Analysis of Overall Survival in Patients with Nonmetastatic Castration-Resistant Prostate Cancer Treated with Vaccine, Nilutamide, and Combination Therapy

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Abstract

Purpose: We reported previously the first randomized study of any kind in patients with nonmetastatic, castrate-resistant prostate cancer. The study employed vaccine, the hormone nilutamide, and the combined therapy (crossover for each arm) with an endpoint of time to progression. We now report survival analyses at 6.5 years from the initiation of therapy with a median potential follow-up of 4.4 years.

Experimental Design: Forty-two patients were randomized to receive either a poxvirus-based prostate-specific antigen (PSA) vaccine or nilutamide. Patients in either arm who developed increasing PSA without radiographic evidence of metastasis could cross over to receive the combined therapies.

Results: Median survival among all patients was 4.4 years from date of enrollment. Median survival exhibited a trend toward improvement for patients initially randomized to the vaccine arm (median, 5.1 versus 3.4 years; $P = 0.13$). Starting from the on-study date, the retrospectively determined subset of 12 patients who initially received vaccine and then later received nilutamide suggested improved survival compared with the 8 patients who began with nilutamide and subsequently were treated with vaccine (median, 6.2 versus 3.7 years; $P = 0.045$). A subgroup analysis of patients randomized to the vaccine arm versus the nilutamide arm showed substantial improvements in survival if at baseline patients had a Gleason score <7 ($P = 0.033$) and PSA <20 ng/dL ($P = 0.013$) or who had prior radiation therapy ($P = 0.018$).

Conclusions: These data indicate that patients with nonmetastatic castration-resistant prostate cancer (D0.5) who receive vaccine before second-line hormone therapy may potentially result in improved survival compared with patients who received hormone therapy and then vaccine. These data also suggest that patients with more indolent disease may derive greater clinical benefit from vaccine alone or vaccine before second-line hormone therapy compared with hormone therapy alone or hormone therapy followed by vaccine. These findings have potential implications for both the design and endpoint analysis of larger vaccine combination therapy trials.

It is estimated that in 2008 over 28,000 men in the United States will die of prostate cancer, making this disease second only to lung cancer in terms of cancer-specific mortality (1). The growing practice of screening for prostate-specific antigen (PSA) has led to increasing numbers of patients being diagnosed with local disease and more patients undergoing treatment with either surgery or local radiation. Approximately 20% to 40% of these patients will develop recurrent disease, manifested by increasing serum PSA, and many will then undergo hormonal treatment. Hormone manipulators, including gonadotropin-releasing hormone agonists and androgen receptor antagonists (ARA), can be used as single agents or in a combined androgen blockade (2). If testosterone suppression fails and serum PSA continues to increase without evidence of metastatic disease (defined as stage D0.5 or nonmetastatic castration resistant disease), patients' treatment options have unproven benefits. Withdrawing ARA temporarily lowers PSA levels in ~11% of patients, although this effect often lasts <6 months (3). Other options for patients with stage D0.5 disease include observation, additional hormone manipulation, or enrollment in a clinical trial with a chemotherapeutic or investigational agent. However, there is currently no standard of care for these patients (2), nor has any treatment been shown to extend survival or prolong time to metastatic disease.

Immunotherapy for prostate cancer, an active field of investigation, uses a wide variety of approaches. PSA, which is expressed by the majority of prostate cancers, as well as by epithelial cells lining the acini and ducts of the prostate gland,

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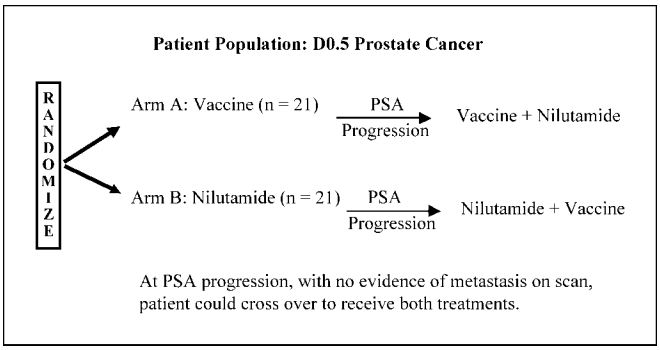

Fig. 1. Study design.

can be an effective target for cancer vaccine therapy (4). Immunization with the live recombinant poxvirus vectors vaccinia and fowlpox allows for the expression of foreign antigens by a transgene encoded directly into various cells of the host, including professional antigen-presenting cells. A particular advantage of using recombinant poxviruses in cancer vaccines is that when a gene for a protein is inserted into a recombinant poxvirus and used as an immunogen, the recombinant protein is much more immunogenic than the same protein used with an adjuvant (5).

We reported previously (6) the first randomized clinical trial in stage D0.5 prostate cancer, wherein patients were initially randomized to receive either the ARA nilutamide or a poxviral vaccine. After 6 months, patients who had an increasing serum PSA but no evidence of metastasis on scan were offered the option of receiving both treatments (Fig. 1). The median time to treatment failure (defined as either disease progression or toxicity requiring discontinuation of treatment) was 7.6 months with nilutamide alone versus 9.9 months with vaccine alone. At treatment failure, 12 of 21 patients randomized to the vaccine arm opted for combination therapy at the time of increasing PSA. After the addition of nilutamide, median time to treatment failure for these 12 patients was 13.9 months for a total of 25.9 months from initiation of vaccine therapy. This suggested that adding hormone therapy after initial vaccine therapy might improve clinical benefit over hormone therapy alone (6). The purpose of the follow-up analysis reported here was to determine whether the time to treatment failure benefit seen in patients who first received vaccine and then received nilutamide resulted in increased overall survival (OS). These findings have potential implication for both the design and endpoint analysis of vaccine combination therapy trials.

Patients and Methods

Patient eligibility and baseline characteristics. In our previously reported randomized phase II trial (6), patients were eligible to enroll if they had documented nonmetastatic castration-resistant prostate cancer determined by increasing serum PSA despite castrate levels of testosterone (<50 ng/dL) with no radiographic evidence of metastatic disease. Patients were required to discontinue treatment with bicalutamide at least 6 weeks before enrollment or treatment with flutamide 4 weeks before enrollment and show a continued increase in serum PSA levels. Further aspects of patient eligibility have been described previously (6). A total of 42 patients were enrolled, 21 randomized to vaccine initially and 21 to nilutamide initially. The trial was approved by the National Cancer Institute Institutional Review Board and conducted at the National Cancer Institute. All study participants signed a consent form that was also approved by the National Cancer Institute Institutional Review Board. Patient demographics are summarized in Table 1.

Treatment regimen. Patients who enrolled on-study were randomized to receive either vaccine alone or nilutamide alone (Fig. 1). Nilutamide was dosed based on standard treatment variables: 300 mg/d for the first month and 150 mg/d thereafter. The vaccine regimen included a priming vaccination on day 1 consisting of two admixed recombinant vaccinia-based vaccines, one containing the transgenes for PSA and the other containing the transgenes for the human T-cell costimulatory molecule B7-1. One month after the priming vaccination, patients were given a monthly boost of a recombinant fowlpox-based PSA vaccine. With each vaccination, 100 μg/d sargramostim (granulocyte-macrophage colony-stimulating factor) s.c. was given at the vaccination site on days 1 to 4 followed by 6 million IU/m^2 aldesleukin (interleukin-2) s.c. in the abdomen on days 8 to 12. Patients were monitored monthly and received restaging computed tomography and bone scans every 3 months. If serum PSA increased on either vaccine or nilutamide alone, with no evidence of metastatic disease on scans, patients were allowed to cross over and receive both treatments. Monitoring and restaging continued on the same schedule as before, and patients remained on-study until PSA increased again or metastatic disease developed.

Survival analysis and statistical considerations. Using standard approaches, we determined current survival status for all patients on the trial. OS was calculated from the date of enrollment on-study to death or the date of last follow-up (April 1, 2007). A secondary OS analysis was done from the development of castration-resistant (D0.5)

Table 1. Baseline characteristics and on-study values

Patient characteristic	Vaccine arm	Nilutamide arm
Median age (range)	69 (51-87)	69 (52-87)
Mean Gleason score (range)	7 (3-9)	7.2 (4-10)
Previous ARA (Casodex or flutamide)		
0	3	4
1	13	10
2	5	7
Orchiectomy	6	4
Median time from diagnosis to enrollment on-study (mo)	10.9	7.8
On-study		
Median PSA (range), ng/dL	8.74 (1.61-292.8)	16.51 (0.74-62.19)
Median PSADT (mo)	3.6	4.3

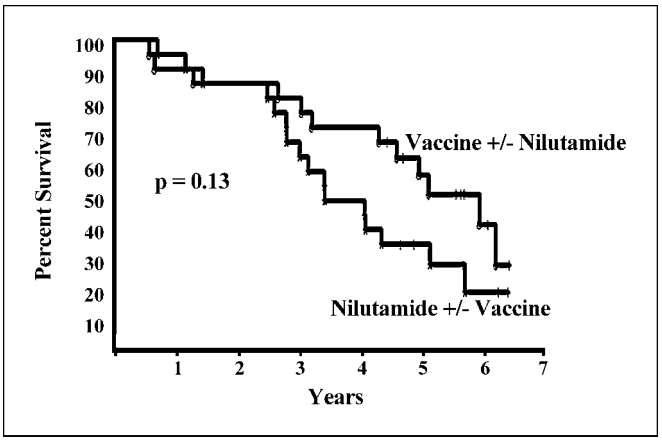

Fig. 2. Survival based on randomization from on-study date. The results suggest a trend toward survival benefit for patients randomized to the vaccine arm.

disease to death or the date of last follow-up (April 1, 2007). The probability of survival as a function of time was determined by the Kaplan-Meier method. A log-rank test was used to determine the statistical significance of the difference between pairs of Kaplan-Meier curves. Exploratory analyses of potential effects within subgroups were done and are reported without formal adjustment; unless the results were suggestive of very strong effects (e.g., if $P < 0.01$), differences found would be considered trends if $P < 0.05$. All P values are two tailed.

Results

Patient characteristics. Median on-study PSA was 8.74 ng/dL (range, 1.61-292.8) in the vaccine arm and 16.51 ng/dL (range, 0.74-62.19) in the nilutamide arm. The median on-study PSA doubling time (PSADT) in the vaccine arm was 3.6 months compared with 4.3 months in the nilutamide arm. There were no significant differences between patient characteristics in the two groups (Table 1). Based on all 42 patients, a retrospective analysis was done from the development of castration-resistant disease at a median potential follow-up of 4.4 years. Of all patients enrolled on-study, the 3-year survival probability from the time of diagnosis of D0.5 prostate cancer was 81%. The median OS for all patients was 5.0 years from the time of diagnosis of D0.5 disease.

Survival analysis of treatment groups. For all patients enrolled on the study, the 3-year survival probability was 71% and the median OS was 4.4 years. Of the patients randomized to the vaccine arm ($n = 21$), the probability of survival 3 years after enrolling on-study was 81%, with a median OS of 5.1 years from time of enrollment. Of the patients randomized to the nilutamide arm ($n = 21$), there was a 62% probability of survival 3 years after enrolling on study, with a median OS of 3.4 years from time of enrollment. There was a trend to increased OS for patients randomized to vaccine versus nilutamide ($P = 0.13$; Fig. 2).

Subgroup analysis of crossover patients. A total of 42 patients were enrolled on study. Of these, 12 patients who were originally randomized to the vaccine arm and 8 patients who were originally randomized to the nilutamide arm crossed over at PSA progression, with no evaluable disease on scans, and began receiving both therapies. The 3-year survival probability from enrollment was 100% for patients initially randomized to vaccine, with nilutamide added at time of PSA progression, with a median OS of 6.2 years (Table 2). The 3-year survival probability was 75% for patients initially randomized to nilutamide, with vaccine added at time of PSA progression, with a median OS of 3.7 years. Thus, the subset of patients who crossed over from vaccine alone to combined therapy had a longer median OS from the on-study date ($P = 0.045$; Fig. 3). OS was also evaluated in these two crossover groups from the date of crossover with the 12 patients treated with vaccine initially, then nilutamide was added, having an OS of 4.8 years compared with 2.8 years for the 8 patients randomized to nilutamide who had vaccine added ($P = 0.028$). However, this analysis was based on small, retrospectively determined cohorts, with the remaining patients not crossing over for one of three reasons: (*a*) they came off study because they developed metastatic disease, (*b*) they came off study as a result of grade 3 toxicity, or (*c*) their disease did not progress either clinically or by serum PSA.

Exploratory subgroup survival analysis from time of enrollment. Whereas Gleason score, on-study PSA, and type of definitive therapy had no effect on survival, as would be expected PSADT >3 months was associated with an improved OS compared with a PSADT ≤3 months ($P = 0.049$). Further subgroup analyses based on baseline characteristics and arm of randomization did reveal substantial differences in OS from time of enrollment (Table 3). Among patients with a Gleason score ≤7, those randomized to the vaccine arm ($n = 12$) had a median OS of 5.9 versus 3.1 years for those randomized to the nilutamide arm ($n = 10$; $P = 0.033$). A confirmed history of radiation therapy favored patients randomized to the vaccine arm [$n = 16$; median OS, 5.9 versus 3.1 years for patients in the nilutamide arm ($n = 13$); $P = 0.018$]. In addition, among patients with an on-study PSA <20 ng/dL, those randomized to the vaccine arm ($n = 10$) had a survival benefit over those randomized to the nilutamide arm ($n = 7$; median, 5.1 versus 2.6 years; $P = 0.013$). Neither prior orchiectomy nor increased PSADT conferred a statistically significant survival benefit for this patient subgroup.

Discussion

To our knowledge, this follow-up analysis of patients with stage D0.5 prostate cancer enrolled in a randomized clinical study is the first published study to provide prospective data

Table 2. Survival of patients receiving vaccine or hormone therapy or both at PSA progression from on-study date

Initial randomization	3-y survival (%)	Median OS (y)
Vaccine	81	5.1
Nilutamide	62	3.4
Crossover at progression	**3-y survival (%)**	**Median OS (y)**
Vaccine then vaccine + nilutamide	100	6.2
Nilutamide then nilutamide + vaccine	75	3.7

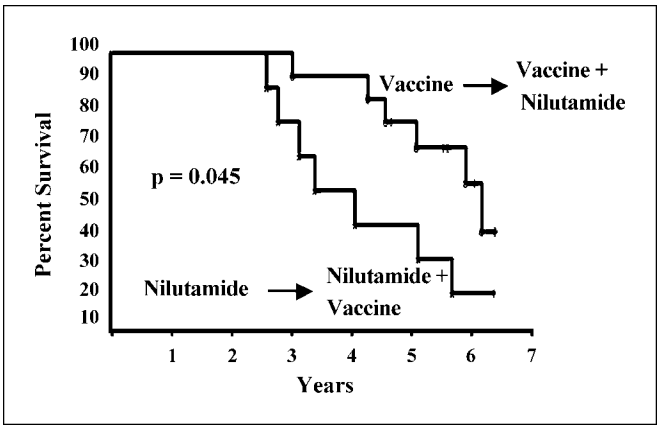

Fig. 3. Survival comparison of the crossover patients. Results show OS benefit from on-study date for patients treated first with vaccine and then with vaccine plus nilutamide, compared with patients treated first with nilutamide and then with nilutamide plus vaccine, suggesting a benefit from combined therapy when vaccine is given early in disease process.

regarding OS in this rapidly increasing patient population. Median OS for all patients enrolled in this study was 5 years, which is consistent with more recent analyses in similar patients (7, 8).

With a median potential follow-up of >4 years, data from this analysis suggest that initial treatment with vaccine may potentially be associated with prolonged survival. A possible explanation for this may be that vaccine therapy initiates a dynamic process of host immune responses that can be exploited in subsequent therapies. Several recently published studies have noted this phenomenon. In a phase I study, 17 patients with advanced-stage cancer received a plasmid/microparticle vaccine directed against cytochrome *P*4501B1. Most patients who developed immunity to *P*4501B1 but required salvage therapy on progression showed dramatic and durable responses to their next treatment regimen (9). In another study, 29 patients with extensive small-cell lung cancer received an adeno-p53 vaccine (10). Patients who received chemotherapy immediately following vaccine therapy showed a high rate (61.9%) of objective clinical responses that were closely associated with induction or augmentation of immune response to vaccine. Finally, a recently completed randomized phase II study at the National Cancer Institute used the same poxvirus-based vaccine approach described in the present study (11). In that trial, 28 patients with metastatic androgen-independent prostate cancer were randomized to receive vaccine alone or vaccine plus docetaxel. Patients in the vaccine-alone arm were allowed to cross over to receive docetaxel at disease progression. The median progression-free survival on docetaxel following vaccine was 6.1 compared with 3.7 months on the same docetaxel regimen but without prior vaccine in a historical control. Similar findings were observed in a randomized multicenter study of the sipuleucel vaccine (12), in which patients in both the vaccine arm (n = 51) and the placebo arm (n = 31) went on to receive docetaxel at progression. There was a striking and statistically significant increase in OS (hazard ratio, 1.90; P = 0.023) with docetaxel treatment in patients having had prior vaccine versus placebo.

As shown in other stages of prostate cancer, for all stage D0.5 patients enrolled in this study, an on-study PSADT ≤3 months resulted in shorter OS compared with patients with a PSADT >3 months (median, 5.1 versus 3.1 years; P = 0.045; ref. 13). However, in this small study, baseline differences in prior therapy, PSA value, and Gleason score did not have an effect on OS. The present follow-up analysis revealed a trend toward improved OS in patients randomized to receive vaccine. An exploratory subgroup analysis done according to treatment randomization suggests which D0.5 prostate cancer patients were more likely to benefit from vaccine-based therapy. Patients with either a baseline Gleason score ≤7 or a baseline serum PSA <20 ng/dL had an apparent increase in OS if they were randomized to the vaccine arm. Both these characteristics are consistent with less pathologically aggressive disease and lower tumor volume. A history of radiation therapy was a predictor that was potentially associated with improved OS in patients randomized to the vaccine arm compared with patients randomized to the nilutamide arm. The prior radiation acting as a positive predictor of survival benefit in the vaccine arm could be due to the fact that prior radiation could have led to tumor cell destruction, which in turn led to cross-presentation of prostate tumor-associated antigens to T cells. Thus subsequent vaccination could actually have been an "immune booster."

Related to this, we have shown previously (14–19) that radiation of tumor can lead to alteration of the phenotype of tumor cells in terms of up-regulation of tumor-associated antigens and also making them more susceptible to T-cell killing. The above data thus suggest that vaccine-based therapy should be used in patients with a lower tumor burden that allows the immune system to mount an effective response (20).

Table 3. Subgroup analysis based on randomized treatment assignment, beginning at on-study date, regardless of crossover, indicates that patients with lower initial Gleason score, lower on-study PSA, and/or history of prior radiation are associated with longer survival with the use of vaccine

Gleason score ≤ 7			
OS	**Vaccine ± nilutamide (n = 12)**	**Nilutamide ± vaccine (n = 10)**	***P***
Median (y)	5.9	3.1	0.033
3 y (%)	83	50	
5 y (%)	57	20	
Prior radiation therapy			
OS	**Vaccine ± nilutamide (n = 16)**	**Nilutamide ± vaccine (n = 13)**	***P***
Median (y)	5.9	3.1	0.018
3 y (%)	87	54	
5 y (%)	61	23	
PSA <20 ng/dL			
OS	**Vaccine ± nilutamide (n = 10)**	**Nilutamide ± vaccine (n = 7)**	***P***
Median (y)	5.1	2.6	0.013
3 y (%)	80	29	
5 y (%)	57	14	

There were 11 patients in this trial who were positive for the HLA-A2 allele and could thus be evaluated using a HLA-A2 PSA peptide. None of the three HLA-A2-positive patients in the nilutamide arm showed induction of PSA-specific T-cell responses either pre- or post-three monthly cycles of therapy. Four of eight patients in the vaccine arm showed at least a 2-fold increase in PSA-specific T cells after three monthly vaccinations, with one patient having a >9-fold increase in PSA-specific T cells. One patient had a 15-fold increase in PSA-specific T cells after 11 months in treatment, and another patient had a 17-fold increase in PSA-specific T cells after 14 months of treatment. This has been described in more detail previously (6) at the ~2-year post-treatment follow-up. None of the patients in this study had previously received chemotherapy. A previous study in patients with metastatic cancers showed a negative association between the number of previous chemotherapy treatments and the magnitude of T-cell response to vaccine ($P = 0.032$; ref. 21). That same study also showed a positive relationship between the magnitude of T-cell response to vaccine and longer time since last chemotherapy ($P = 0.005$). Thus, patients who had received multiple cycles of chemotherapy, or who had received chemotherapy shortly before initiating vaccine therapy, mounted less effective immune responses to vaccine.

Of the 20 crossover patients in this study, the 12 patients who crossed from vaccine to nilutamide at PSA progression had improved OS from enrollment compared with the 8 patients who crossed from nilutamide to vaccine ($P = 0.045$). This suggests that for patients with D0.5 prostate cancer who receive combination therapy, the greatest benefit may be derived by those who receive vaccine early in their treatment program. There is also increasing evidence that androgen deprivation therapy may potentiate immune responses in prostate cancer (22). Androgen deprivation therapy increases infiltration of the prostate by both cytolytic and antigen-presenting T cells within 4 weeks of administration (23). The greater influx of T cells to the prostate may be the result of increased antigen presentation to the T cells (24).

The survival analysis presented here has several limitations. The crossover component does not allow for any conclusions about the efficacy of vaccine alone in the D0.5 population, and survival analyses for crossover patients are potentially biased because they include only the subset of patients retrospectively determined to have received a crossover treatment. Furthermore, this subgroup analysis selects for healthier patients and eliminates patients with rapidly progressing disease. However, this does not affect the OS for all patients randomized in the study. Also, the small number of patients in each arm makes definitive conclusions problematic, increases the possibility of undetected imbalances between the two arms despite randomization, and limits the interpretation of subgroup analyses. Finally, although the two arms were relatively well balanced, at time of enrollment, patients in the vaccine arm had a longer time from diagnosis of D0.5 disease and a slightly lower PSADT. These two factors may have actually favored OS for the patients enrolled in the nilutamide arm. However, even accounting for these limitations, it is clear that patients with tumor characteristics consistent with slow growth and small volume, and who received vaccine earlier in their treatment regimen, may exhibit improved OS.

Based on the results reported here, we have initiated a randomized study in D0.5 prostate cancer patients using a PSA-based vaccine combined with ARA therapy upfront versus ARA therapy alone to determine whether combination therapy can provide clinical benefit by delaying onset of metastatic disease and extending OS. The vaccine in this study is a next-generation poxviral vaccine consisting of PSA plus a triad of costimulatory molecules (B7-1, ICAM-1, and LFA-3) designated TRICOM. This study involves a primary vaccination with recombinant vaccinia-based PSA-TRICOM and multiple booster vaccines with recombinant fowlpox-based PSA-TRICOM. PSA-TRICOM is safe and has a proven ability to mount T-cell-specific responses (25). This study is currently accruing patients at the National Cancer Institute.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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