Bone-Targeted Therapy

Zielgerichtete Knochentherapie

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Abstract

Bisphosphonates and denosumab are well established components of the therapy for osteoporosis and osseous metastases. Their relevance in the adjuvant situation for breast cancer patients is being discussed in part controversially due to the heterogeneous nature of the available data. In particular, it appears that post-menopausal women benefit from an adjuvant therapy with bisphosphonates. In the present contribution we discuss the clinical relevance of osteoprotective therapy in the metastatic and adjuvant settings. Above all the current AGO guidelines on osteo-oncology and bone health have been taken into consideration for recommendations to implement the available data.

Zusammenfassung

Bisphosphonate und Denosumab sind fest etablierter Bestandteil der Therapie der Osteoporose und der ossären Metastasierung. Ihr Stellenwert in der adjuvanten Situation bei Mammakarzinompatientinnen wird aufgrund der heterogenen Datenlage teilweise kontrovers diskutiert. Insbesondere scheinen die postmenopausalen Patientinnen von der Bisphosphonattherapie in der Adjuvanz zu profitieren. In diesem Beitrag soll die klinische Relevanz der osteoprotektiven Therapien im metastasierten und adjuvanten Setting diskutiert werden. Bei den Empfehlungen für die Umsetzung der Daten wurden insbesondere die aktuellen AGO-Empfehlungen zur Osteoonkologie und zur Knochengesundheit berücksichtigt.

Introduction

Bisphosphonates (BP) and denosumab are by now well established components in the therapy for breast cancer. For a long time the main field of use of BP was as therapy for bone metastases; they reduce the prevalence of skeletal complications such as fractures, pain and hypercalcaemia. In the meantime, however, BP are also gaining importance in the adjuvant situation: here they can be employed for osteoprotection and as treatment for the therapy-associated osteopenia under systemic therapy, particularly under endocrine therapy. Their role as protection against metastasis in the adjuvant situation is being discussed controversially due to the heterogeneity of the available data. In the present contribution we attempt to give a survey of the use and risks of bisphosphonates and denosumab in the therapy for breast cancer.

BP are analogues of the naturally occurring pyrophosphates. They are administered orally or intravenously, in the latter case administration of the newer bisphosphonates, such as zoledronate, should take at least 15 minutes. For oral use, BP should be taken in the fasting state in order not to endanger their low bioavailability. The new substance for osteoprotection, denosumab, is a human monoclonal RANKL antibody that is available for subcutaneous injection.

As a rule, treatment with BP/denosumab is well tolerated. Among the most frequent side effects are acute phase reactions, nephrotoxicity and hypocalcaemia. On oral administration of BP gastrointestinal complaints can typically occur [1]. A rare but severe complication of therapy with i. v. BP and denosumab is the development of osteonecrosis of the jaw [2]. AGO recommendations for the prevention of this complication include, among others, dental treatment and good dental hygiene prior to starting the therapy and the avoidance of elective dental interventions during the therapy. The side effects mostly occur in patients with osseous metastases since not only bisphosphonates but also denosumab are administered in markedly higher doses for this indication

Table 1 Prevention of osteoporosis – Recommendations of AGO and the German Umbrella Organisation for Osteoporosis [Dachverband Osteologie (DVO)].

Intervention	AGO recommendation
Sports/physical activities	++
Avoidance of immobilisation	++
Calcium (1 000–1 500 mg/d) in case of restricted uptake with food	++
Vitamin D_3 (800–2 000 U/d)	++
Cessation of smoking, only moderate consumption of alcohol	++
Avoidance of a BMI < 20 kg/m^2	++

Table 2 Drug therapy for osteoporosis and bone metastases.

Drug	Dosage	
	indication: osteoporosis*	indication: bone metastases
Clodronate	–	1 600 mg p. o. daily 1 500 mg i. v. qw3/q4w
Pamidronate	–	90 mg i. v. qw3/q4w
Ibandronate	150 mg p. o./monthly	50 mg p. o. daily 6 mg i. v. qw3/q4w
Zoledronate	5 mg i. v./yearly	4 mg q4w → 4 mg q12w possible after 1 year
Denosumab	60 mg s. c. every 6 months	120 mg s. c. q4w
Alendronate	70 mg p. o./weekly	–
Risedronate	35 mg p. o./weekly	–

* Only those drugs are listed for which the AGO assesses their use with "++"

than for osteoporosis therapy or as prophylaxis in the adjuvant situation (**Table 2**).

Bisphosphonates and Denosumab in the Therapy for Osteoporosis

Osteoporosis is of major relevance not only for the management of elderly patients but also must be taken into consideration in the therapy for breast cancer: substances such as the aromatase inhibitors or GnRH analogues can induce osteoporosis. The current S3 guidelines on osteoporosis (www.dv-osteologie.org) call for basic diagnostic tests together with control of the bone mineral density for women undergoing therapy with aromatase inhibitors (especially those over 60 years of age).

The occurrence of possible complications can be reduced by the timely recognition of osteopenia or manifest osteoporosis with subsequent therapy. **Table 1** provides a summary of useful measures for the prevention of and therapy for osteoporosis. The recommendations for initiating drug therapy for osteoporosis are summarised in tabular form in the S3 guidelines on osteoporosis and depend not only on bone mineral density but also on co-morbidities and co-medications. The available drugs and their dosages are presented in Table 2. A major mechanism of action of BP and denosumab involves the inhibition of osteoclasts. When the osteoclasts are inhibited there is at least an initial increase in osteoblast activity. This leads to an increase in the bone mineral content and thus also an increase in bone density.

Bisphosphonates and Denosumab in the Metastatic Situation

In cases of bone metastases a distinction is made between osteolytic and osteoblastic metastases. These can lead to different complaints and complications: as a result fractures, compression of the spinal cord or pain can occur. As a consequence, treatments such as radiotherapy or surgical stabilisation in cases of a risk for fractures may be necessary. In particular, osteolytic metastases can lead to disorders of mineral metabolism with a potentially life-threatening hypercalcaemia due to excessive bone degradation. BP and denosumab act against this process by inhibition of osteoclasts.

The efficacy of various bisphosphonates in the metastatic setting has been evaluated in a Cochrane meta-analysis [3]. All bisphosphonates reduce the risk of skeletal complications (pathological fractures, bone pain) by ca. 15% (p = 0.001); the risk reduction is especially high for intravenous zoledronate (41%). This was confirmed in 2014 in the **ZICE trial** (zoledronate versus ibandronate comparative evaluation) [4]. The efficacy of denosumab has been proven in several clinical trials; two recently published meta-analyses showed that denosumab more effectively reduces the risk of skeletal complications than i. v. zoledronate [5,6]. The overall and disease-free survival rates were not different.

Up to now, life-long continuation of BP therapy in the initial dosage is recommended for all patients with bone metastases. However, the results of the **OPTIMIZE-2 trial** presented at the ASCO Congress in 2014 revealed that women who had already received monthly zoledronate infusions for several years could continue the therapy in a once every three months regime; the lengthening of the interval between the individual administrations in this randomised double blind study had no influence on the incidence of skeletal complications [7]. Particularly beneficial was the reduction of undesired side effects: in the group receiving zoledronate every 12 weeks no osteonecrosis of the jaw (vs. 1% in the control group) and fewer nephrological complications (7.9 vs. 9.6%) were observed. These new findings have already been included in the currently updated AGO recommendations (**Table 2**).

Bisphosphonates in the Adjuvant Situation

In the meantime better clinical outcomes through the adjuvant administration of bisphosphonates have been demonstrated in clinical trials [8–10] (**Table 3**). The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) presented in the course of the San Antonio Breast Cancer Symposium in 2013 a meta-analysis of 41 randomised trials which included a total of 17 751 patients. Various BPs were used in the individual trials. The meta-analysis confirmed that postmenopausal women benefit from the administration of bisphosphonates: in this group the therapy can reduce the risk of distant metastases from 21.9 to 18.4% (p = 0.0003) and the breast cancer mortality risk from 18.3 to 15.2% (p = 0.004). This effect was independent of the bisphosphonate administered. No clinical benefit was seen in the entire collective (pre-, peri- and postmenopausal women) [11].

Table 3 Clinical relevance of bisphosphonate therapy in the adjuvant situation.

Study/ clinical trial	N	Bisphosphonate	Duration of therapy	Adjuvant therapy	Follow up	Premenopausal	Postmenopausal
Powles	1 069	clodronate p. o.	2 years	CTX ± endocrine	66 months	yes (OS, bone metastasis-free survival)	
Kristensen	953	pamidronate p. o.	4 years	CTX	n. d.	no	
Diel	302	clodronate p. o.	2 years	CTX ± endocrine	103 months	yes (OS)	
Saarto	299	clodronate p. o.	3 years	CTX ± endocrine	120 months	no	
AZURE	3 360	zoledronate i. v.	5 years	CTX ± endocrine	84 months	no	yes (DFS, OS)
NSABP-B34	3 323	clodronate p. o.	3 years	CTX ± endocrine	91 months	no	yes (> 50 yrs. DFS, but not OS)
GAIN	3 023	ibandronate p. o.	2 years	dose-dense dose-intense CTX	39 months	no	no (trend > 60 years)
ABCSG-12	1 803	zoledronate i. v.	3 years	endocrine (Tam vs. AI + GnRH-Anal.)	94 months	yes (DFS: p = 0.042) OS: p = 0.064	
ZO-FAST	1 065	zoledronate i. v.	5 years	endocrine (AI)	60 months	–	yes (DFS)

CTX = chemotherapy, AI = aromatase inhibitors, OS = overall survival, DFS = disease free survival

Zoledronate in the Adjuvant Situation

The initial aim of the **ZO-FAST trial** (Zometa-Femara Adjuvant Synergy Trials) was to investigate the osteoprotective effect of zoledronate under an aromatase inhibitor therapy; the follow-up analysis revealed a better survival for patients in the zoledronate group [8]. In this phase III trial the postmenopausal patients were randomised into two groups: one group was treated up-front with zoledronic acid 4 mg i. v. every 6 months; patients in the other group received zoledronic acid only after the occurrence of a fracture or a decrease in bone mineral density. After a follow-up of 60 months the recurrence rate in the first group could be reduced by 34% (HR = 0.66; p = 0.0375). Also those patients who received zoledronic acid after a decrease in bone density or after the occurrence of a fracture had a significant advantage with regard to disease-free survival compared to the other patients who did not receive zoledronic acid (HR = 0.46; p = 0.0334). No significant difference was seen between the two groups with regard to overall survival, even when there was a trend to better overall survival in the group with the immediate administration of zoledronic acid.

In the **ABCSG 12 trial** (Austrian Breast and Colorectal Cancer Study Group Trial 12) the addition of zoledronic acid to endocrine therapy in premenopausal patients was studied. 1803 patients in stages I and II received the GnRH-analogue goserelin (3.6 mg every 28 days) and were randomised between tamoxifen 20 mg/d vs. anastrozole 1 mg/d with or without zoledronic acid (4 mg every 6 months over a period of altogether 3 years). The addition of zoledronic acid improved the efficacy of the endocrine therapy: after an average follow-up of 94.4 months the zoledronate therapy was able to reduce the recurrence risk by 3.4% and the mortality risk by 2.2% [9, 12].

In the **AZURE trial** (does Adjuvante Zoledronate redUce REcurrence in early breast cancer?) 3360 breast cancer patients with a risk of recurrence were randomised into two groups. The intervention group received zoledronic acid 4 mg i. v. in addition to the standard therapy, at first six times every 3–4 weeks, followed by eight times every 3 months and then five times every 6 months. After an average follow-up of 84 months it could be shown that the administration of the bisphosphonate had reduced the occurrence of osseous metastases. However, in the entire collective no significant differences in disease-free, overall and distant metastasis-free survival could be seen between the two groups. A subgroup analysis, however, did show that patients who were more than 5 years post-menopause markedly benefited from the administration of zoledronate: in this group the bisphosphonate therapy led to a significant improvement in disease-free survival [13].

Clodronate in the Adjuvant Situation

In the meantime four randomised trials on the impact of clodronate on clinical outcome are available. In the largest trial, **NSABP-B34**, 3323 patients were treated with 1600 mg clodronate or placebo over 3 years [14]. After a follow-up of 8.4 years no differences were seen in disease-free or overall survival. Patients older than 50 years benefited with regard to disease-free interval and bone metastasis-free survival, but no influence on overall survival could be seen in this subgroup. In the study reported by **Diel et al.** 302 patients with primary breast cancer in whom tumour cells could be detected in bone marrow at the time of diagnosis were examined [15]. The detection of disseminated tumour cells is accompanied by an increased risk for the occurrence of distant metastasis [16]. After a follow-up of 103 months a significant improvement in overall survival was seen for the patients receiving clodronate (1600 mg p. o. over 2 years): in this arm the mortality rate amounted to 20.4% as compared to a rate of 40.7% in the control arm. The significant reduction in the occurrence of osseous or visceral metastases and the significant improvement in disease-free survival, as seen in the interim evaluations at 36 and 55 months, however, could no longer be detected after the follow-up of 103 months [17]. Although **Powles et al.** in their study with oral administration of clodronate, on the other hand, could not demonstrate a significant benefit with regard to a reduction of visceral metastases, the patients on clodronate did show a better 5-year bone metastasis-free survival [18]. The study of **Saarto et al.** did not show any benefits for the adjuvant administration of clodronate [19].

Other Bisphosphonates in the Adjuvant Situation

In the course of the German **GAIN trial** (German Adjuvant Intergroup Nodal Positive Study) 2015 patients with node-positive non-metastatic disease were randomised after conclusion of che-

motherapy: one group received ibandronate 50 mg p.o. daily for two years, the other group underwent only the standard therapy. Ibandronate had no effect on disease-free or, respectively, overall survival. There was merely a non-significant trend towards better disease-free survival for the administration of ibandronate in the subgroups of younger (under 40 years) and older patients (over 60 years) [20].

Practical Conclusions

Bisphosphonates are a group of osteoprotective substances with few side effects and are so an essential component of breast cancer therapy. For all patients and especially for all those with an increased danger for tumour-therapy induced loss of bone mass, the possibilities of osteoprotection should be discussed. A survey can be found in the current AGO guidelines. Among the options are the so-called life-style factors (physical activity, cessation of smoking, alcohol abstinence), avoidance of underweight and supplementation with vitamin D/calcium. In addition there are the well-established possibilities for drug therapy with bisphosphonates and denosumab [21].

Bisphosphonates and denosumab play an undisputed role in the treatment of bone metastases. Here also the AGO recommendations provide exact details about the various substances. For women who have already been taking zoledronate and who have a stable disease, the interval between doses can be prolonged from every 4 weeks to every 12 weeks [21].

The adjuvant administration of bisphosphonates is still being discussed since the relevant available data are in part contradictory. In the interdisciplinary S3 guidelines on diagnostics of, therapy for and follow-up of breast cancer published in 2012, no position is taken on the administration of bisphosphonates in the adjuvant setting. The recommendations in the upcoming version must be awaited [22]. In the AGO recommendations on osteo-oncology and bone health published in February 2015, the adjuvant administration of bisphosphonates to improve the survival of postmenopausal women is recommended (this option is evaluated with "+"). The recommendation is supported by data from the EBCTCG meta-analysis. The optimal duration of therapy still needs to be defined. In the available trials adjuvant bisphosphonate therapy is generally carried out for 2–5 years [21].

Conflicts of Interest

None.

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