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Bouman, E.W.

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Bone-targeting radiopharmaceuticals as monotherapy or combined with chemotherapy in patients with castration-resistant prostate cancer metastatic to bone; a review

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Abstract

In patients with metastatic castration-resistant prostate cancer, bone is the most common site for metastases. Due to their osteoblastic character, these lesions are very suitable for treatment with bone-seeking radiopharmaceuticals (RPs). Nowadays, radium-223-chloride is the only RP with a proven benefit in overall survival (OS), while the β-emitting RPs are used for pain palliation. In the past, many trials investigating RPs alone, or in combination with chemotherapy have been performed. Due to different designs, characteristics of included patients and used chemotherapeutical and radiopharmaceutical regimens, interpretation of the promising data and positioning of RPs in the treatment of metastatic prostate cancer has become difficult. In this review, we provide an overview of the existing data per radiopharmaceutical with a focus on the different RPs in combination with chemotherapy. Furthermore, we aim to clarify the benefits on pain response and quality of life. At last, we focus on the optimal timing and use of biomarkers in the treatment of patients with castration-resistant prostate cancer with radiopharmaceuticals.

Introduction

Prostate cancer is the most common cancer in elderly men, with bone as the most common site for metastases[1]. These lesions cause pain and fractures, impair the quality of life, increase the costs of treatment and are a major cause of death[2]. For patients with metastatic castration resistant prostate cancer (mCRPC) several therapeutic options exist, including hormonal treatment, bisphosphonates, RANK-ligand inhibitors, chemotherapy, immunotherapy and external beam radiotherapy[3], all with their own benefits, limitations and side effects. The osteoblastic character of these bone lesions makes them suitable for treatment with bone-targeting radiopharmaceuticals (RPs) as well. Bone-targeted treatment can be accomplished with calcimimetic agents (like radium-223-chloride and strontium-89-chloride) or with phosphonate-based radiopharmaceuticals (like samarium-153-EDTMP and rhenium-188-HEDP). Therefore, osteoblastic features of metastases are required to acquire potential benefit. After osteoblastic targeting, the radionuclides in these therapeutic radiopharmaceuticals deliver their energy only over a short range, thereby sparing healthy tissue.

In clinical practice, both alpha-emitting (radium-223-chloride) and beta-emitting RPs (strontium-89- chloride, samarium-153-EDTMP and rhenium-188 HEDP) are used. The main differences between these RPs are the maximum range of radiation (<0.1 mm for radium-223-chloride versus 2.5-10 mm for the beta-emitting RPs) and the maximum energy (5.78 MeV for radium-223 versus 0.81-2.12 MeV for the beta-emitters). Besides, compared to radium-223-chloride which has a relative long half-life (11.4 days), RPs as rhenium-188-HEDP (half-life 0.7 days) and samarium-153-EDTMP (half-life 1.9 days), provide the possibility of higher dosing, achieving a higher dose rate, possibly leading to an increased cell death (Table 1)[4, 5]. Alfa-emitting particles travel in straight lines, causing a higher linear energy transfer (80-100 keV/µm) than beta-emitting particles which scatter around leading to a lower linear energy transfer (0.2 keV/µm).

Table 1 physical characteristics of radionuclides

Radionuclide	Half-life (days)	Energy (MeV)	Emission	Range (mm)
strontium-89	50,57	1,46	β	6,6
samarium-153	1,90	0,71	β/γ	3,1
rhenium-186	3,75	1,07	β/γ	4,5
rhenium-188	0,70	2,12	β/γ	10,2
radium-223	11,43	5,72	α	<0,1

Hereby, the same dose of alfa-emitting RPs are more likely to cause double-strand DNA breaks than beta-emitting RPs (more single strand DNA breaks that are less viable to cause cell-death). On the other hand, from traditionally external beam radiotherapy it is known that the same dose of radiation given in one fraction is more effective than the same dose obtained from continuous low-dose administration, which might be in favor of the beta-emitting RPs[5].

Traditionally, the beta-emitting RPs have been used for pain palliation. Since a survival benefit has been proven for radium-223-chloride, treatment with RPs has become more common[6]. Besides, some studies suggest that there might be a survival benefit for the other RPs as well, although no large phase III trials have been performed to prove this yet[7, 8]. Furthermore, the combination of RPs with chemotherapy or hormonal therapy is a promising treatment option[9, 10].

In this field with a variety in treatment options, RPs are still underutilized which might be explained by a poor understanding of the appropriateness and full potential of this treatment by treating oncologists, and the incorrect assumption that radionuclides are only useful in patients with extensive bone disease. Also, a fear for hematologic side effects might still exist, although several trials show that this is usually limited and tend to recover quickly after treatment[11, 12]. Concerns about an initial pain flair might exist, and although this occurs in 10-20% of the patients, the intensity is usually mild, transient and predictive of a good response[13].

As the existing evidence is based on trials with a wide variance in design, patient populations, treatment combinations and sample size, the aim of this review is to provide an overview of the relevant trials and evidence in this field.

Monotherapy with radiopharmaceuticals

As described above, RPs can be used for survival benefit and/or pain relief. In this chapter, we will review the efficacy of the different radiopharmaceuticals for both indications. The results for monotherapy are summarized in Table 2 (survival), result for the combination with chemotherapy are displayed in Table 3 (survival) and Table 4 (PFS, PSA response and pain relief).

Table 2 Effect of monotherapy with radiopharmaceuticals on survival

Trial	Radiopharmaceutical	N	Randomization	OS months (range)	p-value
Buchali 1988[18]	Strontium-89-chloride 75 MBq	49	placebo:strontium 1:1	2-year survival;4% versus 46%	<0,05
Parker 2013[6]	Radium-223-chloride 50 kBq/kg	921	placebo:radium 1:2	11,3 versus 14,9	<0,001
Alva 2017[14]	Radium-223-chloride 50 kBq/kg	145	Retrospective	15,7 (13,0-22,5)	NA
Wong 2017[15]	Radium-223-chloride 50 kBq/kg	64	Retrospective	12,9 (1,1-34,2)	NA
Palmedo 2003[7]	Rhenium-188-HEDP 40,7 MBq/kg	64	Randomized: 1 or 2 doses	7,0 versus 12,7	0,043
Biersack 2011[8]	Rhenium-188-HEDP 2.96-3.33 MBq	50	Retrospective; 1,2 or 3 doses	4,5 vs 9,98 vs 15,66	0,0001
Denis-Bacelar 2017[16]	Rhenium-186-HEDP (increasing dose)	57	Retrospective; phase I/II trials	15,7	NA

Table 3 Overall survival in different combinations of radiopharmaceuticals and chemotherapy

Trial	Radionuclide	Chemotherapy	Randomization	N	OS (months)	p-value
Sciuto 1996[10]	Sr-89 148MBq (1x)	carboplatin day 7+21 (1x) (seq.)	Sr-89 mono (1x) versus Sr-89+carbo(1x)	30	5,7 vs 8,1 months	NS
Sciuto 2002[24]	Sr-89 148MBq (1x)	cisplatin (1x) (conc.)	Sr-89 mono (1x) versus Sr-89+cis(1x)	70	6 vs 9 months, NS	0,3
Tu 2001[26]	Sr-89 2.035MBq/kg (1x)	doxorubicin (6x) (after induction schedule) (conc.)	doxo mono (6x) versus doxo+Sr-89(1x) (randomization after response to induction)	72	**16,8 vs 27,7**	**0,0014**
James 2016[28]	Sr-89 150 MBq (1x)	docetaxel (10x) (seq.)	doc vs doc+ Sr -89 (1x) vs doc+Sr-89 (1x)+ZA	757	Sr89: 18,17 vs 16,59 (no Sr89)	0,34
Amato 2008[27]	Sr-89 4mCi	doxorubicin+ketoconazaol or paclitaxel+estramustine (conc.)	not randomized	29	22,67 (1,83-57,3+)	NA
Ricci 2007[29]	Sm-153 37 MBq/kg (1x)	estramustine 3 times daily or mitoxantrone (max 6 cycles) (seq. versus conc.)	retrospective: Sm-153 mono (15) vs Sm-153 + chemo 3-5 months later vs Sm-153 + chemo within 1 month	15 14 16	**10 versus** **11 versus** **30**	**0,0008** **0,023**
Fizazi 2009[34]	Sm-153 37 MBq/kg (1x)	docetaxel weekly (6x) (conc.)	phase II non-randomized	43	29 (95%CI 22-31)	NA
Autio 2013[35]	Sm-153 37 MBq/kg (1x)	docetaxel every 3 weeks (max 10) (conc.)	phase II non-randomized	30	14,3 (10,3-24,0)	NA
Borso 2014[36]	Sm-153 37 MBq/kg (1x)	docetaxel every 3 weeks (max 10) (seq.)	phase II non-randomized	30	19,9 (12,6-22,8)	NA
Dodewaard 2017[9]	Re-188 40 MBq/kg (2x)	docetaxel every 3 weeks (max 10) (seq.)	docetaxel vs docetaxel+re-188	88	ITT: 21 (18,72-23,28) vs 23,7 (15,78-31,63) PP: **21,0 (13,61-28,39) vs 33,8 (31,75-35,85**)	0,828 **0,012**
Morris 2017[41]	Ra-223 50kBq/kg (5x)	docetaxel every 3 weeks (max 10)	docetaxel vs docetacel+ra-223	53	NA	NA

Table 4 PFS, PSA and pain response in different combinations of radiopharmaceuticals and chemotherapy

Trial	Radionuclide	Chemotherapy	Randomization	PFS (months)	PSA response	pain response	p-value
Sciuto 1996[10]	Sr-89 148MBq (1x)	carboplatin day 7+21 (1x) (seq.)	Sr-89 mono (1x) vs Sr-89+carbo(1x)	NA	NA	**58,3% vs 86,6%**	**0,025** (pain response)
Sciuto2002[24]	Sr-89 148MBq (1x)	cisplatin (1x) (conc.)	Sr-89 mono (1x) versus Sr-89+cis(1x)	NA	NA	**63% vs 91%, duration: 60 vs 120 days**	**<0,01** **0,002** (pain response)
Tu 2001[26]	Sr-89 2.035MBq/kg (1x)	doxorubicin (6x) (conc.)	doxo mono (6x) versus doxo+Sr-89(1x)	7,0 vs 13,9	81% vs 94%	NA	NA
James 2016[28]	Sr-89 150 MBq (1x)	docetaxel (10x) (seq.)	doc vs doc+ Sr -89 (1x) vs doc+Sr-89 (1x)+ZA	**HR 0,85 (0,73-0,99)**	NA	NA	**0,03 (PFS)**
Amato 2008[27]	Sr-89 4mCi	doxorubicin+ketoconazaol or paclitaxel+estramustine (conc.)	not randomized	11,27 (1,83-29,53)	NA	NA	NA
Ricci 2007[29]	Sm-153 37 MBq/kg (1x)	estramustine 3 times daily or mitoxantrone (max 6 cycles) (seq. versus conc.)	retrospective: Sm-153 mono (15) vs Sm-153 + chemo 3-5 months later vs Sm-153 + chemo within 1 month	NA	**5,7% vs** 35,7% vs **43.7%**	**53,3% vs** 71,4% vs **87,5%**	**0,0235*** (PSA) **0,038*** (pain)
Fizazi 2009[34]	Sm-153 37 MBq/kg (1x)	docetaxel weekly (6x) (conc.)	phase II non-randomized	15 (11-29)	77%	69%	NA
Autio 2013[35]	Sm-153 37 MBq/kg (1x)	docetaxel every 3 weeks (max 10) (conc)	phase II non-randomized	7 (3,7-8,8)	80%	NA	NA
Borso 2014[36]	Sm-153 37 MBq/kg (1x)	docetaxel every 3 weeks (max 10) (seq.)	phase II non-randomized	9,1 (7,8-9,9)	82,10%	NA	NA
Dodewaard 2017[9]	Re-188 40 MBq/kg (2x)	Docetaxel every 3 weeks (max 10) (seq.)	docetaxel vs docetaxel+re-188	ITT: 8,6 (7,86-9,34) vs 9,8 (7,70-11,91) PP: 10,3 (8,81-11,80) vs 12,2 (10,49-13,91)	51,9% vs 56,6%	NS	0,38 (PFS) 0,147 (PSA)
Morris 2017[41]	Ra-223 50kBq/kg (5x)	docetaxel every 3 weeks (max 10)	docetaxel vs docetacel+ra-223	4,8 (2,8-5,6) vs 6,2 (2,8-8,8)	NA	NA	NA

Survival

As it stands, radium-223-chloride is the only radiopharmaceutical that has been investigated in a large phase III trial with survival benefit as primary endpoint. In the phase III ALSYMPCA trial , 921 patients with mCRPC who had received, were not eligible to receive or rejected docetaxel were randomized in a 2:1 ratio between radium-223-chloride or placebo[6]. Radium-223-chloride (50 kBq/kg) was administered every 4 weeks for 6 cycles in the experimental treatment arm. The median overall survival (OS) of 14.9 months in the radium-223 group, was significantly better than the 11.3 months in the placebo group (hazard ratio 0.70 (95% CI 0.58-0.83, P<0.001). In addition, the time to first symptomatic skeletal related event was prolonged in the radium-223-chloride group (15.6 months versus 9.8 months, hazard ratio 0.66 (95% CI 0.52-0.83) P<0.001). In the intervention arm, 25% of the patients reported a meaningful improvement in quality of life (defined as an increase of ≥10 points on the FACT-P questionnaire), versus 10% of the patients in the placebo group (p=0.02). No difference in grade 3-4 adverse events was observed. Unfortunately, this trial did not report data about pain relief.

Recently, these results were confirmed by two retrospective studies, providing post-approval data for radium-223-chloride.

In the analysis of Alva et al., 145 non-trial mCRPC patients from five different centers were included[14]. Seventy percent of the patients had a Gleason score ≥8, 46.5% had received prior abiraterone and/or enzalutamide, 40% received concurrent abiraterone or enzalutamide, and 53% had had prior chemotherapy. Median OS was 15.7 months (95% CI 13.0-22.5 months). In the 72 patients who had reported baseline pain, the pain level (measured by VAS score) decreased in 37 patients (51%) and increased in 5 patients (7%) after the first cycle of treatment.

Wong et al. included 64 patients in a comparable retrospective trial[15]. In this group, the median OS was 12.9 months (range 1.1-34.2 months), and the time to first skeletal related event 4.4 months (range 0.2-20.3 months). In contrast to the study of Alva et al., the results in this trial seem to be slightly inferior to the reported outcomes in the ALSYMPCA trial. However, patients differed in terms of age (74 versus 71 years), ECOG performance status (PS 0-1 in 77% versus 87%) and had had more extensive prior treatment.

For other RPs, placebo controlled trials with survival as primary endpoint (like the ALSYMPCA trial) have not been performed. However, an overall survival benefit of RPs in the treatment of mCRPC is suggested in several studies.

For rhenium-188-HEDP, Palmedo et al. showed, although as a secondary endpoint, that repeated administration of rhenium-188-HEDP resulted in a significant survival benefit compared to a single injection[7]. In this prospective randomized phase II trial, 64 patients were randomized between 1 or 2 injections of 40.7 MBq/kg rhenium-188-HEDP. The median overall survival was significantly longer for patients who had received two injections; 7.0 months versus 12.7 months, p=0.043.

These data were confirmed by a retrospective analysis, which divided 60 patients into 3 groups (group A; 19 patients who had received 1 injection; group B: 19 patients who had received 2 injections and group C: 22 patients who had 3 or more injections)[8]. The mean survival was 4.50 months (95% CI 2.92-6.08) for patients in group A, 9.98 months (95% CI 5.65-14.31) in group B and 15.66 months (95% CI 9.33-22.0) for patients in group C (P<0.001). Due to the retrospective character of this trial, we should be aware of a possible selection bias. It is possible that the patients in the best clinical condition received the most treatment cycles, thereby influencing the results of this study.

For rhenium-186-HEDP, a post-hoc analysis showed a better survival for patients treated with a higher dose of rhenium-186-HEDP[16]. In this trial, data of 57 patients treated with rhenium-186-HEDP in phase I and II dose escalating trials were collected. The median OS since start of treatment was 15.7 months for the entire cohort (1- and 2 year survival rates 72% and 31%). Total administered activity above 3.5 GBq was associated with an increased survival, compared to administered activities below 3.5 GBq (61% reduction of death risk, HR 0.39 95% CI 0.10-0.58 P=0.002) with a median overall survival of 20.1 compared to 7.1 months. As the dosing of the rhenium-186-HEDP depended on the time of entry in a trial, selection bias seems to be less likely in this trial.

In 2015, Tunio et al. performed a meta-analysis of RCT's that compared radiopharmaceuticals with placebo or radiation therapy in terms of OS, pain control, symptomatic skeletal events (SSE), toxicity and Quality of Life[17]. This meta-analysis included 8 articles (1877 patients), investigating strontium-89-chloride, samarium-153-EDTMP, rhenium-186-HEDP and radium-223-chloride in patients with CRPC metastatic to bone. Seven articles reported OS and toxicity, all RCT's reported pain control and SSE and three also reported QoL. Two RCT's showed a significant improvement in the OS, five reported no difference and one RCT showed better survival in the control arm. The pooled odds ratio (OR) of these trials was not significant (0.84, 95% CI 0.64-1.04).

A side note to the OS results must be made; one of the two trials with a significant improvement of OS was the previously described ALSYMPCA study, which accounted for almost half of the number of patients in this meta-analysis (921 of 1877 patients).

Therefore, it is very likely that radium-223-chloride has a large influence on the overall results.

In the trial of Buchali et al., treating 49 randomly selected patients either with strontium-89-chloride (n=25) or placebo (n=24), the survival rate after 2 years was better in the intervention group (46% versus 4%, P<0.05), OR 0.21 (95% CI 0.05-0.91)[18]. Although this is a small trial and the OR has a wide confidence interval, it was well randomized and blinded, with reliable statistics showing this significant improvement in survival.

In contrast to radium-223-chloride and strontium-89-chloride, a survival benefit for samarium-153-EDTMP and rhenium-186-HEDP could not be proven. However, the trials investigating these RPs were underpowered to show this effect.

Pain palliation

Since their introduction, RPs are well-known for their proven benefit on bone pain due to osteoblastic metastases. While external beam radiotherapy is suitable for patients with only a limited number of symptomatic metastases, RPs are useful for patients with more extensive bone disease. A complete and useful summary of this quality of RPs is given in the systematic review of Van Dodewaard-de Jong et al.[4]. In total, 36 RCT's and prospective cohort studies including patients with CRPC and osteoblastic bone metastases treated with strontium-89-chloride, samarium-153-EDTMP, rhenium-186-HEDP, rhenium-188-HEDP or radium-223-chloride were found. In summary, treatment with strontium-89-chloride (12 articles) resulted in a pain response of 50-60% (range 35-92%). Pain responses for samarium-153-EDTMP (9 articles), rhenium-186-HEDP (13 articles) and rhenium-188-HEDP (3 articles) were slightly higher with response percentages around 70% (range 38-89%). For radium-223-chloride a pain response was seen in 50-60% (7 articles). However, a head-to-head comparison of the pain response between the different radiopharmaceuticals has not been performed.

In 26 articles, hematologic toxicity was reported. In 15 trials, grade 3-4 leukopenia or neutropenia was not observed, whereas the incidence was between 1-25% in 11 other articles. No grade 3-4 thrombopenia was seen in 14 trials and varied between 1-21% in the other 12 trials. The highest percentages of hematologic adverse events were reported in trials using higher than standard dosages of the RPs. No relevant differences between the radiopharmaceuticals were seen in terms of safety or adverse events.

A second meta-analysis was performed by Tunio et al. (strontium-89-chloride, samarium-153-EDTMP, rhenium-186-HEDP and radium-223-chloride) in which 6 out the 8 included

articles were also selected in the meta-analysis of Van Dodewaard et al.[17]. All 8 articles (1877 patients) analyzed the symptomatic skeletal events (SSEs) rate; this was significantly lower in patients treated with RPs ($p<0.0001$, pooled OR 0.36, 95% CI 0.51-0.78). Three articles also reported the functional mobility and QoL, which significantly improved ($p=0.006$, OR 0.71, 95% CI 0.55-0.91).

After these meta-analyses, the results of a real-world observational study became available[19]. Fifty-six patients with CRPC and painful bone metastases, who had received rhenium-188-HEDP as regular treatment, were included. The 25 breast cancer patients described in this article are not included in this review. Forty patients received one injection, 15 patients two and 1 patient three injections. A clinically relevant pain reduction was seen in 69% of the treated patients (mean VAS score pre-treatment 5.7±0.4 versus 3.2±0.4 after 4 weeks and 4.0±0.6 after 8 weeks, $p<0.05$). Also, 68% of the patients experienced a significant improvement in QoL (mean QoL score pre-treatment 40±2.8, versus 54±3.3 and 47±4.0 after 4 and 8 weeks respectively. The most profound improvements were seen in the subscales pain, physical functioning and fatigue. A grade 3 thrombopenia was seen in 5.3% of the patients, a transient leukopenia grade 3 occurred in 3.6% (no interventions needed). No grade 4 adverse events were observed.

Radiopharmaceuticals combined with chemotherapy

With the undeniable benefits of RPs alone, the question arises if there would be even more benefit when RPs are combined with another proven beneficial treatment, e.g. chemotherapy. The idea of a radio sensitizing effect of the RPs in combination with chemotherapy originates in the beneficial combination of radiotherapy with chemotherapy in the treatment of head and neck and lung cancer[20, 21]. Combination therapy can be deployed in two different ways. When both agents are used sequentially, the additional effect of the added agent can be found in attacking cells which were less sensitive to or less accessible for the standard used agent. In the case of concurrent treatment, chemotherapy induces re-assortment of tumor cells in the radiosensitive phase of the cell cycle (G2/M phase), thereby increasing the radiosensitivity of tumor cells and the effect of radiation therapy[22]. Nowadays, for prostate cancer, this radiosensitizing principle has been systematically explored, combining rhenium-188 and two taxanes (docetaxel and cabazitaxel) in three human prostate carcinoma cell lines.[23] Based on the colony-forming assay, all three agents showed a significant dose-dependent cell kill in all cell lines. A significant additive effect (*i.e.* enhanced toxicity by combining chemotherapy and

radiation) was proven for the combination of rhenium-188 with both taxanes. Although synergism could not been proven, additivity establish a proof-of-mechanism and is preclinical trials a favorable outcome for clinical translation. So, this trial encourages further research with this combination.

The first combination trials treated patients with a single injection of a RP (strontium-89-chloride) and low-dose chemotherapy. In later trials, when more effective chemotherapy became available, dosages of chemotherapy were increased until standard chemotherapy schedules were combined with single or multiple doses of RPs. This chapter summarizes the developments and results of combination therapy with the different RPs and different chemotherapy regimens. Data about OS are summarized in Table 2, data about PFS, PSA response and pain relief are outlined in Table 3.

Strontium-89-chloride

One of the first combination trials was the trial of Sciuto et al. including 30 patients with painful bone metastases (23 prostate cancer, 7 breast cancer)[10]. Fifteen patients were treated with strontium-89-chloride (148 MBq) alone and 15 patients received a combination of strontium-89-chloride (148 MBq) at day 1 followed by carboplatin 100 mg/m^2 at day 7+21 (sequential treatment). Pain response was significantly better in the latter group (58.3% versus 86.6%, p=0.025). The slight difference in median OS (5.7 versus 8.1 months) did not reach statistical significance.

The same was found for the concurrent combination of strontium-89-chloride with a low dose of cisplatin administered at the same day. Seventy patients with mCRPC were randomized to treatment with 148 MBq strontium-89-chloride and 50 mg/m^2 cisplatin or placebo[24]. Pain relief occurred in 91% of the patients in the cisplatin arm, versus 63% in the placebo arm (p<0.01) with a median duration of 120 versus 60 days (p=0.002). Progression of bone disease occurred in 27% versus 64% of the patients (p=0.04). No difference in survival was found (median OS 9 months combination arm, 6 months placebo arm, p=0.30).

Both described studies showed a significant better pain response, but had no statistical power for overall survival. Furthermore, these trials used a relatively low dose of chemotherapy. In addition, there is no proven survival benefit of platinum containing chemotherapy in prostate cancer. Later trials increased the dose of chemotherapy to regular schedules.

After proving the safety and feasibility of the combination of strontium-89-chloride and doxorubicin,[25] in 2001, Tu et al. reported improved survival for the addition of strontium-

89-chloride to a chemotherapy schedule containing doxorubicin, estramustine and vinblastine[26]. In total, 103 patients received induction chemotherapy (doxorubicin combined with ketoconazole, alternating with estramustine and vinblastine) weekly. After completion of 2 or 3 induction cycles, patients with stable or responding disease (n=72) were randomized for consolidation therapy with doxorubicin alone (n=36), or combined with a concurrent single dose of strontium-89-chloride of 2.035 MBq/kg (n=36). Median time to progression in the strontium-89-chloride group was 13.9 months, versus 7.0 months in the control arm. Median OS was 27.7 versus 16.8 months (p=0.0014).
These results are supported by the phase II trial of Amato et al. who included 29 patients of whom 27 received concurrent strontium-89-chloride on day 1 of week 1, in addition to an alternating schedule of doxorubicin plus ketoconazole and paclitaxel plus estramustine in cycles of 8 weeks[27]. The median PFS was 11.27 months (range 1.83-29.53) with an OS of 22.67 months (range 1.83-57.73+). No additional toxicity was observed.
Despite these positive results, the abovementioned chemotherapeutic regimens are not used anymore, as docetaxel and cabazitaxel became standard chemotherapy for mCRPC.

Docetaxel alone versus docetaxel plus strontium-89-chloride (sequentially administered) and/or zoledronic acid (ZA) was investigated in the TRAPEZE trial[28]. The primary endpoints of this randomized, open-label phase III trial were clinical progression free survival (CPFS) and cost-effectiveness, with SRE-free interval, pain-progression free interval (PPFI), total SRE's and OS as secondary endpoints. All patients received docetaxel 75 mg/m^2 every three weeks. Patients in arm A received docetaxel monotherapy, patients in arm B received ZA 4 mg together with docetaxel (and every 4 weeks after finishing docetaxel treatment until progression), patients in arm C received a single injection of strontium-89-chloride 150 MBq 28 days after the 6th administration of docetaxel and patients in arm D received strontium-89-chloride and ZA as described above. In total, 757 patients were included of whom 349 (46%) completed 10 cycles of docetaxel. In the strontium-89-chloride arm, 67% (253 patients) did receive strontium-89-chloride. In the intention-to-treat analysis, cPFS did not reach statistical significance for strontium-89-chloride or ZA. However, Cox regression analysis adjusted for all stratification variables showed benefit of the addition of strontium-89-chloride on cPFS (HR 0.85, 95% CI 0.73-0.99, p=0.03). There was no effect on OS for strontium-89-chloride (HR 0.92 95% CI 0.79-1.08, p=0.34) nor ZA. Also for PPFI and SRE free interval, no significant effect was found for strontium-89-chloride. ZA showed a significant prolongation of SRE-free interval. It was concluded that the benefit of the addition of strontium-89-chloride to docetaxel was not large enough to

change clinical practice, as the only effect was prolongation of4 cPFS with 1 month, without benefit in OS or SRE's.

Samarium-153-EDTMP

The first report of the combination of samarium-153-EDTMP with chemotherapy was a retrospective trial including 45 patients with mCRPC[29]. Patients were divided in 3 groups: treatment with samarium-153-EDTMP 37 MBq/kg monotherapy (group A, 15 patients), treatment with samarium-153-EDTMP 37 MBq/kg and chemotherapy (estramustine 280 mg three times/day or mitoxantrone 12mg/m^2 every 3 weeks plus prednisone) between 3-5 months after administration of samarium-153-EDTMP (group B, 14 patients) or samarium-153-EDTMP plus above mentioned chemotherapy within 1 month (group C, 16 patients). Patients in group C had a significant favorable clinical response (87.5% versus 53.3%, p=0.0388) and median OS (measured from the day of administration of samarium-153-EDTMP) of 30 months was significantly better in group C than in group B (11 months, p=0.023) and in group A (10 months, p=0.008). This is consistent with the fact that no survival benefit has been proven for estramustine or mitoxantrone alone. In conclusion, there seems to be at least an additive effect for the combination of chemotherapy and samarium-153-EDTMP.

As docetaxel became standard first-line chemotherapy in 2004, all later trials combined samarium-153-EDTMP with docetaxel.

This started with several phase I trials, all proving that the combination of docetaxel and samarium-153-EDTMP in different schedules is feasible and safe[30-33].

Weekly docetaxel 35 mg/m^2 plus 2 cycles of samarium-153-EDTMP 37MBq/kg (administered once a month at the same day as docetaxel, i.e. concurrent treatment) was proven to be well tolerated and safe by two phase I trials, which included 30 patients[30, 31].

Two other phase I trials investigated the combination of docetaxel 75 mg/m^2 every 3 weeks either with samarium-153-EDTMP 37 MBq/kg every 6 weeks or samarium-153-EDTMP 37 MBq/kg together with the first and fourth administration of docetaxel. Both schedules were found to be feasible and safe. A maximum tolerated dose was not reached. In the group treated with samarium-153-EDTMP every six weeks, patients received an average of 5.6 docetaxel doses (range 1-13) and 2.9 samarium-153-EDTMP doses (range 1-6). In the trial with samarium-153-EDTMP together with the first and fourth docetaxel dose, patients received an average number of 3.6 docetaxel dosages (range 2-6) and 1.5

injections of samarium-153-EDTMP (range 1-2). A dose limiting toxicity (grade 3 thrombopenia) occurred twice at two different dose levels.
In conclusion, the combination of docetaxel and samarium-153-EDTMP is feasible and safe, even with docetaxel in regular doses.

Although the efficacy of these combinations has not been tested in a randomized phase II or III trial, three single arm phase II trials provide some information about the OS and PSA response in mCRPC patients treated with samarium-153-EDTMP plus docetaxel.

In the first trial, 43 patients with a response or stable disease after 4 cycles of docetaxel 70 mg/m^2 plus estramustine 10 mg/kg/day were included[34]. Further treatment consisted of a consolidation regimen of docetaxel 20 mg/m^2/week for 6 weeks plus a single concurrent injection of samarium-153-EDTMP 37 MBq/kg at week 1. A PSA response, defined as >50% decline, was seen in 77% of the patients, a pain response in 69%. The PSA-PFS was 6.4 months with a cPFS of 15 months. The median OS was 29 months (95% CI 22-31 months), with a 1-year survival of 77% and a 2-year survival of 56%. An important side note to these remarkable good results must be made; only patients with a response or stable disease after 4 cycles of regular docetaxel were included, after which docetaxel was continued in these proven taxane-sensitive patients.
In the second phase II trial, docetaxel 75 mg/m^2 every 3 weeks was combined with, concurrent, samarium-153-EDTMP 37MBq/kg every 9 weeks[35]. Thirty patients received a median number of 6.5 cycles docetaxel and 2.5 doses samarium-153-EDTMP. Half of the patients were taxane naïve, 36.7% were taxane refractory and 13.3% did receive taxane before but was not considered to be refractory. Median PFS was 7.0 months (95% CI 3.7-8.8 months) and OS was 14.3 months (95% CI 10.3-24.0 months). In the subgroups, PFS and OS were 8.2 months (95% CI 5.7-13.7 months) and 23.4 months (95% CI 13.8-42.7 months) for taxane-naïve patients, 7.0 months (95% CI 3.2-11.5 months) and 19.4 months (95% CI 5.6-30.3 months) for taxane-exposed patients and 3.5 months (95% CI 0.7-8.0 months) and 9.6 months (95% CI 4.8-13.5 months) for taxane refractory patients respectively.
A third phase II trial showed the results of 30 mCRPC patients who received samarium-153-EDTMP 37 MBq/kg, plus sequentially administered docetaxel 75 mg/m^2 4 weeks later, followed by regular dosed docetaxel.[36] The median number of docetaxel cycles was 8. The biochemical response rate was 82.1%, the median PSA-PFS was 9.1 months (95% CI 7.8-

9.9) with a median OS of 19.9 months (95% CI 16.9-22.8). No additive toxicity was observed.

In comparison, in the registration trial of docetaxel, an OS of 18.9 months (95% CI 17.0-21.2 months) for docetaxel monotherapy was found, with a >50% PSA decrease in 45% of the patients[37].

Rhenium-186-HEDP and rhenium-188-HEDP

As far as we know, three phase I studies combining rhenium-186-HEDP or rhenium-188-HEDP with chemotherapy have been performed. In the first trial rhenium-188-HEDP was combined with capecitabine[38]. Twelve patients were treated in different dosing schedules, with 14 days of capecitabine 2500 mg/m^2 orally (divided into two doses) followed by concurrent rhenium-188-HEDP 37 MBq/kg two days later at the highest dose level. One out of six patients experienced a dose limiting toxicity (unrecovered bone marrow suppression; anemia grade 3, thrombocytopenia grade 4 and leukopenia grade 2), probably due to progressive disease. In conclusion, this combination was feasible and safe, with capecitabine 2500 mg/m^2 plus rhenium-188-HEDP 37 MBq/kg being the maximum tolerated dose. As far as we know, the recommended phase II trial has not been performed yet.

The second phase I trial combined docetaxel with sequentially administered rhenium-186-HEDP[39]. Fourteen patients were treated in a dose escalating schedule with docetaxel 75 mg/m^2 combined with increasing dosages of rhenium-186-HEDP (1250 MBq up to 2500 MBq) after the third and sixth cycle of docetaxel. One dose limiting toxicity (DLT) occurred in dose level three (thrombopenia grade 3 >10 days), without any DLTs in the expansion cohort. The last dose level could not be started due to retraction of the RP from the market. It was, nonetheless, concluded that the combination in the last tested dose level was feasible and safe.

This phase I study was followed by a randomized phase II trial, which randomized 88 patients between docetaxel 75 mg/m^2 with (46 patients) or without (42 patients) two injections of rhenium-188-HEDP[9]. Rhenium-188-HEDP was sequentially administered after the third cycle (in a dose of 40 MBq/kg) and the sixth cycle (in a dose of 20 MBq/kg) of cabazitaxel, followed by a four week period before administration of the next docetaxel administration. With a median follow-up of 18.4 months, median PFS was 8.6 months (95% CI 7.86-9.34) in the control arm and 9.8 months (95% CI 7.70-11.91) in the combination arm, p=0.38. Median OS was 21.0 (95% CI 18.72-23.28) months versus 23.7

months (95% CI 15.78-31.63) p=0.83. Because of higher than expected dropout rate and a significant amount of patients who did not receive two cycles of rhenium-188-HEDP, a per-protocol analysis was performed including only patients who fulfilled the whole treatment schedule (n=21 in the control group and 19 in the intervention group). The median PFS was also comparable in this analysis (10.3 months versus 12.2 months, p=0.147). However, addition of rhenium-188-HEDP showed an improved OS (21.0 months versus 33.8 months, p=0.012). Also, for patients with a high alkaline phosphatase (≥220 U/L), addition of rhenium-188-HEDP resulted in a significant better PFS (9.0 months, 95% CI 3.92-14.08 months versus 6.2 months, 95% CI 3.08-9.32 months, p=0.005). This might suggest that rhenium-188-HEDP is more effective in patients with more extended bone metastases.

Pain scores at baseline were already low in both groups, and after three cycles of docetaxel pain scores declined to median VAS scores of 1-2. Therefore, no additional effect of rhenium-188-HEDP could be observed, as this was introduced after cycle 3 of docetaxel.

This research was continued in patients with a more advanced stage of disease and more severe pain, where cabazitaxel was combined with rhenium-188-HEDP in a phase I trial[40]. In 12 patients, the combination of cabazitaxel 25 mg/m^2 with rhenium-188-HEDP 40 MBq/kg after the second and fourth cabazitaxel cycle, followed by a four week interval until the next administration of cabazitaxel, appeared to be feasible and safe. A phase II trial with this combination is currently recruiting.

Radium-223-chloride

Radium-223-chloride has been combined with docetaxel in a phase I/II randomized controlled trial (RCT), published in two abstracts[41]. In this trial, 53 patients were randomized between radium-223-chloride 50 kBq/kg (5 cycles) plus docetaxel 60 mg/m^2 (10 cycles) versus docetaxel 75 mg/m^2 alone (10 cycles). This combination proved to be feasible and safe. Median PFS in the combination arm was 6.2 months (95% CI 2.8-8.8 months) versus 4.8 months (95% CI 2.8-5.6 months) in the docetaxel monotherapy arm (NS). Due to the small patient numbers and preliminary data, further analysis on this combination is warranted.

An early access, open label, single arm phase 3b trial explored the possible concurrent combination of radium-223-chloride with enzalutamide and/or abiraterone in 839 patients[42]. The median OS of the treated patients was 16 months (95% 13-NA), after a median follow up period of 7.5 months. During the radium-223-chloride treatment, 189

patients (27%) received abiraterone, 35 patients (5%) received enzalutamide and 15 (2%) received both. No extra treatment-emergent adverse events were observed in this group.

Timing of treatment with radiopharmaceuticals

At this moment, no clear evidence exists about the optimal sequence and combination of available treatment options, and the place of RPs in this field. Concerns might rise about the influence of previous treatment on the safety and efficacy of RPs, as well as the effect of RPs on later treatments. Although no randomized trials are available, some observations and subgroup analyses can provide insight.

The first trial describing the effects of RPs on further treatment is the follow-up trial of Tu et al (initial trial described above), using strontium-89-chloride in a consolidation regimen[43]. In this trial, 34 patients with a response to induction chemotherapy, were treated with strontium-89-chloride plus 6 weekly doses doxorubicin. Five (15%) of these patients developed bone-marrow failure (defined as at least one of the following parameters; platelet count ≤20.000/μL, absolute neutrophil count ≤500/ μL and/or a hypoplastic marrow with <25% of normal cellularity) during follow-up. The median time between strontium-89-chloride and bone marrow failure was 23 months (6-53 months), whereas median OS was 25 months. For all 5 patients, bone marrow failure was likely to be due to bone marrow infiltration. In total, 31/34 patients (91.1%) were able to receive at least one more chemotherapeutical regimen (consolidation with doxorubicin excluded). It was concluded that in this subset of patients, strontium-89-chloride plus chemotherapy did not lead to serious or permanent bone marrow damage, and that further treatment with chemotherapy after RPs remains a reasonable option.

This was also observed in a prospectively defined follow-up trial of the ALSYMPCA cohort[44]. Of all patients included, 142 patients treated with radium-223-chloride and 64 patients from the placebo cohort received subsequent chemotherapy. Docetaxel was administered in 70% and 72% of the patients (radium-233-chloride and placebo groups), followed by mitoxantrone (16% and 20%), cyclophosphamide (10% and 11%), estramustine (4% and 8%) and carboplatin (3% and 5%). The duration of the first post-radium-223-chloride chemotherapy was comparable between both groups (4.6 versus 4.2 months), as was the dropout rate of patients. The median baseline values for neutrophils and platelets (at start of chemotherapy) were somewhat lower in the radium-223-chloride group ($3.6x10^9$ versus $4.5\ x10^9$ and $215.0\ x10^9$ versus $235.5\ x10^9$ respectively). Although generally low (<10%) and not significant, hematologic adverse events grade 3-4 tended to be more common in

radium-223-chloride pre-treated patients (anemia in 8% versus 4% of the patients, p=0.509, neutropenia 10% versus 2%, p=0.112, thrombocytopenia 6% versus 2%, p=0.438). Median OS was comparable between patients who were and who were not previously treated with radium-223-chloride (16.0 months versus 15.8 months, measured from first day of chemotherapy until date of death).

The other way around, a pre-specified subgroup analysis of the ALSYMPCA trial investigated the effect of previous docetaxel on the efficacy of radium-223-chloride[45]. Of the 921 randomized patients, 526 (57%) had received previous docetaxel (352 in the radium-223-chloride arm, 174 in the control arm) and 395 (43%) had not (262 in the radium-223-chloride arm, 133 in the placebo arm). Although the study was not powered for this subgroup analysis, the use of radium-223-chloride provided a significant benefit in OS in both docetaxel pre-treated (median OS radium-223-chloride 14.4 months versus placebo 11.3 months, HR 0.70, 95% CI 0.56-0.88, p=0.002) and docetaxel naïve patients (median OS radium-223-chloride 16.1 months and placebo 11.5 months, HR 0.69, 95% CI 0.52-0.92, p=0.01). Grade 3-4 adverse events occurred in 62% (docetaxel) and 54% (no docetaxel) of the patients, and the incidence of grade 3-4 thrombocytopenia during radium-223 treatment was higher in docetaxel pre-treated patients (9%) than in docetaxel naïve patients (3%).

Biomarkers

As many treatment options exist in mCRPC, the availability of a good set of early and predictive biomarkers to select the right treatment for mCRPC patients would be very helpful[46].

Unfortunately, most of the currently used biomarkers are more prognostic than predictive for treatment response to RPs.[47] Several trials, with different designs (post-hoc analysis of the ALSYMPCA trial, some retrospective analyses and a phase IIIb early access program) showed more or less the same prognostic markers for OS in mCRPC patients treated with RPs[14, 15, 42, 48, 49]. These markers include baseline alkaline phosphatase (ALP), baseline lactate dehydrogenase (LDH), baseline PSA, baseline hemoglobin, ECOG performance score, ≤5 bone metastases, no prior chemotherapy, pain level at start of treatment and the number of radium-223-chloride treatment cycles.

In terms of treatment response, a favorable OS was found for patients with a confirmed decline in total ALP (tALP) and LDH 12 weeks after start of radium-223-chloride. The median OS of 400 patients with a tALP decline was 17.8 months versus 10.4 months in 97

patients without decline, with a 55% lower risk of death in the first group (HR=0.45, 95% CI 0.34-0.61, P<0.0001). In 196 patients with a decline in LDH, median OS was 19.5 months, versus 14.5 months in 227 patients without decline, with a lower risk of death of 45% (HR=0.55, 95% CI 0.42-0.73, P<0.0001). Greater LDH increase was associated with a rapidly increasing risk of death.[48] However, despite these results, the proportional treatment effect (PTE) was relatively low, with broad confidence intervals (tALP PTE=0.34 95% CI 0.-0.746; LDH PTE=0.07, 95% CI 0-0.211; PSA PTE= 0, 95% CI 0-0.082). A PTE of 0.34 means that the tALP decrease accounts for approximately 34% of the survival benefit of radium-223-chloride, with a strong degree of surrogacy suggested if the lower boundary of the 95% CI is above 0.5.

Multivariate analysis showed that the impact of PSA changes (week 12) on survival was negligible.

These results suggest that changes in tALP from baseline might be a potential surrogate parameter for survival. However, this did not meet statistical surrogacy requirements.

A marker for response during treatment with radium-223-chloride might be found in circulating tumor cells (CTC)[50]. The CTC count is a well-known predictive and prognostic biomarker in mCRPC in general. In the trial of Suarez et al., blood samples of 46 patients treated with radium-223-chloride monotherapy were collected at baseline, at cycle 3 and at progression. At baseline, 50% of the patients had a CTC count >5. Of the patients with a CTC count ≤5 at baseline, 87% remained on treatment after cycle 3, versus 54% of the patients with a baseline CTC count >5, p=0.09. A CTC response (defined as >50% decline from baseline or CTC ≤5) was seen in 8 patients (29%), stabilization in 12 patients (42%) and progression in 8 patients (29%). Patients with a CTC count ≤5 at the beginning of cycle 3 had a higher chance to stay on treatment: 88% versus 50% of the patients with a CTC count > 5, p=0.04.

Future research

As described in the previous paragraphs, treatment with RPs is a promising, yet underutilized, treatment option for patients with CRPC metastatic to bone. Although the use of RPs has become common practice, many ideas and suggestions of earlier trials need further investigation. At this moment, many trials are ongoing or will open soon. Here we provide a selection of the trials that are likely to enrich our knowledge about RPs. The combination of radium-223-chloride with either enzalutamide or abiraterone is under investigation in different trials.

A phase IIa trial (NCT02034552) randomized 68 patients with mCRPC (≥2 lesions at bone scan) between radium-223-chloride, radium-223-chloride plus enzalutamide and radium-223-chloride plus abiraterone and prednisone. The primary endpoint is bone scan response at 24 weeks. Secondary endpoints include radiologic progression free survival, SSE-FS, and OS. This study fulfilled the inclusion and is expected to be completed in July 2018. This trial will provide information about the safety and effectivity of the mentioned combinations, providing evidence for the rationale of further research.
The upfront combination of radium-223-chloride with enzalutamide is under investigation in a phase III trial (NCT02194842), which aims to randomize 560 asymptomatic or mildly symptomatic CRPC patients to enzalutamide alone or the combination with radium-223. The primary endpoint is radiologic PFS with OS, time to first symptomatic skeletal event and influence on later treatments among the secondary endpoints.
A somewhat similar phase III trial combining radium-223-chloride with abiraterone versus abiraterone plus placebo, the ERA223 trial (NCT02043678), was stopped and unblinded due to significant imbalances concerning treatment emergent fractures, SSE-FS and total death events. This turned out to be in disadvantage of the combination treatment arm.

In terms of retreatment with radiopharmaceuticals, the results of a phase II trial (NCT01934790) are awaited. Patients (n=45) who fulfilled 6 cycles of radium-223-chloride without any SAE or adverse event grade 3-4 that led to treatment discontinuation, were retreated with 6 cycles of radium-223. Inclusion and treatment have been fulfilled and the results are awaited. As far as we know, this is the first trial investigating the feasibility of retreatment with RPs. Unfortunately, the effect on overall survival is not addressed in this study.

In the field of combination therapy with chemotherapy, the ReCab II trial is ongoing. Patients who progressed during or after treatment with docetaxel are randomized between cabazitaxel monotherapy or cabazitaxel plus 2 cycles of sequentially administered rhenium-188-HEDP. The primary endpoint is PFS, with OS, pain response and QoL as secondary endpoints.

Also, a large Dutch multicenter study (RaRe study) with a head-to-head comparison between radium-223-chloride and rhenium-188-HEDP will start this year (2018). In a 1:1 randomization, 402 patients will either be treated with 3 cycles rhenium-188-HEDP every 8 weeks or with radium-223-chloride 6 cycles every 4 weeks. Primary endpoint is OS, with PFS, pain response, QoL and cost-effectivity as secondary endpoints.

Discussion

The above described trials show that RPs are a promising and viable treatment option for patients with bone-metastatic CRPC.

For radium-223-chloride, a survival benefit of 3.6 months compared to placebo is proven in a randomized phase III trial. This is confirmed by two retrospective trials, performed after registration of radium-223-chloride.

For the β-emitting radiopharmaceuticals, an effect on survival has only been suggested, as no sufficient RCTs have been performed so far. However, increasing the number of injections or the total dose of a RP, does improve the OS. The RaRe trial, in which the effect on OS of radium-223-chloride and rhenium-188-HEDP will be compared 1:1, will open soon. This trial will probably clarify the effect of rhenium-188-HEDP on survival definitely.

In terms of pain palliation, the benefit for the different RPs is indisputably proven. Although for patients with only a limited number of symptomatic bone metastases external beam radiotherapy might be a suitable modality, for patients with more extensive bone disease radiopharmaceuticals are capable of treating all lesions at once. Although in literature the responses seems to be slightly higher for the beta-emitting radiopharmaceuticals, a randomized trial performing a head-to-head comparison between agents is necessary to clarify if any difference exists.

Several trials prove that both the sequential and concurrent combination of chemotherapy and RPs is feasible and safe, even with normal dosed chemotherapy regimens. Some of these trials showed an improved survival when an RP was added to chemotherapy.

As docetaxel and cabazitaxel are the currently used chemotherapeutic regimes in mCRPC, combining RPs with these agents is the most interesting option. The negative results of the Trapeze trial, adding strontium-89-chloride to a normal schedule of docetaxel, might be due to the timing and dose (single injection) of the RP, together with a high drop-out in the intervention arm. As strontium-89-chloride was administered after the sixth cycle of docetaxel, early dropout and progressive disease resulted in only 67% of the intended patients receiving strontium-89-chloride. More or less the same applies to the Taxium II trial (rhenium-188-HEDP added to docetaxel), in which the per-protocol analysis showed promising results.

From trials, we might conclude that several factors are important to achieve the optimal benefit of the combination of RPs and chemotherapy. In the first place, timing of the RPs

is important as specific targeting of the bone lesions is one of the characteristics of this treatment. After several cycles of chemotherapy, bone activity in the metastases might have lowered, thereby reducing the accumulation and effects of RPs. Second, as described above, repeated injections and higher dosages resulted in more effect in monotherapy studies, which probably applies to combination treatment as well. Also, patient selection might be important as patients with the highest extend of bone disease seem to benefit the most of RPs. In the now open ReCab II trial (cabazitaxel with or without rhenium-188-HEDP), these factors are taken into account, thereby probably providing more insight in the optimal combination of these agents.

Only little is known about the timing of treatment with RPs. At this moment, clinical performance, complications of the bone metastases and patients preference might be the most important factors in decision making. As severe toxicity is rare, and often not clinically relevant to the patient, the use of RPs can be considered in late stages of the disease as long as the bone marrow function is adequate. Combining chemotherapy with RPs might be considered in patients in a good clinical condition with extended bone metastases. However, for the combination of rhenium-188-HEDP with cabazitaxel, results of the ReCab II trial should be awaited.

For a better selection and prediction of treatment effect, a good set of predictive biomarkers is indispensable. Although changes in tALP, LDH and CTC count during treatment are promising predictive biomarkers, more evidence is needed before these can be used in clinic. Besides, the markers are only testes after 3 cycles of radium-223-chloride, while a prediction of response early in the treatment schedule would be more useful.

Conclusion

The use of RPs has several benefits in the treatment of CRPC with bone metastases. Nowadays, radium-223-chloride is primarily used for its OS benefit, which has not been proven for β-emitting RPs yet. Therefore, β-emitting RPs are mainly used because of their indisputable analgesic effects. The combination of RPs with chemotherapy (especially docetaxel and cabazitaxel) is feasible and safe. Although some trials do show a benefit in OS for this combination, further evidence from RCTs is needed.

Further research is needed to determine the timing of treatment with RPs, as well as the role of ALP, LDH, CTC and possible new biomarkers as early predictors of treatment benefit.

In conclusion, RPs are a valuable treatment option for mCRPC patients with osteoblastic bone metastases. More research is warranted to determine the optimal timing and combination with other modalities of RPs in the treatment of metastatic prostate cancer.

Clinical Practice Points

- Bone metastasis of castration-resistant prostate cancer are due to their osteoblastic character really suitable for treatment with bone-seeking radiopharmaceuticals.
- At this moment, a survival benefit has only been proven for the alpha-emitting radiopharmaceutical radium-223-chloride. The beta-emitting radiopharmaceuticals have a proven, well-known effect on pain palliation. A sufficient RCT with beta-emitting radiopharmaceuticals with survival as primary endpoint has not been performed yet. However, several trials suggest a benefit in overall survival for these agents as well.
- The combination of the different radiopharmaceuticals with several chemotherapy schedules is feasible and safe. At this moment, a synergistic effect of this combination is very plausible, although not yet proven in large RCTs. This might be due to shortcomings in the protocol, dosing schedule or drop-out rates in these trials.
- Little is known about the optimal timing of radiopharmaceuticals; before, during or after chemotherapy. At this moment, the performance status of the patient and the degree of metastases and complications should be leading.
- Several trials are ongoing, which will clarify the effect of beta-emitting radiopharmaceuticals as monotherapy or combined with chemotherapy on overall survival. Besides, more data will be acquired on timing of radiopharmaceuticals, and the use of biomarkers.

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