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P99. DENOSUMAB AND CANCER CELL MIGRATION

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Denosumab, a human monoclonal antibody to receptor activator of nuclear factor-?B ligand, suppresses bone resorption and a potential treatment for bone destruction in metastatic cancer. Denosumab may have an additional effect on cancer than the previously demonstrated bone-protective effects. Explanations for the possibly longer survival with denosumab treatment in cancer patients include both indirect and direct effects on tumor cells. An indirect effect may derive from the symbiotic relationship between tumor cells and the bone marrow in which both bone destruction and tumor growth are stimulated. In this relationship, tumor cells secrete different factors that promote production of RANKL.The increased expression of RANKL in the tumor environment leads to increased formation and survival of osteoclasts and results in osteolytic lesions. Osteolysis results in the release of growth factors derived from bone.These growth factors increase the production of parathyroid hormone-related protein or directly promote tumor growth. Another hypothesis is that denosumab may improve survival by directly inhibiting RANKL on RANK-expressing tumor cells, which has been demonstrated also for breast cancer cells in vivo and for a number of other tumor cell lines like lung cancer cells in vitro. RANKL inhibition may have a direct antineoplastic effect on lung cancer cells via apoptosis activity.
Bone destruction increases local extracellular calcium concentrations, which have also been shown to promote tumor growth and the production of parathyroid hormone-related protein. Denosumab may indirectly affect skeletal tumor progression by targeting osteoclasts and disrupting this interaction between tumor cells and the bone microenvironment. RANKL inhibition has been shown to reduce bone osteolysis and skeletal tumor burden and to enhance antitumor efficacy of other therapies on skeletal tumors.
This observation may point toward potential effects of denosumab beyond the skeleton. Preclinical evidence indicates that RANKL inhibition can reduce distant metastasis, and that this effect is potentially independent of osteoclast inhibition.

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