Study of Adverse Effect Profile of Zoledronic Acid Infusion Among Patients with Cancer: A Retrospective Analysis

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Abstract

Background: Zoledronic acid (ZA) is widely used in the management of cancer-related bone events. It, however, might be associated with serious adverse effects.

Objectives: To evaluate ZA adverse effects and changes in biochemical parameters related to ZA toxicities among patients with cancer.

Methods: Ninety-eight oncology patients, who were prescribed ZA intravenous (IV) infusion, were interviewed to assess whether they experienced ZA related symptoms, including acute events and serious adverse effects. ZA’s effects on the serum levels of different biochemical parameters were retrospectively assessed by checking patients’ electronic medical records.

Results: The most commonly reported adverse effects were: myalgia (48%), bone pain (36.7%), influenza-like symptoms (34.7%), headache (31.6%), and pyrexia (22.4%) with decreasing frequency of such adverse effects upon repeated infusions. Serious side effects including jaw osteonecrosis, cardiac, and renal problems were not reported. A small, but statistically significant reduction in serum calcium, creatinine, and total protein levels was observed upon comparing levels before and after the first IV infusion of ZA (P ≤ 0.031). No significant change was recorded with other serum electrolytes including phosphorus, sodium, potassium, and magnesium as well as urea levels (P ≥ 0.271). No significant difference was determined in terms of final serum levels of all parameters in comparison to pre-treatment (P ≥ 0.059), except for potassium, where a significant reduction was observed (P = 0.003). Notably, the mean values of all parameters were within the normal range.

Conclusions: ZA acute events resolved with symptomatic treatment and reduced with repeated IV infusions. ZA appears as a safe treatment modality for skeletal-related events among patients with cancer and the reported adverse effects should not affect patients’ compliance.

Keywords: Zoledronic Acid, Diphosphonates, Safety, Neoplasms, Patients, Serum, Electrolytes

1. Background

Nitrogen-containing bisphosphonate compounds bind to osteoclasts and suppress the mevalonate pathway, resulting in inhibition of osteoclast function and thereby bone resorption (1). Zoledronic acid (ZA) is the most frequently used intravenous (IV) bisphosphonate with multiple clinical applications (2). It has been approved for the treatment of postmenopausal osteoporosis (3) and Paget’s disease of bone (4). ZA has also many clinical applications in the oncology field. These include treatment of metastatic bone diseases (5), malignancy-related hypercalcemia (6), cancer therapy-induced bone loss (7), and multiple myeloma (8).

More than 90% of patients with cancer at advanced stages might have bone metastasis (9, 10). As a result, patients may suffer from skeletal-related events (SRE) such as hypercalcemia, bone fracture, severe bone pain, and spinal cord compression (11). Administration of IV ZA in patients with breast and prostate cancers that are metastatic to bone caused a significant reduction in bone pain and other SRE. In addition, ZA increased bone mineral density and patients’ overall survival (5, 12-18). ZA also demonstrated positive effects in patients with cancers that are less metastatic to bone including advanced lung, thyroid, and renal cell carcinoma (19-21).

A retrospective analysis of 256 patients with cancer who received ZA, demonstrated occurrence of severe ad-
verse effects including: hypocalcemia (n = 22, 8.5%), renal dysfunction (n = 19, 7.4%), jaw osteonecrosis (n = 4, 1.5%), and symptomatic hypocalcemia (n = 2, 0.7%) (22). Conversely, results from one retrospective study among breast cancer patients with bone metastasis showed that such events rarely encountered with ZA administration (23). ZA infusion also resulted in atrial fibrillation in postmenopausal osteoporosis patients (24). However, most of ZA adverse effects were described as acute phase responses (25). These mainly included: pyrexia, musculoskeletal, gastrointestinal (GI), eye inflammation, and other general adverse effects (3, 25, 26). Additionally, ZA treatment resulted in significant changes in biochemical parameters such as serum calcium, phosphorus, and creatinine levels (23, 24, 27).

The positive therapeutic outcomes of ZA in patients with cancer necessitates encouraging its use among these patients. Minimal or absence of major adverse effects with ZA would likely add more valuable recommendations for ZA prescription and improve patients’ compliance. Genetic variations among different ethnicities may however contribute to variation in drug adverse effects profile in different populations (28). Accordingly, it is prudent to investigate the adverse effect profile of ZA among various clinical settings in populations. To the best of our knowledge, evaluation of different aspects of ZA safety profile as well as its effects on biochemical parameters among patients with cancer has not been studied in Jordan.

2. Objectives

This study aimed at (1) evaluating the adverse effects of ZA among patients with cancer and (2) assessing ZA effects on the serum levels of different biochemical parameters related to ZA toxicities.

3. Methods

3.1. Study Design and Subjects

This retrospective cohort study was conducted among patients with cancer receiving IV infusion of ZA (Zometa) at the chemotherapeutic unit in King Abdullah University Hospital (KAUH) Jordan. The study was approved by the Research Committee and the Institutional Review Board (IRB) of Jordan University of Science and Technology (JUST)/Jordan (IRB approval no. 9/118/2018). Written informed consent was obtained from all subjects before being interviewed at the chemotherapeutic unit. The total number of patients who received ZA and enrolled in this study was 98 patients during October 2018 to December 2019.

3.2. ZA Adverse Effects

Patients were interviewed to assess whether they have experienced ZA related symptoms, including acute events such as myalgia, bone pain, influenza-like symptoms, headache, pyrexia, gastrointestinal (GI) symptoms (nausea, vomiting, diarrhea, abdominal pain, and heartburn), visual, and hearing symptoms as well as serious adverse effects (jaw osteonecrosis, cardiac and renal problems, or allergic reactions). Patients were characterized based on their age, gender, smoking status, cancer type, indications for ZA infusion, frequency of infusions, and a number of ZA cycles. After the interview, the electronic medical records of the enrolled patients were retrospectively assessed to confirm the documentation of adverse effects reported by these patients.

3.3. ZA Adverse Effects with Multiple Infusions

In order to assess the frequency of ZA adverse effects with repeated infusions, patients who were treated with ZA for more than 6 cycles (n = 44 patients), were evaluated regarding the occurrence of ZA adverse effects after the first, second to sixth, and more than six infusions.

3.4. Effects of ZA on Biochemical Parameters

The effects of ZA treatment on the serum levels of different biochemical parameters were retrospectively assessed by checking patients’ electronic medical records. These include calcium, phosphorus, sodium, potassium, magnesium, total protein, creatinine, and urea. The clinical laboratory testing for the aforementioned biochemical parameters was done according to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Levels were evaluated at 3 occasions: first, baseline records before the first infusion of ZA (pre-treatment); second, post-treatment of first infusion/before the second infusion; and third, the final level at the date of patient’s interview.

Statistical analysis was performed using GraphPad software (GraphPad prism, Prism8 for windows, version 8). Data on biochemical parameters were expressed as mean ± standard deviation. The Paired t-test was used to compare data between the first and the second readings, as well as between the first and the third readings. The P value less than 0.05 was considered as statistically significant.

4. Results

4.1. Patients’ Characteristics

In this study, 98 patients with cancer who have been prescribed ZA (Zometa) were interviewed at the chemotherapeutic unit of KAUH. The characteristics of
these patients are summarized in Table 1. Of these patients, 9 were male, and 89 were female. The median age was 56.5 years (age range = 33 - 82 years). Among these patients, 12 were smokers at the time of the interview, while 86 patients were non-smokers.

Table 1. Characteristics of the Patients Demographics, Cancer Types, and Intravenous ZA Treatment among Patients with Cancer (Total Number of Patients = 98)

| Patients Characteristics | Values |
|--------------------------|--------|
| Gender                   |        |
| Female                   | 89 (90.8) |
| Male                     | 9 (9.2)  |
| Age, y                   | 56.5 (33 - 82) |
| Smoking status           |        |
| Smoker                   | 12 (12.2) |
| Non-smoker               | 86 (87.8) |
| Primary cancer type      |        |
| Breast                   | 82 (83.7) |
| Prostate                 | 6 (6.1)  |
| Multiple myeloma         | 4 (4.1)  |
| Liver                    | 3 (3.1)  |
| Bone metastasis with unknown primary | 2 (2) |
| Ovarian                  | 1 (1)   |
| Indication for ZA infusion |        |
| Bone metastasis          | 66 (67.3) |
| Cancer therapy induced osteoporosis | 32 (32.7) |
| Frequency of ZA infusions |        |
| Every 1 month            | 66 (67.3) |
| Every 6 months           | 32 (32.7) |
| Number of ZA cycles      | 5.5 (1 - 36) |

Abbreviation: ZA, zoledronic acid.
*Values are expressed as No. (%) or median (range).

4.2. ZA Adverse Effects

The adverse effects recorded in patients with cancer who received ZA are summarized in Table 2. The most common adverse effects were acute events including myalgia (48%), bone pain (36.7%), influenza-like symptoms (34.7%), headache (31.6%), and pyrexia (22.45%). In addition, patients developed GI problems including nausea (21.4%), vomiting (10.21%), diarrhea (10.21%), heartburn (7.14%), and abdominal pain (6.12%). Symptoms related to eye were reported by 14.3% of the patients (redness, pain, and a single case of cataracts). Hearing problems such as tinnitus and hyperacusis were reported by 13.3% of patients. Most of the aforementioned symptoms were self-limiting without the need for medical intervention. However, antipyretics were prescribed to treat pyrexia and influenza-like symptoms. Further, pain killers (acetaminophen/paracetamol) were prescribed for management of myalgia, bone pain, and headache in mild-moderate cases. Tramadol was prescribed in limited cases of severe bone pain and myalgia. All patients reported that GI problems were tolerated without the need for medications. Patients who complained of eye symptoms were referred for ophthalmologic consultation.

Table 2. Zoledronic Acid Adverse Effects among Patients with Cancer (Total Number of Patients = 98)

| Adverse Effects          | Values |
|--------------------------|--------|
| Myalgia                  | 47 (47.96) |
| Bone pain                | 36 (36.73) |
| Influenza like symptoms  | 34 (34.69) |
| Headache                 | 31 (31.63) |
| Pyrexia                  | 22 (22.45) |
| Eye symptoms             | 14 (14.29) |
| Hearing symptoms         | 13 (13.27) |
| Nausea                   | 21 (21.43) |
| Vomiting                 | 10 (10.21) |
| Diarrhea                 | 10 (10.21) |
| Heartburn                | 7 (7.14)  |
| Abdominal pain           | 6 (6.12)  |

*Values are expressed as No. (%).

Serious ZA adverse effects such as jaw osteonecrosis, cardiac, renal or allergic problems were not reported.

4.3. ZA Adverse Effects with Multiple Infusions

The occurrence of ZA adverse effects with multiple infusions was evaluated among patients who were treated with ZA for more than 6 cycles (n = 44 patients). Figure 1
verse effects are not fully understood. However, it has been
underlying mechanisms contributing to the previous ad-
accepts from previous studies on the safety profile of ZA
myalgia, bone pain, influenza-like symptoms, headache,
assessment of ZA adverse effects, acute events including
the patient's compliance toward treatment (29). Upon
(67%) and cancer therapy-induced osteoporosis (33%). ZA
received ZA IV infusions for treatment of bone metastasis
among patients with cancer, we interviewed patients who
five infusions were within the normal levels for all evalu-
infusion resulted in a significant reduction in total protein
level (P = 0.008), but no significant difference was found in
infusion groups. Alternatively, the administration of the first
injection was observed upon the comparison of final treatment
with pre-treatment levels (P = 0.003). Regarding creati-
ine, a significant reduction was observed between pre-
treatment and after the first infusion (P = 0.031). However,
elevation in creatinine levels was observed in the final
reading compared to pre-treatment, although it was sta-
tistically insignificant (P = 0.059). No statistically signifi-
cant difference was found in serum urea level between in-
fusion groups. Furthermore, administration of the first
infusion resulted in a significant reduction in levels of other serum
electrolytes including phosphorus, sodium, potassium, and
magnesium between the pre-treatment and after the first
infusion (P ≥ 0.27) as well as to the final treatment (P ≥
0.075), except for potassium, where the significant reduc-
tion was observed upon the comparison of final treatment
with pre-treatment levels (P = 0.003). Regarding creati-
ine, a significant reduction was observed between pre-
treatment and after the first infusion (P = 0.031). However,
elevation in creatinine levels was observed in the final
reading compared to pre-treatment, although it was sta-
tistically insignificant (P = 0.059). No statistically signifi-
cant difference was found in serum urea level between in-
fusion groups. Alternatively, the administration of the first
infusion resulted in a significant reduction in total protein
level (P = 0.008), but no significant difference was found in
the final reading (P = 0.577). Notably, all readings of differ-
ent infusions were within the normal levels for all evalu-
ated parameters.

5. Discussion

With intent to assess the adverse effects profile of ZA
among patients with cancer, we interviewed patients who
received ZA IV infusions for treatment of bone metastasis
(67%) and cancer therapy-induced osteoporosis (33%). ZA
treatment is recommended for the well-established ben-
eficial effects; however, major adverse effects may affect
the patient's compliance toward treatment (29). Upon
assessment of ZA adverse effects, acute events including
myalgia, bone pain, influenza-like symptoms, headache,
and pyrexia were identified. These are in accordance with
findings from previous studies on the safety profile of ZA
among oncology and osteoporosis patients (25, 30). The
underlying mechanisms contributing to the previous ad-
verse effects are not fully understood. However, it has been
suggested to be caused by the increased levels of inflam-
atory mediators such as interleukin-6 and tumor necro-
sis factor-α as a result of gamma delta T cells activation (31).
Notably, according to interviewed patients, these adverse
effects were self-limiting, tolerable, and/or resolved with
symptomatic treatment. Since patients' compliance was
not affected, no further investigation was committed.

ZA was reported to be associated with increased risk of
jaw osteonecrosis (22), a rare but significantly incapacitat-
ing adverse effect. Jaw osteonecrosis was not reported in
the current study. This is in agreement with results from
other studies that investigated the use of ZA for breast can-
cer patients with bone metastasis and female patients with
osteoporosis (23, 26). This finding might be attributed to
the meticulous oral and dental examination of patients at
KAUH to assess any pre-existing condition that may require
surgical dental treatment following ZA treatment which
may result in jaw osteonecrosis. Our records have shown
that patients have maintained good oral hygiene as well as
performed required dental and periodontal prophylactic
treatments before and during ZA therapy.

ZA' association with renal toxicity was previously re-
ported in other studies and was correlated with doses ex-
ceeding 4 mg given over less than 15 minutes of adminis-
tration time (32). In the current study, ZA was administered
in 4 mg doses within 100 ml 5% dextrose for a period of 30
minutes. Although no renal impairment was documented
for any of the patients in this study, medical problems that
might increase the risk of renal dysfunction should be con-
sidered carefully when prescribing bisphosphonates, espe-
cially diabetes mellitus, hypertension, advanced age and
on medications that may have negative impact on renal
functions (23). In addition, evaluation of renal function
should be routinely performed for all patients undergoing
ZA treatment with sufficient hydration being highly rec-
ommended (23).

Although cardiac-related adverse effects such as atrial
fibrillation were reported in female patients with osteo-
porosis (24), the subsequent studies described no effects of
ZA on cardiac rhythm (26), which was also observed among
the patients of the current study. In addition, allergic reac-
tions or infusion site reactions such as erythema, pruritis,
or pain were not reported, which supports previous studi-
(26).

In this study, we reported that the frequency of ZA
acute events was reduced with repeated infusions. How-
ever, the trend of reduction was less observed regarding
eye problems. Ocular complications were described as id-
iosyncratic and may occur shortly after, or weeks, months,
or even years after ZA treatment (33). Therefore, all patients
who complained of eye symptoms were referred for oph-
thalmologic consultation. However, our findings regard-
The frequency of Zoledronic acid adverse effects with repeated infusions. Columns from left to right show the frequency for zoledronic acid adverse effects for the first (1st), second to sixth (2-6) and more than six (>6) infusions. Analysis was done among patients received more than six infusions (n = 44).

Table 3. Serum Levels of Biochemical Parameters Before and After Zoledronic Acid Intravenous Infusions among Patients with Cancer

| Biochemical Parameter, Unit | Normal Serum Levelb | Pre-Treatment (Baseline) | After the First Infusion/Before the Second Infusion | P Value Pre-Treatment (Baseline) | At Date of Interview (Final Level) | P Value Available Data |
|----------------------------|----------------------|--------------------------|-----------------------------------------------------|---------------------------------|-----------------------------------|-----------------------|
| Calcium, mmol/l.           | 2.20 - 2.55          | 2.38 ± 0.12              | 2.31 ± 0.33                                         | < 0.0001                        | 2.31 ± 0.12                      | 0.636                 | 96                  |
| Phosphorus, mmol/l.        | 0.81 - 1.45          | 1.19 ± 0.23              | 1.18 ± 0.78                                          | 0.889                           | 1.19 ± 0.23                      | 0.147                 | 89                  |
| Sodium, mmol/l.            | 135 - 153            | 140.06 ± 3.02            | 140.33 ± 3.22                                        | 0.470                           | 140.06 ± 3.02                    | 0.860                 | 97                  |
| Potassium, mmol/l.         | 3.70 - 5.40          | 4.43 ± 0.45              | 4.38 ± 0.46                                          | 0.400                           | 4.43 ± 0.45                      | 0.003                 | 97                  |
| Magnesium, mmol/l.         | 0.66 - 0.99          | 0.83 ± 0.1               | 0.81 ± 0.1                                           | 0.271                           | 0.83 ± 0.1                       | 0.075                 | 93                  |
| Total protein, g/L         | 64 - 83              | 73.58 ± 7.17             | 71.55 ± 5.90                                         | 0.008                           | 73.58 ± 7.17                     | 0.577                 | 94                  |
| Creatinine, mmol/l.        | 62 - 115             | 62.25 ± 14.23            | 59.86 ± 14.41                                        | 0.031                           | 62.25 ± 14.23                    | 0.059                 | 96                  |
| Urea, mmol/l.              | 2.86 - 8.21          | 4.86 ± 1.91              | 4.66 ± 1.73                                          | 0.290                           | 4.86 ± 1.91                      | 0.965                 | 96                  |

aValues are expressed as mean ± SD.

bNormal ranges are according to The International Federation of Clinical Chemistry and Laboratory Medicine.

The effect of ZA treatment on the serum levels of different biochemical parameters was also assessed as they could indicate the presence of underlying problems that might be asymptomatic or not reported by patients such as renal failure and hypocalcemia. However, according to the findings, ZA had no significant effect on investigated parameters. Patients at KAUH are usually prescribed prophylactic oral calcium and vitamin D before ZA treatment, which might give explanation for calcium levels being unchanged with ZA infusions. Furthermore, it might explain why the phosphorus level is also unchanged since the mechanism of ZA induced hypophosphatemia has been suggested to be caused by secondary hyperparathyroidism as a result of the hypocalcemia (35). The results of the present study suggested that the absence of asymptomatic or unreported adverse effects such as renal failure and hypocalcemia. These findings support previous studies and suggest that ZA is a safe modality in the treatment of SRE among patients with cancer (3, 23, 24).

Observations from this retrospective, single-center
study need to be confirmed by studying a larger cohort of patients, ideally in prospective studies from multiple hospitals. Other limitations might include heterogeneity in gender distribution, cancer type, and indications for ZA treatment.

5.1. Conclusions

Within the limitations of this study, the findings demonstrated that ZA treatment in patients with cancer was not associated with major adverse effects even with multiple infusions. ZA acute events such as myalgia, bone pain, influenza-like symptoms, headache, and pyrexia were self-limiting and reduced with repeated infusions. In addition, ZA had no significant effect on the serum levels of biochemical parameters linked to medication toxicities. Stringent pre-infusion screening of co-morbidities is highly recommended to reduce the incidence of serious adverse events such as renal failure, atrial fibrillation, and jaw osteonecrosis.

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Footnotes

Authors’ Contribution: Study concept and design: LE. Acquisition of data: AA, AAA, HA, SB, and FA. Analysis and interpretation of data: LE, HB, and AA. Drafting of the manuscript: LE. Critical revision of the manuscript for important intellectual content: LE, HB, AA, AAA, HA, SB, and FA. Statistical analysis: LE, HB, and AA. Administrative, technical, and material support: LE. Study supervision: LE.

Conflict of Interests: All authors report no conflict of interest in this work.

Ethical Approval: The study was approved by the Research Committee and the Institutional Review Board (IRB) of Jordan University of Science and Technology (IRB approval no.: 9/118/2018).

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Informed Consent: Written informed consent was obtained from all subjects before being interviewed at the chemotherapeutic unit.

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