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Review

International society of geriatric oncology (SIOG) clinical practice recommendations for the use of bisphosphonates in elderly patients

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ABSTRACT

A society of geriatric oncology (SIOG) task force reviewed information from the literature (in PubMed) on bisphosphonates in elderly patients with bone metastases until December 2005. Additional pertinent data were obtained from the manufacturers.

Bisphosphonates are recommended in the elderly with bone metastases to prevent skeletal-related events. Intravenous formulations are preferred for the treatment of hypercalcaemia. It has been recognised that zoledronic acid, ibandronate and pamidronate can effectively contribute in relieving metastatic bone pain. Creatinine clearance should be monitored in every patient, and a less renally toxic agent should be used where evidence of similar efficacy is available. The assessment and optimisation of hydration status is recommended. Due to the risk from osteonecrosis of the jaw, routine oral examination and treatment of dental problems by a dental team is recommended before bisphosphonates.

Physicians should choose the most appropriate bisphosphonate. Safety precautions are particularly important in elderly patients. Further research is needed in this population.

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1. Introduction

In elderly cancer patients with bone metastases, the use of bisphosphonates to prevent skeletal-related events (SREs) warrants special consideration, due to physiologic decline and comorbidities that require the use of several concomitant

drugs. Many elderly patients have impaired renal function or renal insufficiency (creatinine clearance <60 mL/min) as a result of age-related kidney function decline and may be at particular risk from renal toxicity. Furthermore, they may have underlying renal impairment related to their disease (especially multiple myeloma).¹ Concomitant medications for

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treatment of the primary cancer, such as some chemotherapies,² also have potential nephrotoxic side effects.

Tolerability issues associated with intravenous (i.v.) bisphosphonates include infusion-site reactions, renal functions deterioration and osteonecrosis of the jaw (ONJ). Although exceptional, elderly patients are at higher risk to develop renal impairment due to reduced hydration, overuse of non-steroidal anti-inflammatory drugs (NSAIDs) for analgesic purposes, and concomitant treatment with antihypertensives, antidiabetic drugs and lipid-lowering agents.

The objective of this publication is to provide clinical practice recommendations for physicians on the indications and safe use of various bisphosphonates in elderly cancer patients with bone metastases. At the time of writing, there were no randomised studies of elderly patients available on which to base recommendations; therefore, data from the available phase III and phase II studies of commonly prescribed bisphosphonates and elderly subanalyses were considered.

2. Prevention of SREs

Table 1 outlines dosing regimens, administration times and indications for some commonly used bisphosphonates.

2.1. Intravenous bisphosphonates

2.1.1. Pamidronate

2.1.1.1. *Recommendations for use.* The infusion rate of pamidronate should never exceed 60 mg/h (1 mg/min). In patients with myeloma and pre-existing renal disease (serum creatinine <265 µmol/L or <3.0 mg/dL) ASCO guidelines recommend no specific change in dosage, infusion time, or interval,³ although it is probably advisable to increase the treatment interval.⁴

Pamidronate dose adjustment is not necessary in mild (creatinine clearance 61–90 mL/min) to moderate renal impairment (creatinine clearance 30–60 mL/min).⁵ Pamidronate should not be administered to patients with severe renal impairment (creatinine clearance <30 mL/min) unless in

cases of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk. Renal function monitoring is currently recommended prior to each dose. In patients receiving pamidronate for bone metastases, who show evidence of renal deterioration, pamidronate treatment should be withheld until renal function returns to within 10% of the baseline value.⁵ Caution is warranted when pamidronate is used with other potentially nephrotoxic drugs.

2.1.1.2. Clinical trial data

2.1.1.2.1. *Breast cancer and multiple myeloma.* Randomised studies of i.v. pamidronate have shown efficacy for the prevention of SREs in patients with metastatic bone disease due to breast cancer and multiple myeloma.^{6–8} In these studies, pamidronate was generally well-tolerated, with few renal adverse events.

Deterioration of renal function has been reported following long-term treatment with pamidronate in patients with multiple myeloma.⁵ However, a study has shown that long-term pamidronate treatment in 22 elderly patients (median age 73 years) with bone metastases was effective and well-tolerated.⁹ There were two cases (9%) of mild reversible renal insufficiency (creatinine 1.7 and 1.6 mg/dL).

2.1.2. Zoledronic acid

2.1.2.1. *Recommendations for use.* Special care should be taken to monitor renal function in the elderly.¹⁰ Pre-existing renal insufficiency¹¹ and multiple cycles of zoledronic acid and other bisphosphonates (e.g. pamidronate) are risk factors for subsequent renal deterioration with zoledronic acid.^{11–14}

Zoledronic acid dose adjustments are required for patients with mild to moderate renal impairment depending on baseline creatinine clearance: >60 mL/min = 4 mg; 50–60 mL/min = 3.5 mg; 40–49 mL/min = 3.3 mg; 30–39 mL/min = 3.0 mg.¹⁵ Zoledronic acid is not recommended in patients with severe renal impairment (<30 mL/min). Renal monitoring guidelines in the prescribing information for zoledronic acid recommend that serum creatinine be measured before each dose and suggest that treatment be withheld in patients with renal deterioration.¹⁵ Factors such as dehydration or the

Table 1 – Commonly used bisphosphonates for the treatment of metastatic bone disease

| | Clodronate (Bonfos [®] ; Ostac [®]) | Pamidronate (Aredia [®]) | Zoledronic acid (Zometa [®]) | Ibandronate (Bondronat [®]) |
|--|---|---|--|---|
| Formulation | Oral tablet or i.v. infusion (rarely used) | i.v. Infusion | i.v. Infusion | Oral tablet or i.v. infusion |
| Administration time (i.v.) | 2–4 h | >2 h | ≥15 min | 1 h |
| Dosing regimen | Oral 1600 mg/day, range 800–3200 mg/day (maximum); i.v. 900 mg every 3–4 weeks | 90 mg i.v. every 3–4 weeks | 4 mg i.v. every 3–4 weeks | 6 mg i.v. every 3–4 weeks Oral 50 mg/day |
| Indication | MBD from breast cancer; multiple myeloma; HCM | MBD from breast cancer; multiple myeloma; HCM | MBD from breast, prostate, lung or other solid tumours; multiple myeloma; HCM | MBD from breast cancer; HCM |
| MBD = metastatic bone disease; HCM = hypercalcaemia of malignancy; i.v. = intravenous. | | | | |

concomitant administration of other nephrotoxic agents should be identified and managed if possible.

2.1.2.2. Clinical trial data

2.1.2.2.1. Breast cancer, multiple myeloma, all solid tumours. The superiority of zoledronic acid compared with pamidronate has been demonstrated by a multiple-event analysis in breast cancer patients.¹⁶ The efficacy of 4 mg i.v. zoledronic acid for the prevention of SREs has been demonstrated in phase III trials of patients with breast cancer, multiple myeloma, hormone-refractory prostate cancer (HRPC) and other solid tumours.¹⁷ In patients with breast cancer, or with solid tumours, the safety of zoledronic acid was reported to be similar to pamidronate or placebo. In patients with HRPC, renal function deterioration occurred in 16/92 (17.4%) patients who received 4 mg zoledronic and in 10/78 (12.4%) patients who received placebo.¹⁵

A sub-analysis of renal function deterioration was conducted in patients aged ≤ 70 years and >70 years from the phase III study. The differences between age groups were similar for 4 mg zoledronic acid and 90 mg pamidronate (Table 2). Within the limits of the data, the elderly kidney is no more sensitive to the nephrotoxic effect of zoledronic acid than the younger kidney.¹⁸

2.1.3. Intravenous ibandronate

2.1.3.1. Recommendations for use. In a multivariate analysis, age was not found to be an independent factor of any pharmacokinetic parameters studied.¹⁹ No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is ≥ 30 mL/min. Below 30 mL/min creatinine clearance, the dose for prevention of SREs in patients with metastatic breast cancer should be reduced to 2 mg every 3–4 weeks, (1-h infusion) to maintain drug exposure levels. Approved product labelling for ibandronate in the European Union recommends monitoring renal function only according to clinical assessment of each patient at the discretion of the physician. There are no dosing restrictions for ibandronate in patients who are receiving concomitant nephrotoxic cancer therapies.

2.1.3.2. Clinical trial data

2.1.3.2.1. Breast cancer and multiple myeloma. The efficacy and safety of i.v. ibandronate for the prevention of SREs are demonstrated in a phase III, placebo-controlled study of patients with breast cancer and in an open-label 2-year extension of this trial.¹⁷ Two-year assessments of time to serum creatinine increase also demonstrated renal safety comparable to placebo.¹⁷

In a subset analysis of the pivotal phase III study of i.v. ibandronate, time to renal function deterioration was investigated in patients aged ≥ 65 years. Twenty-two percent (35/

158) of patients were ≥ 65 years in the placebo group, compared with 25% (39/154) of patients in the ibandronate 6 mg group. At 2 years, deterioration was similar between ibandronate and placebo (9% versus 6% with placebo; Fig. 1¹⁸). These data may suggest that ibandronate has renal tolerance comparable to placebo even when administered in the elderly, although this is unproven.

2.2. Oral bisphosphonates

2.2.1. Clodronate

2.2.1.1. Recommendations for use. Clinical trials have included patients over 65 years, and no adverse reactions specific to this age group have been reported. There are no special dosage recommendations in the elderly. In patients with severe renal impairment (creatinine clearance 10–30 mL/min), the daily dose should be reduced to half the usual dose, i.e. 800 mg. Clodronate is contra-indicated in patients with creatinine clearance <10 mL/min.

2.2.1.2. Clinical trial data

2.2.1.2.1. Breast cancer, multiple myeloma. Clinical trials of oral clodronate have established its efficacy in patients with breast cancer and multiple myeloma.^{19–22} Although oral clodronate has been available for many years, it may not be as effective as i.v. pamidronate.²³

A high incidence of gastrointestinal adverse events and difficulty swallowing the capsules/or large tablets commonly contributes to non-compliance with oral clodronate.^{24,25}

2.2.2. Oral ibandronate

2.2.2.1. Recommendations for use. No dose adjustment is necessary in elderly patients, or in patients with mild or moderate renal impairment where creatinine clearance is ≥ 30 mL/min. Below 30 mL/min creatinine clearance, the recommended dose is 50 mg weekly to maintain drug exposure levels. Oral bisphosphonates should not be administered with food. Ibandronate tablets should be taken after an overnight fast (at least 6 h) and at least 30 min before the first food or drink of the day.²⁶

2.2.2.2. Clinical trial data

2.2.2.2.1. Breast cancer. Oral ibandronate has been shown effective and well tolerated in two phase III trials, and in an open-label extension study, of patients with breast cancer.¹⁷ In these trials, 50 mg of oral ibandronate was well-tolerated with few gastrointestinal adverse events. No patients withdrew because of difficulties in swallowing the tablets.¹⁷

2.2.3. Approach in elderly patients

Physicians should take care to choose the most appropriate bisphosphonate with the best safety profile. Head-to-head

Table 2 – Percentage of patients who experienced renal function deterioration with 4 mg i.v. zoledronic acid and 90 mg pamidronate according to age

| Treatment | Age ≤ 70 yr (%) | Age >70 yr (%) | Difference between age groups (95% CI) |
|----------------------|----------------------|------------------|--|
| Zoledronic acid 4 mg | 9.1 | 7.5 | -1.6 (-10.1, 6.9) |
| Pamidronate 90 mg | 8.2 | 8.2 | -0.1 (-8.6, 8.4) |

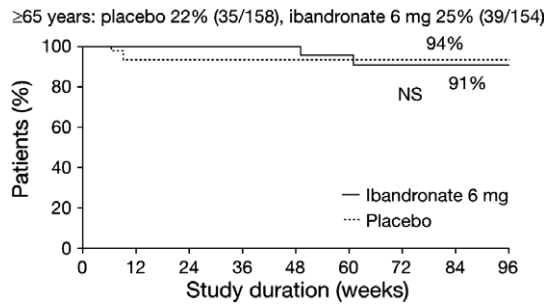


Fig. 1 – Time to renal function deterioration with i.v. ibandronate (6 mg) and placebo in the patients aged ≥ 65 years of age with metastatic breast cancer.¹⁸

trials of bisphosphonates would help to determine relative efficacy and safety profiles. Information on the cost-benefits of bisphosphonates also would aid with treatment choice.

The panel recommends that bisphosphonates should only be given to patients with life expectancy ≤ 90 days for uncontrolled pain. In terminally ill patients with hypercalcaemia, only selected cases should receive bisphosphonates, and this should be discussed first with the patients and/or their families.

3. Bisphosphonates for the palliation of metastatic bone pain

Elderly patients may experience more pain than younger people, although they may be less likely to complain of it.²⁷ The elderly suffer from different causes of pain because of polyopathy.²⁸

Bone metastases are the most common cause of cancer-related pain, especially in the advanced stage of disease. Pain caused by bone metastases is a serious clinical challenge. It has a relevant impact on the quality of life and performance status of patients, and causes disability, occurring at rest or typically during movement.

3.1. Pamidronate

3.1.1. Breast cancer, multiple myeloma, and prostate cancer

The effect of i.v. pamidronate on pain from bone metastases has been investigated in several randomised controlled trials. In patients with breast cancer or multiple myeloma, i.v. pamidronate (45 or 90 mg, every 3 or 4 weeks) was shown to significantly decrease pain and improve the quality of life.^{6,7,29} However, in a combined analysis of two placebo-controlled studies of men with prostate cancer, there were no significant or sustained differences in self-reported pain, analgesic use, or mobility between patients treated with pamidronate or placebo.³⁰

3.2. Zoledronic acid

3.2.1. Breast cancer, HRPC and other solid tumours

Decreases in pain scores from baseline were observed after 12 months in a study of zoledronic acid versus pamidronate in patients with advanced multiple myeloma and breast cancer.¹⁷ In this study, analgesic scores either remained stable

or were reduced. Pain scores were also reduced in two randomised studies of zoledronic acid versus placebo in patients with advanced breast cancer, and in patients with solid tumours (other than breast or prostate cancer) and pain at baseline.¹⁷ In a randomised, phase III study of patients with HRPC and bone metastases, patients receiving zoledronic acid reported fewer increases in pain and analgesic scores than those receiving placebo.¹⁷

The palliative effects of zoledronic acid to relieve bone pain have also been demonstrated in four non-blinded studies in patients with metastatic bone disease due to various primary malignancies.^{31–34}

3.3. Ibandronate

3.3.1. Breast cancer

In three phase III studies, 6 mg of i.v. ibandronate (infused every 3 or 4 weeks) and 50 mg of daily oral ibandronate were shown to significantly reduce pain scores below baseline for up to 2 years.¹⁷ The mean increase in analgesic use was also lower in the ibandronate group compared with placebo (not significantly different).¹⁷

In an open-label, pilot study, intensive ibandronate treatment (4 mg infused over 2 h for 4 consecutive days, 16 mg total dose) significantly reduced bone pain scores within 7 days ($P < 0.001$) in patients with opioid-resistant bone pain (from a variety of tumours; mainly breast).¹⁷ Pain reductions were sustained over the study period.

3.3.2. HRPC and urological cancer

Although ibandronate is not registered for treating bone metastases from HRPC or other urological cancers, the efficacy and safety of loading-dose ibandronate (6 mg infused over 1 h on 3 consecutive days, 18 mg total dose) has been investigated in two, open-label, non-randomised, phase II trials. There was a significant reduction in the mean visual analogue scores for metastatic bone pain from baseline on Day 3 (both were $P < 0.001$), which remained below baseline throughout the remainder of the trials.¹⁷ There were no reports of renal adverse events.

3.4. Approach in elderly patients

A multidisciplinary approach should be taken to the treatment of bone pain in elderly patients. Interventions may include any combination of the following: analgesic drugs, chemotherapy and radiotherapy, hormone therapy, radionuclide therapy, bisphosphonates, cementoplasty, kyphoplasty, surgical stabilisation and/or psychiatric care. Bisphosphonates should not be considered as an alternative to analgesics. However, ibandronate, zoledronic acid and pamidronate have been shown to be useful in the management of metastatic bone pain. Depending on the situation in patients with severe pain, who are unable to move easily, it may be better to start treatment with an oral bisphosphonate at home (e.g. ibandronate or clodronate) in association with analgesic drugs and switch to an i.v. formulation and hospital treatment once mobility has improved or if compliance with oral ibandronate becomes uncertain. However, the need to sit remaining upright for at least 30 min should also be considered in

administration route selection. Cost considerations should not generally affect the decision to administer the most appropriate therapy for each patient.

4. Bone markers as a clinical endpoint

Bone marker levels appear to correlate with the severity of bone pain, and the extent of bone metastases.^{35,36} Studies have also shown that the collagen breakdown product N-terminal cross-linked type 1 collagen telopeptide (NTX) levels can predict the occurrence of SREs in patients with bone metastases, and the response to bisphosphonate therapy.^{36–40} A 12-week, head-to-head, open-label trial of breast cancer patients with bone metastases demonstrated similar effects of oral ibandronate (50 mg/day) and i.v. zoledronic acid (4 mg infused over 15 min every 4 weeks) on biochemical markers of bone turnover.^{41,42}

ASCO guidelines state that 'currently, only radiographic evidence of bone metastases is a reliable stratifier of future risk of bone complications'.⁴³ The use of bone markers to determine the schedule of treatment is currently being tested in the UK in a large phase III trial (BISMARK).

5. Adjuvant use and use for cancer treatment-induced bone loss

Preliminary clinical data suggest that bisphosphonates may prevent cancer-treatment-induced bone loss.⁴⁴ ASCO guidelines currently recommend that the bone health of patients at risk of osteoporosis due to their age or their breast cancer treatment is regularly and routinely assessed.⁴³

Elderly patients are particularly at risk for treatment-induced bone loss and for a given bone mineral density they are more likely to sustain a fracture. Assessment of bone mineral density before and at occasional intervals during endocrine treatments is recommended with intervention with bisphosphonates if bone mineral density falls into the osteoporotic range. In case of significant bone loss, an earlier intervention can be recommended if other risk factors for osteoporotic fractures are also present.

Bisphosphonates may also be beneficial as adjuvant therapy.⁴⁴ A subanalysis of elderly patients from a study of adjuvant clodronate in women with primary operable breast cancer⁴⁴ comprised 13.7% of patients from the original study who were aged 65 years or older.¹⁸ Dyspepsia was statistically more common in patients receiving clodronate who were over 65 years. There were no significant differences in serum creatinine levels between clodronate and placebo groups, regardless of patient age.

Trials are ongoing with i.v. zoledronic acid, oral clodronate and oral ibandronate. ASCO does not currently recommend starting a bisphosphonate in women at any stage of non-osseous disease, outside of clinical trials, regardless of whether there is a high risk of bone metastases in the future.⁴³

6. Renal safety

In order to avoid renal toxicity with pamidronate or zoledronic acid, creatinine clearance should be calculated in every patient prior to each dose, even when serum creatinine is

within the normal range. In patients treated with ibandronate, renal monitoring is at the physician's discretion. Renal function deterioration with i.v. bisphosphonates may be related to the peak dose and infusion time.¹⁷ Therefore, in patients predisposed to renal insufficiency it is important to use recommended infusion times and doses. Care must be taken in selecting the most appropriate i.v. bisphosphonate. For a particular indication, physicians should preferentially choose the most effective bisphosphonate with the lowest risk of renal toxicity. All bisphosphonates have the potential to cause renal toxicity; however, there is increasing evidence that i.v. ibandronate is less toxic than other bisphosphonates.¹⁷ Further actions should be taken to reduce the risk of nephrotoxicity with i.v. bisphosphonates in the elderly; these include avoiding or limiting nephrotoxic agents during bisphosphonate therapy, wherever possible using a less renally toxic drug, and preferentially using agents that have practical recommendations for patients with renal insufficiency. It is therefore necessary to review other drugs being taken. It is also recommended that physicians should assess and optimise the hydration status of elderly patients. Patients can be hydrated by fluids administered orally, intravenously or by hypodermoclysis.⁴⁵

Oral bisphosphonates are not commonly associated with renal toxicity, so may be a viable treatment alternative in some circumstances (i.e. patients who have completed i.v. chemotherapy). Depending on the treatment indication, caution is warranted because some oral bisphosphonates are not as effective as their i.v. counterparts; however, this does not seem to be the case for ibandronate. Non-compliance with oral treatment can also be a problem, and may be a particular issue for elderly patients. Studies are needed that specifically investigate long-term safety and bisphosphonate compliance within elderly cancer patients.

7. Osteonecrosis of the jaw

ONJ may occasionally present as a serious and distressing clinical complication in cancer patients with bone metastases. ONJ is most often associated with i.v. bisphosphonates, but also described with oral therapy (in osteoporosis). A large proportion are patients with multiple myeloma or breast cancer; dental intervention has occurred in 80% of them.⁴⁶

According to the American Academy of Oral Medicine,^{47,48} dentists and physicians should work collaboratively to find the best approach to prevent and manage ONJ. As the elderly have more dental problems, they may be at particular risk from ONJ. Prior to commencing treatment with i.v. bisphosphonates, it is recommended that patients should be seen by a dentist and any oral disease should be stabilised. Patients who have been given oral bisphosphonates within the last 3 months should also have a dental evaluation.⁴⁹

A recent prospective study assessed ONJ in patients who received bisphosphonates since January 1997.⁵⁰ ONJ was observed in 17 of 252 patients. In addition, the study revealed that the length of exposure to bisphosphonates (pamidronate or zoledronic acid) appeared to be the most important risk factor for the occurrence of ONJ. There may be a greater risk with zoledronic acid than with pamidronate that ONJ will de-

velop sooner. Research is needed into the incidence of, and also how to prevent and treat ONJ in patients receiving bisphosphonates. Caution is warranted with prolonged therapy. Research is also needed to define the optimal duration of therapy and frequency of infusions.

8. Conclusion

There are limited data on the use of bisphosphonates in elderly cancer patients. While the use of bisphosphonates is recommended in these patients, care should be taken that the most appropriate bisphosphonate is used. Safety precautions are important in an elderly population, particularly with regards to renal safety and ONJ.

Research is needed on when to stop bisphosphonates; the role of bisphosphonates in patients with an expected survival of less than 3 months, and the role of bisphosphonates in patients with non-lytic metastases. Future studies should additionally investigate the efficacy and safety of bisphosphonates when integrated with other therapies (e.g. Samarium [Sm 153]-lexidronam), and to determine the value of decreasing the frequency of treatment in low-risk patients.

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