Original Article
Immunotherapy in anaplastic thyroid cancer

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Abstract: Anaplastic thyroid cancer (ATC) is one of the worst human malignancies, with an associated median survival of only 5 months. It is resistant to conventional thyroid cancer therapies, including radioiodine and thyroid-stimulating hormone suppression. Cancer immunotherapy has emerged over the past few decades as a transformative approach to treating a wide variety of cancers. However, immunotherapy for ATC is still in the experimental stage. This review will cover several strategies of immunotherapy and discuss the possible application of these strategies in the treatment of ATC (such as targeted therapy for tumor-associated macrophages, cancer vaccines, adoptive immunotherapy, monoclonal antibodies and immune checkpoint blockade) with the hope of improving the prognosis of ATC in the future.

Keywords: Immunotherapy, anaplastic thyroid cancer, immune checkpoint blockade, tumor-associated macrophages, oncolytic virus and neoantigens

Introduction
Anaplastic thyroid cancer (ATC) is the most aggressive malignancy among all thyroid cancer subtypes, with a disease-specific mortality approaching 100% [1]. Conventional therapeutics for thyroid cancer include surgery, chemotherapy and radiation treatment, but none of these methods can provide satisfactory efficacy in ATC, so the median survival of patients from diagnosis is still approximately 5 months [2-4].

With the rapid development of and collaborations between oncology, immunology, and molecular biology, great progress has been made in tumor immunotherapy research. James P Allison and Tasuku Honjo were awarded the Nobel Prize in Physiology or Medicine 2018 for their outstanding contribution in promoting immunotherapy in cancer treatment. According to a comprehensive analysis of the clinical immune-oncology landscape, there were more than 2,000 immuno-oncology agents in clinical or preclinical stages until 2017; furthermore, there were 3,042 active clinical trials of these agents enrolling a total of 577,076 patients [5]. Immunotherapy has become an important means of treatment for many cancers, such as melanoma, non-small-cell lung cancer (NSCLC), and urothelial carcinoma [6-10]. Up to October 2018, the FDA has approved 7 immune checkpoint inhibitors that can be used for a variety of cancer treatments based on the results of related clinical trials [11]. Immunotherapy brings hopes for the treatment of ATC [12, 13]. Here, we reviewed the potential strategies of immunotherapy for ATC, aiming to provide comprehensive information on immunotherapy for this intractable carcinoma.

Targeted therapy for tumor-associated macrophages
Tumor-associated macrophages (TAMs) are derived from circulating monocytes differentiated in the tumor microenvironment [14] (Figure 1A). TAMs have two phenotypes, namely, M1 TAMs, which contribute to immune control over tumors, and M2 TAMs, which promote tumor progression and impair antitumor activity mediated by the immune system [15]. TAMs have been
Figure 1. A. Monocytes migrated to tumor microenvironment from blood circulation attracted by CSF1, VEGF-A and CCL2, and differentiated into TAMs (M2 type). M2 TAMs can promote tumor cell proliferation and contribute to disease progress. B. Target therapy for CSF1, VEGF-A and CCL2 to inhibit the recruitment of TAMs from blood circulation, as a result, restricting the pro-tumor function of M2 TAMs and inhibiting tumor cell proliferation.

found to correlate with the immune-suppressive microenvironment in human gliomas and enhance stemness of breast cancer cells [16, 17], which indicates that targeting TAMs is a practical method in gliomas and breast cancer treatment.
In ATC tissues, TAMs represent more than 50% of nucleated cells and are the only type of lymphocyte. All of these TAMs belong to the M2 phenotype [18]. Because a high density of TAMs is closely related to the aggressiveness and invasiveness of ATC, TAMs have been considered a prognostic biomarker for ATC [19, 20]. Considering that TAMs constitute an unusually high proportion of all nucleated cells and form a dense and diffuse network in the tumor microenvironment of ATCs, as identified under electron microscope [18], targeting TAMs may be a feasible way to treat ATCs. Here, we will discuss the strategies for targeting TAMs in ATC.

**Inhibiting recruitment of TAMs**

During acute inflammatory reactions, monocytes are recruited into tissues from peripheral blood. In this process, chemoattractants and their receptors contribute to the recruitment of these monocytes to inflamed tissues [21, 22]. In the tumor environment, tumor-derived chemoattractants play critical roles in recruiting monocytes into tumors and contribute to the subsequent differentiation of monocytes into M2 TAMs; as such, developing agents to block these chemoattractants has been proposed as a rational way to treat cancer [23] (Figure 1B).

Colony-stimulating factor-1 (CSF1) is a major lineage regulator for most populations of macrophages, playing an important role in recruiting monocytes in many tumors [24-26]. Previous studies have reported that genetic deletion of CSF1 from several models of cancer results in delayed initiation (cervical cancer), progression (breast and pancreatic cancer) and metastasis (breast cancer) associated with the loss of TAMs [27]. CSF1 has been found to be overexpressed in human tissue samples of thyroid tumors, and the expression levels were higher in advanced thyroid cancer than in inactive papillary thyroid cancer (PTC) [28]. In addition, CSF1/CSF1R signaling is required for TAM recruitment and can be pharmacologically targeted to impair PTC initiation [29]. Regarding ATC, the relative expression of CSF1 was higher in ATC cell lines than in PTC cell lines; moreover, both qPCR and microarray data revealed that the expression of CSF1 and its receptor was higher in metastatic ATC cells than in primary ATC cells [30]. These results indicate that the grade of malignancy of thyroid cancer is positively correlated with the expression level of CSF1 and that targeting CSF1/CSF1R signaling may be an effective method in ATC treatment.

Vascular endothelial growth factor A (VEGF-A) can lead to massive infiltration of TAMs into the tumor [31]. Salajegheh A found upregulation of VEGF-A expression in ATC tissues, which indicated that suppression of VEGF-A might also be a potential strategy to inhibit recruitment of TAMs in ATC [32].

Chemokine (C-C motif) ligand 2 (CCL2) is expressed in many cancers, including thyroid cancer [33, 34]. CCL2 can act as a chemotactic factor for monocytes; thus, they can migrate to the tumor region and differentiate into TAMs [35]. P53, a cancer suppressor gene, was reported to play an important role in binding to CCL2 [36]. In addition, p53 mutation was only found in ATC but not in other types of thyroid cancer [37]. It is reasonable to speculate that targeting CCL2 in p53-mutated ATCs may be a promising treatment, but further research is needed to verify this idea.

Due to the critical role of these chemokines in recruiting TAMs, inhibiting chemokine signaling could be considered a therapeutic approach for the treatment of ATC in the future [34].

**Repolarization of TAMs from the M2 phenotype to the M1 phenotype**

Some scholars argue that tumor tissues have both M1 and M2 TAMs, and the ratio of M1/M2 determines the function of all TAMs. Namely, when the ratio is greater than 1, M1 TAMs accounts for most of the TAMs, and antitumor activity will dominate, in contrast, when the ratio is less than 1, M2 TAMs and thus protumor activity will dominate [38]. Repolarization of M2 TAMs into M1 TAMs has been a widely accepted strategy of immunotherapy for TAMs in ATC [39]. Repolarization is not an independent result of immunotherapy; rather, it is always accompanied by the inhibition of TAM recruitment [15]. Banerjee S demonstrated that heat-killed Mycobacterium indicus pranii (Mw) could induce repolarization of TAMs toward the M1 phenotype in vitro but failed to show this in vivo. Furthermore, Mw combined with a GITR antibody (DTA-1) could repolarize M2 TAMs toward the M1 phenotype in vivo and
restrict the progression of advanced-stage melanoma [40] (Figure 2). Whether this combination could be used in ATC requires further investigation. Many researchers have found other ways to repolarize M2 TAMs toward the M1 phenotype in ovarian cancer and NSCLC, but none of these means have been applied in an ATC animal model [41, 42]. Since the mechanism of TAM repolarization is still elusive, clarification will require continued efforts.

Cancer vaccines

Cancer vaccines are an important form of immunotherapy. They target defined antigens to induce or expand cancer-specific T cells and rely on DNA, RNA, proteins or peptides [43]. Cancer vaccines can target neoantigens and tumor-associated antigens (TAAs). Neoantigens are uniquely expressed in tumor cells, while TAAs are typically proteins present in normal tissues but overexpressed in cancers [44].

Cancer neoantigens are derived from somatic mutations present in different cancer cells, and these neoantigens are considered significant targets for cancer immunotherapy because of their immunogenicity and lack of expression in normal tissues.

Next-generation sequencing (NGS) can identify the mutational landscape of cancer and is the starting point of cancer neoantigen identification [44]. In a recent study, researchers analyzed the genetic alteration patterns of 196 ATC clinical samples and found the two most commonly mutated genes in ATC: TP53 (65%) and TERT (65%). Moreover, after comparing mutation frequencies in ATC and differentiated thyroid cancer (DTC), they identified that their ATC cohort was characterized by an increased frequency of mutations in tumor suppressor genes (TP53, NF2, NF1, and RB1) and PI3K/AKT pathway genes (PIK3CA and PTEN). Furthermore, the authors summarized all the pathways and genes that were altered more frequently in ATC than in differentiated thyroid cancer (DTC) [45]. Their findings provide meaningful genome-level information and can help us to identify neoantigens in ATC. There are many ongoing clinical trials of cancer vaccines for the treatment of different cancers, including breast carcinoma, gastric carcinoma, bladder carcinoma, glioblastoma, kidney cancer, leukemia, lung cancer and melanoma [46].

Peptide/protein platforms are the most common but not the only vaccine platform. Here, we discuss another two types of cancer vaccines that may be used for ATC treatment in the future.

Dendritic cell (DC) vaccines

DCs are potent antigen-presenting cells in the immune system, and mature DCs can elicit
immune stimulation and promote antitumor reactions in the tumor microenvironment [47, 48]. DC vaccines are based on patient-derived DCs armed ex vivo with cognate antigen and costimulatory cues from ligands present on the antigen-presenting cell (APC) surface [49]. Mature DCs loaded with tumor-specific antigen were used in a previous study as a vaccine to treat medullary thyroid carcinoma and proved valid in animal models and some patients [50-53]. Furthermore, a phase I clinical study demonstrated that DC immunotherapy could be administered to thyroid cancer patients without substantial side effects [54]. Landa I reported that ATC had a greater mutation burden than poorly differentiated thyroid cancer and well-differentiated thyroid cancer [55], suggesting that ATC had a greater chance of harboring tumor neoantigens. Intriguingly, researchers from Argentina found that triiodothyronine could potentiate antitumor responses by bolstering DC-mediated T cell activation during tumor growth in a melanoma mouse model [56], suggesting that DC vaccine-based treatment may be more effective in thyroid cancer than in other tumors due to the high density of triiodothyronine stored in thyroid follicles. The biggest obstacle for applying DC vaccines in ATC is the lack of a tumor-specific antigen at present. With the development of NGS technology and exploration of neoantigens in the future, application of a DC vaccine in the treatment of ATC will be possible.

**Oncolytic virus vaccines**

Oncolytic virus (OV) therapy is based on the selective replication of viruses in cancer cells and their subsequent spread within a tumor without damage to normal tissue [57]. OVs exert antitumor action through a dual mechanism of selective tumor cell killing and induction of systemic antitumor immunity.

There are two kinds of OVs. The first consists of viruses that naturally replicate preferentially in cancer cells and are nonpathogenic in humans, often due to elevated sensitivity to innate antiviral signaling or dependence on oncogenic signaling pathways. The second consists of viruses that are manipulated genetically for use as vaccine vectors. Until now, many OV therapies have been reported to be effective against ATC cell proliferation, such as dl922-947, Newcastle disease virus, and poxviruses. Interestingly, dl922-947 has been proven to not only suppress tumor growth but also switch M2 macrophages toward a pro-inflammatory M1 phenotype in an ATC mouse model [58-60].

OVs may break the tolerogenic tumor microenvironment and induce a long-lasting CD8 T cell-mediated antitumor response, thereby acting as vaccines [61]. Previous studies have reported that OV infection can counteract cancer-mediated immune evasion by altering the cytokine milieu and the type of immune cells within the tumor microenvironment; these activities will promote immune-mediated tumor cell recognition and eradication [62, 63]. In addition, the lysis of cancer cells can result in the release of tumor-specific antigens (TSAs) that may have been previously hidden from the immune system because of restricted presentation, consequently triggering powerful antitumor immunity against TSAs [64, 65].

Previous studies have shown that OV vaccines have some efficacy in controlling ATCs both in vivo and in vitro [59, 66]. Based on the results of previous clinical trials, the first oncolytic virus, the HSV-1-based talimogene laherparepvec (T-VEC), was approved for the treatment of nonresectable melanoma in the USA and Europe. Here, we list a collection of clinical trials about the therapeutic effectiveness and safety of OVs in advanced or metastatic solid tumors. ATC patients meet the inclusion criteria of all these clinical trials (**Table 1**).

**Adoptive immunotherapy**

Adoptive cell transfer (ACT) is an immunotherapy that relies on the active in vivo recruitment of sufficient numbers of antitumor T cells with the functions necessary to mediate cancer regression [67]. There are two kinds of ACT methods: the first type uses natural host cells that are expanded ex vivo and infused into patients with malignant diseases, and the second method uses infused autologous T cells that have been genetically engineered with chimeric antigen receptors (CARs), which enable these T cells to specifically identify and kill tumor cells to treat different malignant diseases [68, 69].

CAR-T cells can recognize TAAs and induce strong antitumor activity, which has been demonstrated in many cohorts suffering from he-
### Table 1. Clinical trials about OVs in the treatment of advanced/metastasis solid tumor

<table>
<thead>
<tr>
<th>Trial</th>
<th>Condition/Disease</th>
<th>Intervention</th>
<th>Phase</th>
<th>Estimated/Actual Enrollment</th>
<th>State of Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00794131</td>
<td>Advanced solid tumor</td>
<td>GL-ONC1</td>
<td>I</td>
<td>43</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT02428036</td>
<td>Solid tumors with superficial lesions</td>
<td>TBI-1401</td>
<td>I</td>
<td>6</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT03866525</td>
<td>Advanced solid tumor</td>
<td>OH2</td>
<td>I</td>
<td>150</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>NCT01598129</td>
<td>Advanced solid tumor</td>
<td>ONCOS-102+cyclophosphamide</td>
<td>I</td>
<td>12</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT03889275</td>
<td>Advanced solid tumor</td>
<td>MEDI5395+Durvalumab</td>
<td>I</td>
<td>164</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>NCT02045602</td>
<td>Advanced solid tumor</td>
<td>VCN-01 with or without Abraxane®/Gemcitabine</td>
<td>I</td>
<td>36</td>
<td>recruiting</td>
</tr>
<tr>
<td>NCT00625456</td>
<td>Advanced solid tumor</td>
<td>Recombinant Vaccinia GM-CSF; RAC VAC GM-CSF (JX-594)</td>
<td>I</td>
<td>23</td>
<td>Completed</td>
</tr>
</tbody>
</table>
matological tumors, such as CD-19-expressing B cell acute lymphocytic leukemia (B-ALL), chronic lymphocytic leukemia (CLL) and B cell non-Hodgkin lymphoma (NHL) [70, 71]. Many studies have shown that CAR-T cells targeting intercellular adhesion molecule-1 (ICAM-1) can exhibit impressive therapeutic efficacy and survival benefits in a mouse model of ATC [31, 72, 73]. This result indicates that ICAM-1 may be a promising target for CAR-T cell treatment for ATC. Identifying neoantigens is the primary task for the development and application of ACT in ATC treatment.

**Monoclonal antibody**

Monoclonal antibodies (mAbs) are antibodies produced by identical immune cells that are all clones of a unique parent cell, and mAbs can target tumor cells specifically by engaging surface antigens expressed in cancers; the interaction of mAbs with antigens induces cellular events, such as apoptosis [74]. mAbs can be used alone or conjugated with other agents, and the antitumor effect will be enhanced by this conjugation [75, 76]. This method was deemed an ideal cancer treatment model because it directly targets malignant cells and exerts little cytotoxic effects on noncancerous cells.

Aberrant lipid metabolism in ATCs has drawn the attention of many researchers in recent years. Copland JA revealed that stearoyl-CoA desaturase 1 (SCD1), an important component in de novo lipid biosynthesis, is overexpressed in ATCs and is critical for ATC cell survival and proliferation, which suggests SCD1 as a novel therapeutic target for ATCs [77]. Moreover, gene array analysis of ATC tissue compared to normal thyroid tissue demonstrated increased expression of the machinery that facilitates de novo fatty acid biosynthesis, including acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN) and a variety of proteins whose roles include fatty acid uptake, transport and metabolism [78].

mAbs have been used for many cancer treatments, such as the rituximab target CD20 in non-Hodgkin B cell lymphoma, the cetuximab target EGFR in NSCLC and the trastuzumab target HER2 in breast cancer [79, 80]. The FDA has approved many mAbs for cancer treatment [75]. The obstacle to applying mAbs in ATC is the current lack of recognized tumor-specific antigens. Advances in NGS technologies have made it possible to compare tumor and normal sequences rapidly and cost-effectively, which provides tremendous help for researchers to explore neoantigens in ATC.

**Immune checkpoint blockade**

The induction of an immune checkpoint receptor on cancer cells could evade immune attack, resulting in tumor proliferation, invasion, and metastasis [81, 82]. PD-1 and CTLA-4 are the most well-studied immune checkpoint receptors at present (Figure 3).

**Programmed cell death protein 1 (PD-1) blockade**

PD-1 inhibitors have been used to treat many cancers, such as melanoma, NSCLC, and renal carcinoma [83-85]. Owing to their efficacy in suppressing tumor growth and inducing tumor cell apoptosis, the Food and Drug Administration has approved many PD-1 inhibitors for the treatment of a variety of cancers, such as pembrolizumab for melanoma and nivolumab for NSCLC [86, 87]. No such drug has been approved for ATC due to a lack of evidence from clinical trials.

PD-L1, the ligand of PD-1, is expressed in 28.6% of ATC patients, a percentage that is higher than that observed in well-differentiated thyroid cancer [88]. The latest statistics from Cantara indicate that the PD-L1 positive rate in ATCs reaches up to 70-90%, and PD-L1 mAb treatment can reduce tumor volume in an ATC mouse model [89]. In a recent study, Goodman AM reported that PD-L1 copy number alterations were found in a small subgroup of diverse solid tumors and may correlate with responses to checkpoint blockade. His data showed that thyroid anaplastic carcinoma has a relatively high frequency of PD-L1 amplification among most solid tumors, which means that ATCs may be more sensitive to PD-L1 inhibitors than solid tumors with a lower frequency of PD-L1 amplification [90].

Brauner E revealed that the expression of PD-L1 in ATCs was correlated with the BRAFV600E mutation; in addition, anti-PD-L1 treatment potentiated the effect of a BRAF inhibitor. Furthermore, the tumor volume was
Several immune checkpoints are overexpressed on T cell surface in anaplastic thyroid cancer microenvironment and their corresponding ligands on tumor cells. Interaction of receptors and ligands lead to inhibition of T cell proliferation and progression of tumor cells. Immune checkpoints inhibitor prevent the combination of immune checkpoints and their ligands, destroying the immune escape mechanism of tumor cell and enhancing anti-tumor activity of NK cells.

Figure 3. A. Several immune checkpoints are overexpressed on T cell surface in anaplastic thyroid cancer microenvironment and their corresponding ligands on tumor cells. Interaction of receptors and ligands lead to inhibition of T cell proliferation and progression of tumor cells. B. Immune checkpoints inhibitor prevent the combination of immune checkpoints and their ligands, destroying the immune escape mechanism of tumor cell and enhancing anti-tumor activity of NK cells.

decreased more strikingly by the combination of these two therapies than by either of these two agents used alone in an ATC mouse model (the tumor volume of the combination group was reduced by as much as 81% compared to that of the placebo group, while it was reduced by 8% and 44% for the PD-L1 mAb group and BRAF inhibitor group, respectively) [91]. Similar therapeutic effectiveness was observed in some clinical cases [92, 93]. Another study has shown that the ratio of CD56\textsuperscript{hi}CD16\textsuperscript{lo/hi} NK cells to all NK cells is higher in the peripheral blood of ATC patients than in patients with other types of thyroid cancer, while the CD56\textsuperscript{lo}CD16\textsuperscript{hi} NK
cells presented higher PD-1 than other kinds of NK cells [94]. Taken together, this information suggests that a PD-L1 inhibitor is a promising treatment for ATC. A list of ongoing clinical trials pertaining to the potential efficacy of this agent for ATC is shown here (Table 2).

**Table 2. Ongoing clinical trials about PD-1/PD-L1 inhibitor used for ATC patients**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Phase</th>
<th>Estimated enrollment</th>
<th>Estimated completion date (month/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03122497</td>
<td>durvalumab</td>
<td>I</td>
<td>12</td>
<td>5/2020</td>
</tr>
<tr>
<td></td>
<td>tremelimumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SBRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02688608</td>
<td>Pembroliumab</td>
<td>II</td>
<td>20</td>
<td>10/2020</td>
</tr>
<tr>
<td></td>
<td>Pembroliumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03211117</td>
<td>With or without surgery</td>
<td>II</td>
<td>3</td>
<td>12/2019</td>
</tr>
<tr>
<td>NCT02936102</td>
<td>PDR001</td>
<td>I</td>
<td>155 (Comprise a cohort of ATC patients)</td>
<td>2/2020</td>
</tr>
<tr>
<td>NCT03181100</td>
<td>Atezolizumab</td>
<td>II</td>
<td>50</td>
<td>7/2023</td>
</tr>
<tr>
<td>NCT03246958</td>
<td>Nivolumab</td>
<td>II</td>
<td>54</td>
<td>3/2025</td>
</tr>
<tr>
<td>NCT02404441</td>
<td>PDR001</td>
<td>II</td>
<td>319 (Comprise a cohort of ATC patients)</td>
<td>5/2020</td>
</tr>
</tbody>
</table>


Cytotoxic T lymphocyte antigen 4 (CTLA-4) blockade

CTLA-4 is another immune checkpoint, also known as CD152. Previous studies found that CTLA-4 is primarily involved in the regulation of T cell activation in lymph nodes and in Treg-mediated suppression of DC activity. A recent study showed that CTLA-4 binding to its ligands could shield cancer cells from cytotoxic T lymphocyte-mediated attack [95]. Anti-CTLA-4 antibodies have shown promising results in cancer treatment, and three antibodies, ipilimumab, tremelimumab and MK1308, have been largely involved in clinical trials [96, 97]. However, one recent study showed that CD80, a ligand of CTLA-4, was downregulated in 9 out of 11 ATC patients [98]. Whether CTLA-4 exerts an immunosuppressive function in ATCs by binding to its ligands remains elusive. Two trials (NCT03122497 and NCT03246958) contained a cohort of ATCs treated with CTLA-4 inhibitors.

In addition, ATC had strikingly more genetic alterations per tumor than any other thyroid cancer subtype [46, 55]. Furthermore, mutation burden is strongly correlated with favorable clinical benefit of checkpoint blockade therapy [99, 100]. From these data provided by other researchers, we surmise that ATC patients are very likely to benefit from immune checkpoint inhibitors and look forward to the outcome of ongoing clinical trials concerning this therapeutic method.

**Future perspective**

ATC is still a challenge for clinical experts due to its dedifferentiated phenotype and aggressive features. Although immunotherapy has been shown as a promising strategy for this intractable cancer, there are many concerns regarding this treatment that need to be resolved.

Response rates to one single method of immunotherapy are not satisfactory in many cancers, and crosstalk between different immunotherapies has been observed in previous studies; for example, in addition to directly assaulting cancer cells, OVs can also cause repolarization of M2 macrophages to M1 macrophages, decreasing TAM density [65]. In addition, TAMs can express cytokines and enzymes that can suppress T cell recruitment and activation, thereby promoting resistance to immune checkpoint inhibition [101]. Researchers have demonstrated that the combination of a CSF1R inhibitor with a CXCR2 inhibitor can significantly reduce tumor growth; moreover, when a PD-1 antibody was added to this combination, it resulted in blockade of tumor growth [102]. We speculate that different immunotherapies may interact reciprocally rather than independently of one another, illuminating the combination of a vari-
Immunotherapy for ATC

ety of different strategies of immunotherapy as a new direction in the future that may enhance antitumor efficacy and contribute to a better prognosis of ATC.

Many immunotherapy methods, such as tumor vaccines, ACT, and mAbs, rely on targeting tumor-associated antigens (TAAs) or neoantigens presented on cancer cells. To date, no single TAA or neoantigen for ATC has been proven valid, but there are a couple of candidates that might become the first, such as ICAM-1, CD47, CD70, autotoxin and CD1d [103-105]. Recent advances in NGS and epitope prediction have made the rapid identification of tumor neoantigens possible. In the future, detecting TAs and neoantigens will be critical for the development of immunotherapy in ATC.

OVs are also very impressive for their ability to inhibit ATC proliferation and progression, although the full mechanism of antitumor action remains elusive. Moreover, the reason why these viruses target cancer cells and do not attack normal tissues is still unknown. Is there a connection between TAs and the OV? Further investigations are needed to provide an explanation of this phenomenon. Nevertheless, OVs are a highly promising approach for cancer treatment, and illuminating the antitumor mechanism of OVs may guide us to exploit newimmunotherapy methods for cancer treatment.

Despite the tremendous success of immune checkpoint inhibitors, there are many patients who still do not respond to immunotherapy or develop therapeutic resistance [106-108]. Insufficient immune activation is considered one of the main reasons for low response rates, and a combination of checkpoint blockers has been proposed to increase the response rates [109]. Furthermore, Ishizuka JJ reported that the ADAR1 gene was critical for resistance to immunotherapy and proved in a melanoma mouse model that loss of ADAR1 could overcome resistance to immunotherapy. In addition, their results showed that loss of function of ADAR1 restored sensitivity to immunotherapy in tumors with a B2m deletion, which means that targeting the ADAR1 gene is an effective immunotherapy strategy even in the absence of a tumor-specific endogenous CD8+ T cell response [110]. There are no immunocytes in the microenvironment of ATCs except M2 macrophages. This seems to be a disadvantage for immunotherapy, but research provides another avenue for immunotherapy, and more importantly, immunotherapy is likely suitable for ATC given the tumor microenvironment of this unique disease (featuring a lack of a tumor-specific endogenous CD8+ T cell response).

Conclusion

Immunotherapy has demonstrated excellent efficacy for some malignancies, such as melanoma, NSCLC, and leukemia. As effective treatments for ATC are still limited, it is urgent to explore new therapies for this untreatable disease. Generally, immunotherapy has not been approved for ATC, but it has shown palpable efficacy in some animal models of ATC. As a promising means for controlling ATC, more attention should be given to the prompt development of future immunotherapies.

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Disclosure of conflict of interest

None.

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