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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 remains 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
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=0.59) [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].
Denosumab 120 mg in breast cancer bone metastases

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 5-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 hypercalcaemia, 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%); osteolytic, 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

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

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 relapsed 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**