

## **MEETING REPORTS**

### **Meeting Report from the Vth International Conference on Cancer-Induced Bone Disease**

**March 20–24, 2005 in Davos, Switzerland**

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The Vth International Conference on Cancer-Induced Bone Disease was held in Davos, Switzerland, March 20–24, 2005. The conference attracted 420 participants, comprising oncologists and basic scientists with expertise in bone and cancer cell biology. This large group made for an exciting program, with lively discussions of the 31 invited and 90 submitted papers reflecting the great interest in the field of cancer invasion and growth in bone that has been stimulated by many recent advances in the field. The occasion was also marked by the inauguration of the Cancer and Bone Society (CABS), an international society dedicated to advancing knowledge of the skeletal manifestations of cancer through its sponsorship of high quality annual scientific meetings. Robert Coleman (Sheffield, UK) was elected President of CABS, with a term extending until 2008, including the next two annual meetings.

#### **The Bone Microenvironment: Effects on Cancer Behavior**

As a result of extensive studies in recent years, scientists have accumulated overwhelming evidence for the validity of Paget's "seed and soil" hypothesis, and it is now possible to explain why certain cancers have a particular propensity to grow in bone and to identify the properties of the "seed" (cancer cells) and "soil" (bone) that facilitate this bone growth. The most prevalent theme of the meeting was the profound influence of growth factors and cytokines, either released from the bone matrix by resorption, or produced by bone cells or the immune

system, on the behavior of cancer cells in bone.

To introduce this theme, the importance of active osteoclasts and bone resorption in cancer establishment in bone was reviewed. Cytokines (e.g., parathyroid hormone-related protein [PTHrP], interleukin 6 [IL-6], IL-11, and others) released by breast cancer cells promote establishment of tumors by influencing host osteoblastic cells to produce receptor activator of NF- $\kappa$ B ligand (RANKL), and the process is amplified by the release of stored growth factors (e.g., transforming growth factor  $\beta$  [TGF- $\beta$ ] and insulin-like growth factor 1 [IGF-1]) during resorption of bone matrix (1). This entire process has come to be called the "vicious cycle" of cancer growth in bone, with establishment, amplification, and perpetuation of the process controlled by local bone environment conditions. Another mechanism by which TGF- $\beta$  contributes to bone-cancer interactions was identified in a study of epithelial mesenchyme transition in bone metastasis. TGF- $\beta$  was found to promote this process by enhancing invasion, whereas bone morphogenetic protein 7 (BMP-7), which maintains the epithelial phenotype in nonmalignant cells, had the reverse (i.e., inhibitory) effect. BMP-7 expression was found to be low or undetectable in invasive cancers, and daily administration of BMP-7 strongly inhibited orthotopic and bone growth of both breast and prostate cancers in a mouse model (2;3).

Modulation of PTHrP in cancer cells by the bone environment has been recognized for some years. In a new twist, the transcription factor Gli2, a mediator of hedgehog signaling in embryonic development, was shown to regulate PTHrP gene transcription. Gli2 stimulated the *PTHrP* promoter fourfold and increased PTHrP mRNA and protein production in breast cancer cells. Overexpressing Gli2 in cells led to increased bone colonization and growth of tumors (1,4). A new effect of the multifunctional PTHrP was also reported: the carboxy-terminal domain of PTHrP (107-139) contains an activity that promotes the production of several DNA repair enzymes in human breast cancer cells (5). A laboratory study with clinical implications included the finding that a heat shock protein 90 inhibitor, now in advanced clinical trials for its antitumor effect, promotes bone metastasis formation by enhancing osteoclast formation in the nude mouse model using MDA MB 231 breast cancer cells. In several mouse and human *in vitro* systems, the drug promoted osteoclast formation in a dose-dependent manner, and in intact mice, the inhibitor increased resorption, resulting in significant bone loss (6).

RANKL production by host bone cells is generally accepted as playing a central role in the process of bone metastasis by enhancing osteoclast formation and activity. An additional potential role of RANKL was suggested by a finding from gene array studies that in RANK-positive breast cancer cells treated with RANKL, production of several osteotropic and angiogenic factors and metalloproteinases was increased (7). Another mechanism by which the tumor necrosis factor ligand family may participate in local cancer-bone interactions was illustrated by the finding that osteoprotegerin (OPG), produced either by tumor or bone, can bind to and inhibit the apoptotic effect of TRAIL/Apo2L, thereby acting to promote tumor survival in the bone microenvironment (8).

Bone may serve in other ways as a receptive host for certain cancers by facilitating their attachment to the ground substance of bone. Involvement of  $\alpha\beta3$  integrin in this process was shown by overexpressing the integrin in human breast cancer cells, which increased the ability of cancer cells to establish and grow in bone (9). Other studies used a low molecular

weight  $\alpha\beta3$  integrin antagonist to prevent tumor establishment and growth in bone (10). Inhibition of c-Src kinase, which results in inactivation of the osteoclast, was as effective as zoledronic acid in preventing and treating bone tumor growth in a metastasis model and also increased animal survival (11). The concept of "osteomimicry" was reintroduced (1;12), and breast or prostate cancer cells were shown to express quite a number of proteins typical of osteoblasts (e.g., osteocalcin, osteopontin, bone sialoprotein, runx 2, twist, PTHrP, and others). A new finding was that  $\beta2$ -microglobulin, a secreted product of prostate cancer cells, contributes substantially to growth and invasion by breast or prostate cells through a protein kinase A-dependent mechanism (12).

In a genomic analysis of systemic breast and prostate cancer progression, very rare cytokeratin-positive (epithelial) cells were identified in mesenchymal bone marrow and isolated by micropipette (13). By carrying out genome analysis after amplification, the investigators were unable to obtain any evidence that primary tumors transmit genetic aberrations to distant tumors, suggesting that different genotypes might be selected by different microenvironments (13). Observations were also made that disseminated cancer cells were extremely different clonally from primary tumors; however, in metastasis, a clear pattern of clonal expansion occurs late in disease.

## Multiple Myeloma

Multiple myeloma was addressed in depth, with presentations of both clinical and preclinical data. The recent availability of a new treatment with a proteasome inhibitor, bortezomib, made the detailed description of the structure and function of the proteasome a most timely contribution to the meeting (14). Clinical and preclinical data on Dickkopf 1 (DKK1) evoked great interest. DKK1, an inhibitor of Wnt receptor complex signaling that binds to lipoprotein receptor-related protein 5 (LRP-5), is produced by myeloma cells and marrow mesenchymal cells. Increased production of DKK1 has been correlated with both the number and severity of resulting bone lesions and implicated in impaired osteoblast function and bone formation in myeloma bone disease (15). Dkk1 production is enhanced by antitumor therapy and glucocorticoids and inhibited by bortezomib. Validation of

Dkk1 as a target was demonstrated in a study of SCID mice in which myeloma cells were implanted among subcutaneously located fetal bone chips. This environment favored the establishment and growth of myeloma cells. Treatment with neutralizing anti-Dkk1 was highly effective in inhibiting osteoclast formation and increasing myeloma apoptosis, resulting in reductions of both bone loss and tumor burden (16).

The role of Dkk1 was also established in murine preclinical models with 5TGM1 and 5T33 cells. As in other studies, proteasome inhibition provided effective therapy by inhibiting Dkk1 formation, resulting in myeloma cell death and inhibition of bone resorption (17). The murine models were also used to show, by immunohistology and *in situ* hybridization, that RANKL, OPG, PTHrP, and osteoclast-inhibitory lectin were produced in the bone lesions. In a noteworthy example of the influence of the bone microenvironment, expression of these proteins in every case was greatest in those parts of the myeloma deposits located most closely to bone (18).

### **Bisphosphonates: Preclinical and Clinical Studies**

The importance of active osteoclasts in solid cancer metastasis and myeloma growth in bone was emphasized in many of the conference presentations. This concept was particularly illustrated by demonstrations of the efficacy of bisphosphonates in osteoclast inhibition, both in preclinical models and clinical diseases with bone invasion. The status of current and planned bisphosphonate trials in cancer-induced bone diseases was reviewed (19), as was their use in breast and prostate cancers and myeloma bone disease (*e.g.*, 20-23). Several bisphosphonates have been shown in trials to be effective in reducing the time to and number of skeletal-related events. However, the most potent of the N-containing bisphosphonates, zoledronic acid, has emerged to date as the most effective of these agents in treating breast and prostate cancer metastases or myeloma. A large comparative trial of zoledronate vs. ibandronate will begin shortly. In addition, several reports have indicated the rapidly achieved benefits of bisphosphonate treatment in obtaining clinically useful pain relief (24;25).

Another matter that was addressed (but not resolved) at the meeting is whether any bisphosphonate has a meaningful direct antitumor effect. *In vitro* data suggest that N-containing bisphosphonates can kill cancer cells in a dose-dependent manner and that this effect can be "rescued" by geranyl geranylate (GGOH), the mevalonate metabolite distal to the drug target farnesyl pyrophosphate synthase (26-28). Other reported *in vitro* effects include the inhibition of angiogenesis and invasion, as well as promising synergism with zoledronate administered after treatment of cells with doxorubicin (20;29). In most of these studies, prenylation of small G-proteins was inhibited, with rescue often attainable with GGOH. Nevertheless, the concentrations required for these effects were usually high, varying between 10 and 100  $\mu$ M. Very high dosing was particularly prevalent in the *in vivo* studies (26;30). In cases in which bisphosphonate treatment of animal models of bone tumor growth resulted in decreased soft tissue tumor mass, perhaps the most likely explanation proposed was that reduction of the bone tumor mass is the primary event, and the decreased soft tissue mass, the logical consequence of that large reduction. There was certainly no clear convincing evidence from any of the clinical trials of bisphosphonates suggesting a beneficial effect on soft tissue metastasis. It was also pointed out in discussion that bisphosphonates have been very widely used in patients with multiple myeloma without any indication of effects on soft tissue metastasis.

### **Clinical Assessment of Bone Resorption and Evaluation of Effects**

The use of bone resorption marker assays (*e.g.*, the N-telopeptide [NTx] assay) in monitoring therapeutic responses was seen as clinically valuable. An intriguing finding was that in patients with prostate cancer metastasis to bone, which is predominantly osteoblastic, NTx values are consistently greater than in patients with bone metastasis from other solid tumors or in those with myeloma. This observation is consistent with data gathered in recent years that osteoblastic metastases require osteoclast participation, just as lytic metastases do. The unanswered question, therefore, is why the resorption parameter is more markedly elevated in these prostate cancer-induced bone metastases. Several presentations suggested that the higher the

NTx level, the greater the risk of bone metastasis, cancer progression, and death (20;27;31;32). In monitoring treatment progress, NTx assays identified patients who were poor responders, a finding that may be useful in recognizing those in whom more aggressive or alternative treatments should be undertaken, including the addition or substitution of new resorption inhibitors.

The topics of bone loss and increased fracture risk in men treated for prostate cancer and women treated for breast cancer with hormone therapies (aromatase inhibitors and gonadotropin-releasing hormone agonists, respectively), as well as with chemotherapy and glucocorticoids, generated considerable interest (33-35). These treatment sequelae were identified as common and serious problems. Current trials are aimed at evaluating preventive and therapeutic measures using resorption marker assays. American Society of Clinical Oncology guidelines currently recommend specific treatment with resorption inhibition in patients with BMD greater than 2.5 SD below the mean. However, these guidelines may need to be reviewed with respect to the relevant trial data, when they become available.

### **Pain**

Metastasis-induced pain was addressed in both experimental and clinical studies and in approaches described in mice that identified neural circuits reflecting specific tumor-induced bone pain (36). Clinical studies were in agreement regarding the efficacy of bisphosphonate treatment in rapidly reducing bone pain from both breast and prostate cancer bone metastases (24;25;31;37). Isotope treatment was also shown to be effective (38). As the efficacy of irradiation in reducing pain in a mouse model seemed to correlate with reduction in tumor size, the data suggested that there might be benefit from combining irradiation with antiresorptive treatment (36).

### **Clinical Management of Metastatic Bone Disease**

An important aim of this meeting was to update the attendees on the latest developments in the clinical management of advanced cancer, with specific reference to metastatic bone disease. The exciting developments in targeted therapies, with particular reference to breast cancer, were

elegantly reviewed (19). Several targeted therapies (both small molecules affecting signal transduction and antibodies to growth factor receptors) are already in clinical use, and a very large portfolio is in early clinical development. Identifying the relevance of the therapeutic target to cell function and survival was seen as essential to the development of targeted therapies. Failure to define the target has handicapped the clinical development of at least one of these novel therapies.

The treatment possibilities in malignancy are expanding rapidly, and overviews of recent advances in the management of multiple myeloma (16), breast cancer (39), and prostate cancer (40) provided the scientists with an insight into the importance of multidisciplinary management and the complexity of clinical care. Extraordinary results with aggressive myeloablative therapy for multiple myeloma were presented by the Arkansas group (16). Using a combination of induction therapy, tandem transplant, proteasome inhibitors, thalidomide, and bisphosphonates (known as "total therapy"), event-free survival rates of 50% at five years were shown to be possible in fit patients with the disease who are younger than age 60 years. The exciting potential for gene expression profiling in individual tumors to more accurately predict outcome and guide treatment choices was also presented (16;39).

International experts in endoprosthetic surgery, spinal reconstruction, interventional radiology, radiotherapy, and positron emission tomography (PET) all contributed to the clinical component of the meeting. The excellent functional results of specialist spinal surgery and the need for earlier referral for surgical assessment were stressed (41). Vertebroplasty and kyphoplasty provide a less invasive alternative for patients with vertebral fractures without neurological compromise or spinal instability and are innovative techniques that are steadily becoming more widely available (42).

Developments in orthopedic prosthetic devices have considerably improved the outcome of surgical management of painful destructive metastatic lesions in the hips, pelvis, and shoulders. Compared with traditional orthopedic devices (e.g., screws, nails, plates, and rods), orthopedic prosthetic devices result in a structurally

more resilient outcome, allowing weight bearing and restoration of function. Selection of patients for prophylactic surgical intervention is difficult and has been based on clinical features and radiographic appearances. However, new data based on computed tomographic assessment of the mechanical properties of bone showed the potential for this technique to more accurately predict fracture risk. Evaluation using biomechanical testing of biopsy specimens in the laboratory (43), followed by clinical evaluation in patients with spinal metastasis, was an elegant demonstration of translational research (44).

The use of PET scanning with 18F-fluorine deoxyglucose in the evaluation and management of skeletal disorders is increasing. The sensitivity for identification of metastasis is high and was shown to be similar to conventional bone scanning, but with the advantage of additional information on function. With effective treatment, lesions previously identified on PET may disappear earlier than on a bone scan or computed tomography (20). The potential for PET to evaluate bone-specific treatments was seen as an important area for future research.

Radiotherapy remains the treatment of choice for painful bone metastasis. Many randomized studies and metaanalyses have suggested similar efficacy of a single fraction of treatment (usually 8 Gray) to more complex protracted schedules, although the latter continues to be preferred in many parts of the world (45). The choice of appropriate endpoints for such trials, the optimum fractionation for retreatment, and the structural effects of different treatment schedules were all discussed. Radioisotope therapy with bone-seeking radiopharmaceuticals provides an effective alternative to external beam radiotherapy and is particularly useful for sclerotic and mixed lesions associated with prostate and breast cancers. With modern agents, such as samarium-153-lexidronam, retreatments are possible, and bone marrow toxicity is sufficiently minor that, contrary to popular opinion, chemotherapy can be given safely after radioisotope therapy (46).

## Summary

New treatment modalities and proposed treatment trials for breast and prostate cancers and myeloma were discussed in a broad forum. All participants appreciated

that basic scientists in bone and cancer biology need to know and understand these clinical approaches, just as clinicians need to understand the experimental approaches associated with these diseases. The importance of the bone microenvironment in the invasion of these cancers into the bone influenced the discussions of virtually all of the work presented throughout the conference, and it was clear that bone disease is a crucial target of interest for the development of new therapies in oncology.

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