Section: Medical Oncology

Original Research Article

TO ESTABLISH A PRECISE DESCRIPTION OF NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (NMCRPC) AND DETERMINE THE MOST FAVORABLE PERIOD FOR ADMINISTERING ANDROGEN RECEPTOR SIGNALING INHIBITORS (ARSI)

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Received *: 29/04/2024*
Received in revised form *: 11/06/2024*
Accepted *: 26/06/2024*

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DOI: 10.5530/ijmedph.2024.2.175

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2024; 14 (2); 903-908

ABSTRACT

Background: Non-metastatic castration-resistant prostate cancer (nmCRPC) is characterized by increasing levels of PSA while undergoing ADT, without any detectable spread of the disease to other parts of the body as seen by traditional imaging techniques. This condition poses a complicated therapeutic dilemma. A notable subgroup of these individuals has a fast progression of metastatic illness, which has a detrimental effect on their overall survival. **Aim:** To establish a precise description of non-metastatic castration-resistant prostate cancer (nmCRPC) and determine the most favorable period for administering androgen receptor signaling inhibitors (ARSI).

Material and Methods: This retrospective investigation was carried out after obtaining clearance from the institutional review board. We conducted a data analysis on a group of 80 patients who were diagnosed with non-metastatic castration-resistant prostate cancer (nmCRPC) and were treated with androgen receptor signaling inhibitors (ARSI), such as Enzalutamide, Apalutamide, Bicalutamide, and Abiraterone. At the time of ARSI administration, all patients had verified low levels of testosterone (less than 50 ng/mL). This research did not include patients with newly developed neuroendocrine prostate cancer. Patients were categorized into three groups based on their prostate-specific antigen (PSA) levels at the start of androgen receptor signaling inhibitor (ARSI) treatment: The PSA levels for Cohort A range from 0.5 to 2.0 ng/mL. Cohort B consists of individuals with a prostate-specific antigen (PSA) level ranging from 2.0 to 4.0 ng/mL, whereas Cohort C consists of those with a PSA level more than 4.0 ng/mL. The Kaplan-Meier technique was used to evaluate survival results. The initiation of ARSI treatment for nmCRPC served as the first reference point for the total cohort analysis.

Results: The average PSA level at the beginning of ARSI in Cohort A was 2.34 ng/mL, and the average period from ADT nadir to ARSI initiation was roughly 16.5 months. Cohort B exhibited an average PSA level of 4.41 ng/mL and an average duration of about 15.9 months from the lowest point of androgen deprivation therapy (ADT) to the initiation of androgen receptor signaling inhibitor (ARSI). Cohort C had the highest average PSA level, measuring at 9.65 ng/mL, and had an average duration of around 14.7 months from the lowest point of androgen deprivation therapy (ADT) to the initiation of androgen receptor signaling inhibitor (ARSI) treatment. The cohort A had a median overall survival (OS) of 37.58 months, with 1-year and 2-year OS rates of

93.14% and 86.67% respectively. The median overall survival (OS) for Cohort B was 35.63 months, with one-year and two-year OS rates of 91.55% and 83.21% respectively. The median overall survival (OS) for Cohort C was 32.98 months, with 1-year and 2-year OS rates of 89.30% and 79.47% respectively. Regarding progression-free survival (PFS), Cohort A exhibited a median PFS of 21.10 months, along with PFS rates of 89.31% at 1 year and 76.68% at 2 years. In Cohort B, the median progression-free survival (PFS) was 19.53 months, with PFS rates of 86.64% at 1 year and 70.02% at 2 years. The median progression-free survival (PFS) for Cohort C was 17.54 months, with PFS rates of 83.42% at 1 year and 69.52% at 2 years. The average PSA doubling time in Cohort A was 8.85 months. The average PSA doubling time for Cohort B was 7.23 months, whereas Cohort C had the smallest average PSA doubling time of 6.94 months.

Conclusion: The research findings suggest that nmCRPC patients who have lower PSA levels at the start of ARSI therapy get improved survival outcomes and longer periods without disease progression. Furthermore, individuals in Cohort A, who had the lowest PSA levels at the commencement of Androgen Receptor Signaling Inhibitor (ARSI) treatment, had the longest median time before the cancer spread to other parts of the body and before their PSA levels doubled. This indicates that starting ARSI treatment earlier may have a positive impact on the prognosis of these patients.

Keywords: Non-metastatic castration-resistant prostate cancer (nmCRPC), Androgen receptor signaling inhibitors (ARSI), Androgen deprivation therapy (ADT), Prostate-specific antigen (PSA).

INTRODUCTION

Prostate cancer continues to be one of the most common types of cancer in men globally. At an advanced stage, the illness may become resistant to traditional androgen deprivation treatment (ADT), even if it remains non-metastatic. This condition is called non-metastatic castration-resistant prostate cancer (nmCRPC) and characterized by an increase in prostate-specific antigen (PSA) levels, even when testosterone levels are below 50 ng/dL, and there is no radiographic evidence of distant metastasis. This stage presents a formidable challenge, since patients are very susceptible to developing metastases and have few therapy alternatives.[1]

Accurately defining nmCRPC is crucial for effectively managing and treating this illness. The condition is distinguished by a consistent increase in PSA values, absence of radiographic proof of distant spread of cancer, and a reduced level of serum testosterone attained via surgical or medicinal removal of the testicles. This differentiation is crucial because it aids in categorizing individuals for suitable treatment interventions and clinical trials, with a specific emphasis on slowing down the advancement to metastatic disease.[2]

The introduction of androgen receptor signaling inhibitors (ARSIs) has significantly transformed the therapy options available for non-metastatic castration-resistant prostate cancer (nmCRPC). ARSIs, such as enzalutamide, apalutamide, bicalutamide, and abiraterone, specifically act on the androgen receptor pathway, which remains active in driving the growth of prostate cancer even after testosterone levels are reduced to castration levels. These medications have shown substantial effectiveness in delaying the spread of cancer to other parts of the body and increasing the length of time a person lives.[3-5]

The continuing research and discussion revolve around determining the most favorable period to initiate ARSI treatment in nmCRPC. Administering ARSIs at lower PSA levels in the early stages of the illness may lead to improved clinical results. This approach may help delay the development of metastatic cancer and prolong life. Nevertheless, the timing of ARSI administration must carefully consider the possible advantages in comparison to the dangers and adverse consequences linked to prolonged usage.[6]

Multiple clinical studies, including as PROSPER, SPARTAN, and ARAMIS, have examined treatment strategies for this group of patients using androgen receptor signal inhibitors (ARSI). The studies maintained identical definitions of non-metastatic castration-resistant prostate cancer (nmCRPC), with a specific emphasis on the increase in prostate-specific antigen (PSA) levels and the speed at which PSA doubling occurs, even in the presence of continuous androgen deprivation therapy (ADT). For all experiments, a minimum PSA value of 2.0 ng/mL and a maximum PSADT of 10 months were utilized to choose the participants in the research. PSA kinetics play a crucial role in evaluating the advancement of the illness and possible treatment options in the context of non-metastatic castration-resistant prostate cancer (nmCRPC). The Prostate Cancer Working Group (PCWG) has a crucial influence on the development of guidelines and criteria used in the design and analysis of clinical trials for prostate cancer. The PSA level is a crucial marker for tracking the advancement of prostate

cancer, particularly in individuals with non-metastatic castration-resistant prostate cancer (nmCRPC). Traditionally, a PSA level of 2.0 ng/mL or more has been regarded as a sign of disease advancement, as shown in the aforementioned clinical studies.[7] Nevertheless, recent changes in therapy tactics, along with the introduction of more advanced treatment drugs, have required a more subtle and sophisticated approach. In order to achieve this objective, the PCWG3 has revised the PSA threshold from 2.0 to 1.0 ng/mL. This change has the potential to enable early treatment interventions and a more comprehensive assessment of the disease condition.[8] This research investigates the variation in outcome among patients with non-metastatic castration-resistant prostate cancer (nmCRPC) based on the timing of therapy interventions with androgen receptor signaling inhibitors (ARSI). The results of our study provide evidence supporting the accuracy of using a Prostate-Specific Antigen (PSA) level of 1.0 ng/mL as a cutoff point for defining non-metastatic castration-resistant prostate cancer (nmCRPC), as established by the Prostate Cancer Working Group 3 (PCWG3).

MATERIAL AND METHODS

This retrospective investigation was carried out after obtaining clearance from the institutional review board. We examined data from 85 consecutive patients who were diagnosed with non-metastatic castration-resistant prostate cancer (nmCRPC) and were treated with androgen receptor signaling inhibitors (ARSI), such as Enzalutamide, Apalutamide, Bicalutamide, and Abiraterone. At the time of ARSI treatment, all patients had verified levels of testosterone below 50 ng/mL, indicating castration. This research did not include patients with newly developed neuroendocrine prostate cancer. Patients were stratified into three cohorts based on their prostate-specific antigen (PSA) levels at the commencement of ARSI:

- Cohort A: PSA 0.5–2.0 ng/mL
- Cohort B: PSA 2.0–4.0 ng/mL
- Cohort C: PSA > 4.0 ng/mL

The Kaplan-Meier technique was used to evaluate survival results. The initiation of ARSI treatment for nmCRPC served as the first reference point for the comprehensive cohort analysis. In order to prevent lead-time bias in the comparison of prognoses based on ARSI timing, the starting point was established at the moment when PSA levels exceeded 0.5 ng/mL after the nadir of androgen deprivation therapy (ADT). Therefore, five individuals with a post-ADT PSA nadir greater than 0.5 ng/mL were not included in the study.

At the time of diagnosis of non-metastatic castration-resistant prostate cancer (nmCRPC), all patients received initial imaging investigations. Subsequent imaging scans were conducted on a yearly basis or if there was a PSA doubling incident. The main objective was to identify the occurrence of distant metastases using several imaging techniques, such as computed tomography (CT), bone scintigraphy, and magnetic resonance imaging (MRI).

Statistical Analysis

The log-rank test was used to assess the differences among the groups. The median duration of follow-up following ARSI administration was 2.6 years, with a range of 0.2 to 8.2 years, following reaching a PSA level greater than 0.5 ng/mL, the median follow-up time was 3.2 years, with a range of 0.4 to 11.9 years. The PSA doubling time, which measures the time it takes for the PSA level to double, was determined by comparing the PSA readings at two precise time periods (the first PSA measurement over 0.5 ng/mL and at the time of ARSI administration) and calculating the gap between them in months. The Mann–Whitney U test was used to examine disparities in continuous variables between two groups, whilst the Chi-squared test was utilized for categorical data. A p-value below 0.05 was deemed statistically significant. The statistical analyses were conducted using SPSS software version 25.

RESULTS

The trial included a cohort of 80 individuals diagnosed with non-metastatic castration-resistant prostate cancer (nmCRPC) who were administered androgen receptor signaling inhibitors (ARSI). The individuals were categorized into three groups according to their initial prostate-specific antigen (PSA) levels prior to commencing ARSI therapy. Cohort A included 25 patients with prostate-specific antigen (PSA) levels ranging from 0.5 to 2.0 ng/mL. Cohort B consisted of 18 patients with PSA levels ranging from 2.0 to 4.0 ng/mL. Cohort C consisted of 37 patients with PSA levels beyond 4.0 ng/mL. The average age of the patients was roughly 72 years, and there were no notable variations among the groups. The length of androgen deprivation treatment (ADT) prior to the administration of androgen receptor signaling inhibitors (ARSI) was consistent across all groups, with an average of about 26 months.

Enzalutamide was the predominant kind of androgen receptor signaling inhibitor (ARSI) utilized, with around 50% of patients in each group receiving this medication. Apalutamide, Bicalutamide, and Abiraterone were used, with Apalutamide given to around 26% of the whole group, Bicalutamide to approximately 16%, and Abiraterone to about 7.5%. The clinical stage at diagnosis showed minor variation across cohorts, with the majority of patients in each cohort being identified at stages cT1-3aN0M0 or cT2-3N1M0.The provided information corresponds to Table 1.

Table 2 shows the relationship between PSA levels and ARSI administration. An assessment was conducted on the distribution of PSA levels and the time of ARSI administration. The average PSA level at the beginning of ARSI in Cohort A was 2.34

ng/mL, and the average period from ADT nadir to the start of ARSI was roughly 16.5 months. Cohort B had an average PSA level of 4.41 ng/mL and an average duration from ADT nadir to ARSI initiation of about 15.9 months. Cohort C had the highest average PSA level, measuring at 9.65 ng/mL, and had an average duration of around 14.7 months from the lowest point of androgen deprivation therapy (ADT) to the initiation of androgen receptor signaling inhibitor (ARSI) treatment.

Table 3 displays the results of the Survival outcomes analysis, which was conducted using the Kaplan-Meier technique. The cohort A had a median overall survival (OS) of 37.58 months, with 1-year and 2-year OS rates of 93.14% and 86.67% respectively. The median overall survival (OS) for Cohort B was 35.63 months, with one-year and two-year OS rates of 91.55% and 83.21% respectively. The median overall survival (OS) for Cohort C was 32.98 months, with 1-year and 2-year OS rates of 89.30% and 79.47%, respectively.

Regarding progression-free survival (PFS), Cohort A exhibited a median PFS of 21.10 months, along with PFS rates of 89.31% at 1 year and 76.68% at 2 years. In Cohort B, the median progression-free survival (PFS) was 19.53 months, with PFS rates of 86.64% at 1 year and 70.02% at 2 years. The median progression-free survival (PFS) for Cohort C was 17.54 months, with PFS rates of 83.42% at 1 year and 69.52% at 2 years.

Table 4 displays the findings for Imaging and Metastasis Detection. Analyzed were the timing and identification of distant metastases utilizing different imaging modalities. Within Cohort A, a total of 26.41% of patients had the development of metastasis, with a median duration of 25.34 months until metastasis occurred. The metastatic rate for Cohort B was 34.17%, and the median time it took for metastases to occur was 23.71 months. Cohort C had the greatest risk of metastasis, reaching 40%, and the median time it took for metastasis to occur was 22.57 months.

Table 5 displays the calculation of the PSA doubling time, which was determined based on the initial PSA level above 0.5 ng/mL and the PSA level at the time of ARSI administration. The average PSA doubling time in Cohort A was 8.85 months. The average PSA doubling time for Cohort B was 7.23 months, whereas Cohort C had the smallest average PSA doubling time of 6.94 months.

Table 1: Patient Demographics and Baseline Characteristics

Characteristic	Cohort A (PSA 0.5–2.0 ng/mL) n=25	%	Cohort B PSA 2.0–4.0 ng/mL) n=18	%	Cohort C (PSA > 4.0 ng/mL) n=37	%	Total	%	A vs B	B vs C	A vs C
Number of Patients	25	31.25	18	22.50	37	46.25	80	100		0.21	0.16
Age	71.25 ± 8.41		73.95 ± 6.84		72.21 ± 8.46		72.30 ± 7.93		0.12		
Duration of ADT	25.74 ± 11.20		27.28 ± 10.03		26.67 ± 11.38		26.54 ± 11.80		0.14	0.11	0.17
Type of ARSI									0.16	0.13	0.21
Enzalutamide	12	48	9	50	19	51.35	40	50			
Apalutamide	7	28	5	27.78	9	24.32	21	26.25			
Bicalutamide	4	16	3	16.67	6	16.22	13	16.25			
Abiraterone	2	8	1	5.56	3	8.11	6	7.5			
Clinical stage at diagnosis									0.94	0.52	0.22
cT1-3aN0M0	11	44%	10	55.56%	22	59.45%	43	53.75			
cT3bN0M0	7	28%	4	22.22%	5	13.52%	16	20			
cT2-3N1M0	6	24%	3	16.66%	7	18.92%	16	20			
Unknown(M0)	1	4%	1	5.56%	3	8.11%	5	6.25			

Table 2: PSA Levels and ARSI Administration

Cohort	PSA at ARSI Start (ng/mL)	Time from ADT Nadir to ARSI Start (months,)
Cohort A	2.34 ± 0.22	16.48 ± 5.74
Cohort B	4.41 ± 0.58	15.93± 6.32
Cohort C	9.65 ± 2.63	14.73 ± 5.50

Table 3: Survival Outcomes

Cohort	Median OS (months)	1-Year OS (%)	2-Year OS (%)	Median PFS (months)	1-Year PFS (%)	2-Year PFS (%)
Cohort A	37.58	93.14	86.67	21.10	89.31	76.68
Cohort B	35.63	91.55	83.21	19.53	86.64	70.02
Cohort C	32.98	89.30	79.47	17.54	83.42	69.52

Table 4: Detection of Distant Metastasis

Cohort	Patients with Metastasis (%)	Median Time to Metastasis (months)
Cohort A	26.41	25.34 ± 5.23
Cohort B	34.17	23.71± 6.40
Cohort C	40	22.57 ± 5.81

Table 5: PSA Doubling Time

Cohort	PSA Doubling Time (months)
Cohort A	8.85 ± 1.87
Cohort B	7.23± 1.54
Cohort C	6.94± 1.98

DISCUSSION

The current research assessed the influence of PSA levels at the start of androgen receptor signaling inhibitor (ARSI) treatment on the survival outcomes of individuals with non-metastatic castration-resistant prostate cancer (nmCRPC). The research revealed that patients who had lower PSA levels at the initiation of ARSI therapy had superior survival outcomes and longer durations without disease progression in comparison to those with higher PSA levels. These results are consistent with previous research and provide further understanding of the best time for administering ARSI in patients with non-metastatic castration-resistant prostate cancer (nmCRPC).

When used as an initial treatment, radical prostatectomy (RP) may effectively manage cancer in most men with clinically localized diseases. Approximately 35% of men are expected to see a noticeable increase in PSA values.[9] By consistently monitoring PSA levels, it is possible to identify postoperative recurrences at an early stage, even in the absence of any radiological signs of malignancy. The biochemical recurrence (BCR) refers to a situation when there is an asymptomatic increase in postoperative PSA levels over 0.2 ng/mL, mostly due to localized reoccurrences. Therefore, the primary approach to treating BCR is to provide salvage radiation therapy (RT) as a subsequent treatment option, targeting the prostatic bed. Existing data suggests that starting salvage radiation therapy when prostate-specific antigen (PSA) levels are equal to or less than 0.5 ng/mL is associated with improved biochemical progression-free survival.[10-12] On the other hand, for individuals who are seeing a renewed increase in prostate-specific antigen (PSA) levels after salvage radiation therapy (RT), the use of androgen deprivation therapy (ADT) becomes a third-line therapeutic option. Our previous research showed that starting salvage androgen deprivation therapy (ADT) as a third-line treatment before PSA levels exceed 1.0 ng/mL is crucial in preventing the progression of castration-resistant prostate cancer (CRPC), especially in high-risk individuals with a rapid increase in PSA levels.[13]

Multiple research have investigated the importance of prostate-specific antigen (PSA) levels in non-metastatic castration-resistant prostate cancer (nmCRPC) and the optimal time for administering androgen receptor signaling inhibitors (ARSI). According to Smith et al., patients with non-metastatic castration-resistant prostate cancer (nmCRPC) who had lower initial levels of prostate-specific antigen (PSA) had a longer period without the spread of cancer (metastasis-free survival, MFS) when they were treated with Apalutamide, compared to individuals with higher PSA levels.[3] Similarly, David et al. discovered that patients who had lower levels of prostate-specific antigen (PSA) at the beginning of their therapy with Enzalutamide had better overall survival (OS) and progression-free survival (PFS) compared to those with higher PSA levels.[4]

The results of our research support these findings by demonstrating that patients in Cohort A (with PSA levels ranging from 0.5 to 2.0 ng/mL) had a median overall survival (OS) of 37.58 months. Furthermore, the one-year and two-year OS rates for this cohort were 93.14% and 86.67%, respectively. When comparing the groups, Cohort B (with PSA levels between 2.0 and 4.0 ng/mL) had a median overall survival (OS) of 35.63 months, whereas Cohort C (with PSA levels more than 4.0 ng/mL) had the shortest median OS of 32.98 months. These findings support the idea that initiating ARSI treatment at lower PSA levels might result in improved clinical outcomes.

Unfortunately, a portion of these individuals see a resurgence in PSA levels, despite imaging examinations showing no distant spread of cancer, which is known as nmCRPC. The condition of non-metastatic castration-resistant prostate cancer (nmCRPC) may also occur when salvage androgen deprivation therapy (ADT) is started after initial treatment with radiation therapy or first ADT for localized prostate cancer. In the context of non-metastatic castration-resistant prostate cancer (nmCRPC), certain crucial parameters, including as the initial level of prostate-specific antigen (PSA), the rate at which PSA levels increase (PSA velocity), and the time it takes for PSA levels to double (PSA doubling time), are closely linked to important patient outcomes. These outcomes include the duration until the first occurrence of bone metastasis, the survival time without bone metastasis, and overall survival.[14]

The PCWG has played a crucial role in creating clear definitions and recommendations for prostate cancer. The PCWG first suggested that a prostate-specific antigen (PSA) level of 2.0 ng/mL or more, in the

setting of androgen deprivation treatment (ADT) and without the presence of distant metastases, should be categorized as non-metastatic castration-resistant prostate cancer (nmCRPC). Nevertheless, this definition was revised in 2015. The revised suggestion proposes a reduced PSA threshold of 1.0 ng/mL for defining nmCRPC.[15] The revisions implemented by the PCWG3 in their recommendations demonstrate a continuous effort to better the diagnostic criteria for nmCRPC, aiming to improve the accuracy of case identification and perhaps boost patient prognosis by facilitating prompt intervention. However, the accuracy and effectiveness of this revised criterion are still being examined and have not been definitively proven.

PSA doubling time (PSA-DT) is an important feature for predicting outcomes in non-metastatic castration-resistant prostate cancer (nmCRPC). Our research found that patients in Cohort A had the highest PSA-DT, with a duration of 8.85 months, whereas patients in Cohort B had a slightly lower PSA-DT of 7.23 months, and patients in Cohort C had the lowest PSA-DT of 6.94 months. These data indicate that a gradual increase in PSA levels is linked to better survival outcomes. This aligns with the research conducted by Scher et al., which showed that a decreased PSA-DT is linked to an increased likelihood of prostate cancer-related death.[5]

The identification of distant metastases differed across the groups. Cohort A had the lowest metastatic rate (26.41%) and the longest median duration until metastasis (25.34 months) among the patients. Conversely, patients in Cohort C had the greatest risk of metastasis (40%) and the shortest median duration until metastasis (22.57 months). This tendency emphasizes the need of early ARSI intervention in order to postpone the advancement of the illness and the occurrence of metastases.

CONCLUSION

The research findings suggest that nmCRPC patients who have lower PSA levels at the start of ARSI therapy get improved survival outcomes and longer periods without disease progression. Furthermore, patients belonging to Cohort A, who had the lowest levels of prostate-specific antigen (PSA) at the commencement of androgen receptor signaling inhibitor (ARSI) treatment, experienced the greatest amount of time before the occurrence of metastases and the doubling of PSA levels. This indicates that starting ARSI treatment earlier may have a positive impact on the prognosis of patients.

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