RESEARCH ARTICLE

Docetaxel use in castrate resistant prostate cancer, how timing of treatment and age of patients affect outcome

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ABSTRACT

Background: New therapeutic strategies have resulted in some uncertainty over the optimum scheduling of treatments in metastatic prostate cancer (MPC) and with the aging population, it is important to assess outcomes in this age group.

Methods: Patients diagnosed with MPC and treated with docetaxel from 2006 to 2016 were identified and their records retrospectively reviewed via electronic clinical and prescribing systems. Number of treatments received pre and post docetaxel, prostate specific antigen (PSA) response, number of cycles and dosing of docetaxel and castrate resistant overall survival (OS) were analysed.

Results: 209 consecutive patients with MPC receiving docetaxel were categorised according to age; younger than 75 years old (n=150), 75-79 years (n=40) and 80 years or over (n=19). Excluding early docetaxel, mean survival times younger to older were 1001, 1045 and 1294 days and PSA response rates were 39%, 38% and 42%. The oldest group received fewer docetaxel cycles (3.8, p=0.006) and less dose (226mg/m2, p=0.004) compared with less than 75 years (5.8 cycles, 409mg/m2) and 75-79 years (5.1 cycles, 341mg/m2). 168 consecutive patients received second line and beyond docetaxel. 48 patients (29%) received docetaxel after 1 or 2 treatments, 105 (63%) after 3 or 4 treatments and 15 (9%) after 5 or 6. PSA response rates were superior in the earliest treated group (61%, p=0.003), compared with 30% and 31% respectively. Median OS was 29 months, 35 months and 42 months earlier to later, not significantly different (p=0.1).

Conclusions: In these MPC patients in routine clinical practice, the 80 years plus age group

received fewer cycles of docetaxel and less dose, but achieved similar PSA responses. In patients who do not receive initial docetaxel, PSA response rates were significantly improved with subsequent earlier use. OS was not significantly different according to age, nor between early and later docetaxel treated patients.

1. Background: Prostate cancer is the most common male cancer in the UK, with more than 47,000 new cases per year in 2015, with over 11,600 deaths from prostate cancer in 2016.[1] Metastatic prostate cancer (MPC) treatment first started with castration, surgical or medical with use of oral oestrogen (stilbestrol) in the 1940s to block the androgens driving the disease.[2] 'Medical Castration' is still the mainstay of treatment today, with luteinising hormone releasing hormone analogues or antagonists (LHRHa) and anti-androgens such as bicalutamide able to maintain disease control for many years in many patients. However, most patients become 'castrate resistant' at some point and need additional anti-cancer treatments to regain disease control.

Docetaxel chemotherapy use can significantly prolong overall survival in metastatic prostate cancer. The TAX 327 study demonstrated a three-month median survival improvement when used with prednisolone, compared with mitoxantrone and prednisolone.[3]

Docetaxel is now an important part of MPC treatment. However, with the advent of other life-extending therapies such as enzalutamide, abiraterone, cabazitaxel and radium-223, [4-7] more information is needed to ascertain when docetaxel is best used, with limited evidence to guide their optimal sequencing. In the UK in 2013-2015, on average each year more than a third (35%) of new prostate cancer cases were in males aged 75 and over. The highest incidence rate is in the over 90yrs and the overall incidence rate has risen by 44% since the 1990s.[1] This increasing incidence rise of prostate cancer in older patients highlights an important population in which to review use of potentially effective, but also potentially toxic docetaxel chemotherapy.[1]

1.1 Docetaxel- Timing of Use: Docetaxel was initially used following castrate resistance. In the group receiving it every three weeks in the TAX 327 trial, it was employed after initial androgen deprivation therapy (ADT), with 68% of patients having received two previous treatments and 23% more than two.[3]

Studies involving earlier use of docetaxel chemotherapy include CHAARTED and STAMPEDE.[8,9] These demonstrated front line use of docetaxel with initial ADT at the time of diagnosis of MPC results in a longer median overall survival gain of between 10 and 13.6 months versus patients receiving no early chemotherapy and waiting for castrate resistance.

The international retrospective CATS database reviewed sequencing of treatment in patients who received all three of docetaxel, cabazitaxel and at least one new androgen-targeted therapy (ARTA- abiraterone or enzalutamide). Docetaxel

administered before ARTA resulted in superior PSA response rates.[10]

LHRHa and antiantidrogens are typically used as initial therapy in MPC to induce castrate levels of testosterone. There is evidence demonstrating a survival gain in MPC supporting use of new androgen-targeted therapies (abiraterone/enzalutamide), radium-223 for bony metastatic disease and cabazitaxel chemotherapy. Other treatments include low dose dexamethasone as per National Institute of Clinical Health and Excellence (NICE) recommendation; mitoxantrone chemotherapy to improve pain and diethylstilbestrol can also be used for treating select patients after approved life extending therapies have been given.[11-13] However, there is limited information on the sequencing of docetaxel. In the UK NICE does not provide specific guidelines on the order in which these treatments should be given, recommending docetaxel use after development of castrate resistant prostate cancer.[11] NHS England in a Commissioning Policy Statement supports docetaxel use with ADT for the treatment of hormone naïve metastatic prostate cancer.[14] Cabazitaxel is recommended by NICE in patients with hormone-relapsed prostate cancer in whom the disease has progressed during or after docetaxel chemotherapy.[11]

Patients might not initially receive chemotherapy, perhaps through patient choice or impaired performance status, later becoming suitable for docetaxel. In these patients there is limited information on sequencing and treatment outcomes for later docetaxel use in routine clinical practice. There is also significant uncertainty in the optimum scheduling of docetaxel with other therapies. For example the CATS database only considers patients who have received docetaxel and cabazitaxel, and does not consider other treatment options such as radium-223.

1.2 Docetaxel- Use in Older Patients: The median age at diagnosis of prostate cancer is 66 years, but the incidence rates rise rapidly with age. It is the third most common cause of cancer death in men over 80 years with 41% of men dying from prostate cancer being between 75-84 years and 30% for men over 85 years.[15]

The International Society of Geriatric Oncology guidelines on the management of prostate cancer recommend basing treatment for men over 70 years according to individual health status and not by age,[16] which is also true of the NICE guidelines.[11] There is however limited information on the treatment tolerance of docetaxel chemotherapy and outcomes in elderly patients in routine clinical practice.

A French retrospective study reviewed 175 patients aged 75 years and over receiving first line docetaxel chemotherapy and concluded docetaxel is active and feasible in elderly patients with a good performance status but did not compare to other age groups.[17]

Older patients were included in recent docetaxel studies. For example, the CHAARTED study did not exclude patients based on age, rather selecting patients with a good performance status of 0-2.[8] The age range in CHAARTED was 36-91 years with a median of 63 years. STAMPEDE had the

same performance status selection criteria with an age range of 40-84 years and median 65 years.[9] From the TAX327 study the OS benefit for patients over 75 years was similar to that for younger patients. The average age of patients was 68yrs, the HRs for younger and older patients were 0.81 and 0.77, respectively, and 0.80 for over 75 years.

There is, however, limited information on treatment tolerance and outcomes in patients 80 years old and over as well as sequencing of MPC treatments in routine clinical practice.

In research presented here we aimed to fill gaps in current research around the timeliness of docetaxel therapy and compare outcomes in the non-up front docetaxel group of patients who later received it, in relation to the treatment point at which it was delivered. We also aimed to compare outcomes in the non-upfront docetaxel group of patients who later received it in relation to specific age groups- younger than 75 years, 75-79 years and 80 years and over to try and guide management in routine practice.

2. Methods: Patients diagnosed with MPC and treated with docetaxel from 01/01/06 to 24/11/16 at Royal Cornwall Hospital, UK, were identified and their records retrospectively reviewed via electronic clinical and prescribing systems. Patients were excluded if they had chemotherapy with their initial ADT.

Information was gathered including patient age at the start of docetaxel chemotherapy and the number of individual treatments received pre- and post-docetaxel. Note that LHRH agonists and anti-androgens such as bicalutamide were typically used sequentially and considered to be two different treatments and androgen withdrawal was not considered a separate treatment. However, individual treatments included other hormonal agents such as enzalutamide, abiraterone with prednisolone and diethylstilboestrol. Single agent steroids were also considered an individual treatment, as were the chemotherapy agents docetaxel, cabazitaxel and mitoxantrone. Radium-223 was also included as a separate treatment. Castrate resistance was defined as an increase in prostate specific antigen (PSA) of 25% or more and an absolute increase of 2ng/ml or more from the nadir, confirmed by a second PSA test, whilst receiving LHRHa or after bilateral orchidectomy.[18]

Patient outcomes were analysed in terms of PSA response (signified by a PSA reduction of 50% or more); the mean number of cycles and dose per course of docetaxel received; Gleason Grade; time from diagnosis to receiving docetaxel; and castrate resistant overall survival (OS). The resulting database containing these patient outcomes was analysed using Microsoft Excel and the mathematical package R (https://www.r-project.org).

3. Results: In all, there were 213 patient records in our database. Of these, three were discounted through having insufficient data whilst another patient was removed due to a lack of clarity around treatment response. Within the remaining 209, 41 received "early" treatments and were discounted.

Timing

The remaining 168 consecutive patients with MCRPC receiving docetaxel were reviewed. There were 48 patients (29%) who received docetaxel after one or two previous treatments, 105 (63%) after three or four previous treatments and 15 (9%) after five or six. There were no patients who received seven or more individual therapies.

Age

Within the 168 patients, three patient age bands were identified;

- younger than 75 years old
  - n=112, (150 less 38 early docetaxel excluded)
- 75-79 years
  - n=37, (40 less 3 early docetaxel excluded)
- 80 years or over
  - n=19, (no early docetaxel exclusions)

3.1 Overall Survival (OS): When comparing mean OS, respective mean survival times for each of the three age groups excluding patients receiving early docetaxel treatment, younger to older were 1001, 1045 and 1294 days (Table 1), with between class difference being insignificant.

Table 1. Average OS post castrate resistance split by age

	Patients	Average survival (days)	
ALL	**209**	**980**	
Age < 75	150	918	(reference)
Age 75 – 79	40	1033	p = 0.33
Age 80 +	19	1294	p = 0.02
Late	**168**	**1045**	
Age < 75	112	1001	(reference)
Age 75 – 79	37	1045	p = 0.73
Age 80 +	19	1294	p = 0.07
Grand Total	**209**	**980**	

Average OS from castrate resistance increased with the number of previous treatments, being 1292 days for the group receiving five or six previous treatments (Table 2). Although average OS from castrate resistance for the earlier treated group (those treated with docetaxel following one or two alternative treatments) was the shortest at 29 months, this was not significantly less (p=0.10) than the intermediate group (following three or four alternative treatments), the reference group.

Table 2. Average OS post castrate resistance split by previous treatments and patient age

Previous Treatments	Patients	Average survival (days)	
1 or 2	**48**	**884**	**p = 0.10**
Age < 75	35	873	
Age 75 – 79	8	858	
Age 80 +	5	985	
3 or 4	**105**	**1076**	**(reference)**
Age < 75	70	1041	
Age 75 – 79	27	1064	
Age 80 +	8	1416	
5 or 6	**15**	**1292**	**p = 0.22**
Age < 75	7	1192	
Age 75 – 79	2	1355	
Age 80 +	6	1388	
Grand Total	**168**	**1045**	

The rate of survival for the 168 patients is demonstrated graphically in Figure 1. By inspection, rates of survival up to 1400 days post castrate resistance are stronger in the later treated groups than among patients receiving one or two previous treatments.

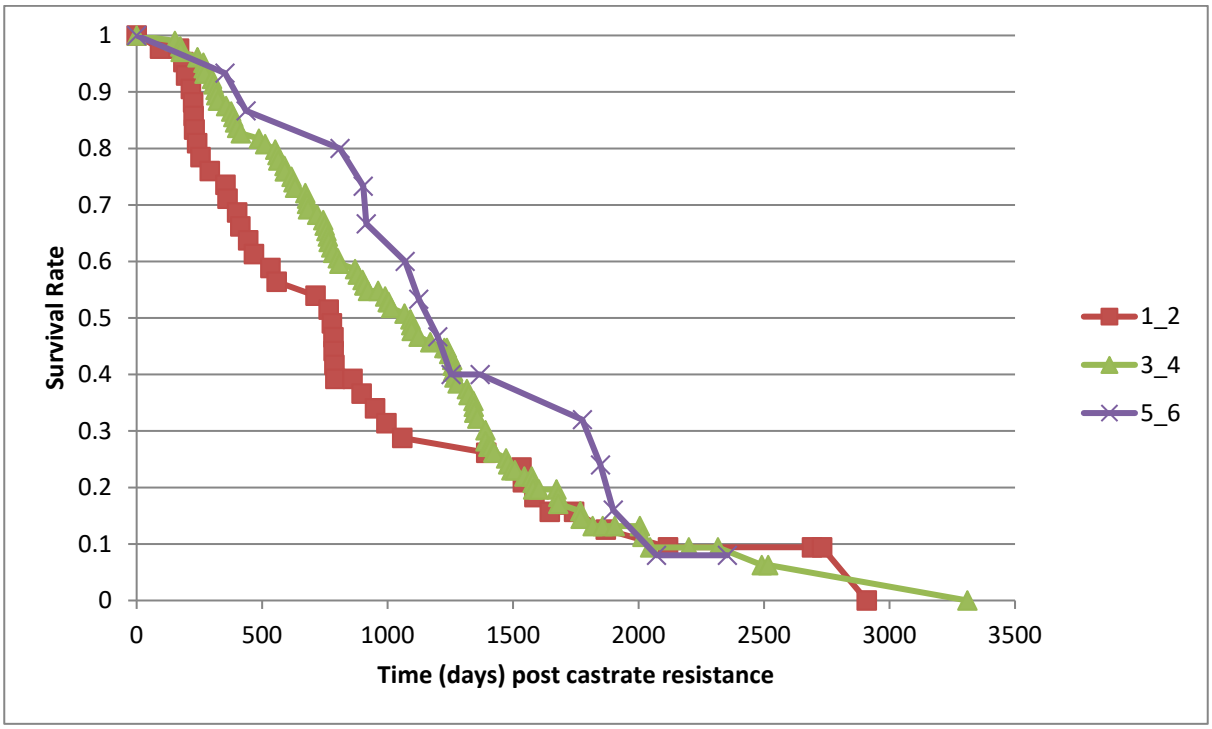

Figure 1 Rates of overall survival for prostate cancer patients split by the number of previous treatments

3.2 Docetaxel treatment cycles and dose size: The overall median number of docetaxel cycles received was 5.5, with more cycles given on average to younger patients (Table 3). The average number of cycles administered to the group of oldest patients was 3.8, significantly less than given to the youngest cohort, the reference category (p=0.01). No statistically significant difference in the cycles existed for patients aged 75 – 79 years versus the reference group.

Table 3. The average number of docetaxel cycles given to the patients split by age and the number of previous alternative treatments

	Patients	**Average Cycles**	
Age < 75	**112**	**5.8**	**(reference)**
Previous treatments			
1 or 2	35	5.9	
3 or 4	70	5.9	
5 or 6	7	5.4	
Age 75 – 79	**37**	**5.1**	**p = 0.15**
Previous treatments			
1 or 2	8	5.6	
3 or 4	27	4.8	
5 or 6	2	6.5	
Age 80 +	**19**	**3.8**	**p = 0.01**
Previous treatments			
1 or 2	5	4.2	
3 or 4	8	4.0	
5 or 6	6	3.3	
Grand Total	**168**	**5.4**	

The group of oldest patients received less dose per course (226mg/m^2, p=0.004) than the youngest group (5.8 cycles, 409mg/m^2) and the intermediate group (5.1 cycles, 341mg/m^2).

To complement their docetaxel, 48 patients (29%) received cabazitaxel as part of their post docetaxel therapy and 25 (15%) received radium-223.

3.3 Gleason Grade: There did not appear to be a significant difference in Gleason Grade between age groups but a trend towards a higher grade in the younger age group. Gleason Grade averaged 8.3 in the youngest age group, 8.3 in the intermediate group and 7.3 for those aged 80 years and above. Gleason Grade averaged 8.0, 7.8 and 8.3, across the three sub-groups defined by the number of previous treatments, earlier- to later-treated respectively.

3.4 Time to Castrate Resistance: The time from diagnosis to castrate resistance was not significantly different according to

previous treatments, averaging 710 days among patients receiving one or two previous treatments; 805 days in patients receiving three or four; and 638 days for patients receiving five or six. Pain and sites of metastatic disease could have acted as confounders, for which we did not have relevant data.[3]

3.5 Dose size and PSA Response: The group treated earliest with docetaxel received a greater mean weighted dose overall and a statistically superior PSA response rate of 61% (p=0.003), compared to the remainder of the cohort. PSA response rates per age group did not show a significant difference at 39% in the youngest group, 38% in the intermediate age group and 42% for the oldest patients.

There was a trend that the older the patient, the more likely docetaxel was the final systemic treatment given at 42% (80 years or over), 32% (75-79 years) and 23% (younger than 75 years).

4. Discussion: Previous evidence has highlighted the importance of timing of docetaxel, with increased benefit in terms of OS being apparent when it is delivered with up-front ADT. There has been less consideration of the timing of later docetaxel within the algorithm of castrate resistant prostate cancer treatments. Our data demonstrates that beyond first line therapy, earlier docetaxel is more likely to result in a PSA response. Lower response rates with later use of docetaxel could be due to prostate cancer cells being exposed to multiple other lines of treatment and developing mechanisms of resistance to therapy over time. Another possibility is the selection of a more chemotherapy insensitive strain, with maintained control of a less resistant component of a heterogenous tumour with prior therapies.

The more unexpected result was that the timing of docetaxel did not impact on castrate resistant OS, given that up-front docetaxel has been shown to improve overall survival regardless of further treatments given. This finding potentially adds weight to the argument for initial docetaxel use in suitable patients with metastatic prostate cancer, improving OS most significantly in this setting. It does not appear from our patient group that second or third line treatment with docetaxel compensates for not receiving it first line, with no significant survival benefit compared with later use. If this finding is a true reflection of prostate cancer behaviour in response to docetaxel chemotherapy it gives clinicians some direction in sequencing therapies for metastatic prostate cancer; in suitable patients docetaxel should be considered with initial ADT. This is in keeping with emerging evidence suggesting that an intensification of treatment in the initial presentation of metastatic prostate cancer can improve outcomes, such as the LATITUDE study, investigating the upfront use of abiraterone with ADT.[19]

Confounding factors have to be considered when interpreting these findings. In reviewing possible disease characteristics influencing these outcomes, a high Gleason Grade might have steered the clinician towards recommending earlier docetaxel chemotherapy, due to a potentially more aggressive disease. However, there was no significant difference in Gleason Grade

between the different timing groups. Another potential confounding factor could have been patients with more indolent disease, i.e. with longer time from diagnosis to castrate resistance and consequently less aggressive disease in vivo. This group may have longer castrate resistant overall survival irrespective of therapy sequencing, but time to castrate resistance was not significantly different between the groups. Furthermore, the patients who have received five or six previous treatments who go on to receive docetaxel may have less aggressive disease, good performance status and/or a low comorbidity score given that they are still well enough to receive chemotherapy at that point, possibly resulting in better survival outcomes overall.

Other potential confounding factors not analysed were sites of metastatic disease and level of pain. Visceral metastatic disease to, for example, the liver would be more likely to have a worse prognosis than to bone alone.[3] The clinician's choice of order of therapies may be affected by the extent of disease and prognosis, with increased disease burden, especially to visceral organs, increasing the chance that a clinician would give docetaxel chemotherapy earlier. This more aggressive disease could result in a shortened, castrate resistant overall survival, possibly diluting the effects of earlier, more efficacious treatment.

A patient's level of pain has been found to be a poor prognostic factor for prostate cancer and clinicians may be more likely to treat a patient in pain with chemotherapy, especially if they are younger.[3] These factors could have influenced outcomes here, with relatively less good outcomes in the earlier treated groups with skewed characteristics, where docetaxel could have been used for more severe symptoms or more extensive disease.

We have only collected data for patients who have received docetaxel rather than all patients diagnosed with metastatic prostate cancer. This highlights the subjective nature of which patients clinicians have decided to treat with chemotherapy, being influenced by many disease and patient characteristics. If the patient has rapidly progressive disease, the patient may not be fit enough for chemotherapy and these patients were not captured in this study. Similarly, patients declining all chemotherapy or excluded from docetaxel use by significant comorbidity are not included, as are patients with extremely sensitive disease to ADT who maintain long term control without multiple lines of therapy.

Patients who receive docetaxel chemotherapy at aged 80 years or over are likely to have a selection bias favouring those with a good performance status and a low level of comorbidity. This group might be expected to also have a better background overall survival resulting in improved outcomes. This selection bias can be inferred from the relatively few patients in the older group being treated with docetaxel for a disease in which incidence increases with age. However, it is noteworthy that this older group receiving docetaxel, for which there is limited published data in the routine clinical practice setting, had comparable outcomes in terms of PSA response and survival

when considered against younger cohorts. We do not have comparison data on the other patients with metastatic prostate cancer aged 80 years or over who were not offered chemotherapy potentially due to poor performance status or comorbidities.

Current evidence suggests that earliest use of docetaxel in castrate sensitive metastatic prostate cancer is optimal. However, this may not be the treatment of choice for all patients. When not given with initial ADT, we can draw from this work that in suitable patients with castrate resistant prostate cancer receiving docetaxel chemotherapy later, it remains an effective treatment option regardless of patient age or number of previous alternative therapies.

These findings may influence the clinical ordering of therapies. If disease response in patients with a high tumour burden is particularly desirable, then earlier use of docetaxel can be considered. However, whilst later introduction of docetaxel chemotherapy may reduce PSA response rate with less overall dose administered, this does not appear to be detrimental to the patient, as long as the patient remains fit enough for later chemotherapy, with castrate resistant overall survival not significantly different between earlier and later treated groups.

5. Conclusions: In routine clinical practice involving patients who do not receive docetaxel with initial ADT, PSA response rates are significantly improved and overall dose received is higher if docetaxel is subsequently used earlier. This finding is in keeping with those within the CATS database but includes patients not receiving cabazitaxel, and also taking account of other therapeutic options. In this patient group however, overall survival was not significantly affected by earlier use of docetaxel, with later docetaxel still maintaining activity, inducing PSA response rates in the region of 30%.

Patients of over 80 years of age received fewer cycles of docetaxel, and less dose per course, but nevertheless achieved similar PSA response rates and castrate resistant OS. Consequently, docetaxel should be considered as a treatment option in suitable patients of 80 years and over. Clinical practice may draw influence from this work with greater consideration for offering docetaxel chemotherapy to the over 80 years population if performance status allows. Some clinicians may be reluctant to offer chemotherapy to this age group but from our findings, with careful patient selection, this age group achieved a similar castrate resistant overall survival compared to younger patients even with a lower response rate and lower chemotherapy dose intensity. Clinicians may be reassured to continue docetaxel chemotherapy as tolerated at a reduced dose in a more elderly population as a PSA response rate comparable to younger patients can still be achieved.

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