A hitherto unreported high incidence of zoledronic acid-induced acute phase reaction in patients with cancer treatment-induced bone loss

The major adverse effect of i.v. administration of aminobisphosphonates (N-BPs) [such as pamidronate and zoledronic acid (ZA)] is the development of an acute-phase response (APR) in about one-third of patients who receive the treatment for the first time [1]. The APR is maximal within 28–36 h of i.v. administration and disappears 2–3 days later, despite continuing treatment. This reaction is characterized by a transient pyrexia and increased circulating levels of interleukin-6 (IL-6), tumor necrosis factor (TNF) and interferon (IFN) [2–4]. The reported incidence is variable, ranging between 10% and 50% in osteoporotic, pagetic and cancer patients according to the type of N-BP administration [5], and also to the different assessment criteria used to classify the APR.

The exact molecular basis for the acute-phase effect is unclear. Some studies have suggested that N-BPs can directly activate and stimulate proliferation of T gamma/delta cells by acting as nonpeptide phosphoantigens [like isopentenyl biphosphate (IPP) or dimethylallyl diphosphate] that bind to the T-cell receptor [6, 7]. Thompson and Rogers [8] have recently demonstrated that potency of N-BPs for activating gamma/delta T cells correlates to potency of these compounds for inhibiting farnesyl-pyrophosphate (FPP) synthase. They hypothesize that internalization of N-BPs by T cells or other peripheral blood mononuclear cells (PBMCs) rapidly leads to inhibition of FPP synthase, causing intracellular accumulation of IPP metabolites upstream of FPP synthase in the mevalonate pathway. PBMCs release or present these metabolites to gamma/delta T cells for their selective activation, proliferation and differentiation to terminal effectors. As a consequence, pyrexia and increased levels of CRP and IL-6 observed *in vivo* may be the effect of the increase in TNF-α and IFN-γ released by gamma/delta T terminal effectors.

In this letter, we report the incidence and the characteristics of ZA-induced acute phase reaction episodes observed in a cohort of 25 patients with history of breast cancer and an osteoporosis (*T* score ≥ -2 standard deviation) secondary to at least 1 year of aromatase inhibitor treatment. The incidence of fever (defined as a transient increase of body temperature >37.5°C with an increase ≥1.0°C at 24 h) in our patients' cohort was 68% (17 of 25 patients). The median temperature was 38.3°C (range 37.5°C–39.4°C). The median time of onset was 12 h, ranging from 8 to 24 h. The median duration of fever was 36 h (range 24–48 h). Finally, the incidence of arthralgia was 72%, that of chills was 12%. The median duration of arthralgia was 36 h (range 14–288).

The incidence of APR observed in our cohort of patients is apparently somewhat higher than those reported in other series of cancer patients treated for the first time with an N-BP. We cannot exclude a pathogenic role of aromatase inhibitors in

affecting the incidence of APR, even if, on the basis of the available literature data, no scientific evidences support this hypothesis. We may assume that the immune system of our osteoporotic patients is more competent than that present in patients with a chronic and advanced disease and that ZA is able to induce a more strong and effective activation and stimulation of proliferation and differentiation of the gamma/delta T-cell population. The following release of acute phase cytokines will be higher and the symptoms stronger. The evaluation of the seric levels of acute phase reaction cytokines and the analysis of gamma/delta T cells in our patients is ongoing. The clinical significance of such observation is unclear, but it could be related to the good prognosis of this subset of patients.

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