MINI-REVIEW

Medical Treatment of Breast Cancer Bone Metastasis: From Bisphosphonates to Targeted Drugs

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Abstract

   Breast cancer bone metastasis causing severe morbidity is commonly encountered in daily clinical practice. It causes pain, pathologic fractures, spinal cord and other nerve compression syndromes and life threatening hypercalcemia. Breast cancer metastasizes to bone through complicated steps in which numerous molecules play roles. Metastatic cells disrupt normal bone turnover and create a vicious cycle to which treatment efforts should be directed. Bisphosphonates have been used safely for more than two decades. As a group they delay time to first skeletal related event and reduce pain, but do not prevent development of bone metastasis in patients with no bone metastasis, and also do not prolong survival. The receptor activator for nuclear factor κB ligand inhibitor denosumab delays time to first skeletal related event and reduces the skeletal morbidity rate. Radionuclides are another treatment option for bone pain. New targeted therapies and radionuclides are still under investigation. In this review we will focus on mechanisms of bone metastasis and its medical treatment in breast cancer patients.

Keywords: Breast cancer - bone metastasis - bisphosphonates - denosumab - targeted therapy

Introduction

   The most common site of breast cancer metastasis is bone; most of the patients whom died because of breast cancer have bone metastasis in postmortem examination (Coleman et al., 1987). Although breast cancer patients with only bone metastasis have a relatively good prognosis, bone metastasis seriously impairs quality of life. Patients with bone metastasis subsequently develop complications due to bone metastasis that needs medical and surgical intervention. These bone related complications, also called skeletal related events (SRE), including pain, pathologic fractures, spinal cord and other nerve compression syndromes and life threatening hypercalcemia are sources of devastating morbidity.

   Metastasis process develops in a stepwise fashion. All steps are very complicated and not yet known exactly. However, we know that lots of molecules play crucial roles in this complicated process including epithelial cell adhesion molecules, matrix metalloproteinases (MMP), integrins, chemokines and several growth factors. More than hundred years ago Paget (Paget 1989) proposed a theory called seed-and-soil hypothesis; cancer cells metastasize to organs if microenvironment is appropriate for their survival. Bone has a huge source of growth factors, cell adhesion molecules and cytokines that makes it fertile soil for metastasized breast cancer cells to survive.

Bone Physiology

   Basically bone is made up of collagen that is mineralized with hydroxyapatite crystals and constantly undergoes remodeling. Under normal physiologic conditions bone resorption and bone formation continues in equilibrium.

   Osteoblasts are derived from multipotent mesenchymal stem cells. Growth factors including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β) and bone morphogenetic proteins (BMPs) induce mesenchymal stem cells to proliferate and differentiate to osteoblasts. Osteoblasts forms new bone and also control the osteoclast formation through expressing receptor activator for nuclear factor κ B ligand (RANKL) and producing osteoprotegerin (OPG). RANKL induces osteoclastogenesis. RANKL-RANK receptor interaction, in the presence of M-CSF, induces fusion of mononuclear precursors to form osteoclast (Boyle et al., 2003). Osteoprotegerin, a decoy receptor for RANKL, inhibits osteoclast differentiation (Simonet et al., 1997).Osteoclastic activity and extent of bone resorption is determined by balance between RANKL and OPG. Parathyroid hormone, parathyroid hormone-related peptide (PTHrP), prostaglandin E2 (PGE2) through receptor EP4, interleukin 6 (IL-6) and IL-11 also stimulate osteoclast production (Kudo et al.,

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2003; Ohshiba et al., 2003; Kayamori et al., 2010).

Metastasis of Breast Cancer Cells to Bone

Vertebrate, metaphysis of long bones and ribs are generally preferred sites for metastasis. Breast cancer cells that express specific adhesion molecules for bone matrix proteins preferentially metastasize to bone.

Bone matrix production and degradation is well balanced under normal conditions. Metastasized breast cancer cell impairs this balance. Tumor derived PTHrP is the main regulator of excess bone degradation. It triggers a vicious cycle that cause osteoclastogenesis, osteolysis and improved malign cell survival and proliferation (Guise, 1997). Stimulation of parathyroid hormone receptor 1 (PTH1) by tumor derived PTHrP activate stromal cells and osteoblasts to produce RANKL, concurrently OPG levels decline. RANKL-RANK interaction and decreased OPG levels together induces osteoclast production in consequence bone degradation increases. With bone degradation bone stored growth factors including insulin like growth factor 1 (IGF1) and TGF-β are released into bone microenvironment (Hauschka et al., 1986). This growth factors and IL-6, IL-11, PGE2, M-CSF, tumor necrosis factor alpha (TNF-α) and PDGF produced by cancer cells or released by osteolysis contribute to the continuation of vicious cycle. All medical treatment modalities are directed to break this vicious cycle.

Bone Directed Therapy

Bisphosphonates

Structure and mode of action: a bisphosphonate molecule contains two phosphorus atoms that attached to a central carbon atom (P-C-P). Bisphosphonates are analogues of inorganic pyrophosphate. They are highly resistant to hydrolysis, therefore bisphosphonates are resistant to biological degradation. Main role of bisphosphonates is to inhibit bone degradation. They divided into two classes as non-nitrogen containing and nitrogen containing (Table 1) (Russell, 2011).

Bisphosphonates selectively binds to the bone mineral. Bisphosphonate molecules are taken up by osteoclast by endocytosis (Baron et al., 2011). Non-nitrogen containing bisphosphonates metabolized to nonhydrolysable ATP analogues that cause osteoclast dysfunction and apoptosis (Frith et al., 2001). Nitrogen containing bisphosphonates inhibit mevalonate pathway that produce important molecules for the post-translational modification (prenylation) of GTP-binding signaling proteins. Main target of nitrogen containing bisphosphonates in this

Table 1. Bisphosphonates

Non-Nitrogen Containing	Nitrogen Containing
Etidronate	Pamidronate
Clodronate	Zoledronate
Tiludronate	Ibandronate
	Alendronate
	Ibandronate
	Risedronate
	Olpadronate

pathway is farnesyl pyrophosphate synthase enzyme. Defective signaling proteins and excess accumulation of metabolites as a result of blockage of this enzyme leads to osteoclast dysfunction and induce apoptosis (Russell, 2011).

Efficacy of bisphosphonates

Historically, there were studies that suggest beneficial effect of bisphosphonates in skeletal metastasis of breast cancer (van Holten-Verzantvoort et al., 1987; Elomaa et al., 1988). The first placebo controlled, randomized study that prove the efficacy of bisphosphonates in breast cancer patients with bone metastasis published in 1993 (Paterson et al., 1993). In this study clodronate significantly reduced SRE. Efficacy of clodronate also demonstrated in other two separate studies (Kristensen et al., 1999; Tubiana-Hulin et al., 2001). Time to the first SRE has been significantly delayed by clodronate therapy in these trials. Pamidronate is another nitrogen containing bisphosphonate that has been found beneficial in breast cancer patients with osteolytic bone metastasis. In two large multicenter randomized placebo controlled studies, in patients receiving cytotoxic therapy and in the other in patients receiving hormonal therapy addition of intravenous pamidronate (90mg 3-4 weeks intravenous) reduced skeletal morbidity and delayed time to first SRE (Hortobagyi et al., 1998; Theriault et al., 1999). Combined follow up results of these two studies at 24 months demonstrated that pamidronate significantly reduced skeletal morbidity rate (2.4 events *vs* 3.7 events, p<0.001) and skeletal complications (51% *vs* 64%, p<0.001). Median time to first SRE was significantly longer (12.7 months *vs* 7.0 months, p<0.001) and pain scores were significantly better in pamidronate arm. Addition of pamidronate to systemic therapy was well tolerated and effective in preventing SRE and symptomatic palliation (Lipton et al., 2000). Recommended pamidronate dose is 2h intravenous infusion of 90mg of drug every 3-4 weeks.

The effects of 4 or 8mg zoledronic acid and pamidronate 90mg in patients with breast cancer bone metastasis or multiple myeloma was compared (Rosen et al., 2001). They also reported analysis of 1130 patients with breast cancer bone metastasis (Rosen et al., 2004). After starting study zoledronic acid infusion time prolonged to 15 minute and 8mg dose reduced to 4mg because of nephrotoxicity. Proportion of patients with an SRE was similar in both treatment arms at the end of 13 months. In patients with lytic bone metastasis, 4mg zoledronic acid achieved 17% relative reduction in the proportion of patients with an SRE compared with pamidronate however this was not significant statistically (p=0.058). Although the primary end point is not reached, in this trail 4mg zoledronic acid delayed time to first SRE (310 days *vs* 174 days, p=0.013) and yielded 20% reduction in the risk of SRE (HR, 0.801; p=0.037) compared to pamidronate. This trial extended to 24 months, 412 patients with breast cancer involved in extended study (Rosen et al., 2003). In subset analysis of patients with breast cancer, the proportion of patients with at least one SRE was still similar in both groups at the end of extension phase. In multiple event analysis 4mg zoledronic acid achieved 20% additional risk reduction in

the risk of developing SRE compared to pamidronate (RR, 0.799; 95%CI, 0.657-0.972; p=0.025). Zoledronic acid (4mg 15 minute intravenous infusion) was well tolerated as pamidronate (90mg 2h intravenous infusion) and SRE risk reduced significantly.

Ibandronate is relatively new bisphosphonate that effective in treatment of bone metastasis. It can be given orally or by intravenous infusion. Efficacy of intravenous ibandronate has been shown in a placebo controlled phase III trial. Six milligrams of ibandronate every 3-4 weeks for 2 years was superior to placebo in terms of skeletal morbidity period rate, new SRE and delaying time to first new SRE, it also reduced pain scores (Body et al., 2003). Oral administration is also effective. In a pooled analysis of two randomized, placebo controlled studies, 50mg oral ibandronate daily reduced the risk of a SRE compared with placebo (HR 0.62, 95%CI:0.48, 0.79; p=0.0001). Need for radiotherapy (0.73 *vs* 0.98, p<0.001) and surgery (0.47 *vs* 0.53, p=0.037) was significantly less in ibandronate group and it was well tolerated except slight upper gastrointestinal adverse effects (Body et al., 2004). (Table 2.)

These large randomized clinical trials suggest that bisphosphonates reduce the risk of developing SRE and delays time to the first SRE in breast cancer patients with bone metastasis. In a mixed treatment metaanalysis zoledronic acid was found to be the most efficacious bisphosphonate in breast cancer patients in reducing SRE. Ibandronate was the second most efficacious bisphosphonate in this metaanalysis (Palmieri et al., 2013). In a recent phase III trial (ZICE trial), oral ibandronate was inferior to infusional zoledronic acid in reducing SRE frequency. Both drugs had similar, acceptable side effect profile (Barrett-Lee et al., 2014). However oral administration of ibandronate can be advantageous for patients who do not want parenteral drugs.

Denosumab

Denosumab is an IgG2 monoclonal antibody that binds to RANKL. Inhibition of RANKL-RANK interaction prevents osteoclast formation and survival. In a phase II study five different doses of denosumab compared. Four weekly 120mg administration of denosumab was the most effective one in suppressing the bone turnover with similar adverse events (Lipton et al., 2007). The largest clinical trial (2046 patients with breast cancer bone metastasis) that compared denosumab with zoledronic acid has been published in 2010 (Stopeck et al., 2010). Denosumab was superior to zoledronic acid in delaying time to first on-study SRE (HR, 0.82; 95%CI, 0.71 to 0.95; p<0.001 noninferiority; p=0.01 superiority) and in reducing risk of multiple SRE (p=0.001). Denosumab was also significantly reduced the skeletal morbidity rate (p=0.004). Overall survival was not different (HR, 0.95; 95%CI, 0.81-1.11; p=0.49) between groups.

Clinical use of bone modifying agents

To initiate bone modifying agent bone metastasis should be documented with plain radiographs or with other imaging methods including bone scan, CT scan or MRI. American Clinical Society of Oncology (ASCO) considers reasonable starting bone modifying agents when bone metastasis is documented with abnormal bone scan and abnormal CT or MRI, with normal plain radiograph. Initiating bone modifying agent only based on abnormal findings on bone scan without any evidence of bone metastasis on plain radiograph, CT scan or MRI outside of a clinical trial is not recommended by ASCO. Even if extraskeletal metastasis is present, ASCO does not

Table 2. Selected Important Clinical Trials

Trial	Agents	Protocol	Important Results
Paterson et al., 1993	Clodronate	1600 mg Daily oral *vs* Placebo	27 %reduction in cumulative SRE p<0.001
Kristensen et al., 1999	Clodronate	800 mg Daily oral *vs* control	Delayed time to first SRE (p=0.015)Lower occurance of fratures (p=0.023)
Tubina-Hulin et al., 2001	Clodronate	1600 daily oral *vs* Placebo	Delayed time to first SRE (p=0.05)Reduce pain intensity and analgesic need (p=0.01)
Hortobagyi et al., 1998	Pamidronate	90 mg every 3-4 weeks, iv. *vs* Placebo	Delayed time to first SRE (p<0.001) Reduced rate of SRE (p<0.001)
Theriault et al., 1999	Pamidronate	90 mg every 4 weeks, iv. *vs* Placebo	Delayed time to first SRE (p=0.049)Reduced skeletal morbidity rate SRE (p=0.008)
Lipton et al., 2000	Pamidronate	90 mg every 3-4 weeks, iv. *vs* Placebo	Delayed time to first SRE (p<0.001)Reduced skeletal morbidity rate SRE (p<0.001)
Rosen et al., 2004	Pamidronate and zoledronic acid	Zoledronic acid 4-8 mg iv. *vs* pamidronate 90 mg iv. every 3-4 weeks	20% risk reduction in the risk of developing SRE compared to pamidronate (p=0.025).
Body et al., 2003	Ibandronate	Ibandronate 2mg iv 3-4 weeks vs ibandronate 6 mg iv. 3-4 weeks vs placebo	6 mg i.v. reduced skeletal morbidity period rate (p=0.004) Delayed time to first SRE (p=0.018) 38% reduction in the number of new bone events
Body et al., 2004	Ibandronate	Ibandronate 50 mg Daily oral *vs* placebo	Reduced mean skeletal morbidity period rate (p=0.004) Reduced risk of SRE (p=0.0001)
Stopeck et al., 2010	Zoledronic acid and denosumab	Zoledronic acid 4 mg i.v. vs. placebo sc. *vs* denosumab 120 mg sc *vs* placebo iv.	Denosumab delayed time to first on study SRE (p<.001 noninferiority; p=0.01 superiority) Reduced risk of multiple SRE (p=0.001) Reduced the skeletal morbidity rate (p=0.004).

*Iv=Intravenous; Sc=Subcutaneous

recommend starting bone modifying agent in the absence of documented bone metastasis (Van Poznak et al., 2011). Because in patients with metastatic breast cancer without bone metastasis, bisphosphonates do not reduce incidence of bone metastasis in cochrane meta-analysis (RR 0.99; 95%CI 0.67-1.47; p=0.97) (Wong et al., 2012). If bone metastasis detected with PET/CT, bone scintigraphy may not be needed (Morris et al., 2010).

Optimal duration and schedule of treatment is not defined. Generally clinical trials evaluated the bone modifying agents up to two years or until unacceptable toxicity. Adhering to the recommended dose and schedule and longer treatment duration is reduces the risk of SRE (Hatoum et al., 2011). Therefore ASCO guideline recommends continuing bone modifying agent until evidence of substantial decline in patient's performance status. We know that bone modifying agents also reduce time to first and subsequent SRE (Van Poznak et al., 2011). Therefore development of a SRE is not an indication to stop bone modifying agent. Another controversial issue is switching to another bisphosphonate after SRE develops. In two phase II studies, it has been shown that patients with skeletal progression or experiencing SRE while on clodranate or pamidronate, switching to more potent bisphosphonates zoledronic acid or ibandronate, may provide pain palliation and may also reduce bone turnover markers (Clemons et al., 2006, Clemons et al., 2008). In another phase II study that evaluate switching, in patients whom urinary N-telopeptide (uNTx) levels are still elevated despite zoledronic acid treatment switching to denosumab reduced uNTx levels significantly then continuing zoledronic acid and patients in switch arm also experienced less SRE (Fizazi et al., 2009). These trials are not enough to recommend switching to another bone modifying agent in case of treatment failure. However switching to more potent agent can be reasonable. Clinicians should decide switching to alternative agent based on individual patient.

Besides delaying time to SRE, bone modifying agents also provide bone pain palliation in patients with breast cancer bone metastasis. Denosumab and zoledronic acid have similar effects in palliating pain but denosumab significantly delays pain worsening in patients who have no or mild pain (Cleeland et al., 2013). All approved bisphosphonates and denosumab are capable of decreasing bone pain caused by breast cancer bone metastasis to some degree. Different pain assessment tools and treatment protocols were used in clinical trial therefore to decide which one is better is not possible (Van Poznak et al., 2011). Current standard care for cancer pain must be applied to all patients with bone pain. Bone modifying agents recommended as an adjunctive therapy for bone pain control, not as a first-line treatment by ASCO (Van Poznak et al., 2011). Bisphosphonates and denosumab does not provide any survival advantage in patients with breast cancer bone metastasis (Wong et al., 2012).

Safety

Osteonecrosis of jaw: Incidence of osteonecrosis of jaw (ONJ) ranges 0.6%-6.2% in breast cancer patients who treated with bisphosphonate. In patients treated with denosumab, ONJ incidence is similar to zoledronic acid (2%-1.4% respectively p=0.39) (Stopeck et al., 2010). Longer duration of therapy, higher cumulative doses, treatment with more potent bisphosphonates (zoledronic acid and pamidronate), history of recent alveolar trauma and inflammatory dental disease are known risk factors for ONJ (Hoff et al., 2008; Hoff et al., 2011). Glucocorticoid treatment or antiangiogenic therapy may also contribute to ONJ development (Saad et al., 2012). Bisphosphonates accumulate in the bone and effect of denosumab on bone become reversible after several months. Therefore beneficial effect of stopping bone modifying agent is unclear in case of ONJ. ASCO recommends dental examination and receiving necessary preventive dentistry before initiation of bone directed therapy. If invasive manipulations that affect bone are indicated initiation of bone directed therapy should be delayed for 2-3 weeks. After initiation of bone modifying agent good oral hygiene should be maintained and invasive dental procedures should be avoided as much as possible (Van Poznak et al., 2011).

Nephrotoxicity

An important adverse event seen with bisphosphonates is nephrotoxicity. Renal toxicity ranges from acute kidney injury with acute renal failure to slowly progressing or nonprogressing renal insufficiency (Hirschberg, 2012). Pamidronate may cause nephrotic syndrome (Markowitz et al., 2001; Sauter et al., 2006). Bisphosphonate related nephrotoxicity is infusion time and dose depended. Zoledronic acid and pamidronate should not be given less than advised duration. Further extension of infusion time does not provide extra protection (Berenson et al., 2011). Dose adjustment should be made according to calculated creatinine clearance (CrCl). Zoledronic acid and pamidronate both are not recommended for patients with renal failure (CrCl <30ml/min). Serum creatinine should be monitored prior to every dose of pamidronate or zoledronic acid and electrolytes, calcium, magnesium and hemoglobin should also be monitored regularly. If renal function deterioration is encountered during therapy, drug should be withheld until renal function returns to within 10 percent baseline (Van Poznak et al., 2011). In ibandronate studies, intravenous and oral, renal adverse effects of treatment were similar with placebo and no one experienced renal failure (Body et al., 2003, Body et al., 2004). Denosumab is mostly cleared through the reticuloendothelial system. Although renal associated adverse effects are nearly equal between zoledronic acid and denosumab, severe renal associated adverse events (1.5% *vs* 0.2%) and renal failure (1.5% *vs* 0.2%) are more frequent with zoledronic acid (Stopeck et al., 2010). In a meta-analysis risk of renal adverse events was found significantly high with zoledronic acid in patients with breast cancer, prostate cancer and other solid tumors (RR 0.76; 95%CI, 0.59-0.98) (Sun et al., 2013). Denosumab may be given to patient with renal impairment cautiously and should be closely monitored for hypocalcemia.

Hypocalcemia and other adverse effects

Calcium homeostasis is disrupted by bone modifying

drugs through inhibition of osteoclastic activity. If any condition that affecting parathyroid hormone secretion or calcium metabolism (surgical hypoparathyroidism, hypomagnesaemic hypoparathyroidism, vitamin D deficiency and renal failure etc.) is present patients become prone to hypocalcemia (Peter et al., 2004; Chennuru et al., 2008). Hypocalcemia and hypophosphatemia are more common with denosumab (Stopeck et al., 2010; Lipton et al., 2012). If no contraindication is present, to prevent hypcalcemia calcium and vitamin D supplementation is recommended to all patients receiving bone modifying agent with breast cancer bone metastasis.

Acute phase response may occur up to three days after administration of intravenous nitrogen-containing bisphosphonate due to increased cytokine production in 15%-30% of patients (Aapro et al., 2008). Generally bisphosphonate naïve patients experience influenza-like symptoms. Severe musculoskeletal pain may occur days or years after initiating bisphosphonate. Discontinuing the causative agent may provide immediate improvement but sometimes may not improve completely (Pazianas et al., 2011). All bisphosphonate especially pamidronate may cause ocular inflammation including conjunctivitis, uveitis, scleritis, episcleritis and iritis. Oral bisphosphonates may cause gastric irritation. Anemia was encountered in nearly one third of patients treated with both zoledronic acid and denosumab (Lipton et al., 2012). Bisphosphonates are associated with increased risk of cardiac arrhythmias including atrial fibrillation and supraventricular tachycardia and stroke (Wilkinson et al., 2010). Pamidronate rarely may cause skin reaction and ototoxicity (Tanvetyanon et al., 2006). In osteoporosis trials incidence of infections complications with denosumab is increased (Anastasilakis et al., 2009). However in cancer patients treated with denosumab or zoledronic acid incidence of infectious complications were similar (Lipton et al., 2012).

Radionuclide Therapy for Breast Cancer Bone Metastasis

Radionuclides are used for palliation of bone pain secondary to mainly osteoblastic bone metastasis of solid tumors. Radionuclide therapy is indicated in patients with multifocal bone metastasis. If external beam radiation is contraindicated or patient suffers from severe pain despite adequate analgesia radionuclide therapy appears as a reasonable palliative modality. Uncontrolled systemic disease, asemptomatic bone metastasis less than three bone metastasis sites, pure osteolytic metastasis, poor bone marrow reserve and less than 60 days of life expectancy are relative contraindications of radionuclide therapy. Absolute contraindications are spinal cord compression, high risk of fracture or pathologic fracture of weight bearing bone, renal failure, pregnancy and breast feeding (Tomblyn, 2012). Strontium-89 hydrochloride (Sr-89), samarium-153 lexidronam (Sm-153) and rhenium-186 hydroxyethylidenediphosphonate (Re-186) are approved radiopharmaceuticals for radionuclide therapy. Phosphorus-32 (P-32) is not used anymore because of severe myelosuppression. After administration

radiopharmaceuticals incorporate into newly formed matrix, extent of incorporation is determined by osteoblastic activity. Therefore painful metastatic sites should be visualized on bone scintigraphy before deciding radionuclide therapy. Strontium has similar properties with calcium therefore it incorporates bone directly. Other isotopes are chelated to organic phosphates to facilitate incorporation to bone. These radiopharmaceuticals deliver local radiation by emitting beta particles. Samarium and rhenium also emit gamma radiation that enables imaging. Another important radiopharmaceutical is alpha emitter radium 223 (Ra-223). It incorporates to bone like strontium. Ra-223 treatment delays time to first symptomatic SRE, prolongs overall survival and also a safe treatment modality in castration resistant prostate carcinoma patients with only bone metastasis (Parker et al., 2013). Efficacy of Ra-223 in breast cancer bone metastasis has been shown *in vivo* and in a mouse model (Suominen et al., 2013).

Most of the studies dealing with radionuclides were carried on patients with prostate cancer (Tu et al., 2001; Oosterhof et al., 2003; Sartor et al., 2004). Patients with breast cancer were also involved in some of the studies. (Fuster et al., 2000; Baczyk et al., 2007). Mentioned all radiopharmaceuticals were found beneficial in palliating painful breast cancer bone metastasis in randomized clinical trials and in case series. In a study 92% of breast cancer bone metastasis patients with refractory to conventional analgesia responded to Sr-89 therapy (Fuster et al., 2000). Generally pain relief occurs 1-3 weeks after administration. One or two days after administration self-limited pain flare may be experienced. Re-186 provides early pain palliation and duration of myelosupression is significantly shorter than Sr-89 (Sciuto et al., 2001). Repeated administration of these radiopharmaceuticals is also safe and effective in patients who benefited from previous administration (Englaro et al., 1992; Kasalicky et al., 1998; Sartor et al., 2007). Transient myelosuppression is the most common toxicity. Generally thrombocytopenia is experienced, significant neutropenia and anemia develops less than thrombocytopenia (Tomblyn, 2012). There was a debate about combined use of bisphosphonate and radionuclides. Nowadays we know that radionuclide therapy (Sr-89, Re-186, Sm-153) combined with bisphosphonates more efficient. (Rubini et al., 2014)

Advances in Treatment of Bone Metastasi

Current medical treatment of breast cancer bone metastasis is bisphosphonates and denosumab. However lots of molecules that target vicious cycle are being investigated. A non-receptor tyrosine kinase Src plays an important role in breast cancer bone metastasis and osteoclastogenesis (Hiscox et al., 2010). Src inhibitor dasatinib that used in chronic myelogenous leukemia also inhibits osteoclastogenesis *in vitro* (Vandyke et al., 2009). Other src inhibitor saracatinib decreased bone resorption markers in a phase I study (Hannon et al., 2012). In two ongoing studies dasatinib (NCT00566618) and saracatinib (NCT00558272) are still investigated in treatment of bone metastasis. In a randomized clinical

trial cathepsin K inhibitor odanacatib suppressed bone resorption markers similar to zoledronic acid after 4 weeks of treatment and well tolerated (Hannon et al., 2012). In the future antibodies that block PTHrP, TGF-β antagonists, proteasome inhibitors and many new molecules targeting vicious cycle will be discussed in treatment of bone metastasis.

Conclusion

Longer survival of patients with breast cancer bone metastasis increases the importance of treatment. Bisphosphonates and relatively new molecule denosumab are mainstay of the treatment. Radionuclides are helpful for pain palliation. There is no molecule that will prevent bone metastasis. New targeted molecules may take place in the treatment of bone metastasis.

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