Bisphosphonate (Zoledronic Acid) Associated Adverse Events: Single Center Experience

Yüksel KUCUKZEYBEK, Gurbuz GORUMLU, Ercument CENGIZ, Cigdem ERTEN, Burcak KARACA, M. Kemal GUL, Bulent KARABULUT, Ulus A. SANLI, Ruchan USLU

Ege University Faculty of Medicine, Department of Medical Oncology, Izmir, TURKEY

ABSTRACT

Zoledronic acid is an efficacy-proven bisphosphonate used in the patients who develop bone metastasis. In our study, we planned to evaluate side effects occurring in the patients who receive zoledronic acid. The records of a total of 5.482 patients diagnosed with solid tumor who were admitted to oncology out-patients' clinic between January 2001 and January 2007 were scanned. It was found that 256 patients received zoledronic acid. Zoledronic acid is administered in 4 mg doses for a period of 15 minutes as intravenous infusion once in 21/28 days. Side effects such as hypocalcemia, symptomatic hypocalcemia, impairment in renal functions and osteonecrosis of the jaw, were evaluated retrospectively. Zoledronic acid was administered due to bone metastasis in 248 patients, malign hypercalcemia in 6 patients and ostoporosis in 2 patients. Four patients (1.5%) were diagnosed with jaw osteonecrosis, 22 patients (8.5%) were diagnosed with hypocalcemia, 19 patients (7.4%) were diagnosed with impairment in renal functions, and 2 patients were (0.7%) diagnosed with symptomatic hypocalcemia. Zoledronic acid is a bisphosphonate which has been proven to reduce complications which may develop depending on the bone metastasis, such as pathological fracture, spinal chord impression andhypercalcemia. On the other hand, side effects may occur in the patients receiving zoledronic acid. It will be appropriate to inform the patients who are planned to start administering zoledronic acid of the benefits to be obtained and the side effects to take place.

Keywords: Zoledronic acid, Jaw osteonecrosis, Hypocalcaemia, Impairment of renal functions

ÖZET

Bifosfonat (Zoledronik Asit) İlişkili Yan Etkiler: Tek Merkez Deneyimi

Zoledronik asit kemik metastazı gelişen hastalarda kullanılan, etkinliği kanıtlanmış bifosfonattır. Çalışmamızda zoledronik asit kullanan hastalarda meydana gelen yan etkilerin değerlendirilmesi planlandı. Ocak 2001 ve ocak 2007 yılları arasında polikliniğe başvuran solid tümör tanılı toplam 5482 hastanın dosyası tarandı. İkiyüzellialtı hastada zoledronik asit kullanımı saptandı. Zoledronik asit 4 mg 15 dakika intravenöz infüzyon şeklinde 21/28 günde bir uygulandı. Hastalarda meydana gelen yan etkiler olan, hipokalsemi, semptomatik hipokalsemi, böbrek fonksiyonlarında bozukluk, çene osteonekrozu retrospektif olarak değerlendirildi. Hastaların 248 inde kemik metastazı, 6 sında malign hiperkalsemi, 2 sinde osteoporoz nedeniyle zoledronik asit başlanmıştı. Dört (1.5%) hastada çene osteonekrozu, 22 (8.5%) hastada hipokalsemi, 19 (7.4%) hastada böbrek fonksiyonlarında bozulma, 2 (0.7%) hastada semptomatik hipokalsemi saptandı. Zoledronik asit kemik metastazına bağlı gelişebilen, patolojik fraktür, spinal kord basısı, hiperkalsemi gibi komplikasyonların gelişimini azalttığı kanıtlanmış bifosfonattır. Diğer taraftan zoledronik asit kullanan hastalarda yanetkiler meydana gelebilmektedir. Zoledronik asit başlanması planlanan hastalara elde edilebilecek faydalar ve ortaya çıkabilecek yan etkiler ile ilgili bilgi verilmesi uygun olacaktır.

Anahtar Kelimeler: Zoledronik asit, Çene osteonekrozu, Hipokalsemi, Böbrek fonksiyon bozukluğu

INTRODUCTION

Bone metastasis develops in 30% of the patients diagnosed with cancer. It mostly develops in breast, prostate, lung, bladder, kidney and thyroid cancers.[1,2] Metastatic bone disease may be terminated with morbidity, pain, increased mobility, pathological fracture, hypercalcemia and spinal cord compression caused by osteoclast activity up-regulation.[3-5] Bisphosphonates (BPs) are analogous of pyrophosphate that is an endogenous regulator of the bone mineralization. BPs prevent osteoclast-associated bone destruction.[6] BPs have been approved for the treatment of cancer-related hypercalcemia and bone involvement by multiple myeloma and solid tumors.[7] Zoledronic acid (ZA) is a nitrogen containing biphosphonate (BP). BPs, containing nitrogen, are more potent as they have side chain including heterocyclic or alkylamine.[8-10] Side effects such as renal failure (RF), hypocalcemia (HC), jaw osteonecrosis (JO), may be observed in association with bisphosphonate usage.[7,11] In our study, we evaluated the records of the patients diagnosed with cancer, who were admitted to Medical Oncology Policlinic at Ege University School of Medicine between 2001 and 2007, and retrospectively examined the resulting side effects after use of ZA.

MATERIAL AND METHOD

The records of the patients diagnosed with cancer who were admitted to Medical Oncology Policlinic at Ege University School of Medicine between January 2001 and January 2007 were evaluated retrospectively. The patients receiving ZA were determined. Subsequently, the patients were evaluated according to the development of side effects for HC, symptomatic hypocalcemia (SHC), RF and JO. ZA is administered in 4 mg doses within 150 cc 5% dextrose for a period of 15 minutes as intravenous infusion once in 21/28 days. Prior to each cycle, renal function tests of the patients were evaluated. HC was defined as serum calcium value being determined below normal limits when serum albumin value is in the normal limits. SHC was determined as tetany development in the patients with lower serum calcium value. RF was defined as increase in creatinine value above normal if the basal creatinine value is normal, or as impairment in creatinine clearance if the basal creatinine value is above the normal. JO was determined clinically and radiologically as required by consulting with dental surgeon of the patient with symptoms such as jaw pain, soft tissue panicula,etc.

RESULTS

The files of 5482 patients who were admitted to our hospital were scanned. It was found that 256 patients received ZA. Characteristics of the patients using ZA are summarized in (the) Table 1. Seventy patients were male and 186 patients were female. The mean age was 54 (83-22) and the average cycle where zoledronic acid is used was found to be 5 (1-49). Distribution of the patients receiving ZA consisted of breast cancer (138), lung cancer (20), bone metastasis with unknown primary (23), prostate cancer (15), kidney cancer (11), gastrointestinal system cancer (12), head-neck cancer (16) cervical cancer (5), bladder cancer (4), sarcoma (4) and the other cancers (8). Two hundred forty eightpatients received ZA due to bone metastasis, 6 patients due to malign hypercalcemia, and 2 patients due to osteoporosis. Side effects occurring in our patients administered with ZA are summarized in Table 2. Four patients (1.5%) were diagnosed with JO, 22 patients (8.5%) were diagnosed with HC, 2 patients (0.7%) were diagnosed with SHC, and 19 patients (7.4%) were diagnosed with impairment in renal functions. Fourpatients who developed JO were diagnosed with kidney cancer (1), breast cancer (1), cervical cancer (1) and prostate cancer (1). JO developed after administration ofaverage 12 (4-32)-cycle zoledronic acid. Mandibular osteonecrosis developed in 3 patients, whereas maxillary osteonecrosis developed in 1 patient. Diagnosis of 2 patients developing tetany were breast cancer. Diagnoses of the patients developing HC were breast cancer (15), prostate cancer (3), lung cancer (2), head-neck tumor (1), carcinoid tumor (1). Sixteen patients diagnosed with a disorder in their renal functions consisted of the patients diagnosed with breast cancer (6), kidney tumor (3), bone metastasis with unknown primary (3), head-neck tumor (2), prostate cancer (2), stomach cancer (1), pancreas cancer (1), and bladder cancer (1). Impairment in renal functions developed after the use of average 8 (3-22)-cycle ZA.

Table 1. Patients' characteristics

Patients' characteristics	Patients (n)	%
Sex		
Female	186	72
Male	70	28
Age		
Range	(22-83)	
Median	54	
Primary tumor site		
Breast	138	54
Lung	20	7
The prostate	15	5
Kidney	11	4
Gastrointestinal system	12	4
Head-neck	16	6
Cervix	5	2
Bladder	4	2
Sarcoma	4	2
Unknown primary	23	10
Other	8	4
Reasons for zoledronic acid administration		
Bone metastasis	248	97
Malign hypercalcemia	6	2
Osteoporosis	2	1
Zoledronic acid administration period (cycle)		
Range	(1-49)	
Median	5	

Table 2. Side effects

	Patients (n)	%
Hypocalcaemia	22	8.5
Symptomatic hypocalcaemia	2	0.7
Disorder in renal functions	19	7,4
Jaw osteonecrosis	4	1.5

DISCUSSION

Osteonecrosis is used to define death of bone marrow cells in the cortical bone marrow cells. The term "oesteonecrosis" is not a disease and used to define the resulting condition related to deterioration of blood supply. JO is characterized with tissue dehiscence, chronical bone devitalization, hypocellularity and lytic radiographical findings which may ocur after the use of pamidronate and ZA.[12] In 2002, the reports with regard to the development of JO after administration of ZA were made to start to FDA.[13] In 2003, Marx et al. reported a series of 36 patients who developed JO after administration of ZA or pamidronate. JO not only results in the clinical findings such as dolorous soft tissue panicula and tooth loss, but is asymptomatic as well.[11] Bomios et al. found incidence of JO to be 6.7% in the study in which 252 patients were evaluated. Furthermore, incidence of JO was found as 1.5% in the patients receiving therapy for a period of 4 to12 months that JO incidence showed an increase by exposure to time and drug, whereas it was found that theincidence increased by 7.7% in those receiving therapy for a period of 37 to 48 months.[14] In the study performed by Murad et al. in which 1951 patients were evaluated, only 2 JO were determined in association with BP administration.[15] JO is observed more in mandibula than maxilla.[16] Also in our study, JO at the rate of 1.5% was found in accordance with the results explained in the literature. Diagnosis of all our patients were made by consulting with dental surgeon due to the symptoms such as jaw pain and distention in the jaw. JO in our patients included in the study took place after administration of average 12 (4-32)-cycle zoledronic acid. Only one of our patients developed maxillary osteonecrosis. Other 3 patients developed mandibular osteonecrosis. Risk factors for the JO were expressed as radiotherapy to the head and neck area, periodontal disease, dental intervention, corticosteroid usage, local or systemic infection and chemotherapy.[17] In the retrospective analysis performed by La Verde et al., the patients administered with ZA, also including those with the history of pamidronate administration, were evaluated retrospectively. Development ratio of the JO was found to be 8.6%. The half of the patients developing osteonecrosis were diagnosed with dental intervention history.[18] No risk factor except for chemotherapy was found

in our study in the patients diagnosed with JO. Today, no guideline was available for managing JO. Although definitive treatment is unknown for the JO, conservative approaches are the recommended treatment options. BP administration is usually stopped after the development of jaw osteonecrosis. However, when it is stopped, there is no study indicating that this has any effects increasing osteonecrosis resolution. On the other hand, temporarily stopping to give BPs may not negatively affect bone metastasis progression.[11,19,20] Before starting the ZA treatment, patients should be informed of performing a dental maintenance. Invasive dental interventions should have been completed 4 to 6 weeks before starting BP therapy and after the intervention, a complete improvement should be ensured. Preventive measures defined to avoid JO from developing are oral cavity examination including a panoramic jaw radiograph, treatment of the possible dental problems before starting to give therapy with ZA, and avoiding invasive dental interventions in the patients receiving BP. Prior to ZA therapy, the patients should be informed of the possible side effects and their benefits to be obtained.[21-22] Our patients applying to our clinic were informed of the side effects before starting to receive ZA therapy. Therefore, the patients included in our study were not administered with any dental intervention not within the physician's knowledge.

Based on the administration of ZA, there may be a disorder in the renal functions. The disorder in renal functions may progress to the end stage renal failure.[7,23] Strong affinity of BPs to metal ions and formation of soluble and insoluble complexes caused by BPs-associated renal toxicity are tried to be explained in such a way that the resulting complexes may cause damages to the kidneys. However, the mechanism of BPs-asociated renal toxicity cannot be explained exactly.[24] The resulting nephrotoxicity related to BPs may occur as acute tubular necrosis and focal segmental glomerulosclerosis.[25] Chang et al. evaluated FDA side effect reports between 2001 and 2003. Consequently, it was reported that RF was found in 72 patients depending on the administration of ZA. Of the patients developing RF, 42 were diagnosed with multiple myeloma and 22 were diagnosed with solid tumor. It was reported that 27 of the reported patients required to be dialyzed and 18 patients died. Renal failure developed approximately 56 days after the administration of ZA. Interestingly, RF developed in 25% of the patients approximately 11 days after the initial dose. After stopping the therapy, a regression was found in serum creatinine values of the patients.[23] In the FDA report reported by Ibrahim et al. in which studies about ZA were evaluated, it was reported that impairment in renal functions were found in at the rate of 8.8 to 15.2% in the patients administered with ZA. It was found that renal toxicity was associated with ZA dose, infusion time and total administered dose.[7] The records of 446 patients administered with ZA were retrospectively evaluated in the study conducted by Mc Dermet et al. The patients were totally administered with 3115 doses of ZA and upon administration of ZA, renal function impairments were found in 9.2% of such patients. The patients, who were observed that their renal functions were disordered, used 4 doses of zoledronic acid in average. Predictive factors for renal function disorders in the patients receiving ZA after the multivariate analysis were found to be age, administered drug dose, NSAID usage, use of chemotherapy including cisplatin, multiple myeloma, infusion time shorter than the recommended and shortening the dose intervals, hypercalcemia, hypertension, diabetes mellitus, presence of chronic renal disease, and being diagnosed with kidney cancer.[26-29] In compliance with data in the literature, impairment in renal functions was found in 7.4% of the patients included in our study. Nine patients diagnosed with disorder in their renal functions were also diagnosed with hypertension, chronic renal failure and diabetes mellitus in addition to malignity. Disorder in renal functions were observed in our patients after the use of average 8 (3-22)-cycle ZA. Regression in creatinine values was found after stopping zoledronic acid. None of our patients required to be dialyzed. On the other hand, a disorder in renal functions at the rate of 6.7 to 11.5 % was found in the patients receiving placebo in the studies for placebo-controlled ZA. As it may also be understood from the results of this study, renal function disorders in the cancer patients may develop depending on the situations, such as advanced stage cancer, chemotherapy, previous BP therapy, concomitant nephrotoxic drug administration, concomitant dehydratation, chronic renal failure, hypertension, diabetes mellitus other than ZA.[30,31] Before

each ZA administration cycle American Society of Clinical Oncology (ASCO) guideline recommends that serum creatinine and electrolyte values of the patients should be analyzed. ASCO guideline suggests decreasing ZA dose in patients with mild to moderate renal impairment. Infusion of ZA for less than 15 minutes is not advised. If a failure in serum creatinine levels occurs without any other identifiable reason , it is suggested to stop ZA and begin the therapy with the same dose after improvement in serum creatinine levels.[32]

Another complication which may develop after administration of BPs is HC. In the study reported by Chennuru et al., 8% SHC was found during the use of ZA in spite of calcium and vitamin D replacement. BP-associated risk factors for HC are reportedas concomitant hypoparathyroidism, vitamin D deficiency and renal failure.[33-37] Of the patients evaluated by us in our study, only 2 (0.7%) were diagnosed with SHC. Twenty two (8.5%) patients were diagnosed with non-symptomatic HC. Our patients had periodically calcium and vitamin D replacement therapy from the beginning of the therapy. Prior to each ZA administration, serum calcium was controlled and the required replacement re-arranged according to the result.

Consequently, bone metastasis develops in 30% of the patients diagnosed with cancer.[1,2] ZA is a BP which has been proven to reduce complications which may develop due to bone metastasis, such as pathological fracture, spinal chord compression and hypercalcemia. On the other hand, side effects such as RF, HC and JO may develop in the patients in association with ZA administration. Therefore, it will be appropriate to inform the patients who are planned to start administering ZA of the benefits to be obtained and the side effects to take place.

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Correspondence

Dr. Yüksel KÜÇÜKZEYBEK

Van Eğitim ve Araştırma Hastanesi

Hematoloji-Onkoloji Kliniği

65100 Van / TURKEY

Tel: (+90.432) 215 76 00

e-mail: yuksel.kucukzeybek@ege.edu.tr