BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 8.01.01 Adoptive Immunotherapy

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Related Policies:

5.21.101-Kymriah (tisagenlecleucel)
5.21.105- Yecarta (axicabtagene ciloleucel)
5.21.155-Tecartus (brexucabtagene autoleucel)
5.21.169- Breyanzi (lisocabatagene maraleucel)
5.21.173- Abecma (idecabtagene vicleucel)
5.90.033- Luxtuma (voretigene neparvovec-rzyl)
8.01.53- Cellular Immunotherapy for Prostate Cancer

Adoptive Immunotherapy

Description

Description

The spontaneous regression of certain cancers (eg, 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 immunotherapy is a method of activating lymphocytes and/or other types of cells for the treatment of cancer and other diseases. Cells are removed from the patient, processed for some period of time, and then infused back into the patient.

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 (IL)-2 and other cytokines. More recent techniques have yielded select populations of cytotoxic T lymphocytes with specific reactivity to tumor antigens. Peripheral lymphocytes are propagated in vitro with antigen-presenting dendritic cells (DC) 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.[5,]

Cellular Therapy and Dendritic Cell Infusions

The major research challenge in adoptive immunotherapy is to develop immune cells with antitumor reactivity in quantities sufficient for transfer to tumor-bearing patients. In current trials, 2 methods are studied: adoptive cellular therapy and antigen-loaded DC infusions.

Adoptive cellular therapy is “the administration of a patient’s own (autologous) or donor (allogeneic) antitumor lymphocytes following a lymphodepleting preparative regimen.”[6,] Protocols vary, but include these common steps:

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

Dendritic cell-based immunotherapy uses autologous DC (ADC) to activate a lymphocyte-mediated cytotoxic response against specific antigens in vivo. Autologous dendritic cells 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-positive T-cells, CD8-positive 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. (See evidence review 8.01.53 for a discussion of DC-based immunotherapy for prostate cancer.)

In an attempt to regulate the host immune system further, recent protocols have used various cytokines (eg, 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.

OBJECTIVE

The objective of this evidence review is to assess whether the use of adoptive immunotherapy in individuals with various malignancies improves the net health outcome.

POLICY STATEMENT

All adoptive immunotherapy techniques intended to enhance autoimmune effects are considered **investigational** for the indications included, but not limited to, cancers associated with Epstein-Barr virus, *Cytomegalovirus*-associated cancers, nasopharyngeal cancer, renal cell carcinoma, gastric cancer, colorectal cancer, hepatocellular carcinoma, non-small-cell lung cancer, melanoma, glioblastoma multiforme, medullary thyroid cancer, pancreatic cancer, and cancers treated with autologous peripheral T lymphocytes containing tumor antigen-specific T cell receptors.

POLICY GUIDELINES

Chimeric antigen receptor T-cell therapies for certain hematologic malignancies (eg, tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel) are discussed separately in evidence review 8.01.63.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Adoptive immunotherapy is a specialized service that may require an out-of-network referral.

FDA REGULATORY STATUS

There are currently no adoptive immunotherapy products within the scope of this review that are U.S. Food and Drug Administration (FDA)-approved. In 2022, the primary analysis of the Netherlands Cancer Institute-sponsored phase 3 M14TIL randomized controlled trial (NCT02278887) was published by Rohaan et al.[7,] This study, comparing autologous TIL therapy with ipilimumab in patients with advanced cutaneous melanoma who had received no more than 1 prior line of therapy, met its primary endpoint of prolonged progression-free survival in TIL recipients. The TIL product was prepared at a local facility and, to date, has not been reported to be associated with regulatory application submissions.

In 2022, a pooled analysis of cohorts enrolled in the phase 2 C-144-01 trial (NCT02360579) was published by Chesney et al.[8,] In this analysis conducted in patients with advanced non-uveal melanoma who had received a median 3 prior lines of therapy, lifileucel, an autologous $CD4^+/CD8^+$ TIL product, demonstrated an overall response rate of 31.4%; with median follow-up of approximately 27 months, median duration of response had not been reached. On the basis of this trial, a Biologics License Application for lifileucel for patients with advanced melanoma was submitted by Iovance Biotherapeutics and accepted by the FDA for priority review, with a Prescription Drug User Fee Act action date of November 25, 2023.[9,]

RATIONALE

Summary of Evidence

Cytotoxic T Lymphocytes

For individuals with Epstein-Barr virus (EBV)-associated cancers who receive cytotoxic T lymphocytes (CTL) , the evidence includes 2 small, prospective noncomparative cohort studies. Relevant outcomes are overall survival (OS) , disease-specific survival (DSS) , quality of life (QOL) , and treatment-related mortality and morbidity. The cohort studies have shown a treatment response to infused CTL directed against cancer-associated viral antigens. To establish efficacy, the following are needed: large, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with *Cytomegalovirus*-associated cancers who receive CTL, the evidence includes a single case series. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. In the absence of a randomized controlled trial (RCT) comparing CTL with the standard of care, no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Cytotoxic-Induced Killer Cells

For individuals with nasopharyngeal carcinoma who receive cytotoxic-induced killer (CIK) cells, the evidence includes a single RCT. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The RCT reported a numerically favorable but statistically insignificant effect on PFS and OS. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with renal cell carcinoma (RCC) who receive CIK cells, the evidence includes multiple RCTs. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The largest of the RCTs reported statistically significant gains in progression-free survival (PFS) and OS with CIK cell-based immunotherapy compared with interleukin-2 (IL-2) plus interferon-α-2. This body of evidence is limited by the context of the studies (non-U.S.) and choice of a nonstandard comparator. The other 2 RCTs have also reported response rates in favor of CIK therapy with an inconsistent effect on survival. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with gastric cancer who receive CIK cells, the evidence includes 2 meta-analyses encompassing non-randomized trials. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Both meta-analyses reported statistically significant effects on OS, DFS, and PFS in favor of immunotherapy versus no immunotherapy. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with colorectal cancer (CRC) who receive CIK cells, the evidence includes a single RCT and 2 meta-analyses. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Results of the RCT showed a statistically significant effect on OS in favor of immunotherapy versus chemotherapy alone. A meta-analysis that included both gastric cancer and CRC found improvements in OS and PFS in favor of CIK or CIK cell/dendritic cell-cytokine-induced killer (DC-CIK) cells compared to chemotherapy alone; another meta-analysis of prospective and randomized studies of CIK or DC-CIK in patients with CRC also showed improvements in survival outcomes compared to non-CIK/DC-CIK treatments. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with hepatocellular carcinoma (HCC) who receive CIK cells, the evidence includes meta-analyses that include RCTs and quasi-randomized trials. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Meta-analyses of these trials have reported improved OS rates when compared to conventional therapies alone, but they are limited by inclusion of studies from Asia only and heterogeneity in comparators. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodological weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with non-small cell lung cancer (NSCLC) who receive CIK cells, the evidence includes multiple RCTs and a systematic review. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. A single systematic review of RCTs reported some benefits in median time to progression and median survival time. The trials assessed in the systematic review were limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodological weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Tumor-Infiltrating Lymphocytes

For individuals with melanoma who receive tumor infiltrating lymphocytes (TILs) , the evidence includes a meta-analysis of randomized trials. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The meta-analysis evaluating TIL with IL-2 in patients with cutaneous melanoma reported an objective response rate of 41%. Pooled 1-year OS rates ranged from 46.1% to 56.5% depending on the IL-2 dose level. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with EBV-associated nasopharyngeal carcinoma who receive TILs, the evidence includes an RCT evaluating TILs as adjuvant therapy. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The RCT evaluating TILs as adjuvant therapy following standard chemoradiation in individuals with EBV-associated nasopharyngeal carcinoma found no difference in PFS or other clinical outcomes compared to patients who received standard chemoradiation alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Dendritic Cells

For individuals with glioblastoma multiforme who receive dendritic cells (DC) , the evidence includes a systematic review of observational studies. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Because of the observational and noncomparative nature of the available evidence, it is difficult to draw any meaningful conclusions. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. Interim results from 1 such RCT have been published but are not informative because the patients were unblinded and results were combined for the treatment and placebo arms. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with NSCLC who receive DC, the evidence includes 2 RCTs and a meta-analysis. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The RCTs have generally reported some benefits in response rates and/or survival. The meta-analysis of these trials also reported a statistically significant reduction in the hazard of death. Most trials were from Asia and did not use the standard of care as the control arm. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodological weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with medullary thyroid cancer (MTC) who receive DC, the evidence includes 1 prospective noncomparative study. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. A small prospective noncomparative study in 10 MTC patients treated with autologous DC has been published. There are no RCTs comparing DC-based adoptive immunotherapy with the standard of care and, therefore, no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with pancreatic cancer who receive DC, the evidence includes a small prospective noncomparative study. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. The study reported on treatment outcomes for 5 patients with pancreatic cancer. Because of the noncomparative nature of the available evidence and small sample base, it is difficult to draw any meaningful conclusions. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Genetically Engineered T Cells

Peripheral T Lymphocytes

For individuals with cancers who receive autologous peripheral T lymphocytes containing tumor antigen-specific T-cell receptors (TCRs) , the evidence includes multiple small observational studies. Relevant outcomes are OS, DSS, QOL, and treatment-related mortality and morbidity. Multiple observational studies have examined autologous peripheral T lymphocytes containing tumor antigen-specific TCRs in melanoma, Hodgkin and non-Hodgkin lymphoma, prostate tumors, and neuroblastoma. Because of the noncomparative nature of the available evidence and small sample size, it is difficult to draw any meaningful conclusion. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

Current guidelines from the National Comprehensive Cancer Network do not include recommendations for adoptive immunotherapy to treat cancers of the bladder[54], central nervous system,[55] head and neck,[56] hepatobiliary system,[57,58] kidney,[55] pancreatic,[59] stomach,[60] thyroid[61], melanoma,[62] or non-small-cell lung cancer.[63]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2011	New policy	
March 2013	Replace policy	Policy updated with literature review, 2 systematic reviews added; primary studies added on cytokine-induced killer (CIK) cells; Refs 1, 3- 6, 24 and 27 added, others renumbered and/or removed. Policy statement now includes cytokine-induced killer (CIK) cells, remains investigational.
March 2014	Replace policy	Policy updated with literature search. References 3, 8, 27, and 31 added. No change in policy statements.
March 2015	Replace policy	Policy updated with literature review through November 2, 2014, references 6-9, 12, 14-17, 41, 46, 52-53, and 56-65 added; reference 55 updated. Rationale reorganized and references renumbered. Cytotoxic T lymphocytes and genetically engineered T cells added to investigational policy statements; "autologous, added to clarify antigen loaded dendritic cells.
June 2016	Replace policy	Policy updated with literature review through November 10, 2015; references 13 and 17-18 added. Section on lymphokine-activated killer cell deleted due obsolete intervention. Policy statements unchanged.
December 2017	Replace policy	Policy updated with literature review through April 25, 2017, and FDA documents accessed subsequent to this date; references 3-10, 23-24, 55-58, and 70 were added.
March 2019	Replace policy	Policy updated with literature review through October 29, 2018; reference 31 added. Policy statements unchanged.
December 2019	Replace policy	Policy updated with literature review through July 25, 2019; Policy statement wording revised to All applications of adoptive immunotherapy evaluated in this policy are considered investigational.
December 2020	Replace policy	Policy updated with literature review through August 31, 2020; references added. "All adoptive immunotherapy techniques intended to enhance autoimmune effects are considered investigational for the indications included, but not limited to cancers associated with EBV, CMV, nasopharyngeal cancer, renal cell carcinoma, gastric cancer, colorectal cancer, hepatocellular carcinoma, NSCLC, melanoma, glioblastoma multiforme, medullary thyroid cancer, pancreatic cancer, and cancers treated with autologous peripheral T lymphocytes containing tumor antigen-specific T cell receptors."
December 2021	Replace policy	Policy updated with literature review through August 24, 2021; no references added. Policy statements unchanged. FDA regulation information removed.
December 2022	Replace policy	Policy updated with literature review through August 24, 2022; references added. Policy statements unchanged.
December 2023	Replace policy	Policy updated with literature review through August 11, 2023; references added. Indication added (TIL in EBV-associated nasopharyngeal carcinoma). Policy statements unchanged.