



CIGNA MEDICAL COVERAGE POLICY

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Subject Adoptive Immunotherapy

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Hyperlink to Related Coverage Policies

Aldesleukin (Proleukin®)
Donor Leukocyte Infusion

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA does not cover adoptive immunotherapy for the treatment of human immunodeficiency virus (HIV) infection or any malignancy because it is considered experimental, investigational or unproven. Adoptive immunotherapy techniques include, but are not limited to:

- 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: The use of interleukin 2 (IL-2) for the treatment of renal cell carcinoma, melanoma, leukemia, and HIV infection is addressed in the CIGNA Coverage Policy Aldesleukin (Proleukin®).

General Background

Adoptive immunotherapy involves the removal of lymphocytes from the patient, stimulation of those lymphocytes to increase their immune capabilities, and transfer of those cells back into the patient to fight cancer. 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. Three adoptive

immunotherapy techniques have been explored: lymphocyte activated killer (LAK) cells, tumor Infiltrating lymphocytes (TILs), and T-cell lymphocytes/dendritic cells (DCs).

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. The adoptive transfer of these cells has shown promise in preclinical models, but clinical experiences have been almost uniformly disappointing (Rosenberg, 2001). Newer concepts in tumor immunology have lessened the importance of the continuing debate over the merits of IL-2/LAK therapy.

Dillman et al. (2009) conducted a case series to evaluate the treatment of glioblastoma multiforme (GBM) with adjuvant intralesional LAK cells (n=33). All patients had completed primary therapy for GBM without disease progression. LAK cells were placed into the surgically exposed tumor cavity following incubation of autologous peripheral blood mononuclear cells with interleukin-2. Prior therapy included surgical resection, partial brain irradiation, gamma knife radiosurgery, and temozolomide chemotherapy. The median time from diagnosis to LAK cell therapy was 5.3 months. The treatment was well tolerated, with an average length of hospitalization of three days. The median survival from the day of LAK treatment was 14.5 months, with a one-year post-LAK survival rate of 66%. The authors concluded that LAK therapy is safe and survival encouraging, and that further evaluation in a phase two trial with intralesional therapies with LAK or carmustine-impregnated wafers is warranted.

Thionunn et al. (2002) reported a case series to determine the efficacy and safety of adoptive immunotherapy administered to 17 patients with recurrent superficial bladder cancer following transurethral tumor resection. Macrophage activated killer (MAK) cells were obtained from autologous mononuclear cells harvested by apheresis and activated with interferon gamma. Six weekly intravesical infusions of approximately 2×10^8 cells each were administered. Additionally, five patients received two or three more infusions at three-month intervals. Follow-up was completed at one year or until tumor recurrence. A total of 112 intravesical infusions were performed. During the 12-month follow-up period, eight patients experienced 11 common toxicity criteria grade one or grade two adverse events, considered possibly related to protocol. No clinically relevant grade one or two laboratory test results were reported while the patients received treatment. In 17 patients, eight tumors recurred compared to 34 recurrences during the year before the first MAK cell infusion. This difference was highly significant ($p \leq 0.0005$). The data suggests that the safety and efficacy of MAK cell therapy is promising. Larger controlled studies are needed to confirm these outcomes, however.

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], 2008). Although TIL therapy was previously thought to be a tumor-specific adoptive immunotherapy, it now appears that TILs may be incapable of homing to the tumor deposits, yielding poor clinical results (Figlin, et al., 1999).

A phase II trial conducted by Besser et al. (2010) evaluated the efficacy and toxicity of adoptively transferred, minimally cultured, bulk TIL (Young-TIL) following lympho-depleting chemotherapy in the treatment of metastatic melanoma in patients refractory to interleukin-2 and chemotherapy (n=20). The Young-TIL technique differs from the TIL technique used in previous studies; a technique that is labor-intensive with a high dropout rate. Young-TIL cultures were successfully generated for 90% of the enrolled patients. Response was measured according to the Response Evaluation Criteria in Solid Tumors. An objective clinical response was achieved in 50% of patients., including two ongoing complete remissions (20+, 4+ months) and eight partial responses (progression-free survival, ranging from 18+ to 3 months. Disease stabilization was seen in four additional patients. Side effects were transient and manageable. The authors stated that these clinical results combined with the simplified process may have a major effect on cell therapy of cancer.

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. The data did suggest however, that there may be some correlation between the number of invaded lymph nodes and TIL treatment effectiveness.

Coppin et al. (2005) in a Cochrane review to evaluate immunotherapy for advanced renal cell carcinoma, compared high-dose IL-2 and Interferon-alpha to other options, with a primary outcome of 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 autolympocyte therapy. The adoptive transfer of these immunocompetent T-cells has been studied in both preclinical and clinical settings. 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 use of antigen-loaded dendritic cells has been explored for the treatment of other malignancies, including lymphoma, myeloma, subcutaneous tumors, melanoma, renal cell cancer, and uterine and cervical cancer

Kondo et al. (2008) conducted a case series to evaluate the clinical efficacy of combination adoptive immunotherapy using MUC1 peptide (MUC1-DC) and cytotoxic T lymphocyte sensitized with a pancreatic cancer, YPK-1-expressing MUC1 (MUC1-CTL) for the treatment of unresectable or recurrent pancreatic cancer (n=20). Patients were treated from 2 to 15 times. One patient with multiple lung metastases experienced a complete response, and five patients had stable disease. The mean survival time was 9.8 months. No grade II-IV toxicity was observed. The authors concluded that immunotherapy with MUC1-DC and MUC1-CTL may be a practical, safe and effective treatment for pancreatic cancer, but randomized controlled trials are needed to confirm the efficacy of this combination adoptive immunotherapy.

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 post-surgical 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.

Kim et al. (2007) conducted a phase I/II trial to evaluate the feasibility, toxicity and clinical efficacy of dendritic cells pulsed with autologous tumor lysate and keyhole limpet hemocyanin in patients with renal cell carcinoma following radical nephrectomy (n=9). Clinical response was evaluated according to the World Health Organization criteria. One patient achieved an objective partial response, five showed stable disease, and three patients showed evidence of partial disease soon after one cycle of immunotherapy. With a median follow-up of 17.5 months, the median time to progression was 5.2 months and the median overall survival was 29 months. The treatment was generally well tolerated with no severe side effects reported. The results from this study suggest that treatment with autologous tumor lysate-pulsed dendritic cells may be well tolerated and may be able to induce anti-tumor immunity in patients with metastatic renal cell carcinoma, but larger, well-designed studies are needed. To date, the optimal subset of patients and mode of maturation, as well as the source of dendritic cell antigen and immunomodulator used, and the route, frequency and dose used have not been standardized.

Although initial results are promising, randomized controlled trials are needed to determine efficacy, patient selection and treatment protocols for adoptive immunotherapy using T-cell lymphocytes/dendritic cells.

Professional Societies/Organizations

American Cancer Society (ACS) (2008): According to the ACS, “lymphocyte activated killer (LAK) cell therapy has shown promising results in animal studies, where it caused shrinkage of tumors in animals with lung, liver, and other cancers. While clinical trials in humans have not yet been as successful, researchers are constantly improving LAK cell techniques. They are testing these newly improved methods against melanoma, brain tumors, and other cancers” (ACS, 2008).

In a statement regarding tumor infiltrating lymphocyte (TIL) therapy, the ACS stated “success with TILs in lab animals has led researchers to try to increase the anti-tumor activity of TILs. Treatments using TILs are being tested in clinical trials for people with melanoma, kidney cancer, and other cancers” (ACS, 2008).

Summary

Investigators have administered lymphokine activated killer (LAK), tumor-activated infiltrating lymphocyte (TIL) cells in combination with intravenous interleukin-2 (IL-2), and tumor-specific T-cells to patients with metastatic renal cell carcinoma, melanoma, breast cancer, and other tumors. No modality-based differences have been seen in the duration of relapse-free interval or overall survival. Studies have failed to show that adoptive immunotherapy results in improved outcomes such as a significant difference in relapse-free interval or overall survival beyond that of IL-2 alone. There is insufficient evidence in the peer-reviewed, medical literature to support the use of adoptive immunotherapy in the treatment of human immunodeficiency virus (HIV) or malignancy.

Dendritic cells (DCs) have shown promise in inducing anti-tumor immunity in some cancer patients. Randomized clinical trials are needed, however, to determine efficacy, patient selection criteria, and treatment protocol. Adoptive immunotherapy with DCs remains experimental, investigational or unproven at this time.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
38999 [†]	Unlisted procedure, hemic or lymphatic system

†Note: Experimental, investigational, unproven and not covered when used to report any adoptive immunotherapy technique.

HCPCS Codes	Description
S2107	Adoptive immunotherapy, i.e. development of specific anti-tumor reactivity (e.g., tumor infiltrating lymphocyte therapy) per course of treatment

ICD-9-CM Diagnosis Codes	Description
042	Human immunodeficiency virus [HIV]
140.0-208.91	Malignant neoplasms
209.0-209.79	Neuroendocrine tumors
230.0-234.9	Malignant neoplasms
	All other codes

***Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

References

1. American Cancer Society. Other active specific immunotherapies. Mar 18, 2008. Accessed Oct 12, 2010. Available at URL address: http://www.cancer.org/docroot/ETO/content/ETO_1_4X_Other_Active_Specific_Immunotherapies.asp?s itearea=ETO
2. Benlalam H, Vignard V, Khammari A, Bonnin A, Godet Y, Pandolfino MC, et al. Infusion of Melan-A/Mart-1 specific tumor-infiltrating lymphocytes enhanced relapse-free survival of melanoma patients. *Cancer Immunol Immunother.* 2007 Apr;56(4):515-26.
3. Besser MJ, Shapira-Frommer R, Treves AJ, Zippel D, Itzhaki O, Hershkovitz L, et al. Clinical responses in a phase II study using adoptive transfer of short-term cultured tumor infiltration lymphocytes in metastatic melanoma patients. *Clin Cancer Res.* 2010 May 1;16(9):2646-55. Epub 2010 Apr 20.
4. Besser MJ, Shapira-Frommer R, Treves AJ, Zippel D, Itzhaki O, Schallmach E, et al. Minimally cultured or selected autologous tumor-infiltrating lymphocytes after a lympho-depleting chemotherapy regimen in metastatic melanoma patients. *J Immunother.* 2009 May;32(4):415-23.
5. Clark J, Atkins M, Urba W, Creech S, Figlin R, Dutcher J, et al. Adjuvant high dose bolus interleukin-2 for patients with high risk renal cell carcinoma: a Cytokine Working Group Randomized Trial. *J Clin Oncol.* 2003 August;21(16):3133-40.
6. Coppin, C; Porzsolt, F; Awa, A; Kumpf, J; Coldman, A; Wilt, T. Immunotherapy for advanced renal cell cancer. *Cochrane Database Syst Rev.* 2005 Jan 25;(1):CD001425. Updated May 18, 2006.
7. Dillman RO, Duma CM, Ellis RA, Cornforth AN, Schiltz PM, Sharp SL, DePriest MC. Intralesional lymphokine-activated killer cells as adjuvant therapy for primary glioblastoma. *J Immunother.* 2009 Nov-Dec;32(9):914-9
8. Dreno B, Nguyen J, Khammari A, Pandolfino M, Tessier M, Bercegeay S, et al. Randomized trial of adoptive transfer of melanoma tumor infiltrating lymphocyte as adjuvant therapy for stage III melanoma. *Cancer Immunol Immunother.* 2002 Sep;51:539-46.
9. Dunn G, Oliver K, Loke D, Stafford N, Greenman J. Dendritic cells and HNSCC:A potential treatment option? (Review). *Oncol Rep.* 2005 Jan;13: 3-10.

10. Figlin R, Thompson J, Bukowski R, Vogelzang N, Novick A, Lange P, et al. Multicenter, randomized, phase III trial of CD8(+) tumor infiltrating lymphocytes in combination with recombinant IL-2 in metastatic renal cell carcinoma. *J Clin Oncol*. 1999 Aug;17(8):2521-9.
11. Hoffman: *Hematology: Basic principles and practice*, 5th ed. Churchill Livingstone, an imprint of Elsevier; 1008.
12. Kasslin AA, Neelapu SS, Kwak LW, Van Kaer L. Immunotherapy. In: Greer JP, Foerster J, Rodgers GM, Paraskevas F, Glader B, Arber DA, Means RT, editors. *Wintrobe's clinical hematology*. Lippincott Williams & Wilkins; 2009.
13. Khammari A, Nguyen JM, Pandolfino MC, Quereux G, Brocard A, Bercegeay S, et al. Long-term follow-up of patients treated by adoptive transfer of melanoma tumor-infiltrating lymphocytes as adjuvant therapy for stage III melanoma. *Cancer Immunol Immunother*. 2007 Nov;56(11):1853-60.
14. Kim JH, Lee Y, Bae YS, Kim WS, Kim K, Im HY, et al. Phase I/II study of immunotherapy using autologous tumor lysate-pulsed dendritic cells in patients with metastatic renal cell carcinoma. *Clin Immunol*. 2007 Dec;125(3):257-67.
15. Kimura H, Iizasa T, Ishikawa A, Shingyouji M, Yoshino M, Kimura M, Inada Y, Matsubayashi K. Prospective phase II study of post-surgical adjuvant chemo-immunotherapy using autologous dendritic cells and activated killer cells from tissue culture of tumor-draining lymph nodes in primary lung cancer patients. *Anticancer Res*. 2008 Mar-Apr;28(2B):1229-38.
16. Kondo H, Hazama S, Kawaoka T, Yoshino S, Yoshida S, Tokuno K, Takashima M, Ueno T, Hinoda Y, Oka M. Adoptive immunotherapy for pancreatic cancer using MUC1 peptide-pulsed dendritic cells and activated T lymphocytes. *Anticancer Res*. 2008 Jan-Feb;28(1B):379-87.
17. Kono K, Takahashi A, Ichihara F, Amemiya H, Iizuka H, Fuji H, et al. Prognostic significance of adoptive immunotherapy with tumor associated lymphocytes in patients with advanced gastric cancer: a randomized trial. *Clin Cancer Res*. 2002 Jun;8(6):1767-71.
18. Lange JR, Fecher LA, Sharfman WH, Alani RM, Mikkilineni R, Topalian SL, et al. Melanoma. In: Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE, editors. *Clinical oncology*. New York, NY: Churchill Livingstone; 2008.
19. Mackensen A, Meidenbauer N, Vogl S, Laumer M, Berger J, Andreesen R. Phase I study of adoptive T-cell therapy using antigen-specific CD8+ T cells for the treatment of patients with metastatic melanoma. *J Clin Oncol*. 2006 Nov 1;24(31):5060-9.
20. Mitchell M, Darrah D, Yeung D, Halpern S, Wallace A, Volland J, et al. Phase 1 trial adoptive immunotherapy with cytolytic lymphocytes immunized against a tyrosine epitope. *J Clin Oncol*. 2002 Feb;20(4):1075-86.
21. Nencioni A, Brossart P. Cellular immunotherapy with dendritic cells in cancer: current status. *Stem Cells*. 2004;22(4):501-13.
22. Ribas A, Butterfield L, Glaspy J, Economou J. Current developments in cancer vaccines and cellular Immunotherapy. *J Clin Oncol*. 2003 Jun;21(12):2415-32.
23. Rosenberg S, Lotze M, Yang J, Topalian S, Chang A, Schwartzentruber D, et al. Prospective randomized trial of high dose interleukin-2 alone or in conjunction with lymphokine activated killer cells for the treatment of patients with advanced cancer. *J Natl Cancer Inst*. 1993 Apr;85(8):622-32.
24. Sereti I, Lane H. Immunopathogenesis of human immunodeficiency virus: implications for immune based therapies. *Clin Infect Dis*. 2001 Jun; 32(12):1738-55.

25. Thiounn N, Pages F, Mejean A, Descotes JL, Fridman WH, Romet-Lemonne JL. Adoptive immunotherapy for superficial bladder cancer with autologous macrophage activated killer cells. J Urol. 2002 Dec;168(6):2373-6.
26. Tuma R, Giannino R, Guirnalda P, Leiner I, Pamer E. Rescue of CD8 T cell mediated antimicrobial immunity with a nonspecific inflammatory stimulus. J Clin Invest. 2002 Nov;110(10):1493-501.

Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	11/15/2007	0225	Adoptive Immunotherapy

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.