

WHERE DOES CHEMOTHERAPY FIT INTO PROSTATE CANCER TREATMENT?

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Abstract

The treatment of metastatic castrate-resistant prostate cancer has changed dramatically in recent years. Several agents have been shown to improve survival in men with castrate-resistant prostate cancer after docetaxel and, for abiraterone acetate and enzalutamide, in chemotherapy-naïve castrate-resistant prostate cancer patients also. These two drugs are now approved and reimbursed in Australia for use in castrate-resistant prostate cancer after docetaxel, or in men unsuitable to receive chemotherapy. It is reasonable to hypothesise that use of these novel survival-prolonging therapies earlier in the treatment course might improve outcomes and this hypothesis is currently being tested in clinical trials. Cytotoxic chemotherapy is often seen as a less desirable treatment strategy and perhaps some men with castrate-resistant prostate cancer are no longer being considered for this treatment. This perception might also lead to changes in management and prescribing practices, including a shift away from multidisciplinary decision-making. However, a careful review of the available literature suggests that this strategy might not be in the best long-term interests of these men and that cytotoxic chemotherapy, rather than being undesirable, might instead be best used as first line management in men able to receive it.

“No cytotoxic drug or combination has been shown consistently to be useful in prostate cancer.”¹ Less youthful readers might recognise that dogma, which was drilled into us as trainees. We learned that prostate cancer did not respond to chemotherapy and this treatment was not worth attempting. We did not understand why and we hoped that one day better drugs or a better understanding of the biology might change things for us. In contrast, today’s trainees might consider advanced prostate cancer to be a disease that is amenable to multiple treatment options, and there are more reviews on this topic than primary papers.² Now we find ourselves in a very different situation – we have chemotherapy that works, but we also have a relative wealth of other modalities, leading some to question if we should use chemotherapy at all, even though we know it can extend survival and improve quality of life.^{3,4}

Our expectations have changed over time. Tannock’s 1996 paper showing the palliative benefit of mitoxantrone and prednisone was a turning point for prostate cancer and indeed the broader field of oncology.⁵ The combination did not demonstrate significant conventional anticancer activity for what was then called ‘hormone-resistant’ prostate cancer, now termed castrate-resistant prostate cancer (CRPC).⁶ This was to the surprise of no-one at all, but the palliative benefits were both statistically and clinically significant. Chemotherapy for CRPC had finally arrived, although not for the reasons we had hoped, and the delivery of active anticancer treatment for palliation of

CRPC was firmly established and became a meaningful trial endpoint.

Effective cytotoxic chemotherapy

Docetaxel was the first cytotoxic agent to challenge the dogma. Two papers published in 2004 established its role, although only the combination of docetaxel and prednisone entered standard clinical practice.^{3,4,7} It is worth reiterating the key points of the landmark TAX327 trial. Docetaxel 75mg/m² every three weeks with prednisone 5mg twice daily, improved survival compared to the previous standard of mitoxantrone and prednisone. The hazard ratio for death was 0.76; if that number sounds familiar, it is because this benefit was comparable to that observed for enzalutamide and for abiraterone acetate (abiraterone) in similar patient populations.^{8,9} Median survival was improved with docetaxel from 16.5 months to 18.9 months, but such figures are much less helpful when explaining benefit to patients. Let us not also forget the other benefits of docetaxel treatment: improved pain control (35% vs 22%); improved quality of life taking into account the toxicity of chemotherapy (22% vs 13%); and better probability of PSA response of 50% or more (45% vs 32%).³ Benefits were perhaps even greater in patients with more favourable PSA levels or kinetics, for those without pain, or those without visceral disease, or older patients.^{3,4,10} Ironically, these are the types of patients many multidisciplinary meetings might consider more suitable for non-cytotoxic treatment approaches.

Docetaxel and prednisone quickly became the standard of care for CRPC, although it took several years for

docetaxel to be reimbursed in Australia and even longer in New Zealand. An unintended consequence of the uptake of docetaxel was that it became a defining moment in the course of a CRPC patient: were they 'post-docetaxel' or 'chemo-naïve'? This of course, was a highly arbitrary definition and subject to many variables that are difficult to control, not the least being that there was (and still is) no clear consensus on when and for whom docetaxel should be used. However, the docetaxel treatment status of the patient rapidly became a dividing line for patient management decisions, as well as for clinical trial design and regulatory approval. Patterns of use of docetaxel shifted as newer agents became available only in the post-docetaxel setting and the patterns will no doubt shift again as reimbursed therapies become available for the chemo-naïve patient.

Progress seemed to stop for a while. Satraplatin was supposed to be the next substantial step forward, but although it improved time to progression of disease or pain, it had no benefit for survival and now has sunk without a trace.¹¹ This did little to instill confidence in cytotoxic drugs, particularly as newer therapies more effectively targeting androgen synthesis and androgen receptor signalling were coming to the fore. Occasional reports have been published indicating benefit for alternative approaches such as metronomic use of cyclophosphamide but these have not entered routine practice.¹² Cabazitaxel was developed on the basis of its activity in taxane-resistant models. The combination of cabazitaxel and prednisone was shown in the post-docetaxel clinical setting to be superior to mitoxantrone and prednisone in terms of survival (TROPIC trial; hazard ratio 0.70; median survival 15.1 months vs 12.7 months), as well as secondary endpoints of response and time to progression.¹³ Toxicity was an initial concern, however further experience has shown that toxicity is relatively low and easily manageable. The recommended starting dose of cabazitaxel may be too high and it is bemusing that growth factor support was recommended instead of altering dose and/or schedule, which would be the approach used for palliative treatment of every other solid cancer. The dose issue is currently being addressed in the PROSELICA study (clinicaltrials.gov identifier: NCT01308580) and the role of cabazitaxel in patients who have not received docetaxel is the subject of the FIRSTANA trial (clinicaltrials.gov identifier: NCT01308567).

Optimal timing of chemotherapy

The TAX327 and TROPIC trial outcomes should give us pause, even while we celebrate access to new non-cytotoxic therapies. Docetaxel improves the hazard ratio of death to 0.76. These same patients who then sequence to cabazitaxel experience a hazard ratio of 0.70. We cannot ignore these numbers. Benefits of similar magnitude are seen with abiraterone or enzalutamide when given after docetaxel,^{8,9} and similar values are found when those drugs are used before docetaxel.^{14,15} However, there is a disturbing thread emerging in the literature to indicate that use of active agents after either abiraterone or enzalutamide might not be associated with the same benefit as initially observed.¹⁶⁻²⁰ We have made unspoken assumptions that benefits of sequential treatment will be additive, but this assumes that the mechanisms of

action and of treatment resistance are independent. This might not be the case. If resistance to androgen receptor-targeted therapies involves mechanisms relevant to the activity of cytotoxic drugs, then the sequence of treatment becomes of critical importance. A similar survival benefit is obtained for both abiraterone and enzalutamide when they are used after docetaxel compared to their use prior to docetaxel. However, the benefit of docetaxel after these agents might be substantially less than the reverse sequence. Given that the median duration of therapy on both agents before chemotherapy is longer than the duration after chemotherapy, for a similar benefit, can it be argued that these agents should be used for the most part only after chemotherapy or if chemotherapy is not appropriate? And where then would cabazitaxel fit into the sequence?

As if that were not enough, we must now consider the implications of the CHAARTED (E3805) clinical trial²¹. CHAARTED brought docetaxel much earlier into the disease sequence, combining it with initiation of androgen deprivation therapy in patients with metastatic castration-naïve prostate cancer. This was controversial, as the regimen combined a cytostatic and cytotoxic approach. The outcomes were extraordinary – six cycles of docetaxel (without prednisone) given with androgen deprivation therapy for metastatic castrate-naïve prostate cancer led to an improvement in the hazard ratio for death of 0.61 for the overall population, with an improvement in median survival from 44.0 to 57.6 months, although the data were relatively immature and were reported after a planned interim analysis after 53% of events. The benefit was clearest for patients with high volume disease (defined as visceral metastases and/or four or more bone metastases with at least one beyond pelvis and vertebral column), where the hazard ratio was 0.6 and median survival improved from 32.2 to 49.2 months. The hazard ratio point estimate for the subset of patients with low volume disease was very similar, but the data are too immature for statistical confidence. Treatment was well tolerated and most patients received the planned number of cycles, 74% without dose modification. Importantly, another similar trial (GETUG-AFU-15) did not show the same outcome and the possible reasons for the discrepancy remain unclear.²² Nevertheless, the CHAARTED trial is already substantially influencing clinical practice.

Many clinicians adopted this approach as standard therapy, perhaps prematurely, although preliminary data reported at ASCO 2015 from four arms of the STAMPEDE trial (clinicaltrials.gov identifier: NCT00268476) provide additional support for the strategy of combining docetaxel with initiation of androgen deprivation therapy.²³ This analysis assessed survival outcomes for 2692 men receiving standard of care (SOC) androgen deprivation therapy for three or more years, compared to SOC plus docetaxel, SOC plus zoledronic acid, or SOC plus both drugs. Docetaxel was given at a dose of 75 mg/m² every three weeks for six cycles, with concomitant prednisolone 10mg daily. The analysis included both M1 and M0 castrate-naïve men; 61% had overt metastatic disease. Survival for the whole population was improved for men receiving docetaxel compared to SOC. The hazard ratio for SOC plus docetaxel was 0.76 (95% confidence intervals 0.63-0.91, p = 0.003) and 0.81 (95% confidence

intervals 0.68-0.97, $p = 0.020$) for SOC plus both drugs compared to SOC. Median survival was 67 months for SOC, compared to 77 months with the addition of docetaxel. No benefit was seen with the use of zoledronic acid.

Sequencing and combinations

The implications of the findings of the CHAARTED and STAMPEDE trials are quite staggering. This is by far the largest effect on survival of any intervention for metastatic prostate cancer since the advent of androgen deprivation therapy. The magnitude of the benefit far exceeds that of docetaxel in the CRPC setting, which implies that the biology of castrate-naïve prostate cancer is fundamentally different in respect of sensitivity to docetaxel and subsequent mechanisms of development of lethal CRPC. Most patients on CHAARTED received treatment in the era when other 'survival-prolonging' therapies were available, as evidenced by the high frequency of use of these agents beyond progression, although not all of the patients in the control arm subsequently received chemotherapy. The findings provide further support for the concept that chemotherapy should be used early rather than late in the disease course. If that is true, then it would be expected that even greater benefits would be seen in the low volume subgroup when data are mature. However, if the principle is true that the treatment might be more effective when used with a lower burden of disease, then one would also predict that even earlier use of docetaxel in the adjuvant setting would provide a similar magnitude of benefit, however this has been shown not to be the case.

CHAARTED also raises several other key points. Firstly, the regimen did not include prednisone and did not assess whether concomitant corticosteroid therapy might further improve outcomes. Inclusion of corticosteroids with docetaxel seemed to enhance the efficacy of treatment in CRPC, but omission of corticosteroids in the CHAARTED population still led to outstanding outcomes. Secondly, the timing of use of docetaxel in this setting is important. It is perhaps not widely appreciated that docetaxel pharmacokinetics are substantially affected by castration status. Clearance of docetaxel in castrate men occurs at approximately double the rate of non-castrate men.²⁴ The CHAARTED regimen recommends four weeks of androgen deprivation prior to the first cycle of docetaxel. Use of docetaxel earlier than this might be associated with unexpected toxicity.

A third implication of the outcomes of these trials is whether we should now consider all patients treated in this way to be 'post-docetaxel' when planning treatment for subsequent castrate-resistant disease. There is as yet insufficient evidence to support this notion. The different biology of docetaxel in the setting of castrate serum levels of androgens, the complex interaction of docetaxel with androgen receptor biology and modifiers of androgen receptor signalling, and the different clinical outcomes when docetaxel is used in the castrate-resistant versus castrate-naïve settings, all indicate that docetaxel treatment in these two clinical states cannot be considered identical. Until high level clinical trial evidence is available, it remains entirely reasonable to consider

docetaxel as a treatment option for these men when their cancer becomes resistant to castration.

Perhaps some clues can be found by looking more carefully at the basic biology and existing clinical data. The mechanism of action of docetaxel remains somewhat unclear, but it has been shown to extend beyond simple stabilisation of microtubules, involving fundamental aspects of androgen receptor biology.^{25,26} Preliminary data suggest that the probability of clinical response to docetaxel correlates with sequestration of the androgen receptor in the cytoplasm of circulating tumour cells.²⁶ Docetaxel treatment of prostate cancers in mice inhibits androgen receptor nuclear localisation and downstream gene expression including PSA, but these effects are not seen if the animals are pretreated with enzalutamide.²⁷ Humans who receive abiraterone before docetaxel are much less likely to respond to docetaxel.^{16,28} Interestingly, in these mice pretreated with enzalutamide, cabazitaxel remains effective,²⁷ suggesting that this drug might be a more logical cytotoxic option in patients who have already received abiraterone or enzalutamide. Some clinical data now exist to support this idea.^{29,30}

Key practice points

Key points for the clinician to understand when choosing and sequencing the available treatment options might include the following:

- Use of abiraterone after enzalutamide assumes that targeting the ligand will be effective after failure of a treatment that effectively blocks receptor activity. This logic may be flawed.
- We know how effective the newer agents are when given after docetaxel, but we have limited information about the activity of docetaxel after the new agents.
- A treatment decision made without appropriate consideration has far-reaching implications. Incorrect choice of the treatment sequence might compromise the ability of the patient to benefit from later treatment options that they will inevitably need. There is little point in changing the sequence of survival-prolonging therapies if by doing so we lose the efficacy of one or more of the agents. We cannot assume that the benefits are additive regardless of sequence.
- These points become even more critical if the pattern of prescribing changes. For example, urologists can easily prescribe abiraterone or enzalutamide, but initial use of docetaxel requires referral to a medical oncologist colleague. The easy option at the beginning might be to the patient's detriment in the end. This highlights the importance of multidisciplinary decision making right from the commencement of therapy and, in the light of CHAARTED and STAMPEDE, perhaps far earlier than we have been accustomed.

What then is the role of chemotherapy for prostate cancer in the current era? We have multiple effective treatment options for CRPC, although none are yet curative. We have no clear evidence to guide us as to the optimal sequence of therapies. We have preclinical and observational data that challenge our underlying assumptions regarding any

cumulative benefit of sequential therapies, as well as the basic biology underlying response and resistance to these therapies. When should a specific therapy start and what should lead us to change treatment? Can we safely and should we combine therapies, such as radium-223 chloride and chemotherapy? There are even more basic questions than these to consider. For example, how many clinicians realise that not all corticosteroids are the same, and that dexamethasone can be a very effective treatment even late in the disease course?³¹

The default answer, and the easy escape for writers of reviews, is to say that more evidence is required and please fund our research. The harsher reality to face is to realise that we all have preconceptions and that we make assumptions all the time based on evidence that might not exist or that we might misunderstand. Chemotherapy was effective in prostate cancer in the 20th century and remains effective in the 21st – if only we knew how to use it correctly.

Conflicts of interest:

IDD is member or chair of advisory boards for the following companies relevant to this paper: Astellas; Bayer; Bristol Myers Squibb; Ipsen; Janssen; Medivation; Sanofi. All payments or honoraria for this work are invoiced by and paid directly to ANZUP Cancer Trials Group, of which IDD is director and chair. No remuneration is received by IDD. CJP has received honoraria and travel support from Sanofi and Janssen.

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