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

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Appendices

ENGLISH SUMMARY

Prostate cancer is the second most common cancer in men worldwide, with over 1 million newly diagnosed cases each year. Until 2012 Docetaxel was the only treatment with a proven survival benefit for patients with metastatic castration-resistant prostate cancer (mCRPC). Over recent years, multiple new anti-cancer agents were introduced for patients with mCRPC. The phase-3 studies evaluating these agents were mostly performed in patients primarily treated with Docetaxel. Many of these agents were developed and evaluated in parallel to each other. Abiraterone and Enzalutamide were two of these drugs, both targeting the androgen receptor (AR). It was unclear what the efficacy and safety was of treating patients who already were treated with one of these two agents, with the other agent. 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. The AFFIRM trial was a phase III trial evaluating the efficacy and safety of Enzalutamide in mCRPC patients previously treated with Docetaxel. However, the efficacy of Enzalutamide in our cohort was worse than those of patients in the AFFIRM trial. Patients had lower Prostate-Specific Antigen (PSA) response rates compared to those in the AFFIRM trial (21% and 54%, respectively) and a shorter progression free survival (PFS) (PFS rates were 12.0 and 36.1 weeks, respectively). Our findings were suggestive of cross-resistance between Abiraterone and Enzalutamide.

Because of the lower response rates and PFS rates, we tried to identify parameters predicting response. In Chapter 3 we report 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. We could distinguish two groups with a relatively high percentage of PSA responses to Enzalutamide treatment. One group with a short time interval between ending Abiraterone and starting Enzalutamide (IAE $<$ 40 days) and one group with longer time interval (IAE $\geq$40 days). In the IAE $<$40 days subgroup, all but one of the Enzalutamide-responders had no response to Abiraterone, while in the IAE $\geq$40 days subgroup, 29% of the Enzalutamide-responders responded to the prior Abiraterone treatment. Moreover, in the $\geq$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 patients treated with Enzalutamide with an IAE of $>$390 days was comparable to Abiraterone-naive patients, as reported in the AFFIRM trial. These results suggest that some patients might be resistant to Abiraterone, but not to Enzalutamide; that some patients might be resistant to both agents and that patients some with an acquired cross-resistance to Enzalutamide might regain sensitivity in time. These findings are hypothetical and need to be evaluated prospectively.

Because efficacy of Enzalutamide in the AFFIRM trial was evaluated as second-line therapy, not many much was known of the tolerability of Enzalutamide in heavily pre-treated patients. In Chapter 4 we retrospectively analyzed patients from our cohort whom received Enzalutamide as fourth- or fifth-line therapy after castration resistance. Enzalutamide was well tolerated and the frequency of adverse events was similar to those reported in the AFFIRM trial. The response rate was 23%, which was comparable to retrospective reports of third-line Enzalutamide. This data was retrospective and hypothesis generating, but did suggest that fourth- or fifth-line treatment was a possible treatment option, even when considering the considerable costs when given on empirical basis.

Almost 70% of the patients with mCRPC develop bone metastases during the course of their disease. Bone metastases and especially the pain associated with them, have a significant impact on quality of life. Symptomatic bone metastases can be treated with bone directed treatment and until 2013 the treatment options were limited to beta-emitting radionuclides, external beam-radiation therapy, bisphosphonates, RANKL inhibitor and surgery. In 2013, results of the ALSYMPCA trial were published, a phase 3 trial evaluating the efficacy of Radium-223 (Ra-223) in men with mCRPC and symptomatic bone metastases without visceral metastases. Ra-223 is a targeted alpha-emitting radionuclide that selectively binds to areas of increased bone turnover. The patients included in the ALSYMPCA trial were either pretreated with Docetaxel or had not received any systemic anticancer therapy after castration resistance. Other agents, like Enzalutamide, Abiraterone and Cabazitaxel were not available during the accrual of the ALSYMPCA. This raised the question whether the results of ALSYMPCA were representative for patients with mCRPC previously treated with systemic anti-cancer agents, other than Docetaxel. In Chapter 5 we report the results of the ROTOR trial, a prospective observational multicenter trial evaluating the efficacy and tolerability of Ra-223 in a non-study population. In 11.3% of the 300 evaluable patients, Ra-223 was the first treatment after castration resistance. Of the pretreated patients, 80.5% was pretreated with Abiraterone or Enzalutamide, while 74% was pretreated with Docetaxel. The 6 months symptomatic skeletal event (SSE) free survival rate was 83%, median PFS was 5.1 months and median Overall Survival (OS) was 15.2 months. Toxicity, 6 months SSE-free survival rate and OS were comparable to those reported in ALSYMPCA. Previous Cabazitaxel treatment' and 'bone-only metastases' were independent predictors of a shorter and longer PFS, respectively, while above median serum lactate dehydrogenase and 'bone-only metastases' were independent predictors of shorter and longer OS, respectively.

These results suggest that in a non-study population Ra-223 treatment: is well-tolerated, is equally effective as in the ALSYMPCA population and that patients not previously treated with Cabazitaxel benefit most from Ra-223.

In the ALSYMPCA trial, health-related quality of life (HRQoL) was also assessed, and patients treated with Ra-223 had a HRQoL benefit over patients treated with placebo. Even though radionuclides are usually given to patients as a treatment for painful bone metastases, effect of Ra-223 on pain and opioid use were not systematically evaluated. Moreover, contemporary patients have significantly more treatment options and are therefore more extensively pretreated, which raises the question if Ra-223 still has a positive effect on HRQoL. The uncertainty of the clinical benefit and effect on pain of Ra-223 causes much uncertainty for both patients and their treating physicians. In Chapter 6 we report results of an integrated analyses on pain, HRQoL and analgesics use in mCRPC patients treated with Ra-223. Of the 300 included patients, 105 were evaluable for both Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Brief Pain Inventory-Short Form (BPI-SF) questionnaires. Forty-five (43%) patients had pain at baseline (PAB; BPI-SF score 5-10 points) and 60 (57%) had no pain at baseline (no-PAB; BPI-SF score 0-4 points), and 78% of PAB patients had an improvement of the BPI-Worst pain subscale during treatment. Ninety-three out of the 300 patients were also evaluable for opioid use, of whom 33 (31,4%) experienced a complete pain response and 55 (58%) experienced an integrated overall clinical response.

Our study showed that a significant proportion of Ra-223 treated symptomatic and asymptomatic, extensively pretreated mCRPC patients experienced an improved HRQoL and a pain response. These results suggest that the majority of contemporary mCRPC patients derives clinical benefit from Ra-223 treatment.

Finally in Chapter 7 we discuss the results presented in this thesis and discuss current and future perspectives.