**Cover Letter to the Editor**

Dear Editor,

Please find enclosed a modified version of my Microreview manuscript “Treatment Advancements for Ovarian Cancer”. To address the concerns and comments raised by two reviewers, I made the following changes to improve and clarify the manuscript. It is my hope these changes make the manuscript acceptable for publication in Microreviews in Cell and Molecular Biology.

Sincerely,

Joye Burroughs

Reviewer 1:

Reviewer 1 helpfully pointed out that I had not fully finished my citations upon submission allowing me to be aware that they needed to be fixed. Upon their recommendation, I reviewed all of my in-text citations and used numbers as identifiers to the references they belong to.

Reviewer 2:

I did not agree with the comments made by Reviewer 2 and carried on writing in the method I saw appropriate despite their recommendation to use more of my own opinions throughout the manuscript. Because of my disagreement with Reviewer 2 and my understanding of the guidelines of this manuscript I chose not to follow their suggestions.

**Treatment Advancements for Ovarian Cancer**

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**Key Words:**

**Abstract**

Ovarian cancer is one of the major causes of cancer related deaths in the United States at around 15,00 death in a year (3). Due to the lack of disease specific symptoms, later identification of disease leads advanced disease causing the standard treatment for advanced ovarian cancer to be debulking surgery alongside chemotherapy (3). New research regarding the identification of serum-based biomarkers (3) alongside virotherapy methods using the measles virus (2) and poly (ADP ribose) polymerase inhibitors (PARP) (4) have the potential to change the standard of care received by patients with advanced and recurrent platinum-resistant ovarian cancer. While many questions remain, PARP coupled with virotherapy techniques and biomarker technology has the potential to change the way ovarian cancer and other late onset cancers are treated leading to the possibility for better outcomes and increased overall survival.

**Introduction**

Ovarian cancer is one of the major leading causes of cancer related deaths in the United States at about 15,000 deaths in a year (3). The standard of care for advanced ovarian cancer is the use of debulking surgery followed by chemotherapy (3). One of the reasons leading to this is that the lack of disease specific symptoms leads to later identification of the condition and ultimately a worsening case for individuals. The common modes of treatment involve surgery and intraperitoneal chemotherapy, however, when considering the use of intraperitoneal chemotherapy and the higher rates of extra-abdominal recurrences, there are concerns as to whether this provides effective control, leading some physicians to question if alternate regimens show comparable survival with less toxicities (1). The use of intraperitoneal chemotherapy saw an initial increase from 0% to 30% from 2003 to 2006 and an additional increase to 50% from 2007 to 2008 showing an increased propensity for this type of treatment in individuals with ovarian cancer (1). The identification of serum-based biomarkers with imaging for early detection of ovarian cancer during routine screenings could potentially improve survival (3). Many groups have found large multi-gene signatures prognostic of outcome in molecularly profiled ovarian tumor samples leading to the possible identification of single-gene prognostic biomarkers to potentially indicate alternative treatments (3). Often these after surgery treatments involve taxane or platinum-based regimens where despite ovarian cancer’s initial sensitivity to platinum-based chemotherapies patients develop resistance and the majority relapse (2). Recent studies using oncolytic measles virus with a sodium iodine symporter as a treatment for drug resistant ovarian cancer was found to be safe with preliminary antitumor activity (2). Because ovarian cancer remains within the peritoneal cavity in around 80% of patients it provides the opportunity to utilize locoregional administration of therapeutics like virotherapy agents (2). Additionally, the use of Poly (ADP-ribose) polymerase (PARP) inhibitors being tested as single agents for treatment in BRCAm cancers has been expanded to test PARP inhibitors as maintenance therapy in a platinum-sensitive setting (4). PARP inhibitors work on the concept of synthetic lethality which is the presence of an inherent cell vulnerability that is not lethal, but when combined with another genetic even may become lethal (4). PARP protein binds to sites of damage on DNA and synthesizes pADPr polymers recruiting additional repair proteins resulting in the release of PARP from DNA, however, inhibition of PARP inhibits the production of polymers so that it is not released from DNA obstructing replication forks causing chain termination (4). Niraparib is a highly selective inhibitor of PARP1/PARP2 nuclear proteins that is metabolized by carboxylesterases that for an inactive metabolite (4). Niraparib is also the first PARP inhibitor to be approved for use as a maintenance therapy after platinum-based therapy in recurrent ovarian cancer (4).

**Recent Progress**

A study conducted by Wright et.al. looked into the use of a combined intraperitoneal/ IV chemotherapy regimen as compared to IV chemotherapy found that the survival benefit was significant with combined intraperitoneal/IV versus IV chemotherapy with few differences few differences in treatment-related toxicities showing intraperitoneal/IV chemotherapy as a feasible treatment for clinical practice (1). However, they did find that individuals who received intraperitoneal/IV chemotherapy were more likely to develop distant metastases at the first recurrence as opposed to intrabdominal relapses which is consistent with previous observational studies, suggesting intraperitoneal/IV chemotherapy is effective within the regions of drug distribution but compromises systemic disease control (1). In a different study concerned with single-gene prognostic biomarkers by Willis et.al., researchers believe that meta-analysis of existing data of ovarian cancer may yield genes to be investigated more closely and could lead to new drug treatments in ovarian cancer patients (3). Overexpressed genes in ovarian tumors are potential biomarkers of prognosis but may also be therapeutic targets if the genes are correlated with poor outcomes where currently overexpression of genes associated with good outcomes could be unintentionally targeted by standard treatments and off-target effects potential drugs individuals may be taking for unrelated health issues (3). They found in their meta-analysis the overexpression of 12 genes and under expression of 20 genes associated with a poor outcome implying genes that may be prognostic as well as potential targets for therapeutic treatments of ovarian cancer (3). Additionally, the use of bioinformatics in conjunction with analysis of literature databases could lead to a more thorough understanding of genes associated with the ovarian cancer tumorigenic process (3). Virotherapy is an approach with mechanisms of action that are not cross resistant with chemotherapy and with conditionally replicating viruses have the potential to overcome limitations of gene transfer approaches using nonreplicating vectors such as limited infection/transduction efficiency (2). Measles virus is a negative-strand enveloped RNA virus where natural infection with the measles virus has been associated with spontaneous tumor regression in individuals with Hodgkin’s disease and non-Hodgkin’s lymphoma (2). In a recent study, Galanis et. al. used the sodium iodine symporter coupled with the measles virus to test for the possibility of treatment in women with platinum-resistant ovarian cancer that had a median of 4 chemotherapy regimens for recurrent disease (2). These researchers were able to confirm the safety of an engineered measles virus strain with the NIS transgene given intraperitoneally in treatment for recurrent ovarian cancer with early evidence of antitumor activity in a phase II trial (2). They found an overall survival of 26.5 months in this group of pretreated individuals compelling and similar to the measles virus-carcinoembryonic antigen virus (MV-CEA) trial at comparably close intervals, comparing favorably with other contemporary series of novel therapeutics in individuals with platinum-resistant or refractory ovarian cancer where the overall survival ranges from 6-12 months (2). Interestingly, the long median overall survival in this study was associated with relatively short median time to progression and the survival benefit could indicate a different mechanism contributing to antitumor effects, such as an immune-based mechanism (2). Even though the intent was to observe oncolytic mechanisms of action, findings indicate immune-mediated antitumor activity where the clinical benefit that individuals derived in context of microscopic residual disease brings up the possibility of an immune-mediated antitumor effect supported by their immune response data (2). Because the majority of individuals with ovarian cancer have neutralizing antibodies against the measles virus, they are studying means to avoid immune capture and ultimately facilitating the delivery of the virus to the tumor like with mesenchymal stem cells for viral delivery (2). The researchers found that intraperitoneal administration of MV-NIS in individuals with recurrent ovarian cancer is associated with compelling survival outcomes that warrant further testing, as well as generating hypotheses surrounding an immune-based mechanism of measles virus action to be studied in future trials (2). This information could lead to possible immune-mediated mechanisms of MV-NIS to guide future steps including combinatorial strategies with other immunomodulatory approaches (2). Along side virotherapy methods to combat platinum-resistance, studies involving PARP inhibitors, specifically Niraparib, have seen some success in patients showing platinum sensitivity following a platinum-based regimen using niraparib as a maintenance therapy. In patients with platinum sensitivity, researchers saw a response rate of 50% with platinum resistant patients showing a response rate of 33% (4). They also found that niraparib maintenance prolonged PFS significantly with both germline BRCA and wild type BRCA patients (4). Ongoing studies will determine if niraparib will be used for both maintenance and treatment in recurrent disease (4).

**Discussion**

While intraperitoneal/IV chemotherapy has increasing success in treating ovarian cancer at the source, the underlying consequences of the increased possibility of recurrence poses the question of efficacy and ethics. While the study conducted by Wright et.al. was in 2015, there are serious repercussions to consider when recommending this form of treatment to individuals leading to an issue of if the benefits outweigh the potential for recurrence, especially when you consider the possibility of resistance to treatment regimens. PARP inhibitors, like niraparib, have seen success in prolonging life span when used as a maintenance therapy to curb recurrence. There is still a lot of unknown surrounding the possibilities of PARP inhibitor therapies mainly due to the recentness of the published work. Despite being well tolerated, there is still the fact of treatment related toxicities that need to be managed thoroughly to avoid effects on outcomes of effectiveness. However, this is not to say that niraparib has more toxicities than other treatment modes, it is just more high maintenance in the monitoring of these effects. Novel discoveries of using viruses, such as the measles virus, as a means of treatment could mean huge things for cancer research, treatment, and potentially the possibility for a cure. This virotherapy technique coupled with the site-specific injection has the potential to change the way physicians treat individuals with recurrent platinum-resistant ovarian cancer as well as the possibility of a more efficient treatment before resistance occurs. This coupled with virotherapy techniques and biomarker technology has the potential to change the way ovarian cancer and other late onset cancers are treated leading to the possibility for better outcomes and increased overall survival. Many questions still loom over these new modes of treatment leading to the need for further advancements and more studies to determine if bioinformatics and, especially, virotherapy are plausible modes of treatment for individuals with ovarian cancer. By combining these technologies, there is the potential for less invasive treatment regimens coupled with fewer toxicities than traditional regimens like debulking surgeries followed by IV chemotherapy regimens. With further studies this technology has the potential to completely change the way treatment regimens are designed as well as establish a new standard for the development of newer, less restrictive treatments ultimately leading to a greater quality of life. With ovarian cancer being one of the major causes of cancer related deaths in women, it is imperative to find better ways to treat individual afflicted with this disease. Some of the shortcomings related to ovarian cancer is the late diagnosis of the disease. This, coupled with the high rates of recurrence makes this form of cancer increasingly volatile. There is so much more that needs to be done to help young individuals afflicted by ovarian cancer and these methodologies are a great step in the right direction, away from outdated and relatively ineffective methods of treatment.

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