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Unexpected effects of biphosphonates in *in vitro* models of activated CLL cells

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Recent studies suggest that the commonly prescribed anti-osteoporosis drugs bisphosphonates (BPs) might also exhibit antitumor activity. We investigated a possible anticancer effect of BPs on B-chronic lymphocytic leukemia (CLL) cells obtained from peripheral blood of 26 CLL patients.

Zoledronate, etidronate and clodronate were administered in vitro simultaneously to following activation stimuli: i) CD40L-expressing fibroblasts, ii) soluble recombinant CD40L produced in our laboratory +IL-4, iii) CpG ODN 2006+IL-15 with or without bone marrow stromal cells (BMSC). CLL cell viability, activation/proliferation were monitored by flow cytometry.

We unexpectedly observed that BPs generated a protective effect from spontaneous apoptosis in 11/26 (42%) patients (viability + 18%-392%) and an augmentation in CLL cell activation/proliferation in 61% of the samples (S+G2M phase: +100%±25). Interestingly, protection from spontaneous apoptosis or increment of cell activation, required the presence of either fibroblasts, BMSC or autologous Nurse Like Cells (NLC).

We thus hypothesized that supportive cells are involved in the BPs effects either through cell-cell interactions with leukemic cells or T cells, or through soluble factors release in the medium. Functional experiments with transwells suggest that stromal cells, in presence of Clodronate, release soluble factors in the medium that may probably concur to the unexpected Clodronate-mediated enhancement of CLL cell activation/proliferation.

This work is in progress and several critical questions on the mechanisms are still unanswered. Nevertheless, the phenomenological data argue that caution should be taken when administering BPs against osteoporosis in elderly persons, who could have Monoclonal B Lymphocytosis or CLL.

Keywords
Bisphosphonates, pro-proliferative effect, stromal cells