Medical Policy Manual

**Topic:** Adoptive Immunotherapy  
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**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**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 or from a donor, processed for some period of time, and then infused into the patient.

**Background**

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 (IL-2) and other cytokines. More recent techniques have yielded select populations of cytotoxic T lymphocytes (CTLs) 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 tumor-infiltrating 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.[1]

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, two 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.”[2] 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 lymphocyte-mediated 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.

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. Please see Cross Reference section below.

**MEDICAL POLICY CRITERIA**

Notes:
- Non-cellular based immunotherapies, including but not limited to IL-2 monotherapy or in combination with other cytokines have been approved by the US Food and Drug Administration (FDA) for the treatment of various malignancies and are addressed in Pharmacy policies. Please see Cross Reference section below.
This policy does not address FDA-approved adoptive immunotherapy, also known as Sipuleucel-T (Provenge®) therapy, to treat asymptomatic or minimally symptomatic, androgen-independent (castration-resistant), metastatic prostate cancer. Provenge® is addressed in the Pharmacy policy, dru216. Please see Cross Reference section below.

I. 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.

II. Other applications of adoptive immunotherapy are considered investigational.

POLICY GUIDELINES

Autologous lymphocytes used as part of adoptive immunotherapy may be harvested in a pheresis procedure or may be isolated from resected tumor tissue.

SCIENTIFIC EVIDENCE

LITERATURE APPRAISAL

Systematic Reviews of Adoptive Immunotherapy Modalities for Various Types of Cancer

Gastric Cancer

In 2015 Shen et al. conducted a systematic review and meta-analysis to evaluate the efficacy and safety of adoptive immunotherapy for the treatment of gastric cancer, including 829 patients from nine small Chinese controlled trials. The adoptive cellular treatments utilized in the trials were: cytokine induced killer (CIKs) (six studies), DC-CIKs (one study), expanded activated autologous lymphocytes (EAALs) (one study) and tumor associated lymphocytes (TALs). In the overall analysis, OS was significantly better in the treated group (OR of 2.64 (95% CI: 2.20–3.18; p < 0.001) and PFS was also significantly improved in the treated group (OR: 3.01; 95% CI: 2.15–4.22; p < 0.001). This improvement remained significant up to five years post-treatment. In addition, increased percentages of CD3+ (MD: 7.76; 95% CI: 2.41–13.12; p < 0.001), CD4+ (MD: 6.40; 95% CI: 2.51–10.29; p < 0.001) and CD4+/CD8+ ratios (MD: 0.38; 95% CI: 0.19–0.56; p < 0.001) were observed in the treated groups compared to controls. The reviewers concluded that although immunotherapy show promise as a treatment modality for gastric cancer, further research on the specific regimens, timing of the immunotherapy, dosage and target antigens are required.

Non-Small Cell Lung Cancer

In 2016 Qian et al. published a meta-analysis of controlled trials to compare the efficacies between adoptive immunotherapy combined chemoradiotherapy and chemoradiotherapy alone in Chinese patients with non-small-cell lung cancer (NSCLC), including seven comparative studies (n=59-339). Adoptive therapy treatments included CIKs (three studies), DC-CIKs (two studies), lymphokine activated killer cells (one study) and tumor infiltrating lymphocytes (one study). Meta-analyses showed that compared with chemoradiotherapy alone, adoptive immunotherapy combined with chemoradiotherapy could improve the 2-year overall survival [odds ratio (OR)=2.45, 95% confidence interval (CI): 1.60-3.75, p<0.001], but not 2-year progression-free survival (OR=1.81, 95% CI: 0.61-
Early stage (OR=3.32, 95% CI: 1.38-7.95, p<0.01) but not advanced (OR=3.75, 95% CI: 0.96-14.68, p=0.057) NSCLC patients were likely to benefit from the adoptive immunotherapy. Most of the adoptive immunotherapy-induced adverse effects were self-limited, mainly including fever, shiver, nausea, and fatigue; and severe toxicities were not observed.

Renal Cell Carcinoma

In 2013, Tang et al. published a meta-analysis of randomized controlled trials (RCTs) to investigate the efficacy of adoptive immunotherapy in patients with metastatic renal cell carcinoma.[5] Four RCTs (three studies published between 1990 and 1999, a fourth study by Liu et al. published in 2012 [discussed below]) met inclusion criteria (total N=469); three RCTs were conducted in the United States and one was conducted in China. Interventions included cytokine-induced killer (CIK) cells, lymphokine-activated killer (LAK) cells, and tumor-infiltrating lymphocytes (TIL). Most adoptive immunotherapy-related adverse reactions were grade 1 or 2 and reversible. In meta-analysis, outcomes were superior for patients treated with adoptive immunotherapy compared with no adoptive immunotherapy, including rates of objective response (pooled risk ratio [RR], 1.65; 95% confidence interval [CI], 1.15 to 2.38; p=0.007; I²=49%), 1-year survival (pooled RR=1.30; 95% CI, 1.12 to 1.52; p<0.001; I²=0%), 3-year survival (RR=2.76; 95% CI, 1.85 to 4.14; p<0.001; I²=46%), and 5-year survival (RR=2.42; 95% CI, 1.21 to 4.83; p=0.01; I²=28%). Heterogeneity across studies was acceptable. However, limitations of the review included varying adoptive immunotherapy protocols and lack of clear descriptions of randomization methods, allocation concealment, blinding, and withdrawals, which may lead to distribution and implementation bias in this meta-analysis.

Hepatocellular Carcinoma

In 2012, Xie et al. performed a meta-analysis of RCTs comparing adoptive immunotherapy with no adjuvant treatment in patients with hepatocellular carcinoma who had undergone curative resection.[6] Six RCTs (published between 1995 and 2009; total N=494) met inclusion criteria. All six trials were conducted in Asia (four in China, two in Japan), with two studies published in the Chinese language. Two trials used CIK cells as adoptive immunotherapy, one used CIK cells plus interleukin-2 (IL-2), and the remaining three used LAK plus IL-2. Outcome measures were 1- and 3-year recurrence and survival rates. Meta-analysis revealed a significantly reduced risk of both 1-year recurrence (odds ratio [OR], 0.35; 95% CI, 0.17 to 0.71; p=0.003), and 3-year recurrence (OR=0.31; 95% CI, 0.16 to 0.61; p=0.001) in patients receiving adoptive immunotherapy. However, no statistically significant difference was observed in 3-year survival rates between the two study groups (OR=0.91; 95% CI, 0.45 to 1.84; p=0.792). It is difficult to reach any conclusions regarding the results of this meta-analysis given the treatment context of the studies, variation in immunotherapy regimens, limited sample size and follow-up period, and low-to-moderate methodological quality of the included trials.

In 2012, Zhong et al. also performed a systematic review of RCTs to evaluate the clinical efficacy of adjuvant adoptive immunotherapy for postoperative patients with hepatocellular carcinoma.[7] Four RCTs (published between 1995 and 2009; total N=423) met inclusion criteria. As with the Xie meta-analysis discussed above,[6] all four trials were conducted in Asia. Three (of four) trials in this review also were included in the Xie meta-analysis. Primary outcomes evaluated in this review were overall survival (OS), disease-free survival (DFS), and recurrence rates. The secondary outcome was adverse effects of treatment/toxicity. Owing to clinical heterogeneity (including operation methods, dose, and type of cytokines) across studies, meta-analysis was not performed. All RCTs reported significantly improved DFS or reduced recurrence rate after treatment with adjuvant adoptive immunotherapy (p<0.05). However, no statistically significant differences were observed in OS between study groups.
across the three trials reporting this outcome. The main adverse effect of adoptive immunotherapy was fever (persistent or transient), reported in three (of four) trials. Conclusions of this systematic review are subject to similar limitations as with the above meta-analysis by Xie et al.

Section Summary: Systematic Reviews of Adoptive Immunotherapy Modalities

Several systematic reviews evaluating RCTs provide limited evidence for improved health outcomes with adoptive immunotherapy due to heterogeneity of adoptive immunotherapy methods, low methodological quality of included trials, and restricted applicability of the findings. In gastric cancer, immunotherapy combined with chemotherapy significantly prolonged OS compared to controls treated with either chemotherapy alone or with another treatment modality. In NSCLC, OS was improved when adoptive immunotherapy was combined with chemotherapy, compared to chemotherapy alone; and these improvements were observed in early stage NSCLC but not advanced stage. In addition, 2-year PFS was similar between treatments. In hepatocellular carcinoma, recurrence rates and DFS were improved with various adoptive immunotherapy treatments compared with controls, but not OS. In renal cell carcinoma, objective response and 1-, 3-, and 5-year survival were improved with various adoptive immunotherapy treatments compared with controls. However, well-designed RCTs with rigorous methods and larger sample sizes are needed to determine efficacy.

Cytotoxic T Lymphocytes (CTLs)

The use of cytotoxic T lymphocytes (CTLs) for adoptive immunotherapy is still in its early stages, with only phase 1/2 trials underway. The body of published evidence for the use of CTLs for adoptive immunotherapy limited to noncomparative studies for various cancers. These studies are described below.

Epstein-Barr Virus–Associated Cancers

In 2014, Bollard et al. conducted an international prospective cohort study of CTL therapy in patients with Epstein-Barr virus (EBV)–positive Hodgkin or non-Hodgkin’s lymphoma.\(^8\) Patients had either active, relapsed disease (n=21) or were in remission with high risk of relapse (n=29). CTLs with activity against EBV antigens were generated by incubating peripheral blood monocytes with EBV antigen-infected dendritic cells. Eleven (52%) of 21 patients with active disease achieved complete response, and two patients (10%) achieved partial response; 2-year event-free survival in this cohort was approximately 50%. Twenty-seven (93%) of 29 patients in remission achieved complete response; 2-year event-free survival was 82%. Immediate or delayed toxicity related to CTL infusion was not observed.

In 2014, Chia et al. studied 35 patients with EBV-positive nasopharyngeal cancer at a single center in China.\(^9\) Patients received standard chemotherapy with gemcitabine and carboplatin followed by EBV-specific CTL infusion. Median progression-free and OS were eight months and 30 months, respectively. One-, 2-, and 3-year OS was 77%, 63%, and 37%, respectively. In comparison, median OS in a group of similar historical controls treated at the same institution with chemotherapy only was 18 to 21 months, and 2- and 3-year OS was 30% to 43% and 16% to 25%, respectively. The most common adverse events associated with CTL infusion were grade 1 and 2 fatigue and grade 1 myalgia. Two patients developed transient fever, and three patients developed grade 1 skin rash. Grade 3 or higher hematological or nonhematological toxicities were not observed during CTL therapy. In a Japanese series of 7 patients who received CTLs for advanced oral and maxillofacial cancers, 1-year survival in patients who
achieved response (n=3) and in those with progressive disease (n=4) were 100% and 25%, respectively, although definitions of response were unclear.[10]

Cytomegalovirus-Associated Cancers

In 2014, Schuessler et al. administered CTLs with or without chemotherapy to 13 patients with recurrent glioblastoma multiforme.[11] CTLs with activity against cytomegalovirus were generated by incubating peripheral blood monocytes with synthetic peptide epitopes. Median OS was 1.1 years (range, 4.4 months to 6.6 years). Adverse events were minor.

Section Summary: Cytotoxic T Lymphocytes

Small, prospective cohort studies in patients with relapsed disease indicated response to infused CTLs directed against cancer-associated viral antigens. Adverse events were mild or moderate. Although a single-center study in Chinese patients with nasopharyngeal cancer reported improved survival compared with historical controls. RCTs are needed to demonstrate net health benefit of CTL therapy.

Cytokine-Induced Killer Cells (CIKs)

To date, cytokine-induced killer cells (CIKs) have been the most common cell type used for adoptive immunotherapy, and have been studied for the largest number of indications. There are several U.S. clinical trials underway for various indications. This evidence review will focus on published comparative studies, including RCTs, evaluating the use of CIKs for adoptive immunotherapy for various indications. These studies are described below.

Lymphomas

In 2016 Wu et al. performed a case-control study of 170 elderly patients with B-cell malignant lymphomas to evaluate health outcomes from CIK-IL2 treatment with standard care in China.[12] Eighty-five elderly patients with B-cell malignant lymphoma were treated with CIK+IL-2, and 85 elderly patients not receiving CIK+IL-2 treatment served as controls. The patients in CIK+IL-2 group and control group were divided into four subgroups according to lymphoma types: diffuse large B cell lymphoma, mucosa-associated lymphoid tissue type, lymphoplasmacytic lymphoma and Hodgkin's lymphoma (HL). The levels of immune markers post-treatment in the four subgroups of CIK+IL-2 group were higher than levels before treatment and the control group post-treatment (p<0.05). The survival time of patients in the CIK+IL-2 group (median 22.36±5.38 months) was significantly longer than the control group (median 16.15±3.62 months).

Nasopharyngeal Carcinoma

In 2012, Li et al. conducted an RCT to evaluate the efficacy of autologous CIK transfusion in combination with gemcitabine and cisplatin (GC) chemotherapy to treat nasopharyngeal carcinoma in patients with distant metastasis after radiotherapy.[13] From September 2007 to August 2008, 60 patients with distant metastasis after radiotherapy were followed up in a university cancer center in China. Patients were randomly divided into two groups; 30 patients in the GC+CIK group received adoptive autologous CIK cell transfusion in combination with GC chemotherapy, and 30 patients in the GC group received chemotherapy alone. One- and 2-year OS were 90% (27/30) and 70% (21/30), respectively, in the GC+CIK group versus 83% (25/30) and 50% (15/30), respectively, in the GC group. Mean OS was 31 months for the GC+CIK group and 26 months for the GC group (log-rank test, p=0.137). Median
PFS was 26 months for the GC+CIK group and 19 months for the GC group (log-rank test, \(p=0.023\)). This small, single-center RCT indicates that the combination of CIK cells and GC regimen chemotherapy may be a viable treatment option for patients with advanced nasopharyngeal carcinoma.

Renal Cell Carcinoma

In 2015, Zhao et al. conducted an RCT in China among operable and inoperable patients with renal cell carcinoma.\[14\] Dendritic cells were also incorporated into treatment. Among the 60 operable patients, the 3-year DFS was 96.7% compared with 57.7% in the control group. PFS was also better in the CIK group (\(p=0.021\)). Among the 62 inoperable patients, OS was better in the CIK group (\(p=0.012\)). There were no severe adverse reactions observed.

In 2013, Zhang et al. conducted a small RCT in China with 20 patients who had unilateral, locally advanced renal cell carcinoma after nephrectomy.\[15\] Patients were randomized 1:1 to postoperative CIK therapy or usual care (chemotherapy with or without radiation therapy, additional surgery, or no further treatment). Method of randomization was not described. At a median follow-up of 44 months, six patients in the CIK group and five controls achieved complete response; two patients in the CIK group and no controls achieved partial response (overall objective response, 80% vs 50% in the CIK and control groups, respectively; Fisher exact test, \(p=0.175\)). Mean PFS was significantly longer in the CIK group, but OS was not (mean PFS, 32 months vs 22 months; log-rank test, \(p=0.032\); mean OS, 35 months vs 34 months; log-rank test, \(p=0.214\)). Adverse events included mild arthralgia, laryngeal edema, fatigue, and low-grade fever in three patients. Grade 3 or higher adverse events were not observed.

In 2012, Liu et al. conducted an RCT to evaluate the effects of autologous CIK cell immunotherapy in patients with metastatic renal cell carcinoma followed up in another university cancer center in China.\[16\] From June 2005 to June 2008, 148 patients were randomized to autologous CIK cell immunotherapy (arm one, \(n=74\)) or IL-2 treatment combination with human interferon-α-2a (arm two, \(n=74\)). The primary end point was OS, and the secondary end point was PFS evaluated by Kaplan-Meier analyses and hazard ratios (HRs) with Cox proportional hazards models. Three-year PFS and OS in arm one were 18% and 61%, respectively, versus 12% and 23%, respectively, in arm two (\(p=0.031\) and <0.001, respectively). Median PFS and OS in arm one were significantly longer than those in arm two (PFS, 12 vs 8 months, \(p=0.024\); OS, 46 vs 19 months, \(p<0.001\)). Multivariate analyses indicated that the cycle count of CIK cell immunotherapy as a continuous variable was significantly associated with prolonged PFS (HR=0.88; 95% CI, 0.84 to 0.93; \(p<0.001\)) and OS (HR=0.58; 95% CI, 0.48 to 0.69; \(p<0.001\)) in arm 1. These findings suggest that CIK cell immunotherapy has the potential to improve the prognosis of patients with metastatic renal cell carcinoma.

Gastric Cancer

Systematic Review

In 2016, Liu et al. published a meta-analysis of controlled trials to investigate the efficacy of CIKs in patients with gastric cancer, including six clinical trials with case-control studies (N= 318 patients receiving CIK cell therapy and 369 patients receiving conventional therapy).\[17\] Included studies were all written in Chinese and ranged in size from 27 to 165 patients. Overall survival (OS) and odds ratio (OR) were analyzed for patients at 1, 2, 3, and 5 years post-CIK cell therapy and post-conventional therapy. Conventional therapy differed between the trials, and included chemotherapy, palliative gastrectomy, 5-FU or 5-HT receptor therapy. CIK cell therapy significantly increased 5-year OS from 27±2.44% to
49±7.62% (p=0.03) and 5-year OR up to 1.77 (p=0.001). The increased 5-year survival rate was also highly correlated with the increased CD3+ T cell number (weighted mean difference [WMD] = 15.43 [95% CI: 5.45–25.41, p=0.002]) and ratio of CD4+/CD8+ (0.44 [95% CI: 0.32–0.56, p < 0.001]) in the CIK treated patients. The heterogeneity between studies and the publication bias were considered low. Adverse events were not addressed. The reviewers concluded that trials of larger sample size are required to obtain more conclusive results regarding the efficacy. In addition, all six clinical trials were reported in China, and data from other countries is still lacking.

Nonrandomized Study

In 2012, Shi et al. published a nonrandomized, comparative study to determine the long-term efficacy of adjuvant immunotherapy with autologous CIK cells in 151 patients with locally advanced gastric cancer.[18] Five-year OS and 5-year DFS for immunotherapy versus no immunotherapy (control group) were 32% versus 23% (p=0.07) and 28% versus 10% (p=0.04), respectively. For patients with intestinal-type tumors, 5-year OS and DFS were significantly higher for immunotherapy (OS, 47% vs 31%; p=0.045; DFS, 42% vs 16%, p=0.02). Larger and well-designed multicenter studies are needed to confirm these findings.

Hepatocellular Carcinoma

In 2015, Lee et al. conducted an RCT in Korea of 230 patients being treated for hepatocellular carcinoma by surgical resection, radiofrequency ablation, or percutaneous ethanol injection.[19] Patients were randomized 1:1 to receive adjuvant CIK cell injections 16 times during 60 weeks or no adjuvant therapy. The primary end point was recurrence-free survival; secondary end points included OS and cancer-specific survival. The median recurrence-free survival was 44 months in the CIK group and 30 months in the control group (p=0.010). OS was longer in the CIK group than in the control group (HR=0.21, p=0.008). Cancer-specific survival was longer in the CIK group than in the control group (HR=0.19, p=0.02). Adverse events occurred more frequently in the CIK group than in the control group, but grade 3 or 4 adverse events did not differ significantly between groups. Adverse reactions associated with CIK included pyrexia, chills, myalgia, and fatigue.

In 2014, Yu et al. conducted an RCT of 132 patients who had previously untreated hepatocellular carcinoma.[20] Patients were randomized 1:1 to receive CIK therapy plus standard treatment (surgical resection in eligible patients, local treatment, or best supportive care) or standard treatment only. At a median follow-up of 19 months, median PFS was 14 months in the CIK group versus seven months in the control group (log-rank test for all comparisons, p=0.019). Estimated 1-, 2-, and 3-year PFS was 56% versus 35% (p=0.004), 36% versus 18% (p=0.004), and 27% versus 18% (p=0.017), respectively. Median OS was 25 months in the CIK group versus 11 months in the control group (p=0.008). Estimated 1-, 2-, and 3-year OS was 74% versus 50% (p=0.002), 53% versus 30% (p=0.002), and 42% versus 24% (p=0.005), respectively. In the subgroup of operable patients, 3-year and median OS did not differ statistically between groups. Common adverse events attributed to CIK therapy were grade 1 or 2 fever, allergy, and headache. Grade 3 or 4 adverse events were not observed. A nonrandomized study from China reported improved PFS in 30 patients who received radiofrequency ablation plus CIK/natural killer cell/gamma delta T-cell (a type of TIL) infusion (median PFS, not reached) compared with 32 patients who received radiofrequency ablation alone (median PFS=12.0 months).[21]

Non-Small-Cell Lung Cancer
In 2014, Wang et al. conducted a systematic review of RCTs of CIK cells for the treatment of non-small-cell lung cancer (NSCLC). Overall, 17 RCTs (total N=1172 patients) were included in the analysis. The studies generally had small sample sizes; the largest had 61 CIK-treated patients and 61 control patients. Most studies also incorporated dendritic cell therapy. A significant effect of CIK was found for median time to progression and median survival time. OS at various time points significantly favored CIK.

**Section Summary: Cytokine-Induced Killer Cells**

Several RCTs from Asia have evaluated the efficacy of CIK cells in different cancer types. These studies have generally reported some benefits in recurrence rates and/or DFS. Several studies of different cancer types report improved OS. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes (for some cancer types), heterogeneous treatment groups, and other methodologic weaknesses.

**Tumor-Infiltrating Lymphocytes (TILs)**

The use of tumor-infiltrating lymphocytes (TILs) for adoptive immunotherapy is underway in several active U.S. clinical trials, most of which are in phase 1 or phase 2. This evidence review will focus on published RCTs evaluating the use of TILs for adoptive immunotherapy for various indications. These studies are described below.

**Melanoma**

In 2011, Rosenberg et al. reported updated results for the patients in the Dudley trial, with median follow-up of 62 months. Ten patients who previously had been classified as partial responders to TIL therapy were reclassified as complete responders by RECIST (1, 3, and 6 patients in the nonmyeloablative, 200 cGy, and 1200 cGy groups, respectively). Of these 20 patients (22% of the original cohort), 19 (95%) had ongoing complete regression longer than 3 years. Actuarial 3- and 5-year survival for the entire group was 36% and 29%, respectively, but for the 20 complete responders, 100% and 93%, respectively. Likelihood of achieving a complete response was similar regardless of prior therapy.

In 2008, Dudley et al. conducted a series of nonrandomized phase 2 studies examining TIL plus IL-2 in patients with metastatic melanoma under various conditions of preinfusion lymphodepletion. A nonmyeloablative 7-day chemotherapy regimen (n=43) was compared with ablative regimens comprising 5-day chemotherapy plus either 200 cGy (n=25) or 1200 cGy (n=25) total-body irradiation. Ninety-five percent of patients had progressive disease after prior systemic treatment. Objective response rates by Response Evaluation Criteria in Solid Tumors (RECIST) were 49%, 52%, and 72%, respectively, and did not differ significantly among groups. Responses occurred at multiple metastatic sites, including brain, and many were durable; 10 patients who achieved complete response had no relapse at a median follow-up of 31 months. Toxicities of treatment occurred primarily in the 1200 cGy group and included a delay in marrow recovery of 1-2 days compared with the other treatment groups, somnolence requiring intubation, renal insufficiency, and posterior uveitis.

In 2007 Benlalam and colleagues randomized 88 patients with stage III melanoma to TIL plus interleukin-2 or interleukin-2 alone following complete tumor resection. This study was based off a previous pilot study performed by the same group in 2002. The investigators studied a panel of 38 tumor-associated antigens by TIL infused in patients in order to determine if treatment outcome
correlates with specific antigens of TIL. The preliminary results indicate that there may be an improved complete response and potentially improved relapse-free survival with Melan-A/MART-1 reactive TIL.

In 1999, Figlin et al. randomized 178 patients with metastatic renal cell carcinoma or resectable renal tumors to adjuvant continuous low-dose IL-2 therapy, with or without additional TIL.[27] TILs were harvested from surgical specimens. Outcomes were similar in both groups, and for this reason the trial was terminated early.

Section Summary: Tumor-Infiltrating Lymphocytes

One small RCT compared TILs plus IL-2 with IL-2 alone in patients with nonmetastatic melanoma and reported no difference between treatment groups in relapse or survival outcomes. Cohort studies in patients with refractory metastatic melanoma demonstrated response rates of 49% and 52% to 72% with TIL plus nonmyeloablative or myeloablative regimens, respectively. Durable responses in the majority of patients who achieved complete response were observed beyond three years. Toxicities appeared primarily associated with myeloablative regimen. Definitive RCTs showing treatment benefit are needed to establish efficacy.

Dendritic Cells (DCs)

Antigen-loaded autologous dendritic cells (ADCs) have been explored primarily in early-stage trials in various malignancies including lymphoma,[28] myeloma,[29,30] subcutaneous tumors,[31] melanoma,[32] NSCLC,[33,34] renal cell cancer,[35] and cervical cancer.[36] A 2012 review article highlighted progress in dendritic cell-based immunotherapy in epithelial ovarian cancer.[37]

Currently, the use of DCs for adoptive immunotherapy is underway in several active U.S. clinical trials, all of which are in phase 1 or phase 2. This evidence review will focus on published RCTs evaluating the use of DCs for adoptive immunotherapy for various indications. These studies are described below.

Hepatocellular Carcinoma

In 2016, Su et al. performed a meta-analysis of RCTs to evaluate the efficacy and safety of dendritic cells (DCs) co-cultured with cytokine-induced killer cell (CIK) immunotherapy combined with transcatheter arterial chemoembolization (TACE) or TACE plus local ablation therapy for hepatocellular carcinoma.[38] The seven randomized controlled trials (RCTs) used DC-CIK + TACE for the treated group and TACE alone for the controls. The one controlled clinical trial that was included used DC-CIK + TACE_RFA for the treated group and TACE+RFA for the controls. In total, 693 patients (N=349 treated and N=344 controls) from eight controlled trials performed in China were included.

Overall study heterogeneity was low. Pooled results showed that DC-CIK immunotherapy combined with TACE or TACE plus local ablation therapy significantly improved overall survival at 1-year (OR = 2.00, p = 0.02) and 2-year (OR = 1.77, p = 0.04) follow-up. An improved overall response rate (ORR) (OR = 1.51, p = 0.03), disease control rate (complete remission + partial remission + stable disease) (DCR) (OR = 1.81, p = 0.01), and quality of life (OR = 3.30, p < 0.0001) were observed in the DC-CIK group. Additionally, the percentage of CD3+ T cells (mean difference [MD] = 21.37, p = 0.005) and the ratio of CD4+/CD8+ (MD = 2.83, p = 0.02) were significantly increased in the DC-CIK therapy group. The only immunotherapy-specific adverse effects reported were mild and transient. However, the reviewers concluded that well-designed RCTs with rigorous methods and larger sample sizes are needed to confirm their findings and determine the best therapeutic combination for HCC. Limitations of this
review include small sample size for all but one included study, no included study was determined to be of high quality, and patient populations in the included studies at different stages of disease. In addition, tumor size, tumor stage, treatment design for inclusion of patients and evaluation of the therapeutic effects varied across the included studies, causing heterogeneity.

**HIV**

In 2016, Jacobson et al. conducted a phase 2B, multicenter, 2:1 randomized, double-blind, placebo-controlled study on 54 HIV patients to assess DC treatment on its ability to reduce viral load.[39] Thirty six patients in the treatment group were injected every four weeks with DC cells loaded with Gag, Rev, Vpr, and Nef RNA molecules from the patient's autologous virus, and 11-12 week viral loads were assessed. There was no difference in viral loads between the treated and untreated patients, and there was no difference in pre- and post-treatment viral loads in treated patients. A greater percentage of the treated patients had cytotoxic T-lymphocyte responses induced in the HIV-specific effector/memory T-cell population. The only adverse event reported was transient, mild (grade 1) local injection site reactions. The authors concluded that despite the induction of HIV-specific effector/memory CD8 T-cell responses, no antiviral effect was seen after the administration of dendritic cells when compared with placebo. Similar nonsignificant results were reported in a smaller RCT conducted by Gandhi et al.[40] For HIV-infected patients, DC treatment needs to be optimized to elicit stronger and long-lasting immune responses in order for this therapy to be effective.

**Multiple Myeloma**

In 2016, Zhao et al. conducted an RCT to investigate the efficacy of dendritic cells and cytokine-induced killer cells (DC-CIK) combined with chemotherapy for treating 42 newly diagnosed patients with multiple myeloma (MM) in China.[41] Twenty patients were randomized to the chemotherapy only group and 22 patients to the immunotherapy (DC-CIK) combined with chemotherapy group. After three weeks post-treatment, the quality of life, clinical index and survival of patients in combined therapy group were better than those of patients in chemotherapy group (p < 0.05); the ratios of immune markers of patients in combined therapy group were significantly lower than those of patients in chemotherapy group alone (p < 0.05). A second study was published by the same group which is likely the same cohort of patients, reporting that levels of IL-2, IL-4, IL-10 and IFN-γ in the DK-CIK + chemotherapy group was higher than in the chemotherapy alone group (p <0.05).[42]

**Glioblastoma Multiforme**

In 2013, Bregy et al. published a systematic review of observational studies of active immunotherapy using ADCs in the treatment of glioblastoma multiforme.[43] Twenty-one studies published through early 2013 were included in this review (total N=403). Vaccination with dendritic cells loaded with autologous tumor cells resulted in increased median OS in patients with recurrent disease (72-138 weeks across eight studies), as well as in those newly diagnosed (65-230 weeks across 11 studies) compared with average survival of 58 weeks. Complications and safety of the vaccine were assessed in all studies. No study indicated any sign of autoimmune reaction. The majority of adverse events were injection site reactions (22%). Other adverse events included fatigue (19.5%), constipation/diarrhea (1.6%), myalgia/malaise (1.6%), shivering (1.4%), and vomiting (0.5%). Because of the nature of the current literature available (ie, case reports, phase 1 and phase 2 clinical trials, prospective studies), the review is subject to publication and selection bias, which has the potential to lessen or amplify the true potential of adoptive immunotherapy. Larger controlled trials are required to assess survival and effect on quality of life of adoptive immunotherapy in this patient population.
Non-Small-Cell Lung Cancer

Systematic Reviews

In 2015 Wang and Wang conducted a systematic review to evaluate the efficacy and safety of dendritic cells co-cultured with cytokine-induced killer cells immunotherapy for the treatment of gastric cancer, including 505 patients from six Chinese RCTs.\cite{44} Compared with control therapies, DC-CIK immunotherapy significantly improved progression-free survival (PFS) [hazard ratio (HR): 0.528, 95% confidence interval (CI): 0.390-0.715, p<0.001], overall survival (OS) (HR: 0.619, 95% CI: 0.487-0.786, p<0.001), and disease control rates (DCR) [relative risk (RR): 1.250, 95% CI: 1.058-1.477, p=0.009]. However, objective response rates (ORR) (RR: 1.190, 95% CI: 0.561-2.526, p=0.650) were not improved in the DC-CIK treated group. The reviewers determined that the risks of adverse events in patients receiving DC-CIK immunotherapy were comparable to those receiving control therapies. The reviewers concluded that further studies are required to adopt routine clinical use of DC-CIK immunotherapy for NSCLC.

In 2014, Chen et al. conducted a systematic review and meta-analysis of RCTs that compared DC-CIK combination immunotherapy with any other treatment (placebo, no intervention, conventional treatment, or other complementary and alternative medicines) for any cancer type and stage.\cite{45} Two included RCTs that compared DC-CIK plus chemotherapy with chemotherapy alone in patients with stage III/IV NSCLC reported OS estimates (total N=150). Pooled RRs favored DC-CIK therapy at 2 years but not at 1 year (RR for 1-year OS=1.38; 95% CI, 1.00 to 1.90; p=0.05; $I^2=35%$; RR for 2-year OS=2.88; 95% CI, 1.38 to 5.99; p=0.005; $I^2=0%$).

Randomized Controlled Trial

In 2012, Shi et al. conducted an RCT at a single university cancer center to evaluate the role of dendritic cell (DC)/CIK combination immunotherapy as maintenance treatment of advanced NSCLC.\cite{33} From October 2008 to June 2010, 60 patients with stage IIIB/IV disease after treatment with four cycles of a platinum-based chemotherapy regimen were randomly divided into two groups. One group was treated with DC-CIK cell therapy (n=30), and the other was a control group who received no adoptive immunotherapy (n=30). Outcome measures were PFS and adverse effects of treatment/toxicity. PFS was 3.2 months in the DC-CIK group (95% CI, 2.9 to 3.5) versus 2.6 months control group (95% CI, 2.39 to 2.73; p<0.05). No significant toxic reactions were observed in the DC-CIK group, including bone marrow toxicity and gastrointestinal reactions. The findings of this small single-center RCT indicate that combination immunotherapy with dendritic cells and CIK cells may offer a viable option as maintenance therapy for patients with advanced NSCLC.

Breast Cancer

Systematic Review

In 2014, Wang et al. performed a systematic review and meta-analysis to evaluate the therapeutic efficacy of dendritic cells (DC) alone, cytokine-induced killer (CIK) cells alone and the combination of DC and CIK cells (DC-CIK) in the treatment of breast cancer.\cite{46} Patient inclusion criteria included: women with metastatic or locally advanced breast cancer, progressive disease, and no standard systemic treatment indicated, life expectancy of >3 months. The main exclusion criteria was radiation therapy or chemotherapy within the previous four weeks. A total of 27 trials, including nonrandomized trials, and
trials with as little as two participants, were included (N=633 patients). Only four trials (n=10, 20, 53, 129) used only DCs, whereas 15 trials used CIK cells and nine trials used both DC and CIK cell in combination. Unfortunately the reviewers performed the analysis on the DC-CIK group compared to non-DC-CIK group (which combined both DC-alone and CIK-alone patients. DC-alone treatment was not analyzed independently of the CIK-alone group, therefore we cannot draw conclusions regarding the therapeutic efficacy of dendritic cells (DC) alone from this review.

Nonrandomized Studies

In 2012, Qi et al. reported the results of a small comparative study to assess the immune response, disease progression, and post-treatment survival of ER/PR double-negative stage II/IIIA breast cancer patients vaccinated with autologous dendritic cells pulsed with autologous tumor lysates, including 31 treated patients and untreated controls.[47] The investigators reported no serious adverse effects and approximately 58% (18/31) of patients were considered to have a positive immune reaction. The 3-year progression-free survival was significantly prolonged: 76.9% versus 31.0% (with vs. without DC vaccine, p < 0.05). However, here was no difference in overall survival between the patients with and without DC vaccine.

In 2012, Koski et al. reported on a small trial to assess the safety and immunogenicity of a novel dendritic cell-based immunization approach for the induction of Th1-polarized anti-HER-2/neu treatment in women with early breast cancer.[48] This trial included 25 treated patients and 11 surgery-only controls. However, the number of treated patients available for various post-treatment analyses ranged from eight to 25. The investigators reported that post-immunization, sensitization of Th cells to at least 1 class II peptide was observed in 22 of 25 treated patients (88%, 95% CI: 68.8 – 97.5%), while eleven of 13 (84.6%, 95% CI: 64 – 99.8%) HLA-A2.1 subjects were successfully sensitized to class I peptides. In addition, anti-HER-2/neu peptide responses were observed up to 52 months post-immunization, although this group contained 11 patients. No comparisons were made between the treated and control groups in terms of outcomes.

In 2007, Czerniecki et al. reported the results of a small trial that assessed outcomes of immunotherapeutic targeting of HER-2/neu with dendritic cells in thirteen ductal carcinoma in situ (DCIS) patients.[49] The vaccinated subjects showed high rates of peptide-specific sensitization for both IFN-gamma-secreting CD4(pos) (11/13 patients, 85%) and CD8(pos) (10/13 patients, 80%) T cells. Seven of 11 evaluable treated patients also showed significantly decreased HER-2/neu expression in surgical tumor specimens compared to unvaccinated controls (n=7), five of which had significant decreases in residual DCIS.

In 2005, Peoples et al. reported the results of a small clinical trial using dendritic cells as part of a HER2/neu Vaccine to Prevent Recurrence in High-Risk Breast Cancer Patients. HLA-A2+ patients (n = 24) were vaccinated using dendritic cells, and HLA-A2− patients (n = 29) were included as untreated clinical controls.[50] The investigators reported that all 24 patients demonstrated clonal expansion of E75-specific CD8+ T cells that lysed HER2/neu-expressing tumor cells. At 22-months follow-up, the disease-free survival was significantly higher in the vaccinated group compared to controls (85.7% vs. 59.8%) but the recurrence rate was not significantly different between groups (8% in treated vs. 21% in controls, p < 0.19). Median time to recurrence in the vaccinated patients was prolonged (11 v 8 months), and recurrence correlated with a weak delayed-type hypersensitivity response.

In 2002 Schirrmacher et al. published long-term follow up (5.2 years) of a previously published comparative study by Ahlert et al.[51,52] In the original 1997 study, 63 patients with primary breast...
cancer and 27 with metastatic pretreated breast cancer were split into groups to test the efficacy of dendritic cell therapy. Each cohort was split into three subgroups with three different cell treatment parameters, with varying cell concentrations and cell viability numbers. The study did not include untreated controls. At long-term follow-up, the group that was treated with the largest number of cells and the most viable cells had had a highly significant long term survival benefit (p=0.004) and significant recurrence free survival (p=0.04) compared to the other treatment groups with reduced cell numbers and reduced viability. Probability of survival at four years was 63% for the group treated with reduced cell numbers, and 94% for the group treated with the largest number of cells and the most viable cells.

Section Summary: Dendritic Cells

Small RCTs have examined the role of adoptive immunotherapy with ADCs in glioblastoma multiforme, NSCLC, medullary thyroid cancer, and pancreatic cancer. All patients had advanced disease; however, treatment protocols varied across studies (eg, coadministration with other types of primed cells and/or chemotherapy). Treatment-associated toxicities were generally acceptable, but response rates varied across cancer types. The RCT in patients with NSCLC showed increased PFS with ADC-CIK adoptive immunotherapy compared with controls. Although results of this RCT and of some observational studies (eg, in glioblastoma multiforme) are encouraging, the overall body of evidence does not demonstrate improved net health outcome in any of the cancers studied.

The evidence for ADC in patients who have breast cancer includes small nonrandomized comparative studies, with treated groups including no more than 65 patients that are primarily, early-stage investigations. Although the preliminary studies suggest that dendritic cell immunotherapy may improve outcomes in patients with breast cancer, the impact of dendritic cell immunotherapy on patient outcomes (eg, increased survival, improved quality of life) has yet to be clarified in large, high-quality RCTs with adequate follow-up in order to show that there is a significant survival advantage for dendritic cell immunotherapy.

Small RCTs have also been published for the use of ADCs in patients with multiple myeloma, with significant differences in overall survival and quality of life in patients treated with ADC plus chemotherapy, compared to those treated with chemotherapy alone. Larger RCTs are needed to definitively determine the efficacy of ADC therapy in these patients.

Small phase 1 and phase 2 RCTs have also been published for the use of ADCs in HIV-positive patients, however these studies are still in the early stages. Although the use of this therapy is a promising alternative to other vaccine therapies for HIV-infected patients, the trials to date have not shown significant antiviral immune responses or a decrease in viral load. Larger RCTs with long-term follow up are needed, as well as protocol optimization to elicit stronger and long-lasting immune responses, in order for this therapy to be effective.

Genetically Engineered T Cells

Engineered T cell–based antitumor immunotherapy uses gene transfer of tumor antigen-specific T-cell receptors (TCR) or synthetic chimeric antigen receptors (CAR). Review articles have highlighted recent progress in this field for solid and hematologic malignancies.[53-55]

The use of genetically engineered T cells for adoptive immunotherapy is still in its early stages, with only phase 1/2 trials underway that have enrolled or expect to enroll small numbers of patients (n<100).
The body of published evidence for the use of engineered T cells for adoptive immunotherapy limited to noncomparative studies for various cancers. These studies are described below.

**TCR Therapy**

**Melanoma**

In 2014 Robbins et al. conducted a pilot trial, including 18 patients with synovial cell carcinoma and 20 patients with melanoma, treated with engineered T cells containing the cancer germline antigen NY-ESO-1.\(^\text{56}\) Eleven of 18 patients with NY-ESO-1\(^{+}\) synovial cell sarcomas (61%) and 11 of 20 patients with NY-ESO-1 positive melanomas (55%) who received the engineered T cells demonstrated partial or complete responses at one-month post treatment. Similar positive results have been reported in other small trials using T cells engineered with melanocyte differentiation antigens, gp100 and MART-1.\(^\text{57}\)

In 2009 in a phase 2 study, Johnson et al. transfected autologous peripheral lymphocytes of 36 patients who had metastatic melanoma with genes encoding TCRs highly reactive to melanoma/melanocyte antigens (MART-1:27-35 and gp100:154-162).\(^\text{58}\) Nine patients (25%) experienced an objective response; eight patients had a partial response lasting three months to more than 17 months; and one patient (in the gp100 group) had a complete response lasting more than 14 months. Treatment toxicities included erythematous rash, anterior uveitis, hearing loss, and dizziness, suggesting that these were attributable to recognition by the genetically modified lymphocytes of normally quiescent cells expressing the targeted cancer antigens; melanocytic cells exist in the skin, eye, and the inner ear. Ideal targets for TCR gene therapy may be antigens that arise in cancers of nonessential organs (eg, prostate, ovary, breast, thyroid) or are not expressed on normal adult tissues (eg, cancer-testes antigens).

**Other Indications**

Additional small phase 1 and phase 2 trials have examined TCR gene therapy in Hodgkin\(^\text{59}\) and non-Hodgkin’s lymphoma,\(^\text{60}\) prostate cancer,\(^\text{61}\) B-cell malignancies,\(^\text{62,63}\) colorectal cancer,\(^\text{64}\) mesothelioma,\(^\text{65}\) and neuroblastoma.\(^\text{66,67}\) There is a large amount of heterogeneity between studies for any single indication, since there are often more than one type of antigen used to engineer the cells. Regardless, large RCTs with standardized treatment protocols and long-term follow up are needed to determine the efficacy of each type of engineered T-cell therapy for each indication.

**CAR Therapy**

CAR therapy generates T cells (CAR-T cells) that express artificial TCRs that bind tumor cell surface antigens but do not need to match the patient’s immune type.\(^\text{55}\)

**B-Cell Malignancies**

**Systematic Review**

In 2015, Zhang et al. conducted a meta-analysis to evaluate the efficacy of CD19-CAR T cells in refractory B cell malignances in Phase I clinical trials.\(^\text{68}\) Fourteen clinical trials (N=119 patients) were included in the analysis of response rate and 12 trials (N= 62 patients) were included in the progression-free survival analysis. The pooled response rate of CD19-CAR T cells was 73% (95% confidence interval [CI]: 46-94%), however significant heterogeneity across estimates of response rates was observed (p < 0.001, I\textsuperscript{2}=88.3%). In subgroup analyses, ALL patients had higher response rates (93%,...
95% CI: 65-100%) than CLL (62%, 95% CI: 27-93%) and lymphoma patients (36%, 95% CI: 1-83%). Lymphodepletion and increasing number of infused CD19-CAR T cells positively correlated with better clinical response. Six-month and 1-year PFS for total 62 patients were 80.0% and 76.3% respectively. The median PFS was seven months. Only lymphodepletion and infused CAR+ T cell number were associated with better prognosis. Further studies to optimize and standardize treatment protocols are needed to improve the efficacy of CD-19 CAR-T cell treatment for these types of malignancies. A second systematic review in 2015 published by Zhu et al., included six of the small trials (n=3 to 15 patients per trial) included in the Zhang review, but reported significantly lower response rates (overall 48%) and six-month and 1-year PFS[69] (43% and 27%, respectively). However, the reviewers regarded these results as therapeutically effective.

Nonrandomized Studies

In 2015, Lee et al. conducted a phase 1 trial in order to define feasibility, toxicity, maximum tolerated dose and response rate in children and young adults with refractory acute lymphoblastic leukemia or non-Hodgkin lymphoma treated with CD19-CAR-T cells.[70] Twenty one consecutively enrolled patients underwent a single infusion, 19 of which received the prescribed dose of CD19-CAR T cells (90% feasibility). Complete response was induced in 70% of patients. Adverse events report were: grade 4 cytokine release syndrome that occurred in three (14%) of 21 patients (95% CI 3·0-36·3), grade 3 fever (nine [43%] of 21 patients), hypokalaemia (nine [43%] of 21 patients), fever and neutropenia (eight [38%] of 21 patients), and cytokine release syndrome (three [14%] of 21 patients). All of these events were reversible.

Preliminary U.S. studies have investigated add-on CAR therapy in eight patients with relapsed chronic lymphocytic leukemia.[71,72] Four (50%) of eight patients achieved complete remission. Adverse events included significant cytokine-mediated toxicities (fever, hypotension, and mental status changes) requiring high-dose, lymphotoxic steroid therapy in three patients who had high tumor burden at the time of CAR therapy.

Other Indications

Small pilot safety and feasibility trials evaluating CAR-T therapies have also been reported for glioblastoma[73], metastatic liver cancer[74,75], HER2-positive tumors[76] (primarily osteosarcoma), AML[77], metastatic renal cell carcinoma[78]. All of the above trials and studies treated between 3-16 patients for each of the indications.

Section Summary: Genetically Engineered T Cells

Small trials of patients with metastatic melanoma reported a 55-60% response rate at 1-month but a 25% response rate at 17 months with TCR gene therapy and broad treatment-related toxicities. Small trials of patients with B-cell malignancies report response rates between 50-80% depending on the specific malignancy. CAR therapy is in a preliminary stage of development, with the majority of published evidence coming from trials with under 20 patients.

REGULATORY STATUS

Adoptive immunotherapy is not a U.S. Food and Drug Administration–regulated procedure.

CLINICAL PRACTICE GUIDELINES
Current clinical practice guidelines from the National Comprehensive Cancer Network do not include recommendations for adoptive immunotherapy to treat cancers of the bladder, head and neck, hepatobiliary system, kidney, pancreas, stomach, breast, thyroid, melanoma, Hodgkin or non-Hodgkin’s lymphomas, or non-small-cell lung cancer.

SUMMARY

There is not enough research to show that adoptive immunotherapies improve outcomes (eg, increased survival, improved quality of life) for patients with any type of cancer. Although some adoptive immunotherapies show promise for certain cancers, the current evidence includes studies with small numbers of patients and there are differences in the types of populations studied (eg, early stage versus advanced disease) and the types of therapies administered. More research is needed with more patients and longer term follow-up. In addition, there are no clinical practice guidelines that recommend adoptive immunotherapy. Therefore, adoptive immunotherapy is considered investigational for any indication.

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OmedaRx Medication Policy Manual: https://www.omedarx.com/policies; NOTE: Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

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