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Medical Policy Manual Medicine, Policy No. 42

Immunological Cellular Therapies and Gene Therapies

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Immunological cellular therapies and gene therapies are methods of treating cancer and other diseases.

MEDICAL POLICY CRITERIA

Notes:

- **This policy does not address the bulleted list of therapies below. Please see the Medication Policy Manual in the Cross References section, below.**
  - Non-cellular based immunotherapies, including but not limited to IL-2 monotherapy or in combination with other cytokines
  - FDA-approved gene and cell therapies (e.g., Luxterna™, Provenge®, Zolgensma®)
  - Chimeric antigen receptor T-cell (CAR-T cell) therapies (e.g., Abecma®, Breyanzi®, Kymriah™, Tecartus™, Yescarda™)

I. Immunological cellular therapies and gene therapies, including but not limited to the following, are considered **investigational**:

A. Adoptive cellular therapy for the administration of cytotoxic T lymphocytes
B. Cytokine-induced killer cells
C. Tumor-infiltrating lymphocytes
D. Antigen-loaded autologous dendritic cells
E. Genetically engineered T-cells

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Autologous lymphocytes used as part of cellular immunotherapy may be harvested in a pheresis procedure or may be isolated from resected tumor tissue.

CROSS REFERENCES

1. Medical Policy Manual: Transplant Table of Contents
2. Medication Policy Manual, Note: Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

ADOPTIVE IMMUNOTHERAPIES

The spontaneous regression of certain cancers (e.g., renal cell carcinoma, melanoma) supports the idea that a patient's immune system can delay tumor progression and, on rare occasions, can eliminate tumors altogether. These observations have led to research into various immunologic therapies designed to stimulate a patient's own immune system.

Adoptive cellular therapy is a method of treatment used to help the immune system fight diseases, such as cancer and infections with certain viruses. T cells are collected from the patient, processed, and returned to the patient. Both nonspecific and specific lymphocyte activation are used therapeutically. Nonspecific, polyclonal proliferation of lymphocytes by cytokines (immune system growth factors), also called autolymphocyte therapy, increases the number of activated lymphocytes.

T Lymphocytes and Killer Cells

Initially, this treatment was performed by harvesting peripheral lymphokine-activated killer cells and activating them in vitro with the T-cell growth factor interleukin-2 (IL-2) and other cytokines. More recent techniques have yielded select populations of cytotoxic T lymphocytes (CTLs) with specific reactivity to tumor antigens. Peripheral lymphocytes are propagated in vitro with antigen-presenting dendritic cells that have been pulsed with tumor antigens. Alternatively, innate tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with IL-2 and anti-CD3 antibody, a T-cell activator. The expansion of TIL for clinical use is labor intensive and requires laboratory expertise. Only a few cancers are infiltrated by T cells in significant numbers; of these, TIL can be expanded in only approximately 50% of cases. These factors limit the widespread applicability of TIL treatment. Recently, cytokine-induced killer cells have been recognized as a new type of antitumor effector cells, which can

proliferate rapidly in vitro, with stronger antitumor activity and a broader spectrum of targeted tumors than other reported antitumor effector cells.[1]

Cellular Therapy and Dendritic Cell Infusions

The major research challenge in immunological cellular therapy is to develop immune cells with antitumor reactivity in quantities sufficient for transfer to tumor-bearing patients. In current trials, two methods are studied: adoptive cellular therapy (ACT) and antigen-loaded dendritic cell infusions.

ACT is "the administration of a patient's own (autologous) or donor (allogeneic) anti-tumor lymphocytes following a lymphodepleting preparative regimen."[2] Protocols vary, but include these common steps:

1. lymphocyte harvesting (either from peripheral blood or from tumor biopsy)
2. propagation of tumor-specific lymphocytes in vitro using various immune modulators
3. selection of lymphocytes with reactivity to tumor antigens with enzyme-linked immunosorbent assay (ELISA)
4. lymphodepletion of the host with immunosuppressive agents
5. adoptive transfer (i.e., transfusion) of lymphocytes back into the tumor-bearing host

Dendritic cell-based immunotherapy uses autologous dendritic cells (ADC) to activate a lymphocyte-mediated cytotoxic response against specific antigens in vivo. ADCs harvested from the patient are either pulsed with antigen or transfected with a viral vector bearing a common cancer antigen. The activated ADCs are then re-transfused into the patient, where they present antigen to effector lymphocytes (CD4+ T cells, CD8+ T cells, and in some cases, B cells). This initiates a cytotoxic response against the antigen and against any cell expressing the antigen. In cancer immunotherapy, ADCs are pulsed with tumor antigens; effector lymphocytes then mount a cytotoxic response against tumor cells expressing these antigens.

In an attempt to further regulate the host immune system, recent protocols use various cytokines (e.g., IL-7 and IL-15 instead of IL-2) to propagate lymphocytes. Protocols also differ in the extent of host lymphodepletion induced prior to transfusing lymphocytes to the tumor-bearing host.

Note: Allogeneic cell transplantation following nonmyeloablative conditioning of the recipient (known as reduced-intensity conditioning [RIC]) also may be referred to as "adoptive immunotherapy" in the literature. However, RIC conditioning cell transplantation relies on a donor-versus-malignancy effect of donor lymphocytes. In contrast, the adoptive immunotherapy techniques described in this evidence review enhance autoimmune effects primarily. The use of RIC in stem cell transplantation is discussed for specific cancers in individual policies related to stem cell transplantation. Please see Cross Reference section above.

GENE THERAPY

Gene therapy is proposed to treat or prevent certain diseases by inserting foreign genetic information into a person's cells. Gene therapies can work by several mechanisms:

- Replacing a disease-causing gene with a healthy copy of the gene
- Inactivating a disease-causing gene that is not functioning properly
- Introducing a new or modified gene into the body to help treat a disease

There are a variety of types of gene therapy products, including but not limited to: plasmid DNA, viral vectors, bacterial vectors, human gene editing technology and patient-derived cellular gene therapy products.

REGULATORY STATUS

Several immunological cellular therapies and gene therapies have received U.S. Food and Drug Administration approval (see Cross References for specific therapies).

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

SYSTEMATIC REVIEWS OF CELLULAR IMMUNOTHERAPY MODALITIES FOR VARIOUS TYPES OF CANCER

Immunological cellular therapies have been investigated for the treatment of relatively common cancers in which novel treatments have been adopted when RCTs show efficacy. The following summary focuses on evidence from systematic reviews that included multiple treatment modalities.

Non-Small Cell Lung Cancer

A 2021 Cochrane review evaluated the evidence for immunotherapy (excluding checkpoint inhibitors) for the treatment of stage I-III non-small cell lung cancer (NSCLC).[3] There were 11 RCTs (total n=5,128) included in the review, which assessed the following immunologic interventions: active immunotherapy Bacillus Calmette-Guérin adoptive cell transfer, TIL, dendritic cell/cytokine-induced killer (DC-CIK), antigen-specific cancer vaccines, and targeted natural killer (NK) cells. Three of the RCTs were limited to patients with unresectable NSCLC, while the others included surgically treated patients. Overall, three of the RCTs were considered to be at a low risk of bias, though there was sponsor involvement in the study design, conduct, and interpretation, one study had an unclear risk of bias, and the other seven were considered to be at high risk of bias. Nine trials were included in the meta-analysis, which

found no evidence of a difference between treatment groups on overall survival, progression-free survival, or adverse events. The review authors concluded that for localized NSCLC, “the current literature does not provide evidence that suggests a survival benefit from adding immunotherapy (excluding checkpoint inhibitors) to conventional curative surgery or radiotherapy.”

Renal Cell Carcinoma

Tang (2013) published a meta-analysis of RCTs to investigate the efficacy of adoptive cellular immunotherapy in patients with metastatic renal cell carcinoma.[4] Four RCTs (three studies published between 1990 and 1999, and a fourth study by Liu (2012), discussed below) met inclusion criteria (total n=469). Three RCTs were conducted in the United States, and one was conducted in China. Interventions included CIK cells, lymphokine-activated killer (LAK) cells, and TIL. Most adoptive immunotherapy-related adverse reactions were grade 1 or 2 and reversible. In meta-analysis, outcomes were superior for patients treated with adoptive immunotherapy compared with no adoptive immunotherapy, including rates of objective response (pooled risk ratio [RR] 1.65, 95% confidence interval [CI] 1.15 to 2.38, p=0.007; I^2=49%), one-year survival (pooled RR 1.30, 95% CI 1.12 to 1.52, p<0.001; I^2=0%), three-year survival (RR 2.76, 95% CI 1.85 to 4.14, p<0.001, I^2=46%), and five-year survival (RR 2.42, 95% CI 1.21 to 4.83, p=0.01, I^2=28%). Heterogeneity across studies was acceptable. However, limitations of the review included varying adoptive immunotherapy protocols and lack of clear descriptions of randomization methods, allocation concealment, blinding, and withdrawals, which may lead to distribution and implementation bias in this meta-analysis.

Hepatocellular Carcinoma

Xie (2012) published a meta-analysis of RCTs comparing adoptive immunotherapy with no adjuvant treatment in patients with hepatocellular carcinoma who had undergone curative resection.[5] Six RCTs published between 1995 and 2009 (total n=494) met inclusion criteria. All six trials were conducted in Asia (four in China, two in Japan), with two studies published in the Chinese language. Two trials used CIK cells as adoptive immunotherapy, one used CIK cells plus interleukin-2 (IL-2), and the remaining three used LAK plus IL-2. Outcome measures were one- and three-year recurrence and survival rates. Meta-analysis revealed a significantly reduced risk of both one-year recurrence (odds ratio [OR] 0.35, 95% CI 0.17 to 0.71, p=0.003), and three-year recurrence (OR 0.31, 95% CI 0.16 to 0.61, p=0.001) in patients receiving adoptive immunotherapy. However, no statistically significant difference was observed in three-year survival rates between the two study groups (OR 0.91, 95% CI 0.45 to 1.84, p=0.792). It is difficult to reach any conclusions regarding the results of this meta-analysis given the treatment context of the studies, variation in immunotherapy regimens, limited sample size and follow-up period, and low-to-moderate methodological quality of the included trials.

A systematic review of RCTs by Zhong (2012) evaluated the clinical efficacy of adjuvant adoptive immunotherapy for postoperative patients with hepatocellular carcinoma.[6] Four RCTs published between 1995 and 2009 (total n=423) met inclusion criteria. As with the Xie meta-analysis discussed above,[5] all four trials were conducted in Asia. Three (of four) trials in this review also were included in the Xie meta-analysis. Primary outcomes evaluated in this review were overall survival (OS), disease-free survival (DFS), and recurrence rates. The secondary outcome was adverse effects of treatment/toxicity. Owing to clinical heterogeneity (including operation methods, dose, and type of cytokines) across studies, meta-analysis was

not performed. All RCTs reported significantly improved DFS or reduced recurrence rate after treatment with adjuvant adoptive immunotherapy ($p<0.05$). However, no statistically significant differences were observed in overall survival (OS) between study groups across the three trials reporting this outcome. The main adverse effect of adoptive immunotherapy was fever (persistent or transient), reported in three (of four) trials. Conclusions of this systematic review are subject to similar limitations as with the above meta-analysis by Xie.

CYTOTOXIC T LYMPHOCYTES

Epstein-Barr Virus–Associated Cancers

Bollard (2014) conducted an international prospective cohort study of cytotoxic T lymphocytes (CTL) therapy in patients with Epstein-Barr virus (EBV)–positive Hodgkin or non-Hodgkin's lymphoma.[7] Patients had either active, relapsed disease (n=21) or were in remission with high risk of relapse (n=29). CTLs with activity against EBV antigens were generated by incubating peripheral blood monocytes with EBV antigen-infected dendritic cells. Eleven (52%) of 21 patients with active disease achieved complete response, and two patients (10%) achieved partial response; two-year event-free survival in this cohort was approximately 50%. Twenty-seven (93%) of 29 patients in remission achieved complete response; two-year event-free survival was 82%. Immediate or delayed toxicity related to CTL infusion was not observed.

Chia (2014) studied 35 patients with EBV-positive nasopharyngeal cancer at a single center in China.[8] Patients received standard chemotherapy with gemcitabine and carboplatin followed by EBV-specific CTL infusion. Median progression-free and OS were eight months and 30 months, respectively. One-, two-, and three-year OS was 77%, 63%, and 37%, respectively. In comparison, median OS in a group of similar historical controls treated at the same institution with chemotherapy only was 18 to 21 months, and two- and three-year OS was 30% to 43% and 16% to 25%, respectively. The most common adverse events associated with CTL infusion were grade 1 and 2 fatigue and grade 1 myalgia. Two patients developed transient fever, and three patients developed grade 1 skin rash. Grade 3 or higher hematological or nonhematological toxicities were not observed during CTL therapy. In a Japanese series of seven patients who received CTLs for advanced oral and maxillofacial cancers, one-year survival in patients who achieved response (n=3) and in those with progressive disease (n=4) were 100% and 25%, respectively, although definitions of response were unclear.[9]

Cytomegalovirus-Associated Cancers

Schuessler (2014) administered CTLs with or without chemotherapy to 13 patients with recurrent glioblastoma multiforme.[10] CTLs with activity against cytomegalovirus were generated by incubating peripheral blood monocytes with synthetic peptide epitopes. Median OS was 1.1 years (range 4.4 months to 6.6 years). Adverse events were minor.

CYTOKINE-INDUCED KILLER CELLS

To date, cytokine-induced killer cells (CIKs) have been the most common cell type used for cellular immunotherapy and have been studied for the largest number of indications. There are several U.S. clinical trials underway for various indications. This evidence review will focus on published comparative studies, including RCTs, evaluating the use of CIKs for adoptive immunotherapy for various indications. These studies are described below.

Lymphomas

Wu (2016) published a case-control study of 170 elderly patients with B-cell malignant lymphomas to evaluate health outcomes from CIK-IL2 treatment with standard care in China.[11] Eighty-five elderly patients with B-cell malignant lymphoma were treated with CIK+IL-2, and 85 elderly patients not receiving CIK+IL-2 treatment served as controls. The patients in CIK+IL-2 group and control group were divided into four subgroups according to lymphoma types: diffuse large B cell lymphoma, mucosa-associated lymphoid tissue type, lymphoplasmacytic lymphoma and Hodgkin's lymphoma (HL). The levels of immune markers post-treatment in the four subgroups of CIK+IL-2 group were higher than levels before treatment and the control group post-treatment ($p<0.05$). The survival time of patients in the CIK+IL-2 group (median 22.36 ±5.38 months) was significantly longer than the control group (median 16.15 ±3.62 months).

Nasopharyngeal Carcinoma

Li (2012) conducted an RCT to evaluate the efficacy of autologous CIK transfusion in combination with gemcitabine and cisplatin (GC) chemotherapy to treat nasopharyngeal carcinoma in patients with distant metastasis after radiotherapy.[12] From September 2007 to August 2008, 60 patients with distant metastasis after radiotherapy were followed up in a university cancer center in China. Patients were randomly divided into two groups; 30 patients in the GC+CIK group received adoptive autologous CIK cell transfusion in combination with GC chemotherapy, and 30 patients in the GC group received chemotherapy alone. One- and two-year OS were 90% (27/30) and 70% (21/30), respectively, in the GC+CIK group versus 83% (25/30) and 50% (15/30), respectively, in the GC group. Mean OS was 31 months for the GC+CIK group and 26 months for the GC group (log-rank test, $p=0.137$). Median progression-free survival (PFS) was 26 months for the GC+CIK group and 19 months for the GC group (log-rank test, $p=0.023$). This small, single-center RCT indicates that the combination of CIK cells and GC regimen chemotherapy may be a viable treatment option for patients with advanced nasopharyngeal carcinoma.

Esophageal Cancer

Yuan (2021) published a meta-analysis of 17 RCTs evaluating the efficacy of CIK cell and DC-CIK cell immunotherapy for esophageal cancer.[13] In these studies, 717 patients received CIK/DC-CIK plus standard therapy (combination therapy), while 699 control patients received only therapy. Ten of the trials evaluated DC-CIK cell immunotherapy and seven evaluated CIK cell therapy alone. All of the studies were performed in China. Combination therapy patients had improved OS (OR 2.57, 95% CI 1.63 to 4.05) and ORR (OR 2.28, 95% CI 1.76 to 2.95) compared to controls.

Renal Cell Carcinoma

Zhao (2015) conducted an RCT in China among operable and inoperable patients with renal cell carcinoma.[14] Dendritic cells were also incorporated into treatment. Among the 60 operable patients, the three-year DFS was 96.7% compared with 57.7% in the control group. PFS was also better in the CIK group ($p=0.021$). Among the 62 inoperable patients, OS was better in the CIK group ($p=0.012$). There were no severe adverse reactions observed.

Zhang (2013) conducted a small RCT in China with 20 patients who had unilateral, locally advanced renal cell carcinoma after nephrectomy.[15] Patients were randomized 1:1 to postoperative CIK therapy or usual care (chemotherapy with or without radiation therapy, additional surgery, or no further treatment). Method of randomization was not described. At a

median follow-up of 44 months, six patients in the CIK group and five controls achieved complete response; two patients in the CIK group and no controls achieved partial response (overall objective response 80% vs. 50% in the CIK and control groups, respectively; Fisher exact test, p=0.175). Mean PFS was significantly longer in the CIK group, but OS was not (mean PFS 32 months vs. 22 months, log-rank test, p=0.032, mean OS, 35 months vs. 34 months, log-rank test, p=0.214). Adverse events included mild arthralgia, laryngeal edema, fatigue, and low-grade fever in three patients. Grade 3 or higher adverse events were not observed.

An RCT by Liu (2012) evaluated the effects of autologous CIK cell immunotherapy in patients with metastatic renal cell carcinoma followed up in another university cancer center in China.[16] From June 2005 to June 2008, 148 patients were randomized to autologous CIK cell immunotherapy (arm 1, n=74) or IL-2 treatment combination with human interferon-alfaα-2a (arm 2, n=74). The primary end point was OS, and the secondary end point was PFS evaluated by Kaplan-Meier analyses and hazard ratios (HRs) with Cox proportional hazards models. Three-year PFS and OS in arm were 18% and 61%, respectively, versus 12% and 23%, respectively, in arm 2 (p=0.031 and p<0.001, respectively). Median PFS and OS in arm 1 were significantly longer than those in arm 2 (PFS, 12 vs. 8 months, p=0.024; OS 46 vs. 19 months, p<0.001). Multivariate analyses indicated that the cycle count of CIK cell immunotherapy as a continuous variable was significantly associated with prolonged PFS (HR 0.88, 95% CI 0.84 to 0.93, p<0.001) and OS (HR 0.58, 95% CI 0.48 to 0.69, p<0.001) in arm 1. These findings suggest that CIK cell immunotherapy has the potential to improve the prognosis of patients with metastatic renal cell carcinoma.

Gastric Cancer

Wang (2018) published a systematic review and meta-analysis of CIK and DC-CIK cell immunotherapy for the postoperative treatment of GC.[17] The study assessed the effect of CIK/DC-CIK treatment for GC after surgery. In total, nine trials that included 1,216 patients were eligible for inclusion in the meta-analysis. Compared with the control group, the HR for OS was 0.712 (95% CI 0.594 to 0.854) and 0.66 (95% CI 0.546 to 0.797) for overall DFS. The risk ratio of the three-year and five-year OS rate was 1.29 (95% CI 1.15 to 1.46) and 1.73 (95% CI 1.36 to 2.19), respectively. The risk ratio for the three- and five-year DFS rate was 1.40 (95% CI 1.19 to 1.65) and 2.10 (95% CI 1.53 to 2.87), respectively. The proportion of patients who were CD3+, CD4+, and CD4+/CD8+ increased in the cellular therapy groups. No fatal adverse reactions were noted. Fever was the most common adverse event in CIK/DC-CIK treatment. Other effects (such as nausea and headache) could be relieved without medication or by a simple treatment. In addition, CIK/DC-CIK therapy reduced bone marrow suppression caused by chemotherapy. The analysis is limited in several ways. First, the difference between the numbers of patients involved in each study may have led to partial differences. Secondly, there were differences in the use of immune cells across different studies. Furthermore, different surgical procedures may have led to different outcomes, thus creating a study bias; patients in stages I to III underwent radical surgery, whereas patients in stage IV underwent palliative surgery.

A meta-analysis by Du (2020) focused on the combination of CIK/DC-CIK immunotherapy with chemotherapy for the treatment of advanced gastrointestinal cancers, which included both gastric cancers and colorectal cancers.[18] Combination therapy was found to be associated with improved OS and PFS compared to chemotherapy alone (RR 1.84, 95% CI 1.41 to 2.40, and RR 1.99, 95% CI 1.52 to 2.60, respectively); subgroup analyses of the outcomes stratified

by gastric cancer and colorectal cancer found results were consistent with the overall results. No significant differences in complete response, partial response, and overall response rates were noted between the groups. In this analysis, quality of life was also assessed using data from three of the included trials. Significantly improved quality of life was observed in the CIK/DC–CIK immunotherapy group compared with the chemotherapy alone group (n=245, weighted mean difference 16.09, 95% CI 1.66 to 30.52). No significant differences were noted between groups for adverse events of interest, such as myelosuppression. The analysis was limited by the presence of potential publication bias leading to negative data being omitted.

Liu (2016) published a meta-analysis of controlled trials to investigate the efficacy of CIKs in patients with gastric cancer, including six clinical trials with case-control studies (n= 318 patients receiving CIK cell therapy and 369 patients receiving conventional therapy).[19] Included studies were all written in Chinese and ranged in size from 27 to 165 patients. OS and OR were analyzed for patients at one-, two-, three-, and five-years post-CIK cell therapy and post-conventional therapy. Conventional therapy differed between the trials, and included chemotherapy, palliative gastrectomy, 5-FU or 5-HT receptor therapy. CIK cell therapy significantly increased five-year OS from 27% to 49% (p=0.03) and five-year OR up to 1.77 (p=0.001). The increased five-year survival rate was also highly correlated with the increased CD3+ T cell number (weighted mean difference 15.43, 95% CI 5.45 to 25.41, p=0.002) and ratio of CD4+/CD8+ (0.44, 95% CI 0.32 to 0.56, p<0.001) in the CIK-treated patients. The heterogeneity between studies and the publication bias were considered low. Adverse events were not addressed. The reviewers concluded that trials of larger sample size are required to obtain more conclusive results regarding the efficacy. In addition, all six clinical trials were conducted in China, and data from other countries is still lacking.

Shi (2012) published a nonrandomized, comparative study to determine the long-term efficacy of adjuvant immunotherapy with autologous CIK cells in 151 patients with locally advanced gastric cancer.[20] Five-year OS and five-year DFS for immunotherapy versus no immunotherapy (control group) were 32% versus 23% (p=0.07) and 28% versus 10% (p=0.04), respectively. For patients with intestinal-type tumors, five-year OS and DFS were significantly higher for immunotherapy (OS 47% vs 31%, p=0.045; DFS, 42% vs 16%, p=0.02). Larger and well-designed multicenter studies are needed to confirm these findings.

Hepatocellular Carcinoma

A systematic review and meta-analysis of CIK cell therapy for hepatocellular carcinoma by Wang (2019) included eight RCTs and 1,038 patients.[21] The results indicated that while CIK treatment was associated with reduced one- and three-year recurrence rates and with survival within five years, it was not associated with six-year overall survival or five-year recurrence.

A meta-analysis by Cao (2019) included seven RCTs and 15 nonrandomized controlled studies (total n=3,756) that compared CIK and dendritic cell (DC) immunotherapy separately or combined to conventional therapy alone.[22] CIK therapy alone was associated with an improvement in OS at six months (RR 1.09, 95% CI 1.03 to 1.16, p=0.005), one year (RR 1.11, 95% CI 1.06 to 1.16, p<0.00001), three years (RR 1.23, 95% CI 1.15 to 1.31, p<0.00001) and five years (RR 1.25, 95% CI 1.14 to 1.36, p<0.00001), while combined therapy with both DCs and CIKs improved OS at one year (RR 3.8, 95% CI 1.29 to 11.22, p=0.02) and five years (RR 1.45, 95% CI 0.99 to 2.12, p=0.05). As with other meta-analyses, all studies evaluating CIK or DC-CIK immunotherapy were conducted in Asia and were limited by the variety of comparators, some of which do not reflect current practice.

Cai (2017) reported the results of a meta-analysis of nine RCTs and three quasi-RCTs that compared outcomes of conventional treatments plus sequential CIK cell treatments with conventional treatments alone (total n=1,387 patients).[23] None of the 12 studies were rated as low risk of bias in all seven domains as assessed by the Cochrane risk of bias tool. Of the 12 RCTs and quasi-RCTs, five reported a statistically significant favorable survival benefit for patients receiving conventional treatments plus sequential CIK cell treatments. All 12 studies were from Asia (one from Japan, one from Korea, and 10 from China). Results of the meta-analysis reported a statistical significant reduction in the hazard of death by 41% (HR 0.59, 95% CI 0.46 to 0.77, p<0.005). However, the heterogeneity among the included studies was statistically significant (p=0.03, I^2=48).

An RCT by Lee (2015) included 230 patients in Korea being treated for hepatocellular carcinoma by surgical resection, radiofrequency ablation, or percutaneous ethanol injection.[24] Patients were randomized 1:1 to receive adjuvant CIK cell injections 16 times during 60 weeks or no adjuvant therapy. The primary end point was recurrence-free survival; secondary end points included OS and cancer-specific survival. The median recurrence-free survival was 44 months in the CIK group and 30 months in the control group (p=0.010). OS was longer in the CIK group than in the control group (HR 0.21, p=0.008). Cancer-specific survival was longer in the CIK group than in the control group (HR 0.19, p=0.02). Adverse events occurred more frequently in the CIK group than in the control group, but grade 3 or 4 adverse events did not differ significantly between groups. Adverse reactions associated with CIK cell therapy included pyrexia, chills, myalgia, and fatigue.

Yu (2014) conducted an RCT of 132 patients who had previously untreated hepatocellular carcinoma.[25] Patients were randomized 1:1 to receive CIK therapy plus standard treatment (surgical resection in eligible patients, local treatment, or best supportive care) or standard treatment only. At a median follow-up of 19 months, median PFS was 14 months in the CIK group versus seven months in the control group (log-rank test for all comparisons, p=0.019). Estimated one-, two-, and three-year PFS was 56% versus 35% (p=0.004), 36% versus 18% (p=0.004), and 27% versus 18% (p=0.017), respectively. Median OS was 25 months in the CIK group versus 11 months in the control group (p=0.008). Estimated one-, two-, and three-year OS was 74% versus 50% (p=0.002), 53% versus 30% (p=0.002), and 42% versus 24% (p=0.005), respectively. In the subgroup of operable patients, three-year and median OS did not differ statistically between groups. Common adverse events attributed to CIK therapy were grade 1 or 2 fever, allergy, and headache. Grade 3 or 4 adverse events were not observed. A nonrandomized study from China reported improved PFS in 30 patients who received radiofrequency ablation plus CIK/natural killer cell/gamma delta T-cell (a type of TIL) infusion (median PFS not reached) compared with 32 patients who received radiofrequency ablation alone (median PFS 12.0 months).[26]

Non-Small-Cell Lung Cancer

Wang (2014) conducted a systematic review of RCTs of CIK cells for the treatment of NSCLC.[27] Overall, 17 RCTs (total n=1,172 patients) were included in the analysis. The studies generally had small sample sizes; the largest had 61 CIK-treated patients and 61 control patients. Most studies also incorporated dendritic cell therapy. A significant effect of CIK was found for median time to progression and median survival time. OS at various time points significantly favored CIK.

TUMOR-INFILTRATING LYMPHOCYTES

The use of tumor-infiltrating lymphocytes (TILs) for adoptive immunotherapy is underway in several active U.S. clinical trials, most of which are in phase 1 or phase 2. This evidence review will focus on published RCTs evaluating the use of TILs for adoptive immunotherapy for various indications.

Melanoma

Dafnil (2019) published a systematic review and meta-analysis that included randomized and non-randomized studies evaluating TIL plus interleukin (IL)-2 in patients with previously treated advanced cutaneous melanoma.[28] Thirteen studies were included in the review, with 410 heavily pretreated patients. TIL therapy was administered with a full nonmyeloablative chemotherapy regimen and separate analyses were performed for low-dose (n=78) and high-dose (n=332) IL-2. The primary endpoint was objective response rates (ORR) and the pooled overall ORR estimate was 41%. The ORR for the high-dose IL-2 group was 43% (95% CI 36% to 50%) and for the low-dose group it was 35% (95% CI 25% to 45%). The analysis additionally compared TIL outcomes with cohorts of patients who were treated with checkpoint blockade immunotherapy. The pooled ORR rates for high-dose IL-2 with TIL (43%) was similar to the ORR rate for nivolumab (44%), but lower than nivolumab/ipilimumab (58%).

DENDRITIC CELLS

Antigen-loaded autologous dendritic cells (ADCs) have been explored primarily in early-stage trials in various malignancies including lymphoma,[29] myeloma,[30, 31] subcutaneous tumors,[32] melanoma,[33-35] NSCLC,[36, 37] renal cell cancer,[38] and cervical cancer.[39] A 2012 review article highlighted progress in dendritic cell-based immunotherapy in epithelial ovarian cancer.[40]

Currently, the use of dendritic cells for adoptive immunotherapy is underway in several active U.S. clinical trials, all of which are in phase 1 or phase 2. This evidence review will focus on published RCTs evaluating the use of ADCs for adoptive immunotherapy for various indications.

Breast Cancer

Wang (2014) performed a systematic review and meta-analysis to evaluate the therapeutic efficacy of dendritic cells alone, CIK cells alone and the combination of dendritic and CIK cells (DC-CIK) in the treatment of breast cancer.[41] Patient inclusion criteria included: women with metastatic or locally advanced breast cancer, progressive disease, and no standard systemic treatment indicated, life expectancy of more than three months. The main exclusion criterion was radiation therapy or chemotherapy within the previous four weeks. A total of 27 trials, including nonrandomized trials, and trials with as little as two participants, were included (n=633 patients). Only four trials (n=10, 20, 53, 129) used only dendritic cells, whereas 15 trials used CIK cells and nine trials used both dendritic and CIK cells in combination. The analysis only compared the DC-CIK group to the non-DC-CIK group (which combined both dendritic cell--alone and CIK-alone patients. Dendritic cell-alone treatment was not analyzed independently of the CIK-alone group, therefore conclusions cannot be drawn regarding the therapeutic efficacy of dendritic cells alone from this review.

Qi (2012) reported the results of a small comparative study to assess the immune response, disease progression, and post-treatment survival of ER/PR double-negative stage II/IIIA breast cancer patients vaccinated with autologous dendritic cells pulsed with autologous tumor lysates, including 31 treated patients and untreated controls.[42] The investigators reported no

serious adverse effects and approximately 58% (18/31) of patients were considered to have a positive immune reaction. The three-year progression-free survival was significantly prolonged: 76.9% versus 31.0% for those with and without the DC vaccine, respectively ($p<0.05$). However, there was no difference in overall survival between the groups.

Koski (2012) reported on a small trial to assess the safety and immunogenicity of a novel dendritic cell-based immunization approach for the induction of Th1-polarized anti-HER-2/neu treatment in women with early breast cancer.[43] This trial included 25 treated patients and 11 surgery-only controls. However, the number of treated patients available for various post-treatment analyses ranged from eight to 25. The investigators reported that post-immunization, sensitization of Th cells to at least one class II peptide was observed in 22 of 25 treated patients (88%, 95% CI 68.8 to 97.5%), while eleven of 13 (84.6%, 95% CI 64 to 99.8%) HLA-A2.1 subjects were successfully sensitized to class I peptides. In addition, anti-HER-2/neu peptide responses were observed up to 52 months post-immunization, although this group contained 11 patients. No comparisons were made between the treated and control groups in terms of outcomes.

Czerniecki (2007) reported the results of a small trial that assessed outcomes of immunotherapeutic targeting of HER-2/neu with dendritic cells in thirteen ductal carcinoma in situ (DCIS) patients.[44] The vaccinated subjects showed high rates of peptide-specific sensitization for both IFN-gamma-secreting CD4(pos) (11/13 patients, 85%) and CD8(pos) (10/13 patients, 80%) T cells. Seven of 11 evaluable treated patients also showed significantly decreased HER-2/neu expression in surgical tumor specimens compared to unvaccinated controls (n=7), five of which had significant decreases in residual DCIS.

Peoples (2005) reported the results of a small clinical trial using dendritic cells as part of a HER2/neu Vaccine to Prevent Recurrence in High-Risk Breast Cancer Patients. HLA-A2+ patients (n=24) were vaccinated using dendritic cells, and HLA-A2− patients (n=29) were included as untreated clinical controls.[45] The investigators reported that all 24 patients demonstrated clonal expansion of E75-specific CD8+T cells that lysed HER2/neu-expressing tumor cells. At 22-months follow-up, the disease-free survival was significantly higher in the vaccinated group compared to controls (85.7% vs. 59.8%) but the recurrence rate was not significantly different between groups (8% in treated vs. 21% in controls, $p<0.19$). Median time to recurrence in the vaccinated patients was prolonged (11 vs. 8 months), and recurrence correlated with a weak delayed-type hypersensitivity response.

Schirrmacher (2002) published long-term follow up (5.2 years) of a previously published comparative study by Ahlert.[46, 47] In the original 1997 study, 63 patients with primary breast cancer and 27 with metastatic pretreated breast cancer were split into groups to test the efficacy of dendritic cell therapy. Each cohort was split into three subgroups with three different cell treatment parameters, with varying cell concentrations and cell viability numbers. The study did not include untreated controls. At long-term follow-up, the group that was treated with the largest number of cells and the most viable cells had had a highly significant long term survival benefit ($p=0.004$) and significant recurrence free survival ($p=0.04$) compared to the other treatment groups with reduced cell numbers and reduced viability. Probability of survival at four years was 63% for the group treated with reduced cell numbers, and 94% for the group treated with the largest number of cells and the most viable cells.

Clear-cell Renal Cell Carcinoma

The results of a phase 3 RCT of an ADC therapy for metastatic clear-cell renal cell carcinoma were reported by Figlin (2020).[48] The trial included 462 patients who were randomized 2:1 to ADC therapy + standard of care (SOC) or SOC alone. The primary outcome was OS. After a median follow up of 29 months, the study was terminated due to lack of clinical efficacy. The median OS was 27.7 months in the ADC group and 32.4 months in the control group (HR 1.10, 95% CI 0.83 to 1.40).

Glioblastoma Multiforme

Bregy (2013) published a systematic review of observational studies of active immunotherapy using ADCs in the treatment of glioblastoma multiforme.[49] Twenty-one studies published through early 2013 were included in this review (total n=403). Vaccination with dendritic cells loaded with autologous tumor cells resulted in increased median OS in patients with recurrent disease (72 to 138 weeks across eight studies), as well as in those newly diagnosed (65 to 230 weeks across 11 studies) compared with average survival of 58 weeks. Complications and safety of the vaccine were assessed in all studies. No study indicated any sign of autoimmune reaction. The majority of adverse events were injection site reactions (22%). Other adverse events included fatigue (19.5%), constipation/diarrhea (1.6%), myalgia/malaise (1.6%), shivering (1.4%), and vomiting (0.5%). Because of the nature of the current literature available (i.e., case reports, phase 1 and phase 2 clinical trials, prospective studies), the review is subject to publication and selection bias, which has the potential to lessen or amplify the true potential of adoptive immunotherapy. Larger controlled trials are required to assess survival and effect on quality of life of adoptive immunotherapy in this patient population.

Hepatocellular Carcinoma

Su (2016) performed a meta-analysis of RCTs to evaluate the efficacy and safety of dendritic cells co-cultured with CIK immunotherapy (DC-CIK) combined with transcatheter arterial chemoembolization (TACE) or TACE plus local ablation therapy (RFA) for hepatocellular carcinoma.[50] The seven RCTs used DC-CIK +TACE for the treated group and TACE alone for the controls. The one controlled clinical trial that was included used DC-CIK +TACE_RFA for the treated group and TACE+RFA for the controls. In total, 693 patients (n=349 treated and n=344 controls) from eight controlled trials performed in China were included.

Overall study heterogeneity was low. Pooled results showed that DC-CIK immunotherapy combined with TACE or TACE plus local ablation therapy significantly improved overall survival at one-year (OR 2.00, p=0.02) and two-year (OR 1.77, p=0.04) follow-up. An improved ORR (OR 1.51, p=0.03), disease control rate (complete remission + partial remission + stable disease) (DCR) (OR 1.81, p=0.01), and quality of life (OR 3.30, p<0.0001) were observed in the DC-CIK group. Additionally, the percentage of CD3+ T cells (mean difference [MD] 21.37, p=0.005) and the ratio of CD4+/CD8+ (MD 2.83, p=0.02) were significantly increased in the DC-CIK therapy group. The only immunotherapy-specific adverse effects reported were mild and transient. However, the reviewers concluded that well-designed RCTs with rigorous methods and larger sample sizes are needed to confirm their findings and determine the best therapeutic combination for HCC. Limitations of this review include small sample size for all but one included study, no included study was determined to be of high quality, and patient populations in the included studies at different stages of disease. In addition, tumor size, tumor stage, treatment design for inclusion of patients and evaluation of the therapeutic effects varied across the included studies, causing heterogeneity.

HIV

In 2016, Jacobson (2016) conducted a phase 2B, multicenter, 2:1 randomized, double-blind, placebo-controlled study on 54 HIV patients to assess DC treatment on its ability to reduce viral load.[51] Thirty-six patients in the treatment group were injected every four weeks with dendritic cells loaded with Gag, Rev, Vpr, and Nef RNA molecules from the patient's autologous virus, and 11 to 12 week viral loads were assessed. There was no difference in viral loads between the treated and untreated patients, and there was no difference in pre- and post-treatment viral loads in treated patients. A greater percentage of the treated patients had cytotoxic T-lymphocyte responses induced in the HIV-specific effector/memory T-cell population. The only adverse event reported was transient, mild (grade 1) local injection site reactions. The authors concluded that despite the induction of HIV-specific effector/memory CD8 T-cell responses, no antiviral effect was seen after the administration of dendritic cells when compared with placebo. Similar nonsignificant results were reported in a smaller RCT conducted by Gandhi.[52] For HIV-infected patients, dendritic cell treatment needs to be optimized to elicit stronger and long-lasting immune responses in order for this therapy to be effective.

Medullary Thyroid Cancer

In a 2009 phase 1 pilot study, 10 patients with metastatic medullary thyroid cancer (MTC) were treated with ADCs pulsed with allogeneic MTC tumor cell lysate.[53] At median follow-up of 11 months, three (30%) patients had stable disease, and seven (70%) patients progressed. No World Health Organization grade 3 or 4 toxicities or autoimmune reactions were observed. Of note, human leukocyte antigen match between patients and tumor cell lines did not predict disease stabilization or progression, suggesting that, should future studies demonstrate efficacy of ADC therapy for MTC using allogeneic tumor lysate, an unlimited source of tumor material may be available for lysate preparation.

Melanoma

Vreeland (2021) published the results of a phase 2b double-blind RCT of a tumor lysate, particle-loaded, dendritic cell vaccine to prevent recurrence in 144 patients with resected stage III/IV melanoma (vaccine n=103, control n=41).[35] After a median follow-up of 19.1, an intention-to-treat analysis found no significant difference in recurrence or in disease-free survival between groups. Adverse event rates were similar for both groups and mostly grade 1 or 2.

Multiple Myeloma

Zhao (2016) conducted an RCT to investigate the efficacy of DC-CIK combined with chemotherapy for treating 42 newly diagnosed patients with multiple myeloma in China.[54] Twenty patients were randomized to the chemotherapy only group and 22 patients to the immunotherapy (DC-CIK) combined with chemotherapy group. After three weeks post-treatment, the quality of life, clinical index and survival of patients in combined therapy group were better than those of patients in chemotherapy group ($p<0.05$); the ratios of immune markers of patients in combined therapy group were significantly lower than those of patients in chemotherapy group alone ($p<0.05$). A second study was published by the same group which is likely the same cohort of patients, reporting that levels of IL-2, IL-4, IL-10 and IFN-γ in the DK-CIK + chemotherapy group was higher than in the chemotherapy alone group ($p<0.05$).[55]

Non-Small-Cell Lung Cancer

Wang (2015) conducted a systematic review to evaluate the efficacy and safety of DC-CIK immunotherapy for the treatment of gastric cancer, including 505 patients from six Chinese RCTs.[56] Compared with control therapies, DC-CIK immunotherapy significantly improved PFS (HR 0.528, 95% CI 0.390 to 0.715, p<0.001), OS (HR 0.619, 95% CI: 0.487-0.786, p<0.001), and disease control rates (RR 1.250, 95% CI 1.058 to 1.477, p=0.009). However, objective response rates (RR 1.190, 95% CI 0.561 to 2.526, p=0.650) were not improved in the DC-CIK treated group. The reviewers determined that the risks of adverse events in patients receiving DC-CIK immunotherapy were comparable to those receiving control therapies. The reviewers concluded that further studies are required to adopt routine clinical use of DC-CIK immunotherapy for NSCLC.

Chen (2014) conducted a systematic review and meta-analysis of RCTs that compared DC-CIK combination immunotherapy with any other treatment (placebo, no intervention, conventional treatment, or other complementary and alternative medicines) for any cancer type and stage.[57] Two of the included RCTs that compared DC-CIK plus chemotherapy with chemotherapy alone in patients with stage III/IV NSCLC reported OS estimates (total n=150). Pooled RRs favored DC-CIK therapy at two years but not at one year (RR for one-year OS 1.38, 95% CI 1.00 to 1.90, p=0.05, I^2=35%; RR for two-year OS 2.88, 95% CI 1.38 to 5.99, p=0.005, I^2=0%).

Shi (2012) conducted an RCT at a single university cancer center to evaluate the role of DC-CIK combination immunotherapy as maintenance treatment of advanced NSCLC.[36] From October 2008 to June 2010, 60 patients with stage IIIB/IV disease after treatment with four cycles of a platinum-based chemotherapy regimen were randomly divided into two groups. One group was treated with DC-CIK cell therapy (n=30), and the other was a control group who received no adoptive immunotherapy (n=30). Outcome measures were PFS and adverse effects of treatment/toxicity. PFS was 3.2 months in the DC-CIK group (95% CI 2.9 to 3.5) versus 2.6 months control group (95% CI 2.39 to 2.73, p<0.05). No significant toxic reactions were observed in the DC-CIK group, including bone marrow toxicity and gastrointestinal reactions. The findings of this small single-center RCT indicate that combination immunotherapy with dendritic cells and CIK cells may offer a viable option as maintenance therapy for patients with advanced NSCLC.

Pancreatic Cancer

Liu (2019) published a systematic review and meta-analysis focused on the DC-CIK immunotherapy for pancreatic cancer.[58] The review included 21 clinical trials and a total of 1,549 patients. The authors reported that DC-CIK treatment improved remission and response rates and overall survival. The adverse reaction rate was 22%.

A 2009 phase 1 study of five patients with inoperable pancreatic cancer reinfused ADCs and lymphokine-activated killer cells with gemcitabine; antigen priming of the ADCs was presumed to occur in vivo from apoptosis of gemcitabine-exposed tumor cells.[59] One patient had a partial response, two had stable disease for more than six months, and two had disease progression. Toxicities included grade 1 anemia and grade 2 leukocytopenia, nausea, and constipation.

GENETICALLY ENGINEERED T CELLS

Engineered T cell–based antitumor immunotherapy uses gene transfer of tumor antigen-specific T-cell receptors (TCR) or synthetic chimeric antigen receptors (CAR). Chimeric antigen receptor therapies are not addressed in this policy. See Cross References above.

Review articles have highlighted recent progress in this field for solid and hematologic malignancies.[60-62]

The use of genetically engineered T cells is still in its early stages, with only phase 1/2 trials underway that have enrolled or expect to enroll small numbers of patients (n<100). The body of published evidence for the use of engineered T cells is limited to noncomparative studies for various cancers.

Melanoma

Robbins (2014) conducted a pilot trial, including 18 patients with synovial cell carcinoma and 20 patients with melanoma, treated with engineered T cells containing the cancer germline antigen NY-ESO-1.[63] Eleven of 18 patients with NY-ESO-1$^+$ synovial cell sarcomas (61%) and 11 of 20 patients with NY-ESO-1 positive melanomas (55%) who received the engineered T cells demonstrated partial or complete responses at one-month post treatment. Similar positive results have been reported in other small trials using T cells engineered with melanocyte differentiation antigens, gp100 and MART-1.[64]

In a phase 2 study, Johnson (2009) transfected autologous peripheral lymphocytes of 36 patients who had metastatic melanoma with genes encoding TCRs highly reactive to melanoma/melanocyte antigens (MART-1:27-35 and gp100:154-162).[65] Nine patients (25%) experienced an objective response; eight patients had a partial response lasting three months to more than 17 months; and one patient (in the gp100 group) had a complete response lasting more than 14 months. Treatment toxicities included erythematous rash, anterior uveitis, hearing loss, and dizziness, suggesting that these were attributable to recognition by the genetically modified lymphocytes of normally quiescent cells expressing the targeted cancer antigens; melanocytic cells exist in the skin, eye, and the inner ear. Ideal targets for TCR gene therapy may be antigens that arise in cancers of nonessential organs (e.g., prostate, ovary, breast, thyroid) or are not expressed on normal adult tissues (e.g., cancer-testes antigens).

Other Indications

Additional small phase 1 and phase 2 trials have examined TCR gene therapy in Hodgkin[66] and non-Hodgkin's lymphoma,[67] prostate cancer,[68] B-cell malignancies,[69, 70] colorectal cancer,[71] mesothelioma,[72] and neuroblastoma[73, 74] There is a large amount of heterogeneity between studies for any single indication, since there are often more than one type of antigen used to engineer the cells. Regardless, large RCTs with standardized treatment protocols and long-term follow up are needed to determine the efficacy of each type of engineered T-cell therapy for each indication.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

Current clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) do not include recommendations for cellular immunotherapy or gene therapy that are within the scope of this policy. NCCN recommendations for CAR-T therapies are not addressed in this policy, see Cross References. NCCN guidelines do not include recommendations for cellular

immunotherapy to treat cancers of the bladder,[75] central nervous system,[76] head and neck,[77] hepatobiliary system,[78] kidney,[79] pancreas,[80] stomach,[81] breast,[82] thyroid,[83] melanoma,[84] or non-small-cell lung cancer.[85]

SUMMARY

Immunotherapies not addressed in this policy include: Non-cellular based immunotherapies, including but not limited to IL-2 monotherapy or in combination with other cytokines; sipuleucel-T (Provenge®); voretigene neparvovec-rzyl (LUXTURNA™); and chimeric antigen receptor (CAR) T-cells. For other cellular immunotherapies, there is not enough research to show an improvement in overall health outcomes (e.g., increased survival, improved quality of life) for patients with any type of cancer. Although some immunological cellular therapies show promise for certain cancers, the current evidence includes studies with small numbers of patients and there are differences in the types of populations studied (e.g., early stage versus advanced disease) and the types of therapies administered. Additional research is needed with more patients and longer follow-up. In addition, there are no clinical practice guidelines that recommend immunological cellular therapies or gene therapies addressed in this policy. Therefore, immunological cellular therapies and gene therapies within the scope of this policy are considered investigational for any indication.

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CODES

Codes	Number	Description
CPT	36511	Therapeutic apheresis; for white blood cells
	37799	Unlisted procedure, vascular surgery (therapeutic leukapheresis)
	96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to one hour
HCPCS	S2107	Adoptive immunotherapy, ie, development of specific antitumor reactivity (eg, tumor infiltrating lymphocyte therapy) per course of treatment

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