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COMMENTARY

Thiocolchicoside a semi-synthetic derivative of the Glory Lily: a new weapon to fight metastatic bone resorption?

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Metastatic bone disease is a serious clinical complication for the treatment of patients with advanced cancer, but few therapeutic options are currently available. Bisphosphonates are an established standard care for these patients, but new treatments are now emerging, including the use of monoclonal antibodies targeting the RANK ligand. In this issue of the *BJP*, Reuter *et al.* provide evidence that thiocolchicoside, a semi-synthetic derivative of the naturally occurring colchicoside, extracted from the seeds of *Gloriosa superba* (Liliaceae), prevented osteoclactogenesis by suppressing RANK ligand-mediated NF-κB activation. Thiolcolchicoside may thus represent an attractive therapeutic option for the management of bone metastatic disease.

LINKED ARTICLE
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Abbreviations
MBD, metastatic bone disease; OPG, osteoprotegerin; RANK, receptor activator of NF-κB; RANKL, RANK ligand

Metastatic bone disease (MBD) often occurs in advanced stages of cancer and is associated with a poor prognosis. MBD causes one of the most distressing set of symptoms of advanced-stage cancers including bone pain, fractures, hypercalcemia, and spinal cord compression. This disease is often accompanied by non-specific symptoms such as anorexia and weight loss. MBD is mostly characterized by osteoclast-mediated bone loss, but aberrant bone deposition, which causes osteosclerotic lesions, can also occur in some types of cancer. MBD results from a dysregulation of bone homeostasis, a physiological *modus operandi* that allows maintenance of bone integrity through a finely-tuned process of formation of new and destruction of old bone.

Bone destruction, also referred to as resorption, is carried out by osteoclasts, whereas bone formation is brought about by osteoblasts. In most cases dysregulation of bone homeostasis in MBD results from a vicious cycle of bone destruction and tumour growth induced by osteoclasts. Less frequently, and depending of the type of tumour, MBD can also arise from bone deposition or osteosclerotic lesions mediated by the persistent activation of osteoblasts. In some patients, especially in breast cancer, MBD can also arise from a mixed phenotype in which both osteoclastic and osteoblastic lesions occur. The prevalence of bone metastasis in patients with advanced breast or prostate cancers can be relatively high with nearly three patients out of four developing MBD (Sturge *et al.*, 2011). Therefore, MBD represents an important challenge in the treatment of advanced cancer.

Conventional treatment of MDB is primarily palliative and based on surgery, radiation, or a limited set of medical compounds including bisphosphonates (alendronate, risedronate, and zoledronic acid), which are inorganic pyrophosphate derivatives. These drugs represent the established standard of care for patients with MBD, with some efficacy in reducing bone pain and skeletal related events in patients.

More recently, because of the growing knowledge of bone biology and to the finding that on particular member of the tumour necrosis factor (TNF)/TNF receptor (TNFR) superfamily receptor-ligand system plays a crucial role in bone homeostasis, novel targeted therapies have emerged to treat patients with MBD. This system comprises the receptor activator of NF-κB, RANK, its ligand (RANK ligand; RANKL) and a soluble decoy receptor for RANKL known as osteoprotegerin (OPG). The new therapeutic option arising from advances in our understanding of the biology of the RANK-RANKL-OPG system and its role in bone morphogenesis and plasticity led to the development of the biotherapeutic drug denosumab (Hadji, 2011), a fully human monoclonal antibody that targets RANKL. RANKL plays an essential role in osteoclast differentiation, maturation and activation. These RANKL-mediated functions are the consequence of stimulation of cells that express RANK on their surface (Anderson *et al.*, 1997; Lacey *et al.*, 1998). RANK is expressed on the surface of osteoclasts and their precursors, whereas RANKL is expressed by osteoblast precursors or other bone stromal cells, as either a membrane bound or a soluble ligand. Binding of RANKL to its receptor RANK on osteoclasts induces osteoclastogenesis through activation of the NF-κB pathway, which in turn results in up-regulation of c-Fos, a key regulator of osteoclast-macrophage lineage determination and bone remodelling (Chiou *et al.*, 2010; Dougall, 2011; Schramek *et al.*, 2011). By preventing the RANK–RANKL interaction, denosumab prevents osteoclastogenesis and hence impairs bone resorption. In the most recent Phase III clinical trials, this antibody has demonstrated greater activity than zoledronic acid in preventing or delaying skeletal related events in patients with advanced cancer, including in multiple myeloma, breast and prostate cancer (Stopeck *et al.*, 2010; Fizazi *et al.*, 2011; Henry *et al.*, 2011). However this therapeutic option is expensive and, as observed with zoledronic acid, denosumab also exhibits serious adverse effects, including necrosis of the jaw, raising real concern about its use to treat MBD (Xie *et al.*, 2011).

Alternative approaches to inhibit the RANK signalling pathway may therefore be necessary in order to limit health care expenditure and serious side-effects, such as osteonecrosis of the jaw. Naturally occurring compounds extracted from medicinal plants or their derivatives that exhibit RANKL-inhibiting activity could represent attractive and alternative approaches to treat MBD. Along these lines, 2-methoxystypandrone, extracted from *Polygonum cuspidatum*, a Chinese herb widely used to cure bone-related diseases in Asia, has been demonstrated to inhibit RANK signalling upstream of NF-κB activation leading to inhibition of osteoclastogenesis (Chiou *et al.*, 2010). In this issue of the BJP, Reuter *et al.*, 2012 provide evidence that other medicinal plant extracts can efficiently suppress osteoclastogenesis induced by RANKL and tumour cells. The authors found that thiocolchicoside, a natural derivative of colchicine and a semisynthetic derivative of the naturally occurring colchicoside extracted from the seeds of *Gloriosa superba* (Liliaceae), also known as the Glory Lily, inhibited RANKL-mediated NF-κB activation in osteoclast precursors thus preventing osteoclastogenesis. This medicinal plant has been used for a long time as a traditional medicinal herb to cure various diseases in Africa and Southeast Asia. The tuberous roots of *G. superba* are commonly used to cure snakebites, skin diseases and ulcers, or to treat inflammation. Its seeds are used for relieving rheumatic and muscle pains (Jana and Shekhawat, 2011). Thiocolchicoside is now available from pharmaceutical companies (Muscoril, Myoril or Neoflax), and is used extensively for its myorelaxant, anti-inflammatory and analgesic properties. Likewise, an early multicenter clinical trial demonstrated the safety of thiocolchicoside administration and its superiority over paracetamol in relieving patients suffering from acute low back pain (Tuzun *et al.*, 2003). More evidence for thiocolchicoside's analgesic properties came from a phase IV clinical study demonstrating that thiocolchicoside efficiently relieved patients suffering from myofascial pain syndrome (Ketenci *et al.*, 2009). Last but not least, thiocolchicoside may also exhibit anti-tumour properties in a large variety of tumour cell lines (Reuter *et al.*, 2010).

Along with these Swiss knife-like properties, the novel anti-osteoclastogenic property of thiocolchicoside (Reuter *et al.*, 2012) ought to attract some interest for future management of MBD or related bone diseases and may represent a new versatile weapon in our arsenal to fight the devastating consequences of cancer on bone homeostasis and integrity.

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