Economic Evaluation of Clodronate and Zoledronate in Patients Diagnosed With Metastatic Bone Disease From the Perspective of Public and Third Party Payors in Brazil

Marcelo Cunio Machado Fonseca, MD, MSc[1,2]; Gabriela Tannus Branco de Araújo, MSc[1,2]; Helder Etto, MSc[2]; Alexandre Schiola, MD[3]; Natália Santoni, PharmD[3]; and Marcio Machado, PharmD, PhD[4]

[1]Federal University of São Paulo, São Paulo, Brazil; [2]Axia.Bio Consulting, São Paulo, Brazil; [3]Bayer Shering Pharma Brazil, São Paulo, Brazil; and [4]University of Toronto, Toronto, Ontario, Canada

ABSTRACT

Background: Metastatic bone disease (MBD) is responsible for >99% of malignant tumors that affect the bone. MBD patients have increased risk of skeletal complications that are often dramatic and result in loss of function or disability, leading to rapid deterioration of quality of life. Bisphosphonates have become the standard therapy for the treatment and prevention of skeletal-related events (SREs).

Objective: The objective of this study was to evaluate the cost-effectiveness of zoledronate and clodronate in the prevention of SREs in patients with MBD.

Methods: A pharmacoeconomic analysis was performed for a hypothetical cohort of patients with MBD to compare the costs and consequences of the use of clodronate and zoledronate for treatment and prevention of SREs in MBD in Brazil. The model was constructed using decision analysis techniques. Costs were described in 5 categories—drugs, physician visits, hospitalizations, surgical/medical care, and laboratory tests—and were reported in 2008 Brazilian reais (1 BRL = 0.54 US dollar). Quality-adjusted life years gained was considered as an outcome. Sensitivity analyses tested model robustness.

Results: The total cost of treatment of MBD in Brazil for a 5-year time-horizon was R$46,313 with clodronate and R$50,319 with zoledronate. The estimated number of quality-adjusted life years was 2.00 and 1.90 for clodronate and zoledronate, respectively. Cost-effectiveness ranking was unchanged when model time-horizon was changed to 1 or 10 years. Univariate analysis revealed the incidence of osteonecrosis as a sensitive parameter in the model. Multivariate analysis confirmed base-case results, in which >60% of model iterations favored clodronate over zoledronate.

Conclusion: The present pharmacoeconomic evaluation, under the premises presented, found that clodronate was dominant over zoledronate from both the public and the private health care perspectives in Brazil. (*Clin Ther*. 2011;33:1769–1780) © 2011 Elsevier HS Journals, Inc. All rights reserved.

Key words: clodronate, economic evaluation, metastatic bone disease, zoledronate.

INTRODUCTION

Metastatic bone disease (MBD) is responsible for >99% of the malignant tumors that affect the bone, and every malignant tumor can eventually metastasize to the bone.[1]

MBD originates more frequently from breast, lung, prostate, kidney, and thyroid cancers, and the prevalence is higher in those with prostate and breast carcinomas (>80% of MBD). Approximately 65% to 75% of patients with breast or prostate cancer will develop bone metastases during the course of their disease.[2] Bone metastases are more commonly located in the vertebrae, ribs, pelvis, and femur. Eventually the location of the primary tumor remains unknown, and only the presence of MBD is identified.[3]

MBD patients have increased risk of skeletal complications that are often dramatic and result in loss of function or disability, leading to rapid deterioration of quality of life. As a result, patients live with the constant possibility of developing skeletal morbidity for a long period of time, which is linked with emotional

Accepted for publication September 20, 2011.
doi:10.1016/j.clinthera.2011.09.025
0149-2918/$ - see front matter

distress.[4] Moreover, patients with MBD have an average survival ranging from <6 months to 48 months; depending on the type of tumor, nearly 5% to 40% of patients reach a 5-year survival.[2]

Clinically, bone pain is the main symptom of MBD and may be accompanied by bone-related events such as local swelling, pathologic fractures, vertebral compression, and, in some cases, hypercalcemia. The injury, however, can progress asymptomatically and become evident only when a pathologic fracture occurs or local swelling appears, which often is associated mistakenly with venous thrombosis.[4,5] The clinical staging of MBD includes laboratory tests such as complete blood count, electrolyte measurement, enzymes dosage, measurement of specific tumor markers, immunoglobulin levels, specific proteins, and hormone dosage.[6]

MDB treatment includes orthopedic follow-up, radiotherapy, and systemic treatment (ie, endocrine therapy, chemotherapy, and bisphosphonates). The main goals of local treatment are pain relief, maintenance or restoration of function, neurologic decompression, and, when possible, local control of tumor growth. The use of radiotherapy alone or in combination with surgical procedures is recommended for the last-mentioned goal, which should take into account the prognosis of the primary tumor, life expectancy, and the patient's general health status.[7,8]

Often used as an adjunct to radiotherapy, bisphosphonates have become part of the standard therapy for the treatment and prevention of skeletal-related events (SREs).[9] However, owing to increased risk of renal toxicity caused by bisphosphonates (predominantly the intravenous forms) and their association with avascular osteonecrosis of the jaw and/or maxilla, monitoring of renal function, performance of an early oral comprehensive examination before the start of treatment, good oral hygiene to prevent infections, and possible tooth extraction are recommended.[10]

Zoledronate and clodronate are 2 bisphosphonates currently approved in Brazil for the treatment and prevention of SREs in MBD; each shows different pharmacologic properties. Clodronate is administered orally in daily doses, whereas zoledronate is administered via intravenous infusions every 4 weeks. A recent meta-analysis of randomized clinical trials showed minimal differences between the 2 treatment options with regard to the reduction in the risk of SREs but suggested that zoledronate is a potentially more efficacious alternative.[11] However, evidence has shown that zoledronate is associated with the occurrence of osteonecrosis of the jaw, which may result in increased health care resource use and costs, as well as a negative impact on patients' quality of life.[12] In terms of treatment costs in Brazil, clodronate and zoledronate are equivalent. All those characteristics lead to uncertainty regarding the relative cost-effectiveness of the 2 comparators in both the public and private markets in Brazil. Thus, the aim of this study was to evaluate the cost-effectiveness of the pharmacologic alternatives zoledronate and clodronate in the prevention of SREs in patients with MBD.

METHODS

A pharmacoeconomic analysis was performed for a hypothetical cohort of patients with MBD to compare the costs and consequences of using clodronate and zoledronate for treatment and prevention of SREs in MBD patients in Brazil. The simulation model was constructed using decision analytic techniques.[13]

The study was set in the Brazilian health care system in 2008. In Brazil there are 2 analytical perspectives to consider, the public from the Ministry of Health and the private from the supplementary medicine system, as these 2 markets show different characteristics and peculiarities, especially cost weights. For both economic perspectives, direct costs presented in 2008 reais (1 BRL = 0.54 USD) were included. The clinical and humanistic consequences considered in the pharmacoeconomic model were life years (LYs) free of SREs and quality-adjusted life years (QALYs), respectively.

A Markov model was designed to represent a cohort of patients diagnosed with MBD. **Figure 1** shows the Markov model used. The pharmacoeconomic model was developed based on the clinical events of the disease in question. Consequently, we identified 4 basic health states for the mathematical model, described later: (1) No SREs: The patient has no SREs and, therefore, is in a state of symptom remission and disease control. In this health state bisphosphonate is administered along with medical follow-up. (2) SREs: The patient has at least 1 of the 3 studied SREs: pathologic fracture, radiation or orthopedic surgery, or hypercalcemia. This health state is characterized by high utilization of medical resources, including surgery, hospitalization, drugs, diagnostic tests, medical follow-up, and others. Each skeletal event was linked to a particular use of medical resources for each specific event. (3) Osteonecrosis: The patient presents an osteonecrosis that may or may not be related to the pharmacologic alternative in use. Treatment ranges from drugs to hy-