Adoptive Immunotherapy and Cellular Therapy

Number: 0641

Policy

Aetna considers adoptive immunotherapy, using either tumor-infiltrating lymphocytes (TILs) or lymphokine-activated killer (LAK) cells that are activated in-vitro by interleukin-2 (IL-2), experimental and investigational for the treatment of the following indications (not an all-inclusive list) due to lack of adequate evidence that it is more beneficial than IL-2 alone:

- Alzheimer disease and other amyloid disorders
- Breast cancer
- Esophageal cancer
- Glioblastoma multiforme
- Head and neck cancer (e.g., nasopharyngeal carcinoma)
- Hepato-cellular carcinoma
- Intractable viral diseases and other infectious diseases
- Lung cancer (including non-small cell lung cancer)
- Malignant glioma
- Melanoma
- Myeloma
- Medulloblastoma
- Neuroblastoma
- Ovarian cancer
- Pancreatic cancer
- Renal cell carcinoma
- Sporadic inclusion-body myositis
- Other malignancies

Aetna considers cellular therapy (including cell therapy, embryonic cell therapy, fresh cell therapy, immune cell therapy, live cell therapy, glandular therapy, organotherapy, and xenotransplant therapy) experimental and investigational for the treatment of the following indications (not an all-inclusive list) due to lack of adequate evidence:

- Acquired immune deficiency syndrome
- Acute lymphocytic leukemia
- Angina
- Arthritis

Policy History

Last Review: 09/28/2020
Effective: 08/20/2002

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- Asthma
Adoptive Immunotherapy

Adoptive immunotherapy involves removing lymphocytes from the patient, boosting their anti-cancer activity, growing them in large numbers, and then returning them to the patient:

Lymphokine-activated killer (LAK) cells: Initial experiments in adoptive immunotherapy involved removing lymphocytes from the blood of a patient and growing them in the presence of the lymphokine interleukin-2 (IL-2), an immune stimulator. The cells were then returned to the patient. These lymphocytes were called LAK cells.

Tumor-infiltrating lymphocytes (TILs): A stronger response against tumor cells is obtained using lymphocytes isolated from the tumor itself. These tumor-infiltrating lymphocytes are grown in the presence of IL-2 and returned to the body to attack the tumor. Researchers are also using radiolabeled monoclonal antibodies for tumor antigens to even more closely identify lymphocytes specific for tumor cells.

* For CAR T therapy, see CPB 0920 - Tisagenlecleucel (Kymriah) (../900_999/0920.html) and CPB 0924 - Axicabtagene Ciloleucel (Yescarta) (../900_999/0924.html).

See also CPB 0377 - Dendritic Cell Immunotherapy (../300_399/0377.html), and CPB 0638 - Donor Lymphocyte Infusion (0638.html).
Adoptive immunotherapy and dendritic cell immunotherapy are forms of cellular therapy, where ex-vivo processed cells are introduced into the body. Adoptive immunotherapy uses immune effector cells (e.g., T cells), whereas dendritic cell immunotherapy uses antigen-presenting cells.

Pre-clinical studies suggested anti-tumor activity could be enhanced by using IL-2 together with ex-vivo activated and expanded autologous lymphocytes. Also, the first objective responses with high-dose bolus IL-2 therapy were noted in patients receiving IL-2 together with LAK cells prepared through in-vitro activation of autologous peripheral blood lymphocytes that were harvested by lymphopheresis, and initially, it appeared that the combination of IL-2/LAK was more active than IL-2 alone.

Clinical studies have failed to demonstrate that the addition of activated LAK cells with IL-2 is any more effective than IL-2 alone. Major IL-2/LAK clinical trials in patients with renal cell carcinoma have been conducted by several groups, including the National Cancer Institute (NCI) Surgery Branch, the Interleukin-2/LAK Working Group, and the NCI-sponsored Modified Group C centers. A subset of the NCI Surgery Branch's patients with renal cell carcinoma and with all patients entered into the Modified Group C trials were randomized to receive IL-2 alone or together with LAK cells. Response rates to IL-2 used alone and together with LAK cells as well as durability of responses did not differ substantially. In a review of the literature, Grimm (2000) concluded that "the data do not support a major contribution of ex vivo activated and adoptively transferred LAK cells to the efficacy of high-dose bolus IL-2 in patients with renal cell carcinoma."

Similar conclusions were reached regarding the adoptive transfer of LAK cells in patients with melanoma treated with high-dose bolus IL-2. Response rates with IL-2/LAK are not different from those observed with high-dose IL-2 alone, and IL-2/LAK therapy in other solid tumors has been disappointing. While attempts to generate LAK at the tumor site remain attractive, Grimm (2000) concluded that the intravenous infusion of LAK is not likely to prove effective in cases beyond the blood-borne metastatic deposits, which appear just as sensitive to interleukin alone.

Grimm (2000) noted that clinical trials conducted with IL-2 and TIL has also been disappointing. Clinical trials of IL-2/TIL have been performed on the basis of the theory that TIL would include those with tumor specific activity, which was somehow suppressed in the vicinity of the tumor. These lymphocytes are produced by placing digested, fresh tumor biopsies into an in-vitro culture with IL-2. Although some early studies have noted response rates using TIL cells together with IL-2 in the 30 to 40 % range, there are no studies comparing responses with TIL cells compared with IL-2 alone.

A Cochrane meta-analysis examined the published evidence for adoptive immunotherapy in renal cell cancer (Coppin et al, 2004). The investigators identified 1 study that compared high dose IL-2 plus LAK cells with high dose IL-2 alone (Rosenberg et al, 1993). Three other studies examined IL-2 given in modified schedules to reduce toxicity but with additions intended to maintain or improve efficacy compared to the high dose IL-2 regimen. The modifiers included TILs (Figlin et al, 1999), or LAK cells (McCabe et al, 1991; Law et al, 1995). The investigators found that examination of individual and pooled response rates showed no clear evidence of enhancement for remission (Peto odds ratio [OR] 0.93, 95 % confidence interval [CI]: 0.50 to 1.74) (Coppin et al, 2004). Likewise for the 3 studies reporting survival, 1-year mortality was not reduced (Peto OR 0.78, 95 % CI: 0.50 to 1.21).
In a phase II clinical study, Kimura and associates (2008) evaluated the effectiveness and toxicity of adjuvant chemo-immunotherapy using dendritic cells and activated killer cells in post-surgical primary lung cancer patients (n = 31). The activated killer cells and dendritic cells (AKT-DC) obtained from tissue cultures of tumor-draining lymph nodes (TDLN) or from TDLN co-cultured with peripheral blood lymphocytes (TDLN-Pb) were used for the adoptive transfer of immunotherapy. Patients received 4 courses of chemotherapy along with immunotherapy every 2 months for 2 years. Three cases were excluded because of refusal by the patients after 1 to 2 courses of immunotherapy. For the 28 cases treated, a total of 313 courses of immunotherapy were administered. The main toxicities were fever (78.0 %), chill (83.4 %), fatigue (23.0 %) and nausea (17.0 %) on the day of cell transfer. The 2- and 5-year survival rates were 88.9 % (95 % CI: 95.9 to 81.9) and 52.9 % (95 % CI: 76.4 to 29.4). 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 feasible and safe, and a large-scale multi-institutional study is needed for assessing the effectiveness of this treatment.

Bernhard and colleagues (2008) stated that the human epidermal growth factor receptor 2 (HER2) has been targeted as a breast cancer-associated antigen by immuno-therapeutical approaches based on HER2-directed monoclonal antibodies and cancer vaccines. These investigators described the adoptive transfer of autologous HER2-specific T-lymphocyte clones to a patient with metastatic HER2 over-expressing breast cancer. The HLA/multimer-based monitoring of the transferred T lymphocytes revealed that the T cells rapidly disappeared from the peripheral blood. The imaging studies indicated that the T cells accumulated in the bone marrow (BM) and migrated to the liver, but were unable to penetrate into the solid metastases. The disseminated tumor cells in the BM disappeared after the completion of adoptive T-cell therapy. The findings of this study suggest the therapeutic potential for HER2-specific T cells for eliminating disseminated HER2-positive tumor cells and propose the combination of T cell-based therapies with strategies targeting the tumor stroma to improve T-cell infiltration into solid tumors.

Rolle and colleagues (2010) noted that glioblastoma multiforme (GBM) is the most common and lethal primary malignant brain tumor. The traditional treatments for GBM, including surgery, radiation, and chemotherapy, only modestly improve patient survival. Therefore, immunotherapy has emerged as a novel therapeutic modality. Current immunotherapeutic approaches for glioma can be divided into 3 categories: (i) immune priming (active immunotherapy), (ii) immunomodulation (passive immunotherapy), and (iii) adoptive immunotherapy.

Chekmasova and Brentjens (2010) stated that adoptive transfer of genetically modified autologous tumor-reactive T cells is a promising novel anti-tumor therapy for many cancers. Ovarian carcinomas in particular appear to be suited to this therapeutic approach based on the fact that these tumors are relatively immunogenic, inducing an endogenous T cell response. Furthermore, the degree to which this endogenous T cell-mediated immune response is evident correlates to long-term patient prognosis following surgery and chemotherapy. To this end, adoptive T cell immunotherapy strategies for the treatment of ovarian carcinomas appear to be particularly promising and are currently being investigated at several centers in both pre-clinical and clinical settings.
Adoptive immunotherapy is also being studied as a means for treating non-malignant conditions such as amyloid disorders (e.g., Alzheimer disease, sporadic inclusion-body myositis) and infectious diseases/intractable viral diseases. However, there is currently insufficient evidence to support the clinical value of these potential applications of adoptive immunotherapy.

Kurusaki et al (2011) stated that APCs play a crucial role in the induction of immune responses. However, the optimal administration route of tumor-specific APCs for inducing effective immunological responses via cancer immunotherapy remains to be elucidated. Human NKT cells are known to have strong anti-tumor activities and are activated by the specific ligand, namely, αGalCer. A total of 17 patients with HNSCC were enrolled in this study. Patients received an injection of αGalCer-pulsed APCs into the nasal, or the oral floor submucosa. Then total body image and single photon emission computed tomography (SPECT) images were examined. The immunological responses including the number of peripheral blood NKT cells, anti-tumor activities and the CD4(+) CD25(high) Foxp3(+) T cells (Tregs) induced following APCs were also compared. APCs injected into the nasal submucosa quickly migrated to the lateral lymph nodes and those injected into the oral floor submucosa dominantly migrated to the submandibular nodes rather than the lateral lymph nodes. An increase in the absolute number of NKT cells and the IFN-γ producing cells was observed in peripheral blood after injection of the APCs into the nasal submucosa, however, these anti-tumor activities were not detected and the increased frequency of Treg cells were observed after administration into oral floor. The authors concluded that these findings indicated that a different administration route of APCs has the potential to bring a different immunological reaction. The submucosal administration of αGalCer into the oral submucosa tends to induce immunological suppression.

In a phase I/II 2-arm trial (Rapoport et al, 2011), a total of 54 patients with myeloma received autografts followed by ex vivo anti-CD3/anti-CD28 co-stimulated autologous T cells at day 2 after transplantation. Study patients positive for human leukocyte antigen A2 (arm A, n = 28) also received pneumococcal conjugate vaccine immunizations before and after transplantation and a multi-peptide tumor antigen vaccine derived from the human telomerase reverse transcriptase and the anti-apoptotic protein survivin. Patients negative for human leukocyte antigen A2 (arm B, n = 26) received the pneumococcal conjugate vaccine only. Patients exhibited robust T-cell recoveries by day 14 with supra-physiologic T-cell counts accompanied by a sustained reduction in regulatory T cells. The median event-free survival (EFS) for all patients is 20 months (95 % CI: 14.6 to 24.7 months); the projected 3-year overall survival is 83 %. A subset of patients in arm A (36 %) developed immune responses to the tumor antigen vaccine by tetramer assays, but this cohort did not exhibit better EFS. Higher post-transplantation CD4(+) T-cell counts and a lower percentage of FOXP3(+) T cells were associated with improved EFS. Patients exhibited accelerated polyclonal immunoglobulin recovery compared with patients without T-cell transfers. Adoptive transfer of tumor antigen vaccine-primed and costimulated T cells leads to augmented and accelerated cellular and humoral immune reconstitution, including anti-tumor immunity, after autologous stem cell transplantation for myeloma.

In a phase II clinical trial, Geller et al (2010) evaluated the tumor response and in-vivo expansion of allogeneic natural killer (NK) cells in recurrent ovarian and breast cancer. Patients underwent a lympho-depleting preparative regimen: fludarabine 25 mg/m(2) × 5 doses, cyclophosphamide 60 mg/kg × 2 doses, and, in 7 patients, 200 cGy total body irradiation (TBI) to increase host immune suppression. An NK cell product, from a haplo-identical related donor, was incubated over-night in 1,000 U/ml IL-2 prior to...
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infusion. Subcutaneous IL-2 (10 MU) was given 3 times/week × 6 doses after NK cell infusion to promote expansion, defined as detection of greater than or equal to 100 donor-derived NK cells/μL blood 14 days after infusion, based on molecular chimerism and flow cytometry. A total of 20 patients (14 ovarian cancer, 6 breast cancer) were enrolled. The median age was 52 (range of 30 to 65) years. Mean NK cell dose was 2.16 × 10⁷ cells/kg. Donor DNA was detected 7 days after NK cell infusion in 9/13 (69 %) patients without TBI and 6/7 (85 %) with TBI. T-regulatory cells (Treg) were elevated at day +14 compared with pre-chemotherapy (p = 0.03). Serum IL-15 levels increased after the preparative regimen (p < 0.001). Patients receiving TBI had delayed hematologic recovery (p = 0.014). One patient who was not evaluable had successful in-vivo NK cell expansion. The authors concluded that adoptive transfer of haplo-identical NK cells after lympho-depleting chemotherapy is associated with transient donor chimerism and may be limited by reconstituting recipient Treg cells. They stated that strategies to augment in-vivo NK cell persistence and expansion are needed.

Weber et al (2011) noted that adoptive T-cell therapy (ACT) using expanded autologous tumor-infiltrating lymphocytes (TIL) and tumor antigen-specific T cell expanded from peripheral blood are complex but powerful immunotherapies directed against metastatic melanoma. A number of non-randomized clinical trials using TIL combined with high-dose IL-2 have consistently found clinical response rates of 50 % or more in metastatic melanoma patients accompanied by long progression-free survival. Recent studies have also established practical methods for the expansion of TIL from melanoma tumors with high success rates. These results have set the stage for randomized phase II/III clinical trials to determine whether ACT provides benefit in stage IV melanoma. These investigators provided an overview of the current state-of-the art in T-cell-based therapies for melanoma focusing on ACT using expanded TIL and address some of the key unanswered biological and clinical questions in the field. Different phase II/III randomized clinical trial scenarios comparing the efficacy of TIL therapy to high-dose IL-2 alone were described. Finally, the authors provided a roadmap describing the critical steps required to test TIL therapy in a randomized multi-center setting. They suggested an approach using centralized cell expansion facilities that will receive specimens and ship expanded TIL infusion products to participating centers to ensure maximal yield and product consistency. If successful, this approach will definitively answer the question of whether ACT can enter mainstream treatment for cancer.

Bielamowicz et al (2013) stated that glioblastoma multiforme (GBM) is the most common and most aggressive primary brain malignancy and, as it stands, is virtually incurable. With the current standard of care, maximum feasible surgical resection followed by radical radiotherapy and adjuvant temozolomide, survival rates are at a median of 14.6 months from diagnosis in molecularly unselected patients. Collectively, the current knowledge suggests that the continued tumor growth and survival is in part due to failure to mount an effective immune response. While this tolerance is subtended by the tumor being utterly "self," it is to a great extent due to local and systemic immune compromise mediated by the tumor. Different cell modalities including lymphokine-activated killer cells, NK cells, cytotoxic T lymphocytes, and transgenic chimeric antigen receptor or αβ T cell receptor grafted T cells are being explored to recover and or redirect the specificity of the cellular arm of the immune system toward the tumor complex. These researchers noted that promising phase I/II trials of such modalities have shown early indications of potential efficacy while maintaining a favorable toxicity profile. Efficacy will need to be formally tested in phase
II/III clinical trials. The authors concluded that given the high morbidity and mortality of GBM, it is imperative to further investigate and possibly integrate such novel cell-based therapies into the current standards-of-care.

Bregy et al (2013) stated that active immunotherapy is a new area of research that may be a successful treatment option for GBM. The focus is on vaccines that consist of APCs loaded with tumor antigen. These researchers conducted a systematic review of prospective studies, case reports and clinical trials to examine the safety and effectiveness of active immunotherapy using dendritic cells in terms of complications, median overall survival (OS), progression free survival (PFS) and quality of life. A PubMed search was performed to include all relevant studies that reported the characteristics, outcomes and complications of patients with GBM treated with active immunotherapy using dendritic cells. Reported parameters were immune response, radiological findings, median PFS and median OS. Complications were categorized based on association with the craniotomy or with the vaccine itself. A total of 21 studies with 403 patients were included in this review. Vaccination with DCs loaded with autologous tumor cells resulted in increased median OS in patients with recurrent GBM (71.6 to 138.0 weeks) as well as those newly diagnosed (65.0 to 230.4 weeks) compared to average survival of 58.4 weeks. The authors concluded that active immunotherapy, specifically with autologous DCs loaded with autologous tumor cells, seems to have the potential of increasing median OS and prolonged tumor PFS with minimal complications. They stated that larger clinical trials are needed to show the potential benefits of active immunotherapy.

Svane and Verdegaal (2014) stated that ACT based on autologous T cell derived either from tumor as tumor-infiltrating lymphocytes (TILs) or from peripheral blood is developing as a key area of future personalized cancer therapy. TIL-based ACT is defined as the infusion of T cells harvested from autologous fresh tumor tissues after ex vivo activation and extensive expansion. TIL-based ACT has so far only been tested in smaller phase I/II studies, but these studies consistently confirm an impressive clinical response rate of up to 50 % in metastatic melanoma including a significant proportion of patients with durable complete tumor eradication. These remarkable results justify the need for a definitive phase III trial documenting the efficacy of this type of T cell-based Advanced Therapy Medicinal Product in order to pave the way for regulatory approval and implementation of TIL therapy as a new treatment standard in oncology practice. TIL-based ACT can, however, only be offered to a limited group of patients based on the need for accessible tumor tissue, the complexity of TIL production procedures, and the very intensive nature of this three-step treatment including both high-dose chemotherapy and interleukin-2 in addition to T cell infusion. To this end, adoptive T cell therapy using peripheral blood mononuclear cell-derived T cells could be a welcome alternative to circumvent these limitations and broaden up the applicability of ACT.

Hepato-Cellular Carcinoma

Mo and colleagues (2017) stated that the role of adoptive immunotherapy (AIT) for patients with hepatocellular carcinoma (HCC) who have received curative therapy is still not well illustrated. In a meta-analysis, these researchers reviewed the current evidence on safety and effectiveness of AIT for patients with HCC who have received curative therapy. They searched PubMed, Embase, Scopus and the Cochrane Library through January 2017 for relevant studies. Mortality and tumor recurrence were compared between patients with or without adjuvant AIT. A total of 8 studies involving 1,861 patients met the eligibility criteria and were meta-analyzed. Adjuvant AIT was
associated with significantly lower mortality at 1 year (relative risk [RR] 0.64, 95% CI: 0.52 to 0.79), 3 years (RR 0.73, 95% CI: 0.65 to 0.81) and 5 years (RR 0.86, 95% CI: 0.79 to 0.94). Similarly, adjuvant AIT was associated with significantly lower recurrence rate than curative therapies alone at 1 year (RR 0.64, 95% CI: 0.49 to 0.82), 3 years (RR 0.85, 95% CI: 0.79 to 0.91) and 5 years (RR 0.90, 95% CI: 0.85 to 0.95). Short-term outcomes were confirmed in sensitivity analyses based on randomized trials or choice of random- or fixed-effect meta-analysis model. None of the included patients experienced grade-4 adverse events (AEs). The authors concluded that the findings of this meta-analysis confirmed the evidence that adjuvant AIT for patients with HCC after curative treatment lowers risk of mortality and tumor recurrence; however, they stated that the findings must be interpreted with caution. They stated that a randomized trial with adequate follow-up is highly desirable. In addition, this study should aim to expand the range of relevant end-points examined, such as quality of life (QOL), duration of hospital stay, and cost-effectiveness; and this study should also examine the possible clinical benefits of multi-modal immune therapies.

This meta-analysis had several drawbacks: (i) the conclusion was based on 4 randomized trials with a low risk of bias and other studies with a high risk bias and was dominated by Asian populations; similar results may not be observed in Western populations, (ii) type of cytokines, number of infusion cycles, and duration of maintenance AIT therapy varied among the included studies, creating substantial heterogeneity for which these investigators could not control using sensitivity analyses, (iii) length of follow-up varied across the studies and in some cases was too short to observe long-term efficacy of adjuvant AIT. As a result, meta-analysis of outcomes at 3 and 5 years had to be conducted on subsets of all included studies, and (iv) some studies did not clearly report procedures for randomization or allocation concealment, increasing the risk of selection or reporting bias. The findings must be interpreted with caution.

Yuan and associates (2017) noted that the harms and benefits of AIT for patients with post-operative HCC are controversial. These investigators updated the current evidence on safety and effectiveness of AIT for patients with HCC who have received curative therapy. Electronic databases were systematically searched to identify randomized controlled trials (RCTs) and cohort studies evaluating adjuvant AIT for patients with HCC after curative therapies. Recurrence and mortality were compared between patients with or without adjuvant AIT. A total of 8 RCTs and 2 cohort studies involving 2,120 patients met the eligibility criteria and were meta-analyzed. Adjuvant AIT was associated with significantly lower recurrence rate than curative therapies alone at 1 year (RR 0.64, 95% CI: 0.49 to 0.82), 3 years (RR 0.85, 95% CI: 0.79 to 0.91) and 5 years (RR 0.90, 95% CI: 0.85 to 0.95). Similarly, adjuvant AIT was associated with significantly lower mortality at 1 year (RR 0.64, 95% CI: 0.52 to 0.79), 3 years (RR 0.73, 95% CI: 0.65 to 0.81) and 5 years (RR 0.86, 95% CI: 0.79 to 0.94). Short-term outcomes were confirmed in sensitivity analyses based on RCTs or choice of a fixed- or random-effect meta-analysis model. None of the included patients experienced grade-3 or grade-4 AEs. The authors concluded that this update reinforced the evidence that adjuvant AIT after curative treatment for HCC lowers risk of recurrence and mortality.

Moreover, these investigators noted that the findings of this meta-analysis that adjuvant AIT significantly reduces recurrence and mortality for post-operative HCC must be interpreted with caution. Surgical method, type of cytokines, number of infusion cycles, and duration of maintenance AIT therapy varied among the included studies, creating substantial heterogeneity for which they could not control using sensitivity analyses. In
addition, length of follow-up varied across the studies and in some cases was too short to observe long-term efficacy of adjuvant AIT. As a result, meta-analysis of outcomes at 3 and 5 years had to be conducted on subsets of all included studies. Some studies did not clearly report procedures for randomization or allocation concealment, increasing the risk of selection or reporting bias. The 4th problem with this meta-analysis was that there were limitations in the original data, which were beyond the these researchers' control, but nevertheless compromise the value of the study. they knew very little about surveillance/screening methodology, diagnostic criteria for HCC, and stage systems for HCC in this meta-analysis. So, a large variability of post-treatment surveillance programs and diagnostic criteria among studies could be expected. The last relevant issue of this meta-analysis was the potential lack of external validity of the results for different populations and settings. All the included studies were conducted on patient populations in Asia. So, a high rate of hepatitis B virus infected patients with or without cirrhosis could be expected. This population may be different in terms of clinical features and co-morbidities from most cases of hepatitis C virus-related or post- non-alcoholic steatohepatitis HCC from US and Europe. These investigators stated that the findings of the present meta-analysis should be verified and extended in further large trials with adequate follow-up. These studies should aim to expand the range of relevant end-points examine (e.g., QOL, duration of hospital stay, and cost-effectiveness); and these studies should also examine the possible clinical benefits of multi-modal immune therapies.

Non-Small Cell Lung Cancer

Mi and colleagues (2016) noted that the effectiveness of IL-2 and induced killer cells for non-small cell lung cancer (NSCLC) is controversial. These researchers evaluated the safety and effectiveness of IL-2 and induced killer cells on NSCLC. Relevant RCTs were searched in Cochrane library (Issue 2, 2013), Web of Science (1980 to March 2013), PubMed (1966 to March 2013), China Knowledge Resource Integrated database (CNKI) (1994 to March 2013), China Biology Medicine database (CBM) (1978 to March 2013), VIP (1989 to March 2013), and Wan Fang databases (1997 to March 2013). There were no language restrictions. After independent quality assessment and data extraction by 2 authors, meta-analysis was conducted by RevMan 5.1 software. A total of 10 RCTs were included; OR, 95 % CI, p value expressed as test group (IL-2 or induced killer cells combined chemotherapy) versus control group (chemotherapy alone), was 2.02 (1.24, 3.29; p = 0.004) for disease control rate; HR (95 % CI; p value), expressed as test group (IL-2 or induced killer cells) versus control group, were 0.60 (0.46, 0.79; p = 0.0003) for OS of post-operative treatment, and 0.77 (0.60, 0.99; p = 0.04) for OS of combination with chemotherapy; MD (95 % CI; p value), expressed as test group (IL-2 or induced killer cells) versus control group (after treatment), were 11.32 (6.32, 16.33; p = 0.00001) for NK cells, 11.79 (2.71, 20.86; p = 0.01) for CD3+ cells, 14.63 (2.62, 26.64; p = 0.02) for CD4+ cells, and -4.49 (-7.80, 1.18; p = 0.008) for CD8+ cells. The authors concluded that the findings of this meta-analysis showed that IL-2 or induced killer cells combination therapy was effective in treating NSCLC and improved OS. Moreover, they stated that further analysis of trials having adequate information and data are needed to confirm these findings.

This systematic review and meta-analysis had several drawbacks: (i) some included in this meta-analysis were not adequate as these did not report the detailed method of random sequence generation and concealment of allocation, and all trials did not mention the use of blinding, (ii) publication bias was a wide phenomenon for all forms of meta-analysis40. Although these investigators searched several databases and no publication bias was detected in the funnel plot analysis,
publication bias might still be a limitation, (iii) the standard preparation process of biological drugs, the combination treatment strategies, the effectiveness of different cell types and other issues (dose strategy, timing, individual therapy of histological types, the long-term survival rate) mentioned above should be further explored with a large sample and rigorous clinical research, and (iv) there were limited data of detail AEs to perform a meta-analysis.

Zeng and associates (2016) stated that AIT has been applied in the treatment of NSCLC patients, but the value of post-operative AIT has been inconclusive largely as a result of the small number of patients included in each study. These researchers performed a systematic review and meta-analysis to address this issue for patients with post-operative NSCLC. PubMed, Embase, Cochrane Library were searched for RCTs comparing AIT with control therapies in post-operative NSCLC patients. The primary end-point was OS; HR was estimated and 95 % CI were calculated using a fixed-effect model. Compared with control therapies, analyses of 4 RCTs (472 patients) showed a significant benefit of AIT on survival (HR 0.61, 95 % CI: 0.45 to 0.84, p = 0.002), and a 39 % reduction in the relative risk of death (no evidence of a difference between trials; p = 0.16, I² = 42 %). In subgroup analyses by treatment cycles and treatment regimen, significant OS benefit was found in combination therapy of AIT with chemotherapy, regardless of whether or not the treatment cycles were more than 10 cycles. The authors concluded that AIT has the potential to improve OS in post-operative NSCLC; these findings suggested that this is a valid treatment option for these patients, and further RCTs are needed.

Zhao and colleagues (2017) noted that although AIT is a novel emerging target treatment for NSCLC, its actual efficacy remains controversial. In a meta-analysis, these investigators evaluated the efficacy of AIT for NSCLC. They systematically searched PubMed, the Cochrane Library, EMBASE, Medline, and Web of Science for relevant parallel RCTs and high-quality observation studies of AIT without any language restrictions. Two investigators reviewed all the texts and extracted information regarding OS, PFS, objective response rate (ORR), and disease control rate (DCR) from eligible studies; sensitivity analyses and subgroup analyses were also conducted to reduce heterogeneity. Of 319 suitable studies, 15 studies (13 RCTs and 2 observation studies) involving 1,684 patients were finally included. Compared to the control therapy (CT) group, the AIT group exhibited better 1-year OS (p = 0.001), 2-year OS (p < 0.001), 3-year OS (p < 0.001), 5-year OS (p = 0.032), 1-year PFS (p < 0.001), and 2-year PFS (p = 0.029). The difference in the ORR (p = 0.293) and DCR (p = 0.123) was not significant between the groups. The subgroup analysis showed that DC/CIK did more benefit to NSCLC patients than LAK and the cycles not associated with AIT efficacy. The authors concluded that AIT could significantly improve the OS and PFS with acceptable toxicity for NSCLC. Nevertheless, further multi-center studies are needed to confirm the conclusion and determine which adoptive immunotherapy is associated with the greatest efficacy.

Huang and colleagues (2019) noted that adoptive T cell immunotherapy with cytokine-induced killer cells (CIKs) has been demonstrated to prolong the survival of patients with advanced NSCLC. These researchers examined if the expansion of effector T cells and the decrease of regulatory T cells (Tregs) that occurred during the ex-vivo generation of dendritic cell-cytokine induced killer cells (DC-CIKs) were associated with improved clinical outcome in patients who received treatment. CIKs were generated ex-vivo over a 28-day period from the peripheral blood apheresis product of 163 patients with advanced cancer (including 30 with NSCLC). CIKs were also generated from an additional cohort of 65 patients with NSCLC over a 15-day period. The PFS
and OS time of patients treated with CIKs was determined by reviewing the patients' medical records. The number of CIKs gradually increased during the culture period and peaked at day 15, followed by a slight decline until day 28. Similarly, the percentages of T cell subtypes associated with anti-tumor activity (CD3+, CD3+CD4+, CD3+CD8+, and CD8+CD28+) peaked at day 15. Although the percentage of CD4+CD25+CD127+ Tregs increased by day 7, a decrease was subsequently observed. Among the 95 patients with NSCLC, those with a post/pre-culture ratio of CD8+CD28+ T lymphocytes of greater than 2.2 had significantly better PFS and OS compared with those with ratios of less than or equal to 2.2. Those with a post/pre-culture CD4+CD25+CD127+ Treg ratio of less than or equal to 0.6 had significantly better OS and PFS compared with those with ratios of greater than 0.6. The peak expansion of CIKs from peripheral blood mononuclear cells occurred at day 15 of ex-vivo culture. PFS and OS were associated with post/pre-culture CD8+CD28+ T lymphocyte ratio of greater than 2.2 and post/pre-culture CD4+CD25+CD127+ Treg ratio of less than 0.6 in the CIKs of patients with advanced NSCLC treated with adoptive T cell immunotherapy. The authors stated that further efforts are underway to optimize the DC-CIK infusion for cancer immunotherapy.

The authors stated that this study had several drawbacks. First, 50 of the patients with NSCLC received chemotherapy prior to the DC-CIK infusions; the number of patients receiving DC-CIK alone was too low to allow subgroup analysis in the current study. Second, despite examining the effect of changes in the major lymphocyte subsets within the DC-CIK infusion during ex-vivo culture on clinical outcome, other cellular components or polymorphisms in cytokines or their receptors on the cells within the DC-CIK infusion may have potentially affected the outcome. These researchers stated that larger numbers of treated patients are needed to evaluate these impacts. They noted that the present study supported the hypothesis that further ex-vivo manipulations of the DC-CIKs may contribute to the development of a consistent cell therapy product with greater anti-tumor activity.

Head and Neck Cancers

Yamasaki et al (2011) noted that Vα24 natural killer T (NKT) cells have potent anti-tumor activity. These researchers performed a phase II clinical study in patients with head and neck squamous cell carcinoma (HNSCC) using ex-vivo expanded Vα24 NKT cells and α-galactosylceramide (αGalCer; KRN7000)-pulsed antigen-presenting cells (APCs) to investigate the efficacy and induction of NKT cell-specific immune responses. The subjects were 10 patients with locally recurrent and operable HNSCC. One course of nasal submucosal administration of αGalCer-pulsed APCs and intra-arterial infusion of activated NKT cells via tumor-feeding arteries was given before salvage surgery. Anti-tumor effects, NKT cell-specific immune responses in extirpated cancer tissue and peripheral blood, safety, and pathological effects were evaluated. Five cases achieved objective tumor regression. The number of NKT cells increased in cancer tissues in 7 cases and was associated with tumor regression. The combination therapy induced NKT cell-specific immune responses in cancer tissues that were associated with beneficial clinical effects.

Huang and colleagues (2017) stated that early-stage and intermediate stage nasopharyngeal cancer (NPC) generally carry a good prognosis, but for patients with recurrent, metastatic disease, options are limited. In a phase I/II clinical trial, these researchers evaluate the effectiveness of Epstein-Barr virus (EBV)-stimulated cytotoxic T-lymphocyte (EBV-CTL) immunotherapy in this patient population. Screening for patients with active, recurrent, metastatic EBV-associated NPC began in February 2007, and the study was closed to accrual in January 2012. After informed consent
was obtained, patients had their blood drawn to initiate manufacturing of the EBV-CTL product. During product manufacturing, patients were placed on interim standard-of-care chemotherapy, and only after disease progression on the interim chemotherapy did patients receive investigational immunotherapy. Patients were re-staged every 2 months until disease progression and then followed for survival. A total of 28 patients were enrolled, and 21 patients were treated. There was 1 complete response achieved, and at the time of last follow-up, the patient had been in remission for more than 8 years since treatment. The median PFS was 2.2 months, and the median OS was 16.7 months. Two other patients, after failing EBV-CTL immunotherapy, unexpectedly demonstrated strong responses to the chemotherapy regimens they had previously failed. Patient EBV viral load and EBV-CTL specificity for tumor-associated viral antigens did not appear to correlate with clinical response. The authors concluded that a durable response was observed with EBV-CTL immunotherapy, but the OS rate for patients with recurrent, metastatic NPC was low. They stated that further research is needed to enhance the effectiveness of EBV-specific immunotherapy in patients with incurable NPC, and to characterize mechanisms for re-facilitation to chemotherapy.

Breast Cancer

Hu and colleagues (2017) stated that breast cancer (BC) is considered a systemic disease with a primarily loco-regional component. The accumulation of basic researches and clinical studies related to cytokine-induced killer (CIK) cells has confirmed their safety and feasibility in treating BC. By searching the PubMed, Embase, CNKI, and Wanfang databases, these researchers conducted a meta-analysis to evaluate the safety and efficacy of dendritic cells (DC)/CIK plus chemotherapy regimen (Exp) compared with chemotherapy (Con) alone regimen for BC. Studies were pooled, and the RR and its corresponding 95% CI were calculated. A total of 11 relevant articles were included in this meta-analysis. These investigators observed that complete response (CR) (RR = 1.54, 95% CI: 1.09 to 2.19, p (heterogeneity)=0.994, I= 0%), partial response (PR) (RR=1.33, 95% CI: 1.11 to 1.59, p (heterogeneity)=0.802, I=0%) and ORR (RR=1.37, 95% CI: 1.20 to 1.57, p (heterogeneity)=0.619, I=0%) in BC patients treatment with DC/CIK plus chemotherapy regimen was improved than that with chemotherapy alone. There was no difference in the incidence of leukopenia, thrombocytopenia, hair loss, nausea/vomiting, hepatic complications, and neurologic complications in BC patient's treatment with DC/CIK plus chemotherapy regimen and with chemotherapy alone. Compared to chemotherapy alone, DC/CIK plus chemotherapy treatment significantly increased CR, PR, and ORR; however, there was no difference between the safeties. The authors concluded that DC/CIK plus chemotherapy treatment may be a valuable new therapeutic option for BC in women. Moreover, they stated that further studies are needed to verify the results of this study, due to the presence of unstable factors.

The authors stated that this study had several drawbacks. First, evaluation of the data set was considered to be too small for visual or statistical examination of publication bias, and the potential existence of such bias could not be determined. Therefore, these researchers assumed that publication bias might have existed. Second, eligibility criteria for inclusion in BC patients were different, which may affect the apparent consistency of the effects in these studies, and led to heterogeneity among studies. Third, potential limitation was that country could also introduce a bias. As increasing number of studies dealing with the treatment of patients with BC with CIK cells were published only in Chinese, so the results of this meta-analysis were based on Chinese patients.
Melanoma

Li et al (2017) examined the efficacy of tumor-infiltrating lymphocytes (TIL) along with interferon-alpha (IFN-α) to treat stage III malignant melanoma (MM) patients in China. Between May 2010 and October 2014, a total of 77 patients of stage III MM who underwent surgery were collected in this study. These patients were divided into 2 groups: patients who received TIL + IFN-α ± RetroNectin-activated cytokine-induced killer cells (R-CIK) in Arm 1 (n = 27) and IFN-α ± R-CIK in Arm 2 (n = 50) as adjuvant therapy. The primary end-points were disease-free survival (DFS) time and DFS rates measured at time-points of 1, 2, and 3 years. The secondary end-points were overall survival (OS) rates measured at time-points of 1, 2, 3, and 5 years as well as OS as evaluated by Kaplan-Meier. The results indicated that the median DFS and OS in Arm 1 were significantly better than those in Arm 2. The data also demonstrated that DFS rate and OS rates in Arm 1 were significantly better than those in Arm 2 at all measured time-points. The authors concluded that patients who underwent surgical excision of stage III MM appeared to enjoy prolonged DFS and OS when treated with TIL + IFN-α compared to IFN-α alone. Moreover, they stated that "In the future, a multicenter randomized phage study will become a better way to reveal the true clinical contribution of TIL combined with IFN-α for the treatment of stage III malignant melanoma".

Foley et al (2018) noted that immunotherapy is a promising method of treatment for a number of cancers. Many of the curative results have been seen specifically in advanced-stage melanoma. Despite this, single-agent therapies are only successful in a small percentage of patients, and relapse is very common. As chemotherapy is becoming a thing of the past for treatment of melanoma, the combination of cellular therapies with immunotherapies appears to be on the rise in in-vivo models and in clinical trials. These forms of therapies include TIL, T-cell receptor, or chimeric antigen receptor-modified T cells, cytokines [interleukin (IL-2), IL-15, IL-12, granulocyte-macrophage colony stimulating factor, tumor necrosis factor-α, interferon-α, interferon-γ], antibodies (αPD-1, αPD-L1, αTIM-3, αOX40, αCTLA-4, αLAG-3), dendritic cell-based vaccines, and chemokines (CXCR2). There are a substantial number of ongoing clinical trials using 2 or more of these combination therapies. Preliminary results indicated that these combination therapies are a promising area to focus on for cancer treatments, especially melanoma. The main challenges with the combination of cellular and immunotherapies are adverse events (AEs) due to toxicities and autoimmunity. Identifying mechanisms for reducing or eliminating these AEs remains a critical area of research. The authors concluded that many important questions still need to be elucidated in regard to combination cellular therapies and immunotherapies, but with the number of ongoing clinical trials, the future of curative melanoma therapies is promising.

Mullinax et al (2018) hypothesized that combining adoptive cell therapy (ACT) with cytotoxic T lymphocyte-associated antigen 4 blockade would decrease attrition and allow more patients to receive TIL. A total of 13 patients with metastatic melanoma were enrolled. Patients received 4 doses of ipilimumab (3 mg/kg) beginning 2 weeks prior to tumor resection for TIL generation, then 1 week after resection, and 2 and 5 weeks after pre-conditioning chemotherapy and TIL infusion followed by interleukin-2. The primary end-point was safety and feasibility; secondary end-points included of clinical response at 12 weeks and at 1 year after TIL transfer, progression-free survival (PFS), and OS. All patients received at least 2 doses of ipilimumab, and 12 of the 13 (92 %) received TIL. A median of 6.5 × 1,010 (2.3 × 1,010 to 1.0 × 1,011) TIL were infused. At 12 weeks following infusion, there were 5 patients who experienced objective response (38.5 %), 4 of whom continued in objective response at 1 year and 1
of which achieved complete response at 52 months. Median PFS was 7.3 months (95% confidence interval [CI]: 6.1 to 29.9 months). Grade 3 or greater immune-related adverse events (AEs) included hypothyroidism (n = 3), hepatitis (n = 2), uveitis (n = 1), and colitis (n = 1). The authors concluded that ipilimumab plus ACT for metastatic melanoma was feasible, well-tolerated, and associated with a low rate of attrition due to progression during cell expansion. They stated that this combination approach serves as a model for future efforts to improve the efficacy of ACT.

These investigators stated that this was the first prospective clinical trial using checkpoint inhibition combined with ACT. With this approach, more patients may be able to complete the therapy and receive TIL infusion, thereby potentially increasing the objective response rate by an intention to treat analysis. Direct comparison between these patients who received checkpoint inhibition and those in prior studies who received TIL alone is not possible. Moreover, the patients in this trial were checkpoint-naive, which is certainly not the case for trial-eligible metastatic melanoma patients at this time. Because of this, currently accruing ACT trials at this institution are designed to include patients that have failed checkpoint inhibitors and also incorporate more recently approved checkpoint inhibitors, specifically anti-PD1 antibodies. Data from these trials will be used to validate the fundamental conclusion from this trial that addition of checkpoint inhibitors to the treatment regimen of ACT is feasible and may increase the efficacy of TIL adoptive transfer for patients with advanced melanoma.

An UpToDate review on “Immunotherapy of advanced melanoma with immune checkpoint inhibition” (Sosman, 2018) does not mention the use of tumor-infiltrating lymphocytes as a therapeutic option.

Furthermore, National Comprehensive Cancer Network’s clinical practice guideline on “Melanoma” (Version 2.2018) does not mention the use of tumor-infiltrating lymphocytes as a therapeutic option.

Medulloblastoma

Orlando and colleagues (2018) stated that medulloblastoma is the most frequent malignant childhood brain tumor with a high morbidity. Identification of new therapeutic targets would be instrumental in improving patient outcomes. These researchers evaluated the expression of the tumor-associated antigen PRAME in biopsies from 60 medulloblastoma patients. PRAME expression was detectable in 82% of tissues independent of molecular and histopathologic subgroups. High PRAME expression also correlated with worse OS. These investigators next examined the relevance of PRAME as a target for immunotherapy. Medulloblastoma cells were targeted using genetically modified T cells with a PRAME-specific TCR (SLL TCR T cells); SLL TCR T cells efficiently killed medulloblastoma HLA-A*02+ DAOY cells as well as primary HLA-A*02+ medulloblastoma cells. Moreover, SLL TCR T cells controlled tumor growth in an orthotopic mouse model of medulloblastoma. To prevent unexpected T cell-related toxicity, an inducible caspase 9 (iC9) gene was introduced in frame with the SLL TCR; this safety switch triggered prompt elimination of genetically-modified T cells. The authors concluded that these findings indicated that T cells genetically modified with a high-affinity, PRAME-specific TCR and iC9 may represent a promising innovative approach for treating HLA-A*02+ medulloblastoma patients.
Le and Thai (2017) noted that research on adult cancer immunotherapy is proceeding at a rapid pace resulting in an impressive success rate exemplified by a few high profile cases. However, this momentum is not readily extended to pediatric immunotherapy, and it is not for lack of trying. Though reasons for the slower advance are not apparent, some issues can be raised. Pediatric cancer patients represent a distinct demographic group whose immune system is inherently different from that of mature adults. Treating pediatric patients with immunotherapy designed for adults may not yield objective clinical responses. These researchers presented an update on adoptive T-cell and natural killer-cell therapies for neuroblastoma and other childhood solid tumors. Additionally, they delineated key differences between human fetal/neonatal and adult immune systems. They hoped this would generate interests leading to the discussion of potential future directions for improving adoptive cancer immunotherapy for children.

**Cellular Therapy**

Barrett (2008) stated that cellular therapy (also known as embryonic cell therapy, fresh cell therapy, glandular therapy, live cell therapy, and organotherapy) refers to various procedures in which processed tissue from animal embryos, fetuses or organs, is injected or taken orally. Products are obtained from specific organs or tissues said to correspond with the unhealthy organs or tissues of the recipient. Proponents of cellular therapy claim that the recipient’s body automatically transports the injected cells to the target organs, where they supposedly strengthen them and regenerate their structure. The organs and glands used in cell treatment include adrenals, brain, heart, kidney, liver, ovary, pancreas, parotid, pituitary, spleen, testis, thymus, and thyroid. Several different types of cell or cell extract can be given simultaneously -- some practitioners routinely give up to 20 or more at once. The author noted that the theory behind cellular therapy is senseless; and the American Cancer Society (ACS) has strongly advised people not to seek it.

According to the American Cancer Society (ACS, 2008), cell therapy (also known as cellular therapy, fresh cell therapy, live cell therapy, glandular therapy, and xenotransplant therapy) entails the injection of processed tissue from the organs, embryos, or fetuses of animals (e.g., cows or sheep). This approach is supposed to repair cellular damage and heal sick or failing organs. Cell therapy is promoted as an alternative therapy for cancer, arthritis, heart disease, Down syndrome, and Parkinson disease. It is also marketed to counter the effects of aging, reverse degenerative diseases, improve general health, increase vitality and stamina, and enhance sexual function. Some practitioners have proposed using cell therapy to treat AIDS patients. However, available scientific evidence does not support claims that cell therapy is effective in treating cancer or any other disease. Moreover, serious adverse reactions can result from cell therapy.

Furthermore, the Centers for Medicare and Medicaid Services states that cellular therapy involves the practice of injecting humans with foreign proteins like the placenta or lungs of unborn lambs. Cellular therapy is without scientific or statistical evidence to document its therapeutic efficacy and, in fact, is considered a potentially dangerous practice. Accordingly, cellular therapy is not considered reasonable and necessary.

Alvarez et al (2013) stated that cell therapy (CTh) is a promising novel therapy for myocardial infarction (MI) and ischemic cardiomyopathy (iCMP). Recognizing AEs is important for safety evaluation, harm-prevention; and this may aid in the design of future trials. These researchers defined the prevalence of peri-procedural AEs in CTh trials in MI and iCMP. They performed a literature search using the MEDLINE.
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Database from January 1990 to October 2010. Controlled clinical trials that compared CTh with standard treatment in the setting of MI and/or ICMP were selected; AEs related to CTh were analyzed. A total of 2,472 patients from 35 trials were included in this study. There were 26 trials including 1,796 patients who used CTh in MI and 9 trials including 676 patients who used CTh in ICMP. Peri-procedural arrhythmia monitoring protocols were heterogeneous and follow-up was short in most of the trials. In MI trials, the incidence of peri-procedural AEs related to intra-coronary cell transplantation was 7.5 % (95 % CI: 6.04 to 8.96 %). Adverse events related to granulocyte colony-stimulating factor (GCS-F) used for cell mobilization for peripheral apheresis was 16 % (95 % CI: 9.44 to 22.56 %). During intra-coronary transplantation in ICMP, the incidence of peri-procedural AEs incidence was 2.6 % (95 % CI: 0.53 to 4.67 %). There were no AEs reported during trans-epicardial transplantation and AEs were rare during trans-endocardial transplantation. The authors concluded that the majority of peri-procedural AEs in CTh trials in MI occurred during intra-coronary transplantation and GCS-F administration. In ICMP, peri-procedural AE were uncommon. They stated that avoiding intra-coronary route for CTh implantation may decrease the burden of peri-procedural AEs; standardization of AEs definition in CTh trials is needed.

Smadja and colleagues (2013) noted that late evolution of peripheral arterial disease results in the apparition of critical limb ischemia (CLI). Surgery is a therapeutic option for patients with chronic disease; however, in most patients, especially those with diabetes mellitus, there are very few options and the clinical evolution is rapidly dramatic. For these reasons, CLI is one of the first diseases treated by genetic or cellular therapies aiming to improve blood flow perfusion in the lower limbs. These investigators described clinical trials on genetic therapy; most of them have been abandoned because of serious side effects, modest effects and major risks. Different types of stem cells are now used for cellular therapy: endothelial progenitor cells, early or late, activated or not, mesenchymal stem cells, embryonic stem cells and human induced pluripotent stem cells.

Teraa and associates (2013) performed a meta-analysis of all RCTs available that studied BM-derived cell therapy compared to standard care with or without placebo in CLI patients and provided summary efficacy data on this approach. A systematic search in the electronic databases of Medline, Embase, and the Cochrane Controlled Trials Register was performed. All studies were critically appraised and data were extracted and meta-analyzed using a random-effects model. Major amputation and amputation-free survival were considered as the primary end-points. A total of 12 RCTs including 510 CLI patients were identified and analyzed. The meta-analysis showed beneficial effects of BM-derived cell therapy on both subjective and surrogate objective end-points, that is, pain score, pain-free walking distance, ankle-brachial index, and transcutaneous oxygen measurements (all p < 0.00001). Overall, the RCTs showed reduced amputation rates in the therapeutic arms of the included trials with a RR on major amputation of 0.58 [95 % CI: 0.40 to 0.84; p = 0.004]. However, when only the placebo-controlled RCTs were considered, the beneficial effect on major amputation rates was considerably reduced and non-significant (RR = 0.78; 95 % CI: 0.40 to 1.51; p = 0.46). Amputation-free survival did not significantly differ between the BM-treated and the control group (RR = 1.16; 95 % CI: 0.92 to 1.48; p = 0.22). The authors concluded that the findings of this meta-analysis underlined the promising potential of BM-derived cell therapy in CLI patients. More importantly, the results of placebo-controlled and non-placebo-controlled RCTs seemed to diverge, which stresses the necessity to use placebo in the control arms of these trials. These
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researchers stated that future well-designed larger placebo-controlled RCTs are needed and should include long-term follow-up data to assess durability of treatment effects.

Lui and Ng (2013) summarized the current evidence on the safety and effectiveness of cell therapy for the treatment of tendinopathy. These researchers performed a systematic literature search using various databases with relevant keywords. Both original animal and human controlled studies, covering any cell type for the treatment of naturally occurring, overuse or collagenase-induced tendinopathy, and with full text available, were included. The quality of all included studies was assessed. Relevant data on study design, safety and efficacy outcomes were extracted. A total of 11 original studies were selected, of which 9 were pre-clinical studies using the collagenase-induced tendon injury model and 2 were clinical studies. Types of cells, scaffolds, dosages and treatment regimens used varied. All the studies performed cell injection once. A critical appraisal of the included studies showed sub-optimal blinding. Cell therapy was generally reported to be safe, except minor complications, in the short-term. Cell therapy was reported to improve tendon architecture in histology but equivocal finding was observed in sonographic/MRI examination, functional and biomechanical performance. The authors concluded that the current evidence was inadequate to make a conclusion whether cell therapy was safe and effective. They stated that further study with adequate sample size and follow-up time, appropriate controls and optimal blinding is needed. Confirmation of finding, using different tendinopathy animal models, by systematic investigation of the effects of cell sources, dosages and regimens on the outcomes, and by the inclusion of tendon pain assessment in both animals and human, is recommended.

Cisbani and Cicchetti (2014) remarked that the hope that cell transplantation therapies will provide an ideal treatment option for neurodegenerative diseases has been considerably revived with the remarkable advancements in genetic engineering towards active cell fate determination in-vitro. However, for disorders such as Huntington's disease (HD), the challenges that researchers face are still enormous. This autosomal dominant genetic disorder leads, in part, to massive neuronal loss and severe brain atrophy which, despite the cell type used, cannot be easily repaired. And before large clinical trials are even considered, investigators must take a critical look at the outcomes of the pilot studies already available, not only from a clinical perspective but also by a careful assessment of what they can learn from the autopsies of HD patients who have undergone transplantation. The authors summarized and discussed the 7 transplantation pilot trials that were initiated worldwide in HD patients more than 10 years ago, with a particular emphasis on the post-mortem analyses of 9 unique cases. Moreover, they described a series of factors, both technical and related to patient selection, that they deem important to predict the outcome of cell grafts in HD therapy.

Liu and colleagues (2014) stated that cell therapy is emerging as a viable therapy to restore neurological function after stroke. Many types of stem/progenitor cells from different sources have been explored for their feasibility and efficacy for the treatment of stroke. Transplanted cells not only have the potential to replace the lost circuitry, but also produce growth and trophic factors, or stimulate the release of such factors from host brain cells, thereby enhancing endogenous brain repair processes. Although stem/progenitor cells have shown a promising role in ischemic stroke in experimental studies as well as initial clinical pilot studies, cellular therapy is still at an early stage in humans. Many critical issues need to be addressed including the therapeutic time window, cell type selection, delivery route, and in-vivo monitoring of their migration pattern. These researchers provided a comprehensive synopsis of pre-clinical
Marquis-Gravel et al (2014) noted that stem cell (SC) therapy improves left ventricular function and dimensions in ischemic heart disease. Few small-scale trials have studied the effects of SC therapy on non-ischemic CMP, the leading cause of heart transplantation in the adults. These investigators examined the effects of SC therapy for non-ischemic CMP by conducting a systematic review of the literature and meta-analysis of RCTs. Medline, EBM Reviews-Cochrane Central Register of Controlled Trials, Embase, and the ClinicalTrials.gov databases were screened for RCTs involving SC for treatment of non-ischemic CMP. Weighted mean differences of improvement of left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD) were calculated using a random effect analysis model. A total of 4 trials were included in this meta-analysis (244 patients). The weighted mean LVEF improvement was 4.87 % (95 % CI: 1.32 to 8.43 %) in the treatment group compared with the control group (p = 0.01). The weighted mean decrease of LVEDD in the treatment group was of -2.19 mm (95 % CI: -5.69 to 1.30) compared with the control group (p = 0.22). On subgroup analysis, results were similar in studies involving peripheral CD34-positive or bone marrow-derived mononuclear cells (p = 0.33 for subgroup differences). The authors concluded that this was the first meta-analysis to show that for the treatment of non-ischemic CMP, SC therapy might improve LVEF, but not LVEDD. They stated that further trials should aim to circumscribe the optimal SC regimen in this setting, and to assess long-term clinical outcomes as primary end-points.

In a phase I clinical trial, Lee and colleagues (2015) stated that chimeric antigen receptor (CAR) modified T cells targeting CD19 have shown activity in case series of patients with acute and chronic lymphocytic leukemia (ALL and CLL) and B-cell lymphomas, but feasibility, toxicity, and response rates of consecutively enrolled patients treated with a consistent regimen and assessed on an intention-to-treat basis have not been reported. In a phase I clinical trial, these researchers defined feasibility, toxicity, maximum tolerated dose (MTD), response rate, and biological correlates of response in children and young adults with refractory B-cell malignancies treated with CD19-CAR T cells. This dose-escalation trial consecutively enrolled children and young adults (aged 1 to 30 years) with relapsed or refractory ALL or non-Hodgkin lymphoma (NHL). Autologous T cells were engineered via an 11-day manufacturing process to express a CD19-CAR incorporating an anti-CD19 single-chain variable fragment plus TCR zeta and CD28 signaling domains. All patients received fludarabine and cyclophosphamide before a single infusion of CD19-CAR T cells. Using a standard 3 × 3 design to establish the MTD, patients received either 1 × 10(6) CAR-transduced T cells per kg (dose 1), 3 × 10(6) CAR-transduced T cells per kg (dose 2), or the entire CAR T-cell product if sufficient numbers of cells to meet the assigned dose were not generated. After the dose-escalation phase, an expansion cohort was treated at the MTD. Between July 2, 2012, and June 20, 2014, a total of 21 patients (including 8 who had previously undergone allogeneic hematopoietic stem-cell transplantation) were enrolled and infused with CD19-CAR T cells; 19 received the prescribed dose of CD19-CAR T cells, whereas the assigned dose concentration could not be generated for 2 patients (90 % feasible). All patients enrolled were assessed for response. The MTD was defined as 1 × 10(6) CD19-CAR T cells per kg. All toxicities were fully reversible, with the most severe being grade 4 cytokine release syndrome that occurred in 3 (14 %) of 21 patients (95 % CI: 3.0 to 36.3). The most common non-hematological grade 3 adverse events were fever (9 [43 %] of 21 patients), hypokalemia (9 [43 %] of 21 patients), fever and neutropenia (8 [38 %] of 21 patients), and cytokine release...
syndrome (3 [14 %] of 21 patients). The authors concluded that CD19-CAR T cell therapy was feasible, safe, and mediated potent anti-leukemic activity in children and young adults with chemotherapy-resistant B-precursor ALL. All toxicities were reversible and prolonged B-cell aplasia did not occur.

Ischemic Heart Disease

Jansen Of Lorkeers et al (2015) stated that in regenerative therapy for ischemic heart disease, use of both autologous and allogeneic stem cells has been investigated. Autologous cell can be applied without immunosuppression, but availability is restricted, and cells have been exposed to risk factors and aging. Allogeneic cell therapy enables pre-operative production of potent cell lines and immediate availability of cell products, allowing off-the-shelf therapy. It is unknown which cell source is preferred with regard to improving cardiac function. These researchers performed a meta-analysis of pre-clinical data of cell therapy for ischemic heart disease. They conducted a systematic literature search to identify publications describing controlled pre-clinical trials of unmodified stem cell therapy in large animal models of myocardial ischemia. Data from 82 studies involving 1,415 animals showed a significant improvement in mean LVEF in treated compared with control animals (8.3 %, 95 % CI: 7.1 to 9.5; p < 0.001). Meta-regression revealed a similar difference in LVEF in autologous (8.8 %, 95 % CI: 7.3 to 10.3; n = 981) and allogeneic (7.3 %, 95 % CI: 4.4 to 10.2, n = 331; p = 0.3) cell therapies. The authors concluded that autologous and allogeneic cell therapy for ischemic heart disease show a similar improvement in LVEF in large animal models of myocardial ischemia, compared with placebo. They stated that these results are important for the design of future clinical trials.

Chronic Kidney Disease

Papazova et al (2015) stated that cell-based therapy is a promising strategy for treating chronic kidney disease (CKD) and is currently the focus of pre-clinical studies. These researchers performed a systematic review and meta-analysis to evaluate the effectiveness of cell-based therapy in pre-clinical (animal) studies of CKD, and determined factors affecting cell-based therapy efficacy in order to guide future clinical trials. A total of 71 articles met the inclusion criteria. Standardized mean differences (SMD) and 95 % CI were calculated for outcome parameters including plasma urea, plasma creatinine, urinary protein, blood pressure, glomerular filtration rate, glomerulosclerosis and interstitial fibrosis. Sub-analysis for each outcome measure was performed for model-related factors (species, gender, model and timing of therapy) and cell-related factors (cell type, condition and origin, administration route and regime of therapy). Overall, meta-analysis showed that cell-based therapy reduced the development and progression of CKD. This was most prominent for urinary protein (SMD, 1.34; 95 % CI: 1.00 to 1.68) and urea (1.09; 0.66 to 1.51), both p < 0.001. Changes in plasma urea were associated with changes in both glomerulosclerosis and interstitial fibrosis. Sub-analysis showed that cell type (bone-marrow-derived progenitors and mesenchymal stromal cells being most effective) and administration route (intravenous or renal artery injection) were significant predictors of therapeutic effectiveness. The timing of therapy in relation to clinical manifestation of disease, and cell origin and dose, were not associated with effectiveness. The authors concluded that the findings of this meta-analysis confirmed that cell-based therapies improve impaired renal function and morphology in pre-clinical models of CKD. They stated that their analyses can be used to optimize experimental interventions and thus support both improved pre-clinical research and development of cell-based therapeutic interventions in a clinical setting.
Heart Failure

Harvey et al (2015) noted that heart failure (HF) is the major cause of mortality worldwide. For more than a decade, cell-based therapies have been developed as treatment for heart disease as an alternative to current therapies. Trials and systematic reviews have assessed the safety and effectiveness of cell therapies in a diverse number of participants and clinical settings. These investigators collated and synthesized evidence from all systematic reviews related to cell-based therapies and HF. A total of 11 systematic reviews were identified through searches of electronic databases up to June 2014. These researchers set out to answer 2 key questions on the effectiveness of cell therapies in HF: (i) What is the overall effect of cell therapies on primary outcomes such as left ventricular ejection fraction (LVEF) and mortality? and (ii) How important is it to define the clinical setting and length of follow-up when assessing cell therapies and HF? The authors concluded that there appeared to be enough evidence to suggest that cell therapies have a moderate, long-lasting effect on LVEF, but the reduction on the risk of mortality observed by some systematic reviews needs to be confirmed in larger, statistically powered clinical trials. Furthermore, they stated that in order to strengthen conclusions, it is important to evaluate clinical evidence for defined clinical settings and to standardize the length of follow-up when comparing outcome data across several trials and systematic reviews.

Orthopedic Disorders

Xu and colleagues (2015) stated that articular cartilage is an avascular tissue that has limited capacity for self-repair. Mesenchymal stromal cells have been considered as potential candidates for cartilage regeneration. However, clinical results of cartilage formation with the use of these cells need evaluation. These researchers evaluated the effect of mesenchymal stromal cell treatment on articular cartilage defects. They searched PubMed, Embase and the Cochrane Central Register of Controlled Trials with key words including "cartilage", "clinical trial", "mesenchymal", "stromal" and "stem cell" up to December 3, 2014. They selected the controlled trial that used treatment with mesenchymal stromal cells on cartilage injury compared with other treatment. These investigators assessed the results of the meta-analysis by means of the error matrix approach. The outcome measures were ranked as comprehensive evaluation index, highest relevance; unilateral evaluation index, medial relevance; and single evaluation index, lowest relevance. A total of 11 trials assessing 558 patients were included in the meta-analysis. Stem cell treatment significantly improved the American Orthopedic Foot and Ankle Society Scale (standard mean difference, SMD, 0.91; 95 % CI: 0.52 to 1.29). The Osteo-Arthritis Outcome Score was also significantly improved in stem cell treatment (SMD, 2.81; 95 % CI: 2.02 to 3.60). Other comprehensive evaluation indexes, such as the American Knee Society Knee Score System (SMD -0.12, 95 % CI: -1.02 to 0.78), the Hospital for Special Surgery Knee Rating Scale (SMD, 0.24, 95 % CI: -0.56 to 1.05) and the International Knee Documentation Committee (SMD, -0.21; 95 % CI: -0.77 to 0.34), appeared to have no significant differences by use of stem cell and other treatments. Overall, there was no obvious advantage regarding the application of stem cells to treat cartilage injury, compared with other treatments. The authors concluded that assessment of the comprehensive evaluation index indicated that there were no significant differences after stem cell treatment. However, assessment of clinical symptoms and cartilage morphology showed significant improvement after stem cell treatment.
In an editorial, Noh and Lee (2015) evaluated the present state of cellular therapy in the field of orthopedics, including clinical trials as well as various research areas. Both the target diseases for cellular therapy and the target cells were reviewed. New methods to activate the cells were interesting to review. Most advanced clinical trials were also included because several of them have advanced to phase III clinical trials. In the orthopedic field, there are many diseases with a definite treatment gap at this time. Because cellular therapies can regenerate damaged tissues, there is a possibility for cellular therapies to become disease modifying drugs. It is not clear whether cellular therapies will become the standard of care in any of the orthopedic disorders (e.g., repair of bone, cartilage and tendon), however the amount of research being performed and the number of clinical trials that are on-going made the authors believe that cellular therapies will become important treatment modalities within several years especially when supplemented with procedures that improve the effectiveness of these treatments.

**Traumatic Brain Injury**

Peng and colleagues (2015) stated that the therapeutic potential of mesenchymal stem cells (MSCs) for traumatic brain injury (TBI) is attractive. These researchers conducted a systematic review and meta-analysis to (i) systematically review the literatures describing the effect of MSCs therapy in animal models of TBI, (ii) determine the estimated effect size of functional locomotor recovery after experimental TBI, and (iii) to provide empirical evidence of biological factors associated with greater efficacy. They conducted a systematic search of PubMed, Embase, and Web of Science and hand searched related references. Studies were selected if they reported the efficacy of MSCs in animal models of TBI. Two investigators independently assessed the identified studies. These investigators extracted the details of individual study characteristics from each publication, assessed study quality, evaluated the effect sizes of MSCs treatment, and performed stratified meta-analysis and meta-regression, to assess the influence of study design on the estimated effect size. The presence of small effect sizes was investigated using funnel plots and Egger's tests. A total of 28 eligible controlled studies were identified. The study quality was modest; between-study heterogeneity was large. Meta-analysis showed that MSCs exert statistically significant positive effects on sensorimotor and neurological motor function. For sensorimotor function, maximum effect size in studies with a quality score of 5 was found in the weight-drop impact injury TBI model established in male SD rats, to which syngeneic umbilical cord-derived MSCs intra-cerebrally at cell dose of (1-5)×10(6) was administered 6 hours following TBI, using ketamine as anesthetic agent. For neurological motor function, effect size was maximum for studies with a quality score of 5, in which the weight-drop impact injury TBI models of the female Wistar rats were adopted, with administration syngeneic bone marrow-derived MSCs intravenously at cell dose of 5×10(6) at 2 months after TBI, using sevofluorane as anesthetic agent. The authors concluded that MSCs therapy may improve locomotor recovery after TBI. However, they stated that additional well-designed and well-reported animal studies are needed to guide further clinical studies.

**Kidney Transplant Recipients**

Sawitzki and colleagues (2020) stated that the use of cell-based medicinal products (CBMPs) represents a state-of-the-art approach for reducing general immunosuppression in organ transplantation. These researchers tested multiple regulatory CBMPs in kidney transplant trials to examine the safety of regulatory CBMPs when combined with reduced immunosuppressive treatment. The ONE Study
consisted of 7 investigator-led, single-arm trials conducted internationally at 8 hospitals in France, Germany, Italy, the UK, and the U.S. (60-week follow-up). Included patients were living-donor kidney transplant recipients aged 18 years and older. The reference group trial (RGT) was a standard-of-care group given basiliximab, tapered steroids, mycophenolate mofetil, and tacrolimus. A total of 6 non-randomized phase-I/II cell therapy group (CTG) trials were pooled and analyzed, in which patients received 1 of 6 CBMPs containing regulatory T cells, dendritic cells, or macrophages; patient selection and immunosuppression mirrored the RGT, except basiliximab induction was substituted with CBMPs and mycophenolate mofetil tapering was allowed. None of the trials was randomized and none of the individuals involved were masked. The primary end-point was biopsy-confirmed acute rejection (BCAR) within 60 weeks after transplantation; AE coding was centralized. The 7 trials took place between December 11, 2012 and November 14, 2018. Of 782 patients examined for eligibility, 130 (17 %) patients were enrolled and 104 were treated and included in the analysis. The 66 patients who were treated in the RGT were 73 % men and had a median age of 47 years. The 38 patients who were treated across 6 CTG trials were 71 % men and had a median age of 45 years. Standard-of-care immunosuppression in the recipients in the RGT resulted in a 12 % BCAR rate (expected range 3.2 to 18.0). The overall BCAR rate for the 6 parallel CTG trials was 16 %; 15 (40 %) patients given CBMPs were successfully weaned from mycophenolate mofetil and maintained on tacrolimus monotherapy. Combined AE data and BCAR episodes from all 6 CTG trials revealed no safety concerns when compared with the RGT. Fewer episodes of infections were registered in CTG trials versus the RGT. The authors concluded that regulatory cell therapy is achievable and safe in living-donor kidney transplant recipients, and is associated with fewer infectious complications, but similar rejection rates in the 1st year; thus, immune cell therapy is a potentially useful therapeutic approach in recipients of kidney transplant to minimize the burden of general immunosuppression.

CAR T Therapy

Almasbak et al (2016) noted that the development of novel targeted therapies with acceptable safety profiles is critical to successful cancer outcomes with better survival rates. Immunotherapy offers promising opportunities with the potential to induce sustained remissions in patients with refractory disease. Recent dramatic clinical responses in trials with gene modified T cells expressing chimeric antigen receptors (CARs) in B-cell malignancies have generated great enthusiasm. This therapy might pave the way for a potential paradigm shift in the way that refractory or relapsed cancers are treated. CARs are genetically engineered receptors that combine the specific binding domains from a tumor targeting antibody with T cell signaling domains to allow specifically targeted antibody re-directed T cell activation. Despite current successes in hematological cancers, this field is only in the beginning of exploring the powerful potential of CAR re-directed T cells in the control and elimination of resistant, metastatic, or recurrent non-hematological cancers. The authors stated that this rapidly developing field meets with considerable challenges that have to be addressed to realize the promise of the CAR T cell therapy for a broader use. While CAR T cell therapies have provided encouraging preliminary signs of efficacy in solid tumors, clinical data so far fail by a large margin to meet expectations for game-changing cell therapy. A major focus of translational research is to improve specificity, efficacy, and safety of CAR T cells to be used in cancers beyond leukemia. Truly tumor specific surface antigens are hardly identified, and the implementation of effective mechanisms to mitigate life-threatening and unexpected off-target toxicities is crucial. Further, issues regarding tumor heterogeneity, tumor immunosuppression, and lack of T cell trafficking and persistence are being addressed to improve efficacy of solid tumor
Combining T cell therapies with immunomodulatory agents, for example, checkpoint inhibitors and cytokines, and/or small-molecular antagonists that block biochemical pathways crucial for tumor growth, constitute exciting opportunities that may have synergistic effects in augmenting anti-tumor responses.

Holzinger et al (2016) noted that in recent years, cancer treatment involving adoptive cell therapy with CAR-modified patient's immune cells has attracted growing interest. Using gene transfer techniques, the patient's T cells are modified ex-vivo with a CAR that re-directs the T cells toward the cancer cells through an antibody-derived binding domain. The T cells are activated by the CAR primary signaling and co-stimulatory domains. Such "second generation" CAR T cells induced complete remission of B cell malignancies in the long-term. In this fast-moving field with a growing number of engineered T cell products, the authors listed about 100 currently ongoing trials that involve CAR T cells targeting hematopoietic malignancies and solid cancer. They discussed major challenges in the further development of the therapy.

Al-Hujaily et al (2016) stated that multiple myeloma (MM) is a disorder of terminally differentiated plasma cells characterized by clonal expansion in the bone marrow (BM). It is the 2nd-most common hematologic malignancy. Despite significant advances in therapeutic strategies, MM remains a predominantly incurable disease emphasizing the need for the development of new treatment regimens. Immunotherapy is a promising treatment modality to circumvent challenges in the management of MM. Many novel immunotherapy strategies, such as adoptive cell therapy and monoclonal antibodies, are currently under investigation in clinical trials, with some already demonstrating a positive impact on patient survival. The authors noted that CAR-T cell therapy has entered successfully into clinical trials and showed some promising results, while CAR-NK cells are still limited to pre-clinical studies at this time. A pilot clinical trial was undertaken using a 2nd-generation recombinant lentiviral vector to generate anti-CD138 CAR-T cells; 5 patients diagnosed with refractory MM were treated. After a follow-up for 7 months, 4 patients were found to have stable disease, and 1 patient with advanced plasma cell leukemia had a reduction of myeloma cells (from 10.5 % to less than 3 %) in the peripheral blood. Data from this study showed that the CAR-T cells homed to the BM. These results suggested that CD138 CAR-T cell therapy for MM is well-tolerated and has potential anti-tumor activity. This research is still underway (ongoing phase I/II study (NCT01886976)).

Sackstein et al (2017) noted that advances in cancer immunotherapy have offered new hope for patients with metastatic disease. This unfolding success story has been exemplified by a growing arsenal of novel immunotherapeutics, including blocking antibodies targeting immune checkpoint pathways, cancer vaccines, and adoptive cell therapy (ACT). Nonetheless, clinical benefit remains highly variable and patient-specific, in part, because all immunotherapeutic regimens vitally hinge on the capacity of endogenous and/or adoptively transferred T-effector (Teff) cells, including CAR T cells, to home efficiently into tumor target tissue. Thus, defects intrinsic to the multi-step T-cell homing cascade have become an obvious, though significantly under-recognized contributor to immunotherapy resistance. Conspicuous have been low intra-lesional frequencies of tumor-infiltrating T-lymphocytes (TILs) below clinically beneficial threshold levels, and peripheral rather than deep lesional TIL infiltration. Therefore, a Teff cell "homing deficit" may arguably represent a dominant factor responsible for ineffective immunotherapeutic outcomes, as tumors resistant to immune-targeted killing thrive in such permissive, immune-vacuous microenvironments. Fortunately, emerging data are shedding light into the diverse mechanisms of immune escape by which tumors restrict Teff cell trafficking and lesional
penetrance. These researchers scrutinized evolving knowledge on the molecular determinants of Teff cell navigation into tumors. By integrating recently described, though sporadic information of pivotal adhesive and chemokine homing signatures within the tumor microenvironment with better established paradigms of T-cell trafficking under homeostatic or infectious disease scenarios, they seek to refine currently incomplete models of Teff cell entry into tumor tissue. The authors further summarized how cancers thwart homing to escape immune-mediated destruction and raise awareness of the potential impact of immune checkpoint blockers on Teff cell homing. Finally, they speculated on innovative therapeutic opportunities for augmenting Teff cell homing capabilities to improve immunotherapy-based tumor eradication in cancer patients, with special focus on malignant melanoma.

Angina

Khan and colleagues (2016) stated that the effect of stem/progenitor cells on myocardial perfusion and clinical outcomes in patients with refractory angina remains unclear because studies published to date have been small phase I/phase-II clinical trials. These researchers performed a meta-analysis of RCTs to evaluate the effect of cell-based therapy in patients with refractory angina who were ineligible for coronary revascularization. Several data sources were searched from inception to September 2015, which yielded 6 studies. The outcomes pooled were indices of angina (anginal episodes, Canadian Cardiovascular Society angina class, exercise tolerance, and anti-anginal medications), myocardial perfusion, and clinical end-points. These investigators combined the reported clinical outcomes (MI, cardiac-related hospitalization, and mortality) into a composite end-point (major adverse cardiac events). Mean difference, SMD, or ORs were calculated to assess relevant outcomes. The analysis showed an improvement in anginal episodes (MD, -7.81; 95 % CI: -15.22 to -0.41), use of anti-anginal medications (SMD, -0.59; 95 % CI: -1.03 to -0.14), Canadian Cardiovascular Society class (MD, -0.58; 95 % CI: -1.00 to -0.16), exercise tolerance (SMD, 0.331; 95 % CI: 0.08 to 0.55), and myocardial perfusion (SMD, -0.49; 95 % CI: -0.76 to -0.21) and a decreased risk of major adverse cardiac events (OR, 0.49; 95 % CI: 0.25 to 0.98) and arrhythmias (OR, 0.25; 95 % CI: 0.06 to 0.98) in cell-treated patients when compared with patients on maximal medical therapy. The authors concluded that the present meta-analysis indicated that cell-based therapies are not only safe but also lead to an improvement in indices of angina, relevant clinical outcomes, and myocardial perfusion in patients with refractory angina. They stated that these encouraging results suggested that larger, phase III RCTs are needed to determine the effect of stem/progenitor cells in refractory angina.

Broncho-Pulmonary Dysplasia

Mobius and Thebaud (2016) noted that despite great achievements in neonatal and perinatal medicine over the past decades, the immature lung remains the most critical organ to care for after premature birth. As a consequence, broncho-pulmonary dysplasia (BPD) remains the most common complication of extreme prematurity. Broncho-pulmonary dysplasia impairs normal development and may cause lifelong morbidities. At present, there is no effective treatment for BPD -- including preventing premature birth. Recent insights into the biology of stem and progenitor cells have ignited the hope of protecting the immature lung, and even regenerating an already damaged lung by using exogenous stem cells or progenitor cells as therapeutics. These therapies are still experimental, and knowledge on the exact mechanisms behind the beneficial effects seen in various animal models of BPD is limited. Nevertheless, early phase clinical trials have started, and encouraging steps towards the therapeutic use of these cells are being made.
Motor Neuron Diseases (e.g., Amyotrophic Lateral Sclerosis)

In a Cochrane review, Abdul Wahid and colleagues (2016) evaluated the effects of cell-based therapy for patients with amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND), compared with placebo or no additional treatment. On June 21, 2016, these investigators searched the Cochrane Neuromuscular Specialized Register, CENTRAL, MEDLINE, and Embase. They also searched 2 clinical trials' registries for ongoing or unpublished studies. They planned to include RCTs, quasi-RCTs and cluster RCTs that assigned people with ALS/MND to receive cell-based therapy versus a placebo or no additional treatment. Co-interventions were allowable, provided that they were given to each group equally. No studies were eligible for inclusion in the review; they identified 4 ongoing trials. The authors concluded that there is currently a lack of high-quality evidence to guide practice on the use of cell-based therapy to treat ALS/MND. There is a need for large, prospective RCTs to establish the effectiveness of cellular therapy and to determine patient-, disease- and cell treatment-related factors that may influence the outcome of cell-based therapy. The major goals of future research should be to determine the appropriate cell source, phenotype, dose, and route of delivery, as these will be key elements in designing an optimal cell-based therapy program for patients with ALS/MND. They stated that future research should also explore novel treatment strategies, including combinations of cellular therapy and standard or novel neuro-protective agents, to find the best possible approach to prevent or reverse the neurological deficit in ALS/MND, and to prolong survival in this debilitating and fatal condition.

Osteoarthritis and Focal Cartilage Defects

Chahla and colleagues (2016) stated that intra-articular cellular therapy injections constitute an appealing strategy that may modify the intra-articular milieu or regenerate cartilage in the settings of osteoarthritis (OA) and focal cartilage defects. However, little consensus exists regarding the indications for cellular therapies, optimal cell sources, methods of preparation and delivery, or means by which outcomes should be reported. These investigators presented a systematic review of the current literature regarding the safety and effectiveness of cellular therapy delivered by intra-articular injection in the knee that provided a Level of Evidence of III or higher. A total of 420 papers were screened; methodological quality was assessed using a modified Coleman methodology score. Only 6 studies (4 Level II and 2 Level III) met the criteria to be included in this review; 3 studies were on treatment of OA and 3 were on treatment of focal cartilage defects. These included 4 RCTs without blinding, 1 prospective cohort study, and 1 retrospective therapeutic case-control study. The studies varied widely with respect to cell sources, cell characterization, adjuvant therapies, and assessment of outcomes. Outcome was reported in a total of 300 knees (124 in the OA studies and 176 in the cartilage defect studies). Mean follow-up was 21.0 months (range of 12 to 36 months). All studies reported improved outcomes with intra-articular cellular therapy and no major AEs. The mean modified Coleman methodology score was 59.1 ± 16 (range of 32 to 82). The authors concluded that studies of intra-articular cellular therapy injections for OA and focal cartilage defects in the human knee suggested positive results with respect to clinical improvement and safety. However, the improvement was modest and a placebo effect cannot be disregarded. The overall quality of the literature was poor, and the methodological quality was fair, even among Level-II and III studies. They stated that effective clinical assessment and optimization of injection therapies will demand greater attention to study methodology, including blinding; standardized quantitative methods for cell harvesting, processing, characterization, and delivery; and standardized reporting of clinical and structural outcomes.
Myocardial Infarction

Wang and colleagues (2018) noted that bone marrow mononuclear cell (BMMNC) therapy has been used as an adjunctive treatment in patients with ST-elevated myocardial infarction (STEMI). However, the therapeutic efficacy of this approach remains controversial. In a meta-analysis, these investigators evaluated the impact of cell therapy on left ventricular function after STEMI. They searched through PubMed and Embase databases till 2017 for all relevant publications using certain search terms; RCTs investigating the effect of BMMNC therapy in patients with STEMI who underwent percutaneous coronary intervention (PCI) were selected. Wall motion score index (WMSI), infarct size, wall thickening, and myocardial perfusion were the endpoints. A total of 24 trials with 1,536 patients were included in this study. Overall, cell therapy reduced infarct size by -2.32 (95 % CI: -4.03 to -0.62; p = 0.007; I²=24 %) and improved myocardial perfusion by -3.04 (95 % CI: -3.94 to -2.15; p < 0.001; I²=0 %).

However, there was no significant difference between treatment group and control group in WMSI or wall thickening. The authors concluded that intracoronary BMMNC infusion was safe for patients with STEMI. It was also associated with improvement of infarct size and myocardial perfusion. Moreover, they stated that further multi-center randomized trials are needed to validate the efficacy of this treatment.

Musculoskeletal Disorders

Piuzzi and colleagues (2019) determined the growth rate and the trends of musculoskeletal cellular therapy trials in the National Institutes of Health (NIH) Clinical Trials Data Bank; analyzed the study design and characteristics; and evaluated which cellular therapies and disease conditions are studied. A systematic review of musculoskeletal clinical trials from 2005 to 2016 using cell-based therapies as the primary intervention was performed through ClinicalTrials.gov. The number of musculoskeletal cell-based clinical trials is increasing, with most being early stage, phase-I/II, and using autologous cells harvested mostly from bone marrow to target cartilage-related diseases. Among the 282 clinical trials identified, only 99 (35.1 %) were completed; 62 of the 99 (62.6 %) did not list any related publications.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “*”:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td></td>
<td>Adoptive Immunotherapy:</td>
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<tr>
<td></td>
<td>Other CPT codes related to the CPB:</td>
</tr>
<tr>
<td>36511</td>
<td>Therapeutic apheresis; for white blood cells</td>
</tr>
<tr>
<td>86357</td>
<td>Natural killer (NK) cells, total count</td>
</tr>
<tr>
<td>88230</td>
<td>Tissue culture for non-neoplastic disorders; lymphocyte</td>
</tr>
<tr>
<td>88237</td>
<td>Tissue culture for neoplastic disorders; bone marrow, blood cells</td>
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<tr>
<td>88239</td>
<td>solid tumor</td>
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<tr>
<td></td>
<td>HCPCS code not covered for indications listed in the CPB:</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<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>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

- A00.0 - B99.9 Certain infectious and parasitic diseases
- C00.0 - D09.9 Malignant neoplasms and malignant carcinoid tumors
- E85.0 - E85.9 Amyloidosis
- G30.0 - G30.9 Alzheimer's disease
- G72.41 Inclusion body myositis [IBM]

Cellular Therapy:

HCPCS codes not covered for indications listed in the CPB:

- M0075 Cellular therapy

ICD-10 codes not covered for indications listed in the CPB (not all inclusive):

- B20 Human immunodeficiency virus [HIV] disease
- C00.0 - D09.9 Malignant neoplasms and malignant carcinoid tumors
- E08.0 - E13.9 Diabetes mellitus
- G10 Huntington's disease
- G12.20 - G12.29 Motor neuron disease
- I10 - I16.2 Hypertensive disease
- I20.1 - I20.9 Angina pectoris
- I21.01 - I22.9 ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
- I24.0 - I25.9 Ischemic heart diseases
- I42.8 Other cardiomyopathies [non-ischemic cardiomyopathy]
- I50.1 - I50.9 Heart failure
- I63.50 - I63.9 Cerebral infarction due to unspecified occlusion
- I70.0 - I70.92 Atherosclerosis
- I73.00 - I73.9 Other peripheral vascular disease [e.g., critical limb ischemia]
- I74.2 - I74.4 Embolism and thrombosis of arteries of the extremities
- I75.011 - I75.029 Atheroembolism of extremities
- I80.00 - I80.209 Phlebitis and thrombophlebitis of extremities
- I82.401 - I82.529 Venous embolism and thrombosis of vessels of lower extremity
- I99.9 Unspecified disorder of circulatory system
The above policy is based on the following references:

Adoptive Immunotherapy


61. Sosman JA. Immunotherapy of advanced melanoma with immune checkpoint inhibition. UpToDate Inc., Waltham, MA. Last reviewed April 2018.


Cellular Therapy

Amendment to Aetna Clinical Policy Bulletin Number: 0641
Adoptive Immunotherapy and Cellular Therapy

There are no amendments for Medicaid.

revised 09/23/2020

Proprietary