INTRODUCTION

Approximately one-third of prostate cancer patients who undergo primary local therapy will experience biochemical relapse documented by rising PSA level.1–3 Salvage radiation may be curative in a portion of prostatectomy patients who experience PSA recurrence.4 However, PSA recurrence following local therapy and salvage treatment is indicative of micrometastatic disease that is no longer curable.5 Because of the high sensitivity of PSA measurement, most biochemically recurrent prostate cancer (BRPC) patients do not initially present with any radiological or physical evidence of local recurrence or distant metastases. In BRPC patients, treatment is aimed at slowing cancer progression. More than 30 clinical trials have evaluated treatments for BRPC patients.6 These treatments range from drugs approved for other indications, Dutasteride,7 Gefitinib8 to natural products including soy9 or diet and exercise;10 to novel targeted agents including immunotherapies and antibodies.11

PSA doubling time (PSADT), defined as the length of time (in months) for the PSA level to double,2 is a controversial end point in clinical trials of BRPC patients. Using PSADT as an intermediate end point in this population is attractive because clinical end points (that is, metastasis-free survival or overall survival) are prolonged, often making trials infeasible. Retrospective studies have shown that PSADT is a strong predictor of metastasis-free survival,12,13 overall survival2 or both.14 However, patients on placebo arms of two randomized controlled trials (RCTs) experienced a significant increase in PSADT that was not induced by any active therapy. In a study of rosiglitazone (n = 106), 73% of placebo patients experienced a >100% increase in PSADT and 31% experienced a >200% increase in PSADT,15 and in a study of celecoxib (n = 78) patients, 20% of placebo patients experienced a >200% increase in PSADT.16 PSADT increases of these magnitudes in patients without medical intervention suggest natural and significant variation of PSADT in BRPC patients. More clinically meaningful, accurate conclusions may result from clinical trial designs informed by the availability of reliable information on the natural variability of PSADT, especially the magnitude of statistical variability in determining PSADT.

To this end, we performed a retrospective analysis of men with BRPC who chose to defer hormonal therapy and were not undergoing other known treatments for prostate cancer until after the occurrence of metastases. We had three goals: (1) to

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BACKGROUND: PSA doubling time (PSADT) is an attractive intermediate end point for assessing novel therapies in biochemically recurrent prostate cancer (BRPC). This study explores whether PSADT calculations are influenced by frequency/duration of PSA measurements, and whether statistical variability leads investigators to find false significant results.

METHODS: In retrospective analyses of two BRPC cohorts: Johns Hopkins Hospital (JHH) patients who deferred therapy and placebo patients on a randomized clinical trial (RCT), we calculated changes in PSADT from early measurements to later measurements using subsets of available PSAs for patients with >6 and >9 PSAs. We simulated hypothetical single-arm trials using randomly selected, 50-patient subsets and simulated two-arm RCTs.

RESULTS: JHH cohort (n = 205) had median follow-up 58 months, median age 61 years and median Gleason 7. PSA variability changed with duration of PSA measurement as median within-patient PSADT increases for men with >6 PSAs ranged from 1.0 to 1.4 months by PSA subset while increases for men with >9 PSAs ranged from 3.9 to 4.1 months. Frequency of measurement did not change PSA variability as PSADT increase was unchanged when odd values were used instead of all values. Approximately 30% of JHH men experienced >200% increases in PSADT. Up to 62% of 50-patient single-arm simulations detected a significant PSADT change, whereas simulated RCTs did not. Results were supported in the RCT placebo cohort; 46% of patients experienced PSADT increases >200%.

CONCLUSIONS: These data suggest that calculated PSADT in BRPC may naturally increase over time in the absence of therapy and may be influenced by duration of PSA follow-up. As a result, single-arm trials could show false significant increases despite the lack of active treatment of these patients. Placebo-controlled RCTs including clinical end points are recommended to screen novel agents in men with BRPC to mitigate bias because of natural PSADT variability.

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The effect of the frequency and duration of PSA measurement on PSA doubling time calculations in men with biochemically recurrent prostate cancer

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ORIGINAL ARTICLE
characterize the natural history of PSADT using a group of patients seen by medical oncologists at the Kimmel Cancer Center at Johns Hopkins Hospital (JHH) and a similar patient population on the placebo arm of a phase II clinical trial; (2) to examine the ramifications of statistical variability in PSADT measurement on the outcome of a series of simulated clinical trials; and (3) to determine whether PSADT calculations in these patients could be influenced by the frequency and duration of PSA measurements.

MATERIALS AND METHODS

We performed a longitudinal observational retrospective analysis of two groups of patients: (1) JHH medical oncology patients—prostate cancer patients seen by JHH medical oncology staff between 1990 and 2010; and (2) ‘placebo patients’—prostate cancer patients who were randomized to the placebo arm of a phase II RCT of an experimentally targeted non-hormonal agent conducted in 41 sites in the United States and Canada.11

JHH medical oncology patients

This retrospective analysis used data extracted from the JHH cancer registry, selecting prostate cancer patients whose paper or electronic records showed medical oncology visits between January 1990 and June 2010, who had undergone local therapy with prostatectomy or radiation (n = 1973). All charts were reviewed to identify those that indicated the patient was experiencing BCRP, and that had at least six PSA measurements ≥ 0.2 ng/ml at least 21 days apart when the patient was not on systemic therapy. Of those excluded, 1569 patients were undergoing systemic therapy (androgen deprivation therapy (ADT) or clinical trials), of whom 309 had six eligible PSA measurements (Figure 1). No patient’s PSA measurements were included in the trial until he experienced biochemical relapse following completion of local therapies including surgery or radiation. Thirty-six patients had salvage therapy at least 1 year before their first included PSA measurement and nine patients had salvage therapy following the last included PSA measurement. For patients who had ADT with local therapy, PSA values were included for 12 months following the completion of ADT. PSA values were included on study until the patient was placed on therapy (for example, ADT or clinical trial). The protocol was approved by the JHH institutional review board. Six PSA measurements were required for inclusion because we were simulating clinical trials in the BRPC patient population. Inclusion criteria for BRPC trials routinely require three PSA measurements for PSADT calculation separately for patients who had radiation as initial therapy. Median follow-up was 58 months in the ‘first-three PSA values versus the remaining PSA remainder and first-three versus remaining odd-numbered values’ (Figure 1). We also calculated median within-patient change (difference) in PSADT for patients where the baseline values were all recorded in the first 12 months after biochemical recurrence, with post-baseline values recorded in the following 24 months. To examine the influence of the number of PSA measurements, we performed the within-patient change in PSADT calculation separately for patients who had ≥ 6 PSA values and those who had ≥ 9 PSA values. PSADT was calculated using the formula $\text{PSADT} = \ln(2)/\text{slope}$ of the linear regression fit of log PSA versus time. Patients experiencing declining PSA values (negative PSADT) were assigned a PSADT of 100 months and included appropriately in the analyses.6,4

To determine how frequently researchers conducting a hypothetical uncontrolled clinical study of an ineffective therapy would encounter a significant change between the subsets of PSA values within patients, we performed 2000 simulations of hypothetical single-arm, 50-patient studies using change in PSADT from baseline as the primary outcome. The computer simulations of hypothetical clinical studies used the actual PSA follow-up data in our database. For each simulated single-arm clinical study, we took a random sample of 50 men in our database. For each sampled man, we computed a hypothetical pre-study PSADT and on-study PSADT and the difference using his observed PSAs in the database. For the 50-patient samples, we then tested whether this difference was zero with the Wilcoxon Signed-Rank test, calling a difference significant if the one-sided P-value was < 0.05. We repeated these hypothetical clinical studies 2000 times and determined the proportion of these simulated studies that reached statistical significance. If there is no difference between the pre-study and on-study PSADTs, then only 5% of the simulated studies should reach statistical significance. Simulations of randomized clinical trials followed a similar procedure, except that these simulations also included assigning each sampled individual to one of two hypothetical treatments. All analyses and simulations were carried out in the R statistical environment. We also calculated the percentage of patients who experienced > 100% and > 200% increases in PSADT.

RESULTS

Patient demographics

Clinical features of the 313 men with BRPC who formed our two analysis cohorts are summarized in Table 1. For the JHH cohort (n = 205), the median baseline PSADT was 13.8 months (range: 2.1–659 months). The majority of patients had Gleason scores ≤ 7, with only 19% above 7. Seventy percent of the JHH patients had radical prostatectomy as their primary therapy, while the rest had radiation as initial therapy. Median follow-up was 58 months and mean and median number of PSA measurements were 12.8 and 10, respectively.

For patients on the placebo arm of the phase II clinical trial (n = 108), median baseline PSADT was 7.1 months (range: 1–100 months). The majority of patients had Gleason scores of ≤ 7, with 25% ≥ 7. All of the placebo patients had radical prostatectomy as their primary therapy; median follow-up was 22 months.

PSADT changes in Johns Hopkins medical oncology patients

In the cohort of JHH medical oncology patients with ≥ 6 PSA measurements (n = 205, Table 2), the median ‘post-baseline’ to ‘baseline’ within-patient increase in PSADT was 1.0–1.4 months. Median percentage 50% of the men experienced a ≥ 100% increase in PSADT and ~ 30% of the men experienced ≥ 200% increase in PSADT. The frequency of significant PSADT lengthening using differences in simulated single-arm studies ranged from 17 to 37% using Wilcoxon Signed-Rank tests to test for increased PSADT. Unlike the single-arm studies, the simulated randomized trials declared a significant difference around 5% of the time, as expected for a 5% level test. Of note, 7 of 205 patients in the JHH cohort experienced declining PSA values (negative PSADT) in the post-baseline period.

For JHH patients with ≥ 9 PSA values (n = 127, Table 3), increases in median within-patient PSADT ranged from 3.9 months in the first-third versus second two-thirds’ comparison to 4.1 months in the first-three versus PSA values versus the remaining PSA...
values’ comparison. The difference in median within-patient PSADT was unchanged at 4.0 months when we removed every other value from the remainder (thereby comparing the first-three values with remaining odd-numbered values). Significant differences were found in 27–62% of 50-patient simulated trials when comparing median within-patient PSADT differences. Furthermore, ~60% of the men in this cohort experienced >100% increase in PSADT and 28–38% of the men experienced >200% increase in PSADT.

PSADT changes in placebo patients

Median treatment duration for patients on the placebo arm of the phase II study was 16.3 months (Table 4). The median baseline PSADT was 7.1 months while the median on-treatment PSADT was 14.9 months. The median within-patient increase in PSADT from baseline to on-treatment was 5.9 months. Increases in PSADT of >100% and >200% occurred in 79 and 46%, respectively, for these patients on placebo.

**DISCUSSION**

This retrospective analysis of patients with BRPC after definitive local therapy illustrates the variability in the natural history of PSA and has significant implications for clinical trial design and interpretation in this population. A hypothetical clinical study of untreated BRPC patients seen by JHH medical oncologists between 1990 and 2010 could show PSADT increasing by ≥4 months in the absence of additional therapy and may be influenced by duration of PSADT follow-up. Confirmatory data come from a randomized phase II clinical trial involving BRPC patients where patients on the placebo arm experienced PSADT increases of nearly 6 months, and in both of these populations ≥50% of patients experienced increases in PSADT >100% and approximately one-third experienced PSADT increases of >200%. These results are consistent with findings in prior studies showing 73% of placebo patients in clinical trials having >100% and 20–31% having >200% increase in PSADT.15,16

The similarity in within-patient increases in PSADT when using every other PSA value versus using all PSA values implies that frequency of measurement will not impact PSA variability. However, the larger within-patient increase in PSADT for the patients with ≥9 PSA measurements versus patients with ≥6 PSA measurements implies that duration of measurement is associated with greater increases in PSADT, and therefore those single-arm trials with longer durations are more likely to reach false conclusions of significance.
randomized comparative trials using randomly sampled untreated patients. In contrast, simulated baseline and showed apparently significant increases despite the median within-patient PSADT change from ‘baseline’ to ‘post-baseline’ PSADT changes. These simulated trials compared from the JHH cohort, showed statistically significant ‘baseline’ to hypothetical single-arm, 50-patient studies, using subsets selected. This was demonstrated when at least 27% and as many as 62% of false positive (that is, might not be at all related to drug activity).

Table 1. Patient demographic and clinical characteristics

| Characteristic                  | Johns Hopkins Hospital data set | Placebo data set |
|---------------------------------|--------------------------------|-----------------|
| Total number of patients (number) | 205                            | 108             |
| Age at diagnosis (years)        |                                |                 |
| Mean                            | 61.5                           | 64.6            |
| Range                           | 45–82                          | 44–86           |
| s.d.                            | 7.2                            | 7.8             |
| Median                          | 62                             | 65              |
| Unknown                         | 23                             | —               |
| Ethnicity (number and percent)  |                                |                 |
| White                           | 156 (76%)                      | NA              |
| African-American                | 43 (21%)                       | NA              |
| Asian/Other/Unknown             | 6 (3%)                         | NA              |
| Pre-operative Gleason score (number and percent) |                     |                 |
| Low grade (scores 4–6)          | 61 (30%)                       | 26 (24%)        |
| Intermediate grade (score 7)    | 82 (40%)                       | 53 (49%)        |
| High grade (scores 8–9)         | 38 (19%)                       | 27 (25%)        |
| NA                              | 24 (12%)                       | 3 (3%)          |
| Mode of primary therapy (number and percent) |                     |                 |
| Radical prostatectomy           | 141 (69%)                      | 108 (100%)      |
| Radiation therapy               | 48 (23%)                       | —               |
| Radiation and hormone therapies | 12 (6%)                        | —               |
| Others                          | 4 (2%)                         | —               |
| Salvage therapy (number and percent) |                     |                 |
| Radiation therapy               | 44 (31%)                       | 46 (42%)        |
| Cryotherapy                     | 1 (1%)                         | 0               |
| Follow-up time (months)         |                                |                 |
| Mean (s.d.)                     | 66.0 (42.0)                    | 22 (8.0)        |
| Range                           | 5.2–184.8                      | 5.8–41.7        |
| Median                          | 58.1                           | 21.9            |
| Initial PSA value (ng ml⁻¹)     |                                |                 |
| Mean (s.d.)                     | 1.2 (2.1)                      | 1.4 (1.2)       |
| Median                          | 0.5                            | 0.9             |
| Range                           | 0.2–14.5                       | 0.3–6           |
| Baseline PSADT (months)         |                                |                 |
| Mean (s.d.)                     | 27.8 (51.8)                    | 10.2 (14.4)     |
| Range                           | 2.1–568.7                      | 1.0–100.0       |
| Median                          | 13.8                           | 7.1             |

Abbreviations: JHH, Johns Hopkins Hospital; NA, not available; PSADT, PSA doubling time.

Thus, these data suggest that uncontrolled single-arm studies using change in PSADT as a primary end point may frequently show a statistically significant lengthening of PSADT that may be a false positive (that is, might not be at all related to drug activity). This was demonstrated when at least 27% and as many as 62% of hypothetical single-arm, 50-patient studies, using subsets selected from the JHH cohort, showed statistically significant ‘baseline’ to ‘post-baseline’ PSADT changes. These simulated trials compared median within-patient PSADT change from ‘baseline’ to ‘post-baseline’ and showed apparently significant increases despite the lack of active treatment of these patients. In contrast, simulated randomized comparative trials using randomly sampled untreated patient trajectories maintained the 5% type I error of a false positive result. Thus, statistically significant increases in PSADT of 6 months or less, or changes of up to 60% in the numbers of patients experiencing 100% increases in PSADT are unlikely to be reliable measures of clinical impact for advancing experimental treatments into randomized phase III trials. Single-arm phase II studies are commonly used to determine whether a treatment has activity against a disease. The significant variability found in this study reinforces the value of including placebo arms in clinical trials in BRPC patient populations.

Smaller changes in median PSADT were seen when the JHH population was expanded to include patients for whom at least six PSA measurements were available: 17–37% of the simulations were significant in this expanded population versus 27–62% in the smaller group with at least nine PSA measurements. The smaller increase in median PSADT differences and the reductions in the percentage of simulated trials that were significant are artifacts of sampling. Patients might have fewer PSA measurements eligible for inclusion in this study if they have more rapidly progressing disease and require early hormone therapy. Therefore, data for the subset of patients with at least nine PSA values may have a bias because they exclude patients with a worse prognosis (that is, a faster PSADT). A second source of similar bias is introduced by our exclusion of patients receiving additional systemic therapies shortly after local therapy, including androgen deprivation. Excluding both of these groups of men retrospectively removes patients non-randomly, and it could be argued that the men removed from the analysis had the most biologically aggressive disease. A further limitation of this data set was the absence of other data on biologic activity that may be affecting the production of PSA over time.

Although patients were excluded if they were on any medications approved for treatment of prostate cancer, available data did not allow us to determine when patients were also taking natural products or other medications (such as non-steroidal inflammatory agents) that could potentially decrease PSA values. Despite this limitation and the biases described above, the natural history of PSADT in BRPC patients with slower PSADTs is illuminating because this is the BRPC patient population most likely to remain on trials of therapies designed to delay the onset of metastases, especially when potential toxicities outweigh the benefits of hormone treatment. This population is targeted in current trials of acai berries, disulfiram, brassica vegetables, kanglaite (Chinese grass seed oil) and vorinostat, all of which are either single-arm or dose-finding studies without placebo arms. In the current setting where no proven therapy exists, a placebo control is appropriate in these trials and appears to be warranted. Although a large single-institution patient population was culled for this study and a second multi-institution trial population provided confirming data, the overall numbers of patients in the analysis are small. The results require additional validation in other cohorts before they can be used as guidance for end point determination in clinical trials.

Conclusion and implications

This retrospective study shows that PSA variability in BRPC patients who are monitored for nine or more PSA measurements, on average 3 months apart, leads to their PSADT naturally lengthening over time even in the absence of treatment. Single-arm trials could therefore show apparently significant increases despite the lack of active treatment of these patients. Thus, using PSADT as the primary end point in clinical trials requires a placebo control in the absence of effective proven therapy, and the magnitude of the benefit needs to be clinically meaningful (for example, ≥6 months). Further, when PSADT change is used as an end point in clinical trials, all PSA values recorded at a specified frequency should be used in computing a baseline PSADT as that is the same protocol that will be used in computing post-baseline...
Table 2. PSADT in months using data from JHH oncology patients who have at least six recorded PSA values

|                          | Mean PSADT (s.d.) | Median PSADT | Median within-patient PSADT difference | Percent of simulations significant | Number (%) of men with >100% increase | Number (%) of men with >200% increase |
|--------------------------|-------------------|--------------|----------------------------------------|-----------------------------------|----------------------------------------|----------------------------------------|
| All values (n = 205)     | 25.1 (30.6)       | 16.6         |                                        |                                   |                                        |                                        |
| First-half versus second-half of values |                   |              |                                        |                                   |                                        |                                        |
| First-half               | 21.6 (19.9)       | 16.8         |                                        |                                   |                                        |                                        |
| Second-half              | 40.7 (99.6)       | 17.0         |                                        |                                   |                                        |                                        |
| Within-patient PSADT difference | 19.1 (95.5)   | 1.0          |                                        | 37%                               | 114 (56%)                              | 56 (27%)                               |
| First-three values versus remainder of values |                   |              |                                        |                                   |                                        |                                        |
| First-three              | 27.8 (51.8)       | 13.8         |                                        |                                   |                                        |                                        |
| Remaining values         | 29.1 (40.1)       | 18.5         |                                        |                                   |                                        |                                        |
| Within-patient PSADT difference | 1.2 (61.3)   | 1.4          |                                        | 17%                               | 114 (56%)                              | 65 (32%)                               |

Abbreviations: JHH, Johns Hopkins Hospital; PSADT, PSA doubling time.

Table 3. PSADT in months using data from JHH oncology patients who have at least nine recorded PSA values

|                          | Mean PSADT (s.d.) | Median PSADT | Median within-patient PSADT difference | Percent of simulations significant | Number (%) of men with >100% increase | Number (%) of men with >200% increase |
|--------------------------|-------------------|--------------|----------------------------------------|-----------------------------------|----------------------------------------|----------------------------------------|
| All values (n = 127)     | 31.9 (36.1)       | 22.2         |                                        |                                   |                                        |                                        |
| First-half versus second-half of values |                   |              |                                        |                                   |                                        |                                        |
| First-half               | 34.5 (63.3)       | 16.1         |                                        |                                   |                                        |                                        |
| Second-half              | 51.2 (122.4)      | 22.1         |                                        |                                   |                                        |                                        |
| Within-patient PSADT difference | 35.1 (46.2)   | 4.1          |                                        | 62%                               | 78 (61%)                               | 36 (28%)                               |
| First-three values versus remainder of values |                   |              |                                        |                                   |                                        |                                        |
| First-three              | 34.5 (63.3)       | 22.3         |                                        |                                   |                                        |                                        |
| remaining values         | 34.5 (63.3)       | 22.3         |                                        |                                   |                                        |                                        |
| Within-patient PSADT difference | 0.6 (74.2)   | 4.1          |                                        | 27%                               | 78 (61%)                               | 48 (38%)                               |
| First-third versus second two-thirds of values |                   |              |                                        |                                   |                                        |                                        |
| First-third              | 34.5 (63.3)       | 16.1         |                                        |                                   |                                        |                                        |
| Second two-thirds        | 51.2 (122.4)      | 22.1         |                                        |                                   |                                        |                                        |
| Within-patient PSADT difference | 35.1 (46.2)   | 4.1          |                                        | 40%                               | 75 (59%)                               | 45 (35%)                               |
| First-three values versus remaining odd-numbered values |                   |              |                                        |                                   |                                        |                                        |
| First-third              | 34.5 (63.3)       | 16.1         |                                        |                                   |                                        |                                        |
| remaining odd-numbered   | 34.5 (63.3)       | 23.3         |                                        |                                   |                                        |                                        |
| Within-patient PSADT difference | -0.5 (67.5)  | 4.0          |                                        | 35%                               | 78 (61%)                               | 45 (35%)                               |

Abbreviations: JHH, Johns Hopkins Hospital; PSADT, PSA doubling time.

Table 4. PSADT in months using data from placebo patients (in months)

|                          | Mean PSADT (s.d. in parentheses) | Median PSADT | Median within-patient PSADT difference | Percent of simulations significant | Number (%) of men with >100% increase | Number (%) of men with >200% increase |
|--------------------------|-----------------------------------|--------------|----------------------------------------|-----------------------------------|----------------------------------------|----------------------------------------|
| Pre-treatment versus on-treatment values |                   |              |                                        |                                   |                                        |                                        |
| All values (n = 108)     | 26.2 (62.1)                      | 12.7         |                                        |                                   |                                        |                                        |
| Pre-treatment            | 10.2 (14.4)                      | 7.1          |                                        |                                   |                                        |                                        |
| On-treatment             | 30.1 (40.5)                      | 14.9         |                                        |                                   |                                        |                                        |
| Within-patient PSADT difference | 19.9 (42.5)  | 5.9          |                                        | 100%                              | 85 (79%)                               | 50 (46%)                               |

Abbreviation: PSADT, PSA doubling time.
PSADT. For instance, one could envision a trial for men with low-risk BRPC in which patients would remain off therapy for the first several months of the study (that is, during a lead-in period), where PSA data would be collected at the same interval (for example, monthly) as would be collected after the initiation of treatment, and analyzed by one central laboratory. Moreover, the frequency of PSA measurement does not appear to affect PSADT determinations, a finding that would be expected given the log-linear relationship between PSA and time in the computation of PSADT. In conclusion, PSADT is a useful measure of PSA dynamics in men with BRPC and should be evaluated only in randomized controlled clinical trials, preferably including conventional clinical and radiological end points that allow for proper validation. In this way, post-treatment changes in PSADT in an active treatment arm and in a placebo arm could both be associated prospectively with clinically meaningful end points such as time-to-first metastasis or metastasis-free survival.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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