Research Article

Real World Patterns of PSA Response and Survival with Abiraterone and Enzalutamide in Metastatic Castrate Resistant Prostate Cancer (mCRPC)

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ABSTRACT

Background: We investigated our institution’s mCRPC enzalutamide or abiraterone patients examining PSA responses and impact of sequencing of these drugs.

Methods: All enzalutamide / abiraterone mCRPC patients (2011-2018) were included. Rates of PSA >50% response (PSA50) were compared. Time to treatment failure (TTF) and overall survival (OS) was analysed as per lines of previous therapy and timing of chemotherapy.

Results: 363 patients included (Enza n=236, Abi n=127), with 15.6 months median follow up. PSA50 was greater in enzalutamide group (58% vs 31% p<0.0005) but TTF was similar for both groups (median Abi 4.2m vs Enza 6m, p=0.965). There was no significant median OS difference between the groups (Enza 13.8m vs Abi 12.5m p=0.065). Number of lines of prior therapy (p=0.735) or timing of chemotherapy before or after Abi/Enza (p=0.21) had no significant OS impact.

Conclusion: Enzalutamide showed higher PSA50 response than abiraterone. Previous lines of therapy or sequencing of chemotherapy with abiraterone / enzalutamide showed no significant survival differences indicating no detriment in either treatment sequence.

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Introduction

There are approximately 11,500 prostate cancer-related deaths every year in the United Kingdom (UK) [1]. The majority of these are due to metastatic disease. After initial androgen deprivation therapy (ADT), metastatic castrate resistant prostate cancer (mCRPC) is defined as progression of prostate cancer despite castrate (less than 50ng/L) levels of testosterone. Novel androgen receptor targeted agents (ARTA) including abiraterone and enzalutamide are in widespread use in mCRPC. Abiraterone- given alongside prednisolone (here onwards called abiraterone or Abi) is an androgen biosynthesis inhibitor of CYP17A1- a key enzyme in extra-testicular and testicular androgen
formation [2]. Enzalutamide (here onwards called Enza) is an androgen-receptor-signalling inhibitor that inhibits androgen receptor translocation, DNA binding and coactivator recruitment [3].

Both these ARTA drugs are in widespread clinical use in the treatment of mCRPC based on several trials demonstrating overall (OS) and progression free survival (PFS) advantage in patients previously treated with docetaxel chemotherapy and pre-chemotherapy groups respectively [4-8]. Chopra et al. indirectly compared abiraterone and enzalutamide using Bayesian modelling from these main trial results (listed above) showing better prostate-specific antigen (PSA) response and PFS for Enza but no OS difference [9]. There have been no randomised published head to head clinical studies comparing the efficacy and toxicity of both Abi and Enza drugs in the pre and post chemotherapy setting. As such there are no indications or guidelines for choosing between one from the other. We also have limited data suggesting superior sequencing of ARTA, chemotherapy and novel agents [10, 11]. George et al. looked at OS and economic burden comparing abiraterone and enzalutamide in 3174 chemo-naive mCRPC patients. This showed similar median OS (Enza 29m and Abi 26m) with reduced overall health care costs for the enzalutamide group [12]. In this study we aim to look at our population of mCRPC patients treated with abiraterone or enzalutamide and examine the impact of the sequencing of either ARTA therapy on the patients’ clinical outcomes.

Materials and Methods

I Study Design and Population

We have collected single institution retrospective data from our ARIA systemic anti-cancer prescribing system for all patients treated at the Royal Cornwall Hospital Oncology centre with either abiraterone or enzalutamide for mCRPC from September 2011 to October 2017. Exclusion criteria were patients treated with abiraterone or enzalutamide in the hormone sensitive metastatic prostate cancer setting in clinical trials. The study had full trust approval- Trust ID 520.

II Data Collection

Patient characteristics were collected including age, number of previous lines of treatment, diagnosis date, Gleason Grade, PSA at treatment initiation, PSA at 4 weeks on treatment, PSA nadir count, treatment cessation date and survival. Patients were excluded if they received Abi or Enza in the metastatic hormone sensitive prostate cancer (mHSPC) setting.

Table 1: Baseline characteristics for Abiraterone and Enzalutamide patients.

|                      | Enzalutamide | Abiraterone | p values |
|----------------------|--------------|-------------|----------|
| Number               | 236          | 127         |          |
| Median age (range) Years | 76 (57 - 93) | 76 (52 - 89) | p = 0.310 |
| Gleason prognostic group distribution: | | | |
| 1                    | 6%           | 8%          | p = 0.576 |
| 2                    | 6%           | 6%          | p = 0.994 |
| 3                    | 8%           | 4%          | p = 0.136 |
| 4                    | 12%          | 6%          | p = 0.075 |
| 5                    | 21%          | 14%         | p = 0.091 |
| Not recorded         | 47%          | 62%         | p = 0.007 |

III Outcome Measures

i Primary Outcome

A. PSA response to treatment- any PSA response (PSAr) and >50% PSA reduction from baseline (PSA50).
B. Overall survival (OS)

a. From time of initiation of ARTA treatment.
b. From time of initial prostate cancer diagnosis and the OS impact of ARTA given pre or post docetaxel chemotherapy.
c. Impact of how many previous lines of therapy before ARTA therapy affected OS.

ii Secondary Outcomes

A. Time to clinical treatment failure (TTF)- defined as the time treatment was stopped by clinician.
B. Time to biochemical failure (TBF)- defined as PSA 25% above nadir count or +2ng/L.

IV Statistical Analysis

For normally distributed data continuous outcomes were presented as means or medians and standard deviations, categorical data were presented as frequencies and proportions. Kaplan Meier and Log-Rank analysis of overall survival and time to treatment failure were performed. Chi-squared testing was performed on the rates of PSA response between the groups and proportions of patients receiving treatment for more than 6 months- significance value was set at p<0.05. Waterfall plots for the individual drugs pre and post chemotherapy use with PSA levels were also performed. Data were analysed with IBM SPSS statistics version 254.0 and R-statistics packages.

Results

In total 363 patients (Enza n=236, Abi n=127) were included with a median follow-up of 15.6 months. Patient characteristics are summarised in (Table 1). Median starting PSA was not significantly different between groups: Abi group 81 ng/L vs Enza group 59 ng/L (p=0.06). Biopsies had not been taken in a significant proportion of patients in both groups: 47% in Enza vs 62% in Abi group.
Patients were heavily pre-treated, with 67% of Enza and 63% of Abi patients having had 3 or more lines of previous therapy. The majority of patients were docetaxel naïve: 79% in Enza and 89% in Abi group.

I PSA Responses

Significantly more PSA responses were seen in the Enza group compared to Abi with PSA50 = 58% Enza vs 31% Abi (p<0.0005). PSAr, again, was more likely in the Enza group (Enza 81% vs Abi 56%- p<0.0005). Maximum PSA changes from ARTA starting level are displayed in the waterfall charts below (Figure 1). PSA responses were higher in the pre compared to post-chemotherapy group which is in line with the previously mentioned COU PREVAIL and AFFIRM studies (Table 2) [5-8].

Table 2: Summary of PSA responses Abiraterone and Enzalutamide groups.

|                        | Enza (n=236) | Abi (n=127) | p-value |
|------------------------|--------------|-------------|---------|
| Proportion with PSA response (any) | 80.1%        | 56.7%       | P < 0.001 |
| Proportion with PSA response >50% | 58.5%        | 30.9%       | P < 0.001 |
| Pre-Docetaxel          | 185          | 90          | P = 0.111  |
| PSA response           |              |             |         |
| Any                    | 152          | 52          | P < 0.001 |
| PSA50                  | 111          | 32          | P < 0.001 |
| Post-Docetaxel         | 51           | 37          | P = 0.111  |
| PSA response           |              |             |         |
| Any                    | 37           | 20          | P = 0.073 |
| PSA50                  | 26           | 7           | P = 0.002 |

![Figure 1: Waterfall chart showing maximal PSA change from baseline in Abiraterone and Enzalutamide groups.](image)

II Survival Results

There was no significant difference in median OS from the start of ARTA treatment between the two drug groups: Enza 13.8m vs Abi 12.5m, (p=0.065) (Figure 2). When comparing survival vs death by different treatments there were more Enza patients alive vs Abi patients (23% vs 8%) p<0.0001.
III Effect of Line of Therapy
The line of mCRPC treatment that ARTA therapy was started on did not influence OS when assessed from date of prostate cancer diagnosis. Median OS of 85m - <3 lines, 90m – 3 lines or 77m for >3 lines of prior therapy (p=0.735) (Figure 3).

IV Sequencing of ARTA with Chemotherapy and OS
In our patients who received chemotherapy (n= 146) there was no significant difference in OS from date of their cancer diagnosis whether the ARTA was given before chemotherapy median OS 85.0 months (95% CI 64.4-105.7m) vs ARTA given after chemotherapy 75.8months (95% CI 66.0 – 85.6) (p=0.21) (Figure 4).
Analysis of OS from diagnosis date looking at the complete patient group (including those patients who did not receive chemotherapy) shows that patients median OS for the group without any prior chemotherapy was higher than those who had prior chemotherapy (p=0.043).

V Treatment Failure Results

There was no significant difference seen in time to clinical treatment failure: Abi 4.2 months vs Enza 6 months (p=0.204) or time to biochemical failure: Abi 3.5 months vs Enza 4.4 months (p=0.965). The clinical treatment failure times were similar for the chemotherapy naïve (Abi 10 months vs Enza 8 months, p=0.60) and post chemotherapy groups (Abi 6 months vs Enza 5 months, p=0.191).

Discussion

In this study we have showed better PSA responses in the enzalutamide group in all settings, but this has not led to significant differences in OS, time to biochemical or clinical treatment failure. The higher PSA responses for enzalutamide are in keeping with findings from previous comparisons of studies by Chopra et al. as discussed earlier and this is now confirmed in our real-world data [9].

In our cohort we had a high proportion of patients without a biopsy which makes it difficult for comparison of Gleason grading between treatment groups. Many patients had been heavily pre-treated with two-thirds having had three or more lines of previous therapy. This may have some impact on subsequent time to treatment failure but the sequencing of treatment with ARTA did not impact on overall survival from cancer diagnosis in the mCRPC setting in our cohort.

A large proportion of patients were given ARTA pre-chemotherapy. This may change over time with increased early docetaxel chemotherapy being used in mHSPC as per the CHAARTED and STAMPEDE study results [13, 14]. Our results demonstrated no detriment to receiving ARTA before chemotherapy as OS was similar in both pre-and-post docetaxel populations. This could be subject to selection bias as patients with higher risk disease or greater symptom burden may have been started on docetaxel earlier in their pathway. It does suggest that patients having ARTA therapy before chemotherapy are not being disadvantaged.

The position of Abi and Enza in the sequence of mCRPC may change with the LATITUDE, STAMPEDE and ENZAMET study results showing benefits similar to chemotherapy in the mHSPC setting [13-16]. This may move the decision to use these drugs in metastatic prostate cancer earlier in the treatment pathway and indeed into the non-metastatic castrate resistant setting: EMBARK, PROSPER, IMAAGEN trials [17-19]. Quality of life in mCRPC is a key factor in treatment selection and selecting the correct treatment for the patient at the correct point in their cancer journey can have a marked impact on their quality of life [20, 21].

I Limitations

This is a retrospective dataset and as such do not have data on significant prognostic markers such as bone pain or quality of life data. We have a significant proportion of patients without a biopsy and hence no Gleason grade. Despite these limitations we feel this is a significant real-world population of mCRPC patients with good PSA and clinical follow up.
II Learning Points

We have shown that clinician choice of drug for a patient with mCRPC does not have a negative impact on OS. Delaying the use of chemotherapy in mCRPC patients may improve patient quality of life and our data would support ARTA use before chemotherapy.

Conclusion

This study showed greater PSA response rates for enzalutamide compared to abiraterone. We saw no major difference in OS when ARTA was started before or after chemotherapy or with number of lines of prior therapy with again no evidence of treatment sequence affecting OS outcome in mCRPC. This indicated it may be reasonable to use ARTA therapy before chemotherapy in the patient’s treatment sequence.

Disclaimer

None.

Conflicts of Interest

John McGrane has received travel and speaking honoraria from Astellas and speaking honoraria from Janssen-Cilag, Deborah Victor has received travel honorarium from Astellas, Michael Rowe has received a travel honorarium from Astellas, Mina Georgieva, Gilberto Lopes, Chong Ming Yeo, Souhi Lebdai, Victor Basset, Julien Blanchereau, Alexandre de La Taille, Vincent Flamand et al (2016) What do we know about treatment sequencing of abiraterone, enzalutamide and chemotherapy in metastatic castration-resistant prostate cancer? World J Urol 34: 617-624. [Crossref]

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