Canadian Agency for Drugs and Technologies in Health

Issues in Emerging Health Technologies

Sipuleucel-T (Provenge®): Active Cellular Immunotherapy for Advanced Prostate Cancer

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Summary

- ✓ **Sipuleucel-T (Provenge®) is an active cellular immunotherapy (therapeutic vaccine) that is designed to stimulate the patient's T-cells to recognize and attack prostate cancer cells that express prostatic acid phosphatase (PAP) antigen.**
- ✓ **Sipuleucel-T demonstrated a survival benefit in men with advanced androgen-independent prostate cancer (AIPC), although this preliminary finding requires confirmation in larger trials.**
- ✓ **Mild to moderate myalgia, chills, fever, and tremor are the most commonly reported adverse events for patients receiving sipuleucel-T. These events generally resolve quickly.**
- ✓ **More studies are needed to evaluate sipuleucel-T in the earlier stages of prostate cancer and in combination with conventional therapies.**

The Technology

Sipuleucel-T (Provenge®, Dendreon Corporation, Seattle, WA) is an active cellular immunotherapy. Active cellular immunotherapies are therapeutic vaccines that can induce new immune responses in patients, to treat pre-existing conditions such as cancer.[1] Antigen-presenting cells (APCs), including dendritic cells, are responsible for sensitizing T-cells to new antigens. In the case of sipuleucel-T, the patient's mononuclear cells, including APCs, are incubated with a fusion protein composed of prostatic acid phosphatase (PAP), an antigen found in 95% of prostate cancers,[2] and granulocyte-macrophage colony-stimulating factor (GM-CSF), a potent immune cell stimulator. The PAP antigen-loaded APCs are administered to the patient and stimulate the patient's immune system to recognize and destroy prostate cancer cells.

Regulatory Status

In late 2006, the US Food and Drug Administration (FDA) accepted a Biologics License Application for sipuleucel-T and assigned it priority review status.[3] In March 2007, the FDA's Office of Cellular, Tissue and Gene Therapies Advisory Committee recommended approval of sipuleucel-T for the treatment of patients with asymptomatic, metastatic, androgen-independent (or hormone refractory) prostate cancer.[4] In May 2007, the FDA requested additional clinical data to support the efficacy claim and additional information regarding the chemistry, manufacturing, and controls section of the Biologics License Application.[5]

Sipuleucel-T does not yet have Health Canada regulatory approval (i.e., a Notice of Compliance) for marketing in Canada.

Patient Group

Prostate cancer is the most common cancer diagnosed in Canadian men.[6] In 2007, an estimated 22,300 new cases will be diagnosed, and approximately 4,300 deaths will occur from this disease. Prostate cancer affects about 0.8% of the adult male population (an estimated 122,400 men in Canada) and has an estimated five-year survival rate of 92%.[6] Deaths from prostate cancer increase with age and most often occur beyond 60 years of age.[6] Most patients are diagnosed at an early stage with cancer that is localized to the prostate. However, nearly a third of patients have advanced or metastatic prostate cancer at diagnosis.[7]

Advanced prostate cancer is defined as disease that has spread to the bone and less commonly to other organs. It is usually associated with an elevated level of prostate-specific antigen (PSA). In progressive disease, PSA values rise after initial therapy.[8] Anti-testosterone or androgen deprivation therapy has been the mainstay of treatment for advanced prostate cancer.[8] Androgens are hormones that promote the development and maintenance of male sex characteristics. In some men, prostate cancer grows in spite of hormone suppression. This is called androgen-independent prostate cancer (AIPC). AIPC is often fatal, with a median survival of 12 to 18 months in patients with metastatic disease.[7]

Current Practice

Localized prostate cancer is most often curable, but currently, there is no curative treatment for the disease if it spreads beyond the prostate.[7] The initial treatment option for metastatic disease is hormonal therapy, primarily anti-testosterone therapy, which includes castration. For patients with AIPC, palliative radiotherapy, bisphosphonate therapy, and chemotherapy are often used.[8,9] Cytotoxic chemotherapy with docetaxel (Taxotere® 75 mg/m^2 intravenously every three weeks) has been shown to reduce serum PSA levels, improve quality of life, provide some pain relief, and prolong median survival by two to three months.[8,10] It is associated with significant but manageable side effects.[7,10]

The Evidence

Most trials of sipuleucel-T have been conducted in men with progressive disease, defined as either rising PSA value, or metastatic or non-metastatic hormone-refractory disease. In a consecutive phase I/II study of 31 patients with AIPC, there was an association between the development of an immune response to prostatic acid phosphatase (PAP) and the time to disease progression.[11] In terms of clinical response, three of 19 men treated on the phase II portion of the study had a ≥50% decline in serum PSA. Another three men had PSA declines of 25% to 49%. The median time to progression was significantly longer in patients who had an immune response compared to those who did not [34 weeks (n=20) versus 13 weeks (n=11), p<0.027].

In a phase II study of sipuleucel-T in 21 patients with metastatic AIPC,[12] two patients had transient PSA decreases of 25% to 50%. One other patient had a complete response to the drug, where their PSA level decreased from 221 ng/mL to undetectable and stayed stable for >4 years. The implication of declining PSA levels for disease-free and overall survival in patients who are treated with therapeutic vaccines is unknown.[1] More studies are needed to determine the value of absolute PSA measurements and PSA kinetics with immunotherapeutic approaches.

A placebo-controlled phase III trial of sipuleucel-T demonstrated a survival advantage with immunotherapy in men with AIPC. A total of 127 patients with metastatic AIPC were randomly assigned in a 2:1 ratio to receive a total of three infusions of sipuleucel-T or placebo every two weeks.[13] There was no significant difference between treatment and placebo groups in the time that it took for the disease to progress (11.7 weeks in the vaccine arm versus 10 weeks in the placebo arm, p=0.052, which was the primary endpoint of the study). An analysis based on 36-month safety data found a statistically significant and clinically important survival advantage of 4.5 months in patients treated with sipuleucel-T compared to the placebo group (median survival of 25.9 months versus 21.4 months, p=0.01). After three years follow-up, the survival rate was 34% for those treated with the immunotherapy compared with 11% for those taking placebo. However, US FDA reviewers expressed some concerns regarding this post hoc analysis and the generalizability of these findings given the relatively small number of patients involved.[14] A pivotal, confirmatory phase III trial in Canada and the US is ongoing.[15]

Adverse Effects

Sipuleucel-T seems to be relatively safe and well tolerated.[1] In the phase I/II study of 31 patients with AIPC, low-grade fever, which was the most common adverse effect, occurred in 13 patients.[11] In another two patients, fever was reported as grade 3 (severe). Other adverse events that were reported as mild (grades 1 to 2) included myalgia (muscle pain), which resolved within one week after infusion; fatigue, sometimes prolonged; and urinary complaints.

In a phase II study, four of 21 patients reported severe (grades 3 to 4) adverse events after infusion, including chills, fatigue, fever, malaise, tachycardia (rapid heart rate), dyspnea (shortness of breath), and vomiting.[12] In the published phase III trial, the vaccine was well tolerated, with the most common side effects including grade 1 rigors, fever, tremor, and feeling cold.[13] Most patients (95%) received all three planned infusions.

Long-term surveillance of side effects, particularly cardiovascular events, will be important for this new class of agents, given patients' advanced age and possible comorbidities.[14]

Administration and Cost

The immunotherapy is prepared fresh for each infusion, with the patient's peripheral blood cells being harvested two days before infusion (leukapheresis) and activated in vitro with a recombinant fusion protein. In clinical trials,[11,16] sipuleucel-T was administered during a 30-minute intravenous infusion in an outpatient setting.

Over a four-week course of therapy, patients received three doses of sipuleucel-T at weeks 0, 2, and 4.[13]

The manufacturer's recommended dose and wholesale price were unavailable. Additional costs would include those associated with the collection of patients' peripheral blood cells for immunotherapy processing, possible transportation to the preparation site and back to the infusion site, and clinic time for intravenous infusion. Because there are no similar active cellular immunotherapies for prostate cancer on the market, comparable costs are unavailable.

A 2004 ECRI Institute *Health Technology Forecast* on cancer vaccines predicted that their financial impact will be high. However, effective vaccines may reduce the need for some existing cancer treatments, possibly reduce treatment-related complications, and if effective, may reduce the costs associated with treating recurrent cancers.[17]

Concurrent Developments

In addition to sipuleucel-T, there are several immunotherapeutic approaches to prostate cancer in phase II to III trials. These include whole cell vaccines (e.g., GVAX; Cell Genesys, San Francisco, CA), viral vaccines (e.g., PROSTVAC-VF; Therion Biologics, Cambridge, MA), and cytokine therapy (e.g., granulocyte-macrophage colony-stimulating factor (GM-CSF)).[18,19] Dendritic cell vaccines based on several prostate-specific antigens are in clinical testing.[19] A monoclonal antibody for prostate cancer (MLN2704; Millenium Pharmaceuticals, Cambridge, MA) is in phase I to III trials.[18]

Rate of Technology Diffusion

The treatment options for metastatic AIPC are limited, so the development of therapies such as cancer vaccines is needed, particularly for older patients who are less able to tolerate chemotherapy.[20] There is some debate about whether chemotherapy or novel immunotherapies, or a combination of both, may be more efficacious as first-line therapy in patients with advanced prostate cancer instead of hormone therapy.[19]

Vaccines may be more beneficial in patients with less advanced disease.[20] The application of sipuleucel-T to patients at earlier stages of the disease requires investigation. One trial (PROTECT or P-11) is evaluating the biological activity of this vaccine in recurrent, hormone-sensitive prostate cancer before the development of metastatic disease.[1]

Implementation Issues

The preliminary clinical data have not clearly established the efficacy of sipuleucel-T, although the FDA's advisory committee agreed that there was "substantial evidence" that the drug is effective and relatively safe.[4] No effect was observed on time-to-disease progression. This outcome measure may be inappropriate for the evaluation of the efficacy of immune therapy, because immune responses to sipuleucel-T are generally not observed until two to three months after the start of therapy.[1]

A second, larger phase III trial, IMPACT (IMmunotherapy for Prostate AdenoCarcinoma Treatment), has been designed with survival as the primary measurable outcome.[21] The results are expected in 2010.[21]

Preliminary evidence suggests that initial treatment with sipuleucel-T, followed by docetaxel, may prolong survival. The optimal timing, sequence, and benefit of sequential therapy remain to be determined.[22]

Because sipuleucel-T is an autologous product, it requires an increased level of coordination and logistics for administration, although it has the advantage of being applicable to most patients (as opposed to therapies that are restricted to certain HLA types or that require tumour procurement).[2] The addition of sipuleucel-T to existing prostate cancer regimens will likely increase the overall treatment costs. The cost-benefit of this treatment cannot be determined until the cost of sipuleucel-T is available.

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