Peer Review File

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Reviewer A

Comment 1: “Discussion”, Page 4, Lines 163-166:

“The enzymes bind to DNA single-strand breaks and activate the base excision repair pathway. PARPi target the PARP family and turn single-strand breaks into double-strand breaks, which are usually repaired by homologous recombination (HR).”

Here, it should be added that when lacking HR deficiency, as in BRCA-mutant cells, DNA double-strand breaks will be processed by alternative but error-prone repair pathway – non-homologous end joining repair (NHEJ) – which lead to the accumulation of genomic instability and ultimately cancer cell death. NHEJ is faster than HR. The authors should also report that beyond the already-known proteins, such as Ku70/80, DNA-PKcs, Artemis, DNA pol λ/μ, DNA ligase IV-XRCC4, and XLF, new proteins are involved in the NHEJ, namely PAXX, MRI/CYREN, TARDBP of TDP-43, IFFO1, ERCC6L2, and RNase H2. Among them, MRI/CYREN has dual role, as it stimulates NHEJ in the G1 phase of the cell cycle, while it inhibits the pathway in the S and G2 phases.

Recommended reference: Boussios S, et al. BRCA Mutations in Ovarian and Prostate Cancer: Bench to Bedside. Cancers (Basel). 2022;14:3888.

Reply 1: Questions and answers raised by the first reviewer provided a clearer description of HR repair and NHEJ repair. I added the description of NHEJ repair in page 8, lines 163-172 of the article.

Changes in the text:“Discussion”, Page 8, Lines 163-172.

Comment 2: “Discussion”, Page 4, Lines 168-171:

“A study suggested that cancer therapy, such as radiotherapy and platinum-based chemotherapy, preferentially involved mutations in genes related to DNA damage response (DDR), which shaped the fitness landscape of clonal hematopoiesis [14].”

For patients with BRCA wild-type tumors and platinum-resistant disease, PARP inhibitors exhibit very low activity as monotherapy. The authors should report that combinations of PARP inhibitors with drugs that inhibit HR may sensitise ovarian cancer with a primary or secondary HR proficiency to PARP inhibitors and potentially expand their use beyond HR-deficient ovarian cancers. Regarding this, PARP inhibitors may be combined separately with anti-angiogenics and immune checkpoint inhibitors as well as with PI3K, AKT, mTOR, WEE1, MEK, and CDK4/6 inhibitors, or even with standard chemotherapy.

Recommended reference: Shah S, et al. Epithelial Ovarian Cancer: Providing Evidence of Predisposition Genes. Int J Environ Res Public Health. 2022;19:8113.

Reply 2: We proposed the therapeutic strategies for platinum-sensitive patients, and the reviewer also proposed the treatment for BRCA wild-type or platinum-resistant patients. So we added this part of content according to the opinion of the first reviewer.

Changes in the text: “Discussion”, Page 8-9, Lines 175-182.

Comment 3: “Discussion”, Page 5, Lines 181-184:

“However, different from olaparib and niraparib, pamiparib is not the substrate of p-glycoprotein (P-gp), which is overexpressed in tumor cells and associated with a variety of antitumor drug resistance.”
Here, it is worthy to be added that technologies of proteomics, such as mass spectrometry and protein array analysis, have advanced the dissection of the underlying molecular signaling events. Within this context, proteomics analysis of ovarian cancer, as well as their adaptive responses to therapy, can uncover new therapeutic choices, which can reduce the emergence of drug resistance and potentially improve patient outcomes.
Recommended reference: Ghose A, et al. Applications of Proteomics in Ovarian Cancer: Dawn of a New Era. Proteomes. 2022;10(2):16.
Reply 3: We have adopted the suggestion of reviewer to add proteomics technology to the discussion.
Changes in the text: “Discussion”, Page 9-10, Lines 199-202.

Reviewer B
Comment 1:
Unique point
The unique point of this case is unclear and suggested to be highlighted in the Abstract, Introduction (need to compare with existing evidence/similar cases), and Discussion. For the authors' reference, is it the first case report to describe AML after PARPi treatment and death in ovarian cancer?
Reply 1: This case is not the first case report to describe AML after PARPi treatment. The purpose to record and publish this case is to alert gynecological oncologists to the serious side effects of PARPi so as to standardize the use of these drugs. Because the application of PARPi is chaotic in China, but many doctors do not pay attention to this problem. We specifically summarized the incidence of AML and MDS in recent clinical studies, so this case is not unique.
Changes in the text: We didn't revise this part.

Comment 2:
Abstract
1) Case Description: It’s suggested to provide more details about the patients, including the patient's demographic information, main symptom, medical and family history, outcomes, and follow-ups.
2) Lessons and Conclusions are almost duplicated. Instead of lessons, it's highly recommended to add a highlight box to summarize the key findings/recommendations, innovation, and potential implications of the study. For your reference: https://gpm.amegroups.com/pages/view/guidelines-for-authors#content-3-3-1 (see template 1)
Reply 2: As suggested by the reviewer, we have revised the content of the case description in the abstract, added the patient's demographic information, main symptom, medical and family history, outcomes, and follow-ups. We have also revised the lessons part as reviewer suggested.
Changes in the text: "Abstract", Page 2, Lines 28-33. "Abstract", Page 2, Line 41.

Comment 3:
Introduction

1) It would be clearer for readers to understand the effect of PARP in tumors if authors specify the mechanism of PARP. Some content in the discussion is suggested to be placed in the introduction.
2) Some claims lack evidence. For example,
The first paragraph in the introduction: " The role of poly (adenosine diphosphate-ribose) polymerase (PARP) in…years or until progression of the disease ".
"Although secondary MDS or AML had been reported earlier, clinicians were still inexperienced in the case of specific patients".
Please check the FULL text to ensure all the statement is evidence-based (not just the above).
Reply 3:
1) The reviewer suggested that the mechanism of PARP would be replaced in the introduction part instead of discussion part. And the reason we did not do that is the mechanism of PARP is complicated and needed to be written at a long length (see Page 8-9, Lines 159-190), which is not suitable for the introduction part. Moreover, PARP inhibitors are widely used in genetically susceptible tumors, such as ovarian, breast, pancreatic, and prostate cancers. Gynecological oncologists would not be unaware of the mechanism of PARP or PARP inhibitors.
2) As the reviewer suggested to check the statement, we did that and the references are given in the below part. But it is not all marked in the manuscript for the limitation on the number of references.
The role of poly (adenosine diphosphate-ribose) polymerase (PARP) in solid tumors is well established in breast cancer (BRCA) pathogenic variant or homologous recombination-deficient (HRD) malignancy[1]. PARP inhibitors (PARPi) have shown clinically significant improvement in progression-free survival in ovarian[2-6], breast[7-8], pancreatic[9], and prostate cancers[10]. Therefore, the European Drug Administration and the US Food and Drug Administration (FDA) approved the clinical application of four PARPi in ovarian, breast, pancreatic, and prostate cancers between 2014 and 2019[11]. PARPi have been recommended as the first-line maintenance therapy for advanced epithelial ovarian cancer and as the maintenance therapy in relapsed ovarian cancer regardless of the initial International Federation of Gynecology and Obstetrics (FIGO) stage by the National Comprehensive Cancer Network and Chinese guidelines to be used for 2 to 3 years or until progression of the disease[12-13].
references
1. Fritz C, Portwood SM, Przespolewski A, ,et al. PARP goes the weasel! Emerging role of PARP inhibitors in acute leukemias. Blood Rev 2021;45:100696.
2. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:1949-61.
3. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1274-84.
4. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2018;379:2495-2505.
5. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2019;381:2391-2402.

6. Penson RT, Valencia RV, Cibula D, et al. Olaparib Versus Nonplatinum Chemotherapy in Patients With Platinum-Sensitive Relapsed Ovarian Cancer and a Germline BRCA1/2 Mutation (SOLO3): A Randomized Phase III Trial. J Clin Oncol 2020;38:1164-74.
7. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med 2017;377:523-33.
8. Litton JK, Rugo HS, Ettl J,et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med 2018;379:753-63.
9. Golan T, Hammel P, Reni M,et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med 2019;381:317-27.
10. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2020;382(22):2091-2102.
11. Mateo J, Lord CJ, Serra V, et al. A decade of clinical development of PARp inhibitors in perspective. Ann Oncol 2019;30:1437-47
12. NCCN clinical practice guidelines in oncology ovarian cancer (Version3.2021).
13. 中国临床肿瘤学会（CSCO）卵巢癌诊疗指南 2022
Changes in the text: We didn't revise this part.

Comment 4: In addition, it is recommended to add a separate "Methods" part in the manuscript to show the search process transparently, specifying the date of search (specified to date, month, and year), the databases, and other sources, search terms used, the timeframe, and inclusion and exclusion criteria. Please see the examples from our journal: https://atm.amegroups.com/article/view/53641/html ; https://atm.amegroups.com/article/view/76493/html .
Reply 4: Thanks for the reviewer's suggestion on writing “Methods”，but our paper is not a systematic review or meta-analysis. Our case is not the same as the examples (https://atm.amegroups.com/article/view/53641/html ; https://atm.amegroups.com/article/view/76493/html) which reviewer listed above. We wanted to report this case to remind oncologists to standardize the use of PARPi and identify serious complications of PARPi as early as possible, not because the case is rare.
Changes in the text: We didn't revise this part.

Comment 5:
Case presentation
1) If applicable, please report the patient’s medical history.
2) "Pamiparib 60mg bid" should also be stated in the case presentation, not just in Fig 1.
3) Please assure all the abbreviations mentioned the first time, such as CSF (line124), t-AML (line 133), etc.
4) Line 135: Please provide detailed information instead of using vague descriptions “symptomatic therapy”.
Reply 5:
1) The patient had no special medical history, so we didn't mention it.
2) As suggested by the reviewer, we have added the usage and dosage of pamiparib in the case presentation.
3) We have mentioned Granulocyte colony-stimulating factor (G-CSF) in line 116 for the first time, so we use the abbreviation in the following context. t-AML is one

of the pathologic subtypes of acute myelogenous leukemia, since the full name of AML has been described in the previous article, we use the abbreviation.
4) Since the hospital where the author worked is a specialized hospital that only have the department of obstetrics, gynecology and pediatrics. The patient was treated in another hospital after she was diagnosed with AML, and we got these information from her daughter instead of medical records. We cannot provide specific content of “symptomatic therapy”.
Changes in the text: "Case presentation", Page 6, Lines 112-114.

Comment 6:
Discussion
It is highly recommended that authors use one separate paragraph to list both strengths and limitations of this case in a logical way.
Reply 6: As suggested by the reviewer, we have added one separate paragraph to list both strengths and limitations of this case.
Changes in the text: “Discussion”, Page 12, Lines 241-251.

Comment 7: A separate part for the conclusion is recommended.
Reply 7: As suggested by the reviewer, we have added a separate part for the conclusion.
Changes in the text: "Conclusion", Page 12, Lines 253-259.

Comment 8:
Figure & Table
1) Fig 1- In the initial treatment, the 6 cycles should be revised to 5 cycles.
2) The timeline is appealing and clearly presents the diagnosis and treatment events. To further make the timeline more informative and stand-alone, would you please provide the results of the diagnostic test? The timeline can add two more lines, one line for CT images, the level of CA125 and the complete blood count in another line. You can refer to our sister journal https://tlcr.amegroups.com/article/view/35939/24197 (see Fig 1)
3) In Fig 2, it's suggested to add arrows to point out the abnormal cells definitely. The arrows need to be explained in the figure legend. In addition, adding scales in H&E figures is highly recommended.
4) In Fig 3, please provide figures with more resolution because current figures are difficult to see clearly. The percentage of cell types in Q1-Q4 needs to be presented. The first diagram (column 1, row 1) has 3 gating, which one relates to the second diagram (column 2, row 1)? It's suggested to replace the current second diagram title with specific gating.
5) In Table 1, it's advised to show those trials mentioned in order of reference or the published year. The full name of all abbreviations should be provided in the legends (e.g., MDS, AML).
Reply 8:
1) Thanks the reviewers for pointing out the error. We have revised Fig 1 the 6 cycles to 5 cycles.
2) The reviewers provided a case with timeline, including computed tomography evaluation. We did not added these part because the point of our case was not to evaluate the efficacy of the drug, but its serious complications.

3) As suggested by the reviewer, we have added arrows to point out the abnormal cells definitely. We also added scales in H&E figures.
4) The flow cytometry test were conducted in another hospital and we do our best but could not get figures with higher quality or the percentage of cell types.
5) As suggested by the reviewer, we have reordered the trials in order of references.
Changes in the text: Please refer to the attachment for the revised figures and table.