Recent therapeutic approaches to treat ovarian cancer

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ABSTRACT

Ovarian cancer is the most deadly and fifth most common cancer in women. Unlike others cancers, ovarian cancer did not undergo major changes in therapeutic strategy. However, recent advances in cell biology, DNA repair mechanism and immunotherapy has improved the survival rate of cancer patients. Even though these mechanisms are potentially working in other cancers, they are still in preclinical trial for ovarian cancer. In this mini review we have updated recent therapeutic strategies in ovarian cancer.

Keywords: Ovarian cancer, Immunotherapy, PARP, GLI1.

1. INTRODUCTION

Cancer is the most deadly disease in the modern world. Transformation of normal cell to cancer cell can be the result of factors including mutation [1], intrinsic signaling factors [2,3] altered signaling that compromise the apoptosis of cell [4–8], compromised DNA repair [9] and etc. Multiple strategies such as novel chemotherapeutic approaches [10–12], microRNA based therapies [13–15], application of bacterial toxins [16–20] and immunotherapeutic [21,22] approaches proved insufficient to reverse the effects of cancer. In certain cases, chemotherapy or radiotherapy used for primary treatment will induce DNA damage [23] in bystander cells [24–27], which may result in inducing second cancers [28].

Several cancers such as ovarian cancer is contributing significantly in the overall outcome of cancer-related deaths. Ovarian cancer is the most deadly and fifth most common cancer in women in the United States [29]. According to NCI estimates, approximately 21,290 new OC cases will be diagnosed in 2015 with 14,180 deaths [30]. Breast cancer, like ovarian cancer affects mostly females, but recent advances in therapeutic strategies like hormone therapy have increased the overall survival. Although survival rates of other cancers have improved significantly, the overall survival rate of OC has not changed in decades, despite improved surgical procedures and powerful chemotherapeutic drugs [31]. First-line chemotherapy for OC involves a platinum drug such as carboplatin alone or in combination with a taxane [32–35]. While most OC patients initially respond to platinum drugs, about 80% of cases present with disease recurrence and develop resistance to platinum drugs, contributing to a poor survival rate. Thus, there is an urgent unmet need for more effective molecular targeted therapeutics to improve survival of OC patients.
2. DNA repair inhibition by PARP

Due to its insidious nature, about 80% of ovarian cancer cases are diagnosed at an advanced stage with intra-peritoneal dissemination or distant metastasis. Although survival rates of other cancers have improved significantly, the overall survival rate of OC has not changed in decades, despite improved surgical procedures and powerful chemotherapeutic drugs. Recently FDA approved the use of the PARP inhibitor (PARPi) Olaparib in the treatment of relapsed ovarian cancer patients with BRCA mutation [36]. This is important as disease recurrence is a major problem for OC patients contributing significantly to the high mortality rates.

Mechanistically, PARPi inhibits the repair of DNA single strand breaks leading to formation of double strand breaks (DSB) during DNA replication. DSB are not repaired in BRCA-deficient cells which lack homologous recombination repair (HR) and ultimately lead to cell death (synthetic lethality) [37,38]. However, the major limitation of PARPi treatment is that only 10 to 15% of OC patients have hereditary BRCA mutation and there are certain mutations in BRCA which do not affect the HR or do not cause synthetic lethality with PARPi.

3. Immunotherapy

Taking advantage of our own immune system to defeat cancer is another promising latest development in cancer. Though most of these approaches have already shown potential results in other cancers, it is still under clinical development in ovarian cancer. Vaccines, antibody treatments, adoptive T cell transfer, oncolytic viruses, checkpoint inhibitors and adjuvant immunotherapies are the various categories for ovarian immunotherapy.

3.1. Antibody treatment

Monoclonal antibodies those are specific to ovarian tumor antigen has been developed. Bevacizumab, which recognizes vascular endothelial growth factor (VEGF) [39], has been currently approved by FDA for ovarian cancer treatment. Various products that target various proteins like folate receptor alpha (Farletuzumab, Mirvetuximab Soravtansine) [40], Trop-2 (IMMU-132) [41], anti-mitotic agent MMAE (DNIB0600A), Delta-like ligand 4 (DLL4) (Demcizumab) [42], and NKG2A receptors (Monalizumab) [43] are in clinical trial for ovarian cancer.

3.2. Checkpoint inhibitors

Natural killer cell is the most important defense against cancer cells especially that escape T-cell defense by downregulating MHC molecules. There are several inhibitory or stimulatory molecules that can prolong natural killer cells defense, which in turn attack and kill cancer cells. Anti-PD1 antibody (pembrolizumab, nivolumab) [44], anti-PD-L1 (durvalumab) [45], Toll-like receptor 8 agonist (motolimod) [46] and CTLA-4 checkpoint inhibitor ( tremelimunab) [47] are in the various stages of clinical trials of ovarian cancer.

3.3 Therapeutic vaccines

Several antigens have been identified in ovarian cancers that are able to activate the acquired immunity. Especially “cancer-testis” antigens, which are expressed only in cancer cells but not in normal cells, have been in use for vaccines therapy. Several vaccines targeting 5T4 antigen (MVA-5T4) [48], NY-ESO-1 protein (CDX-1401) [49], IDO1 inhibitor (epacadostat) [50], Toll-like receptor 3 (Poly-ICLC) [51], p53 [52] and HER2 antigen [53] are currently in clinical trial for ovarian cancer.

3.3. Adoptive Cell Transfer

Adoptive cell transfer is a therapeutic approach based on the T-cell’s ability to kill cancer cells [54]. In brief, T-cells were isolated from cancer patients by leukapheresis. Then these T-cells were modified either by changing their genetic information or by exposing them to chemicals. Both the methods will improve their anti-cancer response. Then these cells will be injected back to the patients. Clinical trials are currently in process for engineered T-cells against NY-ESO-1 protein, MAGE-A3 antigen [55] and mesothelin [56].

3.4 Oncolytic Viruses

Another technology that uses immunological approach for cancer treatment is oncolytic viruses. Basically, this technique uses virus that will trigger tumor cells to self-destruct and thereby initiate greater immune response against cancer. Currently measles virus is in clinical trials for ovarian cancer [57].

3.5 Adjuvant immunotherapies

These are the substances that when used in combination will enhance the immune response. For
example, an IDO1 inhibitor (epacadostat) enhances and restores proliferation of dendritic cells (DCs), NK cells, and T-lymphocytes [58].

4. CONCLUSION

While individual therapeutic strategies show positive influence on ovarian cancer treatment, combination therapy raises the hope much further. Recent study showed that high grade serous ovarian cancer patients whom are exposed to pre and post chemotherapy showed increased immune activation [59]. In many cancer patients, immune system is suppressed to escape immunology mediated anti-cancer effect. However, combination of drugs that target two different mechanisms in ovarian cancer seems more positive. For example, combination of both chemotherapy and immunotherapy may have potential response towards ovarian cancer therapy. Similarly combination of Olaparib (PARP inhibitor) and Cediranib (VEGFR inhibitor) showed increased synthetic lethality in serous ovarian cancer patients even with wild type BRCA [60]. Similarly, BKM120, a drug that blocks PI3 kinase is also in clinical trial in combination with olaparib for ovarian cancer treatment [61]. All these results show combination therapy works better than individual treatments. However finding the right combination that effectively inhibits ovarian cancer will be a tough challenge. Identifying novel targets and combining them with other therapeutic agents will be a better approach for ovarian cancer therapy in future.

Conflicts of Interest

There are no conflicts of interest.

References


