Dr. Wouter Hoff

Editor-in-Chief

*Microreviews in Cell and Molecular Biology*

April 24, 2022

Dear Dr. Hoff,

I would like to submit a microreview article entitled, *Ovarian Cancer and Recent Progress in its Prognosis and Treatment* for consideration by *Microreviews in Cell and Molecular Biology.*

I can confirm the following article to be original work. It has not been published in any other journals, and is not under consideration for publication by any other journals either.

The contents of this paper explores the recent developments in the treatment of ovarian cancer, including the use of olaparib and bevacizumab. The explanation of the studies conducted on these treatments is significant because the current treatments of ovarian cancer are not sufficiently effective, and these treatments provide the potential to revolutionize ovarian cancer treatment.

I have no conflicts of interest to disclose.

Please address all concerns regarding this manuscript to hallie.baker@okstate.edu .

Thank you for your consideration of this manuscript.

Sincerely,

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**Ovarian Cancer and Recent Progress in its Prognosis and Treatment**

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Key Words: ovarian cancer, epithelial ovarian cancer, microRNA, biomarker

**Abstract**

The nature of ovarian cancer lends itself to difficulties in its diagnosis until the late stages of the disease when treatment has the inability to be as successful as it could be if started in earlier stages. This leads to the frequent relapse of many ovarian cancer patients along with difficulties in treatment. Ovarian cancer affects females and is the most common gynecologic malignancy. Several recent studies have lent themselves to the inquiry of more efficient ways to treat patients of ovarian cancer and reduce the risk of relapse and resistance to chemotherapy drugs from their prolonged use. Specifically, the use of the PARP inhibitor, olaparib, has been shown to significantly increase the length of time ovarian cancer patients are able to persist without further progression of the disease after the completion of chemotherapy treatments. Additionally, there have been steps taken to identify certain microRNAs circulating in the blood plasma of ovarian cancer as indicative of the length of progression-free survival as well as response benefits to certain ovarian cancer treatments such as bevacizumab. Thus, allowing patients and medical providers to make better informed decisions about prognostic measures and course of treatment of ovarian cancer.

**Introduction**

Ovarian cancer is a gynecologic malignancy with a worldwide prevalence, affecting one in every 78 women throughout their lifetime. While it is largely prevalent in women over the age of 40 years old, it is highly ranked as the cancer attributing for 2.3% of cancer mortalities, and ranks number five in the cancers causing the most deaths across the world. This incredibly common disease is marked by the presence of malignant tumors in the ovaries, and is often coupled with tumors in the fallopian tubes and/or peritoneum. Among females, it is the seventh most common malignancy and will cause deaths in one out of every 108 women.

 There are several risk factors accompanying ovarian cancer, many of which are common among other cancers affecting women. These risk factors include being middle-aged, family history of ovarian cancer, history of breast, uterine, or colon cancer, obesity, endometriosis, fertility issues, and BRCA1 or BRCA2 mutations. Overall, ovarian cancer is typically caused by biological carcinogens rather than their physical or chemical counterparts.

 Several symptoms signify the presence of ovarian cancer, however these symptoms are not particularly unique to this disease and are often mistaken for other gynecological issues. Fatigue, abdominal pain, pain with sexual intercourse, back pain, irregular periods, and constipation can all by symptoms of ovarian cancer. As a result of the ambiguity of these factors, ovarian cancer is often not diagnosed until advanced stages, putting patients at a much higher risk of mortality than if the disease would have been diagnosed and treatment could have begun in stages I or II. The search for more efficient ways to identify and diagnose ovarian cancer in females is a vital area of study that has benefited from several advancements in recent years.

**Recent Progress**

Significant strides in the prognosis and treatment of ovarian cancer, specifically epithelial ovarian cancer, have been made within the past five years. Most notably, the use of miRNA as a predictive biomarker of ovarian cancer and advancements in the treatment of ovarian cancer are findings that could possibly change the outlook of ovarian cancer for many current and at-risk patients.

 Currently, there are three different methods that allow for the diagnosis of ovarian cancer including pelvic exams, ultrasounds of the vaginal canal, and taking measurements of the protein CA125, a cancer antigen. However, there are several drawbacks to our current methods of diagnosis, seeing as the symptoms of ovarian cancer are often non-distinct and this leads to the diagnosis of ovarian cancer in the late stages of disease progression. This makes the treatment of ovarian cancer an especially delicate affair and puts many patients at risk of relapse and subsequent chemoresistance. In light of this, a more effective treatment of ovarian cancer is consistently sought after. Malignant tumors rely on the availability of blood, oxygen, and nutrients to support rapid growth, and these factors are sustained by the presence of several growth factors including the key mediator, vascular endothelial growth factor (VEGF). The drug bevacizumab is a VEGF inhibitor that is currently used in conjunction with chemotherapy to increase the efficacy of treatment. In cancerous tumors, polyadenosine diphosphate-ribose polymerase, or PARP, is used by the body to repair damage to the DNA in cancer cells, supporting their continued growth and the progression of the disease. In recent years, the efficacy of the use of olaparib, a PARP inhibitor, has been studied in combination with bevacizumab in the treatment of ovarian cancer. One study in particular, published in the New England Journal of Medicine, implemented the use of olaparib in addition to bevacizumab in a group of ovarian cancer patients and compared the progression-free survival benefit to patients who took a placebo and bevacizumab after receiving chemotherapy treatment. Over the course of 24 months, participants of the study were administered either olaparib or the placebo unless disease progression or toxic effects occurred. The results of this study conveyed a clear significant difference in the length of progression-free survival between the two groups with 15.8 months in the groups receiving the placebo and 21.1 months in the group receiving olaparib. Several subgroups were examined throughout the duration of this study, including patients with or without the tumor BRCA mutation and patients with HRD-positive or HRD-negative tumors, all of which had longer progression-free survival among the groups receiving the olaparib drug.

 In addition to these remarkable advancements in the treatment of ovarian cancer, there are also ways to predict the efficacy of therapy through biomarkers. Such biomarkers consist mainly of microRNA, whose dysregulation is commonly associated with all types of cancer throughout the various stages and mechanisms of tumor growth. The associated microRNA can be easily found circulating in the blood in stable levels of unaffected individuals, making it an efficient biomarker of disease factors when these levels are unstable. In a recent study, microRNAs were profiled in the blood plasma samples of 207 patients with epithelial ovarian cancer. The patients were divided into two groups, a discovery cohort (patients in the upper and lower quartiles of progression-free survival) and a validation cohort (remaining patients), in order to examine the microRNAs associated with progression-free survival. These groups were then further broken down by treatment to assess the predictive qualities of microRNAs in the efficacy of treatment. This study’s main goal was to accomplish the identification of microRNAs circulating in the plasma of ovarian cancer patients at risk of relapse as well as the identification of which microRNAs predict the benefit of the use of bevacizumab in conjunction with chemotherapy. All 207 blood samples were tested for the abundance of 754 different microRNAs using quantitative real-time PCR, and the conclusive results were promising. Among patients in the discovery group, those with shorter progression-free survival were reported to have significantly higher amounts of circulating microRNAs, miR–1274A, miR-141, miR-200b, miR-200c, miR-520c-5p, and miR-520d-5p than those with longer progression-free survival. In particular, four micro-RNAs were found to be associated with survival in significant amounts, including miR-1247A, miR-141, miR-200b, and miR-200c. While these were the results related to the prognosis of ovarian cancer, there were also promising results on the evaluation of microRNA levels as a predictive treatment factor. There were no significant differences in the discovery group, however in the validation group it was found that the microRNA miR-200c was associated with patients who had significantly higher rates of survival when taking bevacizumab with chemotherapy rather than just chemotherapy on its own.

**Discussion**

Patients with ovarian cancer are often diagnosed in the late stages of disease progression due to the complicated nature of ovarian cancer and its vague symptoms. Many of these afflicted individuals are at high-risk for relapse and undergoing multiple rounds of treatment leads to the possibility of becoming resistant to chemotherapy drugs. While this information provides concern for the possible complications involved in treating ovarian cancer, the recent progress that has been made in this field regarding treatment shows promising developments that could greatly improve these issues.

 The studies discussed in the previous section outline different advancements in the treatment of ovarian cancer using PARP inhibitors and microRNAs as prognostic and predictive biomarkers. The use of olaparib as a PARP inhibitor in addition to bevacizumab in the regulation of ovarian cancer in patients in the post-chemotherapy phases of treatment was shown to significantly increase the length of progression-free survival than in patients who took only bevacizumab. These findings could greatly improve the regulation of the disease in a group of individuals who are already at high-risk for relapse, and improve their quality of life. The various groups examined in this study also show that olaparib increased progression-free survival time in those who have and do not have the BRCA mutation and in those with HRD-positive tumors. Although, without a group using olaparib as the sole means of therapy it makes it difficult to decisively conclude if the results seen in the patients with HRD-positive tumors because the increased progression-free survival benefit could be attributed to the combined effects of both bevacizumab ad olaparib, not olaparib as a monotherapy. While the results show promise, there needs to be more research done in this area in order to definitively determine how this affects people with HRD-positive tumors.

 With the advancements in management of ovarian cancer in patients post-chemotherapy, the use of microRNAs as biomarkers has proved to be a reliable avenue of determination for the prognosis and prediction of how ovarian cancer patients will respond to this treatment. The aforementioned microRNA, mi-RNA-200c was noted as a significant indicator of patients who will have increased success using bevacizumab as treatment alongside chemotherapy. Using blood samples to examine for microRNA abundance is an inexpensive and efficient way to assist patients and medical professionals in making decisions about course of treatment in ovarian cancer and prognostic measures, thereby giving them the ability to identify the risk of relapse. For patients who are at low-risk for relapse, using microRNAs as a biomarker to discover this could allow them to avoid the possible side-effects of continued treatment when it is not necessary. While this study gave insight into prognostic measures and the benefits of using bevacizumab in conjunction with chemotherapy, further research should inquire into different types of treatment and whether or not their efficacy can be determined through the use of microRNA abundance as a biomarker.

Each of these significant advancements in these areas of ovarian cancer offer new techniques for better treatment and prognostic measures. They also allow for the increased efficiency of the way in which we approach and treat patients with ovarian cancer.

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