Citation: IBMS BoneKEy **10**, Article number: 312 (2013) | doi:10.1038/bonekey.2013.46

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MEETING REPORT

12th International Conference on Cancer-Induced Bone Disease

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IBMS BoneKEy **10,** Article number: 312 (2013) | doi:10.1038/bonekey.2013.46; published online 3 April 2013

Meeting Report from the 12th International Conference on Cancer-Induced Bone Disease, Lyon, France, 15–17 November 2012

The 12th International Conference on Cancer-Induced Bone Disease was held in Lyon, and organized by Conference Chair, Professor Philippe Clezardin (UMR1033, INSERM, France). This conference brings together basic scientists in bone cell and cancer biology with clinical oncologists, providing a forum for discussion of the key issues in the pathophysiology and management of cancers that involve the skeleton, such as skeletal metastases, osteosarcoma and the osteolytic bone disease associated with multiple myeloma. Highlights of the meeting included a focus on micrometastasis with a spirited round-table discussion, complexities of the microenvironment, including the pre-metastatic niche, and advances in targeted therapies, with special consideration given to the understudied area of complications such as pain and cachexia.

Bone Marrow Microenvironment and Cancer Stem Cells

The meeting commenced with a session on pre-metastatic niches and cancer stem cells. Illaria Malanchi (London Research Institute, UK) demonstrated the importance of interactions between cancer stem cells and the pre-metastatic niche, with the intrinsic potential of the cancer stem cells to expand at the metastatic site dependent upon extrinsic signals from the niche.[1] Infiltrating tumour cells were found to induce stromal periostin expression in the metastatic site, which in turn was found to increase Wnt signalling within the cancer stem cells and promote metastatic colonization. The emerging critical role for cancer stem cells within disease pathogenesis identifies this discrete cell population as a potential therapeutic target. This was discussed by Christophe Ginestier (Centre de Recherche en Cancerologie de Marseille, France), who used the stem cell marker aldehyde dehydrogenase (ALDH) to isolate and characterise cancer stem cells.[2] ALDH-positive cells were both tumorigenic and metastatic to bone and lung *in vivo*, with gene expression profiling revealing a 'cancer stem cell' profile. Overexpression of the interleukin-8 receptor CXCR1 was observed in ALDH-positive cells, and subsequent blockade of CXCR1 using a small molecule inhibitor, repertaxin, was found to reduce tumour growth and metastasis in primary human xenografts. Sohail Tavazoie (Rockerfeller University, USA) highlighted the increasing evidence for the importance of microRNAs in the metastatic process.[3] Upon identification of a set of miRNAs for which expression was lost during the development of breast cancer metastasis, subsequent studies revealed distinct mechanisms for the suppressive effects of two microRNAs. miR355 was found to suppress genes, including *SOX4* and *tenascin C*, resulting in a reduction in invasion and migration, whereas miR126 was found to suppress genes, including *IGFBP2*, *MERTK* and *PITPNC1*, which led to the inhibition of metastatic endothelial recruitment, a key property of metastatic cells.

Over recent years, it has been increasingly clear that it is not just the osteoblasts and osteoclasts that interact with tumour cells and promote bone disease, but that other cells within the specialised bone microenvironment are also critical to disease progression. One cell type that remains understudied in the context of bone metastases is the osteocyte. A comprehensive overview of osteocyte biology was provided by Lynda Bonewald (University of Missouri-Kansas City, USA), including the potential for cross-talk between tumour cells and osteocytes.[4] The ability of vascular endothelial cells to convert to mesenchymal stem cells via the process of endothelial–mesenchymal transition, and the molecular mechanisms involved were detailed by Bjorn Olsen (Harvard Medical School, USA).[5] These included both paracrine and autocrine vascular endothelial growth factor (VEGF) signalling, where intracellular VEGF was shown to regulate the balance between osteoblasts and adipocytes. The haematopoietic stem cell niche, and its regulation by mesenchymal stem cells, including the contribution of stroma-derived CD146 and CXCL12, was explored by Paolo Bianco (University of Rome, Italy).[6]

Studies now provide compelling evidence for the involvement of cells of the immune system, including B cells, T cells and myeloid-derived suppressor cells, in the pathogenesis of cancer-induced bone disease. Using a murine model of melanoma bone metastases, Roberta Faccio (Washington University, USA) revealed the significance of T cells in bone metastases, whereby mice with impaired T-cell function and dysfunctional osteoclasts (PLC$\gamma 2^{-/-}$) had an increase in tumour burden despite protection from bone loss.[7] PLCγ2 was primarily expressed on myeloid-derived suppressor cells, and was suggested to regulate T-cell suppression via β-catenin. The complex role of the immune system within the myeloma bone marrow microenvironment was detailed by Massimo Massaia (University of Torino, Italy), who introduced the ability of zoledronic acid to expand dendritic cells from patients with myeloma.[8] This led to accumulation of isopentenyl pyrophosphate, activation of $\gamma\delta$T cells and myeloma cell death. Important differences were highlighted between cells isolated from peripheral blood versus bone marrow.

Bone Marrow Micrometastasis

The development of bone metastases is largely due to the development of clinically undetectable micrometastases present in secondary organs at the time of primary diagnosis. Kathy Weilbaecher (Washington University School of Medicine, USA) provided an update on disseminated tumour cells (DTCs) in breast cancer metastasis, including the evidence that adding zoledronic acid to neoadjuvant chemotherapy reduced the proportion of patients with detectable DTCs.[9] Many questions remain regarding the potential for DTCs, including whether agents that target DTCs may improve survival. In support of this, the hedgehog signalling pathway inhibitor LDE225 is now in a phase II clinical trial designed to study the effect of LDE225 on DTCs and disease-free survival in patients with breast cancer. Brigitte Rack (Munich University Hospital, Germany) reviewed the clinical relevance of circulating tumour cells (CTCs), including the SUCCESS clinical trial, where CTCs were detected in 21.5% of patients, and were found to be an independent predictor of disease-free survival.[10] Advances in our understanding of the clinical relevance, biology and technical challenges in detection were further discussed and debated in the expert round-table discussion by Kathy Weilbaecher, Klaus Pantel (University Medical Center Hamburg-Eppendorf, Germany), Kenneth Pienta (University of Michigan, USA) and Catherin Alix-Panabieres (Le Center Hospitalier Universitaire de Montpelier, France). Areas of discussion included the limitations of the CellSearch platform based solely on targeting epithelial cell adhesion molecule, concerns about the current assays ability to detect low cell number, the appealing concept of CTCs as a 'liquid biopsy', which remains unproven but results to date are encouraging, and the potential for mobilization of DTCs from the bone marrow to the circulation using AMD3100, and whether this renders them a better drug target. The overriding desire of the panel was to improve the technology to identify and target the necessary cells at a single-cell level.

Bone-targeted Therapies

Considerable attention was given to advances in therapeutics, including those currently in use and those in development. An elegant overview of the 'vicious cycle' of cancer-induced bone disease and the different approaches that can be taken to disrupt this cycle was provided by Philippe Clezardin, with the interactions between the tumour and the bone marrow microenvironment likened to an 'evolving ecosystem' by Ken Pienta.[11,12] Pienta presented a role for CCL2 and tumour-associated macrophages in prostate cancer, and revealed how targeting CCL2 had strong effects to reduce tumour burden and bone disease in murine preclinical models of prostate cancer bone metastases, leading to translation to the clinic in a phase II window trial of an anti-CCR2 antibody in patients with bone metastases. The concept of marker-driven precision therapy, including second-generation steroid synthesis inhibitors, such as abiraterone and enzalutamide, and the significance of androgen-receptor expression, was discussed by Eleni Efstathiou (MD Anderson Cancer Center, USA). Mike Rogers (Garvan Institute, Australia) summarised the multiple actions of bisphosphonates in cancer-induced bone disease, including the more recent evidence for effects on $\gamma\delta$T cells and myeloid-derived suppressor cells.[13] In addition to the novel emerging therapeutic approaches, updates were provided on the anti-resorptive drugs, such as the monoclonal antibody directed against receptor activator of nuclear factor-κb ligand (RANKL), denosumab, where Lorenz Hofbauer (Dresden University, Germany) described its use in osteoporosis and skeletal metastases, and highlighted the numerous proposed mechanisms of action of RANKL within the tumour-bone microenvironment.[14] The use of adjuvant bisphosphonates in early breast cancer was discussed by both Michael Gnant (Medical University of Viennna, Austria) and by Robert Coleman (University of Sheffield, UK), who gave the Greg Mundy Memorial Lecture.[15,16] Although bisphosphonates have long been used to treat the osteolytic bone disease associated with skeletal metastases of breast cancer, it is only recently, however, that evidence is emerging to suggest that they may also modify the course of the disease when used in the adjuvant setting. Of particular interest is the increasing evidence of the importance of the menopausal status, whereby subgroup analyses of large randomised studies demonstrate a beneficial effect of bisphosphonates in post-menopausal women on both disease-free and overall survival. Combination therapy was also discussed by Robert Coleman, with retrospective analysis from the AZURE trial, demonstrating a greater reduction in tumour size when chemotherapy was combined with zoledronic acid.

Advances in imaging technologies were presented by Max Lonneux (Chirec, Belgium), who highlighted the preclinical and clinical applications of positron-emission tomography scanning in monitoring bone metastases, including the use of multiple tracers to monitor bone disease and tumour burden.[17]

The final sessions of the meeting addressed a frequently understudied area, that of the complications associated with cancer-induced bone disease. Advances in our understanding of the molecular mechanisms that mediate muscle weakness, or cachexia, were presented by Theresa Guise (Indiana University, USA). Guise demonstrated that not only was there significant muscle dysfunction associated with the renowned MDA 231 murine model of breast cancer bone metastases, but that this could be reduced by targeting the ryanodine receptor channel.[18] Marie Fallon (University of Edinburgh, UK) summarised some of the current challenges in treating

cancer-induced bone pain, including trying to identify those patients that are likely to respond to palliative radiotherapy and the use of somatosensory testing.[19] A thought-provoking presentation on quality of life in patients with cancer-induced bone disease was given by Lesley Fallowfield (University of Sussex, UK).[20]

Summary

The multidisciplinary nature of this conference, encompassing basic and clinical research from bone biology and oncology, provided an excellent environment within which to advance our understanding of the pathophysiology, detection, prevention and treatment of cancer-induced bone disease.

Conflict of Interest

The author declares no conflict of interest.

References

1. Malanchi I, Santamaria-Martinez A, Susanto E, Peng H, Lehr H-A, Delaloye J-F *et al.* Metastasis is… when cancer stem cells fine their niches. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S1).
2. Ginestier C. Targeting breast cancer stem cells. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S3).
3. Tavazoie S. Suppression of metastasis by miRNAs. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S2).
4. Bonewald L. Could the osteocyte be playing a role in cancer metastasis. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S22).
5. Olsen B. Vascular endothelial cells as a source of stem cells for osteoblast differentiation. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S23).
6. Bianco P. The niche and bone metastasis – what are we missing? *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S24).
7. Faccio R. Immune regulation of the tumor/bone vicious cycle. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S17).
8. Massaia M. The bone marrow in multiple myeloma: a paradigm example of concurrent cancer-induced bone disease and immune dysfunction. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S18).
9. Weilbaecher K. CTC and DTC-markers of response and prognosis or new therapeutic targets? *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S6).
10. Rack B. Circulating tumour cells predict survival in early breast cancer patients. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S7).
11. Clezardin P. Future strategies of molecular targeted therapies for the treatment of bone metastases from solid tumors. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S11).
12. Pienta K. Targeting the tumour ecosystem: inhibiting CCL2 as an example of targeting chemokines to inhibit cancer-host interactions. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S12).
13. Rogers M, Shay G, Hornick M, Weilbaecher K. The paradigm of bone-seeking anti-resorptive drugs: evidence that myeloid cells other than osteoclasts are also cellular targets of bisphosphonates in vivo. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S30).
14. Hofbaeur L. Antiresorptive agents in skeletal metastasis and osteoporosis. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S31).
15. Gnant M. Bone-targeted agents impact on relapse and mortality in early breast cancer. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S32).
16. Coleman R. Bone targeted treatments in early cancer – has the seed and soil hypothesis been fulfilled? *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S36).
17. Lonneux M. PET-scan in monitoring bone metastases. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S28).
18. Guise T, Waning D, Mohammed K, Andersson D, John S, Juarez-Camacho P *et al.* Cancer-associated muscle dysfunction: role of ryanodine receptor 1 remodeling. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S37).
19. Fallon M. Cancer-induced bone pain. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S40).
20. Fallowfield L. Quality of life issues related to bone metastasis and antiresorptive compunds. *IBMS BoneKEy* 2012;**9**:193 (Abstract no. S41).