Minodronate, a new nitrogen-containing bisphosphonate, was developed in Japan. It was the first drug to demonstrate significant prevention of vertebral fractures in Japanese patients with osteoporosis in a phase III doubleblind comparative study. As a result of positive data from clinical trials in Japan minodronate was granted a Japanese marketing approval for the treatment of osteoporosis on January 21, 2009. In vitro studies demonstrated that minodronate is one of the most potent inhibitors of bone resorption among currently available bisphosphonates. Preclinical studies demonstrated the inhibitory effect of minodronate on the decrease in the bone mineral density (BMD) in ovariectomized rats, dogs and monkeys. Daily oral minodronate was safe, well tolerated and effective in reducing vertebral fracture risk in postmenopausal women with established osteoporosis. The effects on lumbar and hip BMD and the safety profile of minodronate are comparable to those of alendronate. These data suggest that minodronate is a promising new potent bisphosphonate for the treatment of osteoporosis [1].

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 [2].

1)
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