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Dramatic and Prolonged PSA Response After Retreatment With a PSA Vaccine

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Introduction

Immunotherapy for prostate cancer has gained momentum with the approval of sipuleucel T for metastatic castration resistant prostate cancer (mCRPC). Another vaccine strategy uses prostate specific antigen (PSA) based viral vaccines and 1 approach to this, PROSTVAC VF (Bavarian Nordic, Kvistgaard, Denmark), involves recombinant vaccinia and fowlpox vaccines engineered to encode the PSA transgene along with 3 human T cell costimulatory molecules (B7 1, LFA 3, and ICAM 1), together designated as TRI COM.¹ In a randomized placebo controlled phase II trial of 125 patients with mCRPC, PROSTVAC VF with granulocyte macro phage colony stimulating factor (GM CSF) was associated with an improvement in median overall survival of 8.5 months compared with placebo.² These data led to an ongoing randomized phase III registration trial of PROSTVAC VF with or without GM CSF in patients with mCRPC (NCT01322490).

An important issue for cancer vaccine therapies is whether retreatment with a second series of vaccinations has any clinical utility. Although booster therapy is commonly given for vaccinations involving antibody response to viral antigens, its role in cellular induced immunity and cancer therapy has not been investigated.

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Disclosure

The authors have stated that they have no conflicts of interest.

We report the case of a patient with a dramatic and sustained decline of PSA levels 4 years after receiving a second treatment with PROSTVAC VF, which was given 5 years after the initial fowlpox/vaccinia PSA vaccination. His response provides impetus for consideration of revaccination strategies.

Case Report

This patient was 60 years old when initially diagnosed with clinical T1c (nonpalpable) prostate cancer on the basis of a PSA level of 11.9 ng/mL (Figure 1, point A). A prostate biopsy specimen revealed Gleason 3 + 4 adenocarcinoma. He was treated with radical prostatectomy and was found to have Gleason 4 + 3 disease involving both lobes of his prostate extending outside the capsule to the inferior margin (stage T3a).

After radical prostatectomy, his PSA level became undetectable (< 0.2 ng/mL) and remained so for 2 years (Figure 1, point B). His PSA level then began to rise over the next 4 years, with a PSA doubling time (PSADT) of approximately 10 months (0.84 years), until reaching 2.6 ng/mL approximately 6 years after prostatectomy (Figure 1, segment 1). A ProstaScint (EUSA Pharma, Langhorne, PA) scan demonstrated abnormal activity only in the prostate bed, and he was treated with external beam radiation therapy to the prostate bed (64.8 Gy). However, his PSA level continued to rise without any apparent effect of the radiation on his PSADT (Figure 1, segment 1).

Seven and a half years after prostatectomy his PSA level had reached 7.7 ng/mL. Staging studies showed no evidence of metastatic disease, and he enrolled in an Eastern Cooperative Oncology Group phase II clinical trial of PSA based vaccines for patients with biochemical progression only after local therapy for prostate cancer.³ He was randomized to vaccination with 3 doses of recombinant PSA expressing fowlpox followed by 1 dose of re combinant PSA expressing vaccinia, each 6 weeks apart. Five months after receiving his last vaccination, his PSA level had risen to 12.9 ng/mL (Figure 1, point C) before gradually declining (Figure 1, segment 2) and reaching a nadir of 4.3 ng/mL (a 67% decrease 9.2 years after prostatectomy) (Figure 1, point D). This nadir was short lived and his PSA level began to rise within 1 year. However, in contrast to his prevaccine PSADT, his doubling time slowed to 2.6 years over the next 5 to 6 years (Figure 1, segment 3).

Approximately 11 years after prostatectomy and 4 years after initial vaccination, the patient had a workup that was again negative for metastatic disease. Given his previous response to the PSA vaccine, a compassionate use single patient institutional review board application for treatment with PROSTVAC VF was filed. This vaccine encodes for TRICOM in addition to PSA, and he was treated with the vaccinia vector once followed by 6 treatments with the fowlpox vector over a 6 month period without any complications. GM CSF was also given at the vaccine injection site on the day of and for 3 days after vaccination.

Although he did not experience an early decline in his PSA level as he did after his first vaccinations, he did experience a slowing in his PSA velocity, and his PSA level plateaued at 24 ng/mL about 16 years after prostatectomy (Figure 1, point E). Since then, his PSA level has declined spontaneously without intervention (Figure 1, segment 4). His most recent PSA

level was 3.5 ng/mL (19.3 years after prostatectomy) (Figure 1, point F), an 85% reduction in PSA level from the maximum value over approximately 3.5 years of decline.

Discussion

To our knowledge this is the only patient to be revaccinated with PSA vaccinia/fowlpox vaccines, with approximately 4.5 years between treatments. He has had a profound and sustained decline in PSA elevation after first having marked improvement in his PSA velocity/doubling time. This patient originally had a PSA doubling time of 10 months and as such would have been expected to have a median actuarial time to metastases of 8 years (from the time of PSA elevation) and a median actuarial time to death after development of metastases of 5 additional years.⁴ However, he has not required hormonal treatment or chemotherapy in almost 18 years since his biochemical recurrence, and therefore his course has greatly exceeded expectations. Because spontaneous declines in PSA levels are rare in the absence of therapy, we believe that the ongoing PSA decline in this patient is caused by the combined effect of both sets of vaccinations. Of note, the patient's testosterone levels have been in the low normal range and much greater than castration levels, arguing against waning testosterone levels causing PSA decline. We have also tested for anti PSA antibodies that could decrease PSA levels by pulling PSA out of circulation. PSA antibodies were not detected on multiple occasions. In studies of PROSTVAC VF, there has been a trend toward improved survival in patients with a greater than 6 fold increase in PSA specific T cell responses.^{5,6} Antigen specific T cell responses were not observed in this patient.

Significant PSA declines are rare after PSA based vaccinia/fowl pox therapy. Of 57 patients treated with PROSTVAC VF in 2 phase I and 1 phase II trials, only 6 patients were reported to have PSA elevation declines of > 30%, and none to the degree observed in this patient.⁶⁹ Of 82 patients randomized to the PROSTVAC VF arm in the larger phase II trial, only 1 patient had a PSA elevation decline of > 80%.² Therefore, to our knowledge, this is the first report of a patient with such a dramatic PSA level decline sustained over as long a follow up period.

It is not known with certainty why this patient benefited after the second series of vaccinations, but the first and second series of vaccinations were not identical. Between vaccinations, the viral vectors were modified to encode TRICOM, which may have promoted a stronger and more sustained immune response.¹⁰ When retreated, a prime/boost strategy was used, with the vaccinia vector administered before boosts with fowlpox vector, which is the sequence now being studied in the ongoing phase III trial of PROSTVAC VF. This sequence may be more effective than the reverse because of a more robust immune response induced by vaccinia and the suitability of fowlpox to boost immune responses because it is not associated with significant neutralizing antibody formation. The patient's second set of vaccinations was also given with GM CSF, and the potential benefit of this is also being investigated in the ongoing phase III trial.

This patient's case may also illustrate a more general boosting effect from a second PROSTVAC administration independent of differences in the composition and administration of the 2 series of vaccinations. The immune related events responsible for the

changes in PSA levels, particularly after the second vaccination series, are unknown, although it is of interest that the decline after the second series of vaccinations did not occur for approximately 3.5 years, consistent with observations that responses to immuno therapy can be quite delayed.¹¹

Conclusion

This case suggests that some patients may benefit from multiple courses of vaccination and that this strategy is not obviously likely to cause toxicity. Identifying which patients are most likely to respond to multiple courses of vaccination is an unmet need, but the reduction in PSA level and the subsequent prolongation of the PSADT in this patient after the initial set of vaccinations may have been predictive of a response to revaccination. Future studies might be able to assess the effect of repeated vaccinations of PROSTVAC VF to see if the results observed in our patient can be duplicated.

References

1. Kim JW, Gulley JL. Poxviral vectors for cancer immunotherapy. *Expert Opin Biol Ther* 2012; 12:463–78. [PubMed: 22413824]
2. Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J Clin Oncol* 2010; 28:1099–105. [PubMed: 20100959]
3. Kaufman HL, Wang W, Manola J, et al. Phase II randomized study of vaccine treatment of advanced prostate cancer (E7897): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2004; 22:2122–32. [PubMed: 15169798]
4. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999; 281:1591–7. [PubMed: 10235151]
5. Vergati M, Cereda V, Madan RA, et al. Analysis of circulating regulatory T cells in patients with metastatic prostate cancer pre- versus post-vaccination. *Cancer Immunol Immunother* 2011; 60:197–206. [PubMed: 20976449]
6. Gulley JL, Arlen PM, Madan RA, et al. Immunologic and prognostic factors associated with overall survival employing a poxviral-based PSA vaccine in metastatic castrate-resistant prostate cancer. *Cancer Immunol Immunother* 2010; 59: 663–74. [PubMed: 19890632]
7. DiPaola RS, Plante M, Kaufman H, et al. A phase I trial of pox PSA vaccines (PROSTVAC-VF) with B7-1, ICAM-1, and LFA-3 co-stimulatory molecules (TRICOM) in patients with prostate cancer. *J Transl Med* 2006; 4:1–5. [PubMed: 16390546]
8. Arlen PM, Skarupa L, Pazdur M, et al. Clinical safety of a viral vector based prostate cancer vaccine strategy. *J Urol* 2007; 178:1515–20. [PubMed: 17707059]
9. Kim JW, Madan RA, Gulley JL. Initial PSA oscillations precede prolonged stable disease in a patient treated with a therapeutic cancer vaccine. *Clin Genitourin Cancer* 2012; 10:43–6. [PubMed: 22019260]
10. Grosenbach DW, Barrientos JC, Schlom J, et al. Synergy of vaccine strategies to amplify antigen-specific immune responses and antitumor effects. *Cancer Res* 2001; 61:4497–505. [PubMed: 11389081]
11. Gulley JL. Therapeutic vaccines: the ultimate personalized therapy? *Hum Vaccin Immunother* 2013; 9:1–3. [PubMed: 23442580]

Clinical Practice Points

- The effect of more than 1 series of vaccination with a vaccinia/fowlpox prostate-specific antigen (PSA) vaccine system has not previously been observed. This case illustrates an unusually good response that is likely related to the combined effect of the vaccinations.
- Changes in PSA levels may occur slowly after vaccination. This patient's PSA response was observed > 4 years after his second series of vaccination.
- Repeated vaccination may be useful in patients with disease progression after an initial response to vaccine therapy.

Figure 1.

Prostate-Specific Antigen (PSA) Values (y-Axis) are in Nanograms/Milliliter (ng/mL), Plotted on the Natural Log Scale; PSA was Measured at 2 Different institutions as Denoted by the 2 Colors. Time (x-Axis) is in Years Relative to Prostatectomy in 1993. The Solid Black Line is a Cubic Spline Smooth. The Dashed Blue Lines are the Linear Segments Fit Using Segmented Linear Regression Modeling to Estimate PSA Level Doubling Time During Different Periods. Annotated Peak and Nadir PSAs and Linear Segments of the Model are Summarized in Table 1
Abbreviation: XRT = Radiation Therapy.

Tabel 1

Timeline of PSA Levels

Point	Linear Segment		Years Since RP	Period	PSA (ng/mL)	Slope	PSA Level Doubling Time (years)	
	Linear Segment	Linear Segment					PSA Level Doubling Time (years)	Linear Segment
A	–	–	0	Before RP	11.9	–	–	–
B	–	–	<2	Nadir after RP	<0.2	–	–	–
C	1	–	2.0 8.3	After RP and salvage XRT	–	+0.83	0.84	–
	–	–	8.3	Peak after PROSVAC VF No. 1	12.9	–	–	–
	2	–	8.3 9.0	Immediately after PROSTVAC VF No. 1	–	1.55	0.45	–
D	–	–	9.2	Nadir after PROSTVAC VF No. 1	4.3	–	–	–
	3	–	9.0 16.1	After PROSTVAC No. 1 and immediately after PROSTVAC VF No. 2	–	+0.26	2.64	–
E	–	–	15.9	Peak after PROSTVAC VF No. 2	24	–	–	–
F	4	–	16.1 19.3	After PROSTVAC VF No. 2	–	0.52	1.34	–
	–	–	19.3	Most recent PSA level measured	3.5	–	–	–

Abbreviations: PSA = prostate specific antigen; RP = radical prostatectomy; XRT = radiation therapy.