

OSTEONECROSIS OF THE JAW IN PATIENTS WITH MULTIPLE MYELOMA TREATED WITH BISPHOSPHANATES

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Abstract: Bisphosphonates are pyrophosphate analogues which inhibit osteoclastic activity. Long term use of bisphosphonates has recently been associated with osteonecrosis of the jaw (ONJ) defined as a three month non-healing defect in the jaw. ONJ is commonly precipitated by a tooth extraction or other stomatological procedure in patients treated with long-term, potent, high dose intravenous bisphosphonates for the management of myeloma, breast or prostate cancer.

The aim of this study was to evaluate the incidence of ONJ in patients with MM treated with bisphosphonates during the last 8 years in our institution and to present the first two cases.

We have analysed 247 myeloma patients diagnosed in our institution in the period 2002–09. Only 190/247 patients (76.9%) were treated with bisphosphonates. The incidence of ONJ in our group of patients treated with bisphosphonates was 2/190 (1%). The most commonly used bisphosphonate was i.v. pamidronate (17.8%) and 46.6% were treated with two or more types of bisphosphonates. Sixty-five patients (34.2%) received oral forms of bisphosphonates; 42.1% patients were treated with i.v. forms of pamidronate, ibondronate or clodronate, and 45 patients (23.7%) received a combination of oral and i.v. forms of bisphosphonates. The mean duration of bisphosphonates therapy was 24.7 ± 17.7 months.

The low incidence of ONJ in our institution could be explained by the rare use of zoledronate, which is the most commonly referred bisphosphonate causing ONJ, and by a relatively shorter duration of bisphosphonates treatment in patients with MM. Despite the fact that ONJ is a rare complication in our institution, preventive measures must be considered.

Key words: multiple myeloma, lytic bone disease, bisphosphonates, osteonecrosis of the jaw (ONJ).

Introduction

Multiple myeloma (MM) is a malignant haematological disease associated with increased bone destruction due to increased osteoclast activity [1]. Bone disease affects more than 70% of patients with multiple myeloma and is associated with pain, pathological fractures and hypercalcaemia [2, 3]. Bone disease is an important morbidity factor in patients with MM, and because of that measures for reducing morbidity from skeletal involvement are important in optimizing and improving a patient's quality of life.

Bisphosphonates are non-metabolized pyrophosphate analogues which inhibit osteoclastic activity [4, 5]. Bisphosphonates have been approved for the treatment and prevention of bone disease in patients with MM and solid tumours [6, 7, 8]. Monthly infusions of bisphosphonates reduce skeletal events and modify the natural history of bone disease in MM. Although no clinical data support long-term efficacy and benefit from bisphosphonates beyond 2 years, patients with, and even without, lytic bone disease continue bisphosphonates therapy indefinitely [6, 9, 10]. Adverse effects associated with the use of bisphosphonates are infrequent and consist of pyrexia, renal function impairment and hypocalcaemia. Long term use of bisphosphonates has recently been associated with osteonecrosis of the jaw (ONJ) and the first cases were reported in 2002 [11, 12, 13, 14]. ONJ is defined as a three month non-healing defect in the jaw, usually in the mandible, rarely the maxilla. ONJ is commonly precipitated by a tooth extraction or other stomatological procedure [15] in patients treated with long-term, potent, high dose intravenous bisphosphonates for the management of myeloma, breast or prostate cancer. ONJ was initially associated with the use of zoledronic acid but occurrences after pamidronate and other bisphosphonates have also been reported [11, 12]. The overall prevalence of ONJ is between 2–6% in patients with these malignancies. Current evidence shows that the risk of ONJ in non-cancerous patients, such as those with osteoporosis, is very low and appears to be comparable with that of the general population [16].

The aim of this study was to evaluate the incidence of ONJ in patients with MM treated with different bisphosphonates during the last 8 years in our institution and to report on the first two cases with ONJ diagnosed in our institution.

Materials and Methods

We analysed 247 myeloma patients diagnosed and treated for multiple myeloma in our institution in the period 2002–09. We used intravenous or oral forms of bisphosphonates such as pamidronate, ibandronate and clodronate.

Most commonly we used pamidronate 90 mg i.v. or ibondronate i.v. 6 mg per month, or oral bisphosphonates such as a standard dose of clodronate or ibandronate. We still do not use zoledronic acid for treatment of bone disease in patients with MM and we had only two patients treated with zoledronate in foreign hospitals.

The following data were collected for each patient: demographics, myeloma isotype and presence or absence of lytic bone disease. Details of disease such as duration, type of myeloma chemotherapy, as well as type of bisphosphonates therapy were analysed for each patient. Patients were treated surgically for ONJ and in both cases biopsy materials were pathohistologically analysed. Both patients received broad spectrum antibiotics (Amoxicillin-Clavulonic acid, Ciprofloxacin etc.) before and after surgery and bisphosphonates therapy was stopped after X-ray signs of ONJ.

Results

Data for all patients with MM analysed in our study (demographics, disease duration, type of chemotherapy and bisphosphonates therapy, etc.) are presented in *Table 1*. We had only two cases of ONJ in patients with myeloma treated with bisphosphonates in our institution. The annual incidence of multiple myeloma in our institution in the period 2002–09 was 30 ± 10.9 cases per year with a minimum 18 patients in 2007 and maximum of 55 patients in 2005. Our institution, the Haematology Clinic, treats most of the patients with MM in the Republic of Macedonia. In the period 2002–09 we diagnosed 247 patients with MM. Of the 247 myeloma patients, 190 (76.9%) were treated with bisphosphonates and 57 (23.1%) did not receive bisphosphonates. The incidence of ONJ in our group of patients treated with bisphosphonates was 2/190 (1%). The most commonly used bisphosphonate as a single agent was i.v. pamidronate while 44/247 patients (17.8%) were treated with pamidronate and 115/247 (46.6%) patients were treated with two or three types of bisphosphonate. Sixty-five patients (34.2%) received oral forms of bisphosphonates; 80/190 (42.1%) patients were treated with i.v. forms of pamidronate, ibondronate or clodronate, and 45 patients (23.7%) were treated with a combination of oral and i.v. forms of bisphosphonates. Almost 50.2% (124/247) patients received thalidomide-based regimens during the course of their disease. The patients' characteristics are presented in *Table 1*.

Table 1 – Табела 1

Clinical characteristics of patients with multiple myeloma
Клинички карактеристике на пацијентима са миеломом

	Patient with myeloma
No of patients (2002–09)	247
Age at diagnosis (y)	
Median	62
Range	46–90 years
Sex	
Male	132 (53.4%)
Female	115 (46.6%)
Duration of myeloma (y)	
Median	3 years
Range	3 months – 12 years
Isotype	
IgG	151 (61.1%)
IgA	52 (21.1%)
Others	44 (17.8%)
Bone lesion	
Yes	196 (79.4%)
No	51 (20.6%)
Duration of bisphosphonates Treatment (months)*	24.7 ± 17.7
Median	24 months
Range	2–84 months
Bisphosphonates type	
Pamidronate	44/247 (17.8%)
Ibandronate	24/247 (9.7%)
Clodronate	7/247 (2.8%)
None	57/247 (23.1%)
Combination of two or more	115/247 (46.6%)
Type of administration of bisphosphonates	
Oral	65/190 (34.2%)
I.v.	80/190 (42.1%)
Combination (oral/i.v.)	45/190 (23.7%)
Chemotherapy	
¹ Melphalan based protocols	81/247 (32.8%)
² Thalidomide based protocols	124/247 (50.2%)
³ Multiple chemotherapy protocols	115/247 (46.6%)
⁴ Observation	13/247 (5.3%)

* values are mean ± SD.

¹ MM patients treated only with protocols based on melphalan like MP (Melphalan/Prednisone); COMP (Cyclophosphamide/Vincristine/Melphalan/Prednisone) or both.

² MM patients treated with protocols based on thalidomide like MPT (Melphalan/Prednisone/Thalidomide); Thalidomide/Prednisone; CTD (Cyclophosphamide/Thalidomide/Dexamethasone).

³ MM patients treated with multiple chemotherapeutical protocols like MP; COMP; MPT; CTD; VAD (Vincristine/Doxorubicine/Dexamethasone) etc.

⁴ MM patients with indolent or smoldering myeloma not treated with chemotherapy or patients with advanced age and comorbidities in whom chemotherapy was not indicated.

Case 1

The first case is a male patient 55 years old, diagnosed with IgA myeloma, stage III according to the Durie-Salmon staging system, in February 2008. He had multiple lytic lesions on bone survey with intensive back pain and signs of renal insufficiency with elevated serum urea and creatinine levels. Renal insufficiency was treated conservatively and there was no need for haemodialysis. Initially he was treated with four cycles of VAD (Vincristine/Doxorubicine/Dexamethasone); haematological remission was not achieved, so he continued with 4 cycles of COMP (Cyclophosphamide, Vincristine, Melphalan, Prednisone) chemotherapy, until Thalidomide became available. From October 2008 he was treated with Melphalan/Prednisone/Thalidomide (MPT) protocol and a standard dose of ibandronate orally (50 mg per day). Therapy with oral ibandronate was stopped due to X-ray signs of ONJ in august 2009 (Fig. 1) and the diagnosis was patohistologically confirmed (Fig. 2). Therapy with broad spectrum antibiotics (Amoxicillin+Clavulonic acid) was started. Now he is treated only with MPT chemotherapy.



Figure 1 – X-ray of patients with multiple myeloma (case 1)
Слика 1 – Ртѓ снимка на ѓациенѓ со миелом (случај 1)

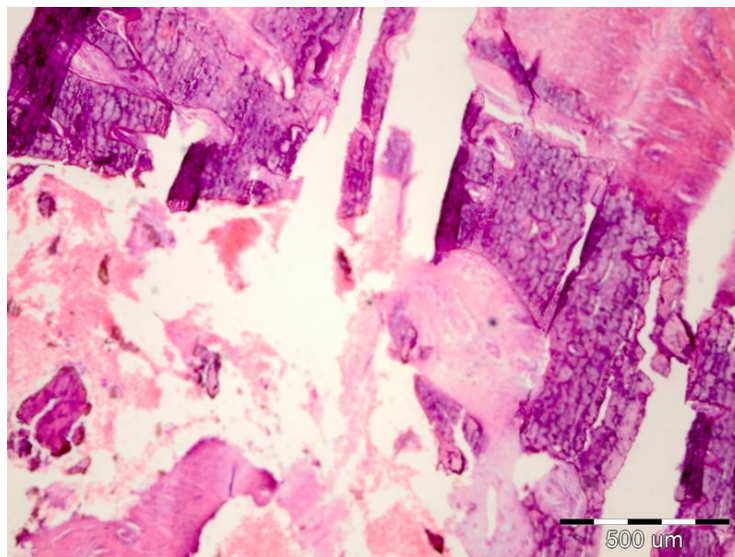


Figure 2 – Pathohistological signs of osteonecrosis in patient with multiple myeloma (case 1)

Слика 2 – Патѹохистѹолошки наод во ѹрилоѹ на остѹеонекроза кај ѹациенѹ со миелом (случај 1)

Case 2

The second case is a female patient, 53 years old, diagnosed with IgG myeloma, stage III, 10 years ago. She had multiple osteolytic lesions at the time of diagnosis. She was treated with multiple chemotherapy regimens. At the beginning she received 17 cycles of COMP (Cyclophosphamide/Vincristine/Melphalan/Prednisone) chemotherapy. Due to aggressive hepatitis B infection chemotherapy was stopped in July 2001 and treatment with Interferon, Lamivudine and small doses of corticosteroids was started. Chemotherapy with Thalidomide/Prednisone and i.v. bisphosphonates was initiated again in June 2004. From August 2004 until October 2009 she received 18 doses of ibandronate i.v. 6mg/per dose and 24 doses of pamidronate i.v. 90 mg/per dose. Due to X-Ray signs of ONJ (Figure 3), bisphosphonates therapy was stopped in October 2009. She was treated surgically in January 2010 with pathohistological proof of ONJ. She was also treated with broad spectrum antibiotics (Amoxicillin+Clavulonic acid) before and after surgery. Now she receives only chemotherapy with Melphalan/Pednisone/Thalidomide.

Both patients have regular check-ups for ONJ and their condition is constantly but slowly improving. In both patients multiple myeloma is active

but under control with monthly doses of MP-Thal chemotherapy protocol. Therapy with bisphosphonates was stopped in both cases.



Figure 3 – X-ray of patients with multiple myeloma (case 2)
Слика 3 – Рџџ снимка на џаациенџи со миелом (случај 2)

Discussion

Clinicians should be aware of this serious complication in all patients receiving long-term treatment with bisphosphonates. Fortunately this complication was rare in our center and we have diagnosed up to now, only two patients with ONJ, one treated with oral ibandronate and one treated with i.v. pamidronate and ibandronate. The low incidence of ONJ in our institution could be explained by the rare use of zoledronate, which is the most commonly referred bisphosphonate causing ONJ [8, 11, 12] and by the relatively shorter duration of bisphosphonates therapy in our patients with MM compared with other studies. Its well known that duration of bisphosphonates treatment is the major risk factor for developing this serious complication [17, 18]. The time of exposure to bisphosphonates was strongly associated with the development of ONJ and this complication is rare in patients receiving bisphosphonates for less than 2 years. The median time of exposure to bisphosphonates and occurrence of ONJ was 39.3 months in the study of Bamias A. *et al.* [18].

ONJ is most commonly reported in patients with MM, but it can occur in all cancer patients treated with bisphosphonates for bone metastatic disease. Other tumours most commonly associated with long-term bisphosphonates therapy are breast cancer, prostate cancer, and other solid tumours [18]. Osteonecrosis of the jaw is a rare complication of bisphosphonates therapy of osteoporosis [16], oral bisphosphonates treatment as well as ibandronate therapy [18].

Bisphosphonates act at sites of active bone remodelling by binding to hydroxyapatite, inhibiting osteoclast development and migratory activity and inducing cell death, thereby decreasing bone resorption without affecting bone mineralization. They accumulate to sites of active bone formation, making the sites more resistant to dissolution by osteoclasts, and are internalized by osteoclasts reducing their survival and modulating the signalling from osteoblasts to osteoclasts [5]. The mechanism of action of bisphosphonates in ONJ remains unclear [19]. First generation bisphosphonates are metabolized and incorporated into adenosine triphosphate-generating toxic analogs, inducing osteoclast apoptosis [20]. Nitrogen-containing bisphosphonates (pamidronate, alendronate, zoledronate and others) are not metabolized; 50% are secreted in the urine unchanged and the rest bind to bone and are slowly released into the circulation. The half-life in the bone could be as long as 10 years [21]. Bisphosphonates disrupt the normal bone homeostasis, resulting in impaired healing that may result in necrosis. Through inhibition of endothelial proliferation, bisphosphonates may interrupt intraosseous circulation and may contribute to development of ONJ [22, 23].

Other significant risk factors for ONJ are invasive dental procedures. Trauma of the mucosa and exposure of the bone to microbial flora creates an acidic inflammatory milieu that causes bisphosphonates detachment from bone in a low pH environment resulting in inhibition of osteoclast activity and enhancing the development of localized osteomyelitis. Preventive measures in patients with MM treated with bisphosphonates reduce the incidence of ONJ [24]. Recommended preventive measures are stomatological examination before bisphosphonates treatment, including X-ray examination, regular stomatological check-ups during bisphosphonates treatment and interruption of therapy two months before planned stomatological procedures such as tooth extraction or other, and antibiotic prophylaxis 2 weeks after tooth extraction or other stomatosurgery.

There is no consensus on management of ONJ. Surgery is potentially curative, but postoperative complications were significant and resulted in more bone exposure. Surgery may exacerbate the process and is avoided whenever possible. Discontinuation of bisphosphonates treatment is recommended but has not significantly helped in improving and resolving ONJ. The condition may

even get worse or reappear months after stopping the treatment. Long-term antibiotic treatment, most often with amoxicillin/clavulonic acid, did not prevent progression in patients with ONJ. ONJ is a rare but long-lasting and difficult to treat condition in cancer patients treated with bisphosphonates. Both patients with ONJ in our institution were treated with broad spectrum antibiotics, surgery and therapy with bisphosphonates was stopped when X-ray signs of osteonecrosis of the jaw were present.

In conclusion, ONJ is an uncommon but long-lasting disorder that occurs mainly in patients with multiple myeloma and solid tumours, treated with intravenous bisphosphonates. High cumulative doses of bisphosphonates, type of bisphosphonates used, poor oral health, and dental extractions may be significant risk factors for ONJ development. Despite the fact that ONJ is a rare complication in our institution preventive measures such as stomatological examination before bisphosphonates treatment, including X-ray examination, regular stomatological check-ups during bisphosphonates treatment and other preventive measures must be considered.

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Резиме

**ОСТЕОНЕКРОЗА НА ВИЛИЦАТА КАЈ ПАЦИЕНТИ
СО МУЛТИПЕН МИЕЛОМ ЛЕКУВАНИ СО БИСФОСФОНАТИ****Павковиќ М.,¹ Петрушевска Г.,² Јовановиќ Р.,² Каранфилски О.,¹
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Бисфосфонатите се пирофосфатни аналози кои ја инхибираат остео-класната активност. Последните неколку години реферирана е поврзаност помеѓу долготрајната употреба на бисфосфонатите и појавата на остео-некроза на вилицата (ОНВ). ОНВ е дефект во коскената структура на вилиците, најчесто на мандибулата кој трае подолго од 3 месеци. ОНВ најчесто се јавува по екстракција на заб или друга стоматолошка процедура кај пациенти со миелом, канцер на дојка или простата кои долго време биле лекувани со интравенски бисфосфонати.

Цел на оваа студија беше да ја анализира инциденција на ОНВ кај болните со мултиплен миелом (ММ), лекувани со бисфосфонати во последните 8 години во нашата институција и да ги прикаже првите два случаи со ОНВ на нашата клиника.

Анализирани се 247 пациенти со ММ дијагностицирани во период од 2002–2009 година. Од 247 пациенти, 190 (76.9%) се лекувани со бисфосфонати. Инциденција на ОНВ во нашата институција е 2/190 (1%). Најчесто употребуван бисфосфонат е и.в. памидронат (17.8%), а 46.6% од болните примале два или повеќе типа на бисфосфонати. Орални бисфосфонати примале 34.2% (65/190) болни, 42.1% примале и.в бисфосфонати како памидронат, ибандронат или клодронат, а 23.7% комбинација од орални и и.в. бисфосфонати. Средното траење на бисфосфонатната терапија во нашата студија е 24.7 ± 17.7 месеци.

Ниската инциденција на ОНВ во нашата институција веројатно се должи на ретката употреба на золендронатот во третманот на коскените лезии кај болните со миелом и на релативно пократкото траење на третманот со бисфосфонати во споредба со други студии. Иако ОНВ е сè уште ретка компликација при бисфосфонатната терапија кај нас, неопходно е да се преземат превентивни мерки за спречување на нејзината појава.

Клучни зборови: мултиплен миелом, литична болест на коските, бисфосфонати, остео-некроза на вилицата.

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