Zoledronic Acid as a Remedy on Clodronate-Resistant Prostate Cancer Patients with Metastatic Bone Pain

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Abstract
To scrutinize the clinical effectiveness and safety of zoledronic acid on the treatment of clodronate-resistant prostate cancer patients with metastatic bone pain.108 clodronate-resistant prostate cancer patients with metastatic bone pain in our hospital from February 2015 to October 2017 were given zoledronic acid therapy per month (4mg zoledronic acid +100 ml saline, infusion time > 15min, treatment for 3 months) All patients underwent QoL (Quality of Life) evaluation precede to zoledronic acid therapy replacement and 1 to 3 months subsequently utilizing the Chinese format of the Visual Analogue Scale (VAS) and EORTC QLQ-BM22 investigation. Also, Analgesic total efficacy, performance status, and adverse reactions were analyzed. After 3 months’ treatment in the comprehensive study population, we found a substantial depletion of bone pain. Thus, 71% patients showed relief and the overall mean VAS (Visual Analogue Scale) scores reduced to 2.1 (95% CI 1.4-2.6, P=0.03). The symptom subscale of EORTC QLQ-BM22 was subsequently reduced to the baseline (PS: 3month p=0.045 PC: 3 months, p=0.02). The Psychosocial Aspects (PA) and Functional Interference (FI) of subscales were higher than the baseline from 2 months onward (PA: 3 months, p=0.03, 2 months, p=0.04; FI: 3 months, p=0.03, 2 months, p=0.03). And the side effects are negligible and acceptable. Zoledronic acid can not only effectively relief the pain but also bring about better practical interference and psychosocial features in clodronate-resistant prostate cancer patients with metastatic bone pain.

Key Words: Zoledronic ACID, Clodronate-resistant, Metastatic bone pain, Efficacy and Safety.

Ácido Zoledrónico como Remedio en Pacientes con Cáncer de Próstata Resistente al Clodronato con Dolor Óseo Metastásico

Resumen
Para analizar la efectividad clínica y la seguridad del ácido zoledrónico en el tratamiento de pacientes con cáncer de próstata resistente al clodronato con dolor óseo metastásico.108 pacientes con cáncer de próstata con dolor metastásico resistente al clodronato en nuestro hospital desde febrero de 2015 hasta octubre de 2017 recibieron terapia de ácido zoledrónico por mes (4 mg de ácido zoledrónico +100 ml de solución salina, tiempo de infusión> 15 min, tratamiento durante 3 meses) Todos los pacientes se sometieron a una evaluación de la calidad de vida (Quality of Life) antes del reemplazo de la terapia con ácido zoledronic y de 1 a 3 meses posteriormente, utilizando el formato chino de Visual Investigación en escala analógica (VAS) y EORTC QLQ-BM22. Además, se analizaron la eficacia total analgésica, el estado de rendimiento y las reacciones adversas. Después de 3 meses de tratamiento en la población de estudio integral, encontramos un agotamiento sustancial del dolor óseo. Por lo tanto, el 71% de los pacientes mostró alivio y las puntuaciones medias en VAS (Visual Analogue Scale) se redujeron a 2.1 (IC 95% 1.4-2.6, P = 0.03). La subescala de síntomas de EORTC QLQ-BM22 se redujo posteriormente a la línea de base (PS: 3 meses p = 0.045 PC: 3 meses, p = 0.02). Los aspectos psicosociales (PA) y la interferencia funcional (FI) de las subescalas fueron superiores a los valores iniciales desde los 2 meses en adelante (PA: 3 meses, p = 0.03, 2 meses, p = 0.04; FI: 3 meses, p = 0.03, 2 meses, p = 0.03). Y los efectos secundarios son despreciables y aceptables. El ácido zoledrónico no solo puede aliviar eficazmente el dolor, sino que también brinda mejores interferencias prácticas y características psicosociales en pacientes con cáncer de próstata resistente al clodronato con dolor óseo metastásico.
1. Introduction

The usual area for metastases is bone in prostate cancer, and a great part of patients will evolve metastases of bone throughout the natural course of their disease. This untreated progression not only exerts unbearable painful on the body but also heavily weighted on cancer-related morbidity and death [1]. The fifth indispensable sign is pain which is related with social and psychosocial function of patient acknowledged as one of the key elements of assessing clinical conditions of patients [2]. Therefore, effective pain control and improved QOL has become the primary challenges for treatment in analgesic oncology which aim is to just to lessen bone pain while reducing unintentional difficulties and side effects.

Today, the treatment of metastatic bone pain remains analgesic by various therapeutic ways. But these treatments are insufficient and the time span shows reaction that censoriously impairs the QoL of patient [3-6]. In this regard, this anguished situation, bisphosphonates have emanated as critical therapeutic modes to cope up with the bone cancer disease [7-9]. While the potentiality of these agents has not yet acknowledged, their application is amplifying. Clodronate belonging to the first generation of bisphosphonates stands out as Non-nitrogen containing, is extensively used all over the globe for its oral agents which is simple and more appropriate. From Sadd’s research, Clodronate had been convinced to improve prostate cancer patients overall long term survival and reduce skeletal-related events [10]. However, with the disease progressed, more and more clinicians would come across such a dilemma; patients in the treatment of the clodronate start to complain about the increasing bone pain because of drug-resistant. By the time, many of them may resort to use or raise the dose of analgesic drugs, even nicotins, neglecting to take into account the serious side effects, such as gastrointestinal disorders, allergy or even addiction. Zoledronate acid, as a third generation bisphosphonate, was well discussed in some studies as the first-line bisphosphonate in the management of the malignant tumor with bone metastases [11-13]. To our knowledge, there was no study to assess the efficiency and well-being of ZA (Zoledronic Acid) for the therapy of clodronate-resistant prostate cancer patients with metastatic bone pain.

Then, in this study, we provided the first evidence to evaluate the efficiency and well-being of ZA (Zoledronic Acid) as a remedy way in the therapy of clodronate-resistant prostate cancer patients with metastatic bone pain.

2. Materials and Methods

2.1. Patients

From February 2015 to October 2017, 108 patients were enlisted for the study; all of them came to prostate cancer outpatient clinics monthly in the affiliated hospital of Wenzhou medical university.

Inclusion criteria: 1. the patients greater than 18 years with life anticipation of more than 3 months. 2. Patients histologically having of prostate cancer, with minimum two radiographic techniques (Electroconvulsive Therapy (ECT) and Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI)) proofs of bone metastases. 3. All of them had been in the treatment of clodronate for more than 3 months. Restart bone pain or to be more aggressive. 4. Patients were need to have castrated levels of (Prostrate-Specific Antigen) PSA (<2ng/mL) during the therapy.

Exclusion criteria: Patients had substantially hepatic, nephritic or non-malignant related diseases; They had done radiotherapy or chemotherapy during the therapy. Previous use of zoledronic acid or other bisphosphates. Paget's diseases, main osteoporosis or hyperparathyroidism.

2.2. Treatment Schedules

After a visit, we conducted a 3 months, prospective, single-arm study. eligible patients were asked to stop taking oral clodronate, but to accept zoledronic acid instead (infused over a 30 min with 4 mg iv) each month; Patients pursued the first-line hormonal treatment and got a calcium extra of vitamin D and 500mg of 400IU everyday. Dexamethasone and other aristocort were not used for their possible palliative effect. The treatment is terminated earlier if and only if they bear critical (Skeletal-Related) SRES situations such as, spinal compression, pathological fractures, or constant and apparent hepatic or renal noxious and also death.

It was managed according to the Declaration of Helsinki and the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human use Guidance for Good Clinical Practice. Also, it was accepted by local Ethical Committee each patient provided written agreement proceeds to study entry.

2.3. Follow Up and Assessment

All the patients more than 3 months, assessed for efficacy and safety monthly. Efficiency was estimated by
analyzing VAS scores and palliative use and also EORTC QLQ-BM22 examination. Safety tests comprised the rates of noxious and the unfavorable occurrences.

A 10-cm VSA (Visual Analog Scale) is used to evaluate the pain patients suffering throughout the trial. The scale comprises of a series of numbers which description is: 0=no pain 2=irritating pain, 4=uncomfortable pain, 6=terrible pain, 8=horrifying pain, and 10=excruciating pain.

The disease symptoms associated to bone metastases are represented by EORTC QLQ-BM22[14]. Reactions, difficulties, and other problems associated to therapy of bone metastases; and supplemental quality of life dimensions that are pertinent across treatment and diagnoses modes. This module had been evaluated by international field study. Results confirmed the sound, reliable, cross-cultural pertinence, and sensitivity, what’s more, patient’s feedback demonstrated QLQ-BM22 is easy to comprehend [15].

To identify the scores of average pain and finished 22-item module every month, the patients asked to jot down the level of pain daily. Both investigations were finished with the aid of an individual who was not connected or self managed by patients. Unfavorable situation was taken as the case lead to stop using for the time being or alter the amount of medication. All clinical results were blind to patients and clinicians.

2.4. Statistical Methods

To compare the means we have used Analysis Of Variance (ANOVA). All statistical surveys were executed by Statistical Package for the Social Sciences (SPSS) V21.0 (SPSS, Chicago, IL). Values are specified, unless otherwise appeared as means ± standard error. The values of P less than 0.05 are taken statistically important. The Wilcoxon test is used to contrast the mean differentiation of pain assessment and Quality of Life (QoL) scales changing when the same persons are studied more than once.

3. Results

3.1. Patient Characteristics

From February 2015 to October 2017, 108 patients were registered and recruited in the hospital for this purpose. Baseline clinical features and demographics beside age baseline Body Mask Index (BMI), Visual Analogue Scale (VAS) scores, Gleason score, Serum creatine, Calcium, Mode of ADT were analyzed (Table 1). The mean age and BMI of the patients were 73.6±7.4 and 23.5±2.1, respectively. About the Gleason score, there was highest percent (59.3%) in G3 (8-10). 28.7% of patients received analgesic therapy. The concentration of serum creatinine and calcium were 79±16.2 (umol/L) and 2.63±0.63 (2.63±0.63), respectively. As for mode of ADT, there was 93.5% on GnRH agonist therapy (Table 1).

Table 1. The clinical characteristics and baseline demographics (n=108)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ±SD</td>
<td>73.6±7.4</td>
</tr>
<tr>
<td>Mean BMI±SD(Kg/m2)</td>
<td>23.5±2.1</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
</tr>
<tr>
<td>G1(5-6)</td>
<td>13(12.0%)</td>
</tr>
<tr>
<td>G2(7)</td>
<td>31(28.7%)</td>
</tr>
<tr>
<td>G3(8-10)</td>
<td>64(59.3%)</td>
</tr>
<tr>
<td>VAS</td>
<td>5.2±2.9</td>
</tr>
<tr>
<td>Patients on</td>
<td></td>
</tr>
<tr>
<td>Analgesic therapy, n=31</td>
<td>31(28.7%)</td>
</tr>
<tr>
<td>Serum creatinine umol/L</td>
<td>79±16.2</td>
</tr>
<tr>
<td>Calcium mmol/L</td>
<td>2.63±0.63</td>
</tr>
<tr>
<td>Mode of ADT</td>
<td></td>
</tr>
<tr>
<td>GnRH agonist therapy</td>
<td>101(93.5%)</td>
</tr>
<tr>
<td>Orchidectomy</td>
<td>7(6.5%)</td>
</tr>
</tbody>
</table>

* clinical characteristics and baseline demographics besides VAS (Visual Analogue Scale) scores, age baseline Body Mask Index (BMI), calcium, Gleason score, Serum creatine, Mode of ADT were analyzed by $\chi^2$ tests.

3.2. The Effect on Pain Control and EORTC QLQ-BM22

The baseline mean Visual Analysis Scale was 5.2 (± 2.9) in CA group. We have taken the up-gradation minimum two point-scales as a rational calculation to spot a noticeable palliative. After 3 months’ therapy we
found a noteworthy depletion of bone pain in the total population of study. Thus, 71.3% patients showed relief and the overall mean Visual Analysis Scale (VAS) scores reduced to 2.1 (P=0.03, 95% CI 1.4-2.6). In prior to the using of zoledronic acid, 31 of 108 patients were on palliative treatment (either non-opioid or opioid). During the follow-up, 18 of 31 were able to discontinue analgesic drug intake, other 6 reduce the dose (P = 0.01) (Figure 1).

**Figure 1.** Visual Analogue Scale

Changes in QLQ-BM22 from baseline through 3 months are presented by 1, 2, 3 months by Fig2a and Fig 2b. High score shows critical level of complications for the symptom scale. At 1, 2 months, PS was lower than the baseline related with a substantial decrease at the third month (PS: 3 month, p=0.045). PC, however, was substantially decreased around a month subsequently contrast with the baseline (3 months, p=0.02; 2 months, p=0.03; 1 month, p=0.03). Refer to the functional scale, a good score means a good status of functioning. Both PA and FI were substantially increased after zoledronic acid therapy replacement compared to the baseline (PA: 3 months, p=0.03, 2 months, p=0.04; FI: 3 months, p=0.03, 2 months, p=0.03, 1 month, p=0.04) (Figure 2).
* P less than 0.05 demonstrates that there is substantially statistical contrast between two groups

**Figure 2.** Assessment of quality life in 108 patients of prostate cancer with bone metastasis cured with the zoledronic acid using the European Organization for Research and Treatment of Cancer (EORTC) QoL Group Bone Metastases Module (QLQ-BM22). The four subscales used in this study are: psychosocial aspects (PA) and functional interference (FI) and the functional scale and pain characteristics (PC) and painful sites (PS) on the symptom scale.

### 3.3. Safety on Adverse Event

The patients were generally well tolerated. There were no significant adverse events associated to therapy throughout the study. The adverse event profiles are shown in the Table 2. Many patients complained about fatigue and myalgia, which occurred in 35 of 108 (32.4%) patients in the 3-month course of the zoledronic acid administration. Renal function deterioration was the most frequent events called for intervention. The changes of renal function from the beginning (79±16.2 Serum creatinine, umol/L) to the revaluation’s end (88 (±18.7) (P= 0.4). Other less common adverse events included gastrointestinal disorders, rash, fever, jaw pain, injection site pain. The average serum calcium measure before therapy was 2.51 ± 0.63 mmol/L and 2.26 ± 0.52mmol/L after treatment, which is still within the normal range. No case of hypocalcemia, fracture or other skeletal related event was observed during the 3-month course (Table 2).

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Zoledronic n=108</th>
</tr>
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<tbody>
<tr>
<td>Fatigue and myalgia</td>
<td>35(32.4%)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>12(11.1%)</td>
</tr>
<tr>
<td>Gastrointestinal disorder (%)</td>
<td>8(7.4%)</td>
</tr>
<tr>
<td>Rash or itch (%)</td>
<td>7(6.5%)</td>
</tr>
<tr>
<td>Fever (%)</td>
<td>2(2%)</td>
</tr>
<tr>
<td>Jaw pain (%)</td>
<td>3( 3%)</td>
</tr>
<tr>
<td>Injection site pain (%)</td>
<td>8(7.4%)</td>
</tr>
<tr>
<td>Hypocalcemia (%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2(2%)</td>
</tr>
<tr>
<td>Sweats</td>
<td>1(1%)</td>
</tr>
</tbody>
</table>

### 4. Discussion

Prostate cancer is the usual cancer in men around the globe and commonly interconnected with metastases of bone. About 10-20% patients of prostate cancer firstly come to clinics for bone pain with a detection of bone
metastatic tumors [16]. Even for those patients who had been diagnosed with prostate cancer at early stage, finished radical prostatectomy without delay, 30% of which would lead to bone metastases eventually [17].

Preceding clinical tests of metastasis of bone greatly considered the skeletal-associated events or overall survival as targeted terminating points. But (VAS) Visual analysis Scale and (QoL) Quality of Life is the preference for all cancer patients too. In cases of breast and prostate cancer, multiple myeloma and in the late stage with bone metastasis, even prolonged life expectation has been reported. So, in the future therapeutic measures and strategies, long-term VAS and QOL assuredly would be taken into account. Thanks to the evolution of the bisphosphonate, the reduction of bone pain as well as skeletal-related events (SRES) has been achieved and prolonged survival time has been reported in cancer patients of prostate with bone metastases [10-13]. In this study, we use the zoledronic acid to remedy clodronate-resistant bone pain, but not analgesic drugs. In view of this meaningful attempt, there is unquestionably a need to identify whether this change would bring about benefits to patients.

First of all, impact on VAS is considered as the most important evaluation for the utility. Obviously, Zoledronate acid, classified as nitrogen-containing, should be more potent than the clodronate in pain control for it, acquires the capability to impede the farnesyl pyrophosphate synthase enzyme which certainly helps in relief of pain caused by tumour cells growth and osteoclast [18]. According VAS outcomes, patients informed that their pain in bones was substantially relieved after 3months’ new treatment compared to the baseline, demonstrating that the zoledronic acid might have a control pain effectively and can fulfill a good task on the clodronate-resistant treatment. This is actually reported by studies in our previous research in an arbitrary trial. 137 patients divided into two groups, with a 3 years follow up, the zoledronic acid group performed better than the clodronate groups with a faster palliative and also in pain control [19]. Another study reported by saad et al, 75% of patients had pain at baseline, and following pain scores lessen during the starting 3 months. The patients who experienced zoledronic acid were noticed to have subsequently little pain scores after 15 months [20]. Though these studies vary in methodologies and objectives, the discerned trend towards pain relief is constant.

The QLQ-BM22 is comprised of four subscales, psychosocial aspects (PA) and functional interference (FI) and the functional scale and pain characteristics (PC) and painful sites (PS) on the symptom scale [21-22]. The Painful Sites subscale can determine whether the pain is systematic or local and also make an assessment of palliative along with a changing in treatment. It is possible to get data competent for a chronological assessment of the treatment by evaluating even if the pain is intermittent or persistent by using PC subscale. The functional interference subscale lets a comprehensive assessment of the pain in tasks of everyday life and the movement restrictions. Finally, the Psychosocial Aspects subscale assesses detailed social and psychological anxieties, related to health conditions and stage of disease. With the enhancement in controlling pain, the range of patients’ movement is no longer limited as before. This is entirely contemplated by the scores upgraded in the functional scale of the EORTC QLQ-BM22. Psychosocial Aspects was subsequently improved after the treatment of 2-3 months and Functional Interference was subsequently improved at all time points on the functional scale. These results show that therapy with the zoledronic acid is competent for normal palliative, and also efficient of contributing to functional (Quality of Life) QoL.

As we know, the clodronate is particularly suitable for those patients who face problem in seeing hospitals or had bad nephritic functions. However, intravenous injection therapy using zoledronic acid is also a comparatively suitable procedure not needing a divided dosage or special preparation, applied with minimum patient control and cause fewer cases of gastrointestinal disorders. In our study, adverse events were lenient to pacify seriousness. Only a few patients conducted dose modification because of jaw pain or renal dysfunction. Other adverse events did not need interventions. These outcomes were identical with those reported by Nirmeen A et al [23]. Therefore, it should be considered as a new try to for clodronate-resistant patients, as compared to an external beam radiation and a treatment substitution to painkiller. On the contrary, it is significant that some studies informed that bone pain after the zoledronic acid was used as the first-line administration [24]. Whether this patient population can be treated by clodronate effectively is interesting but still unknown.

5. Study Limitations

There are still significant limitations in this study. First, though a probable design was chosen, this study had a moderate size of 108 patients only with a single arm. The following period after the zoledronic acid treatment was relatively short (3 months), might not enough to evaluate the unknown side effects. Moreover, it is difficult to analyze the result of the zoledronic acid precisely, for both QOL and VAS are depending on patients themselves which could easily being influenced by individual feelings. Finally, we did not assess the efficiency and well-being of the double-dose administration of the zoledronic acid for the clodronate-resistant patients. Nonetheless, the successive accretion of our patients and our therapy algorithm consistency underscores the usefulness of our outcomes.
6. Conclusions

For the first time, the study show that the zoledronic acid can not only effectively lessens the pain of clodronate-resistant prostate cancer patients with bone metastases, but also brings about better functional advantages and psychosocial situations in this population of patients. The side effects are negligible and acceptable. Hence, it could be a better choice for the clodronate-resistant patient to use the zoledronic acid first, but not analgesic drugs directly.

References


