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Assessing the quality of life of patients with metastatic castration-resistant prostate cancer with bone metastases receiving [^{223}Ra]$RaCl_2$ therapy

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Abstract

[^{223}Ra]$RaCl_2$ dichloride treatment in patients with metastatic castration-resistant prostate cancer (mCRPC) is associated with improved overall survival (OS) and a delay in the time to the first symptomatic skeletal-related event. The aim of this study was to evaluate the quality of life (QoL) of patients with mCRPC receiving [^{223}Ra]$RaCl_2$ treatment using the European Organization for Research and Treatment of Cancer (EORTC) validated questionnaire form.

Thirty patients with mCRPC were included in this study. The patients were administered the EORTC QLQ-C30 (version 3.0) questionnaire at 5 time points: before [^{223}Ra]$RaCl_2$ treatment, after the first cycle, after the third cycle, after the fifth cycle, and at the end of the treatment.

Median age at diagnosis was 65.2 years (range, 49.1–75.5). There was a significant 25% drop in the median alkaline phosphatase levels: 101 U/L (range, 58–594) vs. 75 U/L (39–649) before and during treatment, respectively ($P = .003$). The median dose of [^{223}Ra]$RaCl_2$ for all patients was 4.1 MBq (range, 3.35–6.55), and the majority of patients received 5 treatment cycles (range 3–6). Seventeen patients were alive at the end of treatment (56.7%). The median OS was 26 months (range, 19.8–32.2). All of the patients filled out the questionnaires at the first 3 time points; the fourth survey included 28 patients, and only 23 patients completed the fifth questionnaire. Compared to the baseline, only the scale "role functioning" showed a temporary worsening after the first therapy cycle ($P = .03$). In subsequent cycles, its mean value rose to initial levels. All other functional and symptom scales, as well as global health status, remained constant over all 5 time points and showed no significant changes ($P > .05$).

[^{223}Ra]$RaCl_2$ therapy does not adversely impair the health-related QoL of patients with mCRPC and bone metastasis. Only patients' role functioning worsened temporarily after the first therapy cycle but stabilized in subsequent treatment cycles.

Abbreviations: ALKP = alkaline phosphatase, EMA = European Medicines Agency, EORTC = European Organization for Research and Treatment of Cancer, FDA = Food and Drug Administration, iPSA = initial prostates-specific antigen, IRB = Institutional Review Board, MBq = Mega Becquerel, mCRPC = metastatic castration-resistant prostate cancer, OS = overall survival, QoL = quality of life, Ra = radium, SRE = skeletal-related event.

Keywords: [^{223}Ra]$RaCl_2$, bone metastases, prostate cancer, quality of life, radionuclide therapy

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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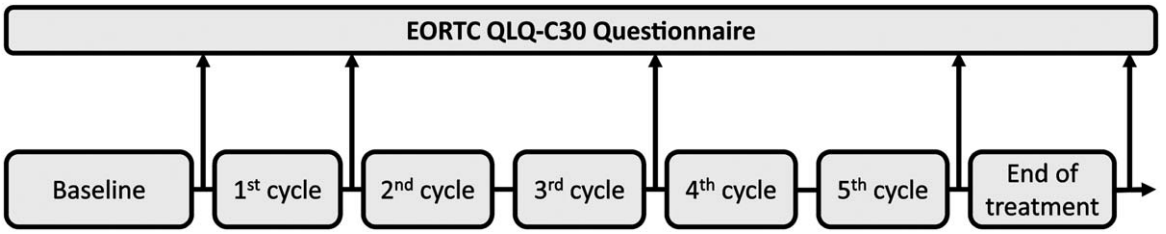

Figure 1. Study design.

1. Introduction

Metastatic castration-resistant prostate cancer (mCRPC) remains a treatment challenge given its resistance to conventional chemotherapies (except for taxanes), and aggressive treatment regimens are usually contraindicated for elderly patient populations.[1]

Bone is one of the most common metastatic sites among patients with prostate cancer (PC)[2]; more than 90% of patients who die from PC have bone metastases.[3] In patients with mCRPC, bone metastases are associated with skeletal-related events (SREs), including fractures that reduce quality of life (QoL)[3] and shorten overall survival (OS), thereby increasing mortality rate.[4] Bisphosphonates (e.g., zoledronic acid) and denosumab have been shown to decrease the risk of SREs. Historically, radionuclide therapy has been used in the treatment of bone metastases with bone-modifying, β-particle-emitting agents (e.g., Re-188-HEDP and Samarium-153-EDTMP), but they have been mainly used for palliative purposes and a clear survival benefit was never shown when applied as monotherapy.[3] Unlike previous radiopharmaceuticals, Radium-223 dichloride has been the first targeted, α-particle-emitting agent with a survival benefit in mCRPC patients with bone metastases, as shown in the ALSYMPCA trial.[5] This study revealed an improved OS as well as a delay in the time to the first symptomatic SRE with the use of [^{223}Ra]$RaCl_2$. As a result, the Food and Drug Administration (FDA) approved [^{223}Ra]$RaCl_2$ in 2013 for the treatment of mCRPC patients with symptomatic bone metastases and no known visceral metastases.[5,6]

Given the importance of evaluating the quality of life of patients receiving radionuclide therapies, the aim of this study was to evaluate the QoL of patients with mCRPC receiving [^{223}Ra]$RaCl_2$ treatment using the European Organization for Research and Treatment of Cancer (EORTC) validated questionnaire.

2. Patients and methods

2.1. Study population and data analysis

[^{223}Ra]$RaCl_2$ therapy has been offered at the University Hospital Bonn for patients with CRPC and bone metastases since 2014. Between March 2014 and June 2016, a total of 83 patients received [^{223}Ra]$RaCl_2$ for treatment purposes at this institution. All of the patients gave informed consent for the radioligand therapy. Retrospective analysis was performed according to institutional ethical guidelines, and the requirement for separate informed consent for this analysis was waived. It is standard practice to give patients the EORTC QLQ-C30 (version 3.0) questionnaire in its validated version to fill out individually during treatment.

Patients who have pathological confirmation of PC and bone metastases and who have returned the filled out forms during their treatment cycles were included in this study. Of the 83 total patients who received [^{223}Ra]$RaCl_2$ therapy during that period, 30 patients fulfilled the inclusion criteria (36%). The filled-out questionnaires were evaluated at 5 time points: before [^{223}Ra]$RaCl_2$ treatment, after the first, third, and fifth cycles and at the end of treatment (Fig. 1).

2.2. Quality-of-life questionnaire

This questionnaire quantitatively assessed different QoL parameters using a 4-point scale (from 1 to 4, where 1 is "not at all" and 4 is "very"). The EORTC QLQ-C30 assesses physical and occupational functioning; fatigue; insomnia; appetite and bowel dysfunction; emotional, cognitive and social functioning; financial difficulties and global health status.

This study was waived by the Institutional Review Board (IRB) at our institution. Using a predesigned case report form, we retrieved the following information: patient demographics, Gleason score and initial prostates-specific antigen (iPSA) levels, PSA and alkaline phosphatase (ALKP) levels before and after therapy with [^{223}Ra]$RaCl_2$, prior therapies (chemotherapy, radiotherapy, hormonal therapy, or surgery) as well as any pain medications taken during [^{223}Ra]$RaCl_2$ therapies. Data of the last follow-up and death (if available) were also collected, and the overall survival (OS) was estimated.

2.3. Statistical analysis

All statistical evaluations were performed using the IBM SPSS Version 24 software. The multivariate scales were calculated after a satisfactory reliability analysis according to the EORTC QLQ-C30 script, and scales with a Cronbach's alpha larger 0.5 are regarded as reliable. Due to their equidistance, individual items (such as dyspnea, insomnia, diarrhea, and constipation) were treated as interval-scaled variables and evaluated parametrically. Descriptive statistics were presented in the form of averages and standard deviations of the scales. Given that at the fourth and fifth time points, 7% and 23% of the patient arches were missing, respectively, a mixed linear model with repeated measures (AR1) was used to evaluate the mean scale differences between the 5 time points. Post-hoc tests of mixed linear models with Bonferroni correction were used to show the difference in scale average at the appropriate time to baseline and calculate *P* values. A Wilcoxon test was performed to assess for significant changes in PSA and ALKP levels pre- and posttreatment, and a log-rank test was used to assess the significance of the number of [^{223}Ra]$RaCl_2$ cycles received on survival outcomes. A cutoff of 5% was assumed to be statistically significant.

3. Results

3.1. Patient characteristics and treatments received

Data from 30 patients were analyzed; their characteristics are summarized in Table 1. The median age at diagnosis was 65.2 years (range, 49.1–75.5), which is close to that at the start of treatment: 70.5 years (range, 51.7–84.3). The median Gleason score was 8 (range, 5–10), and the median PSA levels before and during treatment were similar: 77.85 ng/mL (range, 1.31–285) and 78.1 ng/mL (range, 0.53–747), respectively (P = ns). There was a significant 25% drop in the median alkaline phosphatase levels: 101 U/L (range, 58–594) vs. 75 U/L (39–649) before and during treatment, respectively (P = .003).

The prior therapies are listed in Table 1. All of the patients received oral hormonal therapy prior to [^{223}Ra]$RaCl_2$, and only 2 patients stopped it during treatment (1 patient was on bicalutamide and another was on enzalutamide prior to treatment). More than half (56.7%) were prescribed analgesic medications during the [^{223}Ra]$RaCl_2$ cycles.

The median dose of [^{223}Ra]$RaCl_2$ for all patients was 4.1 MBq (range, 3.35–6.55), with the majority of patients receiving 5 treatment cycles (range, 3–6). Patients would fill the questionnaire 1 day before the designated treatment cycle. The time interval between cycles was 4 weeks.

Seventeen patients were alive at the end of treatment (56.7%). The median OS of the patients was 26 months (range, 19.8–32.2). Of the 13 deceased patients, 9 patients completed all cycles of treatment, and of the 17 patients alive at the last follow-up, 13 completed all cycles of treatment. In our cohort, completing the 6 cycles of [^{223}Ra]$RaCl_2$ treatment was not associated with improved survival (P = .175).

Table 1

Patient characteristics.

Number of patients	30
Median age at initial diagnosis (range)	65.2 (49.1–75.5)
Median age at start of treatment (range)	70.5 (51.7–84.3)
Diagnostic tests	
Median Gleason score (range)	8 (5–10)
Median PSA level before treatment ng/mL (range)	77.9 (1.3–285)
Median PSA level during treatment ng/mL (range)	78.1 (0.5–747)
Median alkaline phosphatase level before treatment U/L (range)	101 (58–594)
Median alkaline phosphatase level during treatment U/L (range)	75 (39–649)
Prior therapies	No. of patients (%)
Surgery	12 (40%)
Chemotherapy	11 (36.7%)
Abiraterone	8 (26.7%)
Bicalutamide	15 (50%)
Enzalutamide	6 (20%)
Bisphosphonate therapy	18 (60%)
Radiation therapy	21 (70%)
Analgesia during Ra-223	17 (56.7%)
Ra-223 treatment	
Median amount of activity (range)	4.1 (3.4–6.6)
Median number of cycles (range)*	5 (3–6)
Patient outcomes	
Alive at end of treatment	17 (56.7%)
Overall survival in months (range)	5.7 (2.1–48.5)

PSA = prostate-specific antigen.

* This also corresponds to the filling of questionnaires, as each patient filled a questionnaire after each cycle.

3.2. Quality-of-life assessment

The patients performed a self-assessment of their QoL before therapy at baseline, after each of the first, third, and fifth treatment cycles, and at the end of treatment. All of the patients were represented at the first 3 time points; the fourth survey included 28 patients and only 23 patients completed the fifth questionnaire. Compared to the baseline assessment, only the QoL scale "role functioning" showed a significant worsening after the first therapy cycle (P = .03; Table 2, Fig. 2). The questions asked in this scale were, "Were you limited in doing either your work or other daily activities?" and "Were you limited in pursuing your hobbies or other leisure time activities?" In subsequent cycles, the mean value of role functioning rose to pretherapy levels. All of the other functional and symptom scales as well as global health status remained constant over all 5 time points with no significant changes (P > .05) (Figs. 2–5). Table 2 presents the averages of the scales and items with the corresponding standard deviations and mean errors.

4. Discussion

In this study, we aimed to evaluate the QoL of patients with mCRPC receiving [^{223}Ra]$RaCl_2$ treatment by using the EORTC-validated questionnaire. Therapy with Radium-223 dichloride has a clear survival benefit for patients with mCRPC and bone metastases, as shown in the ALSYMPCA trial.[5] This trial revealed an improved OS as well as a delay in the time to the first symptomatic SRE with the use of [^{223}Ra]$RaCl_2$. The dose regimen of [^{223}Ra]$RaCl_2$ is 55 kBq per kg body weight, given in 6 intravenous injections at 4-week intervals.[3] The same 4-week time interval was used in our study. The most common adverse drug reactions in patients receiving [^{223}Ra]$RaCl_2$ include nausea, diarrhea, vomiting and peripheral edema, and the most common hematologic laboratory abnormalities were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. The ALSYMPCA trial also highlighted the favorable safety profile of [^{223}Ra]$RaCl_2$.[5]

There have been promising results in terms of tolerance and safety with concurrent administration of [^{223}Ra]$RaCl_2$ with docetaxel or anti-androgen therapies.[7–9] However, recent preliminary data of an ongoing, double-blind, placebo-controlled phase III trial in mCRPC comparing [^{223}Ra]$RaCl_2$ with a placebo, both given in combination with abiraterone and prednisone/prednisolone, have indicated that concomitant use may be associated with increased risk of death and fractures. Thus, the European Medicines Agency (EMA) has recommended that such combination therapy should be restricted.[10,11] Safety-related warnings and precautionary information were accordingly updated in [^{223}Ra]Ra dichloride's FDA label.[12] The patient population we retrospectively examined had been offered [^{223}Ra]$RaCl_2$ before such warnings were officially issued.

Nowadays, the most important target of therapy is sufficient control of the patient's symptom burden, thereby stabilizing or improving health-related QoL. Evaluation of QoL is of central importance in cancer patients, as it influences the choice of the appropriate treatment approach that causes the least possible harm to the patients. The findings of our primary analysis showed that overall QoL, as assessed by the scale "global health status," quantitatively improved in the course of [^{223}Ra]$RaCl_2$ treatment, particularly after the third cycle and at the end of treatment (Fig. 3), but such changes are not statistically significant.

Table 2

Analysis of EORTC scales at baseline, after first, third, and fifth therapy cycles, and at the end of treatment.

EORTC scale	Baseline	After first cycle	After third cycle	After fifth cycle	End of treatment
Global health status					
Global health status					
Average	55.83	56.11	60.28	57.76	61.23
SD	26.99	23.36	24.53	24.49	22.28
SEM	4.93	4.26	4.48	4.47	4.07
P value*	–	1.00	1.00	1.00	1.00
Functional scales					
Physical functioning					
Average	66.89	68.22	69.11	67.59	63.77
SD	29.53	26.48	28.31	27.76	28.98
SEM	5.39	4.83	5.17	5.07	5.29
P value	–	1.00	1.00	1.00	1.00
Role functioning					
Average	60.56	51.67	55.56	52.87	57.25
SD	31.40	34.00	35.11	34.23	37.21
SEM	5.73	6.21	6.41	6.25	6.79
P value	–	.03	1.00	.39	.91
Emotional functioning					
Average	62.50	66.39	67.78	64.08	62.68
SD	25.21	23.92	26.15	25.89	29.40
SEM	4.60	4.37	4.77	4.73	5.37
P value	–	.61	.61	1.00	1.00
Cognitive functioning					
Average	80.00	80.00	80.00	82.18	81.16
SD	26.77	23.33	22.06	20.38	26.26
SEM	4.89	4.26	4.03	3.72	4.79
P value	–	1.00	1.00	1.00	1.00
Social functioning					
Average	66.67	65.56	65.56	65.52	68.12
SD	32.46	34.45	32.14	32.71	29.26
SEM	5.93	6.29	5.87	5.97	5.34
P value	–	1.00	1.00	1.00	1.00
Symptom scales/items					
Fatigue					
Average	46.67	48.89	48.89	47.89	44.93
SD	31.75	29.41	31.10	32.14	30.05
SEM	5.80	5.37	5.68	5.87	5.49
P value	–	1.00	1.00	1.00	1.00
Nausea and vomiting					
Average	6.11	8.89	7.22	7.47	7.97
SD	11.14	17.36	10.43	11.43	15.79
SEM	2.03	3.17	1.90	2.09	2.88
P value	–	1.00	1.00	1.00	1.00
Pain					
Average	48.33	46.67	42.22	42.53	45.65
SD	39.96	37.75	36.02	35.24	39.00
SEM	7.30	6.89	6.58	6.43	7.12
P value	–	1.00	1.00	1.00	1.00
Symptoms—single items					
Dyspnea					
Average	21.11	26.67	32.22	33.33	28.99
SD	28.34	26.84	26.96	30.09	27.16
SEM	5.17	4.90	4.92	5.49	4.96
P value	–	1.00	.26	.21	1.00
Insomnia					
Average	40.00	34.44	32.22	37.93	33.33
SD	36.51	34.45	35.54	34.18	34.82
SEM	6.67	6.29	6.49	6.24	6.36
P value	–	.69	.61	1.00	1.00
Appetite loss					
Average	20.00	16.67	24.44	22.99	17.39
SD	27.12	25.89	32.68	28.32	24.35

(*continued*)

Table 2

(continued).

EORTC scale	Baseline	After first cycle	After third cycle	After fifth cycle	End of treatment
SEM	4.95	4.73	5.97	5.17	4.45
P value	–	1.00	1.00	1.00	1.00
Constipation					
Average	25.56	21.11	17.78	17.24	15.94
SD	33.54	30.93	28.68	30.37	29.93
SEM	6.12	5.65	5.24	5.54	5.46
P value	–	.98	.51	.73	1.00
Diarrhea					
Average	6.67	6.67	11.11	9.20	11.59
SD	16.14	18.36	18.22	23.40	23.80
SEM	2.95	3.35	3.33	4.27	4.35
P value	–	1.00	1.00	1.00	1.00
Financial difficulties					
Average	17.78	15.56	15.56	17.24	17.39
SD	22.71	22.71	27.31	27.63	24.35
SEM	4.15	4.15	4.99	5.04	4.45
P value	–	1.00	1.00	1.00	1.00

EORTC = European Organization for Research and Treatment of Cancer, QoL = quality of life, SD = standard deviation, SEM = standard error of the mean.
* *P* values comparing scales after each cycle to baseline values.

The analysis of the different subscales of the EORTC QLQ-C30 allowed for a more differentiated evaluation of the different aspects of well-being. In the primary analysis, particularly emotional and physical functioning, pain, insomnia, and constipation improved; this finding was clinically relevant, albeit not statistically significant.

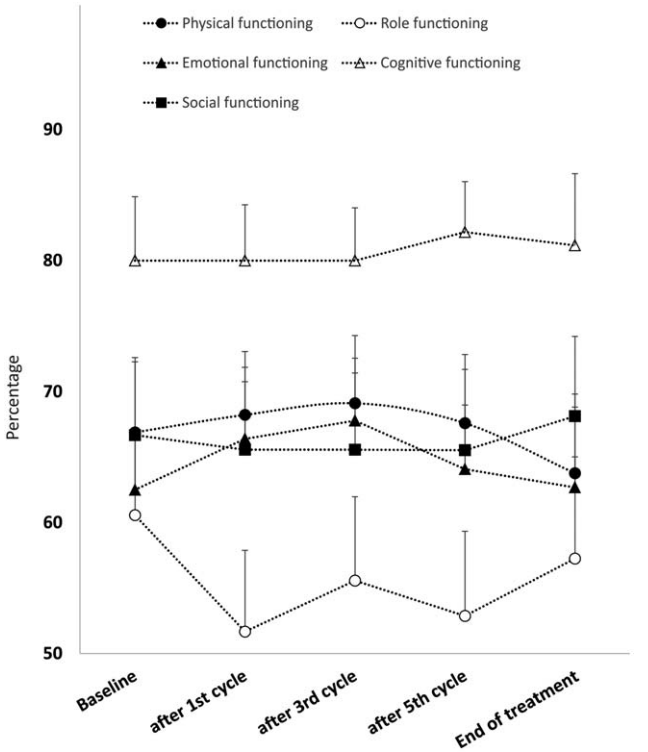

Figure 2. Changes in QoL functional scales over time. Values are presented as mean ± standard error of the mean. QoL scale "Role Functioning" showed a significant worsening after the first therapy cycle ($P = .03$).

The subscale "emotional functioning" asks about the interference of the physical condition or treatment with mood, such as feeling worried, tense, depressed, or irritable. The subscale "physical functioning" assesses patients' mobility and the need for support in basic activities of daily life. From this study, we can infer that [^{223}Ra]$RaCl_2$ treatment has a relatively stabilizing effect on patients by improving their emotional state and physical function. This suggests that the core symptoms of depression and anxiety disorders did not worsen, and that patients' physiological well-being remained stable. However, in a study published by Di Vincentis et al,[13] psychological status did not show significant variations during [^{223}Ra]$RaCl_2$ treatment in their patient population, and no association was found between psychological status and pain relief. This goes to show the

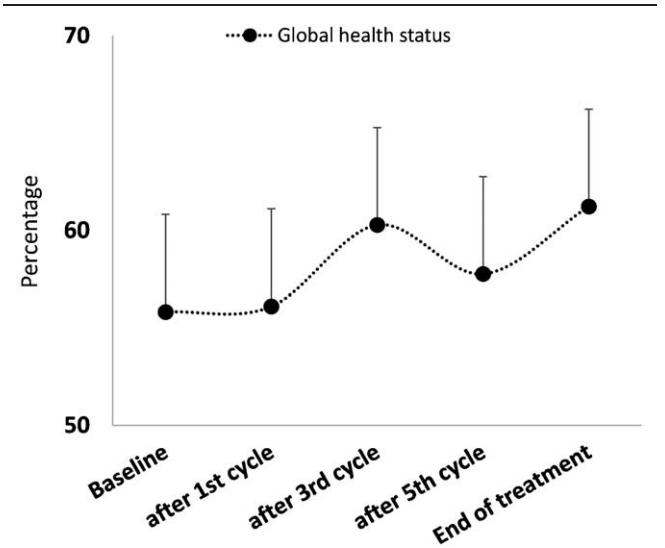

Figure 3. Changes in global health status over time. Values are presented as mean ± standard error of the mean, these increased in the course of Ra-223 treatment.

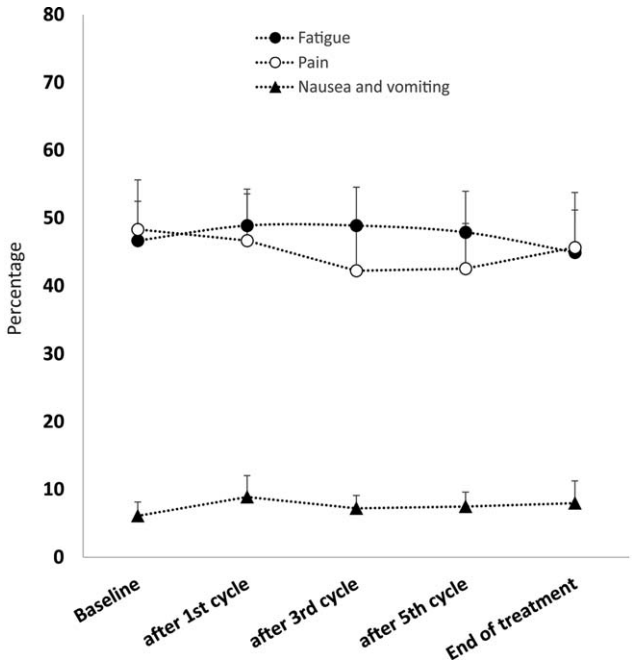

Figure 4. Changes of symptom scales over time. Values are presented as mean ± standard error of the mean, these remained relatively stable in the course of Ra-223 treatment.

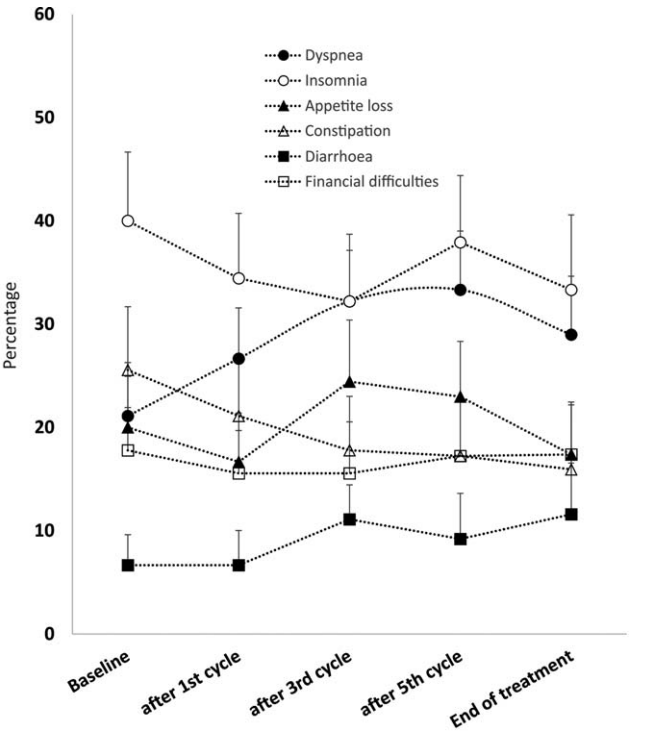

Figure 5. Changes of symptom scales over time. Values are presented as mean ± standard error of the mean.

importance of the psychological aspect in QoL evaluations and the need for a multidisciplinary approach to evaluate patients' emotional states and needs.

In a further step of the analysis, we compared the QoL at baseline with scores after the first, third, and fifth cycles and at the end of treatment. Emotional and physical functioning improved during the course of treatment but dropped after the end of therapy (Fig. 2), whereas social functioning remained relatively the same. Such changes are not statistically significant in our sample. However, role functioning decreased during the course of treatment, and the drop after the first cycle is particularly significant in our study ($P = .03$).

Looking at the physical symptom scales in detail, we can see that pain decreased during the course of the treatment, and fatigue seemed to increase slightly, while nausea and vomiting remained relatively unchanged (Fig. 4). On the other hand, insomnia and constipation showed marked improvement during the course of treatment, while symptoms of dyspnea and diarrhea partially increased (Fig. 5). The stabilization of symptoms without their worsening in the course of treatment may additionally contribute to a positive treatment experience and support a feeling of self-efficacy, which is highly associated with mental well-being.

Furthermore, comparing the pre- and posttreatment levels of ALKP for the 23 patients who received all 5 cycles of treatment, there was a clear decrease in ALKP levels for these patients (from a median of 101 U/L to 75 U/L pre- and posttreatment, respectively; $P = .003$). This indicates a significant reduction in osteolytic activity brought about by the stabilizing effects of [^{223}Ra]$RaCl_2$ on the bone matrix.

Seventeen patients were alive at the end of treatment (56.7%), and our cohort had an OS of 26 months (range, 19.8–32.2). There are obviously many factors that influenced survival in this cohort of patients, such as the burden of the disease and the types of treatments received, among others. In our cohort, completing the 6 cycles of [^{223}Ra]$RaCl_2$ treatment was not associated with improved survival ($P = .175$).

Our study was limited due to the relatively low numbers of patients recruited from a single care center. We only used EORTC-validated questionnaires in this study, and such methodology evidently comes with its own biases. Also, not all patients filled out all of the questionnaires at every time point, as some experienced progression of their symptoms. All of this limits the external validity of the findings and makes it difficult to detect small effects of treatment on QoL. However, our study is valuable in its longitudinal assessment of outcomes over several therapy cycles, which allows for differentiated evaluation of changes in QoL during the course of treatment.

5. Conclusion

[^{223}Ra]$RaCl_2$ therapy does not adversely impair the health-related QoL of patients with mCRPC and bone metastasis. Only patients' role functioning worsened temporarily after the first therapy cycle but stabilized in subsequent treatment cycles.

Author contributions

Acquisition of data: Miriam Sraieb, Hojjat Ahmadzadehfar,
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Miriam Sraieb, Nader Hirmas, Hojjat Ahmadzadehfar, Ken Hermann.
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Miriam Sraieb, Nader Hirmas, Hojjat Ahmadzadehfar, Milka Marinova, Rupert Conrad.

Conception and design: Miriam Sraieb, Hojjat Ahmadzadehfar.
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Study supervision: Miriam Sraieb, Hojjat Ahmadzadehfar.
Writing, review, and/or revision of the manuscript: Miriam Sraieb, Nader Hirmas, Rupert Conrad, Milka Marinova, Markus Essler, Ken Herrmann, Hojjat Ahmadzadehfar.

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