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Bisphosphonic acid acts as Gamma/Delta T cell activating antigen and has direct cytotoxic activity against pancreatic carcinoma cells

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Background

T cells bearing the Gamma9/Delta2 T cell receptor (TCR) constitute two to ten percent of peripheral blood T lymphocytes. They have recently raised much interest as non-MHC restricted effector cells against a variety of tumors. Gamma/Delta T cells are known to be stimulated by phosphoantigens without the need of professional antigen presenting cells. Furthermore, it is described that incubation with phosphoantigens increases their proliferation rate rapidly.

Materials & Methods

Apoptotic and anti-proliferative effects of two bisphosphonates (pamidronate and zoledronic acid) against eight different ductal pancreatic carcinoma cell lines were measured by Annexin-V/PI stain and MTT assay. Gamma/Delta T cells were enriched from peripheral blood of healthy donors and expanded by stimulation with anti-CD3 and IL-2. Cytotoxic activity of Gamma/Delta T cells of age of 14 days was tested against these cell lines. In the next step, we pulsed tumor cells prior to the ^{51}Cr release assay with bisphosphonates.

Results

Zoledronic acid induced even at lower concentrations inhibition of proliferation. Incubation with a 3 μM solution inhibits proliferation to 11–93%. Cell lines susceptible for this treatment had a higher apoptosis rate. Gamma/Delta T cells showed cytotoxic activity against pancreatic cell lines (cell lysis of 24–37% at an effector to target ratio of 80:1). Inhibition of proliferation correlated significantly with susceptibility against Gamma/Delta T cells ($P < 0.003$). Pulsing of target cells with bisphosphonates prior to the cytotoxicity assay increased the lysis rate (41–87%).

Discussion

Zoledronic acid has even at concentrations which could be achieved by normal dosage an anti-proliferative and apoptotic effect. Cell lines which are susceptible for bisphosphonates were also susceptible for treatment with Gamma/Delta T cells. The efficacy of Gamma/Delta T cells could be further enhanced by pulsing tumor cells with bisphosphonates.

Conclusion

At least for some pancreatic carcinoma cells a bisphosphonate-based therapy maybe useful, particular in combination with adoptive transfer of Gamma/Delta T cells