Optimizing the sequence of metastatic castration-resistant prostate cancer treatment options

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Chapter 7

Summarizing discussion and future perspectives

SUMMARIZING DISCUSSION

Until 2012 Docetaxel was the only treatment with a proven survival benefit for patients with metastatic castration-resistant prostate cancer (mCRPC). After 2012, multiple new agents were introduced, all in patients primarily treated with Docetaxel. Abiraterone Acetate (hereafter referred to as Abiraterone) and Enzalutamide are both androgen-signalling-targeted inhibitors.[1] Cabazitaxel is a second generation taxane and Radium-223 dichloride (hereafter referred to as Radium-223) is a targeted alpha therapy that selectively binds to areas of increased bone turnover. [2, 3] Since the new second line treatment options were developed simultaneously, at the time of approval there was no information available whether mCRPC patients would benefit more from one new agent over another. To date, still no head to head comparisons between treatment options for patients who progressed during or after docetaxel treatment are available, and therefore it is not clear which sequence of treatments would be optimal.

In **Chapter 2** we retrospectively evaluated the efficacy and tolerability of Enzalutamide in patients pre-treated with at least Docetaxel and Abiraterone. We concluded that Enzalutamide was well tolerated in this population, and that the adverse-events were similar to those reported in the AFFIRM trial, where Enzalutamide was evaluated as a treatment of mCRPC patients previously treated with docetaxel. However, patients had lower PSA response rates when compared to patients included in the AFFIRM trial (21% and 54% had a serum PSA decrease of ≥50% from the value at start of treatment, respectively) and a shorter progression free survival (PFS) (PFS survival rates were 12.0 and 36.1 weeks, respectively).[4] The CARD-trial, a multicenter, open-label, randomized trial evaluated efficacy of androgen-signalling-targeted inhibitors (Abiraterone/ Enzalutamide) in patients previously treated with Docetaxel followed by cross-over to the other androgen-signalling-targeted inhibitor. It was reported that Cabazitaxel was superior to the androgen-signalling-targeted inhibitor in terms of imaging-based PFS and Overall Survival (OS). A post-hoc analysis showed that patients treated with Enzalutamide after prior Docetaxel and Abiraterone had better imaging-based PFS when compared to patients treated with Abiraterone after prior Docetaxel and Enzalutamide naïve-patients treated with Abiraterone. No OS was reported for these post-hoc analyses. [5] Results from the CARD-trial and several other prospective and retrospective trials, including our study, suggest cross-resistance between Abiraterone and Enzalutamide. [1, 4–9]

There are multiple mechanisms of resistance to androgen-signalling-targeted inhibitors described.[10] Several of these proposed mechanisms are, both systemic and intratumoral upregulation of androgens, androgen receptor (AR) overexpression, amplifications, mutations and splice variants, alteration of pathways involved in cross-talk with AR signaling, neuroendocrine transformation and immune system deregulation.

In recent years, much research attention was drawn to aberrant AR signalling caused by AR splice variants. In these splice variants, the AR protein has a transactivating N-terminal but is missing the C-terminal ligand binding domain. Even though there is no binding domain, the AR receptor is still capable of activating target genes without being activated by androgens.[11–13] AR splice variant 7 (AR-V7) is found to be one of the most commonly expressed AR splice variants in both clinical and preclinical studies.[10] Multiple studies have shown that the presence of AR-V7 is a predictor of poor response to androgen-signalling-targeted inhibitors, but is not a predictor for response to taxane chemotherapy.[12] Antonarakis et al reported that AR-V7 could be present prior to the start of androgen-signalling-targeted inhibitor, but also that some patient converted from AR-V7-negative to AR-V7-positive during treatment. It is likely that this conversion is an important survival mechanism of prostate cancer cells to androgen-signalling-targeted inhibitors, which explains resistance and cross-resistance to androgen-signalling-targeted inhibitor.

In **Chapter 3**, we retrospectively identified parameters predicting response to Enzalutamide in patients previously treated with Abiraterone and docetaxel. In this study, a response was defined as a serum PSA decrease of ≥50% from the value at start of treatment We found that higher Gleason-scores, shorter PSA-doubling time and a longer time interval between ending Abiraterone and starting Enzalutamide were associated with response to Enzalutamide treatment. When the time interval between end of Abiraterone and start of Enzalutamide treatment was more specifically evaluated, we could identify two groups with a relatively high percentage of PSA responses to Enzalutamide treatment. One group with a short time interval (< 40 days) and one group with longer time interval (≥40 days) between the two agents. With the exception of one patient, none of the Enzalutamide responders in the <40 days group had a PSA response on the prior Abiraterone treatment, while in the ≥40 days group, 29% of the Enzalutamide responders responded to the prior Abiraterone treatment. Moreover, in the ≥40 days subgroup a linear relation could be identified between time interval between end of Abiraterone and start of Enzalutamide and PSA response to Enzalutamide. The PSA response rates of mCRPC patients on Enzalutamide with an interval of >390 days was comparable to Abiraterone-naive patients as reported in the AFFIRM trial.[7, 14] These results are suggestive of different cross-resistance patterns and with that possible differences in molecular mechanisms of resistance. Patients might be resistant to Abiraterone, but not to Enzalutamide, patients might be resistant to both agents and patients with an acquired cross-resistance to Enzalutamide might regain sensitivity in time. In the CARD trial patients who were treated with androgen-signalling-targeted inhibitors before Docetaxel had a lower chance of progression on third line androgen-signalling-targeted inhibitor treatment when compared to patients who received Enzalutamide/Abiraterone after Docetaxel and directly crossed-over to third line Enzalutamide/Abiraterone.[5] These results of the CARD trial might supports our finding and hypothesis that in time, cross-resistance between the androgen-signalling-targeted inhibitors is reversible. We hypothesize that the acquired cross-

resistance is an energetically unfavorable state and prostate cancer cells might reverse to a higher level of testosterone dependence upon cessation of AR targeted therapy in time. [7]

In **Chapter 4** we evaluated whether Enzalutamide was viable as a fourth- or fifth- line treatment option for men with castration resistant prostate cancer. Patients in our cohort were all treated with Docetaxel and Abiraterone, and at least a third-line treatment option. Third- and fourth-line treatments were Cabazitaxel in most cases, while a few patients were treated with Ra-223. We found that while the PSA response rates were much lower than those reported in the AFFIRM trial (23% and 54%, respectively), they were similar to response rates of other studies evaluating third-line Enzalutamide.[6, 15–17] Surprisingly, the median OS in our cohort (40.1 weeks) was longer compared to other reports of third-line Enzalutamide therapy in Docetaxel and Abiraterone-native patients (21.7 and 32.6 weeks)[6, 15–17]. This might be explained by survival bias, caused by the selection of patients for fourth- or fifth-line Enzalutamide treatment, who probably have a more protracted course of the disease.[17]

Radium-223

In 2013, the ALSYMPCA phase III trial reported a survival benefit, longer time to symptomatic skeletal Events (SSE) and better quality of life in mCRPC patients treated with Ra-223 compared to placebo, rendering Ra-223 the only radionuclide treatment with a survival benefit in mCRPC patients.[18] Although, patients previously treated with Docetaxel (Doc) as well as patients not-treated with Doc were included in ALSYMPCA, none of these patients had been treated with androgen-signalling-targeted inhibitors or Cabazitaxel. These newer generation drugs became available after accrual of the ALSYMPCA trial was completed.[14, 19–21] This raised the question whether the results of ALSYMPCA were representative for present patients treated with Ra-223.

In **Chapter 5**, we report the results of ROTOR, a prospective registry of Ra-223 treated mCRPC patients in the Netherlands. Even tough patients in our cohort were more heavily pretreated, the OS was comparable to the patients in the treatment arm of the ALSYMPCA trial (15.2 months and 14.9, respectively). A likely explanation is that in the Netherlands mostly patients with good performance scores were selected for Ra-223 treatment. This is reflected by the lower frequency of Eastern Cooperative Oncology Group (ECOG) ≥2 performance scores and lower baseline serum Prostate Specific Antigen (PSA) and alkaline phosphatase (ALP) levels when compared to the ALSYMPCA cohort. Toxicity was similar as reported in the ALSYMPCA trial.

There was no association between prior Abiraterone or Enzalutamide treatment and PFS or OS, but both in univariate and multivariate cox-regression analysis, previous Cabazitaxel treatment was associated with a less favorable PFS and OS. The association between prior chemotherapy and shorter survival has previously been reported in two retrospective studies. [22, 23] Moreover, a retrospective trial, assessing clinical correlates associated with response, confirmed our

finding that prior treatment with Abiraterone or Enzalutamide had no negative effect on OS.[22] These results suggest that in a non-study population, Ra-223 treatment is well-tolerated, equally effective as in the ALSYMPCA population and that patients not previously treated with Cabazitaxel benefit most from Ra-223.

Radionuclides in prostate cancer treatment were historically indicated for painful bone metastases, but an OS benefit of these beta-emitters was not established.[24] The ALSYMPCA trial evaluated patient-reported quality of life. Pain was not assessed with a questionnaire validated to assess pain, but with the pain related sub-questions of the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaires. Moreover, use of analgesics were not used in the pain evaluation, even though this is recommended by the International Bone Metastases Consensus Working Party (IBMCWP).[25, 26] In **Chapter 6** we report outcomes of integrated Health- Related Quality of Life (FACT-P questionnaire), Pain (BPI-SF questionnaire) and opioid use (free text) in a non-Study Cohort of mCRPC patients treated with Ra-223. Hundred and five patients were evaluable for patient reported outcomes. The percentage of evaluable patients experiencing a complete pain response, partial response, indeterminate response or experienced progressive pain during Ra-233 treatment were 31.4%, 26.7%, 33.3% and 5.7%, respectively. Integrated analysis of analgesics questionnaires, FACT-P and BPI showed that 55 patients (57.9%) had a complete pain response or partial pain response and a better HRQoL a better HRQoL or no change in HRQoL. Multivariate analyses suggested that pain at baseline (PAB) and more Ra-223 treatments were significantly associated with a higher probability of a pain response and a better or no change in HRQoL. These results suggest that Ra-223 affects HRQoL and pain in a contemporary mCRPC population. Moreover, our results suggest that patients with pain benefit more from Ra-223 than patients without, but this has to be evaluated in a placebo-controlled trial benefit.

Because Ra-223 is well tolerated it is attractive to explore combinations with another systemic anti-cancer treatment which is not limited to bone metastases. Several studies combining Ra-223 with other agents have been conducted and are being conducted.[27] The ERA-223 trial, was prematurely terminated because of higher mortality and fracture rates in the Ra-223 arm in combination with Abiraterone.[28] This resulted in an advice from the Pharmacovigilance Risk Assessment Committee (PRAC) and the European Medicines Agency (EMA) to restrict the use of Ra-223 to third line treatment or to patients with no other treatment options. They concluded that the mortality was not because of the interaction between Ra-223 and Abiraterone, but probably caused by Ra-223 alone. They also raised concerns about Ra-223 promoting lymph node and visceral metastases.[29, 30] The number of patients in ALSYMPCA and ERA-223 with lymph node metastases have not been made public and therefore a post-hoc analysis of this subgroup could not be performed. Our results do not support the advice given by the PRAC and EMA, since prior treatment with Cabazitaxel was associated with a shorter PFS (chapter 5), while no such

associations were found for prior treatment with Abiraterone or Enzalutamide. The association with chemotherapy and shorter survival has also been reported in several retrospective studies.[22, 23] Alva et al, report that patients in their cohort had a shorter survival when they had prior chemotherapy, but prior treatment with Abiraterone or Enzalutamide had no negative effect on OS.[22] More research is needed to confirm these findings. When confirmed, they would contradict the advice of the EMA to give RA-223 to patients as a third-line treatment or later, as Doc will be a first- or second line treatment for most patients.

FUTURE PERSPECTIVES

In recent years many advances have been made in the treatment of metastasized prostate cancer. These advances include new drugs, like treatment with immunotherapy and Poly ADP-ribose polymerase (PARP) inhibitors. Also new combinations of frequently used drugs are being evaluated. Currently, there are several ongoing studies evaluating the efficacy of newer androgen-signalling-targeted inhibitors and targeted therapies. Here we will discuss recent advances in combination of systemic therapies, immunotherapy and PARP-inhibitors in men with mCRPC.

Combination studies

The efficacy of suppressing serum testosterone in men with advanced prostate cancer was first reported in 1941.[31] Until 2015, treatment of patients with metastasized prostate cancer consisted of ADT until the prostate cancer became castration resistant, after which patients were treated with Docetaxel. In 2015, the CHAARTED trial reported a significant improvement of overall survival by combining Docetaxel with ADT in men with metastatic prostate cancer.[32] These results were confirmed in the STAMPEDE trial in 2016.[33] These spectacular results made many physicians and researchers curious to the efficacy of other combinations with ADT. Several trials have been published evaluating the efficacy of Enzalutamide plus ADT and also Abiraterone plus ADT in metastatic hormone sensitive prostate cancer. These trials show similar results, however to date no prospective study has made a direct comparison of ADT plus Docetaxel, Abiraterone or Enzalutamide. [34–36]

In the metastatic castration-resistant setting, there have been several trials evaluating combination of systemic agents.

A recently published phase 2 trial evaluating tolerability of the combination of Abiraterone and Enzalutamide reported manageable safety profiles. However, PSA-decline rates were similar to those reported in COU-AA-302 (Abiraterone/prednisone monotherapy) and PREVAIL (Enzalutamide monotherapy, but time to progression was shorter in the phase-2 trial.[37] The efficacy of this combination is being evaluated in a phase III trial (NCT01949337).

Preliminary results of two phase 2 trials evaluating the combination of Docetaxel and Enzalutamide and Cabazitaxel and Enzalutamide show promising results. The definitive results of both trials have not been published yet. [38, 39]

A trial similar to ERA-223 is being performed with Enzalutamide instead of Abiraterone. An interim analysis reported there to be no increased fracture and mortality rate in patients treated with the combination.[40] A major difference between ERA-223 and this trial is that patients in this trial were required to use bone health agents, like Denosumab and bisphosphonates. A clinical trial evaluating the combination of Ra-223 and Docetaxel is also being performed, results are also pending.

Immunotherapy

Treatment with Sipuleucel-T, an autologous dendritic cell vaccine, did result in longer OS when compared to placebo, but had no significant effect on PFS.[41] Sipuleucel-T has not been available in Europe since 2015, but is still available in the United States of America.

In several other malignancies, treatment with immunotherapy has yielded significant responses.[42] These treatments were also evaluated in patients with prostate cancer. However, most of the results were disappointing. In 2014, results of treatment with Ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen 4 (CTLA4), in patients with mCRPC progressing after Docetaxel was published (Ipi 043 trial). The authors reported an increased PFS, but failed to show a significant OS benefit.[43] Another trial evaluating efficacy of Ipilimumab in Docetaxel naïve-mCRPC patients also failed to show a significant OS benefit (Ipi 095 trial).[44] A recently published long-term survival update of the Ipi 045 trial did report a significant survival benefit after 2 years follow-up, however only a select group of patients seemed to benefit from Ipilimumab. Definitive biomarkers to select these patients have not yet been identified.[45]

Keynote-199 was a phase-2 trial evaluating Pembrolizumab, a checkpoint inhibitor which targets programmed cell death protein 1 (PD-1), in mCRPC patients. Preliminary results were disappointing, with only a small fraction of the patients having a response (5% of the patients had a complete or partial response). [46, 47] The Check-mate 650-trial is a phase-2 trial evaluating nivolumab , a programmed cell death ligand (PDL-1) inhibitor, and ipilimumab, results are yet to be published. However, preliminary data of this study suggested that Docetaxel naïve patients have a better response than Docetaxel pre-treated patients (25% and 10% of the patients had a complete or partial response, respectively). These results are underwhelming when compared to results from other malignancies with the same treatment regiment, while grade 3-4 toxicity was common.[46, 48] The reason why prostate cancers responds poorly to immunotherapy is not fully understood. In other cancer types, microsatellite instability-high (MSI-H) and deficient mismatch repair pathway (dMMR) have proven to be biomarkers predicting response to immune checkpoint

blockade, like Pembrolizumab and Nivolumab.[49] The prevalence of MSI-H and dMMR is low in prostate cancer, this could explain the disappointing results of immune checkpoint inhibitors in patients with mCRPC.

PARP inhibitors

In prostate cancer, the relevance of genes involved in DNA damage repair (DDR) pathways, notably BRCA1/2, ATM and CDK12 genes, have only recently been recognized. These mutations are present in 10% of the primary tumours and 25% of metastases, with BRCA2 being the most common.[50] In other tumours with DDR defects, Poly ADP-ribose polymerase (PARP) inhibitors and platinum-based chemotherapy have proven to be effective. There is anecdotal evidence that mCRPC patients with BRCA2 germline mutations respond well to platinum based chemotherapy.[50] To date several phase 1 and phase 2 studies have been published of Olaparib and Veliparib, both PARP-inhibitors. Results of a phase 2 trial evaluating the PSA-response in mCRPC patients treated with the combination of Veliparib and Abiraterone/prednisone, compared to Abiraterone/prednisone monotherapy were published. This trial failed to show superiority of the combination when compared to Abiraterone monotherapy in the entire population. [51, 52]

There are a few phase 2 and one phase 3 trials evaluating efficacy of Olaparib. The TOPARP-A study, a phase 2 trial evaluating Opalarib monotherapy in heavily pretreated mCRPC patients, whom had not undergone genetic testing. The authors reported a 33% response rate in the entire population. Subgroup analysis revealed high response rates (88%) in patients with DDR. The TOPARP-B study, evaluated two different dosages of Olaparib monotherapy in mCRPC patients with pathogenic DDR alterations. They reported response rates of 54% and 39% in the high and low dose groups, respectively. Subgroup analyses revealed response rates of 83% for patients with BRCA1/2 mutations. [51, 53, 54]

The PROfound trial, a phase 3 trial evaluating Olaparib in mCRPC patients with a wide array of mutations in genes involved in homologous recombination DNA repair, pretreated with an androgen-signalling-targeted inhibitor and comparing it with androgen-signalling-targeted inhibitor after prior treatment with an androgen-signalling-targeted inhibitor. Response rates of 22% and 4% were reported in the Olaparib and control group, respectively. Patients treated with Olaparib also had longer overall survival rates (17.3 and 14.0 months, respectively). Toxicity was more prevalent in the Olaparib group when compared to the control group. Twenty-three percent of the patients in the Olaparib group required dose reductions, 20% discontinued due to an adverse event and in 4% of the patients treatment was interrupted because of an adverse event.[55, 56] With that, approval of Olaparib as the first targeted therapy for the treatment of mCRPC patients is expected in the near future.

CONCLUSION

Unlike a decade ago, when there was just one life prolonging treatment for mCRPC, we now have an arsenal of treatment options available. Before writing this thesis, there was much uncertainty with regards to sequencing of treatment options for mCRPC patients. Throughout this thesis some of these uncertainties have been addressed, while many still remain. New sequencing studies, new indications and new agents have provided us with new questions on the optimal treatment sequences. I believe that there is no "one size fits all" drug sequence and that the future lies in personalized cancer treatment, where the optimal treatment sequence will dependent on patient, disease and genetic characteristics.

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