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Abiraterone acetate, enzalutamide and their sequence for castration-resistant prostate cancer

Adherence, survival and hospitalization analysis of a medical claims database

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Summary
Objective To analyze drug adherence, overall survival (OS) and hospitalization rates of patients with castration-resistant prostate cancer (CRPC) treated with arbiraterone acetate (AA), enzalutamide (ENZ) and their sequence in a real-life setting.
Methods The database of the largest public insurance company in Austria was analyzed. All CRPC patients with at least one prescription of AA and/or ENZ between September 2013 and August 2016 in the pre-chemotherapy and post-chemotherapy setting were extracted and matched to the Austrian death and hospital admission statistics. Drug adherence was estimated by the medication possession ratio (MPR).
Results Data of 457 patients (mean age: 74.4 ± 8.5 years) were analyzed. The mean MPR was 90% for AA, 85% for ENZ and 88% for the sequence therapy cohort. The median overall survival (OS) of the entire cohort was 21 months: 15 months for AA, 24 months for ENZ, 26 months for the sequence group, and 10 months for the sequence group after switching. In the post-chemotherapy setting, the median OS was 14 months in AA treatment (mean: 15.8 ± 0.9 months), 19 months in the ENZ treatment (mean: 17.2 ± 1.4 months) and 25 months in the sequence group (mean: 22.7 ± 0.8 months). Median OS in the pre-chemotherapy setting was 25 months (mean: 21.5 ± 1.1 months), 18 months in AA treatment group (mean: 18.9 ± 1.5 months) and 17 months in ENZ treatment group (mean: 18.2 ± 1.9 months). Only 43 (9.4%) patients were not hospitalized during the course of the study. On average patients spent 13% of their remaining life span in hospital care (median 8%, range: 1–34%).
Conclusion This Austrian prescription database allows some insights into the outcome of CRPC patients treated with AA and ENZ and their sequence in a real-life setting. Drug adherence was satisfactory, OS was shorter for AA and ENZ as compared to the pivotal phase III trials.

Keywords Medication adherence · Castration-resistant prostate cancer (CRPC) · Overall survival (OS) · Abiraterone acetat (AA) · Enzalutamide (ENZ)

Introduction

The recent introduction of arbiraterone acetate (AA) and enzalutamide (ENZ) has revolutionized the management of castration-resistant prostate cancer (CRPC), both in the pre-chemotherapy and post-chemotherapy settings [1]. The pivotal phase III trials of both drugs showed a moderate survival benefit in the range of 3 months as compared to placebo [2–5]. There are considerable concerns that the optimistic phase III data do not adequately reflect the real-life situation [6]. Therefore, data generated in a real-life setting might offer insights into the generalizability of clinical trial data. While registries still provide an incomplete picture due to the selection of centers and patients, prescription databases might better reflect the real-world scenario.

This group recently reported on a series of patients who received AA for CRPC in the post-chemotherapy setting by analyzing the prescription database of the largest public insurance company in Austria (Wiener Gebietskrankenkasse, WGKK) [7]. A substantially shorter overall survival (OS) could be demonstrated

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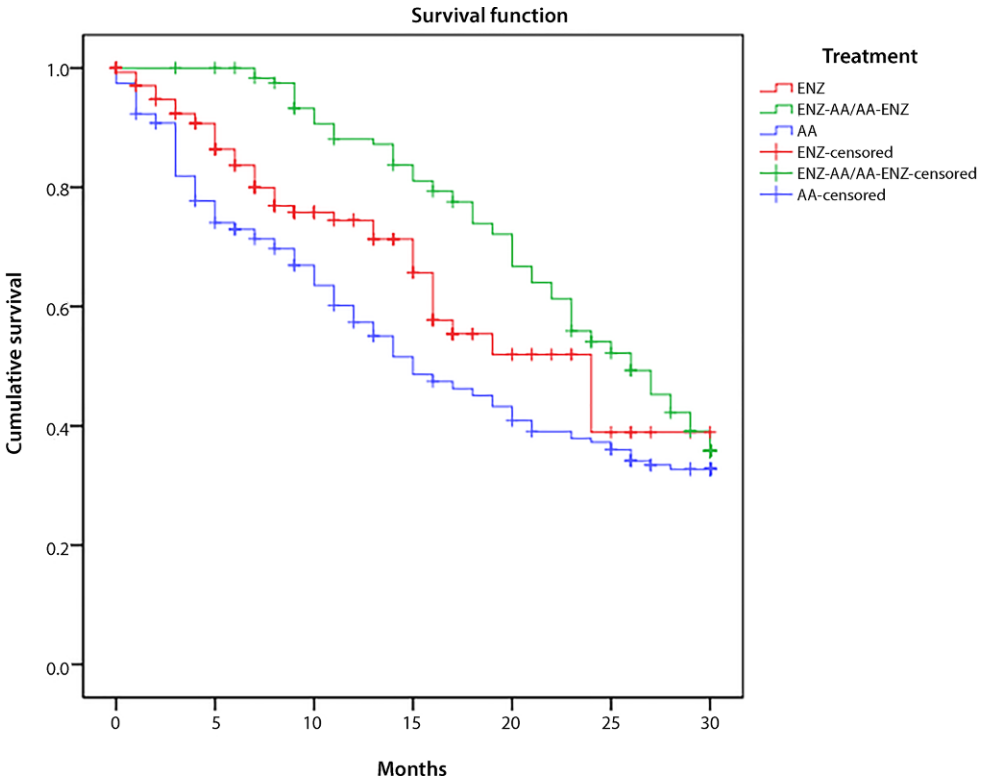

Fig. 1 Overall survival in the entire cohort depending on treatment strategy. *ENZ* Enzalutamid, *AA* Abiraterone acetate

in real life as compared to the registry phase III trial [7]. The high prevalence of CRPC as well as the cost of these drugs emphasize the economic impact of drug adherence, prescription pattern and generalizability of clinical trial data.

In this study the analysis mentioned above is now expanded by updating AA patients and by adding patients who have received ENZ and a sequence of AA and ENZ. This study evaluated (i) adherence rates for AA, ENZ and the sequence of therapy in patients with CRPC in Austria, (ii) the overall survival of CRPC receiving AA, ENZ and the sequence therapy in a real-life setting and (iii) hospital admission rates in this cohort.

Material and methods

The prescription database of the largest public insurance company in Austria was reviewed. We have isolated all patients with at least one prescription of AA, ENZ from September 2013 to August 2016. The following data were extracted from this database: age, date of the first AA and ENZ prescription, number of AA, ENZ prescriptions, number of hospital admissions, length of hospital admissions. This database was matched to the Austria death and hospital admission statistics. Adherence was calculated using the medication possession ratio (MPR) [8]. The MPR is the sum of all days of AA, ENZ, sequence of AA and ENZ supplied within a given period, divided by the total number of days in that period. There is no consensus standard for what constitutes adequate adherence. Some trials consider rates of greater than 80% to be acceptable [9, 10].

Statistical analysis

The SPSS 17.0 package for Windows (SPSS, Chicago, IL, USA) was used for statistical analysis and all the values were expressed in terms of means ± SD, for the efficacy analysis. Survival time was calculated from the initiation of AA, ENZ, sequence of AA and ENZ and the date of death. Patients alive were assessed at the last known follow-up date. Overall survival (OS) rates were estimated using the Kaplan-Meier method.

Results

Patient characteristics

Data of 457 patients with CRPC with at least 1 prescription of AA and/or ENZ were analyzed. Mean patient age was 74.4 ± 8.5 years including ≤60 years: $n = 26$ (5.7%), 61–70 years: $n = 114$ (24.9%), 71–80 years: $n = 196$ (42.9%) and >80 years: $n = 121$ (26.5%). A total of 195 patients received AA and 139 ENZ as a monotherapy, and 123 patients a sequence of both drugs (ENZ-AA $n = 13$, AA-ENZ $n = 110$). Moreover, 112 patients were availabe for calculation of survival after the time of switching. The mean duration of treatment of the entire cohort ($n = 456$) was 11.3 ± 9.7 months (range: 0–30 months). Treatment duration for AA

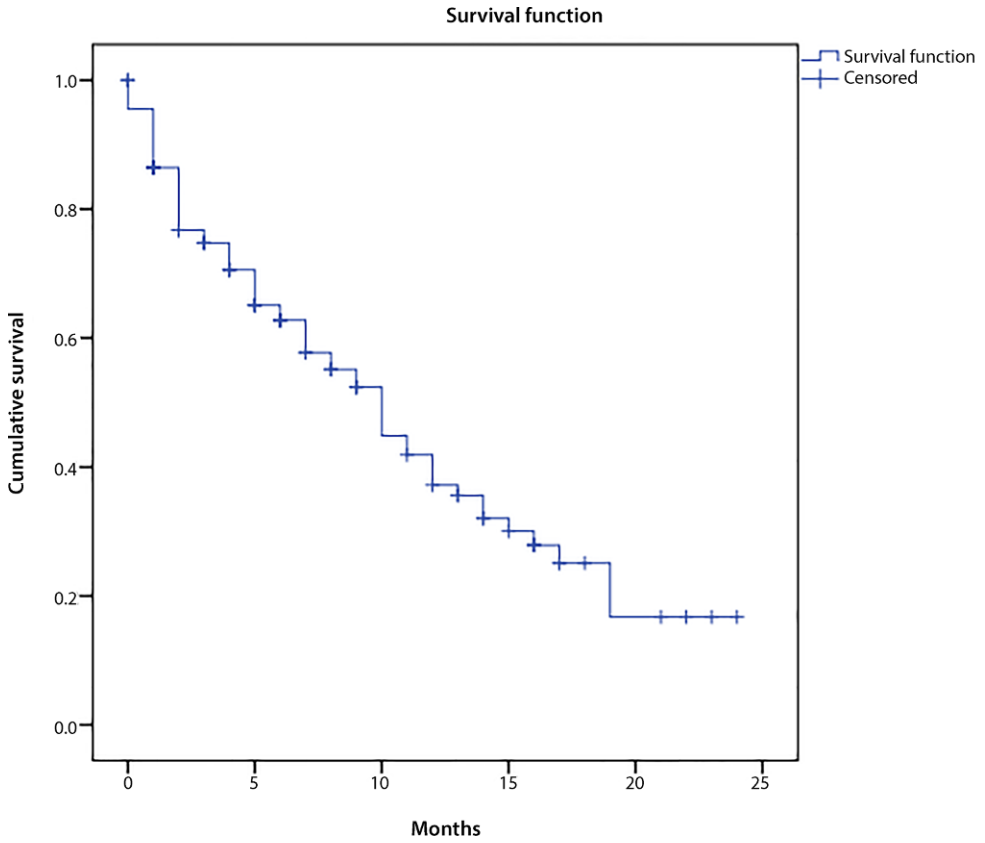

Fig. 2 Overall survival in the sequence group after time point of switching

was 9.5 ± 10.2 months (range: 0–30 months), for ENZ 7.6 ± 6.6 months (range: 0–26 months) and for the sequence therapy 18.1 ± 8.19 (range: 3–30 months).

Drug adherence

The MPR of the entire cohort was 90%: ≤60 years: 91%, 61–70 years: 90%, 71–80 years: 89%, 81–90 years: 89%. MPR of the AA treatment group was 88%: ≤60 years.: 89%, 61–70: 88%, 71–80: 87%, 81–90: 87%. MPR of the ENZ treatment group was 85%: ≤60 years: 85%, 61–70: 85%, 71–80: 85%, 81–90: 85%.

Overall survival

Median OS in the entire cohort was 21 months (mean; 18.8 ± 0.5 months; Fig. 1), the median OS for AA was 15 months (mean: 16.7 ± 0.8 months), 24 months (mean: 19.7 ± 1.1 months) for ENZ, and 26 months (mean: 23.4 ± 0.6 months) in the sequence cohort. A separate analysis on survival in the sequence cohort calculated from the time point of switching showed a median survival of 10 months (mean: 10.8 ± 0.9 months; Fig. 2).

In the post-chemotherapy setting, the median OS was 14 months in AA treatment group (mean: 15.8 ± 0.9 months), 19 months in the ENZ treatment group (mean: 17.2 ± 1.4 months) and 25 months in the sequence group (mean: 22.7 ± 0.8 months; Fig. 3). Moreover, median survival in the pre-chemotherapy setting was 25 (mean: 21.5 ± 1.1 months); 18 months in the AA treatment group (mean: 18.9 ± 1.5 months) and 17 months in the ENZ treatment group (mean: 18.2 ± 1.9 months). Mean overall survival in the sequence treatment group was 25.1 ± 1.3 months (Fig. 4).

The OS decreased with advancing age: ≤60 years (mean: 21.5 ± 2.345 months), 61–70 years (mean: 19.4 ± 1 months), and 71–80 (mean: 19.5 ± 0.8 months), >80 years (mean: 16.5 ± 1 months).

Hospital admissions

In Austria the vast majority of chemotherapies for CRPC are given on an outpatient basis in urological or oncological institutions. For reimbursement reasons these patients are admitted on a day-case basis and are included in the hospital admission statistics. Therefore, we have deleted all admissions for 24h or less from further analyses. Of all 456 patients only 43 (9.4%) were not hospitalized during their remaining life span. The number of hospital admissions (after deleting all admissions for 24h or less) was as follows: 1×: 162, 2×: 155, 3×: 152, 4×: 130, 5×: 130 and >5×: 120. On average, patients spent 13% of their life span in hospital care (median 8%, range: 1–34%). The mean length of total hospital stay was 39.4 ± 36.8 days in the AA treatment group, 26.3 ± 25.8 days in the ENZ

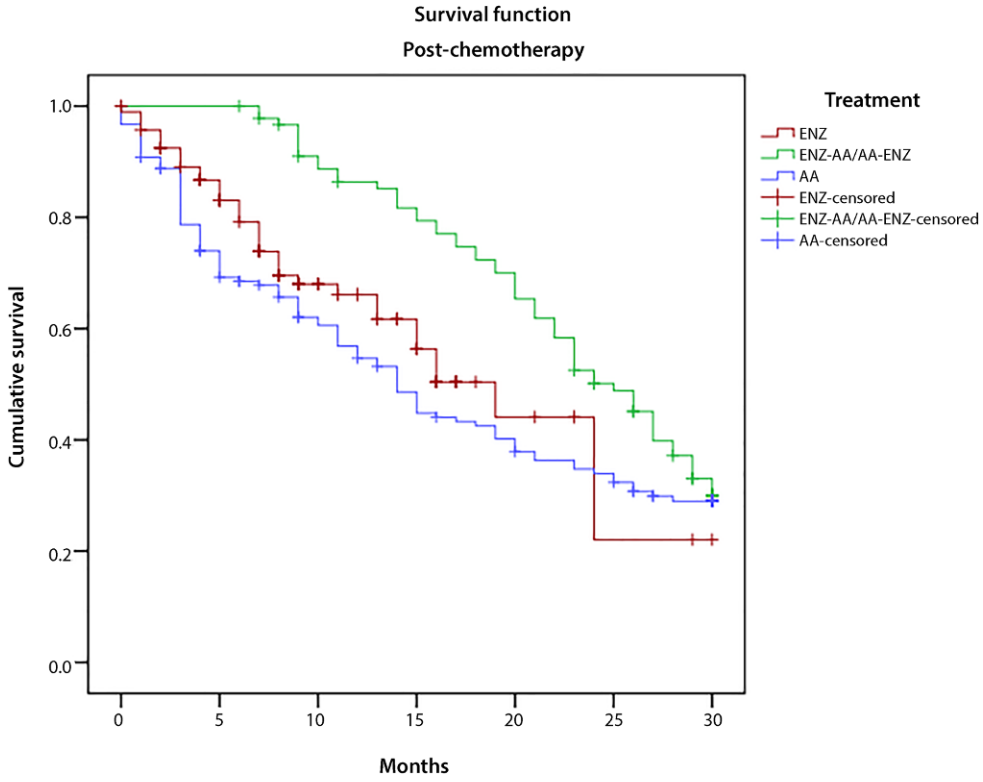

Fig. 3 Overall survival in the post-chemotherapy setting depending on treatment strategy

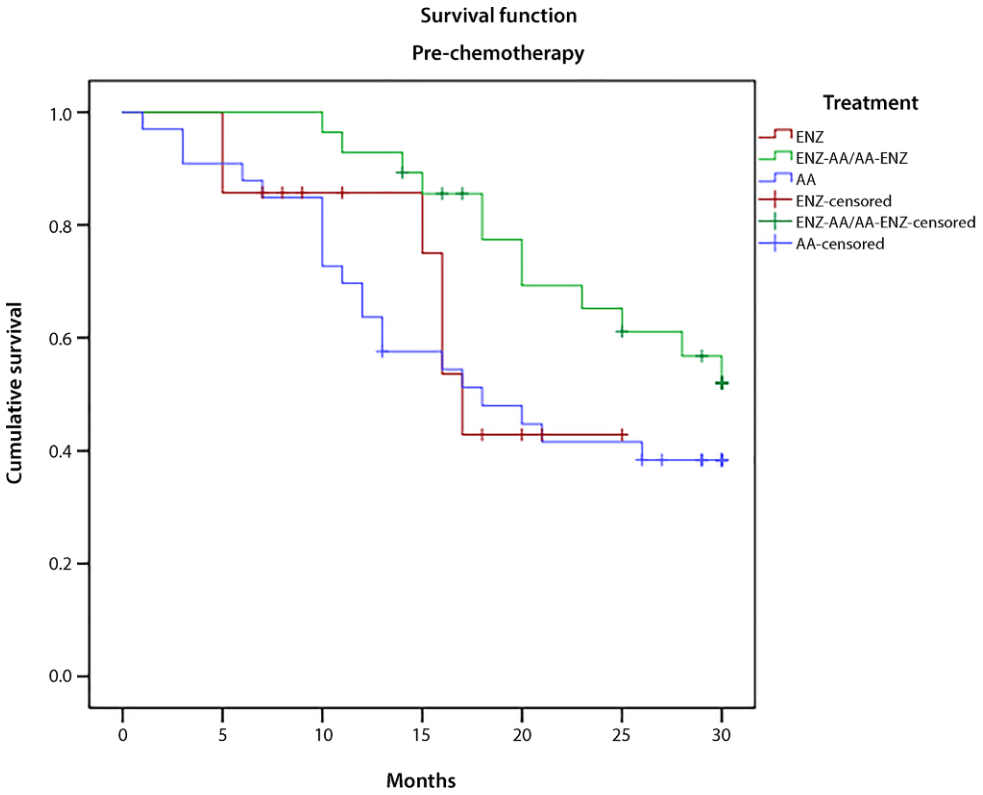

Fig. 4 Overall survival in the pre-chemotherapy setting depending on treatment strategy

treatment group and 66.5 ± 59.5 days in the sequence treatment group.

Discussion

In this study we report (i) a high adherence to AA and ENZ monotherapy as well as their sequence, (ii) lower OS under AA and ENZ in comparison to the pivotal registry trials and (ii) a high rate of hospitalization. The pros and cons of this methodological approach (analysis of a medical claims database) have already been described in detail in our previous paper and are therefore not detailed here [7]. A limitation of this study is the retrospective character, which among other things leads to missing data on comorbidities, admission diagnoses, and other influencing variables. Moreover, to evaluate the survival of each drug without sequence, there were unfortunately fewer patients in the ENZ to AA sequence group.

Adherence to medical treatment is a complex and multifaceted process that can substantially alter the outcome of therapy [11–15]. There are no studies available on the adherence to ENZ or a sequence strategy of AA and ENZ outside clinical trials, but only few for AA. Smith et al. [9] analyzed pharmacy claims of the Canadian Saskatchewan Cancer Agency. All patients with at least one AA prescription were eligible and a total of 86 patients were followed for a minimum of 6 months. Optimal drug adherence was achieved in 82.6% of patients with 79.1% reaching an MPR of at least 90%. At 6 months, the mean MPR was 89.6% (median 100%) and after 12 months 86.6% (median 99.5%). Lafeuille et al. [10] studied this issue by analysing two large-scale US administrative health care claims databases. The mean age of the patients was 72.2 years and the mean MPR was 93% (median 98%). The mean MPR in our series was 94.8 ± 11.9 (median 100%) with no relevant impact of patient age. Herein the mean MPR was highest for AA, followed by the sequence therapy and ENZ but in all three arms >75%. Taken together, the three studies mentioned above and the current one with more than 1,000 patients indicate that the adherence to AA and ENZ in a real-life setting is satisfactory. The reason for the different adherence rates between AA and ENZ seen in our series remains unclear.

As already indicated, there are major concerns that survival data generated by pivotal trials or registries do not reflect the real-life setting [3, 16–20]. Ryan et al. [3] published a double-blind, placebo-controlled study of 1.088 patients treated with AA in the pre-chemotherapy setting with a mean OS of 27.2 months. In our analysis the OS of patients with AA in the pre-chemotherapy setting was substantially shorter (mean OS 18.9 ± 1.5 months). Beer et al. (PREVAIL trial) [5] reported on the registry trial for ENZ in the pre-chemotherapy setting and the median OS was 32.4 months in the ENZ group. In our study survival in the ENZ pre-chemotherapy setting was substantially shorter (17 months). In the post-chemotherapeutic setting de Bono et al. [21] reported a median survival of 14.8 months and Fizazi et al. [4] reported a median survival of 15.8 months under AA. In our study median OS was 14 months in the group treated with AA after chemotherapy. For ENZ in the post-chemotherapy setting Scher et al. (AFFIRM trial) [2] reported a median OS of 18.4 months, comparable to the median OS of 19 months in our series.

The pathomechanisms behind the shorter OS in real life as compared to phase III trials are most likely multifactorial. These data suggest that patient selection in real life is substantially less stringent than in a phase III trial. In our study age of patients was important, OS decreased with increased age of patients. In comparison to the phase III trials, patient age seemed to be slightly higher in all groups in our study. Mean age and range in our study: pre-chemotherapy AA 73.0 ± 12.2 years (range 44–92 years), post-chemotherapy AA 74.6 ± 8.8 years (range 37–91 years), pre-chemotherapy ENZ 76.1 ± 8.3 years, post-chemotherapy ENZ 74.7 ± 8.9 years; median age in phase III trials: pre-chemotherapy AA 71.0 years (range 44–95 years) [3], post-chemotherapy AA 69 (42–95) [4] pre-chemotherapy ENZ 72 (43–93) [5], post-chemotherapy 69 (41–92) [2].

The third aspect of this study was to analyze hospital admissions and length of hospitalization after initiation of AA, ENZ and the sequence therapy. In the Austrian health care system, patients spent a considerable time of their remaining life in hospital care. Only 43 (9.4%) patients were not hospitalized under AA or ENZ; however, these data have to be interpreted in the context of the Austrian health care system, where admission to hospital care is liberal and free of charge to the patient. Furthermore, there is no incentive to dismiss patients as early as possible.

The optimal sequence of anticancer drugs for CRPC is not yet known. No anticancer drug for CRPC has proven superior to another as first-line treatment, and the exact impact of prior treatment on drug effectiveness is unknown. Better biomarkers for treatment selection and evaluation of response to treatment will be needed to personalize the optimal sequence for each individual patient.

Conclusion

The analysis of an Austrian prescription database provides some insights in the outcome of patients treated with AA, ENZ and sequence therapy for CRPC in a real-life setting. Drug adherence was satisfactory and OS shorter as compared to the pivotal phase III trials. The hospitalization rate within this cohort was substantial.

Conflict of interest B.M. Al-Ali, K. Eredics, S. Madersbacher, and I. Schauer declare that they have no competing interests.

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