Original Article

Optimal Timing of Bisphosphonate Administration in Combination with Samarium-153 Oxabifore in the Treatment of Painful Metastatic Bone Disease

Nigora Rasulova, Vladimir Lyubshin[1], Dauranbek Arybzhanov[2], Sh. Sagdullaev[3], Valery Krylov[4], Marat Khodjibekov

Department of Nuclear Medicine, Republic Specialized Center of Surgery, [1]Private Clinic "Summit", Tashkent, Uzbekistan, [2]Department of Chemotherapy and Endovascular Oncology, South Kazakhstan Oncological Clinic, Shimkent, Kazakhstan, [3]Department of Combined Therapy, Regional Tashkent Oncology Clinic, Tashkent, Uzbekistan, [4]Department of Radionuclide Therapy, Medical Radiological Research Center, Obninsk, Russia

Abstract

While bisphosphonates are indicated for prevention of skeletal-related events, radionuclide therapy is widely used for treatment of painful bone metastases. Combined radionuclide therapy with bisphosphonates has demonstrated improved effectiveness in achieving bone pain palliation in comparison to mono therapy with radionuclides or bisphosphonates alone. However, there are conflicting reports as to whether bisphosphonates adversely influence skeletal uptake of the bone-seeking radiotracers used for therapy. Recent studies analyzing influence of Zoledronic acid on total bone uptake of Samarium-153 EDTMP (Sm-153 EDTMP) by measuring cumulative urinary activity of Sm-153 on baseline study, as well as in combination with bisphosphonates (administrated 48 hours prior to Sm-153) did not provide any statistically significant difference in urinary excretion of Sm-153 between the two groups. It may be noted that the exact temporal sequence of bisphosphonate administration *vis a vis* radionuclide therapy has not yet been studied. One of the side effects of bisphosphonates is transient flare effect on bone pain. Radionuclide therapy may also have similar side effect. Keeping in view the above the current study was designed with the main objective of determining the exact timing of bisphosphonate administration in patients receiving combined therapy so as to achieve optimal efficacy of bone pain palliation. Ninety-three patients suffering from metastatic bone pain who received combination therapy with Sm-153 oxabifore (an analog of Sm-153 EDTMP) and Zoledronic acid were divided into three groups according to the timing of Zoledronic acid administration: Group I: 39 patients who received Zoledronic acid 7 or more days prior to Sm-153 oxabifore treatment; Group II: 32 patients who received Zoledronic acid 48-72 hours prior to Sm-153 oxabifore treatment and Group III: 22 patients who received Zoledronic acid 7 days after Sm-153 oxabifore treatment. Sm-153 oxabifore was administered to all patients at the standard bone palliation dose of 37 MBq/kg body weight. All patients received Zoledronic acid before and after treatment in standard dosage of 4 mg every 28 days. WB bone scan, CT, and MRI were performed before treatment in all patients to exclude cord compression and vertebral fractures. Pain scores and quality of life (QOL) measurements were recorded meticulously in all patients. In groups I, II, and III, pain relief occurred in 10.4 ± 3.1 (Range = 5-15); 3.1 ± 1.1 (Range = 1-5) and 22 ± 5.1 (Range = 15-35) days, respectively, following radionuclide therapy. There was statistically significant difference between pain score in all groups before and after treatment as well as statistically significant difference in time to pain relief onset between Group II and other groups of patients ($P < 0.0001$). Based on our results we concluded that administration of Zoledronic acid 48-72 hours prior to Sm-153 oxabifore treatment helps in achieving better pain relief, as well as at the shortest time interval from the start of therapy.

Keywords: Bone pain palliation, Sm-153 oxabifore, Zoledronic acid

Access this article online

Quick Response Code:

Website: www.wjnm.org

DOI: 10.4103/1450-1147.113939

Introduction

It has been reported that up to 60-90% of patients with bone metastases would experience severe bone pain in the terminal stages of their disease.[1] For prevention of skeletal-related events majority of patients now receive infusion of bisphosphonates. The new generation of

Address for correspondence:
Dr. Nigora Rasulova, Head of Nuclear Medicine Department, Republic Specialized Center of Surgery, Str.Farkhadskaya 10, Tashkent - 100115, Uzbekistan. E-mail: niga_r@mail.ru

bisphosphonates exhibits highly potent inhibitory activity on osteoclasts. These compounds are also known to provide pain relief. A previous randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma had shown an increase in pain and analgesic scores more in patients who received placebo than in patients who received zoledronic acid. Zoledronic acid at 4 mg given as a 15-minute infusion was well tolerated, but the 8-mg dose was associated with renal function deterioration.[2]

Radionuclide therapy is widely used as an effective modality in the management of bone pain. Bone seeking radiopharmaceuticals like Samarium-153 EDTMP, Sr-89, etc., have affinity for skeletal tissue and when administered intravenously they concentrate in areas of increased bone turnover,[3] localizing in active bone and mainly at metastatic lesions, allowing site-directed radiotherapy.[4] Combined treatment with both pharmaceuticals, i.e., Zoledronic acid and radiopharmaceutical may improve palliative care and enhance overall efficacy of bone pain palliation.[5-8]

Some authors have demonstrated that the combination of both treatments is globally more effective as compared to either one in isolation.[5-7] However, there are conflicting reports to suggest that bisphosphonates could inhibit the uptake of radiolabeled phosphonates in bone metastases.[9-14] To this effect in one specific study analyses of the cumulative activity of radiotracer excreted in the urine of hormone-refractory prostate cancer patients who were treated with Sm-153 EDTMP were carried out. The patients were first treated with Sm-153 EDTMP followed by Zoledronic acid after 48 hours. The authors reported no statistically significant difference in radioactivity between the two urine samples and concluded that Zoledronic acid does not influence Sm-153 EDTMP uptake by the osteoblastic bone lesions. Nevertheless, they reported musculoskeletal side effects of Zoledronic acid which include bone pain (55%), myalgia (23%0, arthralgia (21%), back pain (15%), and limb pain (14%).[7,15] Radionuclide therapy may also lead to transient flare effect on bone pain.[15] The purpose of our study was to seek further clarification about the combined therapy, especially for determining the exact temporal sequence of bisphosphonates administration in patients receiving combined therapy in order to achieve optimal efficacy of bone pain palliation by comparing different regimes of Zoledronic acid administration in combined treatment of widespread bone metastases with Samarium-153 oxabifore (Oxa-bis ethylennitrilo-tetramethyl phosphonic acid-ETMP).

Materials and Methods

Patients

Ninety-three patients with widespread bone metastases who received combined treatment of Sm-153 oxabifore and Zoledronic acid were divided into three groups according to the timing of Zoledronic acid (Zometa) administration.

Group I consisted of 39 patients (32 females and 7 males, aged 35-71, mean age 54,4 + 8.0) with multiple skeletal metastases from prostatic (N = 7) and breast carcinoma (N = 32) received Zoledronic acid 7 and more days prior to Sm-153 oxabifore treatment. Group II consisted of 32 patients (21 females and 11 males, age 38-72, (mean age 57.1 ± 9.7), all with multiple skeletal metastases from prostate (N = 10), breast (N = 20), and kidney (N = 2) cancers. They received Zoledronic acid 48-72 hours prior to Sm-153 oxabifore treatment. Group III consisted of 22 patients (20 females and 2 males, age 29-66, mean age 53 ± 10.3) with bone metastases from breast (N = 20), prostate (N = 1), and gastric (N = 1) carcinomas. In this group, patients received Zoledronic acid 7 days after Sm-153 oxabifore treatment [Table 1].

Pain assessment was based on visual analog scale (VAS), with 0 representing no pain and 10 representing intolerable pain. Initially there was no significant difference in mean objective pain score according to VAS system between groups of patients at the time of Sm-153 oxabifore administration.

Computed tomography (CT) and magnetic resonance imaging (MRI) examinations were performed before treatment in all patients to exclude cord compression and vertebral fractures.

Sm-153 oxabifore therapy

Inclusion criteria in brief for therapy were (1) intense uptake around painful metastases on recent (3-4 weeks before

Table 1: Patient population and initial status of pain score before Sm-153 Oxabifore administration

	Group-I N=39	Group-II N=32	Group-III N=22
Male:Female	7:32	11:21	2:20
Mean Age (Years)	54.4±8.0	57.1±9.7	53±10.3
Age Range (Years)	35-71	38-72	29-66
Breast Carcinoma	32	20	20
Prostate Cancer	7	10	1
Renal Cancer	-	2	-
Gastric Cancer	-	-	1
Mean objective pain score at the time of oxabifore administration (VAS=0-9)	7.89±0.33	8.03±0.36	8.27±0.33

P: I-II >0.5; I-III >0.1; II-III >0.3

treatment) Tc-99m methylene diphosphonates (MDP) whole body (WB) bone scan, (2) hemoglobin >90 g/L, (3) white blood cell count >4 × 10^9/L, and (4) platelet count of >100 × 10^9/L.

Prior to the administration of the radiopharmaceutical the patients received information both orally and in written pamphlet about the procedure, including an explanation of the therapeutic procedure and radiation protection guidelines; estimated time when to expect possible pain relief, a warning that transient flare effect of pain may occur, and a note on general radiation protection guidelines. Sm-153 oxabifore was administered to all patients at the standard bone palliation dose of 37 MBq/kg body weight. Whole body post-treatment scans were obtained within 3-6 hours after Sm-153 oxabifore administration in all patients.

All patients received Zoledronic acid before and after treatment as per the protocol in standard dosage, 4 mg every 28 days under control of serum urea and creatinine levels. To calculate creatinine clearance we used Cockroft and Gault formula, where creatinine clearance in ml/min= |(140 – age) x weight (kg) x C/plasma creatinine × 0:814)| in which C = 1 if male, C = 0.85 if female; plasma creatinine in µmol/l).

Since Zoledronic acid may lead to renal toxicity we excluded from this study patients with creatinine clearance <50 ml/min because they would have needed to change into other bisphosphonate instead of taking Zoledronic acid. Types and doses of prescribed analgesics as well as VASs were recorded.

Statistical analysis

The acquired results were expressed as the mean + SEM for each index. Comparison of data among various groups was performed with Student's unpaired *t*-test. A $P < 0.05$ was considered statistically significant.

Results

In patients belonging to Group I pain relief started around 10.4 ± 3.1 days (min 5d, max-15 d) days after Sm-153 oxabifore administration. Transient flare effect of pain was registering twice: First after Zoledronic acid administration and later after Sm-153 treatment [Figure 1].

In Group II pain relief occurred earlier by 3.1 ± 1.1 days (min-1d, max-5d) after combined therapy. In most of the patients in this group, post-therapy flare effect of pain occurred mostly following Zoledronic acid administration and not after Sm-153 oxabifore treatment.

Patients belonging to Group III took a much longer time to feel the benefit of therapy. In this group pain relief occurred after a much longer period of about 22 ± 5.1 days (min-15d, max-35d) following combined treatment. Transient flare effect on pain could be noticed in this group of patients twice; once after Sm-153 oxabifore administration and again after administration of Zoledronic acid.

The comparison of VAS among all groups of patients after treatment revealed statistically significant differences in pain score between patients belonging to Group II and rest of the patients belonging to Groups I and III [Figure 2].

According to the visual analyses of Tc-99m MDP bone scans and Sm-153 oxabifore post treatment scans, no significant difference could be noticed in all groups of patients between the diagnostic Tc-99m MDP and post therapy Sm-153 Oxabifore scans [Figure 3].

Discussion

Several studies in the past have reported the comparable efficacy of radionuclide therapy alone *vis a vis* combined therapy with bisphosphonates

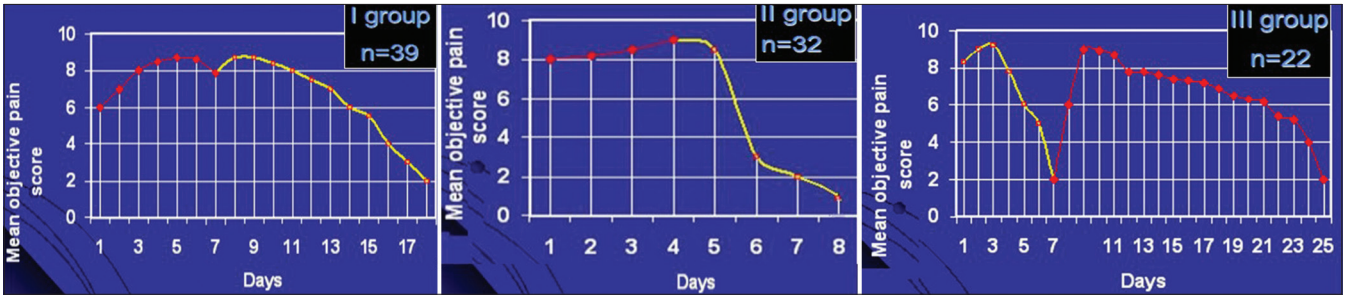

Figure 1: Response to therapy in the three different groups with regard to pain relief. In group I pain relief occurred around 10.4+3.1 (Range=5-15) days after Sm-153 oxabifore treatment. Transient flare effect of pain was registering twice: After Zoledronic acid administration (Red segment) and after Sm-153 treatment (Yellow segment). In group II pain relief occurred earlier by 3.1+1.1 (Range=1-5) days after combined therapy. In most of the patients in this group post-therapy flare effect of pain occurred mostly following Zoledronic acid administration and not after Sm-153 oxabifore treatment. In group III pain relief started after a prolonged time, of about 22 +5.1 (Range=15-35) days following combined treatment. Transient flare effect on pain could be noticed in this group of patients twice; once after Sm-153 oxabifore administration and again after administration of Zoledronic acid

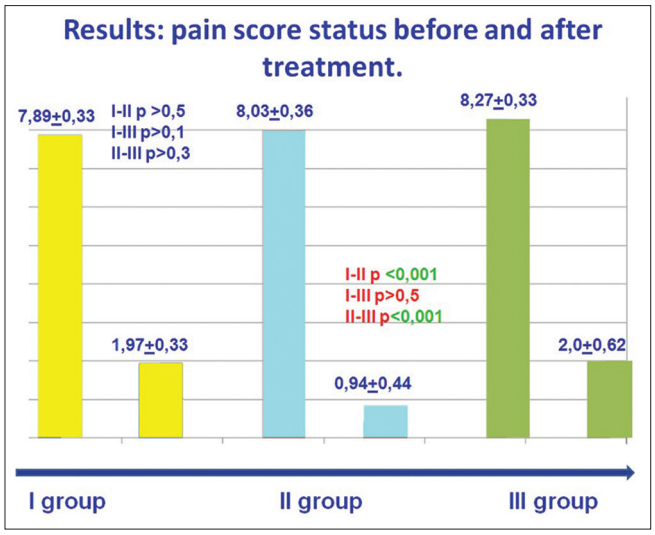

Figure 2: Comparison of VASs in all three groups of patients after treatment revealed statistically significant differences in pain score between patients belonging to group II and rest of the patients belonging to groups I and III

using a number of radio-conjugates including Sr-89 Chloride, Sm-153 EDTMP and Re-186 HEDP.[5,6,13,15] All studies have demonstrated better efficacy of combined therapy (Radionuclide + Bisphosphonates) compared to radionuclide therapy alone. Combined therapies resulted in quicker response to pain palliation, better pain relief, and better quality of life in all studies. All studies have reported that combined therapy is feasible and safe. All studies reported comparable toxicity with regard to hematological toxicity.

However, none of the studies, to the best of our knowledge has addressed the timing of bisphosphonates administration in relation to the radionuclide therapy; whether to give bisphosphonates before or after radionuclide administration; if so how long before or after.

In the current study we observed significant reduction of the pain score across all groups. But the best results with regard to onset of response and degree of pain relief were seen in the group of patients who received Zometa 2-3 days prior to Sm-153 oxabifore administration.

Conclusion

Based on our results we concluded that (1) combined therapy with beta emitting radionuclides and bisphosphonates (Zoledronic acid) is better than radionuclide therapy alone; (2) bisphosphonates do not influence skeletal uptake of Sm-153 oxabifore and (3) administration of Zoledronic acid 48-72 hours prior to Sm-153 oxabifore treatment gives the best results with regard to faster onset of response, higher degree of pain relief and better quality of life. However, it may be noted that our study was conducted in a smaller group of patients. For a better understanding of the pathophysiology of combined therapy, a more comprehensive study may be required in a larger group of patients in the future.

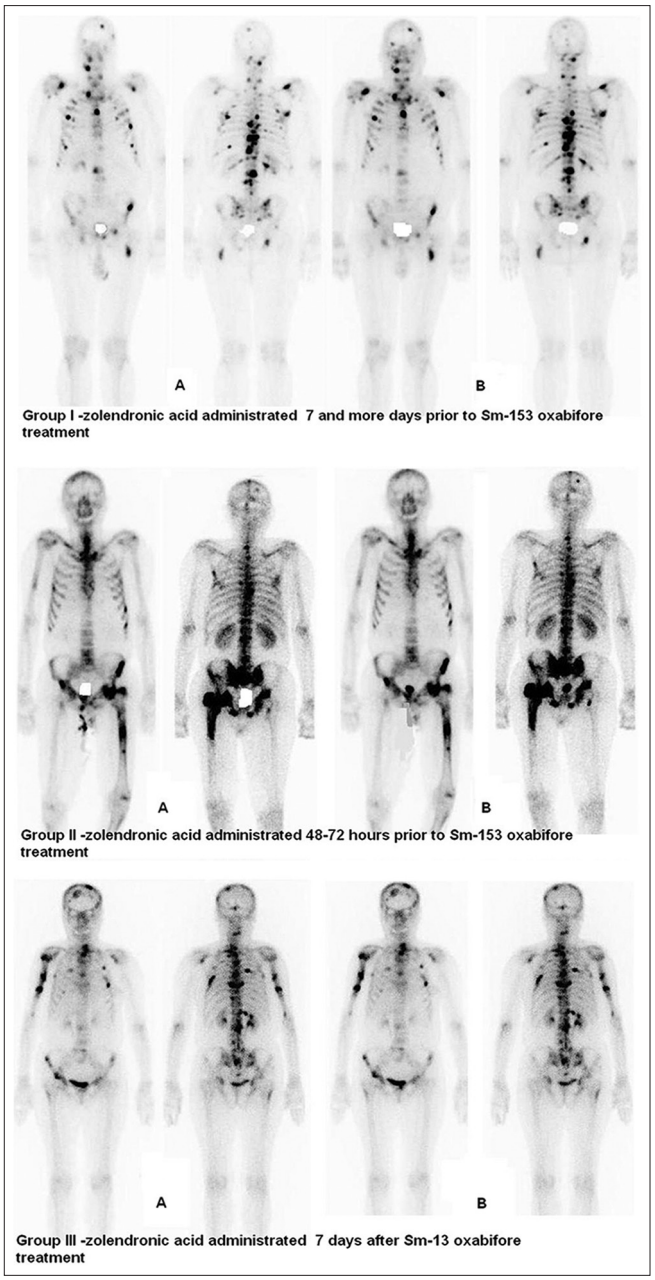

Figure 3: Examples of Paired THERONOSTIC Images of Tc-99m MDP pre-therapy diagnostic whole body bone scans (Column-A) and post-therapy Sm-153 Zoledronic Acid whole body scans (Column B) in patients belonging to Groups I (top panel), II (middle panel) and III (bottom panel). Visual examination of scans did not reveal ny significant difference between the diagnostic and post therapy scans in all three groups

References

1. Mercadante S. Malignant bone pain: Pathophysiology and treatment. Pain 1997;69:1-19.

2. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, *et al*. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94:1458-68.
3. Goeckeler WF, Edwards B, Volkert WA, Holmes RA, Simon J, Wilson D. Skeletal localization of samarium-153 chelates: Potential therapeutic bone agents. J Nucl Med 1987;28:495-504.
4. Bayouth JE, Macey DJ, Kasi LP, Fossella FV. Dosimetry and toxicity of samarium-153-EDTMP administered for bone pain due to skeletal metastases. J Nucl Med 1994;35:63-9.
5. Storto G, Klain M, Paone G, Liuzzi R, Molino L, Marinelli A, *et al*. Combined therapy of Sr-89 and zoledronic acid in patients with painful bone metastases. Bone 2006;39:35-41.
6. Koutsikos J, Leondi A. Treatment efficacy of combined bisphosphonates and 186Re-HEDP treatment in cancer patients with bone metastases. Eur J Nucl Med Mol Imaging 2008;35:1392-3.
7. Lam MG, Dahmane A, Stevens WH, van Rijk PP, de Klerk JM, Zonnenberg BA. Combined use of zoledronic acid and 153Sm-EDTMP in hormone-refractory prostate cancer patients with bone metastases. Eur J Nucl Med Mol Imaging 2008;35:1392-3.
8. Bodei L, Lam M, Chiesa C, Flux G, Brans B, Chiti A, *et al*. EANM procedure guideline for treatment of refractory metastatic bone pain. Eur J Nucl Med Mol Imaging 2008;35:1934-40.
9. Hommeyer SH, Varney DM, Eary JF. Skeletal nonvisualization in a bone scan secondary to intravenous etidronate therapy. J Nucl Med 1992;33:748-50.
10. Krasnow AZ, Collier BD, Isitman AT, Hellman RS, Ewey D. False-negative bone imaging due to etidronate disodium therapy. Clin Nucl Med 1988;13:264-7.
11. Sandler ED, Parisi MT, Hattner RS. Duration of etidronate effect demonstrated by serial bone scintigraphy. J Nucl Med 1991;32:1782-4.
12. Carrasquillo JA, Whatley M, Dyer V, Figg WD, Dahut W. Alendronate does not interfere with Tc-99m methylene diphosphonate bone scanning. J Nucl Med 2001;42:1359-63.
13. Marcus CS, Saeed S, Mlikotic A, Mishkin F, Pham HL, Javellana T, *et al*. Lack of effect of a bisphosphonate (pamidronate disodium) infusion on subsequent skeletal uptake of Sm-153 EDTMP. Clin Nucl Med 2002;27:427-30.
14. Pecherstorfer M, Schilling T, Janisch S, Woloszczuk W, Baumgartner G, Ziegler R, *et al*. Effect of clodronate treatment on bone scintigraphy in metastatic breast cancer. J Nucl Med 1993;34:1039-44.
15. Available from: http://www.drugs.com/sfx/zoledronic-acid-side-effects.html [Last accessed on 2013 Jun 02].

How to cite this article: Rasulova N, Lyubshin V, Arybzhanov D, S, Krylov V, Khodjibekov M. Optimal Timing of Bisphosphonate Administration in Combination with Samarium-153 Oxabifore in the Treatment of Painful Metastatic Bone Disease. World J Nucl Med 2013;12:14-8.

Source of Support: Nil. **Conflict of Interest:** None declared.