Original article

Epidemiological characteristics and survival in patients with de novo metastatic prostate cancer.

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Abstract: The real-world outcomes of patients with metastatic prostate cancer (mPCa) are largely unexplored. We investigated the improvements in overall survival (OS) and cancer-specific survival (CSS) in patients with de novo mPCa in latest years. The USA SEER Research Data (2000-2017) were analyzed using the SEER*Stat software. The Kaplan-Meier method and Cox regression were used. Patients with de novo mPCa were allocated to 3 cohorts based on year of diagnosis: A (2000-2003), B (2004-2010), C (2011-2014). Maximum follow-up was fixed to 5 years. Overall, 26434 patients were included. Age, race and metastatic stage significantly affected OS and CSS. After adjustment for age and race, patients in cohort C showed 9% reduced risk of death (HR: 0.91 [95% CI, 0.87-0.95], p<0.001) and 8% reduced risk of cancer-specific death (HR: 0.91 [95% CI, 0.87-0.95], p<0.001) compared to those in cohort A. After adjustment for age, race and metastatic stage, patients in cohort C showed an improvement in OS and CSS compared to cohort B (HR: 0.94 [95% CI, 0.91-0.97], p=0.001 and HR: 0.89 [95% CI, 0.85-0.92], p=0.001). Patients with M1c disease had a more pronounced improvement in OS and CSS compared with the other stages. No differences were found between cohort B and C. In conclusion, the prognosis of de novo mPCa remains poor with a median OS of 30 months and a median CSS of 35 months. Limited OS and CSS improvements were observed in latest years.

Keywords: Prostatic Neoplasms/mortality, Prostatic Neoplasms/epidemiology, SEER Program

1. Introduction

The treatment landscape of metastatic prostate cancer (mPCa) has completely changed over the last decades. In 2004, docetaxel was the first drug to demonstrate an overall survival (OS) benefit of 2.4 months in mPCa compared to mitoxantrone and was approved for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC)[1]. Cabazitaxel showed a similar OS increase compared to mitoxantrone and became a second-line treatment option for mCRPC in 2010[2]. Subsequently, abiraterone acetate and enzalutamide were approved in both post-docetaxel[3,4] (2011-2012) and in pre-docetaxel mCRPC[5,6] (2013-2014), reporting OS advantages between 4.0 and 4.8 months compared to placebo. Docetaxel was also introduced for the hormone-sensitive phase of mPCa (mHSPC) in 2015[7]. Several androgen-receptor signaling inhibitors (ARSi) – abiraterone, enzalutamide and apalutamide – have then been approved for the treatment of mHSPC[8].
Although the aforementioned randomized trials showed significant survival improvements in the first and second-line of mCRPC, the real-world survival benefit in the population of patients outside of clinical trials is largely unexplored. In addition, the potential cumulative benefit on survival that can derive from the temporal sequence of different treatment strategies is currently unknown.

Given the introduction of chemotherapy in 2004 and of ARSi since 2011, we hypothesized that a significant difference in OS and cancer-specific survival (CSS) was detectable among patients with newly diagnosed mPCa diagnosed in 3 treatment eras: pre-docetaxel 2000-2003 (Cohort A), docetaxel 2004-2010 (Cohort B) and ARSi + cabazitaxel 2011-2014 (Cohort C).

2. Results

2.1. Study cohort

Our selection criteria identified 26434 patients with de novo mPCa diagnosed between 2000 and 2014. Of these, 6047 were diagnosed between 2000 and 2003 (cohort A), 11815 between 2004 and 2010 (cohort B), 8572 between 2011 and 2014 (cohort C). The main characteristics of study population are summarized in Table 1. Overall, 68.3% of patients were ≥65 years. The percentage of patients younger than 75 years was higher in cohort B and C compared to cohort A (32.4% and 33.4% vs. 28.5%). The majority of patients were white (62.7%), followed by black (19.4%) and Hispanic (11.6%). Metastatic classification (AJCC 6th edition) was available for cohort B and C. The majority of patients were M1b (72.7%), with a significant difference between cohort B (70.1%) and C (76.4%). The median follow-up was 25, 26 and 29 months in cohort A, B and C respectively, with a median follow-up of censored patients of 60, 60 and 51 months.

Table 1. Basal characteristics of patients.

|                        | Number of patients (%) |
|------------------------|------------------------|
|                        | Total 2000-2003 2004-2010 2011-2014 |
| **Age (years)**        |                        |
| 15-54                  | 2087 (7.9) 474 (7.8) 970 (8.2) 643 (7.5) |
| 55-64                  | 6323 (23.9) 1250 (20.7) 2857 (24.2) 2216 (25.9) |
| 65-74                  | 7892 (29.9) 1804 (29.8) 3391 (28.7) 2697 (31.5) |
| 75-84                  | 7099 (26.9) 1862 (30.8) 3268 (27.7) 1969 (23.0) |
| ≥85                    | 3033 (11.5) 657 (10.9) 1329 (11.2) 1047 (12.2) |
| **Total**              | 26434 (100) 6047 (100) 11815 (100) 8572 (100) |
| **Race**               |                        |
| White                  | 16513 (62.7) 3830 (63.5) 7361 (62.5) 5322 (62.3) |
| Black                  | 5111 (19.4) 1227 (20.3) 2279 (19.3) 1605 (18.8) |
| American Indian/Alaska Native | 170 (0.6) 31 (0.5) 76 (0.6) 63 (0.7) |
| Asian or Pacific Islander | 1484 (5.6) 329 (5.4) 680 (5.8) 475 (5.6) |
| Hispanic               | 3066 (11.6) 614 (10.2) 1377 (11.7) 1075 (12.6) |
| **Total**              | 26344 (100) 6031 (100) 11773 (100) 8540 (100) |
| **Metastatic stage**   |                        |
| M1a                    | 1097 (5.6) - 610 (5.3) 487 (5.9) |
| M1b                    | 14301 (72.7) - 8011 (70.1) 6290 (76.4) |
| M1c                    | 4265 (21.7) - 2811 (24.6) 1454 (17.7) |
| **Total**              | 19663 (100) - 11432 (100) 8231 (100) |

2.2. Clinical outcome and prognostic variables
In the 26434 patients analyzed for OS, the median values for OS in cohort A, B and C were 26 (95% CI, 25.0-27.0), 26 (95% CI, 25.3-26.7) and 30 (95% CI, 29.1-30.9) months (Figure 1A). In the 26032 patients analyzed for CSS, the median values of CSS were 31 (95% CI, 29.7-32.3), 31 (95% CI, 30.1-31.9) and 35 months (95% CI, 32.4-33.6) (Figure 1B). The detailed age-standardized 1- to 5-year OS and CSS are shown in Figure 2.

Age, race and metastatic stage (this latter was only analyzed in cohort B and C) were identified as significant prognostic factors at univariate analysis and were included in the multivariable models.

Figure 1. Kaplan-Meier estimations of OS (a) and CSS (b) according to cohort allocation. P-value from log-rank test.
2. Multivariable models

The multivariable models for OS and CSS showed a substantial increased risk of death according to age, with the highest risk in patients ≥85 (Table 2 and 3). Black patients showed a slightly higher risk of death compared to white, whereas Asians/Pacific Islanders showed better outcomes compared to white. 9% decreased risk of death and 8% decreased risk of cancer-specific death were found in cohort C compared to cohort A (HR: 0.91 [95% CI, 0.87-0.95], p<0.001 for OS and HR: 0.92 [95% CI, 0.88-0.96], p<0.001 for CSS), whereas no statistically significant differences in OS and CSS were found between cohort A and B. Exploratory multivariable models were also performed in cohort B and C to include the metastatic stage classification (AJCC 6th edition), which was found to be associated with distinct OS and CSS outcomes (Table S1 and S2). In these multivariable models, significant OS and CSS advantages were reported in cohort C compared to cohort B (HR: 0.94 [95% CI, 0.91-0.97], p=0.001 for OS and HR: 0.89 [95% CI, 0.85-0.92], p<0.001 for CSS). In the exploratory subgroup
analysis comparing the OS and CSS of cohort C vs. cohort B, a significant interaction was found among the subgroups of AJCC metastatic classification. More pronounced OS and CSS advantages in cohort C were shown in M1c patients compared to patients with metastases that were limited to nodes or bone (M1c: HR: 0.87 [95% CI, 0.81-0.94], interaction p=0.014 for OS and HR: 0.81 [0.75-0.88], interaction p=0.015 for CSS) (Table 4).

Table 2. Multivariable analysis for OS.

| Age (years)  | Number of patients | HR  | 95% CI      | Lower | Upper | p     |
|--------------|--------------------|-----|-------------|-------|-------|-------|
| 15-54        | 2081               | 0.98| 0.92        | 1.04  |       | <0.001|
| 55-64        | 6300               | 1.03| 0.97        | 1.09  |       | 0.515 |
| 65-74        | 7857               | 1.42| 1.34        | 1.50  |       | 0.286 |
| 75-84        | 7078               | 2.18| 2.04        | 2.32  |       | <0.001|
| ≥85          | 3028               |     |             |       |       | <0.001|

Table 3. Multivariable analysis for CSS.

| Age (years)  | Number of patients | HR  | 95% CI      | Lower | Upper | p     |
|--------------|--------------------|-----|-------------|-------|-------|-------|
| 15-54        | 2049               | 0.94| 0.88        | 0.99  |       | <0.001|
| 55-64        | 6216               | 0.93| 0.88        | 0.99  |       | 0.048 |
| 65-74        | 7720               | 1.20| 1.12        | 1.27  |       | 0.033 |
| 75-84        | 6979               | 1.74| 1.62        | 1.87  |       | <0.001|
| ≥85          | 2987               |     |             |       |       | <0.001|

| Race         | Number of patients | HR  | 95% CI      | Lower | Upper | p     |
|--------------|--------------------|-----|-------------|-------|-------|-------|
| White        | 16376              | 0.93| 0.88        | 0.99  |       | <0.001|
| Black        | 5053               | 1.09| 1.04        | 1.13  |       | <0.001|
| American Indian/Alaska Native | 167 | 1.01 | 0.83 | 1.23 | 0.922 |
| Asian or Pacific Islander | 1423 | 0.73 | 0.67 | 0.78 | <0.001 |
| Hispanic     | 2932               | 0.95| 0.91        | 1.00  |       | 0.076 |

| Year of diagnosis | Number of patients | HR  | 95% CI      | Lower | Upper | p     |
|-------------------|--------------------|-----|-------------|-------|-------|-------|
| 2000-2003 (Cohort A) | 5928              |     |             |       |       | <0.001|
| 2004-2010 (Cohort B) | 11599             | 0.99| 0.95        | 1.03  |       | 0.596 |
| 2011-2014 (Cohort C) | 8424              | 0.92| 0.88        | 0.96  |       | <0.001|
Table 4. Subgroup analysis of OS and CSS between cohort C and B.

| Metastatic stage | 2011-2014 (Cohort C) vs. 2004-2010 (Cohort B) | Number of patients | HR | 95% CI | p |
|------------------|---------------------------------------------|-------------------|-----|--------|---|
| OS               |                                             |                   |     |        |   |
| M1a              |                                             | 1088              | 1.09| 0.93   | 1.28 | 0.014* |
| M1b              |                                             | 14250             | 0.96| 0.92   | 0.99 |        |
| M1c              |                                             | 4254              | 0.87| 0.81   | 0.94 |        |
| All\(^1\)        |                                             | 19592             | 0.94| 0.91   | 0.97 | 0.001 |
| CSS              |                                             |                   |     |        |   |
| M1a              |                                             | 1069              | 1.01| 0.85   | 1.20 | 0.015* |
| M1b              |                                             | 14050             | 0.91| 0.87   | 0.95 |        |
| M1c              |                                             | 4189              | 0.81| 0.75   | 0.88 |        |
| All\(^1\)        |                                             | 19308             | 0.89| 0.85   | 0.92 | <0.001 |

Multivariable models including age and race were used to compute the hazard ratios (HR) and their 95% confidence intervals (CI) for OS and CSS in the metastatic subgroups of patients diagnosed in 2011-2014 vs 2004-2010. *p value for interaction; \(^1\)Multivariable model including age, race and metastatic stage for OS and CSS (Cohort C vs. Cohort B).

3. Discussion

Several randomized trials demonstrated that both chemotherapy and ARSi provide significant survival benefit in mPCa\[1-8\]. However, the real-world survival outcomes of patients with mPCa remain largely unexplored.

In the present SEER-based analysis, we investigated whether the introduction of both chemotherapy and ARSi in mCRPC had substantially changed the real-world OS and CSS in the population of patients with de novo mPCa diagnosed in the United States of America (USA) in 3 different treatment eras (2000-2003 vs. 2004-2010 vs. 2011-2014).

More than 26000 patients diagnosed between 2000 and 2014 were included in our analysis, of these 6047 were diagnosed in pre-docetaxel era (cohort A), 11815 in post-docetaxel era (cohort B), and 8572 in post-ARSi era (cohort C) (Table 1). We found that age had a significant impact on patients’ OS and CSS (Table 2 and 3). In the multivariable model, patients older than 85 showed a double risk of dying compared to patients between 15 and 54 years old and the hazard ratio for death was also significantly unfavorable in patients aged 75-84. Although this figure might be at least in part attributable to the reduced expected survival, older patients may also be less likely to receive the same treatments as their younger counterparts, especially chemotherapy. Therefore, our data suggest the significant efforts should be spent to specifically improve the outcomes of the older and frail population of patients with mPCa.

We did not find a significant difference in the OS and CSS between cohort A and cohort B (Figure 1). Conversely, we observed a statistically significant improvement in the OS and CSS of patients included in cohort C, who showed a decreased risk of death of 9%, a decreased risk of cancer-specific death of 8%, and a median OS gain of 4 months compared to cohort A. The comparison of cohort C with cohort B, adjusted for metastatic stage, also demonstrated a OS improvement of 6% and a CSS improvement of 11%. When compared with the other metastatic stages, we found that patients with M1c disease showed the worst survival, but had a more pronounced OS and CSS improvement in the newer ARSi era compared to M1a or M1b patients (Table 4). Although the reason for this observation remains unknown, the presence of visceral metastases might lead to more aggressive pharmaceutical
approaches and more adherence to treatment that could result in increased benefit compared to the other stages.

The median OS benefit of chemotherapy and ARSi in randomized trials for mCRPC was 2-4 months in first-line[1,5,6] and 4-5 months in second-line[3,4]. Therefore, a more robust OS and CSS benefit would have been expected in cohort C after the introduction of these agents in clinical practice. However, the degree of benefit seen in clinical trials does not necessarily translate into the real-world setting. Screen failure rates on trials are relatively high, and can easily affect the ultimate generalizability of trial results to the real world population.

In addition, our study is based on patients diagnosed with de novo mHSPC, who were supposed to receive ADT as a first-line treatment for metastatic disease, and subsequently docetaxel or ARSi as a first-line treatment for mCRPC. The number of patients who died without receiving a first-line treatment for mCRPC or refused therapies for mCRPC is unknown. The information on number of lines of treatment, type of treatment, disease burden, number and site of metastases were not available and are important limits of our analysis. In addition, we acknowledge that some patients could have received chemotherapy or ARSi outside of the defined treatment eras in the context of clinical trials or some years after mPCa diagnosis.

A recent analysis compared 590 patients with mCRPC diagnosed and treated in two treatment eras (2004-2007 vs. 2010-2013) at Dana-Farber Cancer Institute[9]. The authors demonstrated 41% decreased risk of death in the newer treatment era, with a median OS gain of 6 months.

In another study, Helgstrand and colleagues analyzed the incidence and mortality data of patients with de novo mPCa included the SEER database and in the Danish Prostate Cancer Registry[10]. In patients diagnosed between 2000 and 2009, the median OS was 22 months in SEER and 30 months in the Danish Registry. The 5-year overall mortality was 80.0% in both registries in the period 2000-2004, remained stable (80.5%) according to SEER in 2005-2008, but decreased to 73.2% according to the Danish Registry in 2005-2009.

Although the monocentric experience of the Dana-Farber Cancer Institute and the Danish data confirm the potential survival gain offered by the newer treatments, the SEER analysis by Helgstrand and colleagues does not show substantial survival changes after docetaxel introduction, and it is consistent with our results. We highlight that the medical costs and the health insurance policies might have significantly reduced the extensive use of ARSi and chemotherapy in the general population of patients with de novo mPCa in the USA, affecting their survival outcomes. Ramsey and colleagues reported that the cumulative incidence of bankruptcy in the first 5 years after prostate cancer diagnosis is 38% (nearly 50% in metastatic stage), and the risk of mortality is almost twice as high among patients with prostate cancer who file for bankruptcy compared with those who do not[11]. Further studies should investigate whether insurance policies or limited access to healthcare services could contribute to such disappointing survival gains observed in the SEER registry after the introduction of chemotherapy and ARSi.

Of note, patients with de novo mPCa show worse time to castration and survival compared to those who relapse after local therapy, irrespective of treatment received[12,13]. Therefore, the intrinsic aggressiveness of de novo mPCa could have also led to decreased survival gains in this patient’s population. Although discouraged by international guidelines in recent years, possible premature discontinuation of ARSi and chemotherapy based on PSA progression without clinical or radiographic progression could have also affected the outcome data of patients diagnosed between 2004 and 2014[14].

Finally, we acknowledge that our study excludes the possible benefit induced by docetaxel or ARSi in mHSPC, given their approval for this setting in the latest years. The earlier use of these agents provided OS gains that exceeded 12 months in the randomized trials for mHSPC[8]. In addition, future analyses could detect additional survival benefits that might be provided by an increased knowledge in the sequencing of agents for mCRPC and by the biomarker-driven selection of patients suitable for specific drugs (i.e., PARP inhibitors)[15,16].
4. Patients and Methods

The SEER*Stat software was used to select patients from the SEER Research Data 2000-2017 [17]. Patients with prostate cancer were identified using the codes for malignant adenocarcinoma (8140/3) and prostate gland (C61.9). Only patients with single tumor in medical history were selected. Metastatic patients were identified using a combo of the American Joint Committee on Cancer (AJCC) classification 3rd and 6th editions. According to the November 2019 submission of SEER data, the study cut-off for survival data was 31 December 2017. In order to minimize potential bias related to different follow-up among the cohorts, the maximum follow-up was fixed to 5 years and patients diagnosed from 2015 onwards were excluded. Patient age, race, year of mPCa diagnosis, metastatic stage and outcome data were included in the case listing session of SEER*Stat. The variables described were analyzed in univariate analysis using Kaplan-Meier curves and log-rank test. A P value ≤ 0.05 was considered statistically significant. Cox proportional hazards model were used to test the effect of covariates on OS and CSS. Only patients who had known values for the variables of interest were included. T-test was applied to compare median values. The IBM software Statistical Package for Social Sciences (SPSS) version 23 and RStudio Version 1.2.5001 were used for data analysis.

5. Conclusions

Our large-scale, retrospective analysis suggests that the real-world OS and CSS have not drastically changed during the last two decades in patients with de novo mPCa diagnosed in the USA. The median OS of these patients remains poor and does not exceed 2.5 years. The lack of data on treatment use does not allow to draw conclusions about the potential survival gain provided by chemotherapy and ARSi in patients treated with these agents. Further studies should investigate the real-world impact on survival of these agents after their introduction in the mHSPC setting and the influence of health insurance policies on the outcomes of patients with mPCa.

Supplementary Materials: The following are available online at www.mdpi.com/xxxx/s1, Table S1: multivariable model for OS in cohort B and C, Table S2: multivariable model for CSS in cohort B and C.

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