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MEETING REPORTS

Meeting Report from the 10th International Conference on Cancer-Induced Bone Disease

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Penelope D. Ottewell

Department of Oncology, University of Sheffield, Medical School, Sheffield, UK

September 2010 saw the 10th International Conference on Cancer-Induced Bone Disease hosted at the Cutlers' Hall in Sheffield, UK. This meeting, organized by the International Bone & Mineral Society, continues to facilitate collaboration and knowledge transfer between clinicians and scientists working in the fields of cancer and bone biology. This year's meeting attracted 274 delegates from 28 different countries and focused primarily on the metastatic spread of breast and prostate cancers to bone as well as multiple myeloma bone disease. For all of these disease states there have been substantial advances in the understanding of mechanisms involved in tumor cell trafficking, colonization and growth in bone; identification of new therapeutic targets; and clinical application of bone-targeted therapy.

The Vicious Cycle

The meeting opened with a tribute to Dr. Greg Mundy, who died tragically in February at 68 years of age. Dr. Mundy had been a world leader in bone research for more than 30 years. During his distinguished career he published 540 papers, reviews and book chapters and mentored more than 150 postdoctoral fellows. Six of Dr. Mundy's former colleagues spoke about some of the many contributions he made to the bone field, including his well-known hypothesis of "the vicious cycle."

The vicious cycle describes how interactions between tumor cells and osteoclasts not only result in osteoclast activation and subsequent bone destruction, but also in aggressive growth and behavior of tumor cells. In this process the production of parathyroid hormone-related peptide (PTHrP) by tumor cells initiates the production of receptor activator of nuclear factor-κB ligand (RANKL) by osteoblasts. This, in turn, activates osteoclast precursors, leading to osteolysis. Destruction of bone during the osteolytic process results in the release of bone-derived growth factors, including transforming growth factor-β (TGF-β) and insulin-like growth factor-1 (IGF-1), and raises extracellular calcium concentrations. These growth factors bind to receptors on the tumor cell surface and activate autophosphorylation and signaling through pathways that involve cytoplasmic mediators of most TGF-β signals (SMAD) and mitogen-activated protein kinase (MAPK). In addition, extracellular calcium binds to and activates calcium pumps. Signaling via these pathways promotes tumor cell proliferation and further production of PTHrP (1).

The vicious cycle is of major importance in the field of cancer-induced bone disease; it is a core hypothesis used for the majority of the research presented at this year's meeting. Much of the basic science has concentrated on investigating ways in which tumor cell-bone cell interactions impact this destructive cycle, and chemicals released during this process, such as PTHrP, are being used or are being investigated for use as markers for cancer-induced bone metastasis in patients. Furthermore, drugs designed to treat cancer-induced bone disease, such as those widely discussed at this year's meeting (zoledronic acid and

denosumab), are aimed primarily at disrupting the vicious cycle.

Premetastatic Niches and Tumor Stem Cells

The hypothesis that tumor development and progression to metastasis are driven by a sub-set of cells termed “tumor stem cells” is now being investigated by a multitude of research groups worldwide. The tumor stem cell theory describes a mechanism of tumor initiation whereby a subset of cells, either stem cells or transient amplifying cells, acquire genetic abnormalities rendering them tumorigenic. These tumor stem cells proliferate indiscriminately, and they are the only cell type capable of forming a primary tumor (2). Therefore, development of metastases requires tumor stem cells to be shed from the primary tumor into the bloodstream and for these cells to home to and lodge at the secondary metastatic site. Evidence presented by Alain Puisiex (INSERM, Lyon, France) demonstrated that cancer stem cells may be formed by reactivation of embryonic transcription factors such as TWIST. N-MYC amplification, in a neuroblastoma model, was shown to be consistently associated with overexpression of TWIST1 resulting in inhibition of p53-dependent apoptotic responses, thereby providing a mechanism by which cancer stem cells gain growth advantages at the primary site and favor early dissemination of tumor cells.

The metastatic process involves tumor cells being shed from the primary site into the blood and/or lymph vessels, survival in the circulation, homing to the metastatic site (bone), extravasation of the circulatory vessels, and survival and growth in the metastatic site (3). The cancer stem cell theory hypothesizes that metastasis-associated molecular alterations are acquired within the primary tumor and then transmitted to disseminated tumor cells (2). Data from Christoph Klein's (University of Regensburg, Germany) laboratory is challenging this theory showing that tumor cell dissemination is an early event occurring during the initial development of the primary tumor. Furthermore, disseminated tumor cells isolated from bone marrow or lymph nodes displayed disparate changes in their genome at all levels, including point mutations, allelic losses and genome-wide chromosomal re-arrangements, compared with the primary tumor. These data indicate not only that specific genetic alterations are required for tumor cells to undergo the different stages of metastasis but also that these genetic alterations are independent of the primary tumor and are acquired ectopically by tumor cells during the metastatic process.

In addition to investigations focused on the genetic alterations involved in metastatic tumor growth in bone, research also focused on novel research technologies for investigating interactions between bone-homing cancer cells and the hematopoietic stem cell niche (4). It is currently hypothesized that development of metastatic tumor growth in bone requires cancer cells to home to the bone microenvironment where cancer stem cells lodge within the hematopoietic stem cell niche, “hijacking” this niche from hematopoietic stem cells. Using a SCID mouse model transplanted with human skeletal progenitors, Paolo Bianco (Sapienza Universita' di Roma, Italy) has created a human hematopoietic microenvironment *in vivo*. Co-transplantation of human cancer cells with human skeletal progenitors leads to the establishment of perivascular, human tumor stroma *in vivo*. This model is now being used for ongoing investigations into the effects of genetic alterations in both skeletal progenitor cells and cancer cells on bone homing and metastatic tumor development. Complementary to this research area, Matthias Lutolf (EPF Lausanne, Switzerland) showed data from studies using novel bioengineering strategies to biochemically and structurally deconstruct *in vivo* adult stem cell niches and to reconstruct them *in vitro.* These artificial stem cell niches are being manipulated to identify relevant niche proteins and molecular pathways that regulate stem cell quiescence, self-renewal and differentiation. From a different perspective, Peter Andrews (University of Sheffield, UK) is utilizing human embryonic stem cells in culture to investigate the

mechanisms that control self-renewal commitment to differentiation and lineage selection to distinguish between normal stem cell fate and mechanisms that play a role in cancer progression. Although many of these research strategies are still in their infancy, tumor stem cells and niche cells clearly have important roles to play in the development and progression of cancer. The field looks forward to seeing some of the results from these new technologies at future meetings.

Novel Therapies for Cancer-Induced Bone Disease: Preclinical Approaches

As described in "the vicious cycle," the tumor-bone microenvironment is abundant in factors that cause cancer cells to thrive. Data shown at this meeting reflected the wide range of therapies that are being developed to target both tumorigenetic and bone remodeling factors including TGF-β, TRAIL, RANKL, members of the Wnt family and small molecule integrins.

Theresa Guise (Indiana University, Indianapolis, USA) demonstrated the importance of experimental design for generating relevant pre-clinical data. Dr. Guise used *in vivo* mouse models to show the effects of combining inhibition of osteoclast activity via TGF-β blockade and targeting metastasis-induced hypoxia signaling through HIF-1α on breast and prostate cancer-induced bone disease. This therapeutic combination was highly beneficial in the treatment of osteoclastic MDA-MB-231 breast cancer cells growing in bone. However, TGF-β blockade increased the growth of osteoblastic LuCAP23.1 prostate xenografts. Interestingly, selecting molecules that target osteoblasts, such as endothelin-1 which suppresses production of the Wnt pathway inhibitor DKK1 to de-regulate new bone formation, is an effective treatment against osteoblastic disease in mouse models. Approaching this issue from a multiple myeloma perspective, David Roodman (University of Pittsburgh, USA) showed data published by Yaccoby *et al*. demonstrating anti-tumor activity and increased bone formation following treatment with an anti-DKK1 antibody (5) and by Edwards *et al*. who showed similar effects in a 5TGM1 model of myeloma following enhancement of Wnt signaling with LiCl (6). Dr. Roodman highlighted how data from these studies has led to further interest in the use of new anabolic approaches for treating myeloma and described new clinical trials currently under investigation. Drugs being tested in patients include an anti-DKK1 human monoclonal antibody, an activin A receptor antagonist, and bortezomib (a proteasome antagonist). These studies came about as a direct result of promising data from pre-clinical studies, emphasizing the important relationship between basic scientists and clinicians that meetings like the 10th International Conference on Cancer-Induced Bone Disease promote.

Bone-Targeted Therapy: A Clinical Perspective

Bisphosphonates have long been used to target cancer-induced bone disease associated with many tumor types including breast cancer, prostate cancer, osteosarcoma and multiple myeloma (7). The nitrogen-containing bisphosphonate zoledronic acid is the most potent one at inhibiting bone resorption and was therefore discussed in the most detail at this year's meeting. Zoledronic acid inhibits bone turnover via inhibition of the mevalonate pathway, resulting in intercellular accumulation of small GTPases and ultimately apoptosis of bone-resorbing osteoclasts (8). The mevalonate pathway is ubiquitous to all cell types, and inhibition of bone resorption breaks the "vicious cycle," thus providing potential mechanisms for both direct and indirect anti-tumor effects of zoledronic acid. This year's meeting featured much debate into the potential use of zoledronic acid as an adjuvant therapy for breast cancer. Rowan Chlebowski (UCLA, USA) gave an overview of recent clinical trials, highlighting data published in 2010 by Mauri *et al*. from 6 adjuvant breast cancer trials in which patients treated with zoledronic acid had lower risk of breast cancer recurrence (9). In addition, work published by Michael Gnant in 2009 demonstrated significant decreases in

disease progression and fewer local regional recurrences and contralateral breast cancers in patients receiving zoledronic acid (10). Dr. Chlebowski further emphasized the potential anti-tumor effects of zoledronic acid by providing evidence from his own trials in which he compared healthy female volunteers with patients given zoledronic acid for treatment of osteoporosis. These trials revealed that women receiving the bisphosphonate had a decreased incidence of breast cancer development, however, as bone loss is associated with lower breast cancer incidence, further investigation of this issue is necessary. Dr. Gnant (University of Vienna, Austria) provided an update regarding the ABCSG-12 trial that compares adjuvant endocrine therapy alone to combination therapy with zoledronic acid. Patients enrolled in this study are now in their 62nd month of follow-up, strengthening the findings that addition of zoledronic acid to either tamoxifen or anastrozole improves disease outcomes in pre-menopausal patients with node-negative and node-positive early breast cancer. Further positive results for anti-tumor effects of zoledronic acid were reported by Jean-Jacques Body (Université Libre de Bruxelles, Belgium) and Gareth Morgan (Royal Marsden Hospital, London, UK) showing survival benefits for patients with bone metastasis from a variety of solid tumors and multiple myeloma, respectively.

Tumor cell-mediated osteolysis is regulated through elevated RANKL within the bone (1). Development of a fully human monoclonal antibody that specifically binds RANKL (denosumab) has initiated considerable interest as to its effects on bone turnover, tumor development and metastases. Clinical trials comparing the efficacy of denosumab with zoledronic acid were presented by Janet Brown (University of Leeds, UK) and Allan Lipton (Penn State University, Hershey, USA). These studies demonstrated advantages of denosumab over zoledronic acid in castration-resistant prostate cancer, breast cancer and other patients with advanced cancers (not including breast or prostate) and multiple myeloma. Denosumab was shown to be better than zoledronic acid at delaying or preventing skeletal-related events in a broad cancer population, however, no effect was observed for overall survival.

Despite the benefits of bisphosphonates and denosumab in treating metastatic bone disease, use of these agents may cause exposed and necrotic bone that is isolated in the jaw. Osteonecrosis of the jaw (ONJ) is a complication that usually presents following dentoalveolar surgery but can occur spontaneously (11). Little is understood about the mechanisms underlying ONJ, however, bisphosphonates and denosumab both inhibit osteoclasts, via different mechanisms. Therefore it is likely that osteoclast inhibition may be a primary event in the pathogenesis of ONJ due to altered bone remodeling or wound healing following dental surgery. Salvatore Ruggerio (SUNY at Stony Brook, USA) gave an overview of the associated risks of prescribing long-term bisphosphonate therapy to patients with osteopenia/osteoporosis and cancer and emphasized the need for the implementation of prevention strategies and establishing an early diagnosis to reduce patient morbidity associated with ONJ. Dr. Brown and Dr. Lipton confirmed that ONJ affects a small but significant set of patients treated with zoledronic acid (1.3% in both studies) and denosumab (1.8% and 1.6%, respectively). Their data also showed that the majority of patients experiencing ONJ had known risk factors, strengthening the argument for patient-screening prior to prescribing osteoclast-targeted treatments.

The 10th International Conference on Cancer-Induced Bone Disease continues to move from strength to strength. This intimate and friendly meeting appeals to clinicians and scientists alike, and we look forward to further discussion regarding existing treatments as well as new insights into cancer-induced bone disease at the next meeting.

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