



The International Society of Geriatric Oncology Task Force on Bisphosphonates in Elderly Patients

a report by

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An International Society of Geriatric Oncology (SIOG) task force composed of Jean-Jacques Body, Rob Coleman, Philippe Clezardin, Carla Ripamonti, Rene Rizzoli and Matti Aapro from, respectively, Université Libre de Bruxelles, Institut Jules Bordet and CHU Brugmann, Brussels, Belgium; Weston Park Hospital, Sheffield, UK; INSERMU 664, Lyon, France; Rehabilitation and Palliative Care Unit, National Cancer Institute of Milan, Italy; University Hospital, Geneva, Switzerland; and Clinique de Genolier, Geneva, Switzerland has reviewed information from the literature on bisphosphonates in elderly patients with bone metastases and this work will be published in the *European Journal of Cancer* in 2007. This short manuscript highlights some of the matters discussed in the forthcoming paper.

Elderly patients are at particular risk of treatment-induced bone loss and for a given bone mineral density (BMD) are more likely to sustain a fracture. Assessment of BMD before and at occasional intervals during endocrine treatments is recommended, with intervention with bisphosphonates if BMD falls into the osteoporotic range. Doses and agents used in this setting are different from those used in cancer patient therapy.

In elderly cancer patients with bone metastases, the use of bisphosphonates to prevent skeletal-related events (SREs) warrants



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Matti Aapro received his medical degree from the Faculty of Medicine, University of Geneva, Switzerland. He was a Fellow at the Arizona Cancer Center in Tucson and was the Founding Chair of the Medical and Radiation Therapy Department at the European Institute of Oncology in Milan. He is presently Dean of the Multidisciplinary Oncology Institute, Genolier, Switzerland. Dr Aapro is the immediate Past President of the Multinational Association for Supportive Care in Cancer (MASCC). Dr Aapro serves as Executive Director of the International Society for Geriatric Oncology (SIOG) and at the Board of the European Organisation for Research and Treatment of Cancer (EORTC). Dr Aapro chairs the scientific and organising committees of UICC's WCC of 2008. Dr Aapro is Editor-in-Chief of *Critical Reviews in Oncology/Hematology* and www.cancerworld.org, as well as Associate Editor of *Annals of Oncology*.

special consideration. Elderly patients are at high risk of developing renal impairment due to reduced hydration, overuse of non-steroidal anti-inflammatory drugs (NSAIDs) for analgesic purposes and concomitant treatment with antihypertensive, antidiabetic drugs and lipid-lowering

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agents. Furthermore, older patients with pre-existing renal impairment may be at an increased risk of renal toxicity associated with intravenous (IV) bisphosphonates. Elderly patients may also confuse the dosing with concomitant oral regimens, so ensuring compliance with oral bisphosphonate therapy can be difficult.

The American Society of Clinical Oncology (ASCO) issued an update on the guidelines for the use of bisphosphonates in 2003. They state that for patients with plain radiographic evidence of bone destruction, IV bisphosphonates are recommended. However, these guidelines were published some time ago and do not mention the use of bisphosphonates such as ibandronate that are not approved in the US. Furthermore, they do not take into consideration the particular needs of elderly patients. At the time of writing there were no randomised studies of elderly patients available on which to base these recommendations; therefore, data from the available phase III studies of commonly

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prescribed bisphosphonates were considered. Where available, subanalyses of phase III studies were used as a basis for recommendations. Clinical end-points taken into account included the prevention of SREs and the treatment of metastatic bone pain.

Hypocalcaemia

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Hypercalcaemia

IV bisphosphonates quickly relieve symptoms of hypercalcaemia such as confusion and severe constipation. Calcitonin (in addition to

Bone Metastases

bisphosphonates) remains useful in patients with severe and symptomatic hypercalcaemia who require a prompt decrease in serum calcium levels. Rehydration is an important part of management, but attention to fluid balance and judicious use of diuretics is required in elderly patients.

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

Prevention of Skeletal-related Events

Randomised studies of IV pamidronate 90mg, infused every three or four weeks have shown efficacy for the prevention of SREs in patients with metastatic bone disease due to breast cancer and multiple myeloma and 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.

In a phase III randomised study of patients with breast cancer and multiple myeloma, intravenous zoledronic acid 4mg infused every three or four weeks showed comparable efficacy to IV pamidronate 90mg for the prevention of SREs. The efficacy of IV zoledronic acid 4mg for the prevention of SREs has also been demonstrated versus placebo in patients with breast cancer, hormone-refractory prostate cancer (HRPC) and other solid tumours. This drug therefore has no cancer-specific indication for its use. As decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

A multidisciplinary approach should be taken to the treatment of bone pain in elderly patients.

Ibandronate (approved in the EU and other countries, but not US Food and Drug Administration (FDA)-approved) has been evaluated in patients with breast cancer and bone metastases and no dose adjustment is necessary for elderly patients. In a multivariate analysis, age was not found to be an independent factor of any of the pharmacokinetic parameters studied. No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is $\geq 30\text{ml/min}$. Below 30ml/min creatinine clearance, the dose for prevention of SREs in patients with breast cancer and bone metastases should be reduced to 2mg every three to four weeks, infused over one hour to maintain drug exposure levels. Approved product labelling for ibandronate in the EU 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 also receiving cancer therapies with nephrotoxic side effects.

Oral bisphosphonates should not be administered with food. Clinical trials of oral clodronate have established its efficacy in patients with breast cancer and multiple myeloma. A high incidence of gastrointestinal adverse events commonly contributes to non-compliance with oral clodronate.

Oral ibandronate (approved in the EU and other countries but not FDA-approved) has been shown to be effective for the prevention of SREs in two phase III studies of patients with breast cancer. In these studies oral ibandronate 50mg was well tolerated. The incidence of mild treatment-related upper gastrointestinal adverse events was low ($\leq 7\%$), and only slightly higher in the ibandronate group than the placebo group.

Peculiarities in Elderly Patients

Physicians should take care to choose the most appropriate bisphosphonate with the best safety profile. Safety precautions are particularly important with the use of bisphosphonates in elderly

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patients. Head-to-head 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. 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 all been shown to be useful in the management of metastatic bone pain.

Safety

Many elderly patients have renal insufficiency and this issue has been discussed above. Recently, various publications have reported the occurrence of bisphosphonate-associated osteonecrosis of the jaw (ONJ). According to the American Academy of Oral Medicine (AAOM), dentists and physicians should work collaboratively to find the best approach to the prevention and management of this complication. As the elderly have more dental problems, they may be at particular risk from ONJ. Prior to commencing treatment with IV bisphosphonates, it is recommended that patients should be seen by a dentist and any oral disease should be stabilised. Caution is warranted with prolonged therapy. Research is also needed to define the optimal duration of therapy and frequency of infusions. ■