

The Effectiveness of Zoledronic Acid and Ibandronic Acid in Delaying Skeletal-Related Events in Multiple Myeloma in Indonesia

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Submitted: 18-11-2019

Revised: 13-06-2020

Accepted: 11-09-2020

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ABSTRACT

Zoledronic acid and ibandronic acid are listed in the Indonesian national formulary to prevent skeletal-related events (SRE) in patients diagnosed with bone metastasis in multiple myeloma (MM), with limited evidence to compare their effectiveness. This study aimed to investigate the effectiveness and safety of zoledronic acid and ibandronic acid in delaying SRE. The method was the retrospective, with data obtained from the multicenter study for MM patients with bone metastasis (aged over 18 years), based on medical records between January 2016 and December 2018. Patients were assigned to zoledronic acid and ibandronic acid groups. The clinical outcome was the next SRE which consists of vertebral/bone fracture, spinal cord compression leading to the need for surgery or radiation, and adverse event (AE) due to 2 years of drugs usage. Result of this research was made up of a total of seventy (70) patients with 40 in the zoledronic acid group, and 30 in ibandronic acid. At median treatment duration of 8 months (range: 2 – 24 month), SRE incident in zoledronic acid and ibandronic acid were 20.0 % and 23.3 % respectively. Furthermore, their mean SRE free survival times were 21 months [95% confidence interval (CI) 19 - 23 months], and 19 months [95% CI, 16 – 22 months], respectively. Also, their time intervals were not significantly different ($p>0.05$). The osteonecrosis of the jaw (ONJ) was AE which occurred more in zoledronic acid than ibandronic acid. The conclusion was zoledronic acid tends to delay SRE time compared to ibandronic acid, although more ONJ occur.

Kata kunci: Multiple myeloma; zoledronic acid; ibandronic acid; SRE; safety

INTRODUCTION

Multiple myeloma (MM) is a haematology malignancy which often occurs with a global mortality rate of 1% compared to cancer incidence. According to the Asian Myeloma Network (AMN), its occurrence in Asia is not significantly different to the west. In Indonesia, its prevalence was the second largest incidence of blood cancer, with a median survival rate of 3 to 10 years ^{1,2}. Tadjoeidin *et al.*, (2011) stated that the characteristics of MM patients in Indonesia were dominated by unemployed, Javanese, with high school education. Most patients had less than 30% plasma cells in their bone marrow, proteinuria, negative Bence Jones, and positive serum monoclonal gammopathy. Nearly 50% of patients had stage IIIA with melphalan/prednisone as the most widely used chemotherapy³.

Metastasis in MM targets bone, therefore, 80% of patients experienced bone metastasis through an osteolytic process, osteoporosis, or fracture at diagnosis ^{4,5}. Patients with bone metastasis experience significant morbidity and mortality with a high risk of skeletal-related events (SRE) such as pathological fracture, spinal cord compression, thereby, leading to the need for radiotherapy and surgery ^{6,7}.

Bisphosphonate is an essential therapy for the prevention of bone metastasis⁸, and this is in addition to the intravenous form of ibandronic acid or zoledronic acid listed in the Indonesian National Formulary⁹. The choice of both drugs was still limited by the minimum head to head comparative research of the two drugs. Several systematic review and meta-analysis had discussed the medicines that were more potent for bone metastasis.

A review of Mhaskar *et al.*, (2010) on the effectiveness of zoledronic acid and ibandronic acid in MM patients showed that these therapies were capable of reducing pathological vertebral fractures, SRE, and pain, but not mortality¹⁰. Palmieri *et al.*, (2013) also gave the same results using a meta-analysis. In multiple myeloma, the SRE incidence rate was 1.43 for zoledronic acid and 2.49 for ibandronic acid, which means that zoledronic acid is associated with a lower incidence of SRE than ibandronic acid⁵.

According to De Cock *et al.*, (2005), discontinuity of both acids use tends to occur due to adverse drug reactions (ADR) or complications. The potential problems need to be studied owing to costs with osteonecrosis of the jaw (ONJ) as an adverse event of using bisphosphonates⁶. A study of the ONJ incidence in zoledronic acid and ibandronic acid on a total of 780 patients stated that 81% had ONJ on zoledronic acid groups and 9% on ibandronic acid group, which was influenced by gender and cancer type¹¹. A retrospective study of medical records showed that renal toxicity in MM patients significantly increased on zoledronic acid compared to ibandronic acid¹²

Research on their effectiveness has never been conducted in Indonesia. Therefore, this study aim at investigating the effectiveness of IV zoledronic acid and IV ibandronic acid as SRE prevention in MM patients to monitor and evaluate its usage. The study was also used in clinical pathways development, in documents that reflect standards and services of both doctors, nurses and other health teams where each intervention is given a systematic record and expected to improve the quality of home care in Indonesia.

METHODS

Study design and data collection:

This study was retrospective research, conducted at the national hospitals under Dr. Sardjito Yogyakarta and Dr. Kariadi Semarang. The two hospitals were chosen because the cancer therapy centers in both hospitals are national references for cancer

therapy and research. Data was taken from medical records, and its collection was through a case report form (CRF) containing the patient's demographic and clinical characteristics, treatments, outcome, and adverse event (AE).

The inclusion criteria were adult patients above 18 years, diagnosed with symptomatic multiple myeloma that used zoledronic acid or ibandronic acid from January 2016 to December 2018. Patients with bone lesions or SRE in the axial skeletal survey were included as the baseline, while those with incomplete medical records were excluded.

The result of previous study were used to estimate the minimum sample size. Menssen *et al.*, (2002) stated that the proportion of SRE in the ibandronic acid group IV compared to placebo was 54.55% versus 52.53%.¹³ The study of Aviles *et al.*, (2013) stated that the proportion of SRE in the zoledronic acid group compared to placebo groups was 14.57 % versus 24.20%.¹⁴

Minimum sample size was estimated using the formula¹⁵:

$$n1 = n2 = \frac{\{Z_{1-\frac{\alpha}{2}}\sqrt{2P(1-P)} + Z_{1-\beta}\sqrt{P_1(1-P_1) + P_2(1-P_2)}\}^2}{(P_1 - P_2)^2}$$

$$Z_{1-\alpha/2} = 1,96$$

$$Z_{1-\beta} = 0,84; P_1 = 0,55; P_2 = 0,15$$

The number of samples for each group (zoledronic acid versus ibandronic acid) according to the formula was a minimum of 21 people. The characteristics of the samples in the two groups were matched based on age, gender, stage of disease, treatment duration, baseline of skeletal, comorbidities and type of chemotherapy. The overall MM patients who used ibandronic acid in two hospitals was thirty (30) people were registered in medical record from 2016 – 2018, so that the characteristics of patients using zoledronic acid were adjusted to match the ibandronic group. Forty (40) patients using zoledronic acid was found with characteristics that match with the ibandronic acid group and have complete medical record data. Sample

acquisition for each groups in this study was representative.

Measurement and definitions:

The outcome was SRE incidence, SRE free survival times and AE. The primary outcome was SRE incidence of and SRE free survival times of all baseline skeletal in total sample of each drug group. The secondary outcomes were SRE free survival times based on baseline skeletal and AE.

The SRE was defined as vertebral/ another bone fractures and spinal cord compression with the need for radiotherapy or surgery. The AE were defined as ONJ, renal disorders and flue like symptoms. The SRE was seen from the results of radiological examination and medical records of patients. The AE was seen from medical records. Clinical outcomes and time intervals were traced from the first use of the drug to the next SRE incident or a maximum of 2 years. Time to event was time to SRE that define as the time interval from the first use of the drug to the date of SRE occurred.

Statistical Analysis:

The analysis was descriptive, with the equal group allocation designed to allow the hypothesis test of the different effectiveness of zoledronic acid and ibandronic acid groups.

The baseline characteristics of patients were compared using Chi-square on the categorical variables and Mann Whitney test or t-test on the continuous variables. Furthermore, descriptive statistics were used to report the patients' characteristics and incidents of SRE and AE.

The SRE incidence was reported as a percentage of SRE. The percentage of SRE was the number of samples of each drug group that experienced SRE divided by the number of samples of each drug group multiplied by one hundred percent. SRE free survival times was estimated by the Kaplan Meier test. Estimation was done by entering data of time to event and percentage of SRE of each groups in Kaplan Meier program. Two-tailed alpha significance less than 0.05 level was used for the analyzes

of the differences of SRE free survival times between the two groups. Sree free survival times were further estimated based on baseline of skeletal.

Adverse event (AE) was reported as a percentage of AE that occurred in zoledronic acid or ibandronic acid groups. The percentage of AE was the number of samples for each group of drugs that have AE divided by the number of samples for each group of drugs.

RESULTS AND DISCUSSION

Characteristics of patients:

Zoledronic acid and ibandronic acid are supportive therapies for MM; however, there is limited evidence in comparing these two drugs. This study was, therefore, conducted to determine their effectiveness using seventy (70) patients diagnosed with MM and bone metastasis. Thirty (30) patients used ibandronic acid. The thirty patients who used ibandronic acid were total users of ibandronic acid in both hospitals that include in the criteria with complete and accessible medical records. The characteristics of patients with zoledronic acid were adjusted to patients with ibandronic acid so that forty (40) patients were found in the zoledronic acid groups with characteristics that matched with ibandronic acid groups.

The research was only done with 70 patients because of the low MM incident in the two hospitals. The new case of MM in Indonesia was small. Globocan (2018) stated that the new cases were 2,717 cases a year. It was the 20th rank of cancer incident in Indonesia¹⁶.

The characteristics are shown in Table I, with Forty (40) patients at the zoledronic acid groups and 30 patients in ibandronic acid groups. There was no significant difference based on age, gender, Durie-Salmon stage, the baseline of skeletal, comorbid and chemotherapy type. The median treatment duration in both groups was 8 months, with the age range between 28–80 years. Men were more than women, with stage 3 greater than stage 2. Bone fracture was the most common

Table I. Characteristics of patients

Character	Zoledronic Acid n=40	Ibandronic Acid N=30	p-value
Age, years (Median (range))	57,5(34 – 80)	58,5(28 – 80)	0.867
Male sex, n(%)	25(62.5)	21(70.0)	0.513
Durie-Salmon stage, n(%)			
2	4(10.0)	2(6.7)	0.622
3	36(90.0)	28(93.3)	0.622
Treatment duration, month (Median (range))	8(2 – 24)	8(2 – 15)	0.303
Baseline of skeletal, n(%)			
Bone lesion	19(47.5)	16(53.3)	0.629
Bone fracture	12(30.0)	6(20.0)	0.343
Spinal cord compression	6(15.0)	6(20.0)	0.583
Combination of SRE	3(7.5)	2(6.7)	0.893
Charlson Comorbidity Index (median (range))	2(0-7)	2(0-6)	0.095
Type of chemotherapy, n(%)			
Melphalan, prednisone	27(67.5)	14(46.7)	0.080
Melphalan, prednisone, thalidomide	6(15.0)	7(23.3)	0.375
Vincristine, doxorubicin, dexamethasone	5(12.5)	8(26.7)	0.131
Thalidomide	2(5.0)	1(3.3)	0.733

SRE, skeletal related event

Mann-Whitney test was used to calculate p-value of treatment duration and Charlson comorbidity indexes. T-test was used to calculate p value of age. Chi square test was used to calculated p-value of gender, Durie-Salmon stage, baseline skeletal and type of chemotherapy.

SRE. Furthermore, the most widely used chemotherapy was melphalan – prednisone combination.

Base on patients characteristic, the majority were men above 50 years, in stage 3 Durie-Salmon stage, using melphalan-prednisone. This research was consistent with previous research which stated the characteristics of MM patients in Indonesia were dominated by male above 50 years, in stage 3 and using melphalan-prednisone³.

The median treatment duration of both drugs was 8 months, which was due to government-guaranteed funding for that duration. Patients usually stop using after eight months because they cannot afford to pay. However, the optimal duration of bisphosphate use was indeed debated due to ONJ incident. Several guidelines suggested its use every month for two (2) years under the

disease progression, bone, toxicity, or other laboratory data¹⁷.

Effectiveness:

The ratio of patients with next SRE in the zoledronic acid and ibandronic acid groups was 20.0% and 23.3%, respectively (Table II). Spinal cord compression and vertebral fracture/another bone fracture often occur in each group. According to Kaplan Meier, the estimated mean SRE-free survival times of zoledronic acid and ibandronic acid were 21 months [95% confidence interval (CI), 19 - 23 months], and 19 months [95% CI, 16 - 22 months] respectively. Zoledronic acid tends to delay the incident by two months later than ibandronic acid with no significant time to the difference (p-value = 0.372 (> 0.05), figure 1).

The SRE-free survival time was further analyzed based on skeletal condition.

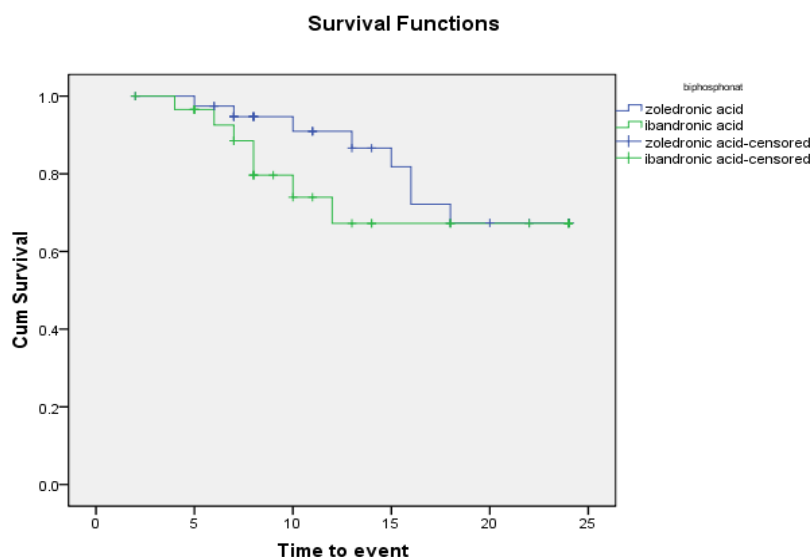


Figure 1. Kaplan Meier estimated SRE free survival time zoledronic acid versus ibandronic acid of all baseline skeletal

Table II. Incidence of SRE in patients subgroups by zoledronic acid or ibandronic acid treatments

Type of SRE	Zoledronic acid (n=40)	Ibandronic acid (n=30)
Vertebral fracture/ another bone fracture, n(%)	3(7.5)	2(6.6)
Need of surgery to bone,n(%)	0(0.0)	1(3.3)
Spinal cord compression,n(%)	5(12.5)	3(9.9)
Combination of SRE,n(%)	0(0.0)	1(3.3)
Total, n(%)	8(20.0)	7(23.3)

SRE, skeletal related event

In patients with bone lesions in the baseline, the mean SRE-free survival times in zoledronic acid and ibandronic acid were 21 months [95% CI, 18 – 24 months] and 18 months [95% CI, 14 – 23 months] respectively (figure 2). While those with SRE in the baseline, it was 20 months [95%CI, 18 – 23 months] and 20 months [95%CI, 15 – 24 months] (figure 3).

In this study, zoledronic acid reduced the risk of SRE 16.5% compared to ibandronic acid in MM patients with bone metastasis. Moreover, zoledronic acid groups have a longer time to SRE than ibandronic acid groups (21 and 19 months). Statistical analysis showed no significant difference between both groups in delaying time to SRE; however, the data showed the benefits of zoledronic acid,

which was felt by patients. It was in accordance with the systematic review of Palmieri *et al.*, (2013) which stated that IV zoledronic acid (4 mg every 3 – 4 weeks) was associated with the lowest SRE incidence rate (1.43) compared with the comparative rates being 2.49 for IV ibandronic acid (6 mg every 3 – 4 weeks)⁵.

Safety:

The most-reported AE was osteonecrosis of the jaw (ONJ) (Table III), which was more common in the zoledronic acid groups. The flue like symptoms and renal disorders were similar in both groups. However, ONJ was more common in the use of zoledronic acid than ibandronic acid. The

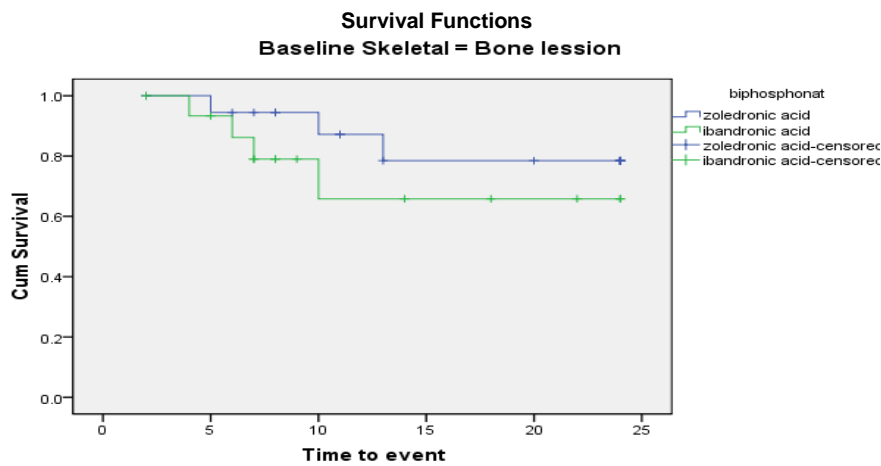


Figure 2. Kaplan Meier estimated SRE-free survival time of zoledronic acid versus ibandronic acid of patients with bone lesions as baseline skeletal

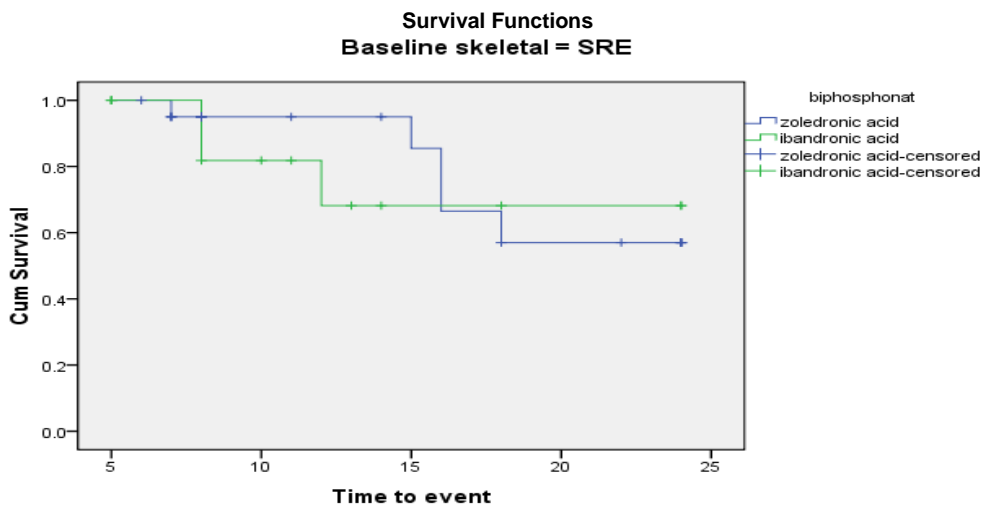


Figure 3. Kaplan Meier estimated SRE-free survival time of zoledronic acid versus ibandronic acid in patients with SRE as baseline skeletal

Table III. Adverse event in patients sub-groups by zoledronic acid or ibandronic acid

Type of Adverse Event	Zoledronic acid	Ibandronic acid
	n=40	n=30
ONJ, n(%)	5 (12.5)	1(3.3)
Renal disorders, n(%)	1(2.5)	2(6.7)
Flue like symptoms, n(%)	1(2.5)	2(6.6)
Total, n(%)	7(17,5)	5(16,67)

ONJ, Osteonecrosis of the jaw

result was in concordance with the study of Gabbert *et al.*, (2014) which reported a total of 780 patients, with 81% experiencing ONJ during the zoledronic acid treatment and 9% during ibandronic acid¹¹.

Many cancer guidelines stated that ONJ is a significant clinical problem associated with long-term use of bisphosphonates. Its frequency is 1-2% of patients each year on monthly intravenous bisphosphonate therapy,

and this risk was reduced by the use of daily oral or intravenous administration with a 3-month schedule. Patients were advised to undergo dental examinations before the administration of bisphosphonate therapy to avoid the incidence of invasive teeth. However, when surgery or extraction of the jaw is unavoidable, prophylactic antibiotics need to be administered. Bisphosphonates need to be stopped until complete healing unless the patient was experiencing symptomatic bone¹⁸.

AE associated with renal disorders was creatinine which increased and was reported in both acid groups. However, Weide *et al.*, 2010 study, was contrary to the previous retrospective results which stated that zoledronic acid significantly increased the risk and incidence of renal impairment compared to ibandronic acid¹².

The research proved that the choice of bisphosphonate therapy must adjusted to the safety of both drugs. Ibandronic acid should be used in MM patients with comorbid kidney disorders or having AE with kidney disorders when using zoledronic acid. Menssen *et al.*, (2002) reported that AE which occurred in ibandronic acid was only hypocalcemia¹³. These results were supported by the study of Terpos *et al.*, (2003) which reported the only incidence of hypocalcemia in ibandronic acid compared to pamidronate (0% versus 9%)¹⁹. While some RCTs reported renal toxicity in the use of zoledronic acid compared to placebo or other bisphosphonates. The RCTs stated that zoledronic acid caused more incident of renal toxicity compared to placebo²⁰⁻²².

Flue like symptoms was reported in both groups. The result was supported by some guidelines that stated intravenous use of bisphosphonate compounds was generally associated with acute phase responses (fever and flu-like symptoms), bone/joint pain, less common side effects such as kidney failure, ocular inflammation and atrial fibrillation¹⁸. However, the results of the study were not in accordance with those of a systematic review which stated that the symptoms of influenza

and the fever incidence of ibandronic acid were slightly lower than zoledronic acid²³.

Overall, the results of the study stated that zoledronic acid could delay the incidences of SRE compared to ibandronic acid in MM patient with bone metastasis with a higher occurrence of ONJ. However, this study still had limitations in terms of patient number and its retrospective which led to lack of controlled comparisons such as RCT, drugs side effect, and the decision on initiation/ continuation of the treatment based on clinical practice preferences of individual physicians.

CONCLUSION

Zoledronic acid tends to delay time to SRE compared to ibandronic acid, with the occurrence of more ONJ. Periodic dental examinations and dental care were recommended during use of both drugs. The renal examination must also be done monthly. The use of both drug must be consider the nephrotoxic potential of the drug. Whenever there were evidence of renal insufficiency, the other drugs with less evidence of renal nephrotoxic must be used.

ACKNOWLEDGEMENTS

This research was received by the Ethics Commission of the Faculty of Medicine, Gadjah Mada University, Yogyakarta, with license number KEPK/FK/0852/EC/2018, as well as that of Kariadi Hospital Semarang (No.034/EC/KEPK-RSDK-2018). We thank all those who participated in this research.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

FINANCIAL SUPPORT

The research is a part of pharmacoeconomics study supported by the Indonesian Health Ministry Scholarship.

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