IBMS BoneKEy. 2010 May;7(5):193-196
http://www.bonekey-ibms.org/cgi/content/full/ibmske;7/5/193
doi: 10.1138/20100447

MEETING REPORTS

Bone Therapeutics: Malignancy – Meeting Report from the IBMS Davos Workshop: Bone Biology & Therapeutics

March 14-19, 2010 in Davos, Switzerland

Olivier Peyruchaud

INSERM U.664, Lyon, France

Bone is the most frequent site of metastasis formation for patients with advanced breast and prostate cancers. These metastases cause skeletal lesions, hypercalcemia due to bone destruction, intractable bone pain, and pathological fractures (1). Bisphosphonates are the current standard of care for patients with bone metastases. The rationale for the use of these powerful anti-resorptive agents was driven by our basic knowledge of the molecular mechanisms that control the progression of bone metastases (2). Osteolytic metastasis is the site of a vicious cycle wherein bone-residing tumor cells stimulate osteoclast-mediated bone resorption and bone-derived growth factors released from resorbed bone promote tumor growth.

Bisphosphonates have proven efficacy in preventing the occurrence of skeletal-related events (SREs) both in preclinical and clinical studies. Bisphosphonates have also been shown to reduce bone pain (3). Andreas Kurth (University Hospital, Department of Orthopedic Surgery, Mainz, Germany) *et al*. (abstracts 81 and 82) presented results showing that a loading dose of ibandronate was well-tolerated and efficient in reducing bone pain. The implication is a reduction in the use of opioids and an improvement in quality of life that may have a great impact on patients in supporting the aggressiveness of more direct anti-tumor therapies.

Conventional chemotherapy that is applied broadly to cancer patients also affects bone physiological regulation and frequently results in bone loss and an increased risk of fractures (4). More frequent use of bisphosphonates would prevent such adverse effects. Ulla Stumpf (University Hospital, Department of Traumatology and Hand Surgery, Düsseldorf, Germany) *et al*. (abstract 94) quantified the deleterious effect of docetaxel on bone mass and strength in rats, which was mitigated with concomitant treatment with ibandronate. Swati Biswas (Vanderbilt University, Nashville, Tennessee, USA) *et al*. (abstract 72) presented data showing that the targeting of the osteolytic vicious cycle with an anti-TGFβ therapy could prevent increased osteolytic lesions in mice bearing MDA-MB-231 tumors and treated with doxorubicin.

The use of bisphosphonates at higher dosing regimens and at higher frequencies in patients with malignant diseases than in those with osteoporosis raises safety concerns, particularly with regard to renal functions. Four clinical studies presented in the Bone Therapeutics: Malignancy poster viewing session by Raoul Bergner (Medizinische Klinik A, Klinikum der Stadt Ludwigshafen, Ludwigshafen, Germany) *et al*. (abstracts 70 and 71), Luc Frimat (Nancy University, Vandoeuvre-les-Nancy, France) *et al*. (abstract 74) and Roger von Moos (Medizinische Klinik, Onkologie und Haematologie, Chur, Switzerland) *et al*. (abstract 78) showed that in multicentric phase III trials of patients with bone metastatic breast cancer or with multiple myeloma, ibandronate (6 mg) administered by IV infusion over 15 min. was without deleterious effect on renal function.

The most serious adverse effect detected in patients treated with bisphosphonates is osteonecrosis of the jaw (ONJ). Cases of ONJ were reported in patients treated not only with bisphosphonates but also with Avastin (an anti-VEGF drug) and with denosumab (an anti-RANKL drug), according to Philippe Clézardin (University

of Lyon, Lyon, France) during the morning session of a satellite symposium sponsored by Novartis Oncology. Vaclav Vyskocil (Bone Disease Center, 2nd Clinic of Internal Medicine, Plzen, Czech Republic) *et al*. (abstract 199) reported cases of ONJ in patients who were treated with oral bisphosphonates (alendronate or clodronate) and also with teriparatide (a PTH peptide). All of these reports indicated that ONJ was not restricted to patients receiving intravenous injections of aminobisphosphonates. Therefore, the reason why affecting bone resorption and angiogenesis interferes with the healing of the buccal epithelium remains unknown. Ian Reid (University of Auckland, Auckland, New Zealand) addressed this question in his talk by showing a reduction of the adhesion of human epithelial cells (Caco-2) over time on bone slices pre-treated with bisphosphonates (abstract 90). Dr. Reid suggested that impaired attachment and survival of epithelial cells to exposed bone in the mouth might favor infections and sustain inflammatory processes. A study presented by Sven Otto (Ludwig-Maximilians-University, Munich, Germany) *et al*. (abstract 87) also referred to the specific characteristics of the mouth environment and suggested that high cumulative concentrations of bisphosphonates and local acidic milieus might play a key role in the pathogenesis of ONJ. Robert Coleman (University of Sheffield, Sheffield, UK) reported that in the phase III trial recently published in the *New England Journal of Medicine* by Gnant *et al*. (5), who analyzed whether neo-adjuvant administration of zoledronic acid would prevent the occurrence of SREs in breast cancer patients on hormonal therapies (tamoxifen and anastrozole), no cases of ONJ were reported. The message is that a careful dental examination of cancer patients is required before involving antiresorptive protocols.

Dr. Coleman also reviewed recent pre-clinical and clinical work suggesting that, in addition to their antiresorptive function, bisphosphonates might also exhibit anti-tumor activity (abstract 27). Since the first studies published by the laboratory of Dr. Clézardin (6) on breast and prostate cancers, direct effects of bisphosphonates *in vitro* have been reported in many cell types. However, until very recently the anti-tumor effect of bisphosphonates *in vivo* outside the bone environment has remained a matter of debate. Dr. Coleman emphasized that experimental animal models might use doses and schedules that are clinically relevant, and take into account exposure time and frequency of administration to address this question. Based on those criteria, recent work published by Ottewell *et al*. (7) demonstrated that sequential administration of doxorubicin followed by zoledronic acid elicited substantial antitumor effects in subcutaneous breast tumors in animals. In the AZURE trial, designed to determine whether the addition of zoledronic acid to neoadjuvant therapy improved disease outcomes, a subgroup received neoadjuvant chemotherapy. Dr. Coleman reported their recent retrospective evaluation of this group of patients comparing the pathological response in primary tumors between treated and untreated groups that suggested a possible direct anti-tumor effect of zoledronic acid in combination with chemotherapy (8). A more convincing clinically-based argument for an anti-tumor effect of bisphosphonates came recently from the previously mentioned study by Gnant *et al*. (5) and discussed by Dr. Coleman. This study demonstrated that the addition of zoledronic acid to adjuvant endocrine therapies improved disease-free survival in premenopausal patients with estrogen-responsive early breast cancer. The reason for this effect was not characterized in this study. Several phase II trials set to address this question are ongoing and the first results should be revealed at the next breast cancer meeting taking place every year in San Antonio. Aminobisphosphonates internalized into monocytes, macrophages or cancer cells are known to alter the mevalonate pathway by blocking FPP synthase (9) leading to the accumulation of isopentenyl pyrophosphate (IPP) and a toxic ATP analog (AppI). Hannu Mönkkönen (University of Eastern Finland, Kuopio, Finland) *et al*. (abstract 86) found that the release of IPP by cancer cells treated with zoledronic acid induced the expansion of a specific subset of human T-lymphocytes (V$\gamma\delta$2 T cells). As presented

orally by Ismahene Benzaid (INSERM U664, Lyon, France) *et al*. (abstract 93), *in vivo* activation of this class of T lymphocytes in animals treated with zoledronic acid induced human breast cancer cell death.

The development of highly powerful anti-osteoporotic therapies will enlarge our arsenal to fight malignant cells in bone tissue. Recent work has revealed that RANKL might contribute to the homing of cancer cells to bone, suggesting that an anti-RANKL targeted therapy would be very beneficial against bone metastases (10). Denosumab, an anti-RANKL fully humanized antibody, is highly potent in inhibiting bone loss and decreasing the risk of osteoporotic fractures (11). Matthew Smith (Massachusetts General Hospital, Boston, Massachusetts, USA) noted that denosumab also has high clinical potential in the context of prostate cancer. Based on a recently completed global study on men receiving androgen deprivation therapy for nonmetastatic prostate cancer, Dr. Smith showed that denosumab significantly increased bone mineral density at all sites and reduced the incidence of new vertebral fractures (abstract 26). Several global randomized trials are ongoing to evaluate the role of denosumab for the treatment and prevention of bone metastases in men with castration-resistant prostate cancer.

In summary, many questions are still unanswered about the mechanisms of action of bisphosphonates as anti-tumor agents, the molecular mechanisms that control the formation and the progression of bone metastases, and the mechanisms that trigger ONJ. However, over the past several years the safety of the use of bisphosphonates in patients with bone diseases has greatly improved. Recent clinical trials have also demonstrated that bisphosphonates used in a neo-adjuvant setting can prevent not only skeletal lesions but also soft tissue metastases and can affect the overall survival of breast cancer patients. Because the mechanisms responsible for that protection have not been elucidated, ongoing clinical trials will tell us more in the near future. Finally, the RANK/RANKL track has emerged as a very attractive and efficient target to treat patients with malignant diseases that affect bone. Results from ongoing clinical trials using denosumab in the context of breast and prostate cancers and in myeloma will also be released soon. Results from all of these ongoing trials will likely aid the development of more powerful, safe and versatile therapeutics for cancer patients with bone alterations.

Conflict of Interest: None reported.

Note: Abstracts from the meeting have been published as a supplement to *Bone*. 2010 Mar;46(Suppl 1):S1-S90.

References

1. Buijs JT, van der Pluijm G. Osteotropic cancers: from primary tumor to bone. *Cancer Lett*. 2009 Jan 18;273(2):177-93.

2. Clines GA, Guise TA. Molecular mechanisms and treatment of bone metastasis. *Expert Rev Mol Med*. 2008 Mar 6;10:e7.

3. Sevcik MA, Luger NM, Mach DB, Sabino MA, Peters CM, Ghilardi JR, Schwei MJ, Röhrich H, De Felipe C, Kuskowski MA, Mantyh PW. Bone cancer pain: the effects of the bisphosphonate alendronate on pain, skeletal remodeling, tumor growth and tumor necrosis. *Pain*. 2004 Sep;111(1-2):169-80.

4. Saad F, Adachi JD, Brown JP, Canning LA, Gelmon KA, Josse RG, Pritchard KI. Cancer treatment-induced bone loss in breast and prostate cancer. *J Clin Oncol*. 2008 Nov 20;26(33):5465-76.

5. Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, Pöstlberger S, Menzel C, Jakesz R, Seifert M, Hubalek M, Bjelic-Radisic V, Samonigg H, Tausch C, Eidtmann H, Steger G, Kwasny W, Dubsky P, Fridrik M, Fitzal F, Stierer M, Rücklinger E, Greil R; ABCSG-12 Trial Investigators, Marth C. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med*. 2009 Feb 12;360(7):679-91.

6. Boissier S, Magnetto S, Frappart L, Cuzin B, Ebetino FH, Delmas PD, Clezardin P. Bisphosphonates inhibit prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrices. *Cancer Res*. 1997 Sep 15;57(18):3890-4.

7. Ottewell PD, Mönkkönen H, Jones M, Lefley DV, Coleman RE, Holen I. Antitumor effects of doxorubicin followed by zoledronic acid in a mouse model of breast cancer. *J Natl Cancer Inst*. 2008 Aug 20;100(16):1167-78.

8. Coleman RE, Winter MC, Cameron D, Bell R, Dodwell D, Keane MM, Gil M, Ritchie D, Passos-Coelho JL, Wheatley D, Burkinshaw R, Marshall SJ, Thorpe H. The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: exploratory evidence for direct anti-tumour activity in breast cancer. *Br J Cancer*. 2010 Mar 16. [Epub ahead of print]

9. Rogers MJ. New insights into the molecular mechanisms of action of bisphosphonates. *Curr Pharm Des*. 2003;9(32):2643-58.

10. Jones DH, Nakashima T, Sanchez OH, Kozieradzki I, Komarova SV, Sarosi I, Morony S, Rubin E, Sarao R, Hojilla CV, Komnenovic V, Kong YY, Schreiber M, Dixon SJ, Sims SM, Khokha R, Wada T, Penninger JM. Regulation of cancer cell migration and bone metastasis by RANKL. *Nature*. 2006 Mar 30;440(7084):692-6.

11. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009 Aug 20;361(8):756-65.