Hormone Refractory Prostate Cancer: Focus on Sipuleucel-T

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Abstract: Sipuleucel-T is a vaccine based on autologous antigen presenting cells that are loaded with an antigen-cytokine (prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor) fusion product. Sipuleucel-T is given intravenous in weeks 0, 2, and 4. Within phase I–III trials, patients with metastatic hormone-refractory prostate cancer have been treated. In these trials an activation of the immune system could be demonstrated. Also, some clinical responses could be documented. Moreover, in a placebo-controlled phase III trial including 127 patients a statistical significantly prolongation of survival was achieved. Side effects from the vaccine are rather mild and included fever, myalgia, fatigue and others. The Food and Drug Administration in the United States requested further data before possible approval of sipuleucel-T.

Keywords: sipuleucel-T, provenge, prostate cancer, immunotherapy, vaccine, prostatic acid phosphatase (PAP), granulocyte-macrophage colony-stimulating factor (GM-CSF)

Introduction

The incidence of prostate cancer U.S. in year 2008 was 186,320 and in the same year 28,660 men died from prostate cancer.[1] The therapeutic options predominantly depend on cancer stage, patient age and co-morbidity. In organ-confined prostate cancer the treatment is radical prostatectomy, external beam radiotherapy, or brachytherapy with curative intention.[2] The associated 5-year overall survival rates are 85% for well and moderately differentiated and 72% for poorly differentiated tumors.[3] Active surveillance is another option and aims to treat (also with curative intention) only patients who are progressive or changed their mind while under surveillance.[4]

In contrast, patients with metastatic prostate cancer have a 5-year overall survival of 23%.[3] Systemic therapy for metastatic disease comprises of different types of hormonal therapies because of the hormone-dependent growth of prostate cancer cells. Today, hormonal therapy is performed by surgical or medical castration (e.g. by administration of gonadotropin hormone releasing-hormone (GnRH) agonists or antagonists) and/or treatment with antiandrogens or other strategies.[5] Approximately 85% of patients with metastatic prostate cancer will respond to initial hormonal therapy. However, at some stage hormonal therapy fails to control prostate cancer growth (i.e. hormone-refractory prostate cancer, HRPC). In these patients, intravenous (iv) chemotherapy with docetaxel in combination with oral prednisone demonstrated some beneficial effect on overall survival (OS).[6] An updated survival analysis showed a median survival of 19.2 months with docetaxel compared to 16.3 months with mitoxantrone (Hazard ratio (HR): 0.79, 95% confidence interval (CI): 0.67–0.93, P = 0.004) Presently, this approved therapy is the most often applied regimen in HRPC.[7] However, therapy beyond docetaxel is often palliative or experimental.

Due to this situation development of alternative treatment strategies such as immunotherapy (e.g. antibody therapy, vaccine therapy) is ongoing. In fact, vaccine therapy of prostate cancer has been increasingly studied over the past years. A number of prostate-specific and tumor-associated antigens (TAAs) have been identified. These include cell surface proteins such as prostate specific membrane antigen (PSMA), prostate stem cell antigen (PSCA), and HER-2neu but also secreted proteins such as prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) and intracellular proteins like G melanoma antigen (GAGE) and others. TAAs are usually presented to T lymphocytes by antigen presenting cells (APCs). The most potent APCs are dendritic cells but other cells such as macrophages and B lymphocytes can also present antigens.[8–10] Dendritic cells account for 0.5% of all circulating

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whites cells but also occur in tissue such as skin (Langerhans cells) and liver (Kuppfer cells). APCs internalize antigens and then present a fragment of the antigen together with major histocompatibility complex (MHC) class-I and class-II molecules. T lymphocytes recognize this complex via the T lymphocyte receptor (signal I) but costimulatory signals such as B7 on APCs and their ligand CD28 on T lymphocytes (signal II) are also required. This process activates T lymphocytes to become cytotoxic in a peptide-specific manner (cytotoxic T lymphocyte, CTL).[8–10]

In a randomized phase III trial it was demonstrated for the first time that a vaccination (sipuleucel-T) can prolong overall survival compared to placebo in patients with HRPC.[11] This review summarizes the available clinical data on sipuleucel-T for the treatment of patients with HRPC.

The Compound

Sipuleucel-T (also APC8015 or Provenge®) is one of the most advanced vaccine approaches for prostate cancer. Sipuleucel-T consists of an antigen (prostatic alkaline phosphatase, PAP) fused through its carboxy terminus to the amino terminus of a cytokine (granulocyte-macrophage colony-stimulating factor, GM-CSF) by a Gly Ser linker.[12] The main reason to use PAP as an antigen for vaccination are that PAP is tissue-specific and that PAP is overexpressed by the majority of prostate cancer cells.[13–15] This antigen-cytokine fusion product is named PA2024.

Autologous APCs are harvested from the peripheral blood of the patient. For this purpose a 1.5 to 2 blood volume leukapheresis is performed. The leukapheresis product undergoes a density centrifugation (first process: buoyant density solution of 1.077 g/ml, 320 mosM, 20 minutes at 1,000 g; second process: buoyant density solution of 1.065 g/ml, 320 mosM, 30 minutes at 805 g) to deplete erythrocytes, granulocytes, platelets, and low-density monocytes and lymphocytes.[12,16] The cell pellet contains dendritic cells (CD54-positive cells), T lymphocytes (CD3-positive cells), B lymphocytes (CD19-positive cells), monocytes (CD14-positive cells), and natural killer cells (CD56-positive cells). CD54 (also intercellular adhesion molecule-1, ICAM-1) is a type I transmembrane molecule and its gene belongs to the immunoglobulin supergene family. Upon activation CD 54 is predominantly expressed at moderate to high levels by endothelial cells, B and T lymphocytes and monocytes. However, the authors predominantly used CD54 as a dendritic cell marker rather than as a marker of activated immune cells. Finally, the cell pellet at a concentration of 1×10^7/ml is exposed to 10 µg/ml PA2024 for 40 h at 37 °C and 5% CO_2 to become APC8015 (or sipuleucel-T).[12,16]

Quality control includes cell number and viability (to be >72%), Gram's stain, allogeneic mixed-lymphocyte reactivity, cell surface marker phenotype, CD54 expression and upregulation, and tests for sterility (40 h), Mycoplasma, and endotoxin (less than 1.4 EU/ml).[12,16]

The final product is transported to the patient at 4 °C and infused iv within 8 h of formulation.

Phase I

The first phase I trial with sipuleucel-T was conducted at the Mayo Clinic.[12] Between December 1997 and July 1998, 13 patients with metastatic HRPC were enrolled. Patients must have had radiographically documented progression (either by bone scan or CT scan) and/or consecutive increases of their PSA levels with the absolute PSA level ≥ 5 ng/ml. Median age of the patients was 67.5 years (range 59–84 years). At baseline median PSA was 323 ng/ml (range 20–921 ng/ml) and median PAP was 22.4 ng/ml (range 9.1–831 ng/ml).[12]

Patients received two iv injections of sipuleucel-T 4 weeks apart followed by three subcutaneous (sc) injections of PA2024 alone 4 weeks apart (patients 1–3: 0.3 mg, patients 4–6: 0.6 mg and patients 7–13: 1 mg). In total, patients received between 1.1 and 5.4×10^9 nucleated cells. These were dendritic cells (18.6% +/– 9.4%), T lymphocytes (65.1% +/– 12%), monocytes (16.6% +/– 7.8%), and B lymphocytes (5% +/– 2.4%). Patients 1–3 received 248 +/– 86×10^6 per m² dendritic cells in the first and 306 +/– 237×10^6 per m² dendritic cells in the second vaccination. Patients 4–6 received 230 +/– 140×10^6 per m² dendritic cells in the first and 147 +/– 49×10^6 per m² dendritic cells in the second vaccination. Patients 7–13 received 325 +/– 155×10^6 per m² dendritic cells in the first and 217 +/– 128×10^6 per m² dendritic cells in the second vaccination.[12]

All patients exhibited some evidence of immunological response to treatment. Proliferation assays against PA2024, PAP, and GM-CSF were performed in 9 patients. After four weeks in these

patients a T lymphocyte proliferation was observed when stimulated with PA2024. There was also a positive result for PAP and GM-CSF stimulation. Furthermore, antibodies against PA2024 and GM-CSF were detected.[12]

Five patients reported mild fever (grade 1–2) and/or chills of less than 24 h. Five patients had myalgia or pain (grade 1–2) for 1–2 days lasting up to one week. Six patients had fatigue (grade 1–2, 1 × grade 3). Four patients reported local reactions at the injections site (grade 1).[12]

Median time to progression (TTP) was 135 days (range 30–274 days). Three of 13 patients had a decline in their PSA level by 50% or more.[12]

Phase II

In a combined phase I/II study sipuleucel-T was given to 31 patients with HRPC at the University of California, San Francisco.[16] Median age of patients was 69 years (range 48–83 years). Median PSA before vaccination was 41 ng/ml (range 3–1, 007 ng/ml). Pretherapeutic results for PAP were not given.

In the phase I part of the trial 12 patients were included for dose escalation (0.2×10^9, 0.6×10^9, 1.2×10^9 to 2×10^9 nucleated cells per m²). In the entire study the median number of nucleated cells infused was 2.1×10^9: There were 11.2% (+/– 11.5%) dendritic cells, 62.3% (+/– 16.4%) T lymphocytes, 7.2% (+/– 4.2%) B lymphocytes, 11.7% (+/– 10.5%) monocytes, and 14.4% (+/– 7.1%) natural killer cells.[16]

All patients developed a T lymphocyte response to the fusion protein PA2024 with a maximum after 2–3 infusions. In contrast, only 10/31 patients had a T lymphocyte response to PAP. Further investigations demonstrated a TH1-response by T lymphocytes because these cells released Interferon-gamma rather than Interleukin-4. Antibodies to PAP and GM-CSF were present in 0% and 33% of patients before vaccination compared to 52% and 81% after vaccination.[16]

There were 15 patients who developed fever (13 × grade 1 or 2, 2 × grade 3) within 2 hours of infusion. Two patients had mild myalgia and one patient had mild fatigue. Five patients had mild urinary symptoms.[16]

Median TTP for patients treated in the phase I part of the trial was 12 weeks and for patients treated in the phase II part 29 weeks. Median TTP in 20 patients with an immune response was 34 weeks compared to 13 weeks in 11 patients without an immune response ($p < 0.027$). Median TTP in patients who received more than 100×10^6 cells per infusion was 31.7 weeks compared to 12.1 weeks in those who received fewer cells per infusion. 3/31 patients had a decline of PSA by more than 50% and 3 other patients by 25%–49%.[16]

Another phase II study was performed at the Mayo Clinic including 21 patients with HRPC.[17] Patients must have had radiographically documented progression (either by bone scan or CT scan) and/or consecutive increases of their PSA levels while the absolute PSA level was supposed to be ≥5 ng/ml. Also, PAP level must have been detectable in patients who had a radical prostatectomy in the past or above the upper limit in patients without surgery in the past. Median age of patients was 72 years (range 57–83 years). Median PSA before therapy was 221 ng/ml (range 21–1,147 ng/ml) and median PAP before therapy was 9.2 ng/ml (range 0.8–291 ng/ml).[17]

Sipuleucel-T was infused iv over 30 minutes at week 0 and 2. The median number of CD54-positive cells was 2.7×10^9 for the first infusion and 3.2×10^9 for the second infusion. Ranges were not given in the publication. Two weeks after the second infusion, patients received three sc injections of 1 mg of PA2024 four weeks apart.[17]

In all patients blood was taken to perform proliferation assays against PAP, PA2024 and GM-CSF as well as serum antibodies against the same molecules. Peripheral blood monocytic cells (PBMCs) collected from patients for at least 16 weeks proliferated upon in vitro stimulation by PA2024. For the patient with responsive disease, PBMCs could be stimulated for 96 weeks. 13/15 patients developed antibodies specific for PA2024 between weeks 4 and 8. Also, antibodies specific for GM-CSF were detected but not for PAP.[17]

The treatment was well tolerated with the most common adverse effects being mild, grade 1–2 rigors and fatigue. However, in 4/21 patients grade 3–4 adverse events including chills, fatigue, malaise, tachycardia, dyspnea, and vomiting after infusion of sipuleucel-T were documented.[17]

Median TTP was 118 days. There was a transient PSA response in 10% of patients. Two patients exhibited a transient 25%–49% PSA decrease. In another patient PSA dropped from 221 ng/ml at baseline to undetectable by week 24 and remained undetectable for 52 months. Parallel to this, his

retroperitoneal and pelvic adenopathy completely disappeared.[17]

Phase III

In 2006, the results of a placebo-controlled phase III study (D9901) comparing sipuleucel-T and placebo were published.[11] There were 127 men with asymptomatic HRPC that were enrolled at 19 U.S. centers between January 2000 and October 2001. Patients were randomized to receive sipuleucel-T iv or placebo iv every 2 weeks, for a total of three doses. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, evidence of progressive disease, radiographic evidence of metastases, and suppressed testosterone due to hormonal therapy. In a central laboratory it was assessed that PAP immunohistochemistry staining was positive in at least 25% of cells.[11]

The primary end point was TTP defined as progressive disease on serial radiographic imaging tests (increase of at least 50% in measurable disease), the appearance of at least 2 new lesions on a bone scan, new cancer-related pain events consistent with progression such as spinal cord compression, nerve roots compression, or pathologic fracture. A central review of imaging test was performed every 8 weeks until week 32 and every 12 weeks thereafter. PSA was neither used to define progression nor to trigger imaging tests.[11]

Median age of patients in the sipuleucel-T group was 73 years (range 47–85 years) compared to 71 years (range 50–86 years) in the placebo group. In the sipuleucel-T group median PSA was 46 ng/ml (range 3.5–3,621) and median PAP was 7 ng/ml (range 0.7–250.5 ng/ml). The comparable values for the placebo group were 48 ng/ml (range 7.9–2,799 ng/ml) and 6.5 ng/ml (range 0.3–163 ng/ml).

The primary study end point was missed (115 patients analyzed, TTP 11.7 weeks with sipuleucel-T versus 10 weeks with placebo, HR = 1.45, 95% CI = 0.99–2.11, p = 0.052). However, a significant delay in TTP in a subset of patients those tumors had a Gleason score of ≤7 was observed.[11]

Results for the second endpoint (i.e. OS) showed statistically significant better results for sipuleucel-T compared to placebo with a median OS of 25.9 months versus 21.4 months (p = 0.01, log-rank; HR = 1.71, 95% CI = 1.13–2.56). At 36 months 34% of patients in the sipuleucel-T group were alive compared to 11% in the placebo group (p = 0.005). For the first time ever, a vaccine approach in prostate cancer resulted in a prolongation of overall survival.[11] After the primary endpoint was reached 56% of patients in the sipuleucel-T group and 63% of patients in the placebo group received some form of chemotherapy. The FDA stated that several analyses showed that was no increased use of chemotherapy in the treatment arm, no delay in chemotherapy use in the placebo arm, and overall survival results appeared similar after adjustment for chemotherapy use in a time dependent covariate model.[18]

Some adverse events were significantly more common in the sipuleucel-T group: rigors (59.8% versus 8.9%), pyrexa (29.3% versus 2.2%), tremor (9.8% versus 0%), and feeling cold (8.5% versus 0%). Grade 1 or 2 adverse events occurred in 70.7% versus 68.9% of patients. Grade 3 or 4 adverse events were documented in 20 patients (24.4%) in the sipuleucel-T group (4 × rigors and 4 × dypnea) and 45 patients (24.4%) in the placebo group. 95% of all patients in the sipuleucel-T group received all infusions. The reason for not-receiving all infusions in the remaining 5% of patients were not given in the publication.[11]

Two other placebo-controlled phase III trials (D9902A and D9902B, the latter is also named IMPACT, i.e. IMmunotherapy for Prostate AdenoCarcinoma Treatment) have been initiated in asymptomatic patients with HRPC.[19] Until December 2002, 99 patients were recruited when the study was stopped due to the findings in D9901 in terms of Gleason score subgroups.[20] Patients with a Gleason score of 7 or less had a TTP of 16 weeks in the Sipuleucel-T arm compared to 9 weeks in the placebo arm (p = 0.002, HR = 2.2, 95% CI = 1.3–3.7). In contrast, for the entire study group only a trend towards a better TTP in the Sipuleucel-T arm was seen (p = 0.065, HR = 1.39, 95% CI = 0.95–2.04).[20] The first part of the study—with TTP as the primary endpoint—was then designated D9902A (the first 98 patients enrolled without regard to Gleason score). In July 2003, the second part of the study (D9902B) including more than 500 patients having HRPC with Gleason score of ≤7 and OS as the primary endpoint was designed.[11,19]

Final analysis of the study D9902A demonstrated an OS of 19 months in the sipuleucel-T group compared to 15.7 months in the placebo group (p = 0.331, log-rank; HR = 1.27). At 36 months

32% of patients in the sipuleucel-T group were alive compared to 21% in the placebo group.[18] Final analysis of 9902B will be performed in 2009.[19]

Discussion

Sipuleucel-T is a vaccine based on autologous APCs that are loaded with a PAP-GM-CSF fusion product. Sipuleucel-T is given iv in weeks 0, 2, and 4 and has been tested within phase I–III trials in patients with HRPC.

Currently, 4 major vaccine techniques are used: vaccination with whole tumor cells, protein and peptide vaccines, viral vector and DNA vaccines and dendritic cell vaccines.[21] Dendritic cells are potent APCs that have the ability to stimulate T lymphocyte immune responses (e.g. CTLs) in animals and humans. Dendritic cells are capable of activating naive CD4-positive and CD8-positive T lymphocytes by antigen presentation on their surface MHC class-I and class-II molecules.[8–10] They are found in most tissues where they exist in an immature state being unable to stimulate T lymphocytes. An antigen capture acts as a signal for the dendritic cells to mature and mobilize to regional lymph nodes, thus allowing for efficient antigen presentation. The capacity to activate T lymphocytes possessed by these mature dendritic cells is related to the presence of a high number of MHC, co-stimulatory and adhesion molecules.[8] Potential disadvantages of this strategy are the great cost and possible logistical problems. Large quantities of peripheral blood mononuclear cells must be obtained for each patient via leukapheresis, and then cultured for several days in the presence of cytokines before being re-infused into the patient.[22,23]

Phase I and phase II trials on sipuleucel T have demonstrated T lymphocyte responses to PA2024, PAP and GM-CSF.[12,16,17] Also, antibodies against these molecules could be detected. Thus, an activation of the immune system through sipuleucel-T can be assumed. However, the type and number of cells showed a rather high variation. This is also the case in other trials. Ragde et al reviewed 7 vaccine trials using DCs in a total of 164 patients with advanced prostate cancer.[9] Antigen sources included peptides, recombinant protein and mRNA. Number of cells injected ranged from 10^5 to 10^{10}. Vaccination was performed iv, sc, intradermally and through intralymphatic injections. The number of vaccinations ranged between 2 to 6. A total of 45 responders (27.4%) were identified in these studies. Clinical response ranged from complete remission to disease stabilization as measured by PSA decline, reduction in PSA velocity and changes monitored by imaging studies such as computerized tomography or bone scans. Treatments were generally well tolerated with mild and transient side effects. No treatment related hematologic, hepatic, renal or neurological toxicity, or clinically evident autoimmune disease were observed. Immunological responses were monitored using in vitro proliferation, ELISPOT, and tetramer assays.[9]

Based on the clinical results of sipuleucel-T (i.e. some PSA response, some improvement in TTP and statistical significant improvement in OS in one randomized phase III trial), Dendreon tried to approve the drug three years ago. In November 2006, Dendreon completed the submission for biological license application (BLA) to the FDA. In January 2007, Dendreon announced that the FDA accepted their application and assigned it priority review status. In March 2007, an advisory committee to the FDA reviewed clinical safety and efficacy data. The 17-member Oncology Drugs Advisory Committee voted 17: 0 that the vaccine is safe and 13: 4 that the vaccine is effective. BLA was, however, denied by the FDA in May 2007 and additional clinical and CMC (Chemistry, Manufacturing and Controls) data were requested. With these data it is likely that Dendreon will resubmit the BLA to the FDA in 2009. The entire preparation is a multi-step process including extraction of blood cells from the patient, transporting them to the vaccine manufacturer, incubating them with recombinant antigen, ensuring sterility of the processed cells, and returning them to the patient for iv infusion. One of the goals of drug before approval is maintaining quality in terms of consistency and purity of the drug.

The question remains at what disease stage sipuleucel-T is to be applied. In the absence of a comparative trial of sipuleucel-T against the standard therapy of HRPC (i.e. docetaxel plus prednisone) one could argue that the approach that needs the most intact immune system could be in first line. With regard to the latter aspect, the most promising scenario would be an adjuvant vaccination with sipuleucel-T in patients with organ-confined disease the most promising approach. The next logical approach would be PSA relapse (also biochemical relapse) after surgery or radiotherapy. In case of approval, the most realistic scenario, however, would be that sipuleucel-T is given to patients with

HRPC and low tumor burden rather than giving sipuleucel-T after chemotherapy with docetaxel has failed. A randomized phase-III trials could also be set up to test sipuleucel-T followed by docetaxel versus docetaxel followed by sipuleucel-T in patients with HRPC. In this setting the primary endpoint should be OS but also additional (and probably important) information about the immune system and its ability to react to a vaccine could be obtained. Also, with such study design of a "sequence therapy" the impact of other second-line therapies such as chemotherapy, antibody therapy, radionuclide therapy and others on OS would be reduced. The impact of second-line therapies on OS in the phase-III trial by Small and co-workers remains open despite the fact that the use of chemotherapy was balanced between the two study arms.[11,18]

Summary

Immunotherapy including vaccine therapy is increasingly studied in patients with prostate cancer. However, it is presently impossible to define the ideal vaccine technique, the ideal patient population, the ideal immune monitoring, and the ideal clinical surrogate parameters.

Measurement of cytokines or T-lymphocyte activation by the ELISPOT technique for instance is easy to perform. Unfortunately, in the majority of trials there is poor correlation between activation of the immune system and clinical outcome. On the other hand, it remains a clear advantage of vaccine techniques that they are usually associated with few side effects.

Presently, sipuleucel-T is one of the most advanced vaccination strategies in prostate cancer. Still, in the near future the best vaccine technique, the best patient population, the best immune monitoring and the best clinical surrogate parameters are to be defined. However, in case of approval it is most likely that most patients with HRPC will receive sipuleucel-T before docetaxel.

Disclosure

The authors report no conflicts of interest.

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