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Side Effects of Bone-Targeted Therapies in Advanced Breast Cancer

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Keywords

Breast cancer · Bone-targeted agents · Bisphosphonates · Denosumab · Adverse events

Summary

In up to 75% of cases, advanced breast cancer patients eventually develop bone metastases with often debilitating skeletal-related events (SREs). Osteoclast inhibitors are commonly used as therapeutic mainstay with clinical studies showing superiority of denosumab over bisphosphonates (e.g., zoledronate) for the prevention of SREs. The present review discusses the adverse event profile of these agents, and addresses the prevention and management of untoward side effects. Adverse events associated with osteoclast inhibitors comprise osteonecrosis of the jaw and hypocalcemia. Hypocalcemia is more common with denosumab, particularly in severe renal dysfunction. During therapy, the appropriate prevention of these adverse events includes close attention to dental health, avoidance of invasive dental procedures, supplementation with calcium and vitamin D unless patients are hypercalcemic, and regular monitoring of relevant serum values. Relating to the risk of nephrotoxicity, bisphosphonates but not denosumab have been incriminated. Therefore, serum creatinine levels should be checked prior to each dose of zoledronate, and in severe renal dysfunction (creatinine clearance < 30 ml/min) zoledronate is contraindicated anyway. Acute-phase reactions are particularly linked to bisphosphonates. Consequently, if these adverse events predominate, switching to denosumab is recommended.

Introduction

In the advanced stage of breast cancer, 65–75% of patients eventually develop bone metastases [1, 2] which often lead to serious and severely debilitating consequences called skeletal-related events (SREs) including pathologic fractures, spinal cord compression, or the need for palliative irradiation or orthopedic surgery. These complications result in poor quality of life due to massive bone pain and functional disability up to loss of autonomy, and finally in decreased patient survival. It goes without saying that these events also entail a significant economic burden [3–6].

Consequently, it is of paramount importance for the patient to prevent SREs in order to sustain functionality, alleviate pain, improve quality of life, and in the end to further prolong survival. For that purpose, besides various local and systemic therapies including radiation, chemotherapeutics and surgical approaches [7, 8], the use of bone-targeted osteoclast inhibitors has led to significant advances [9, 10]. Osteoclast inhibitors comprise 2 classes of agents, the bisphosphonates and the fully human monoclonal antibody denosumab. Bisphosphonates are chemically related to inorganic pyrophosphate, and are particularly bone-active agents as they are preferentially adsorbed onto hydroxyapatite crystals in the extracellular matrix of bone. From there, bisphosphonates are taken up by osteoclasts and induce apoptotic processes [11, 12]. Third-generation nitrogen-containing bisphosphonates, such as zoledronic acid, are much more potent than earlier compounds [13]. On the other hand, denosumab binds to the receptor activator of nuclear factor κB ligand (RANKL) which then binds to its receptor, RANK, located on the osteoclast cell surface, thus interfering with normal osteoclast activation and leading to decreased bone-destructive processes [14, 15].

Despite the overall beneficial effects of osteoclast inhibitors, these therapies, like any medication, are not without un-

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toward effects. Therefore, to facilitate an adequate medical decision making, we here review the adverse event profile of the 2 classes of bone antiresorptive agents in advanced breast cancer [9, 12, 16–18]. In the adjuvant therapy setting of early-stage breast cancer patients, the incidence of similar side effects appears to be lower due to reduced doses and frequencies of osteoclast inhibitors administered [19].

Side Effects of Osteoclast Inhibitors

Comparative studies of intravenous zoledronic acid and subcutaneous denosumab in patients with metastatic breast cancer [20, 21] and prostate cancer [22, 23] reported similar adverse event profiles. Side effects encountered most frequently were acute-phase reactions, nephrotoxicity, hypocalcemia, and osteonecrosis of the jaw (ONJ). These will be discussed below in more detail. Very rare adverse events in the gastrointestinal tract are seen exclusively during oral bisphosphonate treatment. Following bisphosphonates, there have also been some few reports of ocular complications in terms of scleritis, uveitis, and conjunctivitis [11, 24–26]. Occasionally, subcutaneous denosumab may induce injection site reactions and other dermatologic conditions such as dermatitis, eczema, and rashes [18, 20]. Rarely, atypical femur fractures have been associated with bisphosphonate and denosumab therapy [23, 27]. So far, no patients have developed detectable levels of neutralizing antibodies against denosumab [20, 22]. In randomized studies of bisphosphonates and denosumab, severe-grade adverse events have occurred with similar frequencies between treatment arms [20, 22]. Likewise, treatment discontinuation secondary to serious side effects was generally similar in patients on zoledronic acid and denosumab [22, 28–30].

Acute-Phase Reactions

Acute-phase reactions are defined as flu-like symptoms including subfebrile temperatures, leukocytosis, chills, flushing, abnormal fatigue, bone pain, arthralgias, and myalgias [31]. In a comparative study, acute-phase reactions during the first 3 days after treatment were seen in about 30 and 10% of breast cancer patients with zoledronic acid and denosumab, respectively [20]. These responses are induced only by nitrogen-containing bisphosphonates (zoledronate, ibandronate, pamidronate) when being administered intravenously. Most acute-phase reactions typically occur in the first 3 days following initiation of treatment, subside rapidly soon after, and often do not recur upon subsequent treatments. The above side effects, although not life-threatening, may be very unpleasant for the patient, and in rare cases lead to termination of the medication.

Management

Symptomatic relief is provided by nonsteroidal anti-inflammatory drugs and antipyretics [24, 32].

Nephrotoxicity

After therapeutic administration, bisphosphonates are either stored in the bones (30–60%) or remain unmetabolized and are excreted renally (for further pharmacokinetic data see [33–35]). In the kidneys, bisphosphonates diffuse passively into tubular cells dependent only on serum concentration and protein binding. Consequently, an accumulation of bisphosphonates in the tubular cells can occur with induction of apoptotic processes and development of acute kidney injury [12, 36–38] due to tubular necrosis, which typically results in a gradual increase in serum creatinine over months that is only slowly reversed after drug discontinuation [11, 39–41]. Of the available bisphosphonates, zoledronic acid has been linked to most of the reported episodes of renal failure [24, 42]. Recovery from zoledronic acid-induced acute tubular necrosis is possible but may be protracted [38].

Patients with pamidronate-associated renal toxicity may present with nephrotic syndrome which apparently is not reversible [11, 24, 43]. Histologically, these cases show collapsing focal segmental glomerulosclerosis, acute tubular injury, or minimal change disease without glomerular pathology [43]. Ibandronate seems to be the bisphosphonate least likely to be linked to renal toxicity [44].

In contrast, in comparative clinical trials of advanced breast cancer patients, denosumab has been associated with highly significantly lower renal deterioration rates than zoledronic acid [20]. Notably, denosumab has no recognized effect on renal function. Conversely, pre-existing renal impairment was shown to have no impact on denosumab efficacy either. Accordingly, in patients with renal function ranging from normal to dialysis-dependent kidney failure, no effect of renal function on denosumab pharmacokinetics and pharmacodynamics could be encountered. Therefore, no denosumab dose adjustment based on glomerular filtration rate seems necessary [18, 21, 45].

Management

Prior to each dose of zoledronic acid, determination of serum creatinine level is required. Bisphosphonate medication should be stopped if the creatinine level increases by $\geq$ 0.5 mg/dl in patients with normal baseline renal function and if the creatinine level increases by $\geq$ 1.0 mg/dl in patients with abnormal baseline renal function. Treatment can be resumed if the creatinine level returns to near baseline values [23]. Zoledronic acid should be dose reduced in patients with impaired renal function (estimated creatinine clearance 30–60 ml/min), and held for creatinine clearance < 30 ml/min [21, 46].

In the case of pamidronate-associated nephrotic syndrome, no standardized therapy exists. Suggested palliative therapies include corticosteroids and angiotensin-converting enzyme inhibitors [11, 24].

General recommendations to reduce bisphosphonate-induced kidney damage comprise maintenance of adequate hy-

dration, avoidance of concomitant nephrotoxic agents, and strict adherence to package insert information.

Upon denosumab administration, in patients with severely impaired renal function – creatinine clearance < 30 ml/min or on dialysis – close monitoring for hypocalcemia and hypophosphatemia is recommended [21, 46]. Clearly, in this patient cohort the experience is very limited as yet.

Hypocalcemia

Hypocalcemia is the most common electrolyte abnormality associated with the use of bisphosphonates and denosumab [24, 47], as this is due to the mechanism of action of antiresorptive agents. In comparative studies, hypocalcemia was documented significantly more frequently with denosumab (5.5–13% of cases) than with zoledronic acid (3.4–6%) [20, 22]. Clinically, hypocalcemic patients may appear lethargic or weak or they may have full-blown tetany [11, 18]. Even fatal cases of denosumab-induced hypocalcemia have been reported, making clear the critical need for adequate calcium and vitamin D supplementation. In a recent trial, the incidence of hypocalcemia due to denosumab was lower in patients who reported taking calcium and vitamin D supplements than among the patients who did not [48]. The risk appears to be greatest in patients with pre-existing hypocalcemia due to impaired thyroid or parathyroid function. The risk of hypocalcemia with denosumab seems also markedly enhanced in patients with renal insufficiency (creatinine clearance < 30 ml/min) [45] and those with extensive osteoblastic bone metastases or hypomagnesemia [49], as well as after bariatric surgery [50]. The onset of hypocalcemia can arise at any time during therapy, and most commonly occurs within the first 6 months of dosing [21].

Management

To avoid the occurrence of hypocalcemia in patients prescribed denosumab or bisphosphonates, serum vitamin D3 and albumin-corrected or ionized calcium levels should be monitored before the first injection/infusion and all subsequent therapies so that hypocalcemia at any point during treatment can be identified and corrected [24, 47, 50]. As the normal conversion of vitamin D to the active form (25-hydroxycholecalciferol to 1.25-hydroxycholecalciferol (calcitriol)), which occurs in the kidneys, is compromised in the condition of renal dysfunction, supplementation with calcitriol has been suggested for the prevention or treatment of hypocalcemia [51].

Breast cancer patients going to be treated with bisphosphonates or denosumab should be normocalcemic at initiation of therapy and then should be regularly supplemented with calcium (1,000 mg/day orally) plus calcitriol (0.25 μg/day orally). If nevertheless hypocalcemia develops, the osteoclast inhibitor should be held, and calcium and calcitriol doses should be adequately adjusted [23, 24, 50].

Osteonecrosis of the Jaw

ONJ is a well-recognized untoward effect associated with the use of both bisphosphonates and denosumab, and comprises osteonecrosis of the mandible and/or maxilla. According to the American Association of Oral and Maxillofacial Surgeons [52], ONJ has been defined as i) the presence of clinically evident necrotic bone exposed through the oral mucosa or facial skin which has persisted despite appropriate management for more than 8 weeks in osteoclast inhibitor-treated patients with ii) no history of irradiation therapy to the jaws. ONJ of this type following the use of bisphosphonates was first described in 2003 [53]. And in 2008, the so-called 'non-exposed variant of jaw osteonecrosis' was first reported [54], which in the absence of frank bone exposure is characterized by the following clinical features: otherwise unexplained jawbone pain, fistula tracts, loose teeth, swelling, and, in advanced cases, pathologic fracture of the mandible [54, 55].

As risk conditions for the development of ONJ in cancer patients treated with antiresorptive therapies, local factors such as dentures, poor oral hygiene, and preceding dental procedures such as tooth extractions have been identified [23]. Additionally, systemic factors like smoking, diabetes, anemia, renal insufficiency, and use of glucocorticoids, chemotherapeutic and anti-angiogenic agents have been implicated. The risk of ONJ seems to be also enhanced upon longer duration and increased doses of antiresorptive drug therapy [55].

In large meta-analyses of comparative trials in metastatic breast cancer patients, within 2 years of treatment no statistically significant difference in the incidence of ONJ could be detected between denosumab (2.0% of cases) and zoledronate (1.4%) [41, 55–57]. Among nitrogen-containing bisphosphonates, there may be a higher risk of ONJ with zoledronate compared with pamidronate or ibandronate [12].

Management

Preventive strategies may reduce the incidence of osteoclast inhibitor-associated ONJ [12, 21, 55, 58–60]. These strategies comprise meticulous examination of the oral cavity and completion of any necessary preventive dentistry prior to treatment. While on osteoclast inhibitors, patients should maintain optimal oral hygiene and, if feasible, avoid invasive dental procedures, e.g., implant or periodontal surgery. If invasive dental surgery is required, it seems prudent, although not yet proved formally, to cease therapy prior to the procedure and to resume treatment not until completion of wound healing.

In the case of manifest ONJ, depending on the stage of disease [23, 55, 58–60], treatment modalities include pain control often requiring opioid medications, antimicrobial mouth rinses (0.2% chlorhexidine digluconate), systemic antibiotics according to microbiologic testing (preferably a broad-spectrum penicillin plus metronidazole), and nutritional support when needed. In advanced-stage ONJ with exposed bone, sur-

gical treatment options such as bone debridement, curettage, sequestrectomy, or resection may be indispensable. Generally, discontinuation of the antiresorptive medication is advised for at least a 1-month postoperative period.

Choice of Adequate Osteoclast Inhibitor

In breast cancer metastatic to bone, clinical trials have shown superiority of denosumab over bisphosphonates for the prevention of SREs (primary endpoint: time to first on-study SRE, secondary endpoint: time to first and subsequent (multiple) on-study SREs [20]). Consequently, denosumab may be useful in patients not sufficiently responding to bisphosphonates, although in this matter the definite scientific evidence is still pending.

In toxicity profiles, denosumab lacks nephrotoxicity and induces acute-phase reactions at a markedly lower rate compared to bisphosphonates. On the other hand, hypocalcemia is more common with denosumab. Rates of ONJ, however, occur similarly frequently with both agents. Therefore, it seems logical that in patients with modest degrees of renal impairment, denosumab may be favored. The same holds true for patients with severe renal dysfunction (creatinine clearance < 30 ml/min), where zoledronate is contraindicated. In the latter cases, however, the risk of enhanced denosumab-induced hypocalcemia needs careful attention.

Eventually, as a point of patient convenience, the subcutaneous administration of denosumab may be preferable to the intravenous route of zoledronic acid.

Conclusion

Bisphosphonates and denosumab, notwithstanding their beneficial effects in bone-metastatic breast cancer, are associated with potential adverse events which occur dependent on dose and frequency of administration. These untoward effects of osteoclast inhibitors may add to the already existing symptom burden for patients. Therefore, to alleviate this burden, an appropriate management is required including the following preventive measures:

i) Acute-phase reactions have been linked particularly to bisphosphonates. Consequently, if these problems predominate, switching to denosumab is recommended.

ii) Relating to the risk of nephrotoxicity, serum creatinine level should be checked prior to each dose of zoledronic acid to allow for appropriate dosing modifications or termination of medication. Patients with severe renal dysfunction (creatinine clearance < 30 ml/min) should not be treated with zoledronate at all. Generally, adequate hydration is to be maintained.

iii) Hypocalcemia appears to occur more often with denosumab than with zoledronic acid. In any case, however, serum calcium and vitamin D3 levels should be monitored before the first drug administration and all subsequent therapies. All patients treated with osteoclast inhibitors should be given supplemental calcium (1,000 mg/day orally) plus vitamin D (calcitriol, 0.25 µg/day orally) unless they are hypercalcemic.

iv) To reduce the risk of ONJ, meticulous examinations of the oral cavity should be performed prior to and during treatment. Likewise, any necessary preventive dentistry should be completed before therapy. While on osteoclast inhibitors, patients should maintain optimal oral hygiene and avoid invasive dental procedures. Whenever ONJ is diagnosed, the antiresorptive therapy should be discontinued and a specialized center consulted.

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