JBUON 2020; 25(4): 1799-1804
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Real-life use of denosumab 120 mg every 12 weeks in prolonged treatment over 2 years of patients with breast cancer bone metastases

Azzurra Irelli[1], Maria Maddalena Sirufo[2,3], Carlo D'Ugo[4], Lia Ginaldi[2,3], Massimo De Martinis[2,3]

[1]Medical Oncology Unit, Department of Oncology, AUSL 04 Teramo, Italy. [2]Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy. [3]Allergy and Clinical Immunology Unit, Center for the diagnosis and treatment of Osteoporosis, AUSL 04 Teramo, Italy. [4]Radiotherapy Unit, Department of Oncology, AUSL 04 Teramo, Italy.

Summary

Purpose: *To analyze the activity and safety of denosumab (DNS) 120 mg every 3 months over 2 years of standard treatment (120 mg SC every 4 weeks) of patients with breast cancer bone metastases in real life.*

Methods: *We prospectively analyzed the activity and safety of denosumab 120 mg every 3 months and 120 mg every 4 weeks in the treatment of 22 patients with breast cancer bone metastases over 2 years of standard treatment. All patients received specific concomitant antineoplastic treatment, chemotherapy or endocrine therapy and/or target therapy. Oral daily calcium (≥500 mg) and vitamin D (≥1000 U) supplement was recommended.*

Results: *Of the 22 patients treated with denosumab, 4 (18.1%) had at least 1 skeletal related event (SRE); 3 (13.6%) had 1 SRE and 1 patient (4.5%) had 2 SRE, all 10% treated with radiotherapy. Overall, no denosumab-related G3 adverse events occurred; in particular, no cases of osteonecrosis of the jaw have been recorded. The decrease in serum calcium levels was mild (G1, 2 patients, 9%), and recovered in a short time (within 2 weeks) with an increase in the oral support of calcium and vitamin D.*

Conclusions: *Denosumab confirms a good activity profile in terms of delaying and preventing SREs in breast cancer patients and a good safety profile. It represents an optimal treatment resource which doesn't necessitate renal function monitoring and has the convenience of a subcutaneous administration.*

Key words: *breast cancer, denosumab, osteoporosis, bone, aromatase inhibitors, bone metastasis, skeletal health*

Introduction

Breast cancer (BC) is the most common malignant disease in females and the second leading cause of cancer death, with an estimated rate of 271,270 new cases in both sexes in the United States in 2019 [1, 2]. Although technical-scientific advances in oncology have led to an increase in the chances of recovery, skeletal localization remain a common complication of cancer whose incidence reaches 75% in BC [3-7] and, in particular, only bone metastases in 17-37% of the cases [8].

Approximately 20-45% of patients diagnosed with early breast cancer will develop metastases [9] and 25-40% will have bone metastases at the onset of cancer [10, 11] and new cancer treatment strategies are always needed [12].

A large cohort study by Harries et al [13] in patients with early BC found that over a mean follow up period of 8.4 years 22% of them developed bone metastases. Median survival time, from the diagnosis of metastatic disease to death was about

Corresponding author: Massimo De Martinis, MD. Department of Life, Health and Environmental Sciences, University of L'Aquila, Piazzale Salvatore Tommasi no.1, 67100, L'Aquila, Italy.
Tel: +39 0861 0861 429862, Fax: +39 0861 211395, Email: demartinis@cc.univaq.it
Received: 06/02/2020; Accepted: 11/03/2020

22 months that reached about 26 months in bone disease only [14]. More recent literature data report a median survival for metastatic disease of 4-5 years [15], and 6 years for bone disease only [16,17].

Growth factors and cytokines secreted by metastatic tumor cells induce osteoblasts to release receptor activator of nuclear factor kB ligand (RANKL). This is a key molecule on the formation, function, and survival of osteoclasts [17-19]. The vicious circle of bone resorption and tumor expansion perpetuates itself by osteoclast bone resorbing activity, growth factors release and tumor cell proliferation [20-25]. A potential therapeutic strategy in early-stage tumors may prevent skeletal colonization by osteotropic cancer cells. Bone targeted therapy (BTT), such as bisphosphonates (BPs) (pamidronate, ibandronate and zoledronate) and denosumab (DNB), influence bone remodeling to preventing related skeletal events (SREs) [26-29]. For SRE we refer to the need for surgery or radiotherapy to the bone, or to the occurrence of pathological fractures or compression of the spinal cord; whether or not we can include hypercalcaemia of malignancy (HCM) [30]. SREs are associated with pain and morbidity that may require patient hospitalization and even with patient mortality [31]. It follows the need for a multidisciplinary management of bone metastases which involves the involvement of medical oncologists, radiologists, radiotherapists and surgeons in order to find the best treatment for each patient [32].

National and international guidelines recommend the use of BTTs from the time of diagnosis of bone metastases even in the presence of asymptomatic disease, in order to prevent the onset of SREs. In fact, the use of a BTT has been shown to improve the patient quality of life [33,34]. The clinical benefit of bisphosphonates lasts as long as they are administered. In fact, bisphosphonates are ingested by osteoclasts which, dying, remove them from the bone. At least 6 months of treatment are required to obtain a benefit in terms of SRE reduction, and 12-24 months for orthopedic surgery [35]. Therefore, the recommended duration of the BTT is at least two years or until adverse events occur. Further studies are useful to better define the duration of treatment, in particular for DNB, which has a completely different mechanism of action from bisphosphonates, being a human monoclonal antibody that binds RANK-L [33].

Stopeck et al have shown how DNB, compared to zoledronic acid, reduces the time to the first SRE by 18%, with a median time to the first SRE of 26.4 months in the group of patients treated with zoledronic acid and 32.4 months in the group of patients treated with DNB [36].

DNB has been shown to reduce the risk of multiple SREs by 23% and also to reduce the rate of skeletal morbidity by 22% (ratio of the number of SREs per patient divided by the patient at risk time). Overall survival and disease progression do not appear to be affected by the use of BTT. Regarding adverse events, the most frequent were hypocalcaemia and toothache during treatment with DNB. Not all patients who reported toothache developed osteonecrosis of the jaw (ONJ). The risk of ONJ was not greater with DNB than with zoledronic acid (p=0.39) [36].

In addition, DNB has proven more effective than zoledronic acid in terms of pain reduction, allowing a smaller percentage of patients to use strong opioids [37-39]. Lipton et al published the cumulative data from three phase 3 studies comparing DNB and zoledronic acid. Patients diagnosed with breast cancer, prostate cancer and other solid tumors and concomitant bone metastases were stratified according to the Eastern Cooperative Oncology Group performance status (ECOG PS), bone metastasis site, number of bone metastases, presence or absence of visceral metastases and urinary N-telopeptide of type I collagen (NTx). DNB significantly reduced the risk of first SRE compared to zoledronate in all subgroups (HR: ECOG PS, from 0.79 to 0.84; localized bone metastases, from 0.78 to 0.83; number of bone metastases, from 0, 78 to 0.84; presence/absence of visceral metastases, from 0.80 to 0.82; urinary NTx level, from 0.73 to 0.86) [40].

Continuing BTT treatment for more than 2 years seems to be useful in terms of time to the first SRE after 2 years and time to the next SRE. Continuing a BTT beyond 2 years may, however, increase the risk of adverse events. No significant differences were found in serious adverse events (such as renal failure, osteonecrosis of the jaw and hypocalcaemia). So, the long-term use of a BTT is effective although it leads to an increase in toxicity, which is still manageable [41,42].

In the literature on osteoporosis, discontinuation of DNS therapy has been associated with spontaneous rebound vertebral fractures.

The exact pathogenetic mechanisms involved in this rebound phenomenon are not known. Since DNS is not incorporated into the bone matrix like bisphosphonates which bind to hydroxyapatite, bone turnover is no longer suppressed once the use of DNS is discontinued and studies subsequently suggest accelerated bone resorption and subsequent rapid loss of BMD [43, 44]. Some individual clinical cases suggest that the rebound effect is reduced in patients treated with bisphosphonates after stopping DNS or before starting DNS [45-47].

Given that DNS doses in cancer are 12-fold higher than the standard dose for osteoporosis, a higher risk of rebound fractures for metastatic patients is conceivable, so much that it is recommended not to stop DNS therapy in high-risk patients or, alternatively, to switch to another therapy, such as a bisphosphonate [42]. What if instead of switching to a bisphosphonate, we proceeded to an escalated dose of denosumab as maintenance therapy?

The escalation dose modality of zoledronic acid was investigated by Amadori et al in a phase 3 work published in 2013; the study involved enrolling 425 breast cancer patients who had one or more bone metastases and had completed 12-15 months of monthly treatment with zoledronic acid in 63 Cancer Centers in Italy. Patients were assigned 1:1 to the 4 mg zoledronic acid arm once every 12 weeks or the 4 mg zoledronic acid arm once every 4 weeks, and were followed for at least 1 year. The zoledronic acid regimen every 12 weeks was found to be no less effective than the zoledronic acid regimen every 4 weeks in terms of number of skeletal-related events per patient per year. The adverse events recorded were consistent with the known safety profile of zoledronic acid. The incidence of renal adverse events was low and similar between treatment groups. Jaw osteonecrosis occurred in four patients in the 12-week group versus three in the 4-week group. So, the extension of the treatment interval did not decrease the occurrence of osteonecrosis of the jaw [48].

In the REDUCE study, patients with breast cancer bone metastases who were not pretreated with DNSs or bisphosphonates were randomized 1:1 to receive DNS every 4 weeks (arm A:177 patients) versus 12 weeks (arm B:174 patients), after a 3-month induction phase with therapy every 4 weeks in both arms. The primary endpoint of the study was non-inferiority for SRE for DNS every 12 weeks compared to 4 weeks. The final data have not yet been published. In 2018, data related to hypocalcaemia, a secondary endpoint, were presented at SABCS 2018. Hypercalcaemia was observed at a rate of 20% in the first 16 weeks (during the induction phase in both arms) and 19% later (by combining data from arms A and B), despite the mandatory integration of vitamin D and calcium; in particular by 25% in arm A and by 12% in arm B. Therefore, after the induction phase, hypercalcaemia was lower in the 12-week arm compared to 4-week arm. This suggests that DNS every 12 weeks has a more favorable long-term safety profile in terms of hypercalcaemia [49].

In the present study, we prospectively analyzed the activity and safety of DNS 120mg every 3 months over 2 years of standard treatment (120mg sc every 4 weeks) of patients with breast cancer bone metastases in real life.

Methods

Patients

Inclusion criteria included: age≥18 years, histopathological diagnosis of breast cancer, radiological confirmation of the presence of at least one bone metastasis, treatment with DNS 120mg every 4 weeks for at least 2 years, normal liver and kidney function, serum calcium corrected with albumin ≥ 8,1 mg/dL and ≤ 10.4 mg/dL and life expectancy ≥ 6 months.

Exclusion criteria: recent (<3 months) oral cavity surgery or untreated inflammatory-periodontal or peri-implant disease.

Previous intravenous bisphosphonate therapy was not allowed.

All patients received specific concomitant antineoplastic treatment (chemotherapy or endocrine therapy and/or target therapy).

All patients received a subcutaneous injection of DNS 120 mg every 3 months.

An oral daily calcium (≥500 mg) and vitamin D (≥1000 U) supplement was recommended.

All patients underwent orthopantomography and dental examination at baseline and every 6 months thereafter.

All patients gave written informed consent to the treatment.

The study was approved by the Internal Review Board of the University of L'Aquila, Italy, (ex "Comitato etico di Ateneo" D.R. n. 206/2013 modified D.R. n. 46/2017) "Ginaldi 15/04/2014". (http://www.univaq.it/include/utilities/blob.php?item=file&table=allegato&id=1925) and conducted in accordance with the 1975 Helsinki Declaration and its subsequent amendments.

Study design

This cohort study aimed to evaluate the safety and efficacy of DNS 120mg every 3 months, after 2 years of treatment according to the standard schedule, in patients with bone metastases from breast cancer.

Patients were in regular follow-up visits until the deadline (December 2019). From enrollment of the first patient to the deadline (December 2019), the study had a median duration of 25 months (range 6-48).

Assessment of outcomes

The definition of SRE included a pathological fracture (not due to major trauma), radiotherapy on a bone segment, bone surgery or spinal cord compression [30]; malignancy hypercalcaemia (HCM) was not considered.

Patient disease was assessed by radiographic imaging (radiography, computed tomography or magnetic resonance imaging) every 3 months or as clinically indicated.

The frequency of SREs after randomization was assessed.

Adverse events were reported every four weeks. All adverse events were coded using Common Terminology Criteria for Adverse Events (CTCAE) V4.03.

Statistics

T-test was used to compare the groups of patients; a p value<0.05 was considered statistically significant. The analysis has been carried out using the statistical software Graphpad Prism version 5.01.

Results

Patients

This analysis evaluated 22 consecutive patients treated with DNS 120 mg every 12 weeks or 120 mg every 4 weeks, until December 2019 at the Department of Medical Oncology, "G. Mazzini " Hospital, Teramo, Italy.

At randomization, the mean age of all DNS-treated patients (22; 100%) was 56 years (range 28-82). Bone only disease: 9 (40.9%); bone and visceral disease: 13 (59%). Bone metastases: multiple, 22 (100%); osteolithic, 14 (63.6%); osteoblastic, 3 (13.6%); mixed, 5 (22.8%). Location of bone metastases: spine, 18 (81.8%); pelvis, 11 (50%); long bones, 7 (31.8%); others, 12 (54.5%).

The clinical characteristics of the patients are shown in Table 1.

Table 1. Clinical characteristics

Clinical characteristics	*Patients n (%)*
Bone-only disease	9 (40.9)
Bone and visceral disease	13 (59)
No. of bone metastses	
1	0
>1	22 (100)
Bone metastases type	
Osteolytic	14 (63.6)
Osteoblastic	3 (13.6)
Mixed	5 (22.8)
Distribution of bone metastases	
Spinal column	18 (81.8)
Pelvis/hip	11 (50)
Long bones	7 (31.8)
Others	12 (54.5)

Table 2. Effectiveness

N SRE	*Patients n (%)*
1	3 (13.6)
>1	1 (4.5)

Safety

Overall, no DNS-related G3 adverse events occurred; in particular, no cases of osteonecrosis of the jaw have been recorded.

The decrease in serum calcium levels was mild: G1 (2 patients, 9%) recovered in a short time (within 2 weeks) with an increase in the oral support of calcium and vitamin D.

Effectiveness

Of the 22 patients treated with DNS, 4 (18.1%) had at least 1 SRE; 3 (13.6%) had 1 SRE and 1 patient (4.5%) had 2 SRE, all treated by radiotherapy (100%) (Table 2).

Discussion

In this study we evaluated the efficacy and safety of DNS, administered at different schedule (120 mg every 12 weeks and every 4 weeks), after at least 2 years of treatment, as supportive treatment in patients with bone metastases from breast cancer in real life.

The data on the efficacy and safety of DNS are interesting and we compared them with those of the pivotal study of Stopeck et al [36] but obviously the limitations of our study must be taken into account; in fact, our patient sample is small and comes from a single institution.

The most interesting aspect of our study is certainly the safety as several side-effects are described with the use of these drugs [50, 51].

No patient experienced renal failure. On the contrary, in the pivotal study, an incidence of renal failure of 0.2% was reported among patients treated with DNS. However, it should be remembered that renal failure does seem to be related to DNS, due to its catabolism by the reticuloendothelial system.

We also reported no cases of ONJ. As mentioned above, all patients underwent orthopantomography and subsequent maxillofacial visit before starting DNS, to identify possible risk factors such as recent alveolar dental surgery (<3 months), periodontal or peri-implant inflammatory disease, removable dental prostheses and incongruous or poor oral hygiene, which could be responsible for a greater pathogenicity of DNS in the oral cavity. Dental checks were repeated every six months.

Hypocalcaemia was mild in our study: G1; more adequate calcium and vitamin D support resolved the event within 2 weeks. Our data are in line with those reported in the pivotal study, in which hypocalcaemia occurred globally in a low

percentage of patients treated with DNS (5.5%) and mainly in the first 6 months of treatment.

It must also be taken into account that our patients were subjected to disease-oriented chemotherapy or hormone therapy ± targeted therapy, which inevitably affect the quality of life in terms of overall safety.

Conclusion

In conclusion, our experience confirms a good activity profile in terms of control of related skeletal events and a good toxicity profile of DNS. We also found that, in addition to a careful basic assessment, the control of the symptoms of the oral cavity canceled the ONJ events. Efficacy data require wider recruitment and a longer observation period, but preliminary results are very interesting.

Conflict of interests

The authors declare no conflict of interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
2. Irelli A, Sirufo MM, Morelli L, D'Ugo C, Ginaldi L, De Martinis M. Neuroendocrine Cancer of the Breast: A Rare Entity. J Clin Med. 2020;9(5):1452. doi:10.3390/jcm9051452
3. D'Oronzo S, Coleman R, Brown J, Silvestris F. Metastatic bone disease: Pathogenesis and therapeutic options: Up-date on bone metastasis management. J Bone Oncol 2018;15:004-4. doi: 10.1016/j.jbo.2018.10.004.
4. Brook N, Brook E, Dharmarajan A, Dass CR, Chan A. Breast cancer bone metastases: pathogenesis and therapeutic targets. Int J Biochem Cell Biol 2018;96:63-78. doi: 10.1016/j.biocel.2018.01.003.
5. Kuchuk I, Hutton B, Moretto P, Ng T, Addison CL, Clemons M. Incidence, consequences and treatment of bone metastases in breast cancer patients-Experience from a single cancer centre. J Bone Oncol 2013;2:137-44. doi: 10.1016/j.jbo.2013.09.001.
6. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001;27:165-76.
7. Fang J, Xu Q. Differences of osteoblastic bone metastases and osteolytic bone metastases in clinical features and molecular characteristics. Clin Transl Oncol 2015;17:173-9. doi: 10.1007/s12094-014-1247-x.
8. Ahn SG, Lee HM, Cho SH et al. Prognostic factors for patients with bone-only metastasis in breast cancer. Yonsei Med J 2013;54:1168-77.
9. Karrison TG, Ferguson DJ, Meier P. Dormancy of mammary carcinoma after mastectomy, J Natl Cancer Inst 1999;91:80-5.
10. Coleman RE. Skeletal complications of malignancy. Cancer. 1997;80:1588-94.
11. Stathopoulos GP, Trafalis D, Kaparelou M. Bone metastasis in breast cancer is treated by high-dose tamoxifen. J BUON 2016;21:1013-5.
12. Irelli A, Sirufo MM, D'Ugo C, Ginaldi L, De Martinis M. Sex and Gender Influences on Cancer Immunotherapy Response. Biomedicines 2020;8:E232. doi:10.3390/biomedicines8070232.
13. Harries M, Taylor A, Holmberg L et al. Incidence of bone metastases and survival after a diagnosis of bone metastases in breast cancer patients. Cancer Epidemiol 2014;38:427-34. doi: 10.1016/j.canep.2014.05.005.
14. Niikura N, Liu J, Hayashi N et al. Treatment outcome and prognostic factors for patients with bone-only metastases of breast cancer: a single-institution retrospective analysis. Oncologist 2011;16:155-64.
15. Kennedy L, Bhatta S, Hechmati G, Buchanan J. Response to Cost-Effectiveness Analysis of Zoledronic Acid Once Per Month, Zoledronic Acid Once Every 3 Months, and Denosumab Once Per Month in Women With Breast Cancer and Skeletal Metastases. J Clin Oncol 2018;36:1051.
16. Jacobson AF, Shapiro CL, Van den Abbeele AD, Kaplan WD. Prognostic significance of the number of bone scan abnormalities at the time of initial bone metastatic recurrence in breast carcinoma Cancer 2001;91:17-24.
17. Briasoulis E, Karavasilis V, Kostadima L, Ignatiadis M, Fountzilas G, Pavlidis N. Metastatic breast carcinoma confined to bone: portrait of a clinical entity. Cancer 2014;101:1524-8.
18. Sirufo MM, Suppa M, Ginaldi, De Martinis M. Does Allergy break bones? Osteoporosis and its connection to allergy. Int J Mol Sci 2020;21:712; doi:10.3390/ijms21030712.
19. De Martinis M, Sirufo MM, Nocelli C, Fontanella L, Ginaldi L. Hyperhomocysteinemia is Associated with Inflammation, Bone Resorption, Vitamin B12 and Folate Deficiency and MTHFR C677T Polymorphism in Postmenopausal Women with Decreased Bone Mineral Density. Int J Environ Res Public Health 2020;17:4260. doi:10.3390/ijerph17124260
20. Irelli A, Sirufo MM, Scipioni T et al. mTOR links tumor immunity and bone metabolism: what clinical implications ? Int J Mol Sci 2019;20:E5841. doi: 10.3390/ijms20235841
21. Ginaldi L, De Martinis M, Saitta S et al. Interleukin-33 serum levels in postmenopausal women with osteoporosis. Sci Rep 2019; doi: 10.1038/s41598-019-40212-6
22. De Martinis M, Sirufo MM, Ginaldi L. Osteoporosis: current and emerging therapies targeted to immunological checkpoints. Curr Med Chem 2019 doi: 10.2174/0929867326666190730113123.

23. De Martinis M, Sirufo MM, Suppa M, Ginaldi L. IL-33/IL-31 axis in osteoporosis. Int J Mol Sci 2020;21:1239. doi: 10.3390/ijms21041239.
24. Ciccarelli F, De Martinis M, Ginaldi L. Glucocorticoids In Patients With Rheumatic Diseases: Friends Or Enemies of Bone? Curr Med Chem 2015;22:596-603.
25. Massimini M, Palmieri C, De Maria R et al. 17-AAG and Apoptosis, Autophagy and Mitophagy in Canine Osteosarcoma Cell Lines. Vet Pathol 2017;54:405-12.
26. Irelli A, Sirufo MM, Scipioni T et al. Breast cancer patients receiving denosumab during adjuvant aromatase inhibitors treatment: who are the "inadequate responders" patients to denosumab? J BUON 2020;25:648-54.
27. Irelli A, Sirufo MM, Scipioni T et al. Denosumab in breast cancer patients receiving aromatase inhibitors: a single-center observational study of effectiveness in adjuvant setting. Indian J Cancer 2020 in press.
28. V Deligiorgi M, Panayiotidis MI, Trafalis DT. Combining immune checkpoint inhibitors with denosumab: a new era in repurposing denosumab in oncology? J BUON. 2020;25:1-14.
29. Fragkoulis C, Gkialas I, Papadopoulos G, Ntoumas K. Current therapeutic options targeting bone metastasis in metastatic castration resistant prostate cancer. J BUON 2016;21:787-91.
30. Van Poznak CH, Temin S, Yee GC et al. American Society of Clinical Oncology. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. J Clin Oncol 2011;29:1221-7.
31. Pereira J, Body JJ, Gunther O et al. Cost of skeletal complications from bone metastases in six European countries. J Med Econ 2016;19:611-8.
32. Rordorf T, Hassan AA, Azim H et al. Central European Cooperative Oncology Group (CECOG); Swiss Group for Clinical Cancer Research (SAKK). Bone health in breast cancer patients: a comprehensive statement by CECOG/SAKK Intergroup. Breast 2014;23:511-25.
33. Santini D, Lanzetta G, Berruti A et al. Linee guida trattamento delle metastasi ossee. AIOM Guidelines, Ed. 2019.
34. Irelli A, Sirufo MM, Scipioni T et al. The VES-13 test as a predictor of toxicity associated with aromatase inhibitors in the adjuvant treatment of breast cancer in elderly patients: a single-center study. Indian J Cancer 2020 (in press).
35. Ross JR, Saunders Y, Edmonds PM, Patel S, Broadley KE, Johnston SR. Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. BMJ 2003;327:469.
36. Stopeck AT, Lipton A, Body JJ et al. Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study J Clin Oncol 2010;28:5132-9.
37. Steger GG, Bartsch R. Denosumab for the treatment of bone metastases in breast cancer: evidence and opinion, Ther Adv Med Oncol 2011;3:233-43.
38. Cleeland CS, Body JJ, Stopeck A et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid, Cancer 2013;119:832-8.
39. Niang U, Kamer S, Ozsaran Z, Haydaroglu A, Kilciksiz S. The management of painful bone metastases with biphosphonates and palliative radiotherapy: a retrospective evaluation of 372 cases. J BUON 2009;14:245-9.
40. Lipton A, Fizazi K, Stopeck AT et al. Effect of denosumab versus zoledronic acid in preventing skeletal-related events in patients with bone metastases by baseline characteristics. Eur J Cancer 2016;53:75-83.
41. Mjelstad A, Zakariasson G, Valachis A. Optimizing antiresorptive treatment in patients with bone metastases: time to initiation, switching strategies, and treatment duration. Support Care Cancer 2019;27:3859-67.
42. Liu C, Wang L, Liu L et al. Efficacy and safety of de-escalation bone- modifying agents for cancer patients with bone metastases: a systematic review and meta-analysis. Cancer Manag Res 2018;10:3809-23.
43. Tyan A, Patel SP, Block S, Hughes T, McCowen KC. Rebound Vertebral Fractures in a Patient With Lung Cancer After Oncology-Dose Denosumab Discontinuation: A Cautionary Tale. Mayo Clin Proc Innov Qual Outcomes 2019;3:235-7.
44. Anagnostis P, Paschou SA, Mintziori G et al. Drug holidays from bisphosphonates and denosumab in postmenopausal osteoporosis: EMAS position statement. Maturitas 2017;101:23-30.
45. Gonzalez-Rodriguez E, Stoll D, Lamy O. Raloxifene Has No Efficacy in Reducing the High Bone Turnover and the Risk of Spontaneous Vertebral Fractures After Denosumab Discontinuation. Case Rep Rheumatol 2018;17:5432751.
46. Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases. J Bone Miner Res 2017;32:1291-6.
47. Florez H, Ramírez J, Monegal A, Guañabens N, Peris P. Spontaneous vertebral fractures after denosumab discontinuation: A case collection and review of the literature. Semin Arthritis Rheum 2019;49:197-203.
48. Amadori D, Aglietta M, Alessi B et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. Lancet Oncol 2013;14:663-70.
49. Müller A, Templeton AJ, Hayoz S et al. and For the Swiss Group for Clinical Cancer Research (SAKK). Abstract P1-18-01: Incidence of hypocalcemia in patients with metastatic breast cancer under treatment with denosumab: A non-inferiority phase III trial assessing prevention of symptomatic skeletal events (SSE) with denosumab administered every 4 weeks versus every 12 weeks: SAKK 96/12 (REDUSE). San Antonio Breast Cancer Symposium; December 4-8, 2018; San Antonio, Texas. https://doi.org/10.1158/1538-7445.SABCS18-P1-18-01.
50. Altundag K. Bisphosphonate-associated orbital inflammation: is it class-specific side effect? J BUON 2017;22:1603.
51. Vomvas D, Vassiliou V, Papavasileiou D, Kalogeropoulou C, Nicolatou-Galitis O, Kardamakis D. Osteonecrosis of the jaw in a patient treated with ibandronate. J BUON 2008;13:441-2.