The Issue of Renal Safety of Zoledronic Acid from a Nephrologist’s Point of View

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Administration of bisphosphonates for cancer bone metastases, especially by the i.v. route, carries a certain, well-established risk of deterioration of renal function [1–9]. Although toxic acute tubular necrosis and collapsing focal segmental glomerulosclerosis have been implicated in the mechanism of renal toxicity [10–12], the pathogenesis is still poorly understood. In patients who have pre-existing chronic kidney disease (CKD) or other risk factors for the deterioration of renal function, for example, multiple myeloma, diabetes mellitus, hypertension, or advanced age, the administration of bisphosphonates is to be carried out with caution to avoid its deleterious effect on kidney function [13, 14].

Renal function monitoring guidelines have been introduced to reduce the incidence of this serious, potentially life-threatening, adverse event, and serum creatinine level measurement has been proposed as the primary parameter to assess renal risk and to provide guidance to avoid renal toxicity when zoledronic acid is administered [15]. However, excessive changes in glomerular filtration rate (GFR)—the most important parameter in assessing kidney function—correspond to only small changes in plasma creatinine concentration when patients have near normal to mildly/moderately impaired renal function [16, 17], making plasma creatinine a poor indicator of the corresponding GFR in the earlier stages of CKD. GFR must decline to approximately half the normal level before the serum creatinine concentration rises above the upper limit of normal [18]. Moreover, the plasma creatinine level underestimates renal impairment in those with reduced muscle mass, including women, children, the elderly, and the malnourished [19], many of whom have underlying malignant diseases. Therefore, serum creatinine level is not the optimal tool for establishing administration guidelines for patients treated with zoledronic acid (Zometa®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, http://www.pharma.us.novartis.com), which is known to cause deterioration of renal function—defined as a ≥0.5 mg/dl increase in serum creatinine concentration in patients with normal baseline levels or a ≥1.0 mg/dl elevation in serum creatinine in patients with abnormal baseline levels (≥1.4 mg/dl)—in about 10% of patients receiving this treatment for their cancer-induced bone disease during the course of their treatment [3, 15].

Creatinine clearance and GFR predicted by the Cockcroft-Gault formula or by the equation from the MDRD study [18, 20, 21] would offer a more reliable approach to indicate renal function impairment and to determine and monitor the stage of CKD during the overall course of zoledronic acid therapy.

What is extremely worrisome is the fact that among the U.S. adult population at large there are an estimated 5.7 million people with GFRs of 60–89 ml/min per 1.73 m², a second group of 7.4 million people with GFRs of 30–59 ml/min per 1.73 m², and another 300,000 people with GFRs of 15–29 ml/min per 1.73 m², many of whom have normal serum creatinine levels and are not even aware of their CKD [22]. Overall, these three groups account for 2.8%, 3.7%, and 0.13% of the U.S. adult population, respectively.
and the three groups combined comprise 13.4 million people. Many of these people develop cancer with bone metastases and become candidates for zoledronic acid treatment. According to another authoritative source, the U.S. National Kidney Foundation Practice Guidelines for Chronic Kidney Disease, the prevalence rates of kidney damage with a mild (60–89 ml/min per 1.73 m²) and moderately decreased GFR (30–59 ml/min per 1.73 m²) are 3% and 4.3%, respectively, among the U.S. adult population, representing 12.9 million people in the U.S. alone [18]. Thus, a greater risk for developing deterioration of renal function can be predicted in 7.3% of the U.S. population resulting from pre-existing CKD when long-term bisphosphonate therapy is carried out. To a certain, but probably much less significant, extent this increase in renal risk holds true for those patients falling into the group with reduced GFR who are receiving bisphosphonates for the treatment of their osteoporosis. Nevertheless, the dose applied and the way it is administered is markedly different, rendering the renal risk of bisphosphonates in osteoporosis treatment likely much less pronounced than the different, rendering the renal risk of bisphosphonates in the dose applied and the way it is administered is markedly different, rendering the renal risk of bisphosphonates in osteoporosis treatment likely much less pronounced than the risk that has already been observed in patients with cancer bone metastases on i.v. bisphosphonate treatment.

The burden of the increased risk for developing serious renal adverse events associated with zoledronic acid treatment has not yet been systematically studied in the earlier stages of CKD, neither in the 30–59 ml/min per 1.73 m² nor in the 60–89 ml/min per 1.73 m² GFR range. Therefore, we lack the knowledge about the extent of risk for a possible shift of GFR from the 60–89 range to the 30–59 range after zoledronic acid administration over 15 minutes. The administered dose of zoledronic acid in itself seems to be of importance as well. The phase III study in breast cancer and multiple myeloma patients with bone lesions [23] compared a 90-mg dose of pamidronate (Aredia®; Novartis Pharmaceuticals Corporation) administered over 2 hours with a 4-mg dose of zoledronic acid administered over no less than 15 minutes, and the assessment was based on a non-inferiority analysis. Regarding the comparability of safety aspects of the zoledronic acid and pamidronate treatment regimens in routine clinical practice, it is hard to assume that the two have identical renal safety profiles, since the GFR threshold for administering a full dose (i.e., 4 mg) of zoledronic acid is 60 ml/min per 1.73 m² while the GFR threshold is 30 ml/min per 1.73 m² for administering a full dose (i.e., 90 mg) of pamidronate.

Therefore, the behavior of kidney function during zoledronic acid treatment in the 30–59 GFR range and the possible impact of zoledronic acid on a change in GFR in this range are poorly elucidated. Prolongation of the 15-minute infusion time might offer a safer delivery of i.v. administered zoledronic acid, preventing, or at least mitigating, adverse renal outcome. This could potentially provide the opportunity for the administration of appropriately dosed and presumably more efficacious zoledronic acid therapy for patients with GFRs <60 ml/min per 1.73 m².

Studies addressing not only the dosing aspects but the duration of administration of i.v. zoledronic acid in the earlier stages of CKD in patients with bone metastases are thus warranted.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
The author indicated no potential conflicts of interest.

REFERENCES


