Drugs of the Future 2005, 30(9): 892-895

CCC: 0377-8282/2005
DOI: 10.1358/dof.2005.030.09.941847

Provenge®

Prostate Cancer Therapy

APC-8015

Autologous dendritic cell product composed of antigen-presenting cells loaded *ex vivo* with the recombinant fusion protein PA2024, consisting of prostatic acid phosphatase (PAP) linked to human granulocyte-macrophage colony-stimulating factor (GM-CSF)

EN: 259673

Abstract

There are few therapeutic options available for the treatment of hormone-refractory prostate cancer (HRPC), but recent advancements in the understanding of immune recognition have resulted in the development of novel vaccine products aimed at inducing prostate-specific T-cell-mediated immunity. Provenge® (APC-8015) is an immunotherapeutic consisting of autologous dendritic cell precursors loaded *ex vivo* with a recombinant fusion protein (PA2024) comprising prostatic acid phosphatase (PAP), an antigen found in 95% of prostate cancers, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Early clinical studies demonstrated good tolerability of the product and T-cell proliferation responses to PA2024. Phase II studies indicated the preliminary efficacy of Provenge®, with increases in prostate-specific antigen (PSA) doubling time and PSA-modulating effects. Subsequent placebo-controlled phase III studies identified advantages for Provenge® in terms of time to disease progression and time to onset of disease-related pain.

Introduction

Prostate cancer is the most commonly diagnosed cancer in men worldwide, accounting for approximately one-fifth of all male cancers, and the second leading cause of death due to cancer in North American men. Between 1988 and 1992, the incidence of prostate cancer increased dramatically as a result of earlier diagnosis following the introduction of prostate-specific antigen (PSA) blood testing. The 5-year relative survival rate for patients whose tumors are diagnosed in the local and regional stages is 100%. In the past 20 years, the 5-year survival rate for all stages combined has increased from 67% to 98% (1, 2).

Approximately 80% of all cases of prostate cancer are hormone-dependent and require androgens to grow and metastasize. Early detection and treatment during the androgen-responsive stage of the disease are critical to prevent progression to hormone-refractory prostate cancer (HRPC), for which there are few therapeutic options available (2). The initial treatment for advanced prostate cancer is suppression of testicular androgen production by pharmacological or surgical castration. Despite a high rate of initial response to androgen deprivation and secondary hormonal manipulation, most patients will eventually develop progressive androgen-independent disease or HRPC (3).

Recent advancement in the understanding of the molecular basis of immune recognition and regulation has generated new possibilities for the successful development of cancer immunotherapies. The identification of prostate-specific or tumor-associated antigens that can be targeted to promote cell injury or death has enabled the construction of vaccines aimed at inducing prostate-specific T-cell-mediated immunity (4). Prostatic acid phosphatase (PAP) is a protein uniquely expressed in prostatic cancer and prostate tissue, and has been targeted in the development of novel vaccine therapies. Provenge® (APC-8015) contains antigen-presenting cells (APCs) loaded with a recombinant fusion protein, PA2024, which consists of PAP linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), a molecule that specifically targets a receptor expressed on the surface of APCs. It is designed to initiate a T-cell-mediated immune response against PAP and is currently in phase III development for metastatic androgen-independent prostate cancer and earlier stage disease, with fast track designation from the U.S. FDA (5).

J.A. McIntyre, D. Fernández. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Clinical Studies

A phase I trial was performed in 18 patients with HRPC to evaluate procedure feasibility, including leukapheresis volume and immune response induced by Provenge® administered on 3 occasions each 2 weeks apart. The most frequently reported adverse event was transient fever. PA2024-specific immune responses, as determined by T-cell proliferation response *in vitro*, were observed in all patients. One patient had a clinical response demonstrated by > 50% shrinkage of several metastatic lymph nodes and a decrease in serum PSA value. There were no significant correlations between the infused cell numbers or leukapheresis volume and safety, efficacy and immune response (6).

Another phase I trial was conducted in 12 men with HRPC treated at 3 dose levels of Provenge® based on treatment-related toxicity. Two cohorts of 3 patients each received 0.2 and 0.6 x 10^9 nucleated cells/m^2, and 6 patients received 1.2 x 10^9 nucleated cells/m^2. The latter dose represented the maximum number of cells that could be prepared. Patients received Provenge® by i.v. infusion monthly for 3 months. Provenge® was prepared for each treatment course by harvesting dendritic cell precursors from peripheral blood following a standard 1.5-2.0 blood volume mononuclear cell leukapheresis. Preparation involved buoyant density centrifugation followed by incubation for 40 h in serum-free, cytokine-free media with PA2024. Provenge® was well tolerated, with mild myalgias in 3 patients and no other treatment-related adverse events. All the patients developed strong T-cell proliferation responses to PA2024 after a single infusion of Provenge®. The T-cell proliferation responses to the fusion protein were maximal after either 2 or 3 infusions of Provenge®. The magnitude of proliferation was related to the dose of dendritic cells infused (7-9).

In a follow-up phase II trial, 19 men were treated with the maximum dose of Provenge® that could be prepared (median number of nucleated cells = 2.1 x 10^9). Patients in this trial had less extensive disease than those in the phase I trial, who were more heavily pretreated. None had metastases identified on bone scan or computed tomography. The median PSA level was also lower in this group (14.5 ng/ml *vs.* 209 ng/ml in the phase I patients). Overall, treatment was also well tolerated and T-cell proliferation responses occurred in all patients after infusion of Provenge®. In terms of response to treatment, patients from the phase I and II trials were assessed together (n=31). Three patients had at least a 50% decrease in serum PSA, and 3 more had 25-49% decreases in PSA. No improvements in bone scans or soft tissue disease were observed. The median time to disease progression for the phase I patients was 12 weeks, and that for the phase II patients was 29 weeks. The median time to disease progression was significantly longer for those patients who developed an immune response compared with those who did not (34 weeks *vs.* 13 weeks), and it was also longer for those patients who received > 100 x 10^6 cells/infusion (31.7 weeks *vs.* 12.1 weeks for patients who received fewer cells) (7).

In another phase II trial, 18 patients with elevated PSA as the only manifestation of progressive prostate cancer were treated with Provenge® on 3 occasions, each 2 weeks apart. Of 12 patients evaluable for response and with a median follow-up of 4 months, 11 patients had stable disease and 1 patient had progression based on PSA criteria (10).

A phase I trial was also performed in men with advanced HRPC to monitor the safety of Provenge® followed by a soluble antigen PA2024 boost, as well as the effects on cellular and humoral immunity. Twelve men received i.v. infusions of 2 doses of Provenge® 1 month apart, followed by up to 3 monthly s.c. doses of the recombinant antigen. Three dose levels of the subcutaneously injected soluble antigen PA2024 (0.3, 0.6 and 1.0 mg) were evaluated in groups of 3 patients. The treatment was generally well tolerated, with 6 patients experiencing transient mild fatigue and 1 prolonged grade 3 fatigue that was temporally related to treatment. Mild reactions at the s.c. injection site were observed in 4 patients. All 11 evaluable patients developed antibody responses to PA2024. Nine patients developed antigen-specific T-cell proliferative responses after administration of Provenge®. There were sporadic treatment-induced decreases in circulating PSA and PAP, but no objective radiographic responses to treatment were observed (11, 12).

A phase II trial was then performed with Provenge® to better define the response, time to progression and survival of men with androgen-independent prostate cancer. Twenty-one patients with histologically documented HRPC that could be evaluated by radionuclide bone scan or computed tomography scan received 2 i.v. infusions of Provenge® 2 weeks apart followed by 3 s.c. injections of 1.0 mg PA2024 1 month apart. Nineteen patients were evaluable for treatment response. The median time to progression was 118 days. Two patients exhibited a transient 25-50% decrease in PSA, while in a third patient PSA fell from 221 ng/ml at baseline to undetectable levels by week 24, remaining so for 4 years. This patient's metastatic retroperitoneal and pelvic adenopathy also resolved. Peripheral blood mononuclear cells collected from patients for at least 16 weeks proliferated upon *in vitro* stimulation with PA2024, indicating the presence of PA2024-specific immune effector cells. The study demonstrated a definite clinical response of HRPC to Provenge® (13).

A further phase II trial was conducted to assess the PSA-modulating effects of Provenge® in patients with androgen-dependent prostate cancer with biochemical progression. Nineteen patients with nonmetastatic recurrent disease, as manifested by increasing PSA levels (0.4-6.0 ng/ml), and who had undergone previous definitive surgical or radiation therapy received 3 infusions of Provenge® (each approximately 1.2 x 10^9 nucleated cells/m^2) 2 weeks apart. Thirteen of 18 patients evaluable for PSA response demonstrated an increase in the PSA doubling time (disease progression), with a median increase of 62% following treatment. The median time to

PSA progression was 11.7 months. No patient exhibited a PSA reduction of at least 50%, but 7 patients showed moderate decreases in PSA ranging from 6% to 33%. No patient developed distant metastases before or at the time of PSA progression. The treatment was well tolerated (14, 15).

In another phase II trial, Provenge® was administered in combination with bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF). Patients with nonmetastatic, recurrent, androgen-dependent prostate cancer, as manifested by a rising PSA (0.4-6.0 ng/ml), and prior definitive surgical or radiation therapy were given 3 intravenous doses of Provenge® and bevacizumab (10 mg) at baseline and at 2 and 4 weeks. Bevacizumab was given every 2 weeks thereafter until toxicity or progressive disease. The combination of Provenge® and bevacizumab demonstrated PSA-modulating activity, with 9 of 21 evaluable patients exhibiting decreases in PSA from baseline ranging from 6% to 72%, and 3 patients showing a decrease of at least 25%. Significant changes in PSA doubling time were observed in the absence of significant decreases in PSA levels (16, 17).

A randomized, double-blind, placebo-controlled phase III trial (D9901) was conducted in men with asymptomatic, metastatic HRPC. A total of 127 men without cancer-related pain and with PAP-expressing tumors were randomized in a 2:1 ratio to Provenge® (n=82) or placebo (n=45) infused at baseline and at 2 and 4 weeks. Bone or CT scans were performed every 8 weeks and patients completed weekly pain logs. The primary endpoint of the study was objective disease progression. Secondary endpoints were disease-related pain and survival. Patients randomized to placebo were able to cross over to Provenge® at the time of disease progression. Patients were followed per protocol for survival for 3 years following randomization. In the overall patient population, there was a trend towards a longer time to progression in the Provenge®-treated patients (11.1 weeks) compared with the placebo group (10.0 weeks), although this difference did not reach statistical significance. In the subgroup of patients with a Gleason score of 7 or less, the time to objective disease progression was significantly longer in patients treated with Provenge® (16.1 weeks) compared to those treated with placebo (9.1 weeks). In this subgroup, patients treated with Provenge® also had an increased time to onset of disease-related pain and a higher T-cell stimulation index in response to Provenge® (49.6 *vs.* 7.26 in patients with a Gleason score of 8 or more). An analysis of baseline patient characteristics revealed that Gleason score was prognostic for increased time to disease progression with Provenge® treatment. Provenge® was well tolerated, the most frequently reported adverse events being grade 1 and 2 rigors, pyrexia and dyspnea. Median overall survival was 25.9 months for patients treated with Provenge® compared with 22.0 months for those on placebo. At 36 months, 33% of Provenge®-treated patients were alive compared with 11% of placebo-treated patients. In patients with a Gleason score of 7 or less, a 6.4-month survival advantage was observed (median survival in Provenge® patients = 28.4 months *vs.* 22.0 months in placebo-treated patients). These data represent the first survival advantage attributed to an immunotherapy product in prostate cancer (18-23).

Other phase III trials of Provenge® are ongoing. A pivotal study (D9902B) is enrolling up to 275 men with asymptomatic, metastatic HRPC with a Gleason score of 7 or less, and a phase III trial in early-stage prostate cancer (P-11; PROTECT [PROvenge Treatment and Early Cancer Treatment]) has completed enrollment. This is a double-blind, placebo-controlled trial measuring PSA progression and the onset of metastatic disease in over 170 men with nonmetastatic, androgen-dependent prostate cancer (24).

Source

Dendreon Corporation (US).

References

1. Jemal, A., Murray, T., Ward, E., Samuels, A., Tiwari, R.C., Ghafoor, A., Feure, E.J., Thun, M.J. *Cancer statistics*, 2005. CA Cancer J Clin 2005, 55: 10-30.

2. Prous Science Drug R&D Backgrounders: *Prostate cancer (online publication)*. Updated September 27, 2005.

3. Small, E.J., Harris, K.A. *Secondary hormonal manipulation of prostate cancer*. Semin Urol Oncol 2002, 20(3, Suppl. 1): 24-30.

4. Havranek, E.G., Whelan, M.A., Greenhalgh, R., Dalgleish, A.G., Pandha, H. *Advances in prostate cancer immunotherapy*. Surg Oncol 2002, 11(1-2): 35-45.

5. *Dendreon plans Provenge BLA filing*. DailyDrugNews (Daily Essentials) Sept 19, 2005.

6. Takaue, Y., Tanosaki, R., Tobisu, K., Kakizoe, T., Mizunuma, Y., Yanagida, M., Kawai, H.. *Antigen-pulsed dendritic cell therapy for the treatment of hormone-refractory prostate cancer: A phase I trial of APC-8015*. Proc Am Soc Clin Oncol (ASCO) 2002, 21(Pt. 2): Abst 1881.

7. Small, E.J., Fratesi, P., Reese, D.M., Strang, G., Laus, R., Peshwa, M.V., Valone, F.H. *Immunotherapy of hormone-refractory prostate cancer with antigen-loaded dendritic cells*. J Clin Oncol 2000, 18(23): 3894-903.

8. Valone, F., Small, E., Peshwa, M.V., Strang, G., Laus, R., Ruegg, C., van Schooten, W. *Phase I trial of dendritic cell-based immunotherapy with APC8015 for hormone-refractory prostate cancer (HRPC)*. Proc Am Assoc Cancer Res (AACR) 1998, 39: Abst 1186.

9. Valone, F.H., Small, E.J., Whisenant, S., Peshwa, M., Strang, G., Laus, R., Ruegg, C., van Schooten, W. *Immunotherapy of hormone refractory prostate cancer with antigen-pulsed dendritic cells: A phase I/II trial*. Proc Am Soc Clin Oncol (ASCO) 1998, 17: Abst 1334.

10. Frohlich, M.W., Small, E.J., Bok, R.A., Gulla, S.P., Valone, F.H., Harris, K.A., Reese, D.M. *Immunotherapy with prostatic acid phosphatase-loaded dendritic cells (Provenge) in prostate cancer patients with serologic progression after definitive local therapy*. Proc Am Soc Clin Oncol (ASCO) 2001, 20(Pt. 1): Abst 750.

11. Burch, P.A., Breen, J.K., Buckner, J.C., Gastineau, D.A., Kaur, J.A., Laus, R.L., Padley, D.J., Peshwa, M.V., Pitot, H.C., Richardson, R.L., Smits, B.J., Sopapan, P., Strang, G., Valone, F.H., Vuk-Pavlovic, S. *Priming tissue-specific cellular immunity in phase I trial of autologous dendritic cells for prostate cancer*. Clin Cancer Res 2000, 6: 2175-82.

12. Burch, P.A., Kaur, J.S., Richardson, R.L., Pitot, H.C., Buckner, J.C., Padley, D.J., Vuk-Pavlovic, S., Strang, G., Valone, F.H., Peshwa, M.V., Gastineau, D.A. *Soluble antigen boost after dendritic cell infusion for immunotherapy of hormone refractory prostate cancer: A phase I trial*. Proc Am Assoc Cancer Res (AACR) 1999, 40: Abst 570.

13. Burch, P.A., Croghan, G.A., Gastineau, D.A., Jones, L.A., Kaur, J.S., Kylstra, J.W., Richardson, R.L., Valone, F.H., Vuk-Pavlovic, S. *Immunotherapy (APC8015, Provenge®) targeting prostatic acid phosphatase can induce durable remission of metastatic androgen-independent prostate cancer: A phase 2 trial*. The Prostate 2004, 60(3): 197-204.

14. Beinart, G., Rini, B.I., Weinberg, V., Small, E.J. *Antigen-presenting cells 8015 (Provenge®) in patients with androgen-dependent, biochemically relapsed prostate cancer*. Clin Prostate Cancer 2005, 4(1): 55-60.

15. Rini, B.I., Beinart, G., Small, E.J., Verjee, S., Hershberg, R.M. *Immunotherapy (APC015) for androgen dependent, biochemically-relapsed prostate cancer*. J Urol 2005, 173(4, Suppl.): Abst 1018.

16. Rini, B.I., Weinberg, V., Bok, R.A., Nguyen, S., Small, E.J. *A phase 2 study of prostatic acid phosphatase-pulsed dendritic cells (APC8015, Provenge®) in combination with bevacizumab in patients with serologic progression of prostate cancer after local therapy*. Proc Am Soc Clin Oncol (ASCO) 2003, 22: Abst 699.

17. Rini, B.I., Weinberg, V., Fong, L., Small, E. *A phase 2 study of prostatic acid phosphatase-pulsed dendritic cells (APC8015; Provenge) in combination with bevacizumab in patients with serologic progression of of prosatate cancer after local therapy*. Prostate Cancer Symp (Feb 17-19, Orlando) 2005, Abst 251.

18. Schellhammer, P.F., Hershberg, R.M. *Immunotherapy with autologous antigen presenting cells for the treatment of androgen independent prostate cancer*. World J Urol 2005, 23(1): 47-9.

19. Small, E., Schellhammer, P., Higano, C., Peshwa, M., Nemunaitis, J., Jones, L., Valone, F. *A phase III randomized, double-blind, placebo-controlled trial of autologous dendritic cells pulsed with prostatic acid phosphatase (APC8015) in men with asymptomatic, metastatic, hormone refractory prostate cancer*. J Urol 2002, 167(4, Suppl.): Abst 1203.

20. Small, E.J., Rini, B., Higano, C., Redfern, C., Nemunaitis, J., Valone, F., Kylstra, J., Schellhammer, P.F. *A randomized, placebo-controlled phase III trial of APC8015 in patients with androgen-independent prostate cancer (AiPCa)*. Proc Am Soc Clin Oncol (ASCO) 2003, 22: Abst 1534.

21. Kylstra, J.W., Nemunaitis, J., Small, E.J., Jones, L.A. *A placebo-controlled phase 3 trial of immunotherapy (APC8015, Provenge®) for androgen independent prostate cancer (AIPC): Evidence that Gleason score predicts immunologic as well as clinical responses to therapy*. Proc Am Assoc Cancer Res (AACR) 2004, 45: Abst 1408.

22. Small, E., Schellhammer, P., Higano, C., Neumanaitis, J., Valone, F., Herschberg, R.M. *Immunotherapy (APC8015) for androgen independent prostate cancer (AIPC): Final survival data from a phase 3 randomized placebo-controlled trial*. Prostate Cancer Symp (Feb 17-19, Orlando) 2005, Abst 264.

23. Small, E., Schellhammer, P., Higano, C., Neumanaitis, J., Valone, F., Hershberg, R. *Results of a placebo-controlled phase III trial of immunotherapy with APC8015 for patients with hormone refractory prostate cancer (HRPC)*. 41st Annu Meet Am Soc Clin Oncol (ASCO) (May 13-17, Orlando) 2005, Abst 4500.

24. *Dendreon completes enrollment in phase 3 PROTECT (P-11) clinical trial of Provenge in early stage prostate cancer*. Dendreon Press Release 2005, June 21.