

# Advances in Adoptive Cell Therapy for Head and Neck Cancer



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## KEYWORDS

- Adoptive cell therapy • Chimeric antigen receptor • T-cell receptor
- Tumor-infiltrating lymphocyte • Oropharyngeal squamous cell carcinoma
- Human papillomavirus • Head and neck cancer

## KEY POINTS

- Tumor-infiltrating lymphocyte and gene-engineered T-cell receptor T-cell therapy targeting human papilloma virus (HPV) viral antigens have each demonstrated the ability to induce tumor regression in patients with HPV-associated epithelial cancer including head and neck cancer.
- Tumor-intrinsic defects in genes important for antigen presentation and interferon response seem to portend resistance to adoptively transferred T cells and may be overcome by earlier treatment with adoptive cell therapy (ACT).
- One approach to enhance the function of adoptively transferred T cells with membrane-tethered cytokines is being explored.
- Further clinical advances using ACT in head and neck cancer may come through targeting of non-HPV antigens including Epstein-Barr virus viral proteins and cancer germline antigens.

## INTRODUCTION

Adoptive cell therapy (ACT) is a promising new treatment modality that has demonstrated clinical activity in hematologic cancers and a subset of solid tumors. The most clinically successful type of ACT thus far has been chimeric antigen receptor (CAR) T-cell therapy. CAR T-cell therapies targeting the lineage-restricted antigen CD19 have been approved by the US Food and Drug Administration (FDA) for the treatment of B cell malignancies.<sup>1–3</sup> CAR T cells express synthetic receptors that engage target antigens on the surface of tumor cells. Clinical application of CAR

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T-cell therapy has thus far been limited to hematologic malignancies because of the lack of cell surface antigens that can be safely targeted in solid tumors.<sup>4,5</sup> Early studies targeting cell surface antigens in solid tumors with CAR T cells resulted in significant toxicity through targeting of vital healthy tissue. A previous study testing CAR T-cell therapy targeting carbonic anhydrase IX in patients with metastatic renal cell carcinoma led to significant on-target, off-tumor toxicity.<sup>6,7</sup> Careful selection of target antigen is necessary to apply this therapy to common epithelial cancers like head and neck cancer.<sup>5</sup>

Tumor-infiltrating lymphocyte (TIL) and gene-engineered T-cell receptor (TCR) T-cell therapies have demonstrated clinical activity in a subset of solid cancers. TIL and TCR T-cell therapy have the advantage of targeting antigens that are from proteins residing inside of the cell or on the cell surface. Therefore, a broad range of tumor-specific antigens can be targeted with highly potent T cells with minimal to no targeting of vital healthy tissue. In TIL therapy, autologous tumor-specific T cells are harvested from resected metastatic tumor deposits. The natural T cells are expanded *ex vivo* to large quantities and administered back to the patient by intravenous infusion. These T cells have been shown to target mutated neoantigens, cancer germline antigens, and viral antigens expressed by cancer cells.<sup>8,9</sup> TIL therapy has its foundation in the successful treatment of metastatic melanoma.<sup>10</sup> Gene-engineered TCR T-cell therapy involves isolation of peripheral blood lymphocytes by apheresis. These T cells are then genetically engineered to express a high-affinity TCR that recognizes a peptide from a tumor antigen in the context of a specific HLA molecule. Early studies with TCR T-cell therapy targeting the cancer germline antigen New York esophageal squamous cell carcinoma-1 (NY-ESO-1) demonstrated clinical activity in patients with synovial cell sarcoma and melanoma.<sup>11</sup> Recent clinical studies testing TIL and TCR-T cell therapy in treatment-refractory human papilloma virus (HPV)-positive epithelial cancers including head and neck cancer demonstrated clinical activity in the last-line setting.<sup>12-14</sup>

## ADVANCES IN ADOPTIVE T-CELL THERAPY IN HEAD AND NECK CANCER

HPV-associated oropharyngeal cancer is a common type of head and neck cancer that harbors viral antigens that can be targeted by ACT.<sup>15,16</sup> These viral antigens are ideal target antigens for T-cell therapy, because they are not present in vital healthy tissue, important for the transformation and survival of cancer cells, and constitutively expressed by cancer cells.<sup>17,18</sup> T cells targeting the viral antigens E6 and E7 have been identified in tumor-infiltrating lymphocytes from cervical cancer specimens, and better clinical outcomes have been associated with T cell reactivity against these antigens, indicating that ACT with HPV-specific T cells may be an effective treatment for HPV-associated cancers.<sup>19,20</sup>

The first attempt to target these antigens with adoptively transferred T cells was with TIL therapy. In a phase II clinical trial, patients with HPV-associated epithelial cancers were treated with autologous TIL generated preferentially from T cell subcultures reactive toward the E6 and E7 viral antigens.<sup>13</sup> Patients received a conditioning chemotherapy regimen of cyclophosphamide 60 mg/kg for 2 days and fludarabine 25 mg/m<sup>2</sup> for 5 days followed by a single infusion of TIL and high-dose aldesleukin. Objective tumor responses were seen in 5 of 18 (28%) patients with cervical cancer and 2 of 11 (18%) patients with other HPV-positive cancers including head and neck. Two of the responses in patients with cervical cancer were complete and have been ongoing now for more than 6 years. One of 5 patients with HPV-associated head and neck cancer had an objective response. The patient was a 60-year-old man with squamous cell

carcinoma of the tonsil. He was previously treated with 6 systemic anticancer agents and had multiple thoracic metastases that were progressing prior to therapy. Following treatment, he had complete regression of his thoracic disease. He subsequently developed new brain metastases that were resected. He has been without evidence of disease now for more than 5 years. Exploratory analysis from this trial demonstrated that administered TILs displaying a greater frequency of HPV-reactive T cells (as measured by the frequency of T cells responding to E6 and E7 peptide stimulation) and higher concentrations of HPV-specific interferon (IFN)- $\gamma$  release correlated with response. Furthermore, the frequency of HPV-reactive T cells in peripheral blood 1 month after treatment correlated positively with clinical response.<sup>13</sup> Viral and nonviral antigens were targeted by the TIL administered to the 2 patients who had complete tumor regression.<sup>12</sup> Based on these results, a multicenter, multicohort, nonrandomized, industry-sponsored trial is being conducted to test TIL therapy (LN-145) in patients with recurrent and metastatic squamous cell carcinoma of the head and neck (NCT03083873).

Gene-engineered TCR T-cell therapy is a next-generation approach to ACT that does not require surgery and creates a cell therapy product with well-defined specificity toward a target antigen. A TCR targeting the HPV16 E6<sub>29-38</sub>-peptide presented in the context of HLA-A\*02:01 was discovered from the tumor-infiltrating lymphocyte in a patient with metastatic HPV16-associated anal cancer.<sup>21</sup> A first-in-human, single-center, phase I/II study was then conducted using this TCR in patients with metastatic HPV16-associated epithelial cancer.<sup>14</sup> In this study, patients received a conditioning chemotherapy regimen followed by a single infusion of autologous peripheral blood T cells genetically engineered to express the HLA-A\*02:01-restricted, HPV16 E6<sub>29-38</sub>-specific TCR (E6 TCR-T cells) and high-dose aldesleukin administered to patient tolerance. The starting dose of cells was  $1 \times 10^9$ , and the highest cell dose was  $1-2 \times 10^{11}$ . Twelve patients were treated (1 patient with head and neck cancer). No autoimmune toxicities or DLTs were observed. There were no acute toxicities associated with cell infusion, and no cytokine storm occurred at any dose level. Two of 12 patients (2 of 9 patients at the highest cell dose) attained objective tumor responses. One patient with metastatic anal squamous cell carcinoma who was previously treated with 5 systemic anticancer agents including TIL therapy experienced a partial response, with complete regression of 1 lung tumor and partial regression of 2 lung tumors. The remaining 2 lung tumors were resected at the time of progression. She has been without evidence of disease now for more than 4 years. All patients demonstrated high levels of peripheral blood engraftment with E6 TCR-T cells following treatment (median 30%, range 4% to 53%). The number of infused E6-reactive T cells did not correlate with response.<sup>14</sup> This study demonstrated the ability of TCR T-cell therapy to mediate regression of metastatic HPV-associated cancers.

The clinical testing of E6 TCR-T cells was followed by the discovery of a HPV16 E7-specific, HLA-A\*02:01-restricted TCR from an infiltrating lymphocyte in a uterine cervix biopsy from a woman with cervical intraepithelial neoplasia.<sup>22</sup> This TCR (E7 TCR) displayed higher functional avidity than the E6 TCR with the ability to recognize cognate peptide at concentrations as low as 10 pmol.<sup>22</sup> The E7 epitope targeted by this TCR was also found to be highly conserved across different strains of HPV16.<sup>23</sup> A phase I clinical trial was conducted testing the E7 TCR in patients with metastatic HPV16-associated cancers. Twelve patients were treated (4 with head and neck cancer), with 6 patients having objective tumor response. These responses included regression of bulky tumors and complete elimination of some tumors in patients. Four of these responses were in patients with disease refractory to PD-1 inhibitors.

There were 2 responses in patients with head and neck cancer. One response was in a 65-year-old man with metastatic squamous cell carcinoma of the oropharynx with tumors in the lungs, pleura, mediastinum, abdominal wall, retroperitoneum, and bone who was previously treated with 6 systemic anticancer agents including a PD-1 inhibitor and TIL therapy.<sup>24</sup> This study demonstrated the ability of E7 TCR T cells to mediate regression of treatment-refractory, widely metastatic epithelial cancers including PD-1 refractory head and neck cancer. An ongoing phase II clinical trial is currently underway at the National Cancer Institute (NCI) Genitourinary Malignancies Branch to further assess the clinical activity of the E7 TCR (NCT02858310).

### **FUTURE OF ADOPTIVE T-CELL THERAPY FOR HUMAN PAPILLOMA VIRUS-ASSOCIATED HEAD AND NECK CANCER**

The TCR T-cell trials in HPV-associated cancers provide a unique model of studying mechanisms of response and resistance by having constrained variation in both T-cell antigen-targeting and tumor antigen expression. Investigation of T-cell factors in these studies did not provide clear insight into mechanisms of treatment failure. However, the investigation of tumor factors revealed tumor-intrinsic defects in antigen presentation and INF response that demonstrated clear mechanisms of tumor resistance. In the clinical trial testing E6 TCR-T cells, 1 tumor from a patient who did not have a response to therapy was found to have loss of HLA-A\*02:01, the antigen presentation molecule required for E6 TCR T-cell recognition of cognate peptide. Another tumor from a patient who did not respond to therapy revealed a truncating mutation in INF-gamma receptor 1, a crucial molecule for tumor sensitivity to T cells. In contrast, a tumor from a patient who did respond to therapy did not have these defects.<sup>14</sup> Similarly, in the clinical trial testing E7 TCR-T cells, 3 resistant tumors demonstrated genetic defects in either HLA-A\*02:01 or B2M (necessary components of the E7 TCR target complex), and 1 tumor demonstrated copy loss with decreased expression of genes important for antigen presentation and IFN response including TAP1, TAP2, IFNGR1, and IFNGR2. Three sensitive tumors did not show genetic defects encoding these molecules. These findings suggest that tumors acquire somatic mutations and copy loss defects that confer resistance to T cell-mediated tumor engagement and effector function.<sup>24</sup> Awareness of the development of immune resistance, especially as cancers evolve over time and through multiple therapies, is driving a movement in oncology toward earlier application of immunotherapy including adoptive T-cell therapy.<sup>25,26</sup> A clinical trial at the NCI Genitourinary Malignancies Branch will test E7 TCR-T cell therapy in stage II/III HPV16-positive oropharyngeal cancer in the induction setting (NCT04015336).

Another approach to increase the efficacy of adoptive T-cell therapy is to combine administration of tumor-specific T cells with cytokines such as interleukin-12 (IL-12), which is a potent activator of the innate and adaptive immune system.<sup>27,28</sup> Unfortunately, systemic administration of IL-12 as a single agent can result in significant toxicity.<sup>29</sup> One strategy is to preferentially localize IL-12 to the tumor through genetic engineering of tumor-specific T cells. Toward this end, a clinical trial treating patients with metastatic melanoma using autologous TIL genetically engineered to secrete IL-12 was conducted. Clinical activity was seen even at low doses of adoptively transferred T cells, but severe IL-12-related toxicity limited the development of this approach.<sup>30</sup> A potentially safer approach has been developed where IL-12 is tethered to the membrane of adoptively transferred T cells using a transmembrane anchor domain. In preclinical mouse models of cancer, adoptively transferred T cells expressing membrane-tethered IL-12 demonstrated increased antitumor efficacy, low

circulating levels of IL-12 and IFN- $\gamma$ , and no weight loss indicating a lack of systemic toxicity.<sup>31</sup>

## ADOPTIVE T-CELL THERAPY FOR NONHUMAN PAPILLOMA VIRUS-ASSOCIATED HEAD AND NECK CANCER

Epstein-Barr Virus (EBV) has been linked to the development of a subset of head and neck cancers and expresses viral proteins that are ideal targets for adoptive T-cell therapy.<sup>5</sup> Adoptive T-cell therapy with EBV-specific cytotoxic T lymphocytes (CTLs) has been studied for decades as a treatment for EBV after transplantation lymphoproliferative disorder occurring after allogeneic hematopoietic stem cell transplantation.<sup>32,33</sup> Clinical trials are testing EBV-specific CTL therapy in patients with EBV-associated nasopharyngeal carcinoma (NCT03769467, NCT02578641). A limitation of EBV-specific CTL therapy is the variable level of T-cell avidity toward the target antigen. In an attempt to consistently target EBV antigens with a significantly large quantity of high-affinity EBV-specific T cells, an active area of investigation is the discovery of high-avidity TCRs targeting EBV viral antigens that could then be tested in patients with EBV-associated diseases such as nasopharyngeal carcinoma.<sup>34</sup>

Cancer germline (CG) antigens are another group of antigens that are rationale targets for ACT. CG antigens are normally expressed by germ cells but can also be expressed by cancer cells. Because germ cells lack expression of MHC class I molecules, they are unable to be recognized by TCRs. Testis-restricted and certain testis-selective CG antigens are rational targets for TCR-T cell therapy.<sup>5</sup> CG antigens have been successfully targeted using TCR T-cell therapy in patients with synovial cell sarcoma and melanoma.<sup>11</sup> Melanoma-associated antigen 4 (MAGE-A4) is a member of a gene family of MAGE proteins. Expression is thought to be restricted to immune-privileged sites and has been found to be expressed in head and neck cancer.<sup>35,36</sup> A clinical trial is testing this TCR in patients with multiple different cancers including head and neck (NCT03132922). Other MAGE protein family members may also be appropriate targets for ACT in head and neck cancer.<sup>37</sup>

Another CG antigen that may be a target for ACT in head and neck cancer is Kitakyushu lung cancer antigen 1 (KK-LC-1). KK-LC-1 (encoded by CT83) is a CG antigen that has been reported to have restricted expression in germ cells and in certain epithelial cancers including lung, gastric, breast, and head and neck.<sup>38-40</sup> A TCR targeting KK-LC-1 was identified from the tumor-infiltrating lymphocyte of a patient with metastatic cervical cancer who had a complete response to TIL therapy.<sup>12,40</sup> The single KK-LC-1 TCR clonotype was the dominant clone in the TIL infusion cell product, comprising 67% of the infused T cells. This TCR clonotype was also present at high levels following TIL therapy, suggesting that it might have contributed to cancer regression in this patient.<sup>12</sup> Preclinical studies demonstrated the ability of T cells genetically engineered to express the KK-LC-1 TCR to mediate regression of KK-LC-1 positive epithelial cancers.<sup>40</sup> These findings support the clinical testing of KK-LC-1 TCR-T cells in patients with KK-LC-1 expressing epithelial cancers including head and neck cancer.

## SUMMARY

The potential for durable regression of highly refractory tumors makes adoptive T-cell therapy a promising treatment modality for head and neck cancer. Recent success of TIL and gene-engineered TCR-T cell therapy in HPV-associated cancers including head and neck highlight the ability of this therapy to treat advanced epithelial cancers. Strategies to overcome tumor-intrinsic mechanisms of resistance to ACT are being

investigated. Further clinical advances using ACT in head and neck cancer may come through targeting of non-HPV antigens including EBV viral proteins and CG antigens.

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