188Re Zoledronic Acid in the Palliative Treatment of Painful Bone Metastases

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Abstract: 188Re Zoledronic acid (188Re-ZA) is new radiopharmaceutical which may have advantages over other bone seeking β-emitters due to high radiation energy of 188Re, and metabolic effect of zoledronic acid.

In the phase I-II of the study therapeutic dosage of 188Re-ZA was estimated. Pharmacokinetics, dosimetry and safety were assessed in the dose escalation study. Twenty-one (3, 3 and 15) breast and prostate cancer patients with multiple painful bone metastases received 35, 45 and 55 MBq of 188Re-ZA respectively. In the next step 42 new patients were randomized in 2 groups (188Re-ZA in dosage of 45 MBq/kg and 89SrCl2 in dosage of 150 MBq) to assess safety and efficacy of the radiopharmaceuticals, the follow up lasted for 9 weeks.

Absorbed dose to the bone marrow is respectively low 0.26±0.06 Gy. The dose escalation study shows that 188Re-ZA the dosage of 55 MBq/kg is safe, no significant hematologic or any other toxicity is observed. 89SrCl2 in a dosage of 150 MBq/kg, as compared to 188Re-ZA in a dosage of 45 MBq/kg demonstrates similar efficacy, but the effect starts faster in 188Re-ZA group. By the end of the follow up some patients demonstrated pain recurrence, this may indicate the need for repeated courses of treatment. Although many patients with widespread bone metastases and the higher base level of alkaline phosphatase were in the 188Re-ZA group, in the majority of cases of both groups stabilization of the disease was achieved and continued for at least two months. Both radiopharmaceuticals demonstrated acceptable safety profile. Although trend in reduction of hemoglobin level was observed, especially in the group of patients with baseline anemia, both radiopharmaceuticals significantly impact on the platelet counts (PLT) only. As it was predicted by dosimetry data, 188Re-ZA in a dose of 45 MBq/kg is safer, by the week 6 the PLT counts in the 188Re-ZA group became almost the same as baseline and even higher in the week 9, while in the 89SrCl2 group in the week 9 PLT counts remained below the baseline; the difference was statistically proven. It seems that patients with breast cancer, in contrast to those with prostate cancer, have benefit (not statistically significant) in overall survival: 20.7 vs 15.6 months regardless dosage or type of radiopharmaceutical.

Keywords: Bone metastases, 188Re-Zoledronic acid, Radiopharmacy, 153Sm-EDTMP, 89SrCl2.

INTRODUCTION

For long time bone seeking radiopharmaceuticals are used to palliate painful bone metastases. Great part of scientific work in this area is focused on prostate and breast cancers. These types of cancers are characterized by frequent multiple bone metastases with no visceral lesions. [1]. Life expectancy of this kind of patients may be relatively long [1], so it is important to preserve their quality of life. Only three bone seeking radiopharmaceuticals are registered in Russia. 89SrCl2 and 153Sm-EDTMP are the most commonly used to decline pain syndrome and reduce analgesic intake. The newest bone seeking agent 223Ra dichloride also has benefit in overall survival of patients with castration resistant prostate cancer and predominantly skeleton involvement [2]. As for 89SrCl2 it is very simple to handle and administer, but it is recommended for use in cases of light to moderate pain syndromes and not widespread (less than 10 metastases) disease [3]. Unfortunately, these types of clinical situation are relatively rare. Due to its physical characteristics 153Sm-EDTMP can be safely used for larger bone involvements, and its effect is faster, so it can help to manage severe pain [3]. As for 223Ra dichloride it is registered only for castration resistant prostate cancer patients and it is the most expensive one [4]. Despite the fact, that 223RaCl2 is the gold standard of care of
patients with multiple bone metastases, due to its high cost it is hardly available for majority of the prostate cancer patients in Russia and around the world. In addition, we still have no recommendations on the use of $^{223}$RaCl$_2$ in cases of other malignancies (not CRPC) with multiple painful bone metastases. Thus, the search for new radiopharmaceuticals is an important challenge. The new radiopharmaceutical based on $^{188}$Re and Zoledronic acid may become an alternative to traditionally used bone seeking agents.

**MATERIALS AND METHODS**

**Preparation of 188Re Zoledronic Acid (188Re-ZA)**

$^{188}$Re perrhenate (radiochemical purity 99.7%, PH 4.1) was obtained from in-house 25 GBq $^{188}$W/$^{188}$Re generator (Institute of Physics and Power Engineering, Obninsk). The generator was eluted with 5-9 ml of 0.9% saline. 1-2 ml of eluate was mixed with the preparation kit of 4 mg zoledronic acid lyophilizate (Pharm-Sintez, Moscow). The solution was heated at 95°C for 30 min, after cooling to room temperature the solution was passed through the sterilizing filter “Millipore” with the diameter of the pores 0.22 micrometers. Then it is added to 15 milliliters of saline solution and applied to patient by syringe pump for 15 minutes.

Quality control of 188Re-ZA was performed using thin-layer chromatography developed with acetone or physiological saline. The levels of impurities detected in patient samples were always less than 5%.

**Study Design**

This study consisted of two parts. The aim of the first part was to assess the maximum tolerated dose of the radiopharmaceutical and estimate therapeutic dose. The first three patients had to receive the drug at a rate of 35 MBq/kg, after 8 weeks of safety assessment in the event of any dose-limiting toxicity (DLT) the group had to be expanded to 6 patients. In case of DLT in 2 subjects, the study had to be completed; otherwise it was necessary to recruit the next group of three with administration activity of 45 MBq/kg. Like in previous situation, in case of DLT the second group also had to be enlarged to 6 patients. If revealed 2 cases of DLT, the therapeutic dosage would be estimated as 35MBq/kg. In another case, it was necessary to recruit the third group of patients (55 MBq/kg), in case of DLT revealed during follow up period, the third group also had to be expanded to 6, if revealed 2 cases of DLT the therapeutic dosage would be estimated as 45 MBq/kg. In case of only one or no DLT revealed the therapeutic dosage would be estimated as 55 MBq/kg. In any case the group of therapeutic activity had to be enlarged up to 15 patients in order to have more statistically significant data. The DLT was equal for the following events: neutropenia of grade IV or fever caused by neutropenia, grade IV platelet counts decrease or grade III thrombocytopenia lasted more than 7 days, any other grade III-V adverse event associated with the use of an investigational drug.

In the second part of the study safety and efficacy of 188Re-ZA had to be assessed in comparison to $^{89}$SrCl$_2$ on a randomized multicenter basis. The history of use of 188Re-HEDP in Russia is limited only to clinical trials, and 186Re-HEDP has never been used. $^{89}$SrCl$_2$ is used in the majority of the nuclear therapy centers in Russia, but only two centers have experience in $^{153,155}$Sm-EDTMP application. Therefore, $^{89}$SrCl$_2$ was chosen as a comparative drug. Changes in quality of life, intensiveness of pain syndrome and metabolic response (according to a bone scan) were selected as effectiveness criteria. After active part of the investigation all patients entered into long term follow up period with assessment of overall survival.

**Inclusion Criteria**

Patients with histologically proven prostate or breast cancer and CT proven multiple (3 or more) painful (required analgesic intake) bone metastases with positive $^{99m}$Tc Zoledronic acid uptake, with no history of visceral metastases and no additional malignances were included in the study. Subjects with changes in hormone therapy, received external beam therapy or chemotherapy 1 month prior to screening were not included. Sufficient bone marrow function was required: platelet count not less than 100 thousand/ml, leukocyte count not less than 3.0 thousand/ml and hemoglobin level not less than 80 g/l.

**Patients**

The study was approved by the local ethics committee. All patients included in the study were informed about the study, possible risks of participation and signed the informed consent form.

According to the study design the first 3 patients with multiple painful bone metastases of prostate or breast cancer received 188Re-ZA in dosage of 35 MBq/kg, as no cases of DLT appeared in follow up
period, the next 3 received 45 MBq/kg, and the third 3 – 55 MBq/kg, after 9 weeks of follow up the third group was enlarged up to 15 patients. All patients had previously done bone scan with $^{99m}$Tc Zoledronic acid, thananostic pare to $^{188}$Re-ZA, 3 or more bone lesions were confirmed in each case. In the first day after administration dosimetry data were collected: 1, 4, 20, 26-28 hours after administration there was anterior and posterior whole body scanning performed (gamma-camera Mediso with high-energy collimator). Regions of interests were processed anterior and posterior: metastatic lesions, significant organs and tissues. Half-life time ($T_{eff}$), fractions of organs and absorbed doses were calculated using MCNP 4 code and program OLINDA/EXM 1.0. Safety assessment performed during the first 3 days after administration and the next 3 received 45 MBq/kg, and the third 3 – 55 MBq/kg, after 9 weeks of follow up the third group was enlarged up to 15 patients. All patients had previously done bone scan with $^{99m}$Tc Zoledronic acid, thananostic pare to $^{188}$Re-ZA, 3 or more bone lesions were confirmed in each case. In the first day after administration dosimetry data were collected: 1, 4, 20, 26-28 hours after administration there was anterior and posterior whole body scanning performed (gamma-camera Mediso with high-energy collimator). Regions of interests were processed anterior and posterior: metastatic lesions, significant organs and tissues. Half-life time ($T_{eff}$), fractions of organs and absorbed doses were calculated using MCNP 4 code and program OLINDA/EXM 1.0. Safety assessment performed during the first 3 days after administration and then weekly up to week 9. For this issue, blood counts, liver and kidney function biomarkers (ALT, AST, creatinine, urea, etc) were obtained. Physical examination, electrocardiogram and urine tests were performed on a regular basis.

For the efficacy assessment 42 patients were included in the study, after screening they were randomized into $^{188}$Re-ZA group and $^{89}$SrCl$_2$ group, 21 subjects for each group. Basic demographic data and screening characteristics of subjects are on the Figure 1. All patients kept a diary of pain and consumption of Analgesics a week prior and during follow up period after administration of 45/kg MBq $^{188}$Re-ZA or 150 MBq $^{89}$SrCl$_2$. In the diary, they daily described their pain in various parts of the body for a 10-point visual analog scale. Quality of life was evaluated using the SF-36 questioner, which was filled prior therapy and on the 28th and 56th day after. Safety control was performed by the method similar to that used in the first part of the investigation. All patients underwent bone scan with $^{99m}$Tc Zoledronic acid in order to assess metabolic response.

**RESULTS**

**Therapeutic Dosage of $^{188}$Re-ZA**

In this study $^{188}$Re-ZA did not demonstrate significant toxicity in any subgroup. In the group received 55MBq/kg of the radiopharmaceutical reversible short term neutropenia grade III was observed only once in breast cancer patient, who previously received multiple cycles of chemotherapy.
Thus, DLT was not observed and $^{188}$Re-ZA can be safely administered in dosage of 55 MBq/kg. However, according to the experts’ opinion, estimated therapeutic dosage was 45 MBq/kg. This opinion was based on the idea that this kind of treatment might be more effective if it is repeated several times with relatively short intervals. The dosage was reduced to avoid any kind of cumulative toxicity in case of multiple cycles.

**Dosimetry**

During the first part of the study dosimetry measurements were carried out. Urine samples demonstrated rapid excretion of the drug, more than 90% excretion accounted for the first 4 hours after administration. Half-life ($T_{eff}$) in bone metastasis (10.7±3.7 h) depended on their size and uptake of the radiopharmaceutical; it was significantly higher than in a whole body (6.3±0.7 h), normal organs and bones. Variation of $T_{eff}$ determines variability of specific absorbed dose, which was adjusted to therapeutic activity of 45 MBq/kg. Absorbed dose in metastases varied from 4.68 to 43.89 Gy (tumor volume ranges from 14 to 70 cm$^3$), which is sufficient to achieve therapeutic effect. Absorbed dose in kidneys (2.73±0.67 Gy) and urinary bladder (4.24±1.52 Gy) were less than maximally acceptable of 10 Gy. In this study, it was found that absorbed dose to the bone marrow was 0.26±0.06 Gy, it is significantly lower than those for other commercially available bone seeking radiopharmaceuticals.

<table>
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<td>WBC decrease</td>
<td>3 (33%)</td>
<td>1 (33%)</td>
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**Figure 2:** List of adverse events possible related to study medication. The data collected during the first part of the study (therapeutic dose determination and safety assessment).
radiopharmaceuticals like $^{153}$Sm-EDTMP (1.1 Gy) or even $^{188}$Re-HEDP (2.0±0.6) [5].

**Safety**

According to the study design administered activity of $^{188}$Re-ZA was ranged from 2.7 to 5.8 GBq. In this study, adverse events were classified according to the NCI CTC AE v 4.0. In generally the therapy was well tolerated (Figure 2), only one serious adverse event (SAE) was reported in the group of 55 MBq/kg. Hormone refractory prostate cancer patient with rapid disease progression and severe pain syndrome (opioid use required) needed to prolong his stay at hospital due to the grade II flu-like syndrome (3 days of fever) and flares phenomenon which decreased his Karnofsky’s scale from 60% to 40%. Two weeks later this patient was pain free with no more opioid intake and 70% Karnofsky’s scale, were not additional treatments of any kind. Unfortunately, 3.6 months later he died due to disease progression. Almost half of the patients noted the flare effect, which was manifested by a slight increase in pain or an increase in analgesics consumption. Flu-like syndrome was documented in 14% of cases. By the end of the follow up period some patients (predominantly with prostate cancer) demonstrated bone pain recurrence that might be an indication for additional treatment cycle. Most common adverse effects which may have any connection to the study drug are listed on the Figure 2.

The most important adverse event of bone seeking radiopharmaceuticals is hematological toxicity. Platelet counts (PLT) is the unique setting which was found to be statistically significantly associated with the therapy. We have also identified significant differences between the two study drugs. Nevertheless, $^{188}$Re-ZA was well tolerated in all subgroups of activity; 9 (60%) and 12 (63%) cases of grade I PLT decrease were found in 55 MBq/kg and 45 MBq/kg subgroups respectively, nadir was registered at the week 4 after the treatment date and the average PLT reduction was 12% (55 MBq/kg) and 17% (45 MBq/kg) respectively; and one case of reversible PLT counts grade II decrease was registered in one prostate cancer patient from the 45 MBq/kg group, his base PLT count was $9 \times 10^9/\mu L$, by the week 9 it rose up to $125 \times 10^9/\mu L$. No difference between the dosages of 45 MBq/kg and 55 MBq/kg (see Figure 3) was found. As for $^{89}$SrCl$_2$, in generally it was also well tolerated. No flu-like syndrome was revealed, flare phenomenon also was not documented, in one case (castration resistant prostate cancer) unexpectedly pancytopenia was developed, which finely led to death. Except this one extraordinary case there was only grade I toxicity in 9 cases (45%). The differences between $^{188}$Re-ZA and $^{89}$SrCl$_2$ are shown on the Figure 4. We presented data on those patients, who successfully completed the study without any protocol deviations, we excluded 2 women with disease progression (found brain metastases and pleura canceramatosis) from $^{188}$Re-ZA drug arm, as for $^{89}$SrCl$_2$ arm, 2 men with progression of the disease, they could not follow the schedule of visits due to worsening of their general condition, 4 other patients missed at least one visit for different reasons and didn’t take part in the evaluations. Remarkable, in the patient with severe PLT counts decrease necessary platelet transfusion at the week 8 of follow up, however this extraordinary case had not any influence on the final analysis. As it shown on the Figure 4, PLT counts are better in the $^{89}$SrCl$_2$ group (but not statistically significantly). At the week 1 unexpected increase in PLT counts in the $^{188}$Re-ZA group was found. $^{188}$Re-ZA acid PLT dynamics curve has a nadir at the week 4, then it goes up, is close to the screening value at the week 6, at the week 9 it is even better than before the treatment. $^{89}$SrCl$_2$ curve also seems to have a slight increase at the week 1, but its nadir is registered at the 5th week, after that the curve goes up slowly and doesn’t reach initial values by the end of the follow up. Multivariate analysis of variance for repeated measures was used to found statistical differences between the two groups, and it was found with p value about 0.024. This distinction is very important for patients, who may need frequent retreatments to manage multiple painful bone metastases or some kind of chemotherapy in case of any needs.

![Figure 3: Platelet count (PLT) dynamics after administration of 55 MBq/kg or 45 MBq/kg of 188Re-ZA. The number of valid (without missing points) cases were 12 and 19 respectively.](image-url)
circumstances, like disease progression, bone marrow involvement and others, in addition to medications can affect the severity of anemia. In all groups of subjects WBC counts fluctuated in normal range, those patients who initially had WBC count higher than normal level tended to have a decline after treatment. In patients, who were heavily pretreated with chemotherapies, some cases of hematological toxicity were documented. In \(^{188}\text{Re-ZA}\) (55 MBq/kg) group 4 cases (27%) of grade I and 2 cases (13%) of grade II reversible WBC decrease was found, in \(^{188}\text{Re-ZA}\) (45 MBq/kg) 5 cases (26%) of grade I WBC decrease were documented, in the \(^{89}\text{SrCl}_2\) group 6 cases (30%) of grade I and 1 case (5%) of grade II WBC decrease were found.

**Efficacy**

The main idea of the efficacy analysis was to evaluate the influence of administration of \(^{188}\text{Re-ZA}\) or \(^{89}\text{SrCl}_2\) on the average severity of pain. For this issue the area under the pain-time curve (AUC) was calculated for the 7 days of screening period and weekly after the treatment. For comparative analysis, the generalized linear model was used. In our small study (19 and 18 valid subjects who completed all diaries in \(^{188}\text{Re-ZA}\) and \(^{89}\text{SrCl}_2\) group respectively) there was not found any statistically significant deference. In both groups, there were some cases with severe pain syndrome which was refractory to treatment demonstrated only aggravation during the follow up period. These few cases have a great impact on the means, thus the medians reflect the real dynamic much more accurately. As one can see on the Figure 5, patients treated with \(^{89}\text{SrCl}_2\) had better initial conditions, in the 1st 3 weeks we can not see any positive changes, this data is well correlated with already known property of \(^{89}\text{SrCl}_2\). From the week 3 the AUC pain-time curve goes down but unfortunately does not reach its nadir. So, we can't make any conclusions neither about decline degree nor about duration of effect. Contrary, \(^{188}\text{Re-ZA}\) demonstrated fast analgesic effect. Feeling better many patients tried to reduce their daily analgesic intake, what was the reason of pain recurrence at the week 2. After this peak the curve continues to decrease till its nadir at the week 5, average of decrease at this point compared to the screening time is 25.47% for the medians and 10.47% for the means. At the end of the follow up period there was a tendency to evidence of pain recurrence followed with a return to analgesics use. At the week 9 only 4 (21%) patients still demonstrated 50% reduce in the index of analgesic intake, while in \(^{89}\text{SrCl}_2\) group at

Figure 4: Platelet count (PLT) dynamics after administration of 45 MBq/kg of \(^{188}\text{Re-ZA}\) or 150 MBq of \(^{89}\text{SrCl}_2\). The number of valid (without missing points) cases were 18 and 15 respectively.
its best time of action 6 (33%) subjects had 50% or more reduction of this index. To conclude, these even not statistically significant tendencies may indicate a need for different therapeutic approaches in use the investigational drugs.

Figure 5: Area under the curve “Pain-Time” (AUC) at the screening week and after administration of investigational or control radiopharmaceutical.

As for quality of life at the week 4 the dynamics of the integral index of quality of life (IQL) was better in $^{188}$Re-ZA group than in $^{89}$SrCl$_2$ one (+10% and +3% respectively). Like in previous analysis results for $^{89}$SrCl$_2$ group were better at the week 9, IQL reached +7%, while in $^{188}$Re-ZA it was measured +6% compared to the screening condition. These differences however did not reach statistical significance. In subgroup analysis, we found that in the breast cancer group $^{188}$Re-ZA was managed to improve physical component of quality of life (-2% at the week 4 and +21% at the week 9), while $^{89}$SrCl$_2$ failed to improve it (-3% at the week 4 and -1% at the week 9). The differences between $^{188}$Re-ZA and $^{89}$SrCl$_2$ arms were statistically significant according to the Wilcoxon test (p <0.05). In male patient group any statistically significant differences were not found.

Metabolic Response

All patients had bone scan with $^{99m}$Tc-ZA prior to the week 9. Alkaline Phosphatase (ALP) was measured weekly before and after the administration. In both groups, more than half patients had wide spread bone metastases (more than 20 lesions), see Figure 1. Unfortunately, we found statistically significant difference between the main and control group in the baseline ALP level, which, as known, correlates with prognosis. In the $^{188}$Re-ZA group it was significantly higher. Generalized linear model was used to assess influence of the therapy on the ALP level, which can reflect metabolic response, see Figure 6. In this study, there was not any differences between initial and follow up ALP level; it was stable in both groups. In individual analysis, by the end of the follow up period we found 2 cases (12%) of ALP progression (more than 30% ALP level increase) and 3 cases (18%) of response (more than 30% ALP level decrease) in the $^{188}$Re-ZA group. In $^{89}$SrCl$_2$ group there were 2 cases of progression (11%) and only 1 responder (5%). As for imaging, we saw generally stable disease or mix response, there were 4 cases (20%) of 2 or more new active bone lesions on bone scan in the $^{188}$Re-ZA group and 5 (25%) in the $^{89}$SrCl$_2$ group. We also found one case (5%) of clear metabolic response (two lesions disappeared) in the control group.

Figure 6: ALP dynamics after administration of $^{188}$Re-ZA (45 MBq/kg) or $^{89}$SrCl$_2$ (150 MBq).

Survival

All patients included in the study and received treatment entered into survival analysis. Some of them unfortunately were lost for long term follow up, but the data is still collected, so this time we can present only preliminary results. We assessed overall survival (OS) in 3 groups of patients: $^{188}$Re-ZA 55 MBq/kg, $^{188}$Re-ZA 45 MBq/kg and $^{89}$SrCl$_2$ 150 MBq. The results are presented on the Figure 7. The curves are very close to each other, median OS was 17.9 months for $^{188}$Re-ZA 55 MBq/kg, $^{188}$Re-ZA 45 MBq/kg and $^{89}$SrCl$_2$ 150 MBq. The results are not statistically significant between the groups, so we tried to compare OS in men (28 subjects) and...
women (35 subjects), see Figure 8. It seems that life expectancy in breast cancer patients (median OS – 20.7 months) is better than in prostate cancer males (median OS – 15.6 months), but the difference is not statistically significant.

Figure 7: Overall survival by groups: $^{188}$Re-ZA 55 MBq/kg, $^{188}$Re-ZA 45 MBq/kg and $^{89}$SrCl$_2$ 150 MBq.

Figure 8: Overall survival in breast and prostate cancer patients after one cycle of bone seeking radiopharmaceutical.

DISCUSSION AND CONCLUSION

$^{188}$Re-ZA is promising radiopharmaceutical for treatment painful bone metastases. Firstly, we noticed a great difference in pharmacokinetic compared to other bone seeking radiopharmaceuticals and even $^{188}$Re-HEDP [5]. Zoledronic acid has the highest affinity to bone lesions (compared to other phosphonates) with minimal accumulation in healthy bones [6]. As result, therapeutic absorbed doses in bone lesions can be achieved with relatively low bone marrow irradiation. Features of the distribution allow using $^{188}$Re-ZA in higher dosages than $^{188}$Re-HEDP: 55 MBq/kg (up to 5.8 GBq) of $^{188}$Re-ZA is safe and acceptable while for $^{188}$Re-HEDP therapeutic activity was estimated as 3.3 GBq [7]. Bone seeking radiopharmaceuticals are well tolerated; well known dose limiting toxicity is a delayed decrease in the number of blood counts, mainly PLT. The decrease in the PLT counts by the week 4 after the administration, apparently, is a common feature of bone seeking radiopharmaceuticals, a similar trend recorded for $^{153}$Sm-EDTMP [8]. In this study, we didn’t found any significant impact on WBC or HGB level of the both drugs, but there was a tendency to HGB level decline, especially in anemic subjects. In this cases anemia may be the consequence of bone marrow involvement and disease progression, previous cytotoxic regimens or malabsorption and malnutrition. The influence of therapy on the severity of anemia remains not clear. But in fact, inclusion criteria were very wide allowing anemic patients with HGB level below 100 g/l to be involved in this study. There were 2 anemic patients with HGB level 86 g/l and 1 patient – 91 g/l. They all demonstrated worsening the anemia down to grade III which reversed by the end of the follow up period only in one case. In contrast, no decline in HGB level in non-anemic persons was found.

According to the study the therapy had clear influence on PLT counts. In previous investigations no difference between various bone seeking radiopharmaceuticals ($^{153}$Sm-EDTMP, $^{188}$Re-HEDP and $^{89}$SrCl$_2$) was found [9]. $^{188}$Re-ZA is the first one that demonstrated preferable safety profile compared to $^{89}$SrCl$_2$. That is very important for planning retreatments or combinations with other cytotoxic regimens. The case of unexpected pancytopenia in previously clinically stable prostate cancer patient also noteworthy. There is not any clear data about limitations in $^{89}$SrCl$_2$ usage, IAEA recommends not to use it in cases with more than 10 bone lesions (according to bone scan) [3], however, no national or other recommendations related to this subject; in the study 57% patients from the control group, who received $^{89}$SrCl$_2$ had more than 20 bone lesions. Thus, that is a question for further investigations. Despite the fact that patients treated with $^{188}$Re-ZA had worse base condition (higher ALP level), than patients of the control group, both radiopharmaceutical demonstrated similar efficacy. But $^{188}$Re-ZA acts faster and there is a tendency to pain recurrence in some cases at the week 9, while analgesic effect of $^{89}$SrCl$_2$ starts two weeks later and by the week 9 it appears to be maximum. Thus $^{188}$Re-ZA is more suitable for those who suffer...
from severe uncontrolled or progressive pain syndrome. Breast cancer patients from the $^{188}$Re-ZA group had statistically significant benefit in physical component of IQL. Both radiopharmaceuticals were able to achieve stabilization in ALP level.

The study is too small to draw any evidence-based conclusions about survival, however, it should be noted that we have not found any significant difference between patients received a single cycle of $^{89}$SrCl$_2$ or $^{188}$Re-ZA in different dosages. It seems that breast cancer patients have better prognosis than prostate cancer ones, in order to prove this, we need more data. In any case, our survival rates look good compared with findings from other studies [10], including large randomized trials like ALSIMPCA trial [11]. That is encouraging and inspires further research in the field of application of bone seeking $\beta$-emitters.

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