



CIGNA HEALTHCARE COVERAGE POSITION

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Subject Adoptive Immunotherapy

Table of Contents

Coverage Position.....	1
General Background	1
Coding/Billing Information	5
References.....	5

Hyperlink to Related Coverage Positions

[Aldesleukin \(Proleukin®\)](#)

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Coverage Position

CIGNA HealthCare 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-activated infiltrating lymphocytes (TILs)
- antigen-loaded dendritic cells

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

General Background

Adoptive immunotherapy is based on the idea that the immune system can delay tumor growth. Treatment of malignancies with adoptive immunotherapy involves the removal of lymphocytes from the patient, the stimulation of those lymphocytes to increase their immune capabilities, and the transfer of those cells back into the patient to fight the 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 exploit adoptive immunotherapy fully have not been completely defined. Three adoptive immunotherapy techniques have been explored.

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.

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 activation with interferon gamma on the last day of culture. The patients received six weekly intravesical infusions of approximately 2×10^8 cells each. Additionally, five patients received two or three more infusions at three-month intervals. Each patient was followed for 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, but larger, controlled studies are needed to confirm these outcomes.

Rosenberg et al. (1993) conducted a randomized, controlled trial (RCT) designed 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. The 181 patients who had metastatic cancer who had failed to respond to standard therapy or who had a disease for which no effective therapy existed received treatment with high-dose IL-2 alone or with LAK cells plus IL-2. Both treatment groups were to receive the same dose of IL-2 administered according to the same schedule. IL-2 doses were omitted depending on the tolerance of the patient. Of the 181 patients, 97 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%). None of 26 patients with melanoma who received IL-2 alone were alive at the end of the study; five of 28 who received IL-2 plus LAK cells were alive, and three continue 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 they are treated with high-dose IL-2 alone or in conjunction with LAK cells. The authors suggest 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. As studies continue, efforts are underway to develop improved immunotherapy using tumor infiltrating lymphocytes (TIL) and gene modified TIL.

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], 2005). 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).

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.

Dreno et al. (2003) reported the results of an RCT 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.

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 reinfusing the cells back into the patient. 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. Initial results are promising, but RCTs are needed to determine efficacy, patient selection and treatment protocol.

Mackensen et al. (2006) reported on a phase I study to test the feasibility, safety, and survival of adoptively transferred Melan-A-specific cytotoxic T lymphocytes (CTL) in melanoma patients. Eleven patients with metastatic melanoma received at least three and up to 10 infusions of Melan-A-specific CTL at two-week intervals. A six-day course of interleukin-2 was given along with each infusion. Adverse effects were reported as mild and included chills and low-grade fever in seven of the patients. No changes in total lymphocyte counts or signs of autoimmunity were reported. Anti-tumor response was reported in three of the 11 patients: one complete regression, one partial regression, and one mixed response (complete regression of one metastatic lesion but progressive disease of one other metastasis). An increase in eosinophil count up to 51% was observed in seven of 11 patients and an elevated frequency of circulating Melan-A tetramer+ T cells up to two weeks in all patients were noted. This study suggested that adoptive transfer of antigen-specific CTL after *in vitro* stimulation with antigen-pulsed DC may be a safe and promising therapy for patients with malignant disease. Study limitations included small sample size, lack of control and the varying number of treatments received by patients.

Nencioni et al. (2005) conducted a literature review to evaluate the induction of antigen-specific immune responses by DCs generated *ex vivo* from peripheral blood monocytes or bone marrow/circulating hematopoietic stem cells cultured in the presence of cytokine cocktails. DCs have been used in numerous clinical trials to induce antitumor immune responses in cancer patients. The studies carried out to date have demonstrated that DCs pulsed with tumor antigens can be safely administered, and this approach produces antigen-specific immune responses. Clinical responses have been observed in a minority of patients. The authors reported it is likely that either heavy medical pretreatment or the presence of large tumor burdens (or both) are among the causes that impair the effectiveness. Hence, the use of DCs should be considered in earlier stages of disease such as the adjuvant setting. Prospective applications of DCs extend to their use in allogeneic adoptive immunotherapy to specifically target the graft versus tumor reaction. DCs continue to hold promise for cellular immunotherapy, and further investigation is required to determine the clinical settings in which patients will benefit most from the use of this cellular immune adjuvant.

Dunn et al. (2005) reported a literature review to assess the number of strategies for patient survival in head and neck squamous cell cancer (HNSCC). One of the strategies is the use of DCs, natural antigen presenting cells capable of stimulating an anti-tumor immune response. The authors report that encouraging work has been performed using these cells as vaccines against a number of tumors, especially melanoma. DC presence in head and neck squamous cell cancers is associated with an improved prognosis; however, due to immunosuppression, these cells do not function efficiently. This prevents the stimulation of an effective antitumor immune response by the patient and allows tumor

growth to continue. The authors reported that as immunodeficiency in cancer patients is multifactorial, it is likely that a combination of approaches to overcome this will be most successful. The current level of knowledge has identified several potential areas on which to base immunotherapy (e.g., increasing DC levels; restoring function and/or pulsing DC with tumor antigens). According to the authors, it is likely that, initially, such immunotherapeutic methods may be helpful as an adjunct to conventional treatment, with the ultimate goal being to harness the immune system as a primary treatment for HNSCC.

Mitchell et al. (2002) conducted a phase 1 (i.e., initial safety) trial to study distribution and toxicity of cytolytic T lymphocytes (CTLs) against a single melanoma epitope. Cluster of differentiation antigen 8 (CD8) T-cells obtained by leukapheresis from 10 patients with melanomas were immunized *in vitro*. *Drosophila* cells transduced intracellular adhesion molecules were used for priming, followed by two rounds of immunization with mononuclear cells as antigen presenting cells. CTLs were infused intravenously (IV) on day one. CTL frequency was measured by limiting dilutions in five patients. Indium 111 (¹¹¹In) labeling and scintigraphy measured distribution of CTL in the next five patients. Five days later, CTLs were infused on four successive days to both groups. Immunohistology of response was judged by biopsies. Infusions were nontoxic. CTLs were undetectable in blood, going to lungs within five minutes. At four, 24, and 72 hours, they were found in the liver and spleen. Lesions were visualized by scintiscans in one responding patient where two subcutaneous nodules were noted at four and 24 hours. A second patient had a partial response and remains alive with disease two years later. CD8 T-cells were found in lesions of responders. Two nonresponders had few CD8 T-cells in their lesions. Whether the CD8 T-cells in lesions of responders were those that were reinfused is uncertain. This study suggested that CTLs immunized against a single melanoma epitope were nontoxic but did not specifically localize to tumor sites. Nevertheless, two patients had disease regression. Additional therapeutic studies with specifically immunized CTL are warranted.

Sereti et al. (2001) reported in review of literature supported by the National Institutes of Health that human immunodeficiency virus (HIV) infection leads to a state of CD4 lymphopenia and generalized immune activation with subsequent development of opportunistic infections and neoplasms. Immune-based therapies, such as treatment with adoptive immunotherapy, are being investigated as potential supplements to antiretroviral therapy. Although these efforts have generated considerable data, there has been little evidence to date of the clinical efficacy of these strategies. RCTs remain critical in evaluating the clinical significance and the role of immune-based therapies in the therapeutic armamentarium against HIV.

According to the National Institutes of Health (NIH) clinical trials database, there are a number of phase 1 and phase 11 trials regarding the use of immunotherapy in malignancies in the early stages (NIH, 2007).

Professional Societies/Organizations

According to the ACS, "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) (2006).

In their statement regarding TIL therapy, the ACS stated that "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, 2006).

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 significant difference in relapse-free interval or overall survival beyond that of IL-2 alone.

Adoptive immunotherapy remains in the investigational stage (Smith, et al., 2003). There is insufficient evidence in the peer-reviewed, scientific literature to support the use of adoptive immunotherapy in the treatment of human immunodeficiency virus (HIV) or cancer.

Dendritic cells (DCs) have shown promise in inducing anti-tumor immunity in some cancer patients. Randomized clinical trials are needed to determine efficacy, patient selection 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
	No specific codes

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]
	Multiple/varied

*Current Procedural Terminology (CPT®) ©2006 American Medical Association: Chicago, IL.

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