Re: Berenson J, Hirschberg R. Safety and Convenience of a 15-Minute Infusion of Zoledronic Acid

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In a recent paper, Berenson and Hirschberg [1] discuss the renal adverse effects of i.v. bisphosphonates in hypercalcemia of malignancy and metastatic bone disease. They claim that zoledronic acid (Zometa®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, http://www.pharma.us.novartis.com) has renal tolerability comparable with those of other commercially available bisphosphonates. This statement is largely unsupported, as zoledronic acid has only been compared with i.v. pamidronate (Aredia®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, http://www.pharma.us.novartis.com) in one head-to-head trial [2]. There are no renal safety data comparing zoledronic acid with other bisphosphonates indicated for metastatic bone disease, such as ibandronate (Boniva®; Hoffmann-La Roche Inc., Nutley, NJ, http://www.rocheusa.com), which has a renal safety profile comparable with that of placebo [3].

On page 325 of the paper, the low incidence of serum creatinine increase with i.v. ibandronate in a clinical trial is said to be similar to that of zoledronic acid in another study [2, 3]. This is misleading, given the indirect comparison and the different definitions of serum creatinine increase used (i.e., “clinically relevant” versus National Cancer Institute Common Toxicity Criteria grade 3). The authors themselves acknowledge that the relative safety of ibandronate and other bisphosphonates is not known (page 326).

The paper also states (on page 320) that renal adverse effects were “largely related to the bisphosphonate backbone shared by all drugs in the class.” At best, we should be cautious in drawing this conclusion, as the underlying mechanism of renal toxicity is still poorly understood. Preclinical studies have assessed the renal safety of bisphosphonates, following experimental evidence in animals that certain doses can damage the proximal convoluted tubules [4]. In the rat model, qualitative differences between bisphosphonates were seen in the type and location of PCT lesions, while intermittent minimally nephrotoxic injections of zoledronic acid (but not ibandronate) resulted in accumulated renal damage [4, 5]. The absence of toxic accumulation with ibandronate may be explained by its relatively short terminal tissue half-life of 24 days [6, 7], versus a soft-tissue half-life for zoledronic acid of 150–200 days [8]. Further studies are warranted.

On page 323 of the paper, the authors refer to collapsing focal segmental glomerulosclerosis, a renal complication of high-dose, long-term pamidronate, yet they do not mention biopsy-confirmed cases of acute toxic necrosis (and renal failure) linked to the recommended 4-mg dose of zoledronic acid [9]. A recent review by the U.S. Food and Drug Administration Adverse Event Reporting System found 72 physician-reported cases of renal failure in patients receiving zoledronic acid in clinical practice [10]. Of these, 27 needed dialysis and 18 died. The review emphasized the need to monitor renal function carefully with this bisphosphonate, as recommended prior to each dose in the product labeling. In their study, Johnson et al. [11] reported that 23% of zoledronic acid–treated patients (14/60) had renal toxicity. Four patients died due to renal complications. In five patients, serum creatinine levels remained elevated (>3 mg/dl) despite discontinuation of zoledronic acid. More recently, a retrospective analysis by

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Received August 12, 2004; accepted for publication November 29, 2004. ©AlphaMed Press 1083-7159/2005/$12.00/0

The Oncologist 2005;10:82-83 www.TheOncologist.com
Mazj and Lichtman showed that serum creatinine was increased in 12% of patients (35/293) treated with bisphosphonates during an 18-month period [12]. The majority of renal events were observed in patients who switched therapy from pamidronate to zoledronic acid (up to 16%). In all age groups, there was a higher incidence of renal events in patients treated with zoledronic acid than in those treated with pamidronate. Currently there are more publications about renal toxicity with zoledronic acid than with any other bisphosphonate [9–13].

Finally, the paper presents a case for the renal safety of zoledronic acid by 5-minute infusion despite the licensed infusion time of 15 minutes. The 5-minute infusion had to be abandoned during phase III trials due to the high risk of renal toxicity [3]. Treatment guidelines say that it is essential that physicians infuse at a rate no faster than 15 minutes every 3–4 weeks and do not attempt to shorten the infusion time, increase the dose, or reduce the dose interval [14]. Berenson and Hirschberg do not make clear the strength and importance of this advice in their paper.

REFERENCES