Re: Treatment outcomes for patients with metastatic castrate-resistant prostate cancer following docetaxel for hormone sensitive disease.

On behalf of my co-authors, thank you for the opportunity to present this manuscript for review in APJCO.

We look forward to your review.

Declarations

Ethics approval and consent to participate

Multisite ethical approval for ePAD was provided by the Royal Melbourne Human Research Ethics Committee on 01/05/2018, prior to commencement of data collection, including a waiver of the requirement for individual patient consent given the retrospective, non-interventional and de-identified nature of the research and the patient group (advanced cancer) HREC/15/MH/352. The study was conducted in accordance with the National Health and Medical Research Council's (NHMRC, Australia) National Statement on Ethical Conduct in Human Research (2007) and was carried out according to the principles of the Declaration of Helsinki.

Consent for publication

The preliminary data has been presented in poster format at American Society of Clinical Oncology meeting, February 15, 2020.

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Availability of data and material

The datasets will be made available from the corresponding author on reasonable request.

Competing interests

Nil

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Nil

Authors' contributions

All authors have contributed significantly to the study conduct and preparation of this manuscript. The study was conceived and designed by AS and AW. Data was acquired and analysed by the ePAD consortium, and interpreted by all authors. The manuscript was drafted by AS and AW and reviewed by and approved by all authors.

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Treatment outcomes for patients with metastatic castrate-resistant prostate cancer following docetaxel for hormone sensitive disease.

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Abstract -

Aim: Optimal treatment for newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC) has evolved, with many patients deriving benefit from the addition of docetaxel to androgen deprivation therapy (D-ADT). This study sought to define the therapy used and associated activity following D-ADT.

Methods: Retrospective analysis of patients with mHSPC treated with one or more cycles of D-ADT who were identified from a prospectively maintained multisite prostate cancer database of patients treated in a community or academic centre setting in Australia. The primary endpoint of this study was first line time to treatment failure (1L TTF) for subsequent treatment of metastatic Castrate Resistant Prostate Cancer (mCRPC), with secondary endpoints of PSA reduction >50% and first line time to treatment failure (1L TTF).

Results:

93 patients received D-ADT for mHSPC, 85 (91%) had subsequent treatment for mCRPC. Median time to mCRPC (biochemical, clinical or radiographic) had been 14.8 mo (95% CI, 11.9 - 16.5). First line treatment was enzalutamide 47 patients (55%), abiraterone 23 (27%), cabazitaxel 7 (8%), docetaxel 4 (5%) and other therapies 4 (5%). Median 1L TTF was 6.3 mo (95% CI, 4.9 - 7.6), PSA>50% reduction was achieved in 32/89 patients (36%), median time from first to second line treatment was 7.3 mo (1.3 - 27.4), which did not differ significantly between treatment groups.

Conclusions: Abiraterone, enzalutamide, cabazitaxel and docetaxel all demonstrate activity following progression on D-ADT. No difference in efficacy was detected between treatment options for mCRPC. Prospective trials investigating the optimal treatment sequence for prostate cancer following progression on D-ADT needed.

Key words: androgen receptor antagonists, docetaxel, prostate cancer

Introduction

Androgen deprivation therapy (ADT) remains the backbone of therapy for metastatic prostate cancer. [1] Docetaxel was the first treatment to prolong survival for mCRPC following the phase 3 TAX327 and SWOG 9916 trials in 2004 based on superiority against mitoxantrone. [2, 3] The earlier use of docetaxel at diagnosis of mHSPC in addition to ADT, termed "chemo-hormonal" therapy, demonstrated a survival benefit for selected patients, supported by large phase three clinical trials and a subsequent meta-analysis. [4-7] A greater magnitude of benefit is demonstrated in high-risk disease, usually defined using the CHAARTED trial criteria as those harbouring high-volume disease (defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis). [4]

There is a lack of prospective data defining the activity and optimal sequencing of therapy for mCRPC after docetaxel for mHSPC. Registration trials for cabazitaxel and the androgen receptor targeted agents (ARTA) enzalutamide and abiraterone for mCRPC were performed without pre-treatment with docetaxel in the hormone sensitive setting. [8-13] In light of this, we sought to explore the activity of first-line (1L) treatment for patients with mCRPC who have received D-ADT in the hormone sensitive setting.

Methods

Selection and description of patients

Patients with mCRPC treated with one or more cycles of docetaxel for hormone sensitive disease who then developed mCRPC between May 2013 and Jun 2019 were identified from the prospectively maintained multisite mCRPC database (ePAD) of patients treated in a community and academic setting in Australia. 1L treatment, clinicopathologic and outcome data were extracted. The ePAD database does not record the volume of patient disease, so the proportion of patients receiving docetaxel for high-volume disease defined by the CHAARTED criteria is unknown. The treating clinician determined candidacy for docetaxel administration.

mCRPC was defined by PSA progression according to Prostate Cancer Clinical Trials Working Group three (PCWG3) criteria, radiographic or clinical disease progression (via investigator assessment), in the setting of ongoing ADT with a serum testosterone level of less than 50 ng/dL (1.7 nmol/L). [14]

Patients who developed mCRPC were analysed based on first line treatment received. All subsequent lines of treatment for mCRPC were recorded.

The primary endpoint of this study was first line time to treatment failure (1L TTF) defined as time from initiation of 1L treatment for mCRPC to cessation at clinician discretion for toxicity, progression, loss of clinical benefit or patient choice. Secondary endpoints were PSA reduction >50% and time from 1L to second-line (2L) treatment initiation. PSA reduction was defined as the PSA decline from the most recent pre-treatment PSA to the nadir value. Time to 2L treatment was assessed as the date of first dose of 1L treatment to date of the first dose of 2L treatment.

Multisite ethical approval for ePAD was provided by the Royal Melbourne Human Research Ethics Committee before the commencement of data collection.

Statistical analysis

Patients who were treated with at least one cycle of docetaxel in combination with ADT were included in this analysis. The data cut-off was 23 July 2019.

Categorical variables were compared between groups using Chi-square test or Fishers exact test; continuous variables were compared using Kruskal-Wallis H test (one-way ANOVA). A P-value of <0.05 was considered significant. Descriptive statistics (mean or median as indicated and 95% confidence interval) were used to summarise patient demographic data and characteristics. Statistical analyses were conducted using SPSS Statistics software ver. 26 (IBM, Armonk, NY, USA). PSA endpoints were compared to historical data from key registration trials in the pre-and-post D setting for mCRPC to contextualise PSA >50% reduction.

Results

93 patients were identified in the ePAD database as having received one or more cycles of docetaxel for mHSPC and had then progressed to develop mCRPC, of which 85 (91%) had subsequent systemic therapy for mCRPC. There was a median follow-up for all patients of 23.7 mo (range 5.5 - 82.9). Table 1 summarises the baseline characteristics of eligible patients. A majority of patients (65%) had presented with de-novo metastatic disease. Of those where Gleason score was known, 58% had

biopsy Gleason ≥ 8. The median time to ADT start from diagnosis of metastatic disease was 0.3 mo (range 0.0 - 14.4 mo), and 80 of 93 (86%) patients completed six or more cycles of docetaxel (median 6). Of 13 patients not completing 6 cycles of docetaxel, 8 stopped due to toxicity and 5 ceased for unspecified reasons.

Of 85 patients who developed mCRPC and received ≥1 line of treatment (Table 2), median time to mCRPC for the cohort was 14.8 mo (range 1.3 - 56.9, 95% CI 11.9 - 16.5) with median time to 1L treatment of 16.3 mo (range 2.1 - 57.2).

Median PSA at the time of starting first therapy for mCRPC was 32.6 ng/mL (95% CI, 17.6-47.7). Eighty-five patients (91%) received at least one further active treatment for mCRPC summarised for primary and secondary outcomes in Table 3, and treatment sequencing in Figure 1.

Most patients (70, 82%) received an ARTA with enzalutamide 47 (55%) or abiraterone 23 (27%) as their first therapy for mCRPC. One patient received a combination regimen that included abiraterone with an AKT inhibitor, and was grouped with the abiraterone group for subsequent analysis. The remaining 15 patients received cabazitaxel (n=7, 8%), docetaxel (n=4, 5%), 4 patients (5%) had other therapy, including 3 with carboplatin-based therapy and 1 receiving unspecified treatment on clinical trial. Median 1L TTF for mCRPC was 6.3 mo (95% CI, 4.9-7.6). Although numerically shortest with docetaxel at 2.4 months, this did not meet statistical significance (p = 0.059).

Choice of first therapy for mCRPC was independent of time to CRPC (p = 0.15), median PSA at the time of metastatic disease diagnosis (p = 0.61), Gleason Score (p = 0.28), prior local treatment (p = 0.45), visceral metastases (p = 0.37) or liver metastasis (p = 0.81).

All regimens demonstrated activity with PSA reduction >50%, with activity comparable to key registration trials in the pre-and-post docetaxel setting (Table 3).

For the other secondary endpoint; time from 1L to 2L treatment, results do not differ significantly based on 1L treatment assignment, with similar interval from 1L to 2L treatment; mean 7.3 mo (p = 0.88).

With regards to subsequent therapy (Figure 1), 36/85 patients (42%) went on to receive second line treatment for mCRPC, 25 (30%) third line, 6 (6%) fourth line, 4 (4%) fifth line, and 2 (2%) sixth line.

Discussion

The regulatory and Pharmaceutical Benefits Scheme reimbursement landscape in Australia allows clinician choice of taxane chemotherapy or ARTA for 1L mCRPC treatment following D-ADT. Treatments conferring a survival advantage for mCRPC include abiraterone, enzalutamide, and cabazitaxel. Docetaxel rechallenge has produced mixed results. Phase 2 evidence in the mCRPC setting revealed meaningful PSA and measurable tumour responses, but data from patients receiving D-ADT from GETUG AFU-15 (in the mHSPC setting) who received 1L docetaxel for mCRPC had a 20% rate of PSA>50% decline and short time to biochemical failure of 4.1 mo.[15,16] However, no prospective evidence exists to guide 1L choice after docetaxel is administered for mHSPC.

Limited retrospective evidence suggests ARTA have activity following D-ADT. A pooled analysis of 102 patients from 3 institutions examined the activity of abiraterone or enzalutamide based on prior receipt of D-ADT. Survival from initiation of ARTA was similar in both groups, suggesting efficacy is agnostic to the prior receipt of D-ADT [17]. Another large multi-institutional study including 136 patients performed a pooled analysis of ARTA against other therapies, demonstrating a radiographic PFS for ARTA of 9 mo, longer than 6-8 mo reported in the post-docetaxel setting but shorter than 17-20 mo observed in a chemotherapy- naïve population. [4-6] The relative activity of ARTA compared to cabazitaxel remained unclear, as few patients (n = 5) received chemotherapy, representing the minority in a pooled cohort of 17 patients (who received heterogeneous treatments including sipulucel-T and Radium 223), making comparison difficult. [18]

Given the lack of prospective evidence, clinical guidelines can provide little direction regarding the choice of therapy following D-ADT, and decisions are based on pragmatic disease and patient factors such as comorbidities (like the development of significant complications from myelosuppression or residual neuropathy from 1L treatment).[19]

Our study cohort received D-ADT at clinician discretion. The proportion of patients with high-volume disease by CHAARTED criteria is unknown, however 65% presented with de-novo metastatic disease, a validated poor prognostic factor. Time to mCRPC was similar to that of patients from D-ADT trials harbouring poor prognostic factors, defined using the CHAARTED high-volume criteria (see Table 4). [4] This retrospective study demonstrates first-line treatment with chemotherapy or ARTA provides meaningful activity for mCRPC in the post D-ADT setting. In our broad Australian population there

was greater use of ARTA compared to taxane chemotherapy, but no differential activity found for either the primary or secondary endpoints.

1L TTF was similar for all agents except docetaxel, but this did not meet statistical significance, limited by small numbers. Reasons for cessation in this small cohort of 4 patients included 2 that ceased for toxicity after 2 doses. A shorter duration on treatment could be expected given a median prior exposure to docetaxel of 6 cycles. Although patients had a median break of 10 months from completing upfront docetaxel, many adverse events are related to cumulative dose, such as peripheral neuropathy, and may not resolve on treatment cessation. The median cycles (administered sequentially for mCRPC) from TAX 327 was 9.5, but "real world" cohorts have reflected a shorter duration of treatment with a median of 7 cycles.[2,19] Concern regarding both lack of efficacy and cumulative toxicity may be factors why clinicians preferentially choose other agents as first line therapy.

PSA >50% reduction is a useful metric to compare activity of agents between trials performed in the pre-and-post docetaxel setting. [21] In this cohort, despite prior docetaxel therapy for mHSPC, PSA>50% reductions were comparable to registration trials for agents in the mCRPC space (see Table 3). As response rates typically decline with increasing lines of therapy, an intermediate PSA>50% reduction between the historical 1st and 2nd line of treatment is intuitive, as patients have received 1 line of treatment in the HSPC, but not the CRPC setting.

Time from 1L to 2L treatment was not significantly different between the cohorts. Of note, pre-treatment with D-ADT did not appear to adversely impact on receipt of further lines of treatment, with the majority of patients receiving second and subsequent lines of treatment for mCRPC, consistent with reported literature [22].

Overall survival is an objective endpoint that would validate the significance of time on treatment and response metrics, but given the relative immaturity of the database and short follow-up (median follow-up was 27.4 mo from diagnosis of metastatic disease to last review), too few events have occurred (19 deaths / 93 patients) to utilise this for a meaningful comparison. Additional follow-up will be useful to accumulate further events and allow for this at a later time point.

The use of carboplatin regimens (which constituted 3 of 4 patients in the "other" group) remains an area of significant interest, often chosen for clinically aggressive variant prostate cancer. As there is additional toxicity associated with a doublet regimen, defining those patients would be of great value in assisting clinical decisions. More work is needed to identify biomarkers of response, given that responses to carboplatin in mCRPC appear to occur independently of the presence or absence of DNA repair defects. [23]

Recent promising work by Hamid et al. utilising gene expression profiling has demonstrated the ability to subtype prostate cancer into luminal (A/B) and basal subtypes. [24] Preclinical work suggested that the luminal subtype may be more susceptible to chemotherapy relative to basal. The luminal B subtype was associated with a worse OS in the CHAARTED clinical trial, but patients gained significant benefit from the addition of docetaxel, whereas basal subtypes did not seem to benefit from the addition of docetaxel. These findings are expected to be validated in independent trial cohorts, and may lay the foundation for clinical use of gene expression profiling to direct patients to an optimal therapy.

Limitations of this study include the retrospective nature which does not permit control over biases, most notably the clinician choice of subsequent treatment for mCRPC. The absence of mature OS data secondary to short median follow-up does not allow an assessment of long-term patient impact.

Overall, this study demonstrates a range of therapy selection as 1L treatment for mCRPC in the real-world setting. All treatments demonstrated activity, and all appear reasonable choices for patients progressing following D-ADT. Future prospective studies are needed to define the optimal treatment sequence following D-ADT, including how to incorporate biomarkers of efficacy and the impact on patient-centred outcomes such as quality of life.

Table 1 Baseline Patient Characteristics

Characteristics	**N (%) Total = 93 (100%)**	
Median age (range)	65 (44 - 81)	
ECOG		
0	56 (60)	
1	28 (30)	
2	4 (4)	
unknown	5 (5)	
Gleason Score		
Unknown	29 (31)	
<=6	3 (3)	
7	7 (8)	
8	11 (12)	
9	37 (40)	
10	6 (6)	
Prior Local Therapy		
None	60 (65)	
Surgery	19 (20)	
Radiation	7 (8)	
Surgery plus radiation	5 (5)	
Unknown	2 (2)	
Median PSA at diagnosis (range)	53 ng/mL (0.67 - 7086)	
Sites of Metastasis		
Visceral	14 (15)	
Bone Only	27 (29)	
Lymph Node only	11 (12)	
Bone+ LN	36 (39)	

Unknown	5 (5)	
Time to start ADT, months	0.33 (0-14.0)	
Number of cycles of docetaxel		
<= 3	6 (6)	
4	3 (3)	
5	4 (4)	
6	77 (83)	
>6	3 (3)	
Reason for not completing 6 cycles docetaxel; 13 (14)		
Toxicity	8 (62)	
Other	5 (38)	

Table 2 Subsequent therapies for mCRPC (n = 85)

	Number of patients (%)
Median time to mCRPC, mo	14.8 mo (range 1.3 to 56.9)
Number of subsequent treatments	
1	85 (100)
2	36 (42)
3+	25 (29)
Initial PSA at time of therapy, ng/mL	32.6 ng/mL (0.289 - 487).
First Line therapy for mCRPC	
Abiraterone	23 (25)
Enzalutamide	47 (51)
Cabazitaxel	7 (8)
Docetaxel	4 (4)

Carboplatin-based	3 (3)
Other	1 (1)

Table 3: First line treatment efficacy

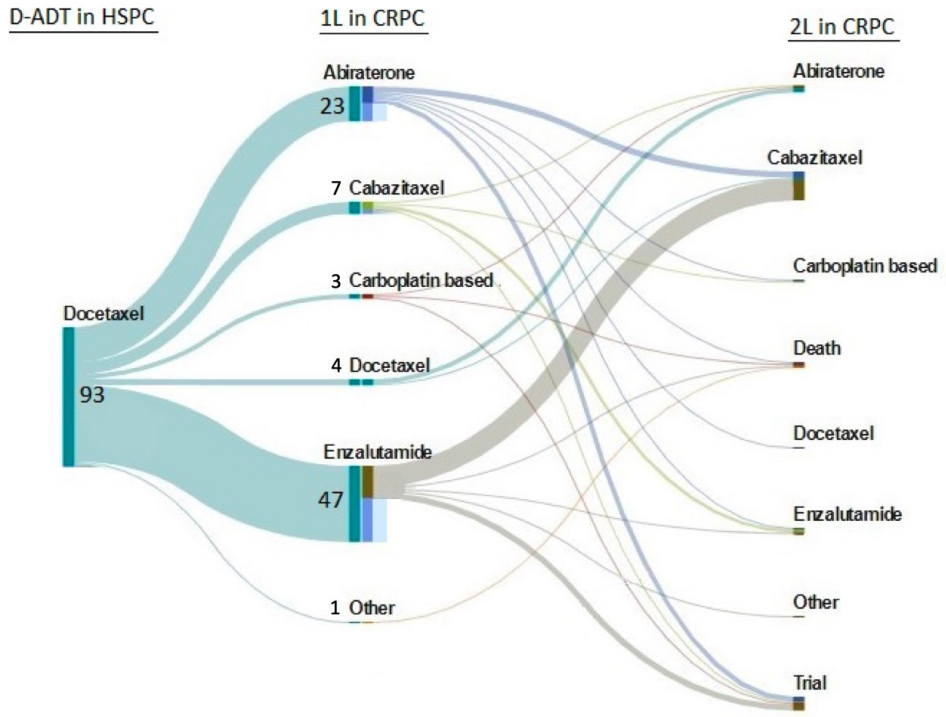
Treatment	Enzalutamide n = 47	Abiraterone n = 23	Cabazitaxel n = 7	Docetaxel n = 4	Other n = 4	
PSA prior to 1L treatment (ng/mL): mean	35.6	36.6	8.9	39.5	6.7	
median	11.5	7.1	10.7	3.3	5	
1L TTF - mo	7.3	7.2	6.0	2.4	3.3	p = 0.059
95% CI	(4.8 - 9.7)	(5.1 - 9.3)	(0 - 12.0)	(1.0 - 3.7)	(1.3 - 5.3)	
Historical pre-D 1L duration – mo	20	16.5	5.1	7.1	N/A	
Historical post-D 1L duration – mo	8.3	5.6	2.8	N/A	N/A	
PSA reduction >50%	26/41	10/19	3/7	3/4	2/4	p = 0.919
	(63%)	(53%)	(43%)	(75%)	(50%)	
Historical pre-D PSA reduction >50%	78%	62%	60%	45%	N/A	
Historical post-D PSA reduction >50%	54%	29%	39%	N/A	N/A	
Pt receiving 2L Rx	16/21	9/13	4/4	4/4	2/3	
	(76%)	(69%)	(100%)	(100%)	(67%)	
1L start to 2L start – mo 95% CI	7.0	6.9	7.7	10.1	5.4	p = 0.88
	(3.8 - 10.3_	(4.2 - 9.5)	(0.2 - 15.3)	(0 - 22.9)	(4.1 - 6.7)	

Table 4: Time to mCRPC from Key Clinical Trials

	Time to mCRPC: mo (95% CI)	
Dataset	**Total Cohort**	**High Volume / Poor Prognostic Pts**
ePAD cohort	14.8	N/A
CHAARTED	19.4 (16.8 to 22.6)	14.9 (12.4 to 17.2)
GETUG-AFU 15	22.9 (19.5 – 28.4)	15.2 (12-21.2)
STAMPEDE	36.7	26.6

*High Volume / Poor Prognosis = visceral (lung or liver) metastases and/or 4 or more bone metastases with at least 1 beyond the pelvis and the vertebral column. [4-6]

Figure 1: Treatment sequencing following D-ADT for HSPC



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Docetaxel chemotherapy in combination with androgen depravation therapy (D-ADT) is an established treatment for patients with newly diagnosed metastatic prostate cancer. The purpose of this study was to define the activity of treatments given following the failure of D-ADT. No significant differences were identified between treatment options. Prospective trials are needed to identify the optimal therapy for patients in this setting.