IN VITRO AND EX-VIVO EFFECTS OF BISPHOSPHONATES ON OSTEOCLASTS AND OSTEOBLASTS PROLIFERATION

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Bisphosphonates (BPs) are currently the most important class of anti-resorptive drugs used to treat metabolic bone diseases, and frequently used in oncology for bone complications. Although, BPs is thought to mainly mediate the reduction of the osteoclast activity, they were found to be capable of stimulating mineralized bone nodule formation in osteoblast cells.

First of all, in this study, we examined the in vitro and ex vivo effects of BPs such as Zoledronic acid (ZOL), Risedronate (RIS) and Alendronate (ALE) at increasing concentrations in: tumoral human cell lines PC3 (prostate cancer) and MG63 (osteosarcoma); preosteoblasts murine cells MC3T3, preosteoclasts cells J774A.1 and RAW267.4 using dehydrogenases activity CCK8 assay, cell viability Crystal Violet (CV) assay, and mineralization assay.

The rank order of efficacy as anti-proliferative compounds evaluated by CV assay in PC3 cells was: ZOL (-28.41%±6.04) ≥ ALE (-24.67%±8.7) ≥ RIS (-21.31%±6,78). In MG63 cells the rank order of efficacy as anti-proliferative compounds evaluated by CV assay was: RIS (-39,31%±1,51) = ZOL (-39,03%±1,68) ≥ ALE (-35,20%±3,21).

The rank order of efficacy as anti-proliferative compounds evaluated by CV assay in J774A.1 cells was: ZOL (-53,18%±2,45) > RIS (-37,96%±3,47) ≥ ALE (-33,71%±3,72).

In RAW 264.7 cells the rank order of efficacy as anti-proliferative compounds evaluated by CV assay was: ZOL (-55,04%±2,98) ≥ RIS (-51,82%±1,50) ≥ ALE (-30,8%±2,3).

Similar effects were obtained by CCK8 assay in all cell lines by novel BPs.

Furthermore, we observed mineralization at lower concentrations with ZOL in differentiated MC3T3 cells.

Also in bone marrow cells derived from tibia and femur of wild type mice in accordance to 3R RULE (DIRECTIVE 2010/63/EU) co-cultured with PC3 we observed a mineralization with ZOL. No cytotoxicity effects were observed in the native bone marrow by novel BPs.

In our experiments ZOL was the most effective compound within the BPs under investigation showing anti-proliferative effects on osteoclasts and inducing mineralization in osteoblasts.