Multidisciplinary treatment of metastatic prostate cancer

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7

Summarizing discussion and future perspective

Introduction

The aim of the studies described in this thesis is to improve the quality of life (QoL) and/or the duration of overall survival (OS) for patients with castration resistant prostate cancer (CRPC). Over the last decades, many new treatment modalities such as stereotactic body radiation therapy (SBRT), new chemotherapeutic agents (docetaxel and cabazitaxel) and radiopharmaceuticals became available[1-6]. All these treatment options have their own indications and timing in the course of the disease. The research in this thesis has focused on either the use of a specific treatment with relatively few side effects to delay a treatment option with long-term side effects (chapter 2), re-use of a proven effective treatment (chapter 3) to create an extra treatment line, or the combination of 2 effective treatment options to improve the QoL and OS (chapter 4 and 5). Overall, in the treatment of patients without curative perspectives, side effects and benefits of a treatment option should always be balanced and discussed with patients before a good decision can be made. In this summarizing discussion, we will discuss the main results and implications for clinical practice per trial. We will also provide a perspective over the possibilities in the future and new options for research.

SBRT to postpone androgen deprivation therapy

For patients with metastases of hormone sensitive prostate cancer, androgen deprivation therapy (ADT) is the standard first-line of treatment[7]. Despite high chances of a good response, ADT has several (long-term) side effects as fatigue, reduced or absent libido, sexual dysfunction and depression as well as insulin resistance and loss of bone mass[8, 9]. For patients with a high volume of disease, the addition of chemotherapy to ADT should be considered as this results in an increase in OS in this patient group[10]. On the other hand, a selection of patients presents with only a few metastases. Oligometastatic disease is typically defined as less than 5 metastases in bone and/or lymph nodes[11, 12]. In this specific patient group, SBRT might stabilise the disease for a while. In this time, ADT might not be needed and can, together with its side effects, be postponed to the moment the disease progresses. In **chapter 2** we describe the results of our retrospective trial in which we compare the ADT-free survival of patients with oligometastatic disease who were regularly treated with SBRT, with a comparable cohort of patients who were treated in a hospital not offering SBRT for this indication. Oligometastatic disease was diagnosed on [18F]fluoromethylcholine ([18F]FCH) PET/CT. For 43 SBRT treated patients and 20 non-

SBRT treated patients, data about the tumor characteristics, time between diagnosis of oligometastatic disease and start of ADT, and time between start of ADT and progression of disease were collected. Seven patients with an oligometastatic recurrence of the disease underwent a second course of SBRT on new metastases. The median time between the diagnosis of oligometastases and start of ADT was 17.3 months (95% CI 13.7-20.9) for SBRT treated patients, compared to 4.2 months (95% CI 0.0-9.0) for the non-SBRT treated patients, P<0.001. Once ADT was started, the median progression free survival (PFS) (development of castration resistant prostate cancer) was comparable between both groups (31.5 versus 26.9 months, P=0.54). However, only a small number of patients could be included in this last analysis (26 versus 19 patients) as the other patients still had stable disease on ADT at the time of analysis. In the patient who underwent a second [18F]FCH PET/CT because of a rising PSA (n=17), no new lesions were found in the high dose radiation field. In 15/17 patients, no [18F]FCH uptake was found in the treated lesions, and the uptake in the metastases of the 2 other patients had strongly diminished. As this is a small, retrospective trial, results should be interpreted with care. Patients were not randomized and start of ADT was determined by the treating physician. However, these results are more or less confirmed by the only prospective randomized trial in this field, the Stomp trial, published in 2018[13]. This phase II study randomized 62 patients with oligometastatic recurrence of hormone-sensitive prostate cancer to a surveillance group with PSA control every 3 months and the intervention group in which oligometastases were treated with metastases directed therapy (MDT) (mostly SBRT, retroperitoneal lymph node dissection in some patients). The median ADT-free survival was 13 months (80% CI 12-17) for the surveillance group versus 21 months (80% CI 14-19) in the intervention group, HR 0.60, P=0.11. The per-protocol analysis showed a median ADT-FS of 12 months (80% CI 7-17 months) versus 21 months (80% CI 16-28 months), HR 0.55, P=0.08. Only 5 patients experienced grade 1 toxicity, grade 2 or higher toxicity has not been reported. As the previous literature consisted of only low grade evidence from small case series, a systematic review published before our trial, concluded that metastases directed therapy MDT is promising, but required validation in clinical trials[14]. With the above described results, we think that MDT became even more interesting for validation in a phase III trial, which should include QoL during treatment and in the ADT free period as one of the endpoints. Besides, a longer follow up period in such a trial will provide more insight in the long-term survival, as our result suggest that progression free interval during ADT is comparable between both groups. This could suggest that survival might be longer by MDT although definitely more evidence is necessary to support this hypothesis.

As in most treatment strategies, the definition and inclusion of the right patient group is most important. Nowadays, more sensitive and specific diagnostic modalities than [18F]FCH PET/CT exist, such as the ^{68}Ga prostate-specific membrane antigen (PSMA) PET-CT and ^{18}Fluoride-PSMA PET-CT[15, 16]. With this new options, patients might be selected even better; patients with more metastases than thought based on the [18F]FCH PET/CT can be excluded whereas patients with 3 or 4 metastases on PSMA PET scan instead of 1 or 2 lesions on [18F]FCH PET/CT, can be treated on all lesions. However, no evidence exists on MDT based on PSMA PET-CT diagnosed oligometastatic disease, so many investigational opportunities exist.

Altogether, MDT is a very promising treatment modality for a carefully defined subgroup of patients. Further investigations should give more insight in the benefits in terms of OS and QoL.

Re-introduction of docetaxel

At some point during ADT, the prostate cancer will become castration resistant. At that moment, a choice should be made between enzalutamide / abiraterone, versus chemotherapy. In case of chemotherapy, docetaxel + prednisone is the first line of treatment[3, 17]. When progression occurs during or after treatment with docetaxel+ prednisone, nowadays the second line of chemotherapy is cabazitaxel+prednisone[4, 18]. At the start of the Recardo trial, described in **chapter 3,** only mitoxantrone+prednisone, for which no survival benefit was proven, was available as second line. So, re-introduction of docetaxel would be interesting. Now cabazitaxel is registered in second line, re-use of docetaxel might still be interesting as an extra treatment line for selected patients. The usual schedule of docetaxel consists of 10 cycles of docetaxel 75mg/m^2 for a maximum of 10 cycles. A proportion of the patients has a good response to docetaxel which can last for several months after treatment. It might be that, especially in patients with a longer response after initial treatment, the tumor is still sensitive to docetaxel. This does, of course, not apply to patients who progress during or shortly after docetaxel containing treatment. This hypothesis is supported by some retrospective data[19-21]. In chapter 3 we describe the results of our randomized phase II trial investigating the re-introduction of docetaxel. Patients with a progression free interval of at least 3 months after initial treatment with docetaxel could be included. As some previous trials suggest a synergistic effect of the combination of carboplatin and docetaxel[22, 23], patients were randomized

between a second course of docetaxel 75mg/m^2 3-weekly (arm A) or 3-weekly docetaxel 60 mg/m^2 plus carboplatin AUC 4 (arm B), both arms included prednisone 5mg twice a day during the whole treatment. The primary endpoint was PFS, with toxicity profile, PSA response and duration of PSA response, tumour response and OS as secondary endpoints. In total, 75 patients were randomized. The median PFS was comparable between both groups; 12.7 months (95% CI 9,9-17.5 months) for docetaxel monotherapy versus 11,7 months (95% CI 8.5-21.0 months) for the combined treatment, P=0.98. The same applies to the OS with 18.5 versus 18.9 months, P=0.79. Although this trial was terminated early due to insufficient recruitment, we consider these results as reliable. This because a conditional power analysis revealed the chance of a significant difference between both groups after completion of inclusion, based on the results of the included patients, is almost zero. We can conclude that addition of carboplatin to docetaxel re-treatment is not beneficial in this patient group. It might be the case that for patients with advanced prostate cancer and gained DNA repair defects (in BRACA 1/2 germline variants), platinum based treatment can be beneficial as this results in covalent adducts with cellular DNA resulting in DNA damage[24]. This might also be the case for patients with anaplastic prostate cancer[25].

In comparison to other post-docetaxel treatment options as abiraterone, enzalutamide, cabazitaxel and radium-223 chloride, the median PFS of 12.7 months in this trial is remarkably long[4, 5, 26, 27]. However, in the patient group included in our trial, the response to first line treatment with docetaxel was also quite long (11.9 and 12.4 months respectively). This suggest a highly selected patient group, which makes it hard to compare our data with the data of post-docetaxel treatment with other agents, as these trials included also patients with a less favorable response to first line docetaxel. So, the median PFS of 11.9 months for re-treatment with docetaxel is still very promising, but a strict selection of patients for this treatment option is necessary.

In the discussion of our published article, we stated that the results of the Recardo trial could also be of interest for patients treated upfront with the combination of ADT and docetaxel, which has become standard of care since the publication of the STAMPEDE and CHAARTED studies[28, 29]. In the meanwhile, follow-up results of patients treated with ADT alone or ADT+docetaxel in the GETUG-AFU 15 study became available[30]. In this retrospective study, data about the first treatment for progression (mainly docetaxel or bicalutamide) were collected from databases and medical records. In total, 134 patients treated with ADT alone and 111 patients treated with ADT plus docetaxel in first line were included, of whom 114 and 82 patients respectively received a second line of treatment

(docetaxel or bicalutamide mainly). The median time between first line treatment and the first treatment for mCRPC was 16 months (95% CI 10-24 months) for the ADT monotherapy group, and 26 months (95% CI 18-36) for patients treated with the combination. A decline in PSA > 50% from baseline after start of docetaxel in first-or second line treatment for mCRPC, was seen in 45% (36/80) of the patients previously treated with ADT, versus 14% (4/29) patients previously treated with the combination of ADT and docetaxel, P=0.07. The median biochemical PFS (bPFS) was 6.0 months (95% CI 4.4-7.7) versus 4.1 months (95% CI 1.3-4.9) respectively. So, in this specific, but in daily life increasing group of patients, rechallenge with docetaxel seems to be effective in only a limited number of patients. However, this is a small retrospective trial so data should be interpreted with care.

Surprisingly, in contrast to previously published articles and our data, no correlation for the efficacy of docetaxel rechallenge was found for the interval between docetaxel containing treatment and progression. One possible explanation might be a difference in included patients. The previously described results all included patients with a longer PFS on docetaxel monotherapy. In patients treated with ADT plus docetaxel, no definite conclusions can be drawn about the role of docetaxel alone, and the sensitivity of the tumor to docetaxel monotherapy. So, also patients with a better response to ADT are included in the group of patients with a longer PFS after initial treatment.

Besides, results for bicalutamide (the second most frequently used treatment in this cohort) were comparable to docetaxel re-treatment with a >50% PSA response in 43% and 17% of the patients (ADT alone versus ADT + docetaxel respectively), and a median bPFS of 5.1 months versus 3.2 months. So, response on bicalutamide was better for patients treated with ADT monotherapy. We would not expect this as the pre-treatment with docetaxel does not necessarily influence the response to bicalutamide (in contrast to the development of docetaxel resistance with pre-treatment). This might suggest a difference between both patient groups, also influencing the results of the docetaxel rechallenge.

As there are, to our best knowledge, no other prospective randomized trials in this field, we should use these data with care. As other studies show good results of a docetaxel rechallenge, we should not put this option aside for patients treated upfront with docetaxel, based on one retrospective trial. Further research is needed to investigate this in a prospective setting and find clinical of biochemical factors that might predict the response to a rechallenge.

Altogether, we think that a docetaxel rechallenge is a promising option in a selected group of patients, somewhere in their treatment schedule, despite several new treatment options.

Radiopharmaceuticals

Beside ADT, abiraterone/enzalutamide and chemotherapy, treatment with radio-pharmaceuticals is another option. Radiopharmaceuticals are radioactive drugs, either linked to bone-seeking ligands as bisphosphonates or with calcimimetic characteristics, that accumulate in regions of increased bone turnover, such as the osteoblastic bone metastases in mCRPC. These agents deliver the radiation precisely at the site of metastases, saving the healthy surroundings of the metastases. Most radiopharmaceuticals consist of beta-emitting particles (samarium, strontium, rhenium), only radium-223 chloride is an alfa-emitting radiopharmaceutical. Traditionally, beta-emitting radiopharmaceuticals are used for their excellent effect in pain palliation in advanced disease, whereas radium-223 chloride is at this moment the only radiopharmaceutical with a proven survival benefit. Despite the large phase III trial showing this survival benefit for radium-223 chloride, most evidence about beta-emitting radiopharmaceuticals consists of small trials including a wide variance of patients and different treatment combinations. In the review described in **chapter four** we provide an overview of the existing literature and define the gaps in our knowledge of this promising treatment modality.

In terms of survival we described, of course, the ALSYMPCA trial, showing a benefit in OS of 3.6 months for radium-223 chloride compared to placebo. These results are confirmed in literature in different trials in different patient populations worldwide[31-33]. For rhenium-188-HEDP two small trials suggest a survival benefit for repeated administration of rhenium-188-HEDP[34, 35]. Based on these results, we will perform a randomized phase III trial investigating this potential effect of rhenium-188-HEDP. This project will be described in more detail in the Future Perspectives of this section.

The effect of radiopharmaceuticals in the treatment of malignant bone pain is undeniably proven, with high response rates and long lasting pain palliation[6].

The theory behind the combination of radiopharmaceuticals with chemotherapy originates in the radio-sensitizing effect of chemotherapy in the treatment of head and neck and lung cancer. Although an in vitro study did not show a synergistic effect for the combination of rhenium-188 with taxanes, the significant additivity that was found in vitro does support

the theory that combination of radiopharmaceuticals with chemotherapy might result in a survival benefit[36].

Despite this theory and results, there are no large randomized trials combining chemotherapy with radiopharmaceuticals showing a survival benefit. This might be due to some shortcomings in the designs of these trials (late introduction of radiopharmaceuticals in the treatment schedule, lower dose of radiopharmaceuticals, single administration of radiopharmaceutical), a higher than expected drop-out rate, and the good results of monotherapy with docetaxel. A way to avoid some of these problems might be inclusion of patients at the moment of the planned administration of the first dose of radiopharmaceuticals to prevent early drop out.

In **chapter five and six** we describe the results of the ReCab I and II trial respectively. In our phase I trial, we proved that the combination of cabazitaxel 25 mg/m^2 with 2 administrations of rhenium-188-HEDP 40 MBq/kg is feasible and save. Both dosages are the standard dose of treatment, in contrast to some previously performed trials as the Trapeze trial and the TAXIUM I & II. However, during our inclusion period, the Proselica trial showed that cabazitaxel 20mg/m^2 is non-inferior to cabazitaxel 25mg/m^2, so we allowed the treating physician to reduce the dose of cabazitaxel if indicated[37].

Unfortunately, the ReCab phase II trial had to be discontinued early due to long lasting delivery problems of the generators needed for the production of rhenium-188-HEDP. However, because of the clear results of the conditional power analysis, we think the results of the 53 included patients are representative and usable. With a median follow-up of 13.4 months, all patients had progressive disease at the time of analysis. The median PFS was 4.8 months (95% CI 2,4-7,2 months) in the standard treatment arm and 6,4 months (95% CI 4,7-8,3) in the intervention arm (P =0.95). As might be expected with these results, also no significant difference was found in OS. The conditional power analysis revealed a chance of 1.6% of a significant difference in PFS after inclusion of the planned 86 patients, which is too low to continue the trial. Previously, we described that in earlier performed trials the moment of inclusion was too early, resulting in a high drop-out range before one or the total of intended dosages of radiopharmaceuticals was administered. The same problem appeared in our trial, as only 65% of the patients received both administrations of rhenium-188-HEDP. Randomization after two cycles of cabazitaxel (just before the first administration of rhenium-188-HEDP) might be of help, although this will not solve the whole problem. All included patients did receive one injection of rhenium-188-HEDP, but in this patient population progression of disease might occur fast, even after an initial response to treatment.

Besides, selection of patients who would benefit most from treatment with radiopharmaceuticals will be very helpful. Unfortunately, we don't have good predictive biomarkers as most of the markers we have are more prognostic than predictive.

Another question in the use of radiopharmaceuticals is the timing of administration. Nowadays, in regular practice they are only used as monotherapy. Some trials show that further treatment following radiopharmaceuticals is feasible and save, thereby opening the possibility of introduction of these agents earlier in the treatment schedule[38, 39]. The other way around, a prespecified subgroup analysis of the Alsympca trial showed that the efficacy of radium-223 chloride was equal in patients who were and who were not previously treated with docetaxel. Recently, the 2 year follow-up data of a phase I/II study investigating a rechallenge with radium-223-chloride were published[40]. In this trial, 44 patients who were treated with a second course of radium-223-chloride were followed for 2 years. Although safety was the primary endpoint, exploratory objectives about response were reported as well. Median radiographic PFS was 9.9 months, median time to PSA progression was 2.2 months with a median OS of 24.4 months. No new safety concerns or drug-related adverse events appeared. So, as retreatment with radium-223 chloride in this small, selected patient group seems save, randomized phase II / III trials with PFS and OS as endpoints, are necessary to investigate the role of the re-use of this expensive but promising treatment option.

Future perspectives of radiopharmaceutical treatment

In the field of combining radiopharmaceuticals with chemotherapy, the DORA trial (NCT03574571) is very interesting. This trial, now including, will show us the results of the combination of docetaxel/prednisone with radium-223-chloride. This trial will set a proof of concept whether it is possible to improve the OS of docetaxel monotherapy (investigating the theory that previous trials have failed due to the effect of docetaxel by itself). Another difference in this trial is the administration of the radiopharmaceutical and chemotherapy simultaneously, where previous trials interrupted the administration of the chemotherapy.

As described above, some small trials suggest a benefit in OS for rhenium-188-HEDP as well. We will investigate this potential in the RaRe trial (NCT03458559). We aim to include 402 patients who will be randomized between 6 injections of radium-223-chloride

50kBq/kg every 4 weeks, or 3 injections of rhenium-188-HEDP 40MBq/kg every 8 weeks. The use of rhenium-188-HEDP instead of radium-223-chloride, if at least a comparable survival benefit can be proven, has several advantages. In the first place, patients only need 3 injections of rhenium-188-HEDP, which reduces the number hospital visits. Thereby, rhenium-188-HEDP has an excellent effect on pain. Although there is no head-to-head comparison between the two agents for this purpose, it seems that the effect on pain is slightly better for rhenium-188-HEDP than for radium-223-chloride. Of course, pain palliation will be a major endpoint in the RaRe trial. Another advantage is that rhenium-188-HEDP is quickly available as it can be produced in hospitals itself, whereas radium-223-chloride needs to be ordered one week in advance due to long transportation logistics. Another very important factor are the costs; the costs for rhenium-188-HEDP are €5000 for 3 injections (the whole treatment) compared to €30.000 for 6 injections of radium-223-chloride (also the whole treatment). So, a cost-effectiveness analysis will be part of the RaRe trial as well.

Conclusion

In conclusion, several treatment modalities exist all with their own limitations and advantages at different moments during the course of metastatic prostate cancer. We think that SBRT in case of oligometastatic disease could be considered to postpone ADT. Rechallenge of docetaxel might be of use for patients with a remarkable good response and tolerance of docetaxel. For the combination of radiopharmaceuticals with chemotherapy is not enough evidence in terms of improvement of OS at this moment. However, radiopharmaceuticals have a remarkable good effect on bone pain, so in selected patients it might be combined if chemotherapy alone does not provide enough pain palliation. For the future, we are awaiting the results of the DORA and RARE trial to learn more about improvement of overall survival by using radiopharmaceuticals alone or in combination with chemotherapy.

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