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Review Article

Advances in immunotherapy and molecular targeted therapy of gestational trophoblastic tumor: current practice and future perspectives

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Abstract: Gestational trophoblastic neoplasia (GTN) is a rare pregnancy-related gynecological malignancy caused by abnormal proliferation of placental trophoblastic cells. It can invade the uterine muscle layer and metastasize early, more common in women of childbearing age. GTN is invasive and can destroy surrounding tissues and blood vessels, causing massive bleeding in uterus and metastatic sites (such as lung, liver, brain, etc.) through blood transfer. Chemotherapy is the main treatment for GTN, and the disease is extremely sensitive to chemotherapy and can be cured by chemotherapy. However, in clinical practice, a large number of patients have failed chemotherapy or even multiple treatments due to drug resistance, recurrence or metastasis of special sites. Therefore, how to individually select the initial chemotherapy regimen and reduce the occurrence of drug resistance is the key to the treatment of high-risk GTN. With the remarkable efficacy of immunotherapy in endometrial cancer, cervical cancer and other diseases, the research on GTN has been further deepened. Therefore, this review discusses the mechanism, methods and efficacy of GTN immunotherapy and molecular targeted therapy, in order to provide new ideas for the diagnosis and treatment of GTN.

Keywords: Gestational trophoblastic tumor, immunotherapy, molecular targeted therapy

Introduction

Gestational trophoblastic neoplasia (GTN) is a group of pregnancy-related gynecological malignancies that originate histologically from placental trophoblastic cells. It is classified as invasive mole (IM), choriocarcinoma (CC), placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). IM and CC are the most common of the four types [1, 2]. The incidence of GTN varies by region and race [3], about 0.6‰ in the United States, 1.4‰ in Europe, 2‰ in Japan [4], and 0.2‰ in South Korea in recent years [5]. However, China itself is a high incidence area of GTN. With the change of fertility control and fertility concept, the overall incidence of GNT decreased significantly, but it still failed to meet the international diagnostic criteria for rare diseases. In recent years, FIGO re-evaluated the new staging and prognostic scoring criteria, and classified the diseases into low risk (0-6 points) and high risk (≥7 points), which is the main basis for the selection of treatment plan in the world at present. For high-risk patients, including extremely high risk (≥12 points), multidrug combination chemotherapy is recommended [6]. In some cases, surgery and radiation therapy are needed. However, there are still 20.0% of patients with drug resistance at the later stage of initial chemotherapy, 5.0%-10.0% of patients with relapse after treatment, and 0.5%-5.0% of patients die due to multiple drug resistance, resulting in poor prognosis of GTN patients [7]. In recent years, with the in-depth study of immunomodulatory molecules in the immune system and tumor microenvironment, tumor immunotherapy has become a treatment method

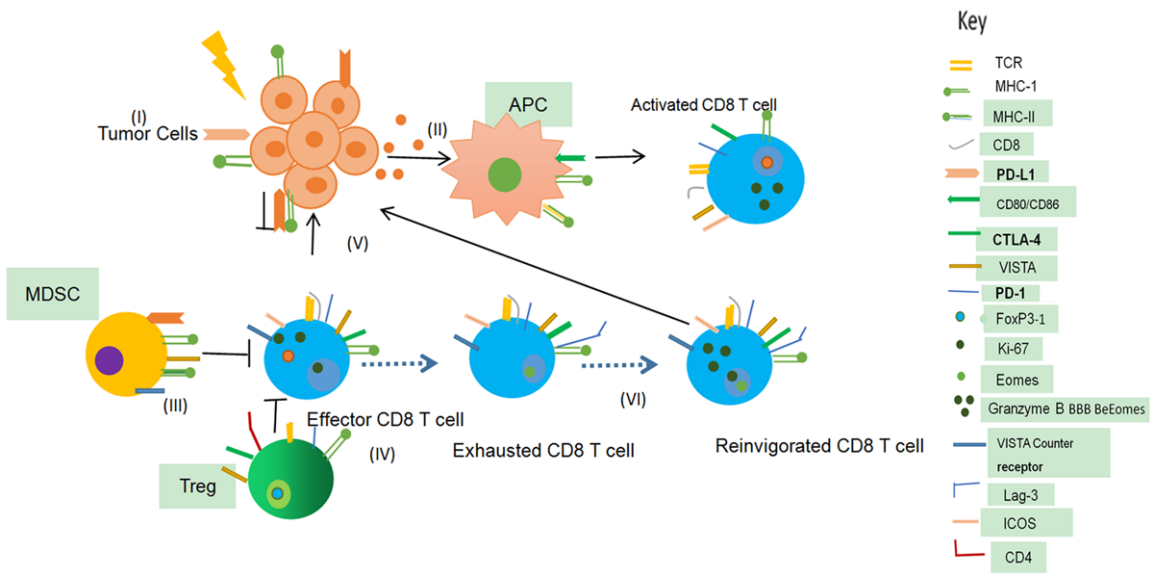

Figure 1. Elizabeth C et al. Mechanisms of immunotherapy. Anti-tumor T cell responses can be regulated in a variety of ways [10], including: (I). Immunological cell death: Tumor cell death induced by radiotherapy or chemotherapy can activate tumor-specific immunity by acting as an antigen or releasing cofactors (II). Vaccines: Peptide, protein, allogeneic or autologous tumor cell vaccines induce tumor-specific responses. Some vaccines use modified cells to coax the immune system into action (III). Enhanced innate immunity: Myeloid cells within the tumor contribute to an immunosuppressive environment (IV). T regs regulation: The treatment either interferes with T regs activity or modifies effector T cells to achieve T regs equilibrium (V). Mobilizing reactive T cells: Immunotherapy enhances T cell infiltration in tumors (VI). Reactivation of exhausted cells: The isolation of an immune inspection site causes exhausted cells to be reactivated to repair cellular proliferative capacity and function. Pd-1--PD-L1 is the main pathway, and other immune negative checkpoints LAG-3, TIGIT and TIM-3 also play a role in cell exhaustion. Note: CTLA-4: cytotoxic T lymphocyte associated antigen-4; VISTA: V-domain Ig suppressor of T cell activation.

for GTN [8]. Currently, there are 5 immune checkpoint drugs targeting PD-1/PD-L1 approved by the Food Drug Administration (FDA), including nivolumab, pembrolizumab, avelumab, durvalumab and atezolizumab [2]. Therefore, this paper reviews the mechanism and efficacy of GTN immune molecular targeted therapy, to provide new ideas for the diagnosis and treatment of GTN.

Mechanism and method of immunotherapy for GTN

In recent years, with the continuous development of medical technology, immunotherapy has been applied in clinical practice and achieved good results. Immunotherapy refers to artificially enhancing or suppressing the immune function of the body when the body is in a low or high immune state, so as to achieve the purpose of curing diseases. The treatment uses its own immune function to kill malignant tumor cells and tissues. It targets the body's own immune system rather than malignant tumor cells and tissues. Previous studies have shown that tumor immune escape is the basis of malignant tendency of tumor, and immune checkpoint is an important mechanism to prevent cell apoptosis [9]. Therefore, immune checkpoint inhibitors developed based on the above principles can effectively prevent immune escape of tumor cells. These immune checkpoint inhibitors include cytotoxic T lymphocyte associated antigen-4 (CTLA-4), programmed cell death 1 (PDCD1) and programmed cell death 1 Ligand 1 (PDCD1LG1). It has been reported that V-domain Ig suppressor of T cell activation (VISTA) is a new member of the negative immune checkpoint B7 family. VISTA mab regulates both T cells and myeloid cells. Based on the cognition that there are multiple immunosuppressive pathways in tumor microenvironment, blocking multiple immunosuppressive pathways simultaneously may achieve the optimal treatment strategy (**Figure 1**) [10]. Immune targets can be divided into two types according to the role of receptor and ligand binding, one is costimulatory molecule, the other is coinhibitory molecule. PD-1

is a costimulatory molecule. In the tumor microenvironment, PD-1 binds to PD-L1 and activates its pathway, thereby inhibiting the activity of T lymphocytes. Once the activity of T lymphocyte is inhibited, it cannot kill tumor cells, which survive by immune escape. The use of PD-1 or PD-L1 inhibitors can block the PD-1/PD-L1 pathway, thereby enhancing the activity of T lymphocytes, enhancing the recognition and killing effect of tumor cells, and ultimately achieving the purpose of anti-tumor [11, 12]. Placental antigen expression in pregnant women makes it a target for immune recognition during pregnancy, while PD-L1 expression maintains pregnancy tolerance. Studies have shown that PD-L1 is expressed in tumor tissues of GTN patients, and most of them are strongly positive [13]. In a scholar's study, immunohistochemical evaluation of 83 pathological tissue samples from gestational trophoblastic disease showed that PD-L1 was widely and strongly expressed in all pathological subtypes. Meanwhile, moderate to severe immune invasion was found in the surrounding area of the tumor, and the expression of PD-L1 was not correlated with FIGO prognostic score and chemotherapy sensitivity of GTN patients [14]. Immunohistochemical analysis of PD-L1 and PD-L2 expression in 112 patients with GTN showed that PD-L1 was expressed in tumor cells of all patients, with moderate to strong PD-L1 expression in 80 patients. PD-L2 was expressed in 87.5% of patients' tumor cells. The expression of PD-L1 and PD-L2 accounted for 39.3% and 30.4% of tumor-related immune cells, respectively [15]. Clinical trials of immune checkpoint inhibitors in GTN are limited. In April 2017, the French Centre for Trophoblastic Diseases initiated a phase II clinical study of immune checkpoint inhibitors in the treatment of drug-resistant trophoblastic tumors (NCT-03135769). The study included two cohorts: low-risk patients who were resistant to single-agent chemotherapy (MTX or ACT-D); Another cohort consisted of patients who were resistant to combination chemotherapy (EMA-CO, EMA-EP, BEP, etc.). PD-L1 antibody Trophimmun (Avelumab IV) 10 mg/kg, once every 2 weeks, was used for 3 courses of HCG consolidation after normal HCG.

The 2018 ESMO Meeting, You et al. reported some results of the low-risk group in the form of wallpaper. After 11.7 months of follow-up, 3 of the 6 patients had complete remission, while the other 3 patients did not respond to the treatment and were in remission after salvage chemotherapy with no serious adverse reactions. This is the first study to use a nontraditional chemotherapy agent to treat low-risk drug-resistant GTN and achieve remission [16]. Ghorani et al. also reported the treatment of paprilizumab in 4 patients with extremely high risk of GTN with liver or brain metastases. In this study, all patients received palizumab 2 mg/kg, 21 d as a cycle, a total of 5 courses, results of 3 patients achieved complete remission, 1 patient died due to disease progression, no class III-IV drug adverse reactions occurred during the treatment, and all patients could tolerate [17]. In 2019, KIM et al. reported 2 cases of extremely high-risk GTN treated with paprilizumab and achieved the same satisfactory efficacy [18]. In this study, one patient was treated with 200 mg of pabulizumab (21 days as a course of treatment). After 5 courses of treatment, imaging examination confirmed complete remission and clinical follow-up was carried out. The other patient had been treated for 3 courses as of press time, and his condition was in complete remission without any class III-IV drug side effects. In 2017, Huang et al. [19] firstly reported a case of stage IV choriocarcinoma with drug resistance who received PD-1 inhibitor (pembrolizumab) and achieved complete remission. Subsequently, Charing Cross Hospital in the UK reported for the first time 4 patients with drug-resistant and recurrent GTN who received PD-1 inhibitor (pembrolizumab) and 3 patients (2 chorionic and 1 PSTT) achieved complete remission with no relapse at 5-24 months of follow-up. Xu et al. study reported that the expression of TILS and HLA-G in tumor tissues may be related to the prognosis of patients [20]. Therefore, the 2018 FIGO Cancer Report suggested that PD-1 inhibitor (pembrolizumab) could be used as a remedial treatment for patients with drug-resistant recurrent GTN [21]. Peking Union Medical College Hospital also reported 8 patients with drug-resistant recurrent GTN receiving PD-1 inhibitor (pembrolizumab) in 2020, with an effective rate of 50%. In addition to the PD-1 inhibitor (pembrolizumab), a recent clinical trial of a PD-1 inhibitor (avelumab) for the treatment of methotrexate resistant low-risk GTN was reported by researchers from the French Centre for Trophoblast Cell Disease, involving 15 patients

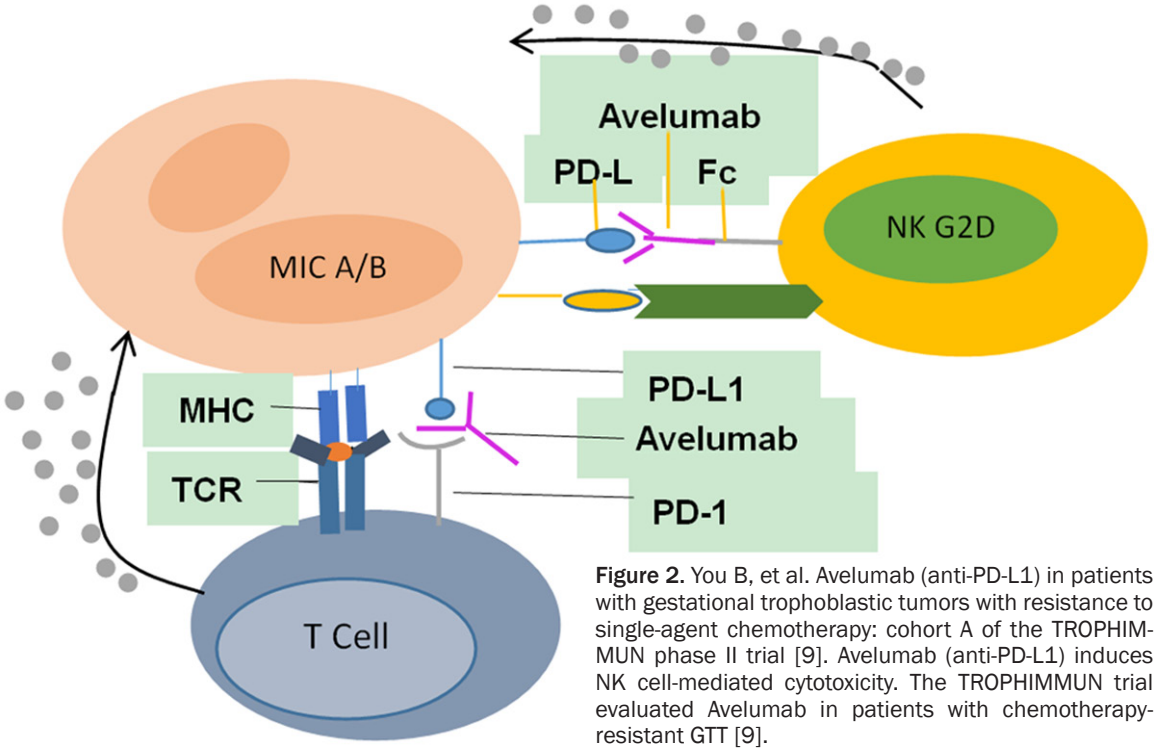

Figure 2. You B, et al. Avelumab (anti-PD-L1) in patients with gestational trophoblastic tumors with resistance to single-agent chemotherapy: cohort A of the TROPHIMMUN phase II trial [9]. Avelumab (anti-PD-L1) induces NK cell-mediated cytotoxicity. The TROPHIMMUN trial evaluated Avelumab in patients with chemotherapy-resistant GTT [9].

with a complete response rate of 53% (8/15) (**Figure 2**) [9]. Paspalj et al. reported the choriocarcinoma showed strong PD-L1 expression. Despite a frustrating response to cytotoxic chemotherapy, she experienced full remission after pembrolizumab and now has a durable response of currently more than two years after the end of treatment [22].

In 2021, it is worth noting that Yang *et al.* reported a single-arm, open-label, phase 2 clinical trial (CAP01) of Carrelizumab combined with apatinib in the treatment of high-risk chemotherapy-resistant or recurrent gestational trophoblastic tumor. Twenty patients (19 chorionic and 1 PTT) were treated with carrelizumab (200 mg/2 weeks) in combination with apatinib (250 mg/once per day) until disease progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR) as assessed by serum HCG levels. The study showed an objective response rate of 55% (95% CI: 32%-77%). The median follow-up time was 18.5 months (IQR: 14.6-20.9), and the median progression-free survival (PFS) was 9.5 months. Median overall survival (OS) was not achieved, with a 12-month OS rate of 90%, and no grade 4 or 5 treatment-related adverse events were reported. This study provides new therapeutic ideas and options for the salvage treatment of trophoblastic tumor. Of course, due to the limited number of patients and the single-arm study, studies with larger samples are needed to further confirm the efficacy and safety (**Table 1**) [23].

It should be recognized that the research on GTN immunotherapy started late, and the mechanism of immune checkpoint inhibitors is not fully understood. For now, some encouraging cases have given researchers confidence, but many cases that do not respond to treatment have not been reported. At present, there are no effective indicators for the efficacy of immunotherapy, so it is necessary to be very careful and fully informed when selecting patients to use immunotherapy.

Molecular targeted therapy for GTN

With the deepening of molecular typing and genetic tumor research and the rapid development of biological targeted therapy drugs, the treatment of malignant tumor has gradually entered the era of precision medicine [24]. In recent years, the clinical application of targeted therapy in GTN has also made breakthrough progress. Studies have shown that deletion of

Table 1. Summary of recent studies on GTN immunotherapy

author	years	Types of GTN	n	Condition and therapeutic effect
You *et al*. [9]	2020	CC	15	Single drug resistance, avelumab treated for an average of 8 cycles, 1 healthy pregnancy, and the efficiency reached 50%.
Ghorani *et al*. [17]	2017	GTN	4	3 patients (2 chorionic and 1 PSTT) achieved complete remission and had no recurrence during 5-24 months of follow-up. Another patient with PSTT combined with ETT had poor disease progression. This study found that the expression of TILS and HLA-G in tumor tissues may be related to patient prognosis.
Huang *et al*. [19]	2017	CC	1	One case with multiple metastases in the head of pancreas, liver (multifocal), mediastinum and lung (multifocal) underwent multi-drug chemotherapy (EMA-CO chemotherapy 4). After the decrease of hCG, the rise of hCG increased after 4 cycles. The decrease of hCG was treated by 2 cycles of Prebrolizumb. After treatment, hCG was normal, liver lesions almost disappeared, and liver enzymes were normal followed by treatment with 50% Prebrolizum B for 4 months.
Choi *et al*. [21]	2019	PSTT/ETT	7	Prebrolizumb for the first time in Asia for the treatment of PSTT/ETT; Effective response rate is 6/7, complete response rate is 5/7.
Xiang Y et al. [23]	2021	CC/PSTT	20	20 patients were treated with carrelizumab in combination with apatinib until tumor progression or unacceptable toxicity. The objective response rate of 55% (95% CI: 32%-77%). The median follow-up time was 18.5 months (IQR: 14.6-20.9), and the median progression-free survival (PFS) was 9.5 months. No grade 4 or 5 treatment-related adverse events were reported.
Chen et al. [24]	2020	GTN	8	Multidrug resistance was observed in 8 patients. Seven of them underwent surgical treatment and were treated with PD-1 inhibitors after surgery, with an average of 9 cycles of treatment. There was no recurrence after 2-7 months of follow-up, and 4 patients had no obvious response and changed to other chemotherapy regimens.
Worley *et al*. [27]	2017	CC		After 2 weeks of ACTD monotherapy, emA-CO + hysterectomy was performed because hCG decreased and increased again. After 7 cycles, the hCG decreased to normal, and the chemotherapy was consolidated for 3 cycles, and the drug was stopped for 1 month. HCG increased again after treatment. Thoracoscopic resection of lung lesions and craniocerebral radiotherapy were performed, followed by TRCl05 and bevacizumab (10 mg/kg) sustained remission for 28 months after 8 cycles.

Note: GTN: Gestational trophoblastic neoplasia; CC: Choriocarcinoma; PSTT: Placental-site trophoblastic tumor; ETT: Epithelioid trophoblastic tumor; hCG: Human chorionic gonadotropin; PFS: Progression-free survival.

two tumor suppressor genes TRIM32 (9Q33.1) and CDH19 (18Q22.1) have been detected in choriocarcinoma specimens [16]. Genetic testing has also identified potential molecular therapeutic targets in patients with chemotherapy-resistant refractory GTN.

VEGF targeted therapy

Angiogenesis plays an important role in various physiological and pathological processes such as embryogenesis, tumor growth, invasion and metastasis. Vascular endothelial growth factor (VEGF), a homodioglycan protein with a molecular weight of about 45 KDa, is characterized by a protein structure containing disulfide bridges and cystine motifs, which is a key mediator of angiogenesis. The binding of VEGF to corresponding receptors can lead to endothelial cell proliferation and tumor neovascularization, and promote tumor growth, invasion and metastasis. Angiogenesis is critical to tumor development and growth, so the important role of VEGF in tumor angiogenesis makes it a reasonable target for anti-tumor therapy [25]. A study analyzed and compared VEGF expression in partial hydatidiform mole, complete hydatiform mole and choriocarcinoma pathological tissues by immunohistochemical method, and found that VEGF expression in choriocarcinoma tissues was higher than that in partial hydatiform mole and complete hydatiform mole, suggesting that VEGF may be involved in the progression of trophoblastic diseases (**Table 2**) [26].

Singh et al. found that VEGFR-2 expression in normal placental tissues was significantly higher than that in hydatidiform mole tissues by analyzing VEGF expression in GTN tissues [26].

Table 2. Summary of recent studies on molecular targeted therapy for GTN

author	years	Types of GTN	n	Condition and therapeutic effect
Sarah G Bell et al. [8]	2021	ETT	1	Sarah G Bell *et al.* report a case of extrauterine epithelioid trophoblastic tumor (ETT, the rarest variant of gestational trophoblastic tumor) that has been stable on nearly two years of pembrolizumab treatment.
Kim GS et al. [18]	2019	GTN	2	One patient was treated with paprizumab (200 mg/kg; 21 days as a course of treatment), and achieved satisfactory efficacy. The other patient has been treated for 3 courses, and also achieved complete remission.
Paspalj et al. [22]	2021	CC	1	The patient experienced full remission after pembrolizumab and has durable response of currently more than two years after end of treatment.
Worley et al. [27]	2018	Refractory CC	1	The patient was treated with bevacizumab (10 mg/kg) and anti-endoglin monoclonal antibody (TRC105), and HCG decreased to normal after 4 courses.
Zhang et al. [32]	2019	CC	1	There was a large amount of CD105 expression in the tumor cells, and after 4 weeks of TRC105 combined with beizumab treatment, the patient's symptoms were significantly improved.
Pires et al. [34]	2019	CC	2	In vitro studies have found that EGFR and HER2 are significantly overexpressed in GTN cells, and lapatinib can significantly inhibit tumor cell growth by regulating the expressions of EGFR and HER2 in GTN.

Note: GTN: Gestational trophoblastic neoplasia; CC: Choriocarcinoma; PSTT: Placental-site trophoblastic tumor; ETT: Epithelioid trophoblastic tumor; EGFR: Epidermal growth factor recept.

The expression of VEGF, Angiopoietin-1 and Angiopoietin-2 in placenta of GTN was significantly higher than that in choriocarcinoma. Moreover, choriocarcinoma tissue showed strong staining intensity for VEGFR-3, confirming high expression of VEGF and its receptor in gestational trophoblastic disease. Antiangiogenic therapy can increase the expression of glycoprotein in endothelial cell, and endothelial cell glycoprotein blockade can increase the expression of VEGF.

Although endothelial glycoprotein expression is limited outside endothelial cells, it is a very specific marker for placental syncytial trophoblast cells and an ideal histopathological marker for choriocarcinoma tissues. In 2018, Worley et al. reported a case of refractory choriocarcinoma treated with bevacizumab and achieved satisfactory clinical efficacy. The patient was a 36-year-old female with low-risk GTN at the time of onset. The early treatment effect was not good, and the chemotherapy regimen was changed for several times. The blood HCG decreased and then increased again, and the disease progressed rapidly with brain metastasis. The patient was treated with bevacizumab (10 mg/kg) and anti-endoglin monoclonal antibody (TRC105), and HCG decreased to normal after 4 courses [27].

CD105 targeted therapy

CD105 is a member of the transforming growth factor-β (TGF-β) receptor superfamily. It has many biological functions in human tissues. At present, studies on this membrane protein are mostly limited to vascular endothelial cells, and due to its role in angiogenesis, anti-vascular therapy targeting this protein is also in progress. Some of them are clinical trials [28, 29]. Studies have found that over expression of CD105 can not only reduce the sensitivity of choriocarcinoma cells to chemotherapy drugs, but also stimulate the increase of cell migration and invasiveness, and inhibit the occurrence of apoptosis of choriocarcinoma cells.

Moreover, *in vitro* experiments have confirmed that bone morphogenetic protein 9 (BMP9) is involved in the occurrence of drug resistance in choriocarcinoma through CD105, and exposing choriocarcinoma cells to high concentration of BMP9 can increase cell resistance to chemotherapy drugs. The BMP9/Smads pathway is a biological pathway in which CD105 reduces the sensitivity of cells to chemotherapy. After analyzing the immunohistochemical and pathological significance of tumor tissues in patients with choriocarcinoma, Wang et al. found that the high expression of CD105 and BMP9 in pathological tissues was correlated with drug

resistance and postoperative recurrence after chemotherapy, but not correlated with the age of onset and other factors. The results of this study suggest that these two proteins may become new auxiliary indicators to predict and evaluate the prognosis of patients with choriocarcinoma [30]. Studies have found that CD-105 is positively correlated with the expression of cytotype and type trophoblast cells [31]. After the successful construction of CD105 expression related nude mouse transplanted tumor model of choriocarcinoma, the growth and protein expression of transplanted tumor in each group were detected. The results showed that the growth rate of CD105 knockdown xenografts in nude mice was slower than that of wild choriocarcinoma, while the growth rate of CD105 over expression xenografts in nude mice was significantly faster than that of wild choriocarcinoma. This study confirmed that the expression of CD105 in choriocarcinoma was positively correlated with tumor growth rate and tumor drug resistance [31]. Therefore, a monoclonal antibody binding to CD105 has been developed to become a new molecular targeted therapy for GTN (TRC105). Zhang et al. conducted genome analysis on tumor cells of a GTN patient, and the analysis results showed that there was a large amount of CD105 expression in the tumor cells, and after 4 weeks of TRC105 combined with beizumab treatment, the patient's symptoms were significantly improved and the condition was in a stable stage [32]. In 2019, Frijstein et al. found that VEGF and its receptors were highly expressed in trophoblastic tumors. Angiogenesis is the basis and prerequisite for tumor cell proliferation and metastasis, and VEGF is one of the important factors controlling angiogenesis, indicating that VEGF and its receptor are expected to become a new therapeutic target for patients with GTN [33].

EGFR targeted therapy

Epidermal growth factor receptor (EGFR), a member of ERBB conserving receptor family, is a transmembrane glycoprotein located on the surface of cell membrane. Other members of the family include HER2/Neu/ErbB2, HER3/ErbB3 and HER4/ErbB4, which affect cell proliferation and signaling.

EGFR plays its role by affecting tumor cell proliferation, invasion, metastasis, and apoptosis. EGFR was highly expressed in GTN tissue. In vitro studies have found that EGFR and HER2 are significantly overexpressed in GTN cells, and lapatinib can significantly inhibit tumor cell growth by regulating the expressions of EGFR and HER2 in GTN [34, 35]. To investigate the expression patterns of C-Erbb2 and Bcl-2 proteins in hydatidiform mole tissues, Missaoui et al. performed immunohistochemical analysis on 220 pregnancies, including 39 aborted tissues, 41 partial hydatidiform mole tissues and 140 complete hydatiform mole tissues. The results showed that c-ErBB2 expression was observed in 3 partial mole tissues and 10 complete mole tissues, and bcl-2 immunostaining was more obvious in partial mole (61%) and complete mole (70.7%) tissues than in aborted tissues [36]. In conclusion, EGFR-related targets are expected to become new targets for the treatment of GTN, but clinical studies on EGFR in GTN are lacking, and the clinical application value of related drugs remains to be further studied.

Occurrence and countermeasures of immune-related adverse events (IRAEs)

Tumor immunotherapy is to activate and enhance the patient's own immune system to play an anti-tumor effect. Various immune checkpoint inhibitors, mainly PD-L1 inhibitors, have shown encouraging efficacy in the treatment of various tumors. Drugs increase the activity of the immune system while producing inflammatory side effects, known as IRAEs. Although any organ system can be involved, immune-related adverse events are more common in the skin, gastrointestinal system, endocrine system, and liver, and less common in the cardiovascular, central nervous system, lung, and blood system. Kane and Friel conducted a meta-analysis of 16 RCTs, and found that the mortality rate of adverse reactions such as bleeding and delayed wound healing caused by drug factors in the treatment of GTN patients with bevacizumab was 2.5%. For vascular endothelial growth factor (VEGF) targeted therapy, bleeding is a common adverse reaction, which not only affects the prognosis of patients, but also increases the difficulty of clinical treatment [37].

The cause of immune-related adverse events may be that PD-L1 inhibitors block immune self-tolerance associated with PD-L1, and

enable reactive T cells in the activated immune system to attack body's self-antigens.

(1) Although the specific mechanism of IRAEs is not yet clear, immune-related adverse events are all caused by the body's over-immunity to normal organs, and the overall incidence and severity of IRAEs with PD-L1 inhibitors are far less than that with traditional radiotherapy and chemotherapy. Mild to moderate (grade I-II) symptomatic treatment of IRAEs can mostly be alleviated. Severe (grade III-IV) IRAEs can be effectively treated by delaying dosing or, in more severe cases, inducing temporary immunosuppression by oral glucocorticoids or immunosuppressive drugs, unalleviated IRAEs should be discontinued permanently [38].

(2) Although targeted drugs such as VEGF/VEGFR receptor inhibitors have shown efficacy in a variety of tumor therapies, the accompanying IRAEs is also an important factor affecting their clinical use. The most common ones are blood pressure and proteinuria, as well as hand-foot syndrome, fatigue, diarrhea, thrombocytopenia and hepatorenal toxicity [39]. For hypertension caused by such drugs, blood pressure should be dynamically monitored, and antihypertensive drugs should be actively used to control blood pressure so that it is not higher than 140/90 mmHg. At present, there is no unified guideline for the use of antihypertensive drugs. Conventional angiotensin converting enzyme inhibitors, angiotensin receptor antagonists and thiazide diuretics can all be used to treat hypertension caused by VEGF/VEGFR receptor inhibitor targeting drugs. Specific use needs to be combined with patients' complications and actual situation. If severe hypertension that cannot be controlled by drugs occurs, medication should be discontinued [39].

Targeted therapy of PI3K/AKT signaling pathway

In addition to the above statements, other targets related to drug resistance in GTN also exist, all of which provide new ideas and targets for the treatment of GTN. Chen et al. examined the gene sequences of 8 patients with GNT, and the results showed that phosphatase and tensin homolog (PTEN), phosphatidylinositol 3-hydroxy kinase (PI3K), protein kinase B (PKB) pathways are closely associated with GNT occurrence and development [40]. It may be a new target for the targeted therapy of trophoblast tumor. Xu et al. showed that External regulatory protein kinase (ERK1/2) can increase the leukemia inhibitory factor (LIF) induced signal transduction and activator of transcription 3 (STAT3) [20]. It can increase the proliferation ability of JEG-3 choriocarcinoma cells and promote the proliferation of tumor cells, but the long-term effects of patients need to be further studied and discussed.

Future prospective

As a pregnancy-related gynecological malignant tumor, GTN often occurs in women of childbearing age. Studies have shown that the incidence in Asia is higher than that in Europe and The United States. At present, the cause of the disease is not very clear, which may be related to race, region, nutritional status, family history, endocrine and other factors. Treatment of GTN has improved significantly in recent decades with classical chemotherapeutic agents. Nevertheless, the discussion and optimization of treatment is still ongoing. In order to find a better balance between achieving the best curative effect and reducing the side effects of treatment, the standardization of treatment should be emphasized, and precise and individualized treatment should be carried out according to the specific situation of patients. With the rise of tumor immunotherapy, trophoblast tumor immunotherapy has become the focus and hotspot of current research, and the research is more focused on immune checkpoint inhibitors and molecular targeted therapy drugs (**Tables 1**, **2**). Although good effects can be achieved, the incidence of adverse drug reactions is still relatively high. At the same time, the mechanism of immune checkpoint inhibitors is not completely clear, so further research and exploration are needed to find more targets and related combined treatment plans, in order to provide new ideas and methods for the treatment of GTN patients.

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Disclosure of conflict of interest

None.

Abbreviations

IM, invasive mole; CC, choriocarcinoma; PSTT, placentalte trophoblastic tumour; ETT, ephelioid trophoblastic tumour; FDA, Food Drug Administration; CTLA-4, cytotoxic T lymphocyte associated antigen-4; PDCD1, programmed cell death 1; PDCD1LG1, programmed cell death 1 ligand 1; VEGF, vascular endothelial growth factor; TGF-β, transforminggrowth factor-β; EGFR, epidermal growth factor receptor; PTEN, phosphatase and tensin homolog; PI3K, phosphatidylinositol 3-hydroxy kinase; PKB, protein kinase B; LIF, leukemia inhibitory factor; STAT3, signal transduction and activator of transcription 3; ORR, the objective response rate; PFS, progression-free survival; OS, overall survival; VISTA, V-domain Ig suppressor of T cell activation.

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