Multidisciplinary treatment of metastatic prostate cancer

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General introduction

Localized disease

Prostate cancer is the most common malignancy in men in Europe[1]. In case of localized disease, treatment may consist of a radical prostatectomy (removal of the entire prostate gland), or radiotherapy. Radiotherapy might be performed as external-beam radiation therapy or brachytherapy in case of patients with a good prognosis[2]. The choice of treatment depends on the risk factors (Gleason score), prostate-specific antigen (PSA) levels at diagnosis and tumor size, combined with the age of the patient, comorbidity and personal preferences[3-5]. Depending on the risk group and lymph node status, adjuvant androgen deprivation therapy (ADT) should be considered to improve the curation rate[6, 7]. However, as prostate cancer often grows slowly without causing local problems, some patients might never need treatment. Especially for older patients or patients with severe comorbidities, active surveillance might be an option as well[8].

Metastatic disease

Despite the intended curative treatment, some patients will develop metastatic disease, or will have advanced or metastasized disease at first presentation. Once distant metastases are present, 5-year relative survival rates drop from nearly 100% for localized or locally advanced disease, to 30% for metastasized disease[9]. Bone is the most common site of metastases of prostate cancer, occurring in up to 90% of the patients with metastatic disease[10]. These bone metastases cause pain and fractures as well as bone marrow insufficiency, impair the quality of life, increase the costs of treatment and are a major cause of mortality [11]. Other common sites of metastases are lymph nodes, lungs and liver. Rare locations of metastases include brain, kidney, adrenal glands, spleen and pancreas.

Treatment in metastatic disease

Hormonal treatment

As the androgen receptor pathway is essential for progression of prostate cancer, the first line of treatment of patients with hormone sensitive metastatic disease is ADT[12]. The aim of ADT is to lower the testosterone levels below 1.7 nmol/L, which is equal to the castration level. This might be achieved by a bilateral orchiectomy, LHRH analogues or antagonists or GnRH antagonists[13]. Side effects of the ADT include fatigue, reduced or absent libido and sexual dysfunction, depression hot flushes, insulin resistance and loss of bone mass[14]. In patients with high volume disease or visceral metastases, the addition of 6 cycles of docetaxel to the ADT should be considered as an overall survival (OS) benefit has been shown for the combined treatment[15, 16].

Despite the ADT, after an average of 14-24 months, patients will show signs of disease progression as a rise in PSA, clinical progression and/or radiological progression; the disease has become castration resistant[17].

Chemotherapy

For patients with metastatic castration-resistant prostate cancer (mCRPC), several treatment options exist. For a long time, CRPC was believed to be insensitive to chemotherapy, although mitoxantrone was registered for palliative treatment as significant pain relief was seen with this therapy. In 2004, two randomized controlled trials showed a significant improvement in OS of 1.9 and 2.4 months in patients treated with docetaxel compared to mitoxantrone [18, 19]. Since these publications, docetaxel is the first line chemotherapy for mCRPC. When progression occurs during or after treatment with docetaxel, a second line of chemotherapy exists in the form of cabazitaxel. Compared to mitoxantrone, a benefit in progression free survival of 1.4 months and in overall survival of 2.4 months was shown[20].

Treatment with abiraterone and/or enzalutamide should be considered before, in between and after chemotherapy, or in patients unfit for chemotherapy. Abiraterone blocks the syntheses of androgens in the tumor as well as the adrenal glands, thereby lowering the androgen levels even further than ADT. In both patients previously treated with docetaxel and chemo-naïve patients, a benefit in OS was seen for Abiraterone compared to placebo (4.6 months and 4.4 months respectively)[21, 22]. Enzalutamide is an androgen-receptor-signaling inhibitor with a strong binding capacity, blocking the signaling pathway of the

androgen receptor. The affirm trial showed significant survival benefit of 4.8 months for enzalutamide compared to placebo in patients with progression of mCRPC after treatment with docetaxel[23]. A trial with chemo-naïve patients with CRPC was prematurely stopped due to a significant benefit in OS for patients treated with enzalutamide compared to placebo (23% reduction in risk of death, hazard ratio 0.77, 95% CI 0.67-0.88, P=0.0002). The median OS was 35.2 months for patients in the enzalutamide group, versus 31.3 months for patients in the placebo arm. Median radiographic PFS was 20.0 months versus 5.4 months, respectively[24, 25].

For patients with high volume disease and/or visceral metastases, the first line treatment is still ADT. However, for these patients, the addition of 6 cycles of docetaxel at the start of treatment should be considered. The CHAARTED trial showed an improvement in median OS of 17 months (32.2 versus 49.2 months, HR 0.60 95% CI 0.45-0.81)) for the combination therapy in this patient group. These results were confirmed by the Stampede trial, with an OS benefit of 10 months for the combination of ADT+docetaxel[16]. Also, the Latitude and Stampede 2 trial, both showed significant OS benefit for the addition of abiraterone, instead of docetaxel, to ADT (HR 0.63 and 0.70 respectively), therefore this combination should be considered as well[26, 27]. For apalutamide, another anti-androgen, a significant benefit was found when combined with ADT compared to ADT plus placebo (OS after 24 months was 82.4% versus 73.5%, 95% CI 0.51-0.89, P=0.005). However, these data need to become more mature before they can be compared to the docetaxel and abiraterone data[28].

Radiopharmaceuticals

Bone metastases in mCRPC are generally osteoblastic metastases, which makes them really suitable for treatment with radiopharmaceuticals. A radiopharmacon is a radioactive compound that will accumulate in parts of the bone with increased osteoblastic activity, i.e. bone metastases. Uptake in the bone metastases can be accomplished either by the use of a calcimimetic drug (radium-223-chloride) or linking the radionuclide to a bisphosphonate (as in rhenium-188- hydroxyethylidene diphosphonate (^{188}Re-HEDP)). Due to the systemic administration of radiopharmaceuticals, all bone metastases can be irradiated simultaneously. Because of the delivery of energy over just a short range, healthy tissue will be relatively spared[29]. For the alpha-emitting radiopharmaceutical radium-223, a significant survival benefit of 2.8 months has been proven, compared to placebo (14.0 versus 11.2 months, HR 0.70, 95% CI 0.55-0.88) [30]. For the beta-emitting

radiopharmaceuticals, a survival benefit has not been proven yet. However, these agents are well-known for the excellent pain relief they can achieve in up to 80-90% of the treated patients [31].

Outline of this thesis

As described above, the first line of treatment for patients with metastatic prostate cancer is ADT, which has serious side effects. At this moment, the detection of metastases is performed by Computed Tomography (CT) and bone scintigraphy. The use of hybrid imaging modalities as [^{18}F]fluoromethylcholine ([^{18}F]FCH positron emission tomography (PET)/CT offers the possibility to detect metastases early in the development of metastatic disease, at relatively low PSA levels. This might result in the diagnosis of metastatic disease when only a few metastases are present. *Chapter two* concentrates on a specific patient population, patients with oligometastatic disease, defined as ≤ 4 metastases. For this group, local treatment might be an attractive treatment option. Stereotactic body radiation therapy (SBRT) is a form of high-dose external radiotherapy delivered in a few fractions with advanced techniques, allowing relative sparing of nearby healthy tissue. This retrospective trial investigates whether treatment with SBRT in oligometastatic hormone-sensitive disease can safely postpone the start of ADT and thereby postpone the side effects of ADT.

The first part of this introduction outlined the rationale of docetaxel as first line of chemotherapy. However, at some point during or after treatment with docetaxel, progression will occur. For patients with a long progression free survival after docetaxel and without severe side effects during treatment, re-introduction of docetaxel might be a favorable treatment option [32, 33]. *Chapter three* describes the results of a phase II trial randomizing patients with a PFS of at least 3 months after initial docetaxel treatment, between re-treatment with docetaxel monotherapy or docetaxel combined with carboplatin. The primary endpoint of this study was the PFS (PSA and RECIST), with toxicity profile, PSA response, tumor response, OS and quality of life as secondary endpoints.

Some trials suggest that the beta-emitting radiopharmaceutical ^{188}Re-HEDP might give an OS benefit besides its excellent results in pain palliation[34]. We investigated the combination of ^{188}Re-HEDP with the second line of chemotherapy; cabazitaxel. *Chapter four* contains the results of the ReCab I trial, a phase I trial investigating the safety and feasibility of this combined treatment. The dose of cabazitaxel was increased until the optimal dose

was reached, in combination with 2 administrations of ^{188}Re-HEDP. This phase I trial is the base of the ReCab II trial, described in *chapter five*. In this open label phase II trial, patients were randomized between cabazitaxel 25mg/m^2 (standard treatment) or cabazitaxel 25mg/m^2 plus ^{188}Re-HEDP 40 MBq/kg after the second and fourth cycle of cabazitaxel. The aim of this trial was to investigate whether standard treatment with cabazitaxel could be optimized by the addition of ^{188}Re-HEDP in terms of PFS and OS, and quality of life.

Chapter six gives an overview of the current knowledge of treatment with radiopharmaceuticals. This review contains summarized information about the different radiopharmaceuticals as monotherapy, but also the different combinations with chemotherapy published in literature. The aim of this review is to clarify the benefits of radiopharmaceuticals in pain relief and improvement in quality of life. It also focuses on the optimal timing and the use of biomarkers in the treatment with radiopharmaceuticals.

Chapter seven compromises a summarizing discussion of the result presented in this thesis. The second part of this chapter describes a future perspective, in which the RaRe trial will be explained. This trial is a randomized phase III trial comparing the radiopharmaceuticals radium-223-chloride and rhenium-188-hydroxyethylidene diphosphonate. If Re-188-HEDP is at least non-inferior to radium-223-chloride, registration of Re-188-HEDP will be accomplished for the same purpose as radium-223-chloride. This will result in a less intensive treatment schedule for mCRPC patients, as re-188-HEDP will be administered 3 times once every 8 weeks, compared to 6 administrations every 4 weeks for radium-223-chloride. In addition, treatment with re-188-HEDP will be markedly less costly than radium-223-chloride. At last, this is the first phase III trial with a head-to-head comparison of the two radiopharmaceuticals in terms of pain palliation and quality of life.

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