Medical Policy
Adoptive Immunotherapy

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Policy Number: 455
BCBSA Reference Number: 8.01.01
NCD/LCD: N/A

Related Policies
- Donor Leukocyte Infusion for Malignancies Treated with Hematopoietic Stem-cell Transplant, #338
- Melanoma Vaccines, #453
- Cellular Immunotherapy for Prostate Cancer, #268

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Adoptive immunotherapy, using adoptive cellular therapy for the administration of cytotoxic T-lymphocytes, cytokine-induced killer cells, tumor-infiltrating lymphocytes, antigen-loaded autologous dendritic cells, or genetically-engineered T-cells is considered INVESTIGATIONAL.

Kymriah™ (tisagenlecleucel), a type of CAR-T cell therapy, is considered INVESTIGATIONAL.

Other applications of adoptive immunotherapy are considered INVESTIGATIONAL.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th></th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>(HMO and POS)</td>
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<tr>
<td>Commercial PPO and</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Indemnity</td>
<td></td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>This is not a covered service.</td>
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</table>
CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following HCPCS code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>S2107</td>
<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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Description

Adoptive immunotherapy uses “activated” lymphocytes as a treatment modality. 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. Initially, this was done by harvesting peripheral lymphokine-activated killer cells and activating them in vitro with the T-cell growth factor interleukin-2 (IL2) 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 that have been pulsed with tumor antigens. Alternatively, innate tumorinfiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with IL-2 and anti-CD3 antibody, a T-cell activator. 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.

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 (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.” 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 ELISA
4. lymphodepletion of the host with immunosuppressive agents
5. adoptive transfer (ie, transfusion) of lymphocytes back into the tumor-bearing host.

Dendritic cell-based immunotherapy uses autologous dendritic cells (ADC) to activate a lymphocytomediated 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 retransfused 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. (See Related Policies links for dendritic cell-based immunotherapy for prostate cancer.)

In an attempt to further regulate the host immune system, recent protocols use 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.

Note: Allogeneic stem 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 stem 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.

Summary
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.

The evidence for adoptive immunotherapy in patients who have various types of cancer includes randomized controlled trials (RCTs) for many of the cancers, nonrandomized comparative studies, and uncontrolled trials. Relevant outcomes are overall survival, disease-specific survival, and treatment related morbidity. Clinical studies using adoptive immunotherapy are primarily small, early-stage investigations for a variety of cancers. The available RCTs are from non-U.S. centers in heterogeneous patient populations and interventions, and have methodologic shortcomings that limit conclusions. Studies of cytotoxic T lymphocytes, lymphokine-activated killer cells, tumor-infiltrating lymphocytes, autologous dendritic cells, and genetically engineered T cells suggest that some adoptive immunotherapies may improve outcomes in some cancer types. However, the impact of adoptive immunotherapy on patient outcomes (eg, increased survival, improved quality of life) has yet to be clarified in large RCTs. Specifically, high-quality RCTs with adequate follow-up are needed to show that there is a significant survival advantage for adoptive immunotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
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<tr>
<td>10/2017</td>
<td>Statement added to clarify that Kymriah™ (tisagenlecleucel) is considered investigational.</td>
</tr>
<tr>
<td>5/2016</td>
<td>BCBSA National medical policy review.</td>
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<tr>
<td></td>
<td>Section on lymphokine-activated killer cell deleted due to obsolete intervention.</td>
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<tr>
<td></td>
<td>Effective 5/1/2016.</td>
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<tr>
<td></td>
<td>New investigational indications described.</td>
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<td></td>
<td>Effective 5/1/2015.</td>
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<tr>
<td>6/2013</td>
<td>The wording of the policy statement under adoptive cellular therapy was changed to include cytokine-induced killer (CIK) cells; however, the intent of both policy statements (i.e., investigational) is unchanged. Effective 6/1/2013.</td>
</tr>
<tr>
<td></td>
<td>No changes to policy statements.</td>
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<tr>
<td>1/17/2012</td>
<td>BCBSA National medical policy review.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References


