Individualized Bone-Protective Management in Long-Term Cancer Survivors With Bone Metastases

Tilman D Rachner,1,2,3 Robert Coleman,4 Peyman Hadji,5,6 and Lorenz C Hofbauer1,2,3

1Division of Endocrinology, Diabetes and Bone Diseases & Center for Healthy Ageing, Department of Medicine III, Technische Universität Dresden, Dresden, Germany
2German Cancer Consortium (DKTK), Partner Site Dresden and German Cancer Research Center (DKFZ), Heidelberg, Germany
3Center for Healthy Aging, Technische Universität Dresden, Dresden, Germany
4Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK
5Frankfurt Center of Bone Health, Frankfurt, Germany
6Philips-University of Marburg, Marburg, Germany

ABSTRACT
Antiresorptive therapy is an important component of a multimodal approach to treating patients with advanced malignancies and metastatic bone disease. Over the past decade, overall survival of affected patients has improved in most cancer entities, and long-term disease control is a realistic goal in many cases. There are emerging clinical studies showing the benefits of an initial antiresorptive therapy using bisphosphonates or denosumab. However, some adverse events of these therapies, such as osteonecrosis of the jaw, correlate with the cumulative doses given, and there is an increasing clinical need for new antiresorptive concepts to treat long-term survivors. This review summarizes the clinical evidence of antiresorptive therapies across different cancers with bone involvement and presents concepts of dose-reduction protocols for long-term survivors with established metastatic bone disease.

KEY WORDS: CANCER; ANTIRESORPTIVES; THERAPEUTICS

Introduction
Bone metastases represent a common finding in patients with advanced breast and prostate cancer, and osteolytic lesions are a hallmark of multiple myeloma. Bone metastases may also occur in many other malignancies, including renal and lung cancers as well as melanoma. (1)

In the presence of established bone metastases, guidelines generally recommend the use of a high-dose antiresorptive treatment to prevent or delay the occurrence of skeletal-related events (SREs). Best established bone-protective agents include the bisphosphonate zoledronic acid (4 mg Q4W) and the receptor activator of NF-κB ligand (RANKL) antibody denosumab (120 mg Q4W). These drugs are well documented to reduce the occurrence of SREs and, in some cases, to positively improve survival. (2)

Although bisphosphonates and denosumab have distinct modes of action, they combine beneficial effects on different aspects of bone health in patients with advanced solid tumors. The more potent amino-bisphosphonates act as inhibitors of the mevalonate pathway. Although many direct anti-cancer properties of amino-bisphosphonates have been repeatedly displayed in preclinical trials, it is now generally accepted that the pharmacological levels required for these effects are unlikely to be achieved in humans (reviewed in Göbel and colleagues (3)). Denosumab is a monoclonal antibody directed against RANKL, and RANKL has been proposed to mediate breast cancer progression and migration of cancer cells to bone (reviewed in Rachner and colleagues (4)). If denosumab has direct effects on tumor biology or solely affects bone remodeling remains under debate. Nonetheless, both bisphosphonates and denosumab have proven efficacious in protecting from drug-induced bone loss and fragility fractures.
In the past, the life expectancy of the majority of affected patients was limited and treatment was usually continued indefinitely. Because trial duration and follow-up has often been restricted to 1 to 2 years, there is little scientific evidence on how to manage the treatment of long-term survivors with bone metastases. However, over the past 10 years, significant progress has been made in treating the underlying malignancies of patients with established bone metastases, resulting in longer overall survival.

Several new treatment approaches for multiple myeloma and prostate cancer have been FDA approved, and sequential therapeutic approaches often allow disease control for many years.

Patients with metastatic melanoma and some forms of lung cancer have benefitted greatly from the introduction of checkpoint inhibitors. These advances have led to a scenario where cancer have benefits from treatment, allowing disease control for many years. However, over the past 10 years, significant progress has been made in treating the underlying malignancies of patients with established bone metastases, resulting in longer overall survival.

Breast cancer–derived bone lesions usually have a predominantly lytic radiographic appearance, and there is general agreement that an antiresorptive treatment should be initiated upon the time of diagnosis. In addition, there is considerable evidence that an adjuvant bone-protective therapy with bisphosphonates significantly reduces the risk of developing bone metastases and death in postmenopausal patients with limited disease at the time of diagnosis. Data on the adjuvant use of denosumab are currently ambiguous, and there is no clear recommendation for the adjuvant use of denosumab for the prevention or delay of bone metastases.

Bisphosphonates

In patients with breast cancer and bone metastases, less potent bisphosphonates such as pamidronate and ibandronate significantly improve bone health. Pamidronate (90 mg i.v. Q-3-W) prolonged the time to first skeletal complication by almost 50% from 7.0 to 13.9 months in a trial with 382 women but did not affect survival. The intravenous application of ibandronate for up to 2 years (6 mg every 3 to 4 weeks), significantly reduced the number of SREs by 38% and prolonged the time to first new bone event. Zoledronic acid is the most potent bisphosphonate available and has been tested in head-to-head trials with other bisphosphonates. In comparison with pamidronate, zoledronic acid reduced the risk of an SRE by an additional 20%. Ibandronate provides an oral alternative but failed to show non-inferiority to zoledronic acid in preventing SREs. Based on these findings and the increasing long-term survival of affected patients, several trials have assessed the efficacy of reducing the dosing of zoledronic acid in the long-term treatment of patients with breast cancer–derived bone metastases (Table 1).

In the open-label phase III “ZOOM” trial, 425 patients were assigned to receive either zoledronic acid in a 12-week (prolonged interval) or 4-week (normal interval) scheme after an initial period of 12 to 15 months of standard treatment. The skeletal morbidity rate was 0.26 (95% confidence interval [CI] 0.15–0.37) in the 12-week group and 0.22 (0.14–0.29) in the 4-week group, and further analyses revealed that the between-group difference was lower than the predefined margin for non-inferiority. Numerically, the number of SREs were comparable with 31 of 209 (15%) and 33 of 216 (15%) of cases in the 12- and 4-week groups, respectively.

In another trial (OPTIMIZE-2), again recruiting patients after treatment for 12 months, zoledronic acid every 12 weeks was non-inferior to a 4-week regimen with 23.2% and 22.0% of patients experiencing an SRE after 1 year of follow-up, respectively.

Search Strategy and Selection Criteria

References for this review were identified through searches of PubMed for articles published from January 1990 to April 2021, by using the terms “bone metastases,” “long-term treatment,” and “clinical trials,” in combination with the terms “dose reduction,” “adverse events,” and “guidelines.” Peer-reviewed articles resulting from these searches and relevant references cited in those articles were reviewed. Only articles published in English were included.

Breast Cancer

Bone metastases secondary to breast cancer are a critical long-term complication with a high prevalence in advanced disease.

| Table 1. Trials Assessing a 12-Week Dosing Interval of Zoledronic Acid in Patients With Established Bone Metastases |
|---------------------------------|---------------|-----------------|------------------|--------------------|-------------------|---------------|
| Trial                          | Entity        | Study design    | Agent            | Result             | Reference         |
| ZOOM                           | Myeloma       | N = 425         | Prospective      | ZA, 12–15 months  | Non-inferior      | Amadori et al. |
|                               | Breast        |                 | OL, non-infer.   | Prior therapy     |                   |                |
|                               | Prostate      |                 |                 |                   |                   |                |
| OPTIMIZE-2                     | N = 403       | Prospective     | ZA, 11–15 months | Non-inferior      | Hertogoyi et al.  |
|                               |               | OL, non-infer.  | Prior therapy    |                   |                   |                |
| CALGB                          | N = 278       | Prospective     | ZA, no prior     | Non-inferior      | Himmelstein et al.|
|                               | Breast        | DB              | Therapy          |                   |                   |                |
|                               | Prostate      |                 |                 |                   |                   |                |

OL = open label; DB = double blind; non-infer. = non-inferiority trial; ZA = zoledronic acid.
More recently, a larger study in 1766 patients, with either breast cancer, prostate cancer, or multiple myeloma, conducted by the Cancer and Leukemia Group B (CALGB), randomized patients at the initiation of bisphosphonate treatment to zoledronic acid every 12 or every 4 weeks. The proportions of the 855 patients with breast cancer presenting at least one SRE were similar (114 [27%] with Q 4-week dosing and 122 [29%] with Q 12-week dosing in both arms; between-group difference −0.02 [99.9% CI −0.13 to 0.09; p = 0.50]). The primary endpoint of non-inferiority was met. However, in the study as a whole, more patients receiving zoledronic acid every 12 weeks required bone surgery within 2 years of enrollment (secondary endpoint) compared with 4-week zoledronic acid.(17)

A recent systematic review and meta-analyses of trials with reduced bisphosphonate dosing regimens in patients with breast cancer was conducted.(18) Four randomized trials with 1721 subjects were included and concluded that the prolonged interval of 12 weeks of zoledronic acid or pamidronate was non-inferior to standard dosing with regard to SREs as well as adverse events.(18) Notably, this meta-analyses also included one trial with pamidronate tested at a reduced dosing interval of 12 weeks compared with the standard interval of 3 to 4 weeks. (19) As a limitation, this relatively short trial (maximum of 48 weeks) only assessed biomarker data but came to the conclusion that there was sufficient data of non-inferiority of a de-escalated regimen to warrant additional trials. (19) Based on these data with pamidronate, and in support of the more extensive data available with zoledronic acid, a general feasibility of reducing long-term dosing of bisphosphonates could be postulated(2) (Fig. 1). (FIG1)

Denosumab

Denosumab (120 mg every 4 weeks) was tested in a pivotal phase 3 trial in comparison to zoledronic acid (4 mg every 4 weeks). In patients with bone metastases secondary to breast cancer, denosumab was superior to zoledronic acid in prolonging the time to first (hazard ratio [HR] = 0.82, 95% CI 0.71–0.95, p = 0.01 for superiority) and time to first and subsequent SRE (HR = 0.77, 95% CI 0.66–0.89, p = 0.001). (20) The use of denosumab for the treatment of breast cancer-derived bone metastases has since become one of the most commonly applied antiresorptive approaches for these patients.

The pharmacology of denosumab is different from that of bisphosphonates. Although bisphosphonates rapidly accumulate in the bone, where they have a long half-life of many years,(21) denosumab only has a serum half-life of <30 days.(22) A direct translation of results from dose-reduction studies with bisphosphonates to denosumab is therefore not possible. However, based on the well-documented sustained suppression of bone turnover using the lower osteoporosis treatment regimen of 60 mg every 6 months, a reduced intensity treatment scheme for long-term survivors with stable metastatic disease may be feasible, and trials are currently running to test this hypothesis.

Most recently, data from the “Rethinking Clinical Trials (REaCT) bone-targeting agents” study (NCT02721433) were published. This study included patients with bone metastases secondary to breast or castration-resistant prostate cancer. Approximately half of the patients received denosumab (56.3%) in either 4- or 12-week intervals and the study met the predefined endpoint of non-inferiority with no significant differences between the different treatment arms. (23) The larger Reduse trial (NCT02051218) is still ongoing and will help to clarify if a dosing reduction in patients with advanced breast and prostate cancer can be recommended.

Prostate Cancer

Bone metastases secondary to prostate cancer display some unique features compared with bone lesions associated with other malignancies. The main difference is that bone metastases...
of prostate tumors commonly form osteosclerotic lesion that have a dense radiographic appearance. Although these lesions have a lower structural quality than healthy bone, associated fracture risk is considerably lower than in patients with osteolytic lesions.\(^{(24)}\) In addition, affected patients tend to have a longer overall survival compared with patients with other cancer entities and bone metastases.

**Bisphosphonates**

Of note, a clinically relevant benefit of antiresorptive treatment has only been found in patients with advanced castration-resistant prostate cancer (CRPC), whereas there was no positive effect of zoledronic acid on the occurrence of SREs or overall survival in patients with castration-sensitive prostate cancer.\(^{(25)}\) Furthermore, data from the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial indicate the addition of zoledronic acid to standard treatment in hormone-sensitive prostate cancer did not improve overall survival.\(^{(26)}\) Among bisphosphonates, only zoledronic acid has been proven to significantly reduce SREs in patients with CRPC.\(^{(27)}\) Compared with placebo, zoledronic acid reduced the risk of SREs by 36% (relative risk [RR] = 0.64, 95% CI 0.485–0.845, \(p = 0.002\)).

Although the majority of dose-reduction trials have been performed in breast cancer or multiple myeloma, some have addressed the issue of reducing dosing of zoledronic acid in patients with prostate cancer and bone metastases. In the largest trial, 689 of the 1822 enrolled patients had prostate cancer. Here, there was no significant difference in the proportion of SREs between the 4-week and 12-week group\(^{(17)}\) (Table 1).

**Denosumab**

A clinical benefit of denosumab is well established in several different settings of prostate cancer. For patients with limited disease undergoing endocrine therapy, denosumab was specifically approved to prevent the deleterious effects of androgen deprivation on bone mass.\(^{(28)}\) Furthermore, adjuvant use of high-dose denosumab significantly delayed the bone metastases-free survival by 4.2 months compared with placebo (0.85, 95% CI 0.73–0.98, \(p = 0.028\)).\(^{(29)}\) However, this clinical benefit came at the cost of a substantial increase in the number of diagnosed patients with an osteonecrosis of the jaw in the denosumab-treated group (5% versus 0%), a figure that is comparable to high-dose denosumab treatment of patients with established bone metastases.

For patients with bone metastases secondary to castration-resistant prostate cancer, denosumab was superior to zoledronic acid in reducing the time to first on-study SRE in a phase 3 trial.\(^{(30)}\) In this trial, 1904 patients were randomized to receive denosumab or zoledronic acid. Median time to first on-study SRE was 20.7 months with denosumab compared with 17.1 months with zoledronic acid (HR = 0.82, 95% CI 0.71–0.95, \(p = 0.008\)) for superiority.\(^{(30)}\) Denosumab given at 120 mg every 4 weeks is now a well-established treatment choice for men with advanced prostate cancer. The Reduse trial is currently ongoing to assess if a longer dosing interval of 120 mg denosumab every 3 months is non-inferior to the current standard treatment (NCT02051218). In the CALGB study,\(^{(17)}\) 689 patients with prostate cancer were included. The probability of experiencing at least 1 SRE within 2 years of randomization was not significantly different between the zoledronic acid 4-week and 12-week groups for patients with prostate cancer (110 [32%] with Q 4 weeks and 102 [30%] with Q 12 weeks; between-group difference 0.02, 99.9% CI –0.10 to 0.15, \(p = 0.59\)).

**Myeloma**

Osteolytic bone lesions are a hallmark of multiple myeloma with an occurrence in 70% to 95% of affected patients.\(^{(31)}\)

**Bisphosphonates**

Multiple trials have been performed to evaluate the clinical benefit of bisphosphonates in multiple myeloma.\(^{(32)}\) Initial trials with clodronate, pamidronate, and ibandronate in the 1990s were conducted as placebo-controlled trials and established a reduction of SREs for clodronate and pamidronate.\(^{(32)}\) Notably, intravenous ibandronate (2 mg/monthly) failed to reduce the rate of SREs.\(^{(33)}\) Trials with zoledronic acid were later conducted as randomized-controlled studies against pamidronate\(^{(13)}\) or clodronate.\(^{(34)}\)

The efficacy of zoledronic acid in reducing SREs in myeloma bone disease was of comparable magnitude to intravenous pamidronate.\(^{(13)}\) Zoledronic acid significantly reduced the number of SREs compared with clodronate (27% versus 35%; HR = 0.74, 95% CI 0.62–0.87, \(p = 0.0004\)).\(^{(35)}\) Furthermore, treatment with zoledronic acid was associated with a survival benefit for affected patients. Zoledronic acid reduced the mortality by 16% compared with clodronate (HR = 0.84, 95% CI 0.74–0.96, \(p = 0.0118\)) with a mean overall survival of 50 months in patients receiving zoledronic acid compared with 44.5 months for those treated with clodronate.\(^{(36)}\) Based on these trial data, it is generally accepted that all patients with newly diagnosed multiple myeloma and osteolytic disease should be treated with an antiresorptive agent. Although head-to-head trials of second-generation bisphosphonates are lacking,\(^{(36)}\) based on the available data, preference should be given to an amino-bisphosphonate over clodronate and the majority of recommendations favor zoledronic acid over other bisphosphonates.\(^{(2)}\)

There is no consensus over the duration of bisphosphonate therapy. However, depending on the baseline characteristics, there is an increasing number of patients with multiple myeloma who can be considered as long-term survivors.\(^{(37)}\) The initial zoledronic acid trials in multiple myeloma were all conducted with the standard dose of 4 mg every 4 weeks.

In the CALGB study, 278 patients with multiple myeloma were included.\(^{(17)}\) The probability of experiencing at least 1 SRE within 2 years of randomization was not significantly different between the zoledronic acid 4- and 12-week groups for patients with prostate cancer (36 [26%] with Q 4 weeks and 29 [21%] with Q 12 weeks; between-group difference \(–0.12\) [99.9% CI \(–0.12\) to \(–0.254\), \(p = 0.14\)].\(^{(13)}\)

With the knowledge of a positive correlation between the cumulative doses of bisphosphonates and the risk of adverse events, recent ESMO guidelines suggest a reevaluation of the bone-protective therapy after 24 months of treatment.\(^{(2)}\) Both the European Myeloma Network (EMN)\(^{(38)}\) and ASCO\(^{(39)}\) recommend that bisphosphonates (or denosumab) are administered for 2 years with continuation only if there is evidence of active myeloma bone disease.

**Denosumab**

Denosumab was assessed in a third pivotal phase 3 trial for patients with myeloma and bone metastases from solid tumors other than prostate and breast cancer.\(^{(40)}\) In this trial, monthly
denosumab at 120 mg was compared with monthly zoledronic acid at 4 mg. Denosumab was non-inferior to zoledronic acid (primary endpoint) in delaying the time to first on-study SRE (HR = 0.84, 95% CI 0.71–0.98, p = 0.0007). However, there was no statistical superiority of denosumab over zoledronic acid (p = 0.06) and no differences with regard to overall survival. Furthermore, an ad hoc analysis suggested a survival disadvantage for patients treated with denosumab (HR = 2.26, 95% CI 1.13–4.50, p = 0.014). Based on these results, denosumab was initially not approved for the treatment of bone lesions in patients with multiple myeloma. Later conducted analyses revealed an imbalance between the baseline characteristics of both groups, and after adjusting for confounders, there was no survival difference between the zoledronic acid and denosumab groups (HR = 1.31, 95% CI 0.80–2.15; p = 0.278). As a response, a recent phase 3 trial was conducted that only included patients with multiple myeloma. This large trial enrolled 1718 patients and met its primary endpoint of non-inferiority of denosumab to zoledronic acid for time to first skeletal-related event (HR = 0.98, 95% CI 0.85–1.14, p = 0.01 for non-inferiority). Consequently, denosumab was approved for the treatment of multiple myeloma by the FDA in 2018. With no clear evidence of superiority of either agent, treatment choice should be made based on a number of considerations. Although costs are higher for denosumab, it does not negatively impact renal function, which may be an advantage, especially for patients with multiple myeloma, who are prone to renal impairment.

Other Malignancies

Data from clinical trials for other solid malignancies, apart from breast and prostate cancer, remain relatively limited.

In a large phase 3 trial, in 773 patients with bone metastases from solid tumors other than breast or prostate cancer, zoledronic acid reduced the rate of SREs compared with placebo. In this trial, the majority of patients had non-small-cell lung carcinoma (~50%), whereas some patients with small-cell lung carcinoma, renal cell carcinoma, and head and neck and thyroid carcinoma were also included. Long-term follow-up of this study confirmed the protective effects of zoledronic acid in this cohort. Four milligrams of monthly zoledronic acid reduced the risk of developing a SRE by −31% (HR = 0.692, p = 0.003). In a retrospective analysis of this study, the effects of zoledronic acid on developing SREs in renal cell carcinoma were investigated. In a subset of 74 patients with renal cell carcinoma, zoledronic acid reduced the proportion of patients with an SRE compared with placebo (37% versus 74%, p = 0.0015).

As mentioned above, a phase 3 trial for patients with myeloma and bone metastases from solid tumors other than prostate and breast cancer showed non-inferiority of denosumab for reducing SREs compared with zoledronic acid but failed to show superiority for denosumab after adjusting for multiplicity. Results from this trial were influenced by the results from the myeloma cohort, and an ad hoc subgroup analysis excluding the patients with multiple myeloma showed a significant benefit for denosumab in delaying the time to first on-study SRE compared with zoledronic acid (HR = 0.81, 95% CI 0.68–0.96).

Furthermore, in an exploratory analysis of this trial, denosumab was associated with an improved overall survival compared with zoledronic acid in patients with metastatic non-small-cell lung cancer. There are no randomized data evaluating schedule or duration of antiresorptive treatments in these other solid tumors.

Approaches to Patients With Disease Progression

Despite a general improvement achieved in treating the underlying malignancies of patients with bone metastases, some patients experience disease progression or SREs while receiving antiresorptive treatment. In these cases, a switch to a different antiresorptive agent is often considered. Although this response maybe conceptually attractive, valid clinical data to support this decision is lacking.

Notably, no new safety signals were found in the open-label extension of the initial phase 3 trials for patients with bone metastases secondary to breast or prostate cancer. In this trial, 342 patients with breast cancer and 128 patients with prostate cancer were switched from zoledronic acid to denosumab for an additional 2 years of open-label extension. Overall survival throughout the duration of the study was comparable between treatment groups. A recently published retrospective cohort study identified patients who were switched from a bisphosphonate to denosumab after suffering from a SRE while receiving treatment and compared them to patients who remained on the same bisphosphonate. Intriguingly, switching to denosumab was associated with a longer time to subsequent symptomatic skeletal event (HR = 0.47, 95% CI 0.25–0.88, p = 0.02).

However, with a lack of prospective trials, there is no general recommendation for switching of antiresorptive therapies in case of a new SRE, and these decisions need to be made under consideration of the individual disease history and prognosis.

Safety Considerations

With an increasing number of long-term survivors with metastatic bone disease, evidence-based clinical approaches are required to provide affected patients with optimal care and a transparent risk-to-benefit assessment. High cumulative doses of bisphosphonates come at the cost of a high risk of developing ONJ. It is especially important to note that precipitating factors are commonly found in those patients developing ONJ. In one study, oral procedures and/or poor hygiene such as dental extractions or periodontal disease were found in 28/29 documented cases. Based on these findings, dental evaluation and treatment, if required, are highly recommended before starting antiresorptive treatment.

Although ONJ has long been the most focused on adverse event of antiresorptive treatment, the occurrence of atypical femur fractures (AFF) is another established adverse event that is associated with a high morbidity. In general, AFF are considered a rare adverse event in patients receiving high-dose antiresorptive therapy for osteoporosis or malignant bone disease. There appears to be a higher risk in patients of Asian descent. However, the majority of publications are case reports or small case series. More recently, a larger study reported an incidence of 0.9% surgically treated cases of AFF (5 of 529 patients) in patients with bone metastases receiving bisphosphonates or denosumab compared with 0 cases in 192 patients not treated with bone-modifying agents. Notably, rates of AFF appeared higher (6.6%) in patients with breast cancer compared with other malignancies. This may in part be explained by hip geometry, and special attention should be paid to AFF in patients with breast cancer. Several other studies have
addressed the same topic. In a retrospective study of patients who had received a minimum of 24 doses of intravenous bisphosphonates for skeletal metastases, the rate of AFF was 4 of 327. Notably, no clear association between dose and duration of therapy was observed in this study.\textsuperscript{(55)} With regard to denosumab, a retrospective multicenter study revealed an AFF incidence of 1.8% (5 of 277) in patients receiving denosumab for bone metastases.\textsuperscript{(55)} In this study, 4 of 5 of patients with AFF had received zoledronic acid before denosumab and 4 of 5 patients had received treatment for more than 3.5 years.\textsuperscript{(55)}

More recently, a systematic review performed by the ECTS was published addressing the medical management of AFF. The authors concluded that only 8 cases of AFF in bisphosphonate naive patients had been published. Four of these cases occurred in the oncology setting after 21 to 42 doses of monthly denosumab.\textsuperscript{(56)} Although ONJ and AFF are adverse events of intravenous bisphosphonates and denosumab, their incidence remains fairly low, especially when compared with the well-documented benefits of these therapies. While in most cases bisphosphonates are paused if ONJ occurs, there is little evidence to prove that this improves healing. In the case of AFF, the recent ECTS recommendations propose to discontinue bisphosphonate treatment to prevent worsening or a new contralateral AFF.\textsuperscript{(56)} In the case of denosumab, any interruption of therapy needs to be weighed against the risk of rebound-associated vertebral fractures (extensively discussed in van de Laarschot and colleagues\textsuperscript{(56)}).

**Approaches to Long-Term Survivors**

Evidence for clinical efficacy in dose-reduction regimens varies depending on substance and tumor entity. Data for a dose reduction of zoledronic acid is best documented for multiple myeloma\textsuperscript{(17)} and breast\textsuperscript{(18)} and prostate cancer.\textsuperscript{(17)} There is an increasing consensus that extending the dosing interval of zoledronic acid to 12 weeks is appropriate in cases where a complete or good partial response has been achieved and the tumor appears controlled.

Importantly, there are data to suggest that patients who have received an initial therapy with a standard dose are less prone to SREs than patients who are started on a reduced dosing scheme (odds ratio [OR] = 0.59, 95% CI 0.47–0.74, \( p < 0.00001 \)).\textsuperscript{(18)} Antiresorptive therapy should therefore be commenced with the standard high-dose/short-interval protocol and reductions should only be considered after a few months (3 to 6 months are generally accepted as adequate).

Lately, ESMO guidelines have proposed an algorithm where an interruption of bisphosphonate therapy can be considered after 24 months in patients with myeloma or oligometastatic disease\textsuperscript{(2)} who have achieved a complete response or good partial response. In patients with multiple bone metastases, a reduced interval of 3 months is recommended for patients who have achieved a complete or good partial response. There is no solid evidence with regard to the duration of this, and individual approaches are required that take tumor status and concurrent osteoporosis into account. In all cases, treatment should be resumed in case of disease progression.

Most recently, physicians increasingly face the clinical situation of how to respond to patients who remain under complete remission to an extent where bone lesions are no longer detectable and systemic therapies (ie, immune therapies) are paused. This clinical situation is not reflected by any clinical trial. However, in these cases, the authors of this review believe that an interruption of bisphosphonate treatment can be considered similar to the recommendations for patients with myeloma or oligometastatic disease.\textsuperscript{(2)}

Data on dose-reduction trials with denosumab are underway, but data are not yet available. Based on the lack of solid data and considering the different pharmacological properties of denosumab, no dose reductions are recommended for denosumab until more data are available. Most importantly, termination of denosumab therapy is associated with a rebound effect that results in strong loss of bone mass and a strongly increased risk of fractures.\textsuperscript{(57)} Denosumab treatment must not be paused or interrupted for a longer period without providing patients with an adequate consolidation concept (in most cases, application of i.v. bisphosphonates).

**Socioeconomic Considerations**

In addition to its clinical importance, the choice of treatment regimen has economic implications. Several studies have tried to assess the effects on modifying the antiresorptive protocol from an economic perspective. A cost-effectiveness analysis compared the different treatment options (zoledronic acid q1M, q3M or denosumab q1M). This study came to the conclusion that costs with denosumab were approximately ninefold higher than with generic zoledronic acid every 3 months, while showing no relevant difference in quality-adjusted life-years.\textsuperscript{(58)} However, results from these studies are highly dependent on the data sets used for analyses and may provide very different results based on study populations, assumed costs and benefits, as well as statistical approach. For example, another study, which was based on SRE reductions reported from the pivotal phase 3 denosumab trials, summarized that, while the direct costs of using denosumab are much higher than for zoledronic acid, the reduced costs associated with bone complications actually favored denosumab.\textsuperscript{(59)} Results from these studies also appear to be at the risk of being biased dependent on their financial sponsor (summarized in Shapiro and colleagues\textsuperscript{(58)} and Koo and colleagues\textsuperscript{(60)}).

**Conclusion**

Enormous progress has been made in treating patients with metastatic bone disease across all entities. The majority of large bisphosphonate trials available have been conducted with zoledronic acid. Undoubtedly, benefits of an antiresorptive treatment outweigh potential adverse events in most cases. However, long-term treatment with these agents increases the cumulative risk of some adverse events, such as ONJ. There is sufficient data to support a reduction in dosing interval to 12 weeks in myeloma and metastases from solid malignancies, although solid data are only available for breast and prostate tumors. Most authors suggest a minimal period of 6 months of standard treatment (ie, monthly injections of zoledronic acid) before a dosing reduction should be initiated. In multiple myeloma and in cases of oligometastatic bone disease, interruption of antiresorptive treatment with bisphosphonates can be considered if patients have achieved a complete or good partial response and the clinical status is deemed as stable after 24 months of treatment.\textsuperscript{(2)} Similar considerations can be made in patients with multiple bone lesions that show a long-term clinical response to treatment.
especially if other adjuvant agents are paused. Resumption of treatment should be initiated in case of disease progression.

Studies investigating different dosing intervals of denosumab are currently being conducted. Until these studies are published, prolonging the intervals of denosumab administration beyond 4 to 6 weeks is not recommended.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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