Survival in Metastatic Prostate Cancer

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The real-world survival trends are largely unexplored in patients with de novo metastatic prostate cancer. A recent population-based analysis provided data about the survival improvements in patients with de novo metastatic prostate cancer diagnosed in USA between 2000 and 2014. Despite the advent of several new drugs, limited improvements in overall and cancer-specific survival were observed in 2011-2014 compared to 2000-2003 and 2004-2010.

Keywords: prostate cancer ; metastatic prostate cancer ; SEER ; survival analysis

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 with mitoxantrone, and was approved for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC)[1]. Cabazitaxel showed a similar OS increase compared with 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 pre-docetaxel mCRPC[5][6] (2013–2014), reporting OS advantages between 4.0 and 4.8 months compared with placebo (Figure 1). 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—were then 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. The ideal population of patients enrolled in clinical trials might overestimate the true benefit induced by approved drugs in the general population of patients with newly diagnosed mPCa. For example, not all patients can receive chemotherapy. Although no specific advice is included in the U.S. National Comprehensive Cancer Network guidelines, the European Association of Urology guidelines recommend that docetaxel should be only offered to mHSPC patients who are fit enough for chemotherapy[9]. Of note, the STAMPEDE trial of docetaxel in mHSPC only included patients fit for chemotherapy and without significant cardiovascular history. Many patients with mPCa in the real-world are elderly with many comorbidities, and they cannot receive chemotherapy [10]. In addition, patients with poor general conditions or poor performance status are often not suitable for aggressive anticancer therapies. Moreover, although some retrospective data have been reported[11], no randomized trial has ever assessed the long-term, cumulative benefit on survival that can derive from the temporal sequence of different treatment strategies. Finally, the U.S. insurance policies or limited access to healthcare services could contribute to producing a discrepancy between the expected survival gain and the real-world data[12].

2. Survival in Patients with Newly Diagnosed Metastatic Prostate Cancer

A recent analysis compared 590 patients with mCRPC, who were diagnosed and treated in two treatment eras (2004–2007 vs. 2010–2013) at the Dana–Farber Cancer Institute[11]. The authors demonstrated a 41% decreased risk of death in the newer treatment era, with a median OS gain of 6 months. In addition, the cumulative benefit from the newer therapies was more pronounced in longer-term survivors and de novo patients. Although this study provided useful information, all patients had castration-resistant disease, only 216 had de novo mPCa, and they were all managed in a top-level institution.

In another study, Helgstrand and colleagues analyzed the incidence and mortality data of patients with de novo mPCa included in the SEER database and in the Danish Prostate Cancer Registry[13]. In patients diagnosed between 2000 and 2009, the median OS was 22 months in SEER and 30 months in the Danish Registry. The five-year overall mortality was 80.0% in both registries in the period of 2000–2004, remained stable (80.5%) according to SEER in 2005–2008, and 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 confirmed the potential survival gain offered by newer treatments, the SEER analysis by Helgstrand and colleagues did not show substantial survival changes after 2004.

In the recent SEER-based analysis (https://www.mdpi.com/2072-6694/12/10/2855), it was 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 in three different time periods (2000–2003—Cohort A, 2004–2010—Cohort B, 2011–2014—Cohort C). Although the patients were allocated to these cohorts regardless of having received a specific treatment, it should be highlighted that docetaxel was approved by the FDA for the treatment of mCRPC in 2004, whereas ARSi was approved from 2011 onwards (Figure 1).

More than 26,000 patients diagnosed between 2000 and 2014 were included in this analysis; of these, 6047 were allocated to Cohort A, 11,815 to Cohort B, and 8572 to Cohort C (Table 1). Age had a significant impact on patients' OS and CSS (Table 2 and Table 3). In the multivariable model, patients older than 85 showed a double risk of dying compared with 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.

It was not identified a significant difference in the OS and CSS between Cohort A and Cohort B (Figure 2). Conversely, a statistically significant improvement in the OS and CSS of patients included in Cohort C was observed. These patients 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 with Cohort A. The comparison of Cohort C with Cohort B, adjusted for the metastatic stage, also demonstrated an OS improvement of 6% and a CSS improvement of 11%. When compared with the other metastatic stages, patients with M1c disease showed the worst survival, but had a more pronounced OS and CSS improvement in the newer ARSi era compared with 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 with the other stages.

The median OS gain 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]. Although this study was not designed to demonstrate the potential benefit of chemotherapy or ARSi, a more robust OS and CSS improvement would have been expected in patients diagnosed in 2011–2014, after the introduction of several agents in clinical practice (Figure 1). A median OS improvement of 4 months in Cohort C compared with Cohort A appears to be quite discouraging. Regardless of cohort analysis, the probability of survival after 3 years from diagnosis was 40.0% in 2000 and 46.8% in 2014 (Figure 3). Similarly, the five-year probability of survival was 24.0% in 2000 and 28.2% in 2012.

3. Limits and Possible Explanations

Significant limits can affect this analysis. The number of patients who died without receiving a first-line treatment for mCRPC or refused therapies for mCRPC was unknown. In addition, the information on the number of lines of treatment, type of treatment, disease burden, number and site of metastases, body mass index, performance status, and comorbidities was not available in the SEER database and these potential confounders were not adjusted in the multivariable model.

However, patients' ineligibility or refusal of anticancer treatments, insurance issues, intrinsic disease aggressiveness, or prior unavailability of drugs in a hormone-sensitive setting might contribute to these disappointing results.

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