

Targeted Therapy of Epithelial Ovarian Cancer: from Single Drug to Combined Strategy

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Abstract: Epithelial ovarian cancer is one of the most lethal disease. However, its prognosis is difficult and most of the patients are in advanced stage when they are diagnosed. What's even worse is that most of them cannot achieve R0 resection only by taking traditional surgery and monotherapy will lead to many adverse reactions. These highlight the significance of using combined strategy. Nowadays, some ongoing trials have shown the feasibility to combine biological drugs including Bevacizumab, Olaparib, Pembrolizumab, TC scheme, and even some new activators. These innovative technologies are expected to enhance the efficacy of treatment and reduce side effects. This review integrates newest trends and technological advancements in targeted therapy, emphasize the potential application of combined drugs. By addressing the challenges faced by traditional surgeries and monotherapy, and underlining the advantages of emerging therapies, this paper provides an insight for research, ultimately increase the possibility of managing epithelial ovarian cancer and give patients a better life.

Keywords: Epithelial ovarian cancer, Combined targeted therapy, Bevacizumab, Olaparib, Pembrolizumab

1. Introduction

Ovarian cancer (OC) is a kind of fatal disease, which is the fifth leading cause of deaths related to cancer among women [1]. The annual number of new cases of OC in China is about 88,400, of which epithelial ovarian cancer (EOC) accounts for 80%~90%. The 5-year survival rate of advanced EOC patients is only 10%~30%, which is pretty low. Its prognosis is also extremely difficult in that about 70% of advanced patients will relapse within 3 years, and it is easy to develop platinum resistance after recurrence, which makes it difficult for follow-up treatment. There is also a 50% rate of being homologous recombination deficient (HRD) at the same time [2].

While by treating with traditional surgery, about 40% of patients with peritoneal metastases in the advanced stage cannot achieve R0 resection; even if they reach R0 resection, about 70% of advanced patients will relapse [3], and there is a also great possibility of having postoperative complications such as intestinal obstruction or infection. At the same time, EOC is less sensitive to radiotherapy, it needs high doses of radiation to achieve effective killing, but these are easy to cause damage to surrounding normal tissues.

These highlight the advantages and significance of targeted therapy. Targeted cancer therapies are drugs that interfere with specific proteins necessary for tumor growth and progression. These agents are designed based on knowledge of cancer-associated molecular alterations [4]. Targeted drugs play a role by interfering with the key molecular events of the disease; they block some growth signaling pathways, inhibit activity of abnormal kinase and suppress the vessels from growing, and so on. These properties avoid ineffective treatment and lead to less severe side effects than traditional therapies and significantly extend progression free survival (PFS) and overall survival (OS) [5]. Targeted drugs have less damage to normal cells than traditional chemotherapy drugs, they accurately attack tumors and provide a new direction for combined treatment, like combining targeted treatment with immunization therapy.

2. Particularity and potential targets

2.1. Abnormal vascular proliferation and hypoxic microenvironment

EOC is a kind of malignant tumor that originate from the surface of the ovary or fallopian tube. It has several key features that are possible to be potential targets. We primarily focus on abnormal proliferation of vessels, hypoxia microenvironment lead to drug resistance, some particular cases with HRD positive, its characteristics of "cold tumour", and peritoneal metastasis.

First, the expression level of VEGF-A in EOC is 10-20 times higher than that of normal tissues [5]. This means that the over-expression of vascular endothelial growth factor (VEGF) will promote the formation and growth of tumor blood vessels and provide tumors with oxygen and nutrition more easily. At the same time, this will also result in vascular structure disorders, like tumor blood vessels being distorted and leaking, which makes it difficult to deliver chemotherapy drugs effectively, so that the treatment of anti-vascular is a possible target therapy to improve the delivery of chemotherapy.

2.2. HRD

Second, because of the over-secretion of VEGF, blood flow will be poor and lead to a hypoxic microenvironment [5]. At this moment, hypoxia-inducing factor (HIF-1 α) will increase steadily. HIF-1 α modifies the ABCB1 gene, increasing the excretion of platinum drugs and bringing about chemotherapy resistance [6]. It is possible to generate an HIF-1 α inhibitor to resist drug resistance. Third, about Homologous Recombination Deficiency (HRD), it indicates Homologous Recombination Repair (HRR) pathway dysfunction in cells, that is, cells cannot repair DNA double-strand breakages (DSBs). So when the PARP inhibitors (PARPi) are used, they prevent the single-strand breaks (SSBs) from repairing, and SSBs will convert into DSBs. HRD cells will die due to the inability to repair DSBs, and normal cells can survive through HRR. Meanwhile, approximately 50% of patients have positive HRD because of some mutations [7]. This characteristic shows the possibility of HRD being a targeted point, as it is an essential predictor of the sensitivity of PARPi in EOC and showcases the usage of PARPi.

2.3. "Cold tumor"

Besides, most EOC are seen as "immune cold tumors", that is, toxic T cells in the tumor have less infiltration, there is a richness of immunosuppressive cells like Treg, and the response rate to immune checkpoint inhibitors (ICIs) is low, especially the expression of PD-1 is low, which is only

10-15% [8] . So we can use some inhibitors to block immune pathways, or we can also activate innate immunity.

2.4. The special transfer of peritoneal metastasis

Last but not least, it is special for EOC that most of the patients are likely to have peritoneal metastasis, which means they have a high trend to have peritoneal spread, and tumor cells will adhere to the peritoneum and form tumor metastasis. Because of this metastasis, MUC16 will show high expression, so that causes immune escape. According to this, there is an apparent need to use Chimeric Antigen Receptor T-Cell Immunotherapy (CAR-T) to modify T cells in vitro and transfer them back into patients' bodies when they have the ability to kill the tumor cells.

3. Biological targeted drugs

3.1. Anti-VEGF drugs

For anti-angiogenic agents, the most common one is Bevacizumab, its product name is Avastin. It targets VEGF-A, and it blocks the combination of VEGF-A and VEGFR to inhibit tumor angiogenesis. Bevacizumab can extend PFS for 3.8 months in the GOG-0218 trial [9].

3.2. PARP inhibitors

For PARPi, Olaparib, product name Lynparza, mainly acts on patients with BRCA mutation or HDR-positive by inhibiting the PARP enzyme targeting PARP1/2 and preventing the repair of SSBs so that it can induce the death of HRD cells in HRD-positive tumors; this is called "Synthetic Lethality" [10]. At the same time, it has shown that PFS will extend to 56 months in patients with BRCA mutation in the SOLO-1 trial.

3.3. Immune Checkpoint Inhibitors (ICIs)

In addition, unlike the traditional small molecule targeted drugs above, there is another kind of targeted drug, which is called macromolecular biologic agents, or they are called, ICIs. For example, Pembrolizumab, product name Keytruda, is an ICI that targets at PD-1. It specifically binds with the PD-1 receptor on the surface of T cells in order to block the PD-1 receptor from binding to the PD-L1 or PD-L2 on tumor cells, so that it can remove T cells' inhibition and restore the immune system's killing function against tumors. As a result, it inhibits the tumor growth. It has shown great feedback that ORR is 8.1% in the KEYNOTE-100 trial [11].

4. Limitations of monotherapy

4.1. Bevacizumab

The first one is Bevacizumab, it has a 20-30% possibility of causing hypertension, as shown in the GOG-0218 test, and 15-20% of causing proteinuria, as shown in the ICON7 Test, and tumors will up-regulate PlGF, FGF, and other alternative pathways to escape the immune system so cause drug resistance [12].

4.2. Olaparib

Similarly, Olaparib has a 40% possibility of causing anaemia in the SOLO-1 Test and a 30-50% possibility of causing fatigue, as shown in the PRIMA Test [9,13]. It has special restrictions on the applicable patients. It is only beneficial for HRD-positive patients or for whom has BRCA mutation, for those Myriad MyChoice data shows that people with GRD-positive had an ORR of 30-40%, accounting for 50% of EOC, but it had poor efficacy in HRD-negative patients, as the ORR is less than 10%. Drug resistance is much more common for Olaparib, 30-40% of patients with BRCA mutations will have a situation that is a BRCA reverse mutation; this will lead to resistance. Furthermore, overexpression of DNA repair protein RAD51 or lack of protein 53BP1 leads to drug resistance too.

4.3. Pembrolizumab

As for Pembrolizumab, because of its characteristics of "cold tumor" which means T cells have insufficient infiltration in EOC, the ORR of monotherapy is only 8-15%, and it also has a 10-15% possibility of causing immune colitis, similarly, 5-10% of causing thyroid dysfunction [14]. At the same time, some immunosuppressive factors (SPIFs), such as TGF- β and Treg are possibly lead to primary or recurrent drug resistance.

5. The future trend: combination therapy

5.1. TC + Bevacizumab

The first way is to combine chemotherapy and targeted therapy together; that is, to combine the TC scheme with Bevacizumab to treat advanced epithelial ovarian cancer. The TC scheme is a kind of chemotherapy method that binds two drugs, Paclitaxel and Carboplatin, together to treat cancer. By dividing patients into the TC chemotherapy group and combined group, while the TC group used the TC regimen for treatment and the combined group used the TC regimen combined with Bevacizumab for treatment, then compare the clinical efficacy, adverse reactions, and miRNA-21, CA125, and inflammatory factor levels before and after treatment of the two groups. Results show that the ORR of the Bevacizumab combination group was higher than that of the TC chemotherapy group ($P < 0.05$), but the comparison of DCR of the two groups showed that the difference between them was not that significant statistically ($P > 0.05$). After treatment, the levels of the two groups of miRNA-21, CA125, and inflammatory factor decreased on average ($P < 0.05$), and the combined group of Bevacizumab was lower than that of the TC chemotherapy group ($P < 0.05$). The incidence of adverse reactions between the two groups was compared, and the difference was not statistically significant ($P > 0.05$) either. We can draw the conclusion that the combination of the TC scheme and Bevacizumab can effectively improve the ORR of patients with advanced EOC, reduce the levels of miRNA-21, CA125 and inflammatory factors, and have good safety [15]. TC chemotherapy directly kills the tumor cells that are dividing rapidly, and Bevacizumab inhibits VEGF, blocks tumor angiogenesis, reduces blood supply, and improves the delivery of chemotherapy drugs. Altogether they can reduce the volume of the tumor, delay drug resistance and reduce the risk of recurrence. Second, as for patients with positive HRD, PARPi and anti-angiogenesis drug combined therapy are suitable.

5.2. Bevacizumab + Olaparib

Similarly, combining Bevacizumab with Olaparib, ongoing trial PAOLA-1 divided HRD-positive patients with BRCA mutation into two groups: the combined group, using Olaparib and Bevacizumab to treat, and the control group treated with Bevacizumab only, respectively. The overall results reveal that HRD-positive patients treated by combined therapy reduce the risk of disease progression by 59% and increase the 5-year survival rate by 17.1%, and patients with BRCA mutation have extended the PFS for 34.1 months [16]. These two drugs contribute to inhibiting tumors by preventing the repair of SSBs, inducing death in HRD tumors, inhibiting VEGF, reducing angiogenesis, improving tumor perfusion, and enhancing PARPi. Altogether, they can kill tumor cells directly and delay drug resistance and inhibit the recurrence of tumors, just like the first method.

5.3. CADM3 activator + Pembrolizumab

The last possible therapy is more novel than these two; that is, to generate a new generation of activators and then combine it with inhibitors. Now the trend is considering developing a CADM3 activator and treating patients with the combination of it and the PD-1 inhibitor Pembrolizumab, which is a kind of ICI. A trial put forward its feasibility by studying the expression of cell adhesion molecule 3 (CADM3) in EOC tissue and cells and found that CADM3 mRNA is abnormally expressed in a variety of cancer tissues, while the expression in EOC tissue is significantly lower than that of normal ovarian tissue. The difference is statistically significant ($P < 0.05$). Other tests and data, like the ROC curve, GO and KEGG enrichment analysis results, Western blot and RT-qPCR results, flat plate clone formation experiment, and Transwell invasion experiment results, all lead to a conclusion that CADM3 is lowly expressed in EOC tissues and cells, the overexpression of CADM3 can inhibit the proliferation, migration, and invasion of EOC cells [17]. CADM3 activator combined with Pembrolizumab can improve T cells' penetration and reduce the expression of PD-L1 to reduce T cell depletion simultaneously. This can not only reduce recurrence of tumors and reduce drug resistance to PD-1 monotherapy but also broaden the applicable population, like PD-L1-negative patients and HRD-negative patients.

6. Conclusion

In conclusion, even though monotherapies, such as PARP inhibitors (PARPi) like Olaparib for HRD-positive patients, anti-angiogenics like Bevacizumab, immune checkpoint inhibitors (ICIs) like Pembrolizumab, and other traditional chemotherapies like TC scheme, have demonstrated some clinical benefits, their limitations including acquired drug resistance, possibility of causing immune escape, narrow applicability, and insufficient biomarkers, these highlight the necessity for combination therapies. Combination approaches, like anti-angiogenics drugs combined with TC scheme or with PARP inhibitors, and immune checkpoint inhibitors (ICIs) combine with new generations of activators to get help from the immune system, they all use complementary mechanisms in order to cover the shortage of each other. To further advance the field, future research should focus on developing some biomarkers to better predict patient responses to these combination therapies. Additionally, optimizing dosing schedules and toxicity management protocols will be crucial for improving treatment tolerability and adherence. These will improve treatment success and reduce the chance of resistance. Ongoing trials that combine specific drugs like Olaparib add Bevacizumab and emerging CADM3 activators and add Pembrolizumab

combination demonstrate the potential to increase the progression-free survival (PFS) of EOC patients. However, challenges still exist, such as there are still some adverse reactions like hypertension, fatigue, and anemia, treatments highly depends on patient selection like their HRD status or PD-L1 expressions,, potential possibility of adjust other signal pathways, addressing drug resistance, and high cost for some patients or some areas with limited resources. Collaborative efforts between researchers, clinicians, and pharmaceutical companies are needed to make these innovative therapies more accessible globally, particularly in resource-limited settings. As we deepen our understanding of tumor biology and resistance mechanisms, next-generation targeted agents and immunotherapies may offer even greater potential for overcoming current limitations. Ultimately, the integration of precision medicine approaches with multidisciplinary care will be key to maximizing therapeutic outcomes while maintaining patients' quality of life. So I believe ultimately, by designing personalized and multi-target treatment plans, these continued innovations promise to redefine the standard of care for epithelial ovarian cancer in the coming decade, and we can transform this fatal disease into a controllable disease and give patients longer and better-quality lives.

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