Summarizing discussion and future perspectives

Introduction

The research of this thesis has been focused to improve systemic treatment for patients with metastatic castration-resistant prostate cancer (mCRPC). In 2004, docetaxel was the first chemotherapeutic agent with a proven survival benefit in patients with mCRPC.\textsuperscript{1,2} Last years many new therapeutic agents have become available.

Sipuleucel-T is an autologous vaccine prepared using the patient’s own peripheral blood mononuclear cells, obtained with leukapheresis and \textit{ex vivo} incubated with a recombinant fusion protein that consists of a prostate antigen and granulocyte-macrophage colony-stimulating factor.\textsuperscript{3} For patients with minimally symptomatic disease, a good performance status and no visceral metastases, treatment with sipuleucel-T results in an overall survival benefit without improving time to progression. A possible explanation for the discrepancy between progression-free survival (PFS) and overall survival might be that vaccination therapy induces deceleration of tumor growth rate over a long period of time instead of eliciting immediate tumor regression. However, a great disadvantage of sipuleucel-T is the complexity of preparation of this autologous product and therefore it is only limited available worldwide (not available in The Netherlands).

Abiraterone is a new androgen synthesis inhibitor that irreversibly binds the CYP17 gene and consequently blocks synthesis of androgens in the tumor and in the testis and adrenal glands.\textsuperscript{4,5} Abiraterone is prescribed in combination with prednisone to prevent side effects caused by mineralocorticoid excess. Enzalutamide is an androgen receptor signalling inhibitor that targets multiple steps in the androgen receptor signalling pathway.\textsuperscript{6} Both abiraterone as well as enzalutamide have been studied first in patients with mCRPC who were progressive on or after treatment with docetaxel.\textsuperscript{4,6} Both hormonal agents resulted in a survival benefit of several months. After these positive results post-docetaxel, abiraterone and enzalutamide were also studied in patients with mCRPC pre-docetaxel, again showing a survival benefit of several months.\textsuperscript{7,9} Cabazitaxel is a novel tubulin-binding taxane drug with proven efficacy in patients with docetaxel-resistant mCRPC.\textsuperscript{10} Compared to mitoxantrone it results in improvement of both PFS as well as overall survival.

Finally, the alpha emitting radionuclide radium-223-chloride has led to further improvement of survival in patients with mCRPC and osteoblastic metastases.\textsuperscript{11} Treatment with radium-223-chloride seems most effective in patients with at least 6 bone metastases and high alkaline phosphatase at baseline. However, the optimal use of radium-223-chloride (either pre- or post-docetaxel) in the treatment of mCRPC needs to be further studied.

With all these new agents available, important progress has been made in the systemic treatment of mCRPC. While these agents were introduced in a relatively short period of time, the appropriate sequence of the different new therapeutic possibilities needs to be determined. And, despite the progress that has been made, median survival of men with mCRPC is still limited and further improvement is warranted. \textit{Chapter two} gives an overview of the new treatment possibilities and discusses the optimal sequence in which these agents could be used. There might be a rational for alternating androgen receptor-targeting agents with chemotherapy because of possible cross-resistance between enzalutamide and abiraterone. Further data about the mechanisms of cross-resistance are necessary and might help to overcome it. The introduction of so many new agents also creates a chance for combination strategies. Currently, several trials combining novel androgen receptor-targeting agents with chemotherapy or radium-223-chloride or trials combining
chemotherapy with radiopharmaceuticals are ongoing. Another focus for future research lies in personalizing care for patients with mCRPC. Translational research using genetic and molecular profiling of tumor cells and imaging techniques will hopefully result in tools to predict response to specific therapies.

**Immunotherapy**

Previous vaccination trials in patients with mCRPC showed improvement of overall survival without prolongation of PFS. As mentioned above, this might be explained by enhanced efficacy of subsequent therapies because of heightened immune status. In chapter three we describe the results of a retrospective analysis of patients with mCRPC who were treated with the immune checkpoint inhibitor ipilimumab and GVAX, an allogeneic vaccine. We collected data on PFS and overall survival after treatment with docetaxel and mitoxantrone. To study whether immune status was related to the efficacy of chemotherapy, frequencies of myeloid and lymphocyte subsets were determined. Median PFS after docetaxel was 6.4 months (range 0.8-11.2), while median PFS after mitoxantrone was markedly longer than expected (4.8 months; range 1.4-13.7 months). High CD8+ICOS+ Tcell/Treg and pDC/mMDSC ratios were associated with relatively long PFS after mitoxantrone, suggesting a correlation between activated immune status and benefit of mitoxantrone. Subsequently we analysed 21 patients from the VU Medical Center who were randomized to GVAX or not in two large phase III trials. Median PFS after docetaxel was 9.9 months for vaccinated patients and 7.1 months for unvaccinated patients. Interestingly, PFS after mitoxantrone (n = 14) was significantly longer in vaccinated patients as compared to controls (5.9 versus 1.6 months; p = 0.0048). Mitoxantrone is a DNA-reactive agent closely related to anthracyclins. Besides the direct cytotoxic effect on tumor cells, anthracyclins may also stimulate the host immune system to attack cancer cells. This process of immunogenic cell death was reported for mitoxantrone and other anthracyclins but not for docetaxel and might explain the improved efficacy of mitoxantrone we found in our retrospective analysis. Of course, the major limitation of our study was the retrospective study design and the relatively small sample size. Our results are hypothesis generating and suggest that patients with mCRPC, previously treated with immunotherapy, experience improved efficacy of mitoxantrone treatment. This is in line with the results from previous trials, in which a survival benefit was seen of immunotherapy without improvement of progression-free survival. It would be interesting to analyse the response to chemotherapy of patients treated in large trials studying any form of immunotherapy (i.e. sipuleucel-T, PROSTVAC-VF and ipilimumab).

**Radiopharmaceuticals**

Bone is the most common site for metastases in patients with mCRPC. Skeletal metastases can lead to significant morbidity, such as bone pain, bone marrow insufficiency and spinal cord compression. Bone-seeking radiopharmaceuticals are radioactive agents that are bound to a ligand that binds to the bone matrix and accumulate in sites of increased bone turnover. After intravenous administration, radiation is delivered specifically to the osteoblastic metastatic sites. Most bone-seeking radiopharmaceuticals are beta-emitting radionuclides, except for radium-223-chloride, which is an alpha-emitter. As mentioned before, radium-223-chloride has proven efficacy in delaying skeletal-related events and results in improvement of overall survival as compared to placebo.
most commonly used beta-emitting radionuclides are strontium-89-chloride, samarium-153-EDTMP, rhenium-186-HEDP and rhenium-188-HEDP. These radionuclides can be used to palliate multifocal pain due to diffuse osteoblastic metastases. Chapter four contains the results of a systematic review evaluating the efficacy of bone-seeking radiopharmaceuticals in palliating malignant bone pain in patients with mCRPC. In total, 36 articles were included in the review of which 13 randomised trials and 23 prospective studies. Of all trials, 10 studies used strontium-89-chloride, 7 samarium-153-EDTMP, 12 rhenium-186-HEDP, 2 rhenium-188-HEDP and 2 radium-223-chloride. Three studies reported on several radionuclides. Only a few trials contained a blinding procedure and several studies contained incomplete follow-up or lack of intention-to-treat analysis. Many different definitions of pain response were used in the trials, and therefore it was not possible to calculate a pooled estimate of pain response to treatment with any of the radiopharmaceuticals. We therefore presented treatment results of the radionuclides as a percentage of pain response (partial and complete response combined; intention-to-treat population whenever possible) with a 95% confidence interval. Pain response rate for strontium-89-chloride was around 50-60% (range 35-92%). For the other beta-emitting radionuclides (samarium-153-EDTMP, rhenium-186-HEDP and rhenium-188-HEDP) slightly higher pain responses were reported (70%; range 38-89%). Repeated administration radium-223-chloride resulted in pain responses of 50-60%, and the best pain responses were seen with the highest dosage of radium-223-chloride. Differences in pain response percentages might be explained by different definitions of pain response and different time points at which pain assessment was performed. Haematological toxicity seems manageable, however this might be influenced by the fact that many of the included studies were performed in patients with only limited previous systemic therapies. Despite the heterogeneity of included studies, the results of this systematic review support the use of radiopharmaceuticals for palliating malignant bone pain from mCRPC. For future studies we suggest to include patients with baseline pain scores of at least 4 on a visual analogue scale/numerous rating scale (0-10), to perform weekly pain assessments for a minimum of 12 weeks, to use a predefined definition of pain response (taking into account use of analgesic requirements) and to report time-points for pain response. Treatment with bone-seeking radiopharmaceuticals can be combined with other systemic therapies. We prefer treatment with a radionuclide with a relatively short halftime (i.e. samarium-153-EDTMP, rhenium-186-HEDP or rhenium-188-HEDP) because recovery time of haematological toxicity is shorter.

Combination therapy

Previous studies indicate that there might be improvement of survival when chemotherapy is combined with radiopharmaceuticals or when radiopharmaceuticals are administered repeatedly. In a randomized study performed by Tu et al median overall survival was significantly increased when chemotherapy was combined with strontium-89-chloride as compared to chemotherapy alone. However, the chemotherapeutic regimen used in this trial consisted of doxorubicin, estramustine and vinblastine instead of the current standard chemotherapy docetaxel. A German study group compared single injection versus two injections of rhenium-188-HEDP in patients with progressive CRPC and bone pain. Median overall survival was better for patients receiving repeated treatment (12.7 versus 7 months; p = 0.043).

Docetaxel

In the Taxium I studie (chapter five) we examined the combination of standard first-line docetaxel with repeated injections of rhenium-186-HEDP in patients with bone metastatic CRPC. A dose
escalation schedule was designed in which docetaxel was given at a standard dosage of 75 mg/m² 3-weekly and rhenium-186-HEDP was administered in increasing activities (1250 MBq up to 2500 MBq) after the third and sixth cycle of docetaxel. Three patients were included in each dose level. Dose limiting haematological toxicity was defined as any grade 4 toxicity lasting more than 7 days or any grade 3 toxicity that did not recover within 10 days. In total 14 men were included in this phase I trial. One dose limiting toxicity (thrombocytopenia grade 3 lasting > 10 days) occurred at dose level 3 leading to expansion of this dose level to six patients. No further dose limiting toxicities occurred, but unfortunately dose level 4 was not started because of production problems of rhenium-186-HEDP. We concluded that it was feasible and safe to give a combination of docetaxel with two injections of rhenium-186-HEDP in declining dosage.

To study whether the addition of a beta-emitting radiopharmaceutical to docetaxel/prednisone improved efficacy of chemotherapy in patients with mCRPC a randomized controlled trial was necessary. Rhenium-188-HEDP is another beta-emitting radiopharmaceutical that is very similar to rhenium-186-HEDP. An important advantage of rhenium-188-HEDP is that it can be produced on-site with a small generator. We therefore continued the Taxium II study using rhenium-188-HEDP instead of rhenium-186-HEDP. Chapter six describes the results of this randomized controlled phase II study that was performed at 7 medical centers in The Netherlands. Patients with bone-metastatic CRPC eligible for first-line docetaxel were randomized between standard docetaxel 75 mg/m² 3-weekly with prednisone 5 mg bd with or without 2 injections of rhenium-188-HEDP after the third and sixth cycle of docetaxel. Primary endpoint of the study was PFS. In total, 88 patients were included in the trial, of whom 46 patients were allocated to combination therapy. In the intention to treat analysis no differences became apparent in PFS, survival and PSA. An interesting finding was that, in the group with a high baseline alkaline phosphatase, median PFS was significantly better with combination treatment (9.0 months) as compared to standard treatment (6.2 months; p=0.005). In the experimental group 8 patients received only one cycle of rhenium-188-HEDP, whereas another 8 patients did not receive rhenium-188-HEDP at all. Because of this relatively high drop-out rate we also performed an exploratory analysis in the per-protocol group (n = 40). Median PFS was comparable between the two groups, but median overall survival in the per-protocol analysis was significantly longer in the experimental group (33.8 months versus 21.0 months, p=0.012).

In general, pain responses were comparable between the two groups, but musculoskeletal pain was reported less frequently in the combination group compared to control (88% versus 68%, p=0.024). Quality of life remained stable during treatment, but after eight cycles there was in increase in fatigue scores in the group that received standard docetaxel which did not occur in the experimental group. Thrombocytopenia was reported only in the experimental group (grade I-II thrombocytopenia occurring in 25% of patients), but platelet count recovered in all patients without causing any serious problems.

Unfortunately this study did not meet its primary endpoint of improving PFS by the addition of rhenium-188-HEDP to standard docetaxel. This might be due to the fact that the study was underpowered. However the per-protocol analysis showed interesting results that support the hypothesis that repeated treatment with radiopharmaceuticals has disease modifying potential. PFS might not be the right endpoint in mCRPC, whereas overall survival should be used. The same was seen with repeated injections of radium-223-chloride in the ALSYMPCA trial. For further studies we suggest to randomize patients after three courses of docetaxel, instead of randomizing at start of
treatment, to prevent high drop-out rates. Finally we suggest to select patients with high alkaline phosphatase at baseline.

**Cabazitaxel**
Most patients in the Taxium II trial were newly diagnosed with mCRPC. Benefit of bone-seeking radiopharmaceuticals might be related to the extent and stage of the disease. Patients with later stage CRPC might respond differently to rhenium-188-HEDP because of more extensive bone metastases. Patients with high baseline alkaline phosphatase seemed to benefit more from combination therapy as compared to standard treatment. The ReCab I trial studied the combination of rhenium-188-HEDP with second-line cabazitaxel in patients with bone metastatic CRPC. The results of this phase I trial are presented in chapter seven. In the Taxium II trial, dosage of the second injection of rhenium-188-HEDP was half the dosage of the first injection. Because no serious toxicity was seen we decided to use full dosages for every treatment cycle of rhenium-188-HEDP in the ReCab I study. Cabazitaxel was administered in climbing dosages from 20 mg/m² to 25 mg/m². Rhenium-188-HEDP was administered after the second and fourth cycle of cabazitaxel. Twelve patients were included, of whom 3 had progressive disease before the third cycle of cabazitaxel. One dose limiting toxicity occurred in dose level 1 after the second cycle of rhenium-188-HEDP: thrombocytopenia grade 3 causing delay of the next cycle of treatment. This cohort was expanded to six patients and no further dose limiting toxicities occurred. Combination therapy with cabazitaxel and rhenium-188-HEDP proved to be feasible and safe with similar toxicity as compared to previous results with cabazitaxel monotherapy.

Following this phase I trial, now a randomized phase II trial is started (the ReCab II trial) comparing standard cabazitaxel/prednisone with or without two injections of rhenium-188-HEDP.

**Conclusion and future perspectives**
In conclusion, beta-emitting radiopharmaceuticals are effective to reduce malignant bone pain in patients with mCRPC. Addition of rhenium-188-HEDP to standard docetaxel/prednisone did not improve PFS. However, the observed survival benefit in the per-protocol analysis of the Taxium II trial warrants further studies on the combined treatment of chemotherapy and radiopharmaceuticals. While repeated treatment with radium-223-chloride already has a proven survival benefit in patients with mCRPC, pain palliation might be better with rhenium-188-HEDP. It would be interesting to compare rhenium-188-HEDP with radium-223-chloride. We plan to perform a randomized controlled trial in patients with mCRPC who have progressed on or after treatment with first-line docetaxel. Patients will be randomized between 3 injections of rhenium-188-HEDP with an 8-week interval and 6 injections of radium-223-chloride with a 4-week interval. Primary outcome will be overall survival. Secondary outcomes will focus on pain palliation, quality of life and also economic issues. Pain will be an important outcome of this trial, because the efficacy of pain palliation by radium-223-chloride is much less established as compared to rhenium-188-HEDP. Economic aspects of both treatments are interesting, because treatment with radium-223-chloride is quite expensive, whereas rhenium-188-HEDP is much cheaper. In the current times of exponential growth of healthcare costs, we have an important obligation to society to explore possibilities to improve cost-effectiveness of cancer treatment.

Another way to improve efficacy of systemic treatments in (prostate) cancer might be found in personalizing cancer care. Many different therapeutic agents are available for treating patients with
mCRPC, but we are not able to predict which therapy will be beneficial to one patient. This means that patients are frequently exposed to side effects of a therapy without having the benefits of the treatment. In addition, this leads to high healthcare costs. It would be a giant improvement if we would be able to match a systemic treatment to the specific genomic or molecular profiles of the patient’s tumor. To establish personalized cancer care into daily practice it is important to collect tumor biopsy material and clinical characteristics of many patients. Large (inter)national studies like the Center for Personalized Cancer Treatment (CPCT) program provide in this critical need.19 Other studies focus on circulating tumor cells or circulating microRNAs. For example, circulating tumor cells can be tested for presence of the nuclear androgen-receptor splice variant 7 (AR-V7). Tumor cells with AR-V7 lack the binding site for androgen, while they retain the activating site that stimulates tumor growth. Presence of the AR-V7 splice variant is associated with resistance to abiraterone and enzalutamide but not to chemotherapy with docetaxel or cabazitaxel.20,21

Also new imaging techniques might contribute to efficacy of systemic treatment of mCRPC. Imaging with 18F-fluorocholine positron emission tomography (FCH-PET) might qualify as early biomarker of response in patients receiving chemotherapy.22 At the VU University Medical Center an imaging study will start this year in patients with mCRPC eligible to second-line cabazitaxel, to assess the predictive value of FCH uptake changes as defined with FCH-PET after one cycle of treatment (compared to baseline).

Currently, much attention is going to a PET imaging technique targeting the prostate-specific membrane antigen (PSMA), for example with gallium-68-PSMA.23 PSMA is a trans-membrane glycoprotein that is highly expressed on prostate cancer cells. PSMA is negatively regulated by androgen and significantly overexpressed in androgen-independent prostate cancer. It has shown to be a predictor for prostate cancer progression, because high expression of PSMA is associated with higher tumor grade and aggressive forms of the disease. Further research is warranted to define the exact role of PSMA-PET imaging in characterization of the disease and decision making for subsequent therapies. In addition, PSMA might serve as a homing target for therapeutic agents such as radioactive nanoparticles.24 The advantage of using PSMA as a homing ligand as compared to bone-seeking radiopharmaceuticals would be, that both bone and soft tissue metastases are treated. PSMA is also intensively studied as a target for immunotherapy.25,26

References


19. www.cpct.nl


