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

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

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Abbreviations; **c-Fos**: Oncogene Fos; **NF-κB**: nuclear factor kappa B; **MBD**: metastatic bone disease; **OPG**: Osteoprotegerin; **RANK**: receptor activator of NF-κB; **RANKL**: RANK ligand

Abstract :

Metastatic bone disease is a serious clinical complication for the treatment of patients with advanced cancer, yet few therapeutic options are currently available. Bisphosphonates are an established standard-of-care for these patients, but new treatments are now emerging, including the use of monoclonal antibodies targeting RANK ligand. In this issue of 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*), prevents osteoclactogenesis by suppressing RANK ligand-mediated NF-κB activation. Thiolcolchicoside may thus represent an attractive therapeutic option for the management of bone metastatic disease.

Main Text

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 nonspecific symptoms such as anorexia and weight loss. MBD is mostly characterized by osteoclastic-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, while 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. Bone metastasis prevalence 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), i.e. inorganic pyrophosphate derivatives. These drugs represent the established standard-of-care for patients with MBD, with some efficacy for reducing bone pain and skeletal related events in patients.

More recently, owing to the growing knowledge of bone biology and to the finding that a particular one of the tumour necrosis factor (TNF)/TNF receptor (TNFR) superfamily receptor-ligand systems plays a crucial role in bone homeostasis, novel targeted therapies have emerged to treat patients with MBD. This system is the one consisting of the receptor activator of nuclear factor kappa-B ligand (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 which targets RANKL. RANKL plays an essential role in osteoclastic differentiation, maturation and activation. These RANKL-mediated functions are the consequence of stimulation of cells that express RANK on its surface (Anderson *et al.*, 1997; Lacey *et al.*, 1998). RANK is expressed on the surface of osteoclasts and their precursors whilst RANKL is expressed by osteoblast

precursors or other bone stromal cells as either a membrane bound or 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 therefore prevents osteoclastogenesis and, hence, impairs bone resorption. In most recent Phase III clinical trials, this antibody has demonstrated superior activity when compared to zoledronic acid in preventing or delaying skeletal related events in patients with advanced cancer, including in multiple myeloma, breast and prostate cancer (Fizazi *et al.*, 2011; Henry *et al.*, 2011; Stopeck *et al.*, 2010). However this therapeutic option is expensive and, similar to zoledronic acid, denosumab also exhibits adverse effects, including necrosis of the jaw, raising some concerns regarding its use to treat MBD (Xie *et al.*, 2011).

Alternative approaches to inhibit the RANK signalling pathway may therefore be privileged in order to limit health care expenditure and osteonecrosis of the jaw. Naturally-occurring compounds extracted from medicinal plants or derivatives thereof 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 BJP, Reuter et al. provide evidence that other

medicinal plant extracts can efficiently suppress osteoclastogenesis induced by RANKL and tumour cells (Reuter *et al.*, 2011). The authors have identified that thiocolchicoside, a natural derivative of colchicine and a semi-synthetic derivative of the naturally occurring colchicoside extracted from the seeds of *Gloriosa superba* (Liliaceae), also known as Glory Lily, inhibits 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. *Gloriosa superba's* tuberous roots 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 *et al.*, 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 superiority as compared to paracetamol in relieving patients suffering from acute low back pains (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-tumoural 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.*, 2011) 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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