Multidisciplinary treatment of metastatic prostate cancer

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A phase II trial of Cabazitaxel with or without Rhenium-188-HEDP in patients with metastatic castration resistant prostate cancer who progressed on or after a docetaxel containing treatment; The ReCab II trial

Submitted

Abstract

Background

Rhenium-188-HEDP is a beta-emitting radiopharmaceutical used for palliation of bone pain for patients with metastatic castration resistant prostate cancer (CRPC). Some trials suggest that treatment with beta-emitting radiopharmaceuticals might also result in a survival benefit. This trial investigated whether the addition of rhenium-188-HEDP to standard treatment with cabazitaxel could result in an improvement of progression-free survival (PFS), overall survival (OS), pain palliation and quality of life (QoL).

Patients and methods

Patients with bone metastases of CRPC were randomized between standard treatment with cabazitaxel 25mg/m^2 every three weeks for 10 cycles, or 10 cycles of cabazitaxel 25mg/m^2 plus two cycles of rhenium-188-HEDP 40 MBq/kg after the second and fourth cabazitaxel administration. The primary endpoint was progression free survival, with overall survival, pain palliation and quality of life as secondary endpoints.

Results

Twenty five patients were included in the standard treatment arm, and 28 patients in the combination arm. We had to put the trial on hold after inclusion of 53 patients, due to production problems of the ^{188}Tungsten-generator which is necessary for the production of rhenium-188-HEDP. An efficacy analysis was performed for the primary endpoint at 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 versus 6.4 months (95% CI 4.7-8.3 months) in the intervention arm (*P* =0.95). A conditional power analysis showed a chance of 1.6% of finding a significant difference between both arms after inclusion of the intended 86 patients, after which we decided to stop the trial. No differences in quality of life or pain relief were observed between both treatment groups.

Conclusion

Addition of rhenium-188-HEDP to cabazitaxel in patients with mCRPC did not result in a benefit in PFS or OS, nor in pain relief or quality of life.

Introduction

In patients with metastatic castration resistant prostate cancer (mCRPC), bone is the most common site of metastases, occurring in more than 90% of the patients[1]. Nowadays, in a rapidly evolving treatment field, cabazitaxel is the recommended chemotherapy in patients who have progressed during or after docetaxel[2]. However, with a median overall survival of 15.1 months for patients treated in the pivotal TROPIC trial for cabazitaxel, the benefit is still moderate. Treatment with radiopharmaceuticals targeting the osteoblastic bone metastases specifically, can also result in a survival benefit in this patient group. This has been shown for Radium-223 chloride, an alfa-emitting radiopharmaceutical[3]. Early studies suggest that treatment of mCRPC patients with the beta-emitting- radiopharmaceutical rhenium-188-HEDP (^{188}Re-HEDP) might result in an OS benefit as well[4, 5].

At this moment, ^{188}Re-HEDP is known and used for its effect on pain palliation in this patient group, with significant and durable pain responses in up to 80% of the patients[6].

Previously, we investigated the combination of ^{188}Re-HEDP with docetaxel (first line chemotherapy) in mCRPC in the Taxium II trial. This combination did not result in an overall survival benefit compared to docetaxel monotherapy[7]. Several factors might be related to the negative outcome of this trial. At first, the study was underpowered due to a higher than expected drop-out rate, even before the first administration of ^{188}Re-HEDP. Furthermore, the dose of the second administration of ^{188}Re-HEDP might have been to low (half of the standard dose). Besides, many other trials combining docetaxel with another agent failed, implicating that docetaxel by itself is a very effective first-line treatment[8-10]. However, a per protocol analysis in this trial showed a significant improvement in OS, suggesting a disease modifying effect of repeated ^{188}Re-HEDP.

Besides the Taxium II trial, some other trials combining beta-emitting radiopharmaceuticals with chemotherapy were negative, which might have been caused by the same problems in the design of these trials[11]. For example, in the Trapeze trial strontium-89-chloride was introduced in the docetaxel schedule after the sixth cycle of docetaxel. This resulted in a drop-out of 33% of the patients before introduction of the investigational agent. Besides, patients receiving the radiopharmaceutical were those with a good response to docetaxel due to drop-out of the non-responders[12]. The hypothesis that docetaxel by itself is so effective that it overrules the effect of ^{188}Re-HEDP is strengthened by some trials showing a OS benefit when the beta-emitting radiopharmaceutical strontium-89-chloride is combined with a less effective

chemotherapeutic regimen (doxorubicin+ketoconazole alternating with estramustine+vinblastine)[13, 14].
In addition to these strontrium-89-chloride trials suggesting a potential effect on OS, some other trials or subgroup analysis did show promising results for beta-emitting radiopharmaceuticals as well[4, 5, 7, 13].

To our best knowledge, ^{188}Re-HEDP or other radiopharmaceuticals have never been combined with cabazitaxel. A trial combining radiopharmaceuticals with cabazitaxel will include a different patient population than previously performed trials, as these patients have a more advanced stage of disease with a higher number and volume of bone metastases.

In our current trial, we build upon the experiences from previous trials by including patients in a more advanced setting (as cabazitaxel is the second line of chemotherapy), introducing ^{188}Re-HEDP earlier in the chemotherapy schedule and in a higher dose. We will investigate the effect of the combination of rhenium-188-HEDP with cabazitaxel on the progression free survival and quality of life in this specific patient population with a generally high volume of osseous metastases. Previously, we demonstrated in a phase I trial that this combination is feasible and save[15].

Patients and methods

Patients

Patients were eligible if they had histologically confirmed prostate cancer that had metastasized to bone and evidence of disease progression during or after treatment with docetaxel. Disease progression was defined either as progression according to the RECIST criteria, or, in case of non-measurable lesions, at least 2 consecutive rises in PSA over a reference value taken at least 1 week apart or appearance of a new lesion[16]. Uptake of ^{99m}Tc-hydroxymethylene diphosphonate in bone metastases at bone scintigraphy was required to establish the osteoblastic character of these metastases. Previous exposure to radiopharmaceuticals was not allowed within 2 months prior to inclusions, and patients had to be cabazitaxel naïve. External body radiation therapy for symptomatic bone metastases was allowed prior to or during trial participation.
The World Health Organization performance status had to be 0-1, age >18 years and an adequate bone marrow function was required (defined as an absolute neutrophil count

(ANC) >1.5x10^9/L, platelet count > 100x10^9/L and hemoglobin >9.0 g/dL) as well as an adequate renal and liver function. The minimal life expectancy was 3 months and patients had to be able to receive cabazitaxel. Patients using LH-RH agonist had to continue their treatment and a serum testosterone <50 ng/dl (<1.7 nmol/L) was required.

In total, 7 medical centers in the Netherlands participated in this randomised phase II trial. The first patient was included in June 2016 and inclusion continued until August 2018. At that moment, we had to put the inclusion on hold due to worldwide production problems of the ^{188}Tunsten-generator which is necessary for the production of ^{188}Re-HEDP.

This study was approved by the institutional review board and medical ethics committee for all participating sites. Informed consent was obtained from all individual participants in the study.

Study Design

The safety and feasibility of the combination of cabazitaxel with ^{188}Re-HEDP was investigated in the phase I part of this trial, as previously published[15].

Before randomization, included patients were stratified for Bone Scan Index (< or ≥50) and including hospital[17]. They were randomly assigned to one of the treatment arms; in arm A patients received a maximum of 10 cycles of cabazitaxel 25 mg/m^2 every three weeks, whereas in arm B an administration of ^{188}Re-HEDP 40 MBq/kg (with a maximum dosage of 3300 MBq) after the second and fourth cycle of cabazitaxel was added. Time between the administration of ^{188}Re-HEDP and the next cycle of cabazitaxel was

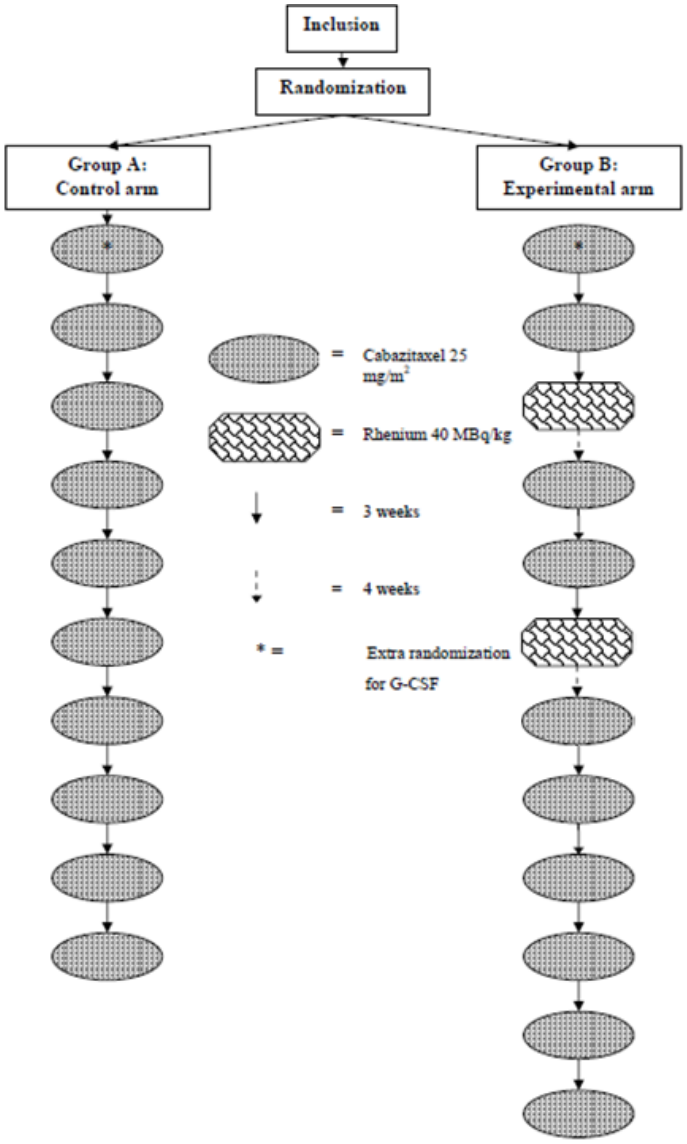

Figure 1 Treatment schedule

4 weeks, taking into account the nadir of thrombocytopenia 4 weeks after treatment[18, 19]. The treatment schedule is summarized in Figure 1. Patients and treating physicians were not blinded. Administration of cabazitaxel took place in the participating hospital. ^{188}Re-HEDP was produced and administered in the Meander Medical Center in Amersfoort, The Netherlands, according to previously published methods[20]. All patients received prednisolone 10mg daily during the treatment phase.

At baseline, a full medical history and physical examination were performed, together with laboratory tests (full blood count, electrolytes, renal and liver function, PSA and testosterone) and imaging (bone-scan and assessment of evaluable disease by chest x-ray or CT and CT of the abdomen). Patients were asked to complete a pain assessment using a visual analogue scale (VAS) and a questionnaire about their quality of life (EORTC QLQ-30). PSA, the VAS score and QLQ-questionnaire were repeated just before every treatment cycle and monthly after completion of treatment until progression of disease occurred. Imaging was repeated pre-cycle 7 and at the end of treatment, and in case of clinical progression or a rising PSA in 2 consecutive measurements.

The primary endpoint in this trial was progression-free survival (PFS), measured from the date of randomization until prove of progression was established. PFS was a composite endpoint of PSA progression (increase in PSA ≥25% and ≥2ng/mL above the nadir, confirmed by a second value 3 or more weeks later), radiographic progression (according to RECIST criteria for soft tissue lesions on CT-scan or the appearance of ≥2 new bone lesions for bone metastases) or death, according to the recommendations of the Prostate Cancer Clinical Trials Working Group 2[21].

Secondary endpoints were OS, PSA response, pain response and impact on QOL and the toxicity profile of both study arms.

Statistical analysis

SPSS Statistics, version 22.0 (IBM) was used for statistical analysis. The primary analysis was planned to be performed as a stratified logrank test. The targeted improvement was a PFS at 4 months of 40% in the control group to 60% in the intervention group. To provide 80% power of detecting the targeted improvement, 39 patients per treatment arm were required. Considering a potential (early) drop-out rate of 10%, a total of 86 patient were planned to be randomized. Time to progression was analyzed using the Kaplan-Meier method. Due the worldwide production problems of the ^{188}Tungsten-generator, necessary for the production of ^{188}Re-HEDP, we were forced to stop inclusions, as described in the

results section. Because of these long-lasting problems, we decided to perform a conditional power analysis of the logrank test, to investigate whether a re-start of the trial would be reasonable.

Results

In total, 53 patients (25 in the standard treatment arm, 28 in the intervention arm) were included between June 2016 and August 2018.

Baseline characteristics were well balanced between both treatment groups (Table 1).

The median number of treatment cycles was 5.8 (range 1-10) in the cabazitaxel group versus 7.2 (3-12) in the intervention arm (p=0.08). In total, 5 patients (20%) completed the whole treatment protocol in arm A, whereas 7 patients (25%) in arm B received at least 10 treatment cycles of whom 4 (14.3%) completed the entire treatment protocol (12 treatment cycles). All patients in the intervention arm received at least one injection with ^{188}Re-HEDP, 18 patients received both planned ^{188}Re-HEDP injections (64.3%).

Median follow up was 13.4 months (range 2.1 – 28.3 months). All patients had progressive disease at the time of the conditional power 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 months) in the intervention arm (P =0.95), Figure 2. With a hazard ratio of 1.018, the conditional power after inclusion of 86 instead of 53 patients would have been 1.6% (range 1.5 – 2.2%). This means that, based on the results of the 53 included patients, the chance of a significant difference between both arms (in either direction) after inclusion of 86 patients would be 1.6%. In other words, after completion of the trial, the chance of a non-significant difference between both arms would be 98.4%. Due to the low number of patients, a subgroup analysis was not possible. This also applies to a per protocol analysis, as only 5 patients in the control arm and 4 patients in the intervention arm could be included in such a calculation.

At the time of analysis, 25 patients were deceased; 12 in the control group and 13 in the intervention arm. The median OS was 21.5 months (95% CI 5.7-37.2 months) in arm A, versus 25.9 months (95% CI 7.8-44.0 months) in arm B, P=0.6 (Figure 3).

Table 1 Baseline characteristics

	Cabazitaxel (n=25)	**Cabazitaxel + rhenium-188-HEDP (n=28)**
Median age (range)	69.8 (49-81)	69.9 (48-79)
Gleason score at diagnosis		
≤6	1 (4%)	1 (3.5%)
7-8	14 (56%)	13 (46.4%)
≥9	10 (40%)	14 (50%)
Median time between first diagnosis PC and inclusion	45.8 (4.0-140.2)	41.8 (16.4-101.8)
WHO performance (%)		
0	1 (4%)	5 (17.9%)
1	12 (48%)	17 (68%)
2	3 (12%)	0
NA	7 (28%)	9 (32%)
Bone scan index		
<50	14 (56%)	14 (50%)
≥50	11 (44%)	14 (50%)
Median number of prior treatment cycles*	2	2
Median biochemical values (range)		
Hemoglobin	7.6 (5.5-8.6)	7.9 (6.1-10.0)
Alkaline phosphatase	203 (64-797)	148 (53-417)
LD	244 (192-709)	215 (182-394)
PSA	151 (10-1201)	110 (28-301)

*systemic treatment for mCRPC including docetaxel

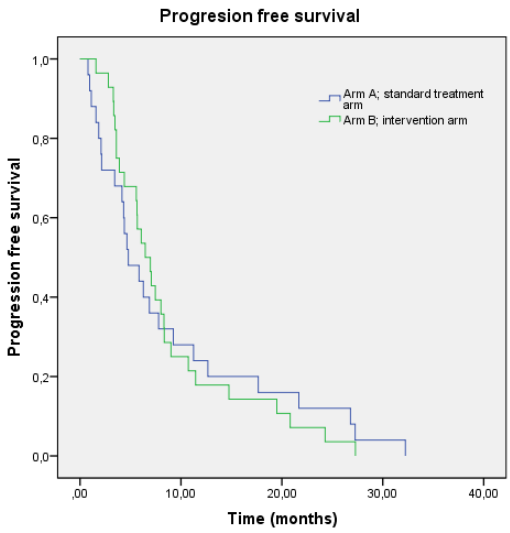

Figure 2 Progression free survival (intention to treat analysis)

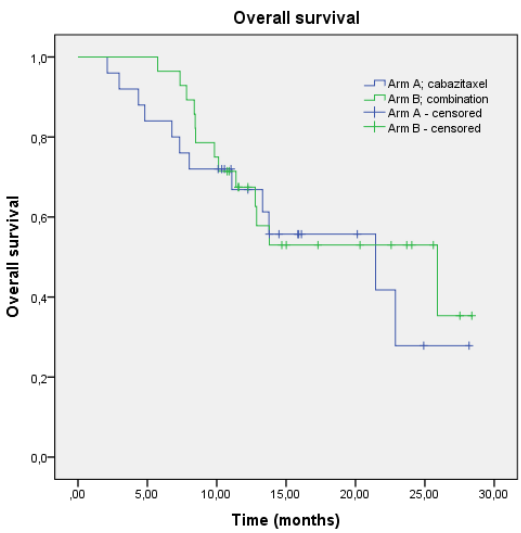

Figure 3 Overall survival

Table 2 Median and mean VAS scores

	Cabazitaxel	**Cabazitaxel + rhenium-188-HEDP**	**Cabazitaxel**	**Cabazitaxel+ rhenium-188-HEDP**	**P-value***
	Median	Median	Mean	Mean	
Baseline (n= 51)	7	3.5	6.0	3.8	0.005
Pre-cycle 4 (n=34)	2	2.5	2.7	3.1	0.67
Pre-cycle 7 (n=17)	4	2	4.4	2.7	0.28
End of treatment (n=38)	5	2	4.9	2.3	0.06

*P-value calculated using independent sample T-test for remaining data

Table 3 Comparison of mean QLQ-30 scores between both treatment arms

	Cabazitaxel	**Cabazitaxel + rhenium-188-HEDP**	**P-value***
Baseline (n= 51)	9.2 (SD 2.2)	10.5 (2.0)	0.046
Pre-cycle 2	10.0 (3.4)	10.68 (1.9)	0.44
Pre-cycle 3	12.3 (1.3)	11.0 (1.7)	0.28
Pre-cycle 4	10.1 (3.4)	10.6 (1.7)	0.59
Pre-cycle 5	11.5 (2.8)	11.1 (2.1)	0.68
Pre-cycle 6	10.8 (2.7)	9.9 (2.2)	0.44
Pre-cycle 7	10.7 (3.0)	10.8 (2.0)	0.95
Pre-cycle 8	12.2 (1.3)	10.2 (2.5)	0.13
Pre-cycle 9	11.3 (2.5)	9.1 (3.3)	0.33
Pre-cycle 10	11.1 (2.1)	11.8 (2.3)	0.57
EOT	9.2 (3.2)	10.2 (2.4)	0.33

Of 51 patients, the VAS score at baseline was documented. The median VAS score of all included patients was 5 (median VAS in the cabazitaxel group 7, in the cabazitaxel plus ^{188}Re-HEDP 3.5). Pre-cycle 4 (so, after 3 cycles of cabazitaxel or 2 cycles of cabazitaxel plus 1 cycle of ^{188}Re-HEDP) the median VAS score declined to 2 in the overall population, to 2 in the cabazitaxel group and 2.5 in the combination arm. Pre cycle 7 (6 cycles cabazitaxel or 4 cycles cabazitaxel + 2 cycles ^{188}Re-HEDP) median VAS score was 4 in the cabazitaxel arm and 2 in the combination arm. At the end of treatment, median VAS score in arm A was 5 and 2 in the ^{188}Re-HEDP arm. Only the difference between treatment groups at baseline was statistically significant (P = 0.005), Table 2.

The scores on the QLQ-C30 questionnaire were significant better in the intervention arm. However, as displayed in Table 3, no significant differences or changes existed between the two groups during or after treatment. We didn't have enough data to draw definite conclusions about the VAS score or QLQ-30 score in the follow up after treatment had been completed.

Also, a safety analysis was performed. All patients in both treatment groups had at least one adverse event of any grade. Anemia occurred in all participating patients. Adverse events of grade 3 or higher occurred 28 times in both treatment groups. Non-hematological adverse events ≥ grade 3 were also equal in both groups with 13 events (table 4). As was expected, thrombocytopenia grade 1-2 was more common in the intervention group, as thrombocytopenia is a well-known side effect of rhenium-188-HEDP. This did not result in an increase in ≥ grade 3 thrombocytopenia. Serious adverse events occurred 27 times in 22 patients, of which 16 were (possibly) related to the treatment (table 5). Thirteen events occurred in arm A (48%) versus 14 in arm B (52%). In both arms, 8 events were treatment related. No grade 5 adverse events related to the treatment were reported.

Discussion

The aim of this trial was to investigate whether the addition of the beta-emitting radiopharmaceutical ^{188}Re-HEDP to standard treatment with cabazitaxel would result in a longer PFS and / or better pain palliation and QoL for patients with castration resistant prostate cancer metastatic to bone, who progressed during or after treatment with docetaxel. We were forced to stop inclusions due to world-wide production problems of the ^{188}Tungsten-generator necessary for the production of ^{188}Re-HEDP. We thus decided to analyze the 53 patients enrolled and calculate the conditional power.

Although median PFS was longer in the combination group, no statistically significant difference in PFS was found between both treatment groups. On top of that, the conditional power analysis, based on the available data revealed a chance of 1.6% of finding a significant difference between treatment groups after inclusion of the intended 86 patients. As we considered this chance was to small, we decided to stop the trial definitely.

We tried to avoid problems in the design of the trial, as learned from previous trials combining radiopharmaceuticals with chemotherapy as described in the introduction. We increased the dose of ^{188} Re-HEDP compared to the Taxium II trial and introduced ^{188} Re-

HEDP earlier in the treatment schedule. Unfortunately, we were not able to complete the trial, resulting in an underpowered study. Although we tried to improve the number of patients receiving the intended dose of the radiopharmaceutical by introducing ^{188}Re-HEDP earlier in the schedule, still 35% of the patients received only 1 injection due to early drop-out. This might have influenced the results, as we know from previous trials that repeated injections of ^{188}RE-HEDP significantly increase the survival compared to a single injection[4].

In future studies, the problem of early drop out might be solved by including and randomizing patients with a proven treatment effect after 2 cycles of cabazitaxel, or another chemotherapeutic agent. This will prevent early drop-out due to progression during the chemotherapeutic treatment and improve the number of patients who might have benefit of the combined treatment accordingly.

In the presented ReCab trial we observed that the PFS of both treatment groups was longer than has been described in previous studies. The registration trial of cabazitaxel, the TROPIC trial, showed a PFS of 2.8 months in the cabazitaxel arm, with an OS of 15.1 months. In the ReCab trial, this is 4.8 and 6.4 months for PFS, and 21.5 and 25.9 months for OS respectively. This difference might be partially caused by the inclusion of a slightly different patient group in the ReCab trial. Although median PSA was more or less comparable, 31% of the patients in the Tropic trial had received at least 2 chemotherapeutic regimens (of whom 15% had received 2 regimes of docetaxel), whereas all patients in the ReCab had been treated with 1 schedule of docetaxel and no other chemotherapeutic agents. Also, patients in the Tropic trial had a relatively low median time of PFS after the last cycle of docetaxel (0.7 months). A difference in the design of the trials might also have influenced the outcome. The Tropic trial implemented CT-scans and bone scans more frequently, which can result in an earlier detection of radiologic progression. Besides, since publication of the Tropic trial in 2010, more subsequent treatment options have become available, which might influence the OS in our trial as well.

We could speculate that the inclusion of a patient group with a better than expected response to cabazitaxel might have influenced or diminished the effects of ^{188}Re-HEDP, as we supposed to be the case for docetaxel as well as described above. However, we don't have evidence for this theory in the case of cabazitaxel.

As we mentioned, this trial was underpowered due to early discontinuation of the inclusion due to logistic problems with the production of the ^{188}Tungsten-generator. This is probably not so relevant for the conclusion, due to the very low conditional power of 1.6%.

A very interesting trial, now open for inclusion, is the DORA trial (NCT03574571). In this trial, docetaxel in first line is combined with the alpha-emitting radiopharmaceutical radium-223-chloride, for which an OS benefit by itself has already been proven. This trial investigates the addition of 6 cycles of radium-223-chloride 55 kBq/kg to docetaxel (60 mg/m^2 3-weekly) versus docetaxel 75mg/m^2. This trial is based on promising data of a phase I/IIa trial, showing that this combination is feasible and save[22]. A total of 53 patients were randomized; patients in the docetaxel+radium-223 group had a more pronounced PSA response and a longer time to PSA progression than patients with docetaxel monotherapy. Thereby, changes in bone maker levels (ALP, P1NP) indicated a better suppression of osteoblastic activity in the combination arm, and an antitumor effect was suggested in both arms by decreasing circulating tumor cells. Another interesting outcome of this phase I trial is the feasibility of concomitant administration of a radiopharmaceutical with chemotherapy, as previous studies mainly used a sequential schedule. This raises the question whether concomitant administration of ^{188}Re-HEDP with docetaxel or cabazitaxel might result in better outcomes, as the administration of chemotherapy is not interrupted by the administration of ^{188}Re-HEDP. Besides, in vitro data showed that taxanes might function as radiosensitizers, which can improve the effect of concomitant administration even more[23].

Participating patients preferred a schedule of cabazitaxel + ^{188}Re-HEDP, as they experience a 'drug-holiday' in the period of administration of ^{188}Re-HEDP due to the low toxicity profile of this agent. However, we were not able to prove a benefit in QoL or pain palliation for the combination compared to cabazitaxel monotherapy. As pain relief by repeated ^{188}Re-HEDP can last for a few months, there might be an effect in VAS and QoL in the period after the end of treatment. As we learned from the Taxium II trial, we tried to gain information of this period. But, as we could expect, many patients developed rapid progression during or after treatment. Combined with the premature termination of the trial, we were unable to collect sufficient data to compare both groups in terms of pain and QoL after the end of treatment.

Overall, at this moment, there is not enough evidence to introduce the combination of chemotherapy and radiopharmaceuticals in clinical practice. In this respect, the results of the DORA trial are eagerly awaited.

Conclusion

Combining cabazitaxel with rhenium-188-HEDP in patients with mCRPC did not result in a benefit in PFS or OS, nor in pain relief or quality of life, compared to cabazitaxel monotherapy.

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