EUROPEAN JOURNAL OF CANCER 43 (2007) 852–858

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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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ARTICLE INFO

Article history:
Received 18 September 2006
Received in revised form
6 December 2006
Accepted 8 December 2006
Available online 26 January 2007

Keywords:
Bisphosphonates
Bone metastases
Bone pain
Clinical practice recommendations
Elderly
SIOG
Renal safety

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.

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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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.12.006

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 insufficiency[11] 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 (Bonefos®;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.) Dosing regimen	2–4 h Oral 1600 mg/day, range 800–3200 mg/day (maximum); i.v. 900 mg every 3–4 weeks	>2 h 90 mg i.v. every 3-4 weeks	⩾15 min 4 mg i.v. every 3–4 weeks	1 h 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.