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Research progress of immunotherapy against anaplastic thyroid cancer

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Anaplastic thyroid cancer (ATC) is the most aggressive type of thyroid cancer. While ATC is rare, its mortality is high. Standard treatments, such as surgery, radiotherapy, and chemotherapy, have demonstrated limited efficacy in managing ATC. However, the advent of immunotherapy has significantly improved the prognosis for patients with ATC. Immunotherapy effectively targets and eliminates tumor cells by using the power of the body's immune cells. The neoantigen is an atypical protein generated by somatic mutation, is exclusively observed in neoplastic cells, and is devoid of central tolerance. Neoantigens exhibit enhanced specificity towards tumor cells and display robust immunogenic properties. Currently, neoantigen therapy is primarily applied in immune checkpoint inhibitors and cellular immunotherapy, encompassing adoptive immunotherapy and tumor vaccines. This study discusses the mechanism, tumor microenvironment, clinical trials, adverse events, limitations and future directions associated with ATC immunotherapy.

KEYWORDS

anaplastic thyroid cancer, immunotherapy, tumor microenvironment, immune checkpoint inhibitors, cellular immunotherapy

1 Introduction

Also known as undifferentiated thyroid carcinoma, anaplastic thyroid carcinoma (ATC) is the most malignant thyroid cancer and one of the most aggressive solid tumors (1). ATC accounts for <2% of thyroid cancers, but >40% of patients have large primary tumors, extrathyroidal spread, and local and distant metastases at the time of diagnosis (2). The median survival after initial diagnosis is approximately four months, and one in five patients survives >12 months. Furthermore, the 5-year survival rate is close to 0% (3). The standard ATC treatment includes surgery, radiotherapy, and chemotherapy. However, ATC is extremely malignant, and the effect of treatment is limited due to its invasiveness, lack of differentiation, and chemoresistance (4, 5). While ATC features gene mutations the incidence rate is lower than that of differentiated thyroid cancer. The signaling pathways in ATC are mainly MAPK, PI3K–AKT–mTOR, and JAK–STAT, which contain important targets such as RET and EGFR. Targeted drugs such as sorafenib,

lenvatinib, dabrafenib, and trametinib have exerted some effects, but drug resistance is the main issue that should be solved (6). Therefore, safer and more effective treatments are needed to improve the prognosis of patients with ATC. The use of immunotherapy to treat solid tumors, including ATC, has become a promising treatment option (7). Immunotherapy has developed rapidly in recent years and yielded significant results in reducing disease recurrence and prolonging patient survival. Moreover, various levels of combined therapy can synergistically combat tumors and minimize side effects. This article reviews the current immune mechanism and immunotherapy of ATC.

2 ATC immunotherapy mechanisms

2.1 Fundamentals of immunotherapy

Tumor immunotherapy uses the body's immune cells to eliminate tumor cells, with T cells being the main effector cells. Tumor elimination by T cells begins with the recognition of tumor antigens (8), which are self-molecules altered by gene mutation, protein truncation, protein misfolding, or abnormal post-translational modification (9). Tumor antigens are divided into tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs) (10).TAAs are macromolecules found on the surface of tumor cells and can also be found in normal tissues. Nevertheless, TAAs are highly expressed in tumors, most of which have central tolerance and weak immunogenicity (11). TSAs, or neoantigens, are not expressed in normal somatic cells and do not exhibit central tolerance. TSAs are more specific to tumor cells and have strong immunogenicity. Neoantigens can be presented on the cell surface and subsequently recognized by T cells under the action of major histocompatibility complex (MHC) molecules, causing T cell activation and promoting T cell-mediated attack and removal of tumor cells (12). Neoantigens contribute to tumor-specific immune responses and have been used as targets for novel, precise, and personalized tumor immunotherapy (13).Currently, neoantigen therapy is mainly used in immune checkpoint inhibitors (ICIs) and cellular immunotherapy (adoptive immunotherapy and tumor vaccines).

2.2 Relationship between tumor microenvironment and ATC

The tumor microenvironment (TME) refers to the environment required for tumor cell appearance and development and contains tumor cells, extracellular matrix, immune cells, and the cytokines, metabolites, and exosomes they release (14). Different organs have biologically unique microenvironments, and different thyroid cancer types also have greatly differing immunological TMEs (15). Immune cells in the ATC TME mainly consist of tumor-associated macrophages (TAMs), tumor-associated mast cells (MCs), dendritic cells (DCs), natural killer cells (NKs), cytotoxic T cells (CTLs), and regulatory T cells (Tregs) (16). However, some scientists believe that ATC only involves cancer cells, macrophages, and vascular endothelial cells and almost no other cells (17). Due to the low prevalence and low possibility of surgery for ATC, most of the current studies address the role of the phenotypic characteristics of tumor-associated immune cells in the pathogenesis or progression of papillary thyroid carcinoma, whereas there are few studies on ATC.

Thyroid cancer has an extremely wide range of TAM density, with TAM density being the highest in ATC (18). TAMs can directly promote tumor occurrence, development, and metastasis by releasing various inflammatory factors, growth factors, and matrix proteases. TAMs can also indirectly promote tumor progression by mediating tumor angiogenesis and immunosuppression (19, 20). TAMs are mainly divided into M0, M1, and M2 types (21). M0 TAMS are usually dormant, while the proinflammatory M1 TAMs mainly produce cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), which inhibit and kill tumor cells. The anti-inflammatory M2 TAMs produce factors such as IL-10 and IL-13, which promote tumor formation and development (22). In ATC, TAMs account for >50% of nuclear cells, and the M2 type is predominant (17). M2-like TAMs accelerate ATC cell metastasis by activating the insulin receptor (IR)-A/insulin-like growth factor 1 receptor (IGF1R)-mediated PI3K–AKT–mTOR pathway and upregulating IGF-1/IGF-2 (23). It is also believed that only ATC contains a branched TAM network to promote ATC invasion through metabolic and nutritional functions (17).

The ATC microenvironment has significantly increased tumor-infiltrating lymphocytes (TILs) as compared with normal thyroid tissues, and most of them are CD8+T cells (24). However, only one investigator demonstrated that CD8+ T cells enhance their killing effect on ATC cells by secreting granzyme, TNF-α, and interferon-γ (IFN-γ) (25). In patients with ATC, NKs kill tumor cells by inducing apoptosis via the release of cytolytic granules (26). MCs are the first immune cells recruited during inflammation and are associated with ATC aggressiveness (27). ATC has a higher number of MCs than other forms of thyroid cancer. By producing IL-6, TNF-α, and CXC chemokine ligand 8 (CXCL8)/IL-8, MCs aid epithelial–mesenchymal transition in ATC cells (28). Galectin-9 aids MC support of ATC cell adhesion, angiogenesis, metastasis, and tumor immune escape (29). Most of the body's professional antigen-presenting cells are termed DCs, yet the amount of DCs in ATC is much lower than that of other thyroid cancers (30, 31).

Soluble mediators such as cytokines and chemokines are mainly released by tumor-infiltrating immune cells and can also be released by cancer cells. ATC cells secrete CXCL9 and CXCL10, which are chemotactic to T cells (24). IL-4 and IL-10 upregulate the anti-apoptotic proteins B-cell lymphoma-2 (Bcl-2) and Bcl-xL to promote ATC cell progression and chemotherapy resistance (32). CXC chemokine receptor 4 (CXCR4) is involved in the local invasion and distant metastasis of ATC cells mediated by stromal cell-derived factor (33). The transcription factor CREB3L1 activates the extracellular matrix signaling pathway, maintains the fibroblast-like characteristics of ATC cells, reshapes the tumor interstitial microenvironment, and drives ATC malignant transformation (34). ATC is also linked to elevated levels of other cytokines, including IL-6, IL-1, granulocyte colony-stimulating factor, macrophage colony-stimulating factor, CXCL8, and CXCR4 (35, 36). One obvious characteristic of ATC is the high percentage of

immunosuppressive cytokines (24). By altering the immunological microenvironment, immunotherapy can reinstate the tumor-killing capacity of anti-tumor immune cells (37).

Single-cell RNA sequencing (scRNA-seq) is a novel technology that enables comprehensive analysis of the cell composition and transcriptional phenotype of malignant cells and surrounding immune cells by examining the transcriptome information of individual cells (38). In one study, scholars used scRNA-seq to distinguish tumor cells from normal cells based on differences in copy number (39). They estimated that the average prediction accuracy for identifying tumor cells was 97%. Lu sequenced the single-cell RNA of ATC patients and classified the cell types (40). They divided the cells into eight main types and found that in patients with ATC, the number of endothelial cells decreased significantly, while the number of myeloid cells increased significantly. Furthermore, they also discovered that ATC cells exhibited overexpression of mesenchymal and glial genes. Compared with papillary thyroid carcinoma, the number of M2 macrophages in ATC significantly increased, while the number of M1 macrophages decreased. In ATC tumors, the total depleted cells account for more than 50% of the T cell population. It is also found that TRα1, as a transcription factor, plays a role in inhibiting tumor growth through various signaling pathways. ScRNA-seq revealed that the induction of PAX8 by TRα1 transformed the cell landscape of ATC from one state to another through a transcription program (41). ScRNA-Seq not only deepens our understanding of ATC cell composition and heterogeneity but also offers new insights for personalized therapy and the development of molecular markers.

3 Application of immunotherapy in ATC

3.1 Immune checkpoint inhibitors

Immune cells have cell surface receptors known as ICIs, which control T lymphocyte activation and effector activities (42). The most well-characterized ICIs are programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4). The other ICIs include lymphocyte activation gene 3, T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain, T-cell immunoglobulin domain and mucin domain 3 (43). A trial of the PD-1 inhibitor spartalizumab in patients with advanced/metastatic ATC reported an overall response rate of 19%, including a complete response of 7% and a partial response of 12%. PD-L1-positive individuals had a higher response rate (29%) than PD-L1-negative patients (0%) (44). An objective response rate of 16% and a 1-year survival rate of 38% were noted for ATC treated with pembrolizumab or nivolumab (45). However, only one patient in a trial using stereotactic body radiation therapy and the CTLA-4 inhibitor tremelimumab or the PD-L1 inhibitor durvalumab for metastatic ATC lived for more than a year (46).Furthermore, additional research reported the efficacy of pembrolizumab and spartalizumab for patients with ATC, which demonstrated the anti-tumor action of ICIs in ATC management (47, 48).

Before starting immunotherapy, most of the patients in these trials receiving ICIs underwent surgery, radiation, chemotherapy, and even targeted therapy. Six patients with metastatic ATC who had not responded to radiation, chemotherapy, or radioiodine therapy were included in a trial evaluating the combination of lenvatinib and pembrolizumab. The results demonstrated that 66% of the patients had a full response, 16% had stable illness, and 16% had progressing disease. The median progression-free survival for all patients was 16.5 months. Half of the ATC patients were still receiving therapy at the time of data cutoff, with treatment durations of 1–40 months (49). Following surgery, a 67-year-old patient with ATC was treated with the PD-1 inhibitor sintilimab in conjunction with the antiangiogenic drug anlotinib. The patient demonstrated notable tumor shrinkage and an 18.3-month maintained remission (50). After receiving combination therapy consisting of the anti-PD-1 antibody camrelizumab and the multitargeted kinase inhibitor famitinib, a patient with locally advanced unresectable ATC underwent postoperative radiotherapy and complete surgical resection after computed tomography demonstrated a partial lesion response after three cycles. The patient demonstrated a very good quality of life about 24 months after diagnosis (51). Another study reported that three patients with ATC died within six months despite treatment with surgery, radiation, and chemotherapy in addition to pembrolizumab (52). Based on the aforementioned trials, it is believed that the treatment effect might also be connected to the duration of treatment overlap. Hence, more research is needed to fully understand the synergistic mechanism and tolerance of combined treatments. Currently, there are several reports on ongoing ATC studies involving PD-1/PD-L1 inhibitor (NCT05453799, and NCT05119296), or PD-1 combined with other treatment (NCT04171622, NCT04675710, NCT05696548, NCT04238624, NCT05659186, NCT03181100, NCT04400474, and NCT04579757). Please refer to Tables 1, 2 for a summary of trials.

Adverse effects are unavoidable when using ICIs. According to NCT02404441, grade 1 or 2 diarrhea, pruritus, exhaustion, and fever were the most frequent treatment-related adverse effects in patients with advanced/metastatic ATC receiving spartalizumab (44). The most common grade 2–4 adverse events were hypertension, fatigue, weight loss/anorexia, oral mucositis, diarrhea, joint/muscle pain, and hand-foot syndrome in six patients with metastatic ATC who were treated with combined lenvatinib and pembrolizumab after all other forms of surgery, chemotherapy, or radiotherapy had failed. However, the lenvatinib-induced adverse effects necessitated treatment stopping in two patients (49). One patient receiving pembrolizumab treatment developed severe grade 4 colitis (bloody stools, severe dehydration, and hypotension), necessitating extensive fluid resuscitation and systemic steroids (53). Despite the ICI adverse effects reported in several studies, most of them can be alleviated with symptomatic therapy. Therefore, ICIs have emerged as a new tool in ATC treatment.

3.2 Adoptive immunotherapy

Adoptive immunotherapy involves injecting immune cells with anti-tumor activity to either directly kill or activate the body's immune response to kill tumor cells. It includes TILs, T cell receptor engineered

TABLE 1 Completed trials of ICIs in ATC.

Title	Population	Treatment	Enrollment	Results	NCT number
PD-1 Blockade in Anaplastic Thyroid Carcinoma	Locally advanced and/or metastatic ATC	Spartalizumab 400 mg IV, once every 4 weeks	42	ORR=19%	NCT02404441
An Evaluation of Clinical Efficacy of Immune Checkpoint Inhibitors for Patients with Anaplastic Thyroid Carcinoma	Locally advanced or metastatic unresectable ATC	Nivolumab,240 or 480 mg IV, every two or four weeks or pembrolizumab, 200 or 400 mg IV, every three or six weeks	13	ORR=16%	Retrospective case
Phase II Trial of Pembrolizumab in Metastatic or Locally Advanced Anaplastic/ Undifferentiated Thyroid Cancer	Metastatic or locally advanced anaplastic/ undifferentiated thyroid cancer	Pembrolizumab 200 mg IV once every 3 weeks	5	ORR=60%	NCT02688608
Phase 2 Study of Pembrolizumab Combined With Chemoradiation Therapy in Anaplastic Thyroid Cancer	ATC and no prior history of neck radiotherapy	Pembrolizumab, 200 mg intravenously (IV) every 3 weeks, combined with chemoradiotherapy (docetaxel/doxorubicin, 20 mg/m2 each IV weekly plus volumetric modulated arc therapy)	3	ORR=0	NCT03211117
A Pilot Study of Durvalumab (MEDI4736) with Tremelimumab in Combination with Image-Guided Stereotactic Body Radiotherapy in the Treatment of Metastatic Anaplastic Thyroid Cancer	Metastatic anaplastic thyroid cancer	Patients will receive durvalumab and tremelimumab together every 4 weeks (one cycle). SBRT delivered to one metastatic site per standard of care using a standard 9Gy x 3 fractions will be given within 2 weeks after the completion of the first cycle. After 4 cycles, patients will then continue with single agent durvalumab every 4 weeks until disease progression or unacceptable toxicity or a total of 12 months from date of initial treatment.	12	Only 1 patient had stable disease beyond 15 weeks	NCT03122496

ORR, overall response rate; IV, intravenous infusion.

T cells (TCR-T), chimeric antigen receptor T cell therapy (CAR-T), and NK therapy. TIL therapy was effective in treating numerous solid tumors, including melanoma, breast, cervical, head and neck, stomach, liver, esophagus, and lung cancers (54). The effect of autologous TILs (LT-145 or LN-145-S1) on patients with ATC and some other cancers is being studied in NCT03449108. As an alternative to TIL therapy, T cells can be isolated from peripheral blood and targeted to tumor cells by transferring synthetic TCR or CAR using gene therapy techniques (55). TCR-T involves transfecting TCR α- and β-chain genes into T cells, which can recognize TSAs. This results in structural alterations in the TCR antigen-binding region of the T cells, enabling them to specifically recognize the corresponding tumor antigens. T lymphocytes expressing specific TCRs can recognize human leukocyte antigen (HLA)–peptide complexes on the surface of tumor cells. Antigenic stimulation signals are transmitted by phosphorylating the intracellular region of the immune receptor tyrosine activation motifs, which activates the T cell immune response (56). Patients with colorectal cancer, synovial sarcoma, and metastatic melanoma demonstrated a notable clinical response to TCR-T. CAR overcomes some of the limitations of TCR. However, the success of CAR-T therapy has been concentrated in hematologic tumors, whereas only partial progression has been observed in solid tumors to date (57, 58). Ongoing studies are evaluating the safety and tolerability of AIC2 CAR-T cells in patients with relapsed/refractory poorly differentiated thyroid cancer and ATC (NCT04420754). Animal studies have demonstrated that adoptive cell therapy based on NKs significantly inhibited metastatic growth in ATC lung metastasis model mice (59). An ongoing study (NCT05194709) is evaluating the efficacy, safety, and pharmacokinetics of anti-5T4 CAR-NK cells in patients with advanced solid tumors, and the NCT03415100 study is evaluating the safety and feasibility of CAR-NK cell therapy targeting NKG2D ligands in patients with metastatic solid tumors.

TIL-treated patients with advanced cutaneous melanoma experienced many adverse events, such as thrombocytopenia, fever, chills, neutropenia, and tachycardia (60). In colorectal cancer, TCR-T causes severe transient inflammatory colitis (61). The most common adverse effects of CAR-T in other tumors are cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (62). Grade 3 cytokine release syndrome also occurred in two patients in a phase I study of CD33 CAR-NK cells in patients with relapsed or refractory acute myeloid leukemia (63). However, the adverse effects of adoptive immunotherapy in ATC are unclear and require further clarification.

3.3 Tumor vaccines

Tumor vaccines can stimulate the body to generate active specific immunity against tumor cells or cells or molecules in the TME that promote tumor growth. ATC typically has a high mutation burden, and most of the neoantigens in ATC can be used for tumor vaccines. Thus, tumor vaccines might be more effective in ATC (64). The current

TABLE 2 Ongoing trials of ICIs and combination with other therapies in ATC.

NCT Number	Study Title	Interventions	Enrollment	Phase	Estimated primary completion date
NCT05453799	A Phase II, Multicenter Study of XmAb20717 in Patients With Metastatic Anaplastic Thyroid Cancer With an Exploratory Cohort in Aggressive Hurthle Cell Thyroid Cancer	Vudalimab	54	II	2024-07-15
NCT05119296	Phase II Trial of Pembrolizumab in Metastatic or Locally Advanced Anaplastic/Undifferentiated Thyroid Cancer	Pembrolizumab	20	II	2024-11
NCT04171622	Lenvatinib in Combination With Pembrolizumab for Stage IVB Locally Advanced and Unresectable or Stage IVC Metastatic Anaplastic Thyroid Cancer	Lenvatinib Pembrolizumab	25	II	2025-08-31
NCT04675710	Pembrolizumab in Combination With Dabrafenib and Trametinib as a Neoadjuvant Strategy Prior to Surgery in BRAF-Mutated Anaplastic Thyroid Cancer	Surgery Dabrafenib Pembrolizumab Trametinib	30	II	2024-06-30
NCT05696548	Phase 2 Study of Nivolumab Plus Lenvatinib for Patients With Unresectable Anaplastic Thyroid Cancer (NAVIGATION Study)	Lenvatinib Nivolumab	51	II	2025-07
NCT04238624	A Pilot Study of the Addition of Cemiplimab, an Antibody to PD-1, to the Treatment of Subjects With BRAF-Mutant Anaplastic Thyroid Cancer Who Are No Longer Responding to Dabrafenib and Trametinib	Cemiplimab	15	II	2024-06-20
NCT05659186	A Phase II Study of the Efficacy and Safety of PD-1 Inhibitor and Anlotinib Combined With Multimodal Radiotherapy in the Second-line Treatment of Recurrent or Metastatic Anaplastic Thyroid Cancer	Tislelizumab Anlotinib Radiotherapy	20	II	2024-12-30
NCT03181100	Atezolizumab Combinations With Chemotherapy for Anaplastic and Poorly Differentiated Thyroid Carcinomas	Atezolizumab Bevacizumab Cobimetinib	50	II	2025-07-31
NCT04400474	Exploratory Basket Trial of Cabozantinib Plus Atezolizumab in Advanced and Progressive Neoplasms of the Endocrine System. CABATEN Study	Cabozantinib Atezolizumab	93	II	2023-12
NCT04579757	An Open-Label Phase Ib/II Study of Surufatinib in Combination With Tislelizumab in Subjects With Advanced Solid Tumors	Surufatinib Tislelizumab	135	I/II	2024-04-30

ATC vaccines mainly include DC vaccines and oncolytic virus (OV) vaccines. Triiodothyronine can enhance DC ability to stimulate cytotoxic T-cell responses, thereby enhancing anti-tumor responses (65). DC vaccines have been successfully used to treat medullary thyroid carcinoma, and the treatment of thyroid cancer might be more effective than that for other tumors (66). OVs use natural or genetically modified viruses to specifically infect and lyse cancer cells but do not harm normal cells. The anti-cancer activities of OVs are derived from multimodal cancer-killing mechanisms. First, OVs infect and replicate in cancer cells, inducing tumor cell lysis and releasing infectious viral progeny that spreads to the surrounding tumor cells. Second, OV-mediated oncolysis of tumor cells initiates the release of tumor-associated antigens, cellular danger-associated molecular pattern signals, and cytokines that promote the maturation of antigen-presenting cells and activate antigen-specific CD4 and CD8 T cell responses. Third, OVs can specifically infect and destroy tumor vascular endothelial cells and stromal cells and destroy tumor blood vessels by promoting endostatin and angiostatin production (67). Furthermore, OVs induced cell death and tumor regression in cultured ATC cells and mouse models and modulated the ATC microenvironment to shift the M2-type TAMs to the proinflammatory M1 phenotype (68, 69). Although adverse events such as fever, injection site reactions, headache, and vomiting occurred in patients with glioma and melanoma treated with the OV vaccine, they were all tolerable (70). Nevertheless, patients with ATC have not received a tumor vaccine. It is expected that the development of DC And OV vaccines will become a means of treating ATC (Figure 1).

4 Application limitations and future directions of ATC immunotherapy

Immunotherapy is a promising treatment for patients with ATC, but some clinical management issues persist. ICIs have had tremendous success, but many patients do not respond to them (71). The cell preparation, expansion, and infusion of TILs are complex which can take a long time for patients (72). TCR is limited by human HLA and must match HLA to be effective, whereas CAR-T can recognize extracellular antigens presented independently of HLA (73). However, CAR-T therapy is subject to inadequate infiltration of CAR-T cells, poor proliferation and durability, toxicity control, and an immunosuppressive microenvironment (74). The NK survival rate and cytotoxicity are significantly reduced by the CAR-binding epitope location and its distance from the surface of CAR-NK cells and by NK sensitivity to freeze-thawing (75). DC vaccines are complex and expensive to

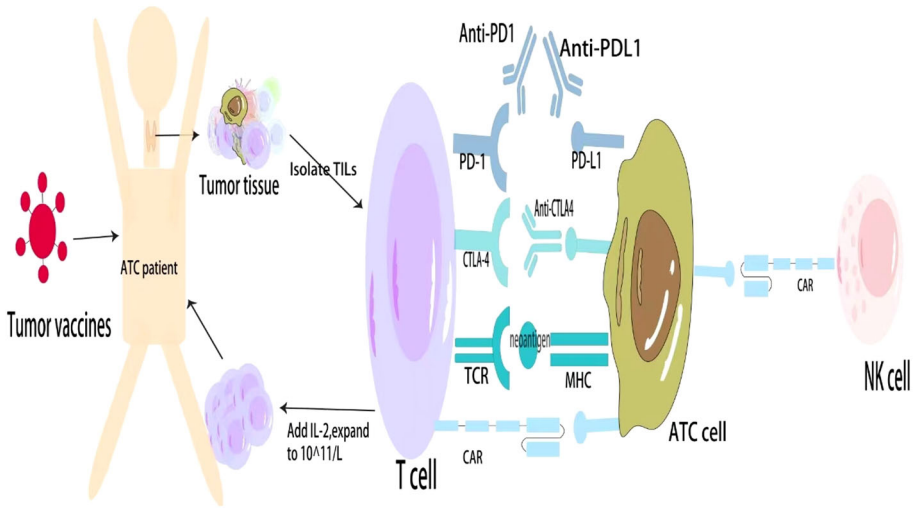

FIGURE 1
General approaches to immunotherapy for ATC. ATC, Anaplastic thyroid cancer; PD, Programmed cell death protein; CTLA, Cytotoxic T lymphocyte antigen; TCR, T cell receptor; CAR, Chimeric antigen receptor; MHC, Major histocompatibility complex; TILs, Tumor-infiltrating lymphocytes; NKs, Natural killer cells.

produce, require ex vivo expansion, maturation, and activation, and have a short half-life *in vivo* (76). Furthermore, the OV vaccines are subject to drug resistance, and the pharmacokinetics, quality control, and detection methods require further investigation (77, 78).

Immunotherapy is the fourth major therapy for cancer treatment and has achieved good results. However, considering the abovementioned adverse effects and limitations, further development and optimization are required. As the effectiveness of a single treatment is currently restricted, surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy can be combined to varying degrees to maximize the advantages of each treatment. Aiming to alleviate symptoms, inhibit tumor cell proliferation, and promote tumor cell apoptosis. Oncolytic herpes simplex virus and BRAF inhibitors enhanced the immune-mediated anti-tumor effect in animal tests, hence improving the survival rate of the ATC mouse model (79). ICIs, targeted therapies, and CAR-T combination therapy demonstrated significant synergistic effects in rectal cancer, non-small cell lung cancer, liver cancer, breast cancer, hematologic neoplasms, and other cancers (80). When the two promising treatments are used in combination, several unknowns remain to be investigated, such as the relative dose, timing, design, and means of overcoming mitigating factors (81). Better preclinical models that more effectively recapitulate the intricate interactions of human immune cells are required to increase the success rate of clinical translation. Given the large presence of TAMs in the ATC microenvironment, targeting TAMs might be a potential ATC treatment. Modifying macrophages with CAR might aid in overcoming immunosuppressive cytokines and upregulate antigen presentation. CAR-M can home in on tumor tissue, have immunity to immunosuppressive TMEs, and lack an immune exhaustion process similar to those of T cells and NKs. Thus, CAR-M might be another potential cell treatment technique (82). CAR-M has been effectively used in animal trials to treat ovarian and breast cancer (83, 84).

5 Conclusion

Currently, several studies indicated that immunotherapy can prolong the survival time of patients with ATC, and combining different therapy modalities has greater efficacy than a single-arm treatment. Combination therapy can impede and regulate tumor growth, lower the risk of adverse effects, and exert synergistic anti-tumor effects. Due to the advancements in understanding the mechanisms of immune action, immunotherapy may progress rapidly, which will be excellent news for most patients with cancer.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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