**Dendritic Cell Immunotherapy**

**Number: 0377**

**Policy**

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers dendritic cell immunotherapy experimental and investigational because the peer-reviewed medical literature does not support its clinical use at this time.

See

- **CPB 0641 - Adoptive Immunotherapy and Cellular Therapy**
- **CPB 0802 - Prostate Cancer Vaccine**

**Background**

Dendritic cells (DCs) are the most potent type of antigen presenting cells and are vital in inducing activation and proliferation of T-lymphocytes. Their unique property has prompted their recent application to therapeutic cancer vaccines. Isolated DCs containing tumor antigen ex-vivo and administered as a cellular vaccine, have been found to induce protective and therapeutic anti-tumor immunity in experimental animals.
The clinical evaluation of DC immunotherapy in humans is in its earliest phases for the treatment of malignancies such as leukemia, lymphoma, melanoma, and certain solid tumors. Specifically, melanoma-associated antigens have been characterized at the molecular level and melanoma vaccine is currently being investigated in clinical trials. Dendritic cells immunotherapy involves isolating dendritic cells from either circulating blood or bone marrow cells from the patient (or HLA-matched donor) and then exposing them to proteins from the patient's cancer cells in order to activate T-lymphocytes. These lymphocytes are grown in bioreactors to be infused into the patient when sufficient numbers have been obtained.

Currently, no conclusions regarding the efficacy of DC immunotherapy can be made from the anecdotal reports reported in the published, peer-reviewed medical literature. Although DC immunotherapy appears to be a promising modality for the treatment of cancer, completion of randomized trials is necessary. Specifically, the appropriate antigen(s), adjuvant(s), dose, route and schedule need to be established. In a review of the evidence, Figdor et al (2004) concluded that "although early clinical trials indicate that [dendritic cell] vaccines can induce immune responses in some cancer patients, careful study design and use of standardized clinical and immunological criteria are needed".

Ardon et al (2012) noted that DC-based tumor vaccination has rendered promising results in relapsed high-grade glioma patients. In the HGG-2006 trial (EudraCT 2006-002881-20), feasibility, toxicity, and clinical efficacy of the full integration of DC-based tumor vaccination into standard post-operative radiochemotherapy were studied in 77 patients with newly diagnosed glioblastoma. Autologous DC was generated after leukapheresis, which was performed before the start of radiochemotherapy. Four weekly induction vaccines were administered after the 6-week course of concomitant radiochemotherapy. During maintenance chemotherapy, 4 boost vaccines are given. Feasibility and progression-free survival (PFS) at 6 months (6 mo-PFS) were the primary end-points. Overall survival (OS) and immune profiling, rather than monitoring, as assessed in patients' blood samples, were the secondary end-points. Analysis has been done on intent-to-treat basis. The treatment was feasible without major toxicity. The 6 mo-PFS was 70.1% from inclusion. Median OS was 18.3 months. Outcome improved significantly with lower EORTC RPA classification. Median OS was 39.7, 18.3, and 10.7 months for RPA classes III, IV, and V, respectively. Patients with a methylated MGMT promoter had significantly better PFS (p = 0.0027) and OS (p = 0.0082) as compared to patients with an un-methylated status. Exploratory "immunological
profiles" were built to compare to clinical outcome, but no statistical significant evidence was found for these profiles to predict clinical outcome. The authors concluded that full integration of autologous DC-based tumor vaccination into standard post-operative radiochemotherapy for newly diagnosed glioblastoma seems safe and possibly beneficial. They stated that these results were used to power the currently running phase IIb randomized clinical trial.

In a systematic review, Tanyi et al (2012) stated that after decades of extensive research, epithelial ovarian cancer still remains a lethal disease. Multiple new studies have reported that the immune system plays a critical role in the growth and spread of ovarian carcinoma. These investigators summarized the development of DC vaccinations specific for ovarian cancer. So far, DC-based vaccines have induced effective anti-tumor responses in animal models, but only limited results from human clinical trials are available. Although DC-based immunotherapy has proven to be clinically safe and efficient at inducing tumor-specific immune responses, its' clear role in the therapy of ovarian cancer still needs to be clarified. The relatively disappointing low-response rates in early clinical trials point to the need for the development of more effective and personalized DC-based anti-cancer vaccines.

Bregy et al (2013) stated that glioblastoma multiforme (GBM), the most common malignant brain tumor, still has a dismal prognosis with conventional treatment. Therefore, it is necessary to explore new and/or adjuvant treatment options to improve patient outcomes. Active immunotherapy is a new area of research that may be a successful treatment option. The focus is on vaccines that consist of antigen presenting cells (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 in terms of complications, median OS, 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 DCs. 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. Moreover, they stated that larger clinical trials are needed to show the potential benefits of active immunotherapy.

Wang et al (2014) noted that glioblastoma multiforme (GBM) has a poor prognosis. In a systematic review and meta-analysis, these investigators analyzed the outcomes of clinical trials that compared immunotherapy with conventional therapy for the treatment of malignant gliomas. PubMed, Cochrane and Google Scholar databases were searched for relevant studies. The 2-year survival rate was used to evaluate effectiveness of immunotherapy. Of 171 studies identified, 6 comparative trials were included in the systematic review. Immunotherapy was associated with a significantly longer OS and 2-year survival compared to conventional therapy. The authors concluded that immunotherapy may improve the survival of patients with GBM.

Chen et al (2014) stated that a new strategy of adoptive and passive immunotherapy involves combining dendritic cells (DCs) with a subset of natural killer T lymphocytes termed cytokine-induced killer (CIK) cells. In a systematic review and meta-analysis, these researchers evaluated the safety and effectiveness of DC-CIK therapy versus placebo, no intervention, conventional treatments, or other complementary and alternative medicines for malignant tumors. These investigators searched PubMed, Medline, Embase, Cochrane, Wangfang, Weipu, CNKI databases and reference lists of articles. They selected randomized controlled trials (RCTs) of DC-CIK therapy versus placebo, no intervention, conventional treatments, or other complementary and alternative medicines in patients with all types and stages of malignant tumor. Primary outcome measures were OS and treatment response. Secondary outcome measures were health-related quality of life (HRQoL) assessment, PFS, and adverse events. A total of 6 trials met the inclusion criteria. There was evidence that chemotherapy + DC-CIK increased the 2-year (risk ratio [RR] 2.88, 95 % confidence interval [CI]: 1.38 to 5.99, p = 0.005) and 3-year (RR 11.67, 95 % CI: 2.28 to 59.69, p = 0.003) survival rates and PFS (RR 0.64, 95 % CI: 0.34 to 0.94, p < 0.0001) in patients with non-small cell lung cancer compared to those treated with chemotherapy alone. DC-CIK therapy appears to be well-tolerated by cancer patients and to improve post-treatment patient health related quality of life. The authors concluded that DC-CIK immunotherapy is a safe and effective treatment for...
patients with malignant tumors. They stated that further clinical trials to provide supportive evidence for the routine use of DC-CIK therapy in clinical practice are needed.

Lombardi et al (2015) stated that plasmacytoid dendritic cells (pDCs) are multifunctional bone marrow-derived immune cells that play a key role in bridging the innate and adaptive immune systems. Activation of pDCs through toll-like receptor agonists has proven to be an effective treatment for some neoplastic disorders. These researchers explored the contribution of pDCs to neoplastic pathology and discussed their potential utilization in cancer immunotherapy. Current research suggests that pDCs have cytotoxic potential and can effectively induce apoptosis of tumor-derived cell lines. They are also reported to display tolerogenic function with the ability to suppress T-cell proliferation, analogous to regulatory T cells. In this capacity, they are critical in the suppression of autoimmunity, but can be exploited by tumor cells to circumvent the expansion of tumor-specific T cells, thereby allowing tumors to persist. The authors concluded that several forms of skin cancer are successfully treated with the topical drug imiquimod, which activates pDCs through toll-like receptor 7. Furthermore, pDC-based anti-cancer vaccines have shown encouraging results for the treatment of melanoma in early trials. They stated that future studies regarding the contributions of pDCs to malignancy will likely afford many opportunities for immunotherapy strategies.

Drakes and Stiff (2016) noted that approximately 80 % of patients with ovarian cancer are diagnosed with advanced disease. Even with cutting edge surgical techniques and the best regimens of standard therapies most patients relapse and die of drug resistant disease within 5 years of diagnosis. Dendritic cell immunotherapy can induce anti-tumor T cell immunity in patients and holds great potential in the era of modern anti-cancer treatment. The authors summarized the important findings in ovarian cancer DC clinical trials, and discussed new directions which may improve the effectiveness of DC immunotherapy. Expert commentary: of this study was “Administration of DC vaccines with other forms of immunotherapy may enhance the efficacy of these treatments, ultimately increasing cures for this disease”.

Artene and colleagues (2016) stated that the bevacizumab and irinotecan protocol is considered a standard treatment regimen for recurrent malignant glioma. Recent advances in immunotherapy have hinted that vaccination with DCs could become an alternative salvage therapy for the treatment of recurrent malignant glioma.
These investigators performed a search on PubMed, Cochrane Library, Web of Science, ScienceDirect, and Embase in order to identify studies with patients receiving bevacizumab plus irinotecan or dendritic cell therapy (DCT) for recurrent malignant gliomas. The data obtained from these studies were used to perform a systematic review and survival gain analysis. A total of 14 clinical studies with patients receiving either bevacizumab plus irinotecan or DC vaccination were identified; 7 studies followed patients that received bevacizumab plus irinotecan (302 patients) and 7 studies included patients that received DCT (80 patients). For the patients who received bevacizumab plus irinotecan, the mean reported median OS was 7.5 (95% CI: 4.84 to 10.16) months. For the patients who received DCT, the mean reported median OS was 17.9 (95% CI: 11.34 to 24.46) months. For irinotecan + bevacizumab group, the mean survival gain was -0.02 ± 2.00, while that for the DCT group was -0.01 ± 4.54. The authors concluded that for patients with recurrent malignant gliomas, DCT did not have a significantly different effect when compared with bevacizumab and irinotecan in terms of survival gain (p = 0.535) and did not improve weighted survival gain (p = 0.620). Thus, this survival gain analysis demonstrated that there is no real clinical benefit for patients undergoing DC vaccination in comparison to those receiving bevacizumab and irinotecan for the treatment of recurrent malignant gliomas.

Tang and colleagues (2017) noted that DCs play a pivotal role in the tumor microenvironment (TME). As the primary antigen-presenting cells in the tumor, DCs modulate anti-tumor responses by regulating the magnitude and duration of infiltrating cytotoxic T lymphocyte responses. Unfortunately, due to the immunosuppressive nature of the TME, as well as the inherent plasticity of DCs, tumor DCs are often dysfunctional, a phenomenon that contributes to immune evasion. Recent progresses in the understanding of tumor DC biology have revealed potential molecular targets that allow researchers to improve tumor DC immunogenicity and cancer immunotherapy. These investigators reviewed the molecular mechanisms that drive tumor DC dysfunction. They discussed recent advances in the understanding of tumor DC ontogeny, tumor DC subset heterogeneity, and factors in the TME that affect DC recruitment, differentiation, and function. The authors described potential strategies to optimize tumor DC function in the context of cancer therapy.

Hargadon (2017) stated that melanoma is a highly aggressive form of skin cancer that frequently metastasizes to vital organs, where it is often difficult to treat with traditional therapies such as surgery and radiation. In such cases of metastatic
disease, immunotherapy has emerged in recent years as an exciting therapeutic option for melanoma patients. Despite unprecedented successes with immune therapy in the clinic, many patients still experience disease relapse, and others fail to respond at all, thus highlighting the need to better understand factors that influence the efficacy of anti-tumor immune responses. At the heart of anti-tumor immunity are DCs, an innate population of cells that function as critical regulators of immune tolerance and activation. As such, DCs have the potential to serve as important targets and delivery agents of cancer immunotherapies. Even immunotherapies that do not directly target or employ DCs, such as checkpoint blockade therapy and adoptive cell transfer therapy, are likely to rely on DCs that shape the quality of therapy-associated antitumor immunity. Thus, understanding factors that regulate the function of tumor-associated DCs is essential for optimizing both current and future immunotherapeutic strategies for treating melanoma. To this end, the author focused on advances in the understanding of DC function in the context of melanoma, with particular emphasis on the role of immunogenic cell death in eliciting tumor-associated DC activation, immunosuppression of DC function by melanoma-associated factors in the tumor microenvironment, metabolic constraints on the activation of tumor-associated DCs, and (the role of the microbiome in shaping the immunogenicity of DCs and the overall quality of anti-melanoma immune responses they mediate. Furthermore, the author highlighted novel DC-based immunotherapies for melanoma that are emerging from recent progress in each of these areas of investigation, and discussed current issues and questions that will need to be addressed in future studies aimed at optimizing the function of melanoma-associated DCs and the anti-tumor immune responses they direct against this cancer.

Bryant and associates (2019) noted that the ability of immune therapies to control cancer has recently generated intense interest. This therapeutic outcome is reliant on T cell recognition of tumor cells. The natural function of DCs is to generate adaptive responses, by presenting antigen to T cells, hence they are a logical target to generate specific anti-tumor immunity. The understanding of DC biology is expanding, and they are now known to be a family of related subsets with variable features and function. Most clinical experience to-date with DC vaccination has been using monocyte-derived DC vaccines. There is now growing experience with alternative blood-derived DC derived vaccines, as well as with multiple forms of tumor antigen and its loading, a wide range of adjuvants and different modes of vaccine delivery. Key insights from pre-clinical studies, as well as lessons learned from early clinical testing drive progress towards improved vaccines. The authors
concluded that the potential to fortify responses with other modalities of immunotherapy makes clinically effective "2nd generation" DC vaccination strategies a priority for cancer immune therapists.

Hepatocellular Carcinoma

Chen and colleagues (2018) stated that DC-based immunotherapy has recently been reported frequently in the treatment of hepato-cellular carcinoma (HCC); however, its efficacy remains controversial. In a systematic review and meta-analysis, these researchers evaluated the clinical efficacy of DC-based immunotherapy on HCC. PubMed, Cochrane Library, Embase and Web of Science were searched to identify clinical trials on DC-based immunotherapy for HCC published up to January 31, 2018. The articles were selected according to pre-established inclusion criteria and methodologic quality, and publication bias were evaluated. A total of 1,276 cases from 19 clinical trials were included. Compared with traditional treatment, further DC-based therapy enhanced the CD4+ T/CD8+ T ratio (standardized mean difference [SMD]: 0.68, 95 % CI: 0.46 to 0.89, p < 0.001); increased the 1-year, 18-month and 5-year PFS rate and the 1-year, 18-month and 2-year OS rate (RR greater than 1, p < 0.05), prolonged the median PFS time (median survival ratio [MSR]: 1.98, 95 % CI: 1.60 to 2.46, p < 0.001) and median OS time (MSR: 1.72, 95 % CI: 1.51 to 1.96, p < 0.001). Adverse reactions were mild. The authors concluded that DC-based therapy not only enhanced anti-tumor immunity, improved the survival rate and prolonged the survival time of HCC patients, but it was also safe. These researchers stated that these findings provided encouraging information for further development of DC-based immunotherapy as an adjuvant treatment for HCC. However, these findings must be interpreted with caution because of the small study numbers, publication bias and the various of study designs, pre-treatment and therapeutic processes of DCs.

Gastric Cancer

Wang and colleagues (2018) noted that immunotherapy is emerging as a new treatment strategy for gastric cancer (GC). However, the safety and efficacy of this technique remain unclear. In a meta-analysis, these investigators examined the effect of cytokine-induced killer cell (CIK)/DC-cytokine-induced killer cell (DC-CIK) treatment for GC after surgery. Hazard ratio (HR), OS rates, and disease-free survival (DFS) rates were calculated using a Mantel-Haenszel (M-H) fixed-effects model (FEM), and results were displayed using forest plots. Publication bias was
assessed by Begg test, and data were presented using funnel plots. Date robustness was assessed by the trim and fill method. Descriptive analysis was performed on T lymphocytes and adverse effects. A total of 9 trials (1,216 patients) were eligible for inclusion in this meta-analysis. Compared with the control group, the HR for OS was 0.712 (95 % CI: 0.594 to 0.854) and 0.66 (95 % CI: 0.546 to 0.797) for overall DFS. The RR of the 3 and 5-year OS rate was 1.29 (95 % CI: 1.15 to 1.46) and 1.73 (95 % CI: 1.36 to 2.19), respectively. The RR for the 3 and 5-year DFS rate 1.40 (95 % CI: 1.19 to 1.65) and 2.10 (95 % CI: 1.53 to 2.87), respectively. The proportion of patients who were CD3+, CD4+, and CD4+/CD8+ increased in the cellular therapy groups. No fatal adverse reactions were noted.

The authors concluded that chemotherapy combined with CIK/DC-CIK therapy after surgery resulted in low HR, and significantly increasing OS rates, DFS rates, and T-lymphocyte responses in patients with GC. These investigators expected more multi-center randomized trials to be performed to verify the efficacy of this technique in the near future. This therapy is a potentially effective strategy for the treatment of GC. Although pre-clinical studies showed that immunotherapy has a significant effect upon GC, many problems need to be solved urgently, for example, is use of immunotherapy combined with chemotherapy more effective? What is the cycle and duration of maintenance of immunotherapy? The authors stated that the prospect of immunotherapy for GC is promising, but more research and a standardized treatment regimen are still needed.

These researchers noted that this study had several drawbacks. First, the difference between the number of patients involved in each study may have led to partial differences. Second, there were differences in the use of immune cells across different studies. The immune responses induced by different immune cells were different and may have had different effects on the development of the disease. Furthermore, different surgical procedures may have led to different outcomes, thus creating a study bias; patients in stages I to III underwent radical surgery, whereas patients in stage IV underwent palliative surgery.

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”*+”:

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Amendment to
Aetna Clinical Policy Bulletin Number: 0377 Dendritic Cell Immunotherapy

There are no amendments for Medicaid.