INTRODUCTION

Androgen deprivation therapy (ADT) with luteinizing hormone-releasing hormone analog (LHRHA) or orchiectomy is the first-line therapy in patients with metastatic prostate cancer. While almost all patients eventually show progression to castration-resistant prostate cancer (CRPC) following ADT administration, the period of ADT efficacy ranges among patients. Recent research suggests that some prostate cancer patients may benefit from the addition of upfront docetaxel chemotherapy. Upfront chemotherapy in prostate cancer patients prolonged progression-free survival time and overall survival (OS). In 2014, Sweeney reported that ADT combined with docetaxel clearly improved OS over ADT alone in men with high volume metastatic prostate cancer. However, previous studies have not been able to identify the patients who should receive ADT and concurrent docetaxel chemotherapy. Identification of patients with a shorter time to CRPC can lead to better development of individual therapy plans. In patients receiving ADT, the target testosterone limit during ADT should be 50 ng dl⁻¹. Even though more than 90% of patients who have received LHRHA for 3 or 4 months can achieve serum testosterone levels <50 ng dl⁻¹, there are still differences in their serum testosterone levels. A recent study of patients with metastatic disease showed that when considered as a continuous variable, serum testosterone levels during LHRHA therapy were associated with OS. The prognostic role of changes in testosterone levels over time was also recently examined. However, the optimal testosterone threshold necessary to induce a better ADT therapy effect remains unknown.

This prospective study was undertaken to explore the prognostic role of serum testosterone levels in a consecutive series of metastatic prostate cancer patients after the first month of maximal androgen blockade therapy. The aim of this study was to assess the relationship between serum testosterone levels at two different cut-off points (50 and 25 ng dl⁻¹) on the patient outcome of time to progression to CRPC. As a secondary aim, we explored whether another cut-off point could more accurately distinguish patients with different prognoses.

PATIENTS AND METHODS

This study included consecutive patients followed prospectively between January 2007 and September 2012 at the Department of Urology, Fudan University Shanghai Cancer Center. The following inclusion criteria were used for this study: histologic diagnosis of prostate adenocarcinoma by biopsy, eligibility for maximal androgen blockade therapy for metastatic disease, adequate compliance with therapy, regular follow-up, normal liver and kidney function, Eastern Cooperative Oncology Group performance status 0–2, adequate hematologic and liver function, Eastern Cooperative Oncology Group performance status 0–2, adequate liver and kidney function, Eastern Cooperative Oncology Group performance status 0–2.
performance status <2, and written informed consent. Exclusion criteria included severe concomitant diseases, liver and/or kidney failure, secondary malignancies, intermittent ADT, and concomitant antineoplastic therapies such as radical prostatectomy, radiation therapy, or chemotherapy. Patients without definite evidence of metastasis were also excluded. Gleason scores were all determined by the same pathologists, who were genitourinary specialists.

ADT therapy consisted of administration of LHRHAs every month or a long-acting formulation of commercially available LHRHAs every 3 months. Bicalutamide was given at a dose of 50 mg daily. Secondary hormonal therapy consisted of the administration of LHRHAs and flutamide 250 mg 3 times a day after bicalutamide withdrawal for 6 weeks.

Serum testosterone levels were measured before and after 1, 3, and 6 months of maximal androgen blockade therapy. Testosterone level was determined based on the screening blood analysis using an automated immunoassay (Access® Testosterone, Beckman Coulter, Fullerton, CA, USA). The assay has a functional sensitivity of 0.13 ng ml⁻¹.

Bone scan was routinely performed in all patients with suspected bone metastasis. If bone scan was not able to confirm the diagnosis, local MRI was performed for further evaluation. Abdominal and pelvic MRI was used to detect lymph nodes and visceral metastasis. Patient follow-up consisted of clinical evaluation and serum PSA measurement every month. Imaging procedures, including pelvic computed tomography and chest radiography, were repeated every 6 months, and bone scans were repeated every 12 months. Two blood samples were collected at every follow-up examination, and the one with the lower testosterone value was used in the statistical analysis.

The endpoint of follow-up was defined as the time from the start of maximal ADT to CRPC. CRPC was detected by an increase in PSA, typically defined as three consecutive increases over nadir in the context of castrate levels of serum testosterone and three consecutive increases of PSA after antiandrogen withdrawal for 6 weeks and secondary hormonal manipulations.

A multivariate Cox proportional hazards model was used to assess the role of serum testosterone in predicting ADT therapy failure after adjusting for validated prognostic parameters such as age, Gleason score, serum testosterone levels, serum alkaline phosphatase, baseline PSA levels, and the existence of metastases other than osseous metastases. Age, serum alkaline phosphatase level, serum testosterone level, and baseline PSA level were included as continuous variables whereas the remaining parameters were analyzed as categorical variables.

We also used a receiver operating characteristic (ROC) curve to identify the cut-off point of testosterone levels that could discriminate, with the best combination of sensitivity and specificity, patients who were expected to experience hormone therapy failure within a year from those who were not. Next, serum testosterone levels, as independent variables, were considered as categorical variables according to the cut-off points ≤25 ng dl⁻¹ and >25 ng dl⁻¹. We carried out the log-rank test to compare the survival curves between the different serum testosterone levels.

Statistical computations were performed using Stata software (version 12.0; StataCorp LP, College Station, TX, USA). All statistical tests were two-tailed, and statistical significance was set at P < 0.05.

RESULTS

The study population included 206 patients. All patients had osseous metastatic lesions but had not received any previous therapy. Histologic diagnosis of prostate adenocarcinoma was made by biopsy. The patient characteristics are shown in Table 1. We excluded patients whose prostate biopsies were not performed in our center owing to the unavailability of the biopsy specimens. Patients with liver or heart dysfunction—and so did not meet our standard inclusion criteria—were also excluded. Approximately 400 patients were excluded.

The median testosterone level before ADT was 443 ng dl⁻¹ (143–910 ng dl⁻¹). The median baseline PSA was 241 ng dl⁻¹ (10.6–5000 ng dl⁻¹). After the first month of ADT, serum testosterone levels were ≤25 ng dl⁻¹ in 98 (47.6%) patients, between 25 and 50 ng dl⁻¹ in 95 (46.1%) patients, and ≥50 ng dl⁻¹ in 13 (6.3%) patients. The median testosterone level after the first month of ADT was 26 ng dl⁻¹ (13–83 ng dl⁻¹). Among the 13 patients with testosterone ≥50 ng dl⁻¹, 10 (4.8%) had a testosterone level between 50 and 60 ng dl⁻¹ and 3 (1.5%) had a testosterone level >60 ng dl⁻¹.

The prognostic role of serum testosterone levels attained during ADT therapy was evaluated by PSA, which was tested every month. The 206 enrolled patients were followed for a median of 14 months and, at the end of this study, all of the patients were still alive and all had progressed to CRPC.

In multivariate Cox regression analysis (Table 2), serum testosterone levels after the first month of maximal ADT were not prognostic of the time of effective hormone therapy but were significantly associated with a tendency to lower the risk of disease progression that was close to attaining statistical significance (adjusted HR, 2.62; 95% confidence interval [95% CI], 0.86–7.99; P = 0.090). Serum testosterone levels ≤25 ng dl⁻¹, however, were significantly associated with a lower risk of progression to CRPC (adjusted HR, 1.46; 95% CI, 1.08–1.96; P = 0.013).

Because the testosterone levels after the first month of ADT exhibited large variations, we used the ROC curve (Figure 1) to find a cut-off level to discriminate between patients who were expected to progress to CRPC in a short period (<14 months) from those who were not. The area under the curve was 0.59 (95% CI, 0.51–0.66). A testosterone value of 25 ng dl⁻¹ offered the best overall sensitivity and specificity (0.56 and 0.59, respectively).

We then performed a single-factor logistic test of testosterone levels. The result showed that time to CRPC was related to testosterone levels (P = 0.020). Accordingly, 98 (47.6%) patients who showed a serum testosterone level of 25 ng dl⁻¹ or less after the first month of ADT had a significantly longer time to CRPC than the remaining patients.

Table 1: Clinicopathologic characteristics of 206 patients

| Characteristics          | Median   | Range   |
|--------------------------|----------|---------|
| Age (year)               | 68       | 38–83   |
| Baseline serum PSA (ng ml⁻¹) | 241     | 10.6–5000 |
| <100, n (%)              | 51 (24.8)|         |
| 100–1000, n (%)          | 117 (56.8)|        |
| >1000, n (%)             | 38 (18.4)|         |
| Baseline serum testosterone (ng ml⁻¹) | 443      | 143–910 |
| Biopsy Gleason score, n (%) | 26 (12.6)|         |
| ≤7                       | 180 (87.4)|        |
| >7                       | 26 (12.6)|         |
| Metastasis, n (%)        |          |         |
| Osseous metastasis       | 206 (100)|         |
| Areas other than the bone metastasis | 26 (12.6) |         |
| Time to progression (month) | 14      | 6–73    |

PSA: prostate-specific antigen; n: number of patients

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108 patients (52.4%), who did not reach these levels \((P = 0.0004)\). Kaplan–Meier survival estimates (Figure 2) also clearly show the different outcomes of the two groups.

A total of 98 patients attained a serum testosterone level of 25 ng dl\(^{-1}\) or less after the first month of ADT. The mean baseline PSA of these patients was 522.8 ng ml\(^{-1}\), the mean time to CRPC was about 19.1 months, and the mean Gleason score was 8.5. In other 108 patients who did not attain a serum testosterone level of 25 ng dl\(^{-1}\) or less, the median baseline PSA was 861.8 ng ml\(^{-1}\), the mean time to CRPC was about 14.6 months, and the mean Gleason score was 8.7. As the patients’ baseline PSA did not follow a normal distribution, we used the Wilcoxon rank-sum test and found that the difference between the two groups for baseline PSA was statistically significant \((P = 0.007)\). We found no statistically significant difference in the Gleason score of these two groups by \(t\)-test \((P = 0.954)\).

As explained previously, we concluded that serum testosterone levels, considered as a categorical variable based on a cut-off value of 25 ng dl\(^{-1}\), were significantly associated with time to CRPC in patients with metastatic prostate cancer.

We also analyzed patients’ baseline serum testosterone and serum testosterone levels after 6 months of ADT (Table 3). Single-factor logistic tests and multivariate Cox proportional hazards models, after adjusting for validated prognostic parameters such as age, Gleason score, serum testosterone levels, serum alkaline phosphatase, baseline PSA levels, and whether other metastases besides osseous metastasis existed, were used again to assess the role of serum testosterone. We found that serum testosterone levels ≤20 ng dl\(^{-1}\) after 6 months were significantly associated with a longer time to CRPC (adjusted HR, 1.99; 95% confidence interval [95% CI], 1.32–2.59; \(P = 0.001\)). The purpose of this study was to identify patients with a shorter effective time of ADT so as to improve individual therapy plans. The parameters that can predict prognosis earlier are more valuable, so we committed to study the serum testosterone levels after the first month of ADT.

In our study, 26 patients had distant metastases in areas other than the bone, including hepatic, pulmonary, mediastinal, and supravacuicular metastases. To further understand the prognostic role of serum testosterone levels in patients who only had bone metastases, we reanalyzed the data after excluding these 26 patients. In the remaining 180 patients, 83 patients (46.1%) attained a serum testosterone level of 25 ng dl\(^{-1}\) after the first month of ADT while 97 patients (53.9%) did not attain these levels. A single-factor logistic test showed that time to CRPC was related to testosterone level \((P = 0.005)\). Kaplan–Meier survival estimates showed that the 83 patients had a longer time to CRPC than the remaining 97 patients \((P < 0.0001)\). In multivariate Cox regression analysis, which included age, Gleason score, serum testosterone level, serum alkaline phosphatase level, and baseline PSA level (Table 4), serum testosterone level as a continuous variable after the first month of ADT was not prognostic of the effective time of hormone therapy (adjusted HR, 2.58; 95% CI, 0.77–8.60; \(P = 0.122\)). However, serum testosterone levels ≤25 ng dl\(^{-1}\) were significantly associated with a lower risk of progression to CRPC (adjusted HR, 1.85; 95% CI, 1.32–2.59; \(P = 0.003\)). Our results did not change when including patients who had only bone metastases.

Figure 1: ROC curve of testosterone after the first month of maximal androgen blockade therapy to identify patients who with shorter valid time.

Figure 2: Time to CRPC in patients undergoing maximal androgen blockade therapy metastatic disease (overall \(P = 0.0004)\).

Table 2: Multivariate Cox analysis of prognostic role of serum testosterone levels after first month of maximal androgen blockade therapy \((n=206)\)

| Variable                          | Time to progression | \(P\) |
|----------------------------------|---------------------|------|
| Testosterone continuous variable|                     |      |
| Testosterone                     | 2.62 (0.86–7.99)    | 0.090|
| Gleason score                    | 1.40 (1.18–1.66)    | 0.000|
| Baseline PSA                     | 1.00 (0.99–1.00)    | 0.057|
| Age                              | 0.98 (0.97–1.01)    | 0.213|
| ALP                              | 0.99 (0.99–1.00)    | 0.439|
| Metastasis other than the bone   | 1.31 (0.86–2.00)    | 0.208|
| Testosterone levels <50 ng dl\(^{-1}\) \((n=193)\) | 1.26 (0.70–2.29)    | 0.438|
| Testosterone                     | 1.42 (1.19–1.69)    | 0.000|
| Baseline PSA                     | 1.00 (1.00–1.00)    | 0.025|
| Age                              | 0.98 (0.97–1.00)    | 0.131|
| ALP                              | 0.99 (0.99–1.00)    | 0.340|
| Metastasis other than the bone   |                     | 0.293|
| Testosterone levels ≤25 ng dl\(^{-1}\) \((n=98)\) | 1.46 (1.08–1.96)    | 0.013|
| Testosterone                     | 1.41 (1.20–1.67)    | 0.000|
| Baseline PSA                     | 1.00 (1.00–1.00)    | 0.101|
| Age                              | 0.99 (0.97–1.00)    | 0.142|
| ALP                              | 1.00 (1.00–1.00)    | 0.606|
| Metastasis other than the bone   | 1.36 (0.89–2.07)    | 0.158|

PSA: prostate-specific antigen; ALP: alkaline phosphatase; CI: confidence interval; HR: hazard ratio; n: number of patients

1.44–2.74; \(P = 0.001\). The purpose of this study was to identify patients with a shorter effective time of ADT so as to improve individual therapy plans. The parameters that can predict prognosis earlier are more valuable, so we committed to study the serum testosterone levels after the first month of ADT.

In our study, 26 patients had distant metastases in areas other than the bone, including hepatic, pulmonary, mediastinal, and supravacuicular metastases. To further understand the prognostic role of serum testosterone levels in patients who only had bone metastases, we reanalyzed the data after excluding these 26 patients. In the remaining 180 patients, 83 patients (46.1%) attained a serum testosterone level of 25 ng dl\(^{-1}\) after the first month of ADT while 97 patients (53.9%) did not attain these levels. A single-factor logistic test showed that time to CRPC was related to testosterone level \((P = 0.005)\). Kaplan–Meier survival estimates showed that the 83 patients had a longer time to CRPC than the remaining 97 patients \((P < 0.0001)\). In multivariate Cox regression analysis, which included age, Gleason score, serum testosterone level, serum alkaline phosphatase level, and baseline PSA level (Table 4), serum testosterone level as a continuous variable after the first month of ADT was not prognostic of the effective time of hormone therapy (adjusted HR, 2.58; 95% CI, 0.77–8.60; \(P = 0.122\)). However, serum testosterone levels ≤25 ng dl\(^{-1}\) were significantly associated with a lower risk of progression to CRPC (adjusted HR, 1.85; 95% CI, 1.32–2.59; \(P = 0.003\)). Our results did not change when including patients who had only bone metastases.
DISCUSSION

The importance of monitoring serum testosterone levels to verify response to ADT was underlined in an expert consensus paper. However, the currently recommended target testosterone level of 50 ng dl$^{-1}$ is not supported by any demonstrated correlation with patient outcome. In our study, 50 ng dl$^{-1}$ cut-off had no prognostic value in the overall cohort of patients. However, a cut-off of 25 ng dl$^{-1}$ significantly correlated with the effective time of hormone therapy, suggesting that a serum testosterone level of ng dl$^{-1}$ can be an effective marker of ADT efficacy.

It is noteworthy that serum testosterone levels maintained a prognostic significance during maximal ADT in patients with osseous metastases. We also used single-factor log-rank tests and an ROC curve to test the relationship between the serum testosterone level after 6 months of therapy and arrived at a similar conclusion.

Although our study provided prognostic information on serum testosterone levels, this does not necessarily mean that serum testosterone levels can be used as a surrogate parameter of ADT therapy efficacy. Our study had several limitations. First, all patients in our study were from Fudan University Shanghai Cancer Center and had a lower survival rate, free of androgen-independent progression, than patients without these increases. Taking a different approach than previous studies, our study explored the prognostic role of testosterone levels after the first month of ADT in patients with metastatic prostate cancer, and we identified a clear relationship between serum testosterone levels and the time to CRPC. The strengths of this study reside in its prospective design and long follow-up period.

In a small proportion of the patients (6.3%) in our series, serum testosterone levels within the castration range were not reached after the first month of ADT with LHRRAs and bicalutamide. These data are consistent with previous studies, in which the proportion of patients whose testosterone levels did not decrease to 50 ng dl$^{-1}$ was 1%–12.5%. However, most of our patients whose testosterone levels did not fall to castration levels had testosterone levels between 50 ng dl$^{-1}$ and 60 ng dl$^{-1}$. The disadvantages of this study and possible interferences with other androgens such as dehydroepiandrosterone sulfate could account for these discrepancies. These limitations notwithstanding the results of serum testosterone levels and patient outcomes support the validity of this assay.

We also attempted to evaluate the prognostic role of testosterone in localized prostate cancer patients with biochemical recurrence after radical therapy; but these patients should receive radical prostatectomy or radical radiation therapy first. Different stages and individual patient differences before operation or radiation therapy influence the effect of radical therapy. Therefore, we only included metastatic prostate cancer patients who had low heterogeneity.

Recent studies have confirmed that docetaxel combined with ADT at the beginning of the treatment can produce better outcomes in some metastatic prostate cancer patients. However, combination therapy is not appropriate for those who have a long progression-free time with ADT alone as the side effects of docetaxel chemotherapy are more severe than for ADT. It is, therefore, important to identify patients with a poor response to ADT. We initially examined patient baseline serum testosterone levels, with the aim of possibly providing an earlier

| Variable | Time to progression | HR (95% CI) | P |
|----------|---------------------|-------------|---|
| Testosterone continuous variable | 1.86 (0.72–4.84) | 0.200 |
| Gleason score | 1.41 (1.19–1.68) | 0.000 |
| Baseline PSA | 1.00 (0.99–1.00) | 0.052 |
| Age | 0.99 (0.97–1.01) | 0.194 |
| ALP | 1.00 (1.00–1.00) | 0.390 |
| Metastasis other than the bone | 1.29 (0.85–1.96) | 0.234 |

| Testosterone levels <50 ng dl$^{-1}$ (n=190) | 1.06 (0.61–1.69) | 0.951 |
| Testosterone levels ≥20 ng dl$^{-1}$ (n=96) | 1.99 (1.44–2.74) | 0.001 |

PSA: prostate-specific antigen; ALP: alkaline phosphatase; CI: confidence interval; HR: hazard ratio; n: number of patients

Table 3: Multivariate analysis of prognostic role of serum testosterone levels after 6 months maximal androgen blockade therapy (n=206)

| Variable | Time to progression | HR (95% CI) | P |
|----------|---------------------|-------------|---|
| Testosterone continuous variable | 2.58 (0.77–8.60) | 0.122 |
| Gleason score | 1.29 (1.08–1.54) | 0.005 |
| Baseline PSA | 1.00 (1.00–1.00) | 0.008 |
| Age | 0.99 (0.98–1.01) | 0.623 |
| ALP | 0.99 (0.99–1.00) | 0.451 |

| Testosterone levels <50 ng dl$^{-1}$ (n=193) | 1.28 (0.65–2.48) | 0.474 |

Table 4: Multivariate Cox analysis of prognostic role of serum testosterone levels in patients who had only bone metastasis after the first month of maximal androgen blockade therapy (n=180)
prognostic guide for individual therapy plans, but we were unable to establish a significant relationship. However, serum testosterone levels after the first month of maximal ADT can still be useful at the beginning of treatment. Our findings can help identify patients that may benefit from the addition of upfront chemotherapy.

The most well-known trials of early use of docetaxel in advanced prostate cancer are the STAMPEDE\textsuperscript{20} and ChaarTed\textsuperscript{21} trials. The ChaarTed trial demonstrated that patients with a high tumor burden could obtain benefit from early use of docetaxel. However, they did not see any difference in low tumor burden patients.\textsuperscript{20} The STAMPEDE trial did not report benefit for patients with a high tumor burden; however, subgroup analysis according to the presence of metastatic lesions showed that both metastatic and nonmetastatic prostate cancer patients could achieve a longer failure-free survival.\textsuperscript{21} Although there is still some controversy about these studies, the value of early chemotherapy in selected hormone-sensitive metastatic prostate cancer patients is becoming clear. Further studies are required to find clinical indicators to identify patients suitable for receiving early chemotherapy.

Based on our findings, we suggest that if testosterone levels can be driven lower with adjunctive therapies, patient overall outcome might be improved. Other drugs, such as abiraterone, may be able to help decrease testosterone to ≤ 25 ng dl\textsuperscript{-1} among patients who do not achieve this level within 1 month on regular ADT and, therefore, may be able to improve their prognosis. LHRH antagonists or switching of LHRHAs can be considered as an alternative. LHRH antagonists appear to offer an effective option in the management of prostate cancer by suppressing testosterone levels and reducing PSA. In contrast to the agonists, LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. In theory, if the testosterone level is more quickly decreased to castrate levels, patients could achieve greater benefits. Other potential advantages of LHRH antagonists versus agonists are the lack of a need for combination therapy with an antiandrogen, simple management without the need to educate patients about antiandrogen use, more targeted therapy, and a more pronounced downregulation of gonadotropins and testosterone.

In our study, all patients used LHRHAs but only half achieved a serum testosterone of ≤ 25 g dl\textsuperscript{-1}. As orchiectomy and LHRH antagonists lower testosterone, in addition to adding docetaxel chemotherapy, these two treatment approaches may offer suitable alternatives. In future clinical trials, docetaxel and abiraterone could be added to treatment for patients who fail to reach testosterone levels of 25 ng dl\textsuperscript{-1} after the first month of ADT. Observing and comparing ADT efficacy and overall survival time will provide additional evidence to support this hypothesis.

We conclude that testosterone levels < 50 ng dl\textsuperscript{-1}, which were previously thought to be sufficient, cannot reveal the effectiveness of ADT therapy. Instead, a threshold of 25 ng dl\textsuperscript{-1} can better predict the effective time of ADT therapy. We believe that our findings can help guide clinical treatment. Previous evidence and the results of our study indicate that it is critical to monitor serum testosterone levels in patients on ADT and to check the efficacy of antiandrogen therapy, as effective serum testosterone suppression might affect prognosis and survival.

CONCLUSION

Previous studies confirmed that serum testosterone levels have a prognostic role in patients with metastatic prostate cancer receiving ADT.\textsuperscript{22} Serum testosterone levels lower than the currently adopted cut-off seem to be associated with the time to CRPC. Serum testosterone levels, therefore, can be a promising surrogate parameter of maximal ADT efficacy in metastatic prostate cancer. Moreover, currently available LHRHAs failed to achieve suppression of testosterone levels in a substantial proportion of patients with prostate cancer in this series. However, the testosterone level cut-off value of 25 ng dl\textsuperscript{-1} after the first month of ADT can distinguish patients who benefit from ADT effectiveness for only a short time from patients who do not. The testosterone level after the first month of ADT can predict metastatic prostate cancer patient prognosis.

AUTHOR CONTRIBUTIONS

YW and BD designed the study, collected, analyzed, and interpreted the clinical data and wrote and revised the manuscript. DWY supervised the project and revised the manuscript. All authors approved the final manuscript.

COMPETING INTERESTS

None of the authors declared competing interests.

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