Nitrogen-containing bisphosphonates (N-BPs), which prevent bone resorption, exert direct and γδT cell (GDT)-mediated antitumor effects against several tumor cell types, including glioblastoma (GBM). However, limited information is available regarding the antitumor effects of N-BPs in GBM. Specifically, the antitumor effects of minodronate (MDA), a third-generation N-BP, in GBM are yet unclear. A study aimed to investigate the antitumor effects of MDA in GBM in vitro and in vivo.

Nakazawa et al performed growth inhibition and apoptosis detection assays using the GBM cell lines U87MG and U138MG. Apoptosis inhibition assays were also conducted. In vivo xenograft assays were performed in highly immunodeficient NOD.Cg-Prkdcscid Il2rgtm1Sug/Jic mice subcutaneously implanted with U87MG and U138MG cells. Growth inhibition and apoptosis detection assays demonstrated that MDA inhibited GBM cell growth via apoptosis, which was markedly enhanced by ex vivo expanded GDT. A pan-caspase inhibitor, z-VAD-fmk, inhibited MDA-induced U138MG apoptosis and MDA/GDT-induced U87MG and U138MG apoptosis. But z-VAD-fmk increased MDA-induced U87MG apoptosis. MDA/GDT-mediated apoptosis was blocked by the anti-T cell receptor (TCR) Vγ9, mevalonate pathway inhibitor, granzyme B inhibitor, and antitumor necrosis factor (TNF)-α. In vivo xenograft assays showed that combined intraperitoneal administration of MDA/GDT induced antitumor effects on unestablished U87MG-derived subcutaneous tumors. MDA exerted direct and GDT-mediated anti-GBM apoptotic effects in a caspase-dependent manner. GDT recognized MDA-exposed GBM cells via TCRVγ9 and induced apoptosis via granzyme B and TNF-α release. Because MDA elicited anti-GBM effects in synergy with GDT in vivo, a combination of MDA and ex vivo-generated GDT could be an effective treatment in patients with GBM [1].

1)
Nakazawa T, Nakamura M, Matsuda R, Nishimura F, Park YS, Motoyama Y, Hironaka Y, Nakagawa I, Yokota H, Yamada S, Tamura K, Takeshima Y, Omoto K, Tanaka Y, Ouji Y, Yoshikawa M, Tsujimura T, Nakase H. Antitumor effects of minodronate, a third-generation nitrogen-containing bisphosphonate, in synergy with γδT cells in human glioblastoma in vitro and in vivo. J Neurooncol. 2016 Jul 8. [Epub ahead of print] PubMed PMID: 27393349.