Limit: 325 words (without title)

SRC kinase inhibition with saracatinib limits the development of osteolytic bone disease in multiple myeloma

Destructive bone lesions due to osteolytic bone disease (OBD) are a major cause of morbidity and mortality in multiple myeloma (MM) patients and the development of new therapeutic strategies is of great interest. In this study, we assessed the effect of SRC inhibition with saracatinib (AZD0530, AstraZeneca) on the development of MM and its associated OBD.

We first determined SRC family kinase expression in the multiple myeloma microenvironment and found that patient-derived MM cells express SRC at low levels and disease stage does not correlate with SRC expression levels. SRC expression was found to increase during osteoclast differentiation and decrease during osteoblast differentiation. Next, we validated an inhibitory role of saracatinib on osteoclast differentiation and function. Saracatinib inhibited the differentiation and polarization of RAW264.7 osteoclasts, reflected by a decrease of CTSK and DC-STAMP levels and a defective actin ring formation and culminating in a complete inhibition of bone matrix resorption. In addition, we found that saracatinib inhibits collagen secretion by MC3T3-E1 osteoblasts.

In vivo, saracatinib did not alter MM bone marrow plasmocytosis in both the 5TGM.1 and 5T2MM murine myeloma models. However, bone destruction was markedly reduced in both models following treatment with saracatinib. In the 5TGM.1 model multiple trabecular bone parameters were restored to levels observed in healthy control mice following saracatinib treatment, including BV/TV, Tb.N. and Tb.Th.. These results were confirmed in the 5T2MM model, which displays a more severe osteolytic bone disease. In addition, saracatinib treatment resulted in an increase in cortical thickness and a decrease in the number and size of cortical lesions in 5TGM.1 mice. These findings were corroborated by histomorphometric analyses.

In conclusion, we report a potent inhibitory preclinical effect of the SRC inhibitor saracatinib on the development of OBD in MM. Our results indicate that saracatinib exerts this effect via blocking of osteoclast function. These findings warrant further study of the feasibility and efficacy of saracatinib to treat OBD in MM patients.