# Adoptive Immunotherapy

## Coverage Policy

Cigna does not cover the following adoptive immunotherapy techniques because each is considered experimental, investigational or unproven, except as noted below in the related Coverage Policy:

- lymphokine activated killer (LAK) cells activated in vitro by recombinant or natural interleukin-2 (IL-2) or other lymphokines
- tumor infiltrating lymphocytes (TILs)
- antigen-loaded dendritic cells

**Note:** For information on coverage of Sipuleucel-T (Provenge®), refer to the applicable Cigna Coverage Policy: Oncology Medications.

## General Background

Adoptive immunotherapy, also called adoptive cellular therapy, involves the removal of lymphocytes from an individual, stimulation of those lymphocytes to increase their immune capabilities, and the transfer of those cells back into the patient. The potential benefit of this therapy depends on the availability of recombinant human cytokines and the ability to collect large enough quantities of stimulated lymphocytes for therapeutic transfer. The principles of cellular immunology needed to fully exploit adoptive immunotherapy have not been completely defined. Adoptive immunotherapy has been proposed as a treatment option for numerous conditions including cancer, human immunodeficiency virus, type I diabetes mellitus and rheumatoid arthritis. Several techniques have been explored, including the use of lymphocyte activated killer (LAK) cells, tumor Infiltrating lymphocytes (TILs), and T-cell lymphocytes/dendritic cells (DCs). At the present time the high-dose bolus IL-2 regimen...
remains the treatment of choice for appropriate patients with access to such treatment and is the gold standard to which other IL-2–based regimens should be compared. The addition of tumor-infiltrating lymphocytes, other cytokines, or chemotherapeutics have failed to improve on the durable partial and complete responses observed with high-dose IL-2 treatment (Lotze, 2011).

Lymphocyte Activated Killer (LAK) Cells
LAK cells are developed by removing peripheral blood lymphocytes and stimulating them with high concentrations of interleukin 2 (IL-2), a cytokine produced by lymphocytes that stimulates both T-cells and natural killer cells. Once there is a large enough quantity of stimulated cells, the cells are transferred back into the patient. Studies have suggested that LAK cells are limited in therapeutic efficacy and have demonstrated no advantage for the administration of LAK plus IL-2 over administration of IL-2 alone (Kasslin, 2014). Newer concepts in tumor immunology have lessened the importance of the continuing debate over the merits of IL-2/LAK therapy. The role of this therapy has not been established for any indication.

Literature Review: There is insufficient evidence to demonstrate the safety and effectiveness of adoptive immunotherapy with lymphocyte activated killer cells for the treatment of any condition, including malignancy and human immunodeficiency virus. Studies have primarily been in the form of case series with small patient populations (n=17–33) (Dillman, et al., 2009; Thionuun, et al., 2002).

Kimura et al. (2015) conducted a phase III, randomized controlled trial (RCT) to investigate postsurgical adjuvant chemotherapy plus immunotherapy (Group A) (n=50) vs. chemotherapy alone (group B) (n=51) for the treatment of non-small cell lung cancer (NSCLC). Patients were age < 76 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1; had adequate bone marrow function, liver function, and renal function; primary NSCLC (including combined-type small cell carcinoma) histology; and pathological of stage IB with tumor sizes larger than five centimeters or with severe vessel invasion and stages II–IV. Non-curative resection cases were included. Immunotherapy consisted of the adoptive transfer of autologous activated killer T (AKT) cells and dendritic cells (DC) obtained from the patients’ own regional lymph nodes. The autologous AKT–DC from the regional lymph nodes of patients had to grow enough to provide more than 7 × 10^9 cells for each course of the therapy. Undetectable tumor cells remaining after the resection of the primary tumor were the target of the immunotherapy. Group A received 12–15 courses of treatment over a two-year period and group B received four courses of chemotherapy. Stage IIIB patients received two courses of induction chemotherapy prior to surgery. Follow-ups occurred for up to five years. The primary end point was overall survival with recurrence-free survival, toxicity, and adverse effects of immunotherapy as secondary end points. The two-year overall survival rates in groups A and B were 93.4% and 66.0%, and the five-year rates were 81.4% and 48.3%, respectively, statistically significant in favor of group A (p=0.0013). The two- and five-year recurrence-free survival rates were also statistically significant in favor of group A (p=0.0020). Adverse events included chills, shivering and fever. There were 19 cases of recurrence in group A and 33 cases in group B. Thirty-five stage IIIB and IV patients were excluded from the study because macroscopic residual tumors remained after surgery, and enough T cells could not be obtained for dosage. Limitations of the study include the small patient population, heterogeneity of the disease stages and lack of sufficient numbers of lymphocytes obtained from patients with stage N2 and N3. Additional data from a large-scale multi-center RCT is needed before the clinical importance of this therapy is determined. The most effective dose for immunotherapy in this population has not been determined.

Rosenberg et al. (1993) conducted a randomized controlled trial to determine whether the administration of lymphokine activated killer (LAK) cells in conjunction with high-dose Interleukin-2 (IL-2) alters response and survival rates compared to those for IL-2 alone in patients with advanced cancer (n=181). Included patients had either metastatic cancer that failed to respond to standard therapy, or had a disease for which no effective therapy existed. A total of 97 patients had renal cell cancer and 54 had melanoma. Median follow-up was 63.2 months. There were 10 complete responses among the 85 assessable patients who received IL-2 plus LAK cells, compared to four among the 79 who received IL-2 alone. Complete response continued in seven patients at 50–66 months. The 36-month survival with IL-2 plus LAK cells was 31%, compared to 17% with IL-2 alone. A trend toward improved survival was seen for patients with melanoma who received IL-2 plus LAK cells (32%) compared to those who received IL-2 alone (15%). Of 26 patients with melanoma who received IL-2 alone, none were alive at the end of the study; five of 28 who received IL-2 plus LAK cells were alive, and three continued in complete response. No difference in survival was seen in patients with renal cell cancer in the two treatment groups. There were six treatment-related deaths (3.3%). The authors concluded that some patients with metastatic cancer have prolonged remission when treated with high-dose IL-2 alone or in conjunction with LAK
cells. The authors noted a trend toward increased survival when IL-2 is given with LAK cells in patients with melanoma, but no trend was observed for patients with renal cell cancer.

Tumor Infiltrating Lymphocytes (TILs)
Tumor tissue contains its own immune system cells called tumor infiltrating lymphocytes. In TIL therapy, tumor infiltrating lymphocytes are removed from the tumor itself and treated with IL-2. These activated cells are then returned to the patient to attack the tumor (American Cancer Society [ACS], 2015). There is insufficient evidence to support the safety and effectiveness of adoptive immunotherapy using tumor infiltrating lymphocytes for the treatment of any condition including melanoma and renal cell cancer. Study populations were small and heterogeneous, and outcomes related to overall survival are variable. At this time, the role of this therapy has not been established for any indication.

Literature Review:
Rosenberg et al. (2011) reported on a trial of 93 patients with measurable metastatic melanoma who were treated with the adoptive transfer of autologous TILs administered in conjunction with interleukin-2 following a lymphodepleting preparative regimen on three sequential clinical trials. Ninety-five percent of the patients had progressive disease following prior treatment. About 85% of study participants had surgically resectable disease. Objective response rates by Response Evaluation Criteria in Solid Tumors (RECIST) in the three trials using chemotherapy alone or with two or 12 Gy irradiation were 49%, 52%, and 72%, respectively. Twenty of the 93 patients (22%) achieved complete tumor regression, and 19 have ongoing complete regressions beyond three years. The actuarial three- and five-year survival rates for the entire 93 patients were 36% and 29%, respectively. For the 20 complete responders, three- an five-year survival rates were 100% and 93%, for the 32 partial responders 31% and 21%, and for the 41 non-responders were 7% and 5%, respectively. Overall follow-up was 62 months. A limitation of the study is the uncontrolled design and lack of comparator.

Dreno et al. (2003) conducted a randomized controlled trial to demonstrate the use of TILs as adjuvant therapy for stage III (metastasis to regional lymph nodes) melanoma. After lymph node excision, patients without any detectable metastases were randomly assigned to receive a two-month course of either TIL plus IL-2 or IL-2 only. The primary endpoint was the duration of the relapse-free interval. Eighty-eight patients eligible for treatment were enrolled in the study. After a median follow-up of 46.9 months, the analysis did not show a significant extension of the relapse-free interval or overall survival for the study population.

Khammari et al. (2007) reported long-term results of the Dreno study. After a median follow-up of 114.8 months, there was no change in the non-significant extension of relapse free interval or overall survival.

In a Cochrane review evaluating immunotherapy for advanced renal cell carcinoma Coppin et al. (2005, updated 2011) compared high-dose IL-2 and Interferon-alpha to other options. The primary outcome was overall survival at one year. They selected randomized controlled trials (RCTs) that included patients with advanced renal cell carcinoma who had utilized an immunotherapeutic agent and RCTs that had reported on remission or survival. The review was separated out into 11 different comparisons. One comparison involved enhancements of IL-2 therapy. One study compared high-dose IL-2 plus LAK cells with high-dose IL-2 alone. Three other studies examined lower dose IL-2 with the addition of modifiers, including TILs or LAK cells. The authors concluded the response rates in these studies demonstrated no evidence of enhancement for remission, and of the three studies that reported survival, one-year mortality was not reduced.

T-Cell Lymphocytes/Dendritic Cells (DCs)
T-cell (also known as dendritic cell [DC]) adoptive immunotherapy involves isolating the DCs, harvesting and exposing the cells to a variety of immunologic stimuli, then re-infusing the cells back into the patient. This process is also called autolymphocyte therapy. Phase I and II trials have explored the use of DCs in treating hormone-resistant prostate cancer. The studies reported that therapy was well-tolerated and resulted in a reduction of prostate-specific antigen (PSA) levels. The role of antigen-loaded dendritic cells has also been explored for the treatment of other malignancies (e.g., lymphoma, myeloma, subcutaneous tumors, melanoma, renal cell, uterine, cervical and non-small cell lung cancer) and autoimmune disorders, such as type I diabetes mellitus and rheumatoid arthritis.

The benefit of DCs to health outcomes has not been established for any indication except as noted for Sipuleucel-T (Provenge®) in the applicable Cigna Coverage Policy: Oncology Medications. Randomized controlled trials are needed to determine safety and effectiveness, patient eligibility criteria, and treatment
protocols, including optimal dosing, route of delivery, and source of antigens for the treatment of other malignancies and autoimmune disorders, including type I diabetes mellitus and rheumatoid arthritis.

**Literature Review:** Han et al. (2014) reported results of a systematic review and meta-analysis of six randomized controlled trials involving 428 individuals with non-small cell lung cancer. Patients in the control group received chemotherapy alone while the experimental group received chemotherapy combined with DC-cytokine-induced killer cells (CIK) immunotherapy. One-year overall survival (OS) was improved in the chemotherapy combined with DC-CIK immunotherapy group compared to that of the chemotherapy alone group (p=0.02); however, the two-year OS was not significantly different between groups p= 0.21). Likewise, one-year progression-free survival (PFS) was significantly prolonged in the DC-CIK immunotherapy group compared to the chemotherapy alone group (p= 0.005); however, there was no significant difference in two-year PFS (p=0.10). Partial response (PR), overall response rate (ORR) and disease control rate (DCR) were considered to assess treatment efficacy. Analysis of the DCR showed significant improvement for the group receiving combination treatment (p=0.06), but no statistically significant improvement between groups was noted for PR (p=0.22) or ORR (p=0.76). Although data suggest short-term improvement in OS and PFS, longer-term outcomes do not reflect sustained benefit. Additional studies reflecting long-term benefit of DC immunotherapy are needed to establish the role of this therapy for the treatment of NSCLC.

Draube et al. (2011) performed descriptive analyses at a study level and individual patient data level on twenty-nine studies involving the use of immunotherapy with mature monocyte derived dendritic cells or immature monocyte derived dendritic cells in 906 patients with prostate or renal cell cancer (RCC). Three studies were randomized phase II studies; the remaining studies were phase I/II. Analysis at study data level revealed that dendritic cell (DC) vaccination led to an antigen-specific cellular immune response in 77% of patients with prostate cancer and 61% of patients with RCC. Specific humoral immune response was detected in 55% of patients with prostate cancer and no patients with RCC. Overall, objective response (complete response + partial response+ mixed response) was observed in 7.7% of patients with prostate cancer and in 12.7% of patients with RCC. The authors concluded that results demonstrated an association between specific cellular immune response and clinical benefit in both prostate cancer and RCC trials. However, there was heterogeneity regarding DC purity and dose, DC subtype, antigen delivery, route of vaccination and quality controls between the studies. DC immunotherapy warrants further investigation in phase III randomized trials.

Kumura et al. (2008) evaluated the efficacy and toxicity of adjuvant chemo-immunotherapy using autologous dendritic cells and activated killer cells obtained from tissue cultures of tumor-draining lymph nodes for the postsurgical treatment of primary lung cancer (n=28). All patients received four courses of chemotherapy along with immunotherapy every two months for two years. Two and five-year survival rates were 88.9% and 52.9%, respectively. The authors concluded that adoptive transfer of activated killer cells and dendritic cells from the tumor-draining lymph nodes of primary lung cancer patients is safe and feasible, and that a large-scale multi-institutional study is needed to evaluate the efficacy of this treatment.

**Systematic Review of Multiple Adoptive Immune Cells**

Qian et al. (2016) conducted a systematic review and meta-analysis of studies that compared chemoradiotherapy alone to chemoradiotherapy plus adoptive immunotherapy for the treatment of non-small-cell lung cancer (NSCLC). Seven articles met inclusion criteria. The articles included clinical trials that investigated the treatment of NSCLC with adoptive immunotherapy with a mean follow-up longer than two years. Outcomes included: death, tumor recurrence, or metastasis. Studies with a sample size of less than 20 subjects were excluded. There was no significant difference in the two-year progression-free survival (PFS) in the combination of adoptive immunotherapy group and the chemoradiotherapy-alone group (p=0.284). The addition of immunotherapy did improve the two-year overall survival rate (p<0.001) of early stage NSCLC patients (p<0.01) but not for patients with advanced disease (p=0.057). Self-limited adverse effects of immunotherapy included: fever, shivers, nausea, fatigue and retention of water and sodium. Limitations of the studies include: the heterogeneity of the types of adoptive immune cells (LAK, TIL, CIK, cytotoxic T lymphocyte, γδ T cells); the combination regimen of the cells; and the short-term follow-ups. The authors noted that multicenter randomized controlled trials with large patient populations are needed to provide reliable data on which to develop guidelines for clinical practice.

**Professional Societies/Organizations**

**American Cancer Society (ACS):** In a statement regarding tumor infiltrating lymphocyte (TIL) therapy, the ACS noted that some early studies have been promising, but its use may be limited due to the inability to get TILs
from patients. Treatments using TILs are being tested in clinical trials in patients with melanoma, kidney cancer, ovarian cancer, and other cancers (ACS, 2015).

Use Outside of the US
Adoptive immunotherapy is noted to be of research interest in the published, peer-reviewed scientific literature.

Summary
The safety and effectiveness of adoptive immunotherapy using lymphocyte activated killer (LAK) cells, tumor-activated infiltrating lymphocyte (TIL) cells in combination with intravenous interleukin-2 (IL-2), and tumor-specific T-cells have been studied in the clinical setting in patients with metastatic renal cell carcinoma, melanoma, breast cancer and other tumors. Clinical studies have failed to show improved outcomes such as a significant difference in relapse-free intervals or overall survival (OS) with the exception of IL-2 alone. Published studies are limited by small, heterogeneous patient populations, and short term follow-up. Large, high-quality controlled clinical trials reporting long-term outcomes are required before results can be translated into routine clinical practice. Professional society support, in the form of published guidelines is lacking.

Dendritic cells (DCs) have shown promise in inducing anti-tumor immunity in some patients with hormone-resistant prostate cancer and non-small-cell lung cancer. DC therapy has also been explored as a treatment of several autoimmune disorders, including type I diabetes mellitus and rheumatoid arthritis; however, data are primarily limited to animal studies. Safety and effectiveness has not been established in human trials. High-quality randomized clinical trials reporting long-term improvement in progression-free- and overall survival are needed to determine safety, effectiveness, patient selection criteria, and optimal treatment protocol.

There is insufficient evidence in the publishes peer-reviewed literature to support the safety and effectiveness of adoptive immunotherapy techniques utilizing LAL cells, TIL cells, or DCs for any indication except as noted for Sipuleucel-T (Provenge®) in the applicable Cigna Coverage Policy: Oncology Medications.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
   2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Experimental/Investigational/Unproven/Not Covered when used to report the adoptive immunotherapy techniques listed in this Coverage Policy for any indication:

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<td>Adoptive immunotherapy, i.e., development of specific anti-tumor reactivity (e.g. tumor-infiltrating lymphocyte therapy) per course of treatment</td>
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References


