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NEWS

The Anti-cancer Activity of Bisphosphonates in the Clinic

Recent IBMS BoneKEy webinar on cancer and bone discussed the need to reconsider the clinical relevance of the vicious cycle

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Introduction

More than a century ago, the English surgeon Stephen Paget proposed the idea that cancer cells from primary tumors spread preferentially to particular organs throughout the body because those organs provide a hospitable environment or "soil" for the malignant cells – the "seed" – to live and grow. This seed and soil hypothesis, a fundamental tenet of today's understanding of cancer metastasis, is well-known to researchers who study cancer and bone, since certain cancers, such as those of the lung, prostate and breast, have a strong tendency to spread to and establish themselves in skeletal tissue. Paget's early hypothesis has been extended recently by investigators who focus on the skeletal complications of malignancy through the concept of the "vicious cycle," where cancer cells that have spread to bone release factors that affect bone cells, resulting particularly in activation of bone-resorbing osteoclasts; these osteoclasts in turn allow the release of bone matrix-derived factors that feed back to the cancer cells, further fueling the latter's growth.

Inhibiting the vicious cycle appears promising as a treatment approach in the cancer setting, but recent clinical trial results examining the effects of bisphosphonates, the bone field's mainstay of treatment for osteoporosis and cancer-induced bone disease, in breast cancer patients suggest that doing so may not always be beneficial. Such was the intriguing conclusion delivered by Robert Coleman during "The Potential Anti-cancer Activity of Bisphosphonates in the Clinic," the seventh IBMS BoneKEy webinar and the first one focused specifically on cancer and bone. Part of BoneKEy's increasing coverage of the cancer and bone field (see BoneKEy Oncology here), this May 25th, 2011 webinar featured a slide presentation by Dr. Coleman, a professor of medical oncology at the University of Sheffield in the United Kingdom, followed by a distinguished panel discussion moderated by Philippe Clézardin, BoneKEy Associate Editor. Focusing on recent results from the AZURE trial, which is examining the effects of adding the powerful intravenous bisphosphonate zoledronic acid to standard therapy in breast cancer patients, Dr. Coleman made the case that it is time to reconsider the relevance of the vicious cycle in the patient setting.

Lines of Evidence Supporting an Anti-cancer Role for Bisphosphonates in the Clinic

In his description of the clinical evidence supporting the use of bisphosphonates as anti-cancer agents, Dr. Coleman first noted that administration of adjuvant bisphosphonates has been associated with improved disease outcomes. For instance, a subgroup of 205 patients with breast cancer in the AZURE trial received neoadjuvant chemotherapy; half of these patients also received zoledronic acid immediately following chemotherapy, and they were compared to the other half of patients receiving only chemotherapy. Compared to patients receiving chemotherapy alone, those who also received zoledronic acid exhibited a statistically significant 44% reduction in tumor size at the time they were to undergo surgery to have tumors removed.

In addition to this finding regarding residual invasive tumor size, the study also found that almost 12% of patients receiving both chemotherapy and zoledronic acid achieved pathological complete remission (where tumors could be detected neither in the breast nor the axillary lymph nodes), while only about 7% of patients in the chemotherapy-only group did so; though this difference was not statistically significant, the study authors stressed this was not surprising considering the small numbers of patients in the study. In short, the results from this subgroup analysis suggest a potential synergistic effect of combining chemotherapy with zoledronic acid, which is consistent with studies suggesting the same in animal models.

The effects of zoledronic acid on disseminated tumor cells (DTCs) within the bone marrow also suggest an anti-cancer effect of bisphosphonates. Indeed, in support of this conclusion, Dr. Coleman pointed to a number of clinical studies showing decreased numbers of DTCs in patients taking zoledronic acid as early adjuvant breast cancer therapy, compared to those receiving only standard therapy. “We know that DTCs are a very powerful prognostic factor for subsequent relapse, so to eliminate DTCs ought to bode well for the future of these patients,” Dr. Coleman said.

In addition to improvements in disease outcomes and with regard to DTCs, Dr. Coleman also pointed to recent epidemiological studies showing prevention of cancer as further evidence for the anti-cancer activity of bisphosphonates. For instance, recent data from the Women's Health Initiative showed a 32% reduction in invasive breast cancer in normal subjects receiving a bisphosphonate for the treatment of osteoporosis, compared to those not receiving one (for more coverage of this and other epidemiological studies of bisphosphonate use and breast cancer incidence, see a recent BoneKEy Commentary by Rowan Chlebowski here and one by Dr. Clézardin here). Similarly, Dr. Coleman noted data presented by Bo Abrahamsen and colleagues last year at the 37th European Symposium on Calcified Tissues in Glasgow that suggests a reduction in colon cancer incidence with use of bisphosphonates. Indeed, their Danish national register-based cohort study of 33,000 osteoporosis patients taking a bisphosphonate (primarily alendronate) and 66,000 matched controls not taking a bisphosphonate documented a 39% reduction in colon cancer death in the alendronate users compared to controls, as well as an overall mortality reduction of 17%. “We know that oral bisphosphonates are quite poorly absorbed, and so in the colon there would be quite significant concentrations of bisphosphonates that may indeed have potential effects either on precursor lesions or even on early cancer lesions by direct effects on cancer cells,” Dr. Coleman surmised.

Another line of evidence – studies of advanced cancer – provide further support for an anti-cancer role of bisphosphonates in the clinic, particularly data from the Medical Research Council (MRC) Myeloma IX randomized controlled trial published in *The Lancet* in December of last year. This study randomized nearly 2,000 patients with newly diagnosed multiple myeloma to receive either 4 mg of intravenous zoledronic acid every 3-4 weeks along with chemotherapy, or 1,600 mg daily of the oral bisphosphonate clodronate along with chemotherapy. Compared to subjects taking clodronate, those who received zoledronic acid exhibited a statistically significant median increase in overall survival of 5.5 months. Dr. Coleman stressed that this difference appeared early in the time course of the disease, with a statistically significant difference appearing after just 4 months. “This suggests that zoledronic acid must be either synergizing with chemotherapy to get a better anti-myeloma response or improving the immune status of patients to allow them to survive the toxicities of chemotherapy,” Dr. Coleman said. Panelist Evangelos Terpos, an assistant professor of hematology at the University of Athens School of Medicine in Greece agreed with the significance of the MRC Myeloma IX findings. “The 5.5-month survival advantage was irrespective of the skeletal-related event reduction that zoledronic acid produced,”

according to Dr. Terpos. “This is the first time that a direct anti-myeloma effect of zoledronic acid has been shown, and it's very exciting.”

The panel discussed in a bit more detail whether such an anti-cancer effect could in fact be a result of a potential beneficial impact on the immune system, an often hypothesized benefit of bisphosphonates in the cancer setting. In the case of multiple myeloma, Dr. Terpos noted that effects on immune cells such as natural killer T cells could potentially mediate the anti-myeloma effects of zoledronic acid, though there isn't enough evidence yet to support this conclusion. Dr. Coleman noted the same potential for an immune system effect of zoledronic acid in the case of breast cancer, though he too stressed that there is little clinical data yet in support of this possibility.

Adjuvant Therapy of Breast Cancer...and Rethinking the Vicious Cycle

After discussing the above studies, Dr. Coleman focused specifically on clinical trials of adjuvant therapy with bisphosphonates in breast cancer, an approach that has captured the attention of the bone and cancer field particularly over the past year or two but that in fact is not a new one. Indeed, in a study by Trevor Powles and colleagues, published in 2006 in *Breast Cancer Research*, over 1,000 patients with primary stage I-III breast cancer were randomized to receive along with standard therapy either 1,600 mg/day of clodronate for 2 years or placebo. Results revealed that compared to placebo, patients receiving clodronate exhibited improvements in bone metastasis-free survival as well as in overall survival, both at 2-year and 5-year timepoints.

While this early study provided important data, the landmark Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12), whose initial results were published in 2009 in *The New England Journal of Medicine*, offered the most compelling data on adjuvant BP use that the cancer and bone field had seen to date. In this clinical trial, panelist Michael Gnant and colleagues randomized just over 1,800 premenopausal patients with endocrine-responsive stage I/II breast cancer to receive the gonadotropin-releasing hormone (GnRH) agonist goserelin and the SERM tamoxifen, or goserelin and the aromatase inhibitor anastrozole, with or without 4 mg of intravenous zoledronic acid administered every 6 months for 3 years. Findings after a median follow-up of almost 48 months published in the *NEJM* article revealed that the addition of zoledronic acid to endocrine therapy resulted in a statistically significant reduction in disease-free survival (DFS) events of 36%. Furthermore, results over a longer follow-up period (a median of 62 months) have now shown a statistically significant 32% reduction in DFS events in the patients who had received zoledronic acid compared to those not receiving the bisphosphonate; Dr. Coleman stressed that this reduction in DFS events included reductions not just in bone metastases but also in metastases at other distant sites as well as in locoregional recurrences, which suggests that zoledronic acid was having an effect beyond just bone and the bone microenvironment. Furthermore, a subgroup analysis of this study has shown that the impact of zoledronic acid on DFS events was much stronger in patients over the age of 40, a finding consistent with results from AZURE, a study coordinated by Dr. Coleman and one to which he devoted the rest of his webinar presentation.

In AZURE, over 3,000 patients with stage II/III breast cancer were randomized to receive either standard therapy (chemotherapy, endocrine therapy, radiation therapy) or standard therapy plus 4 mg of zoledronic acid; patients in the latter group initially received 6 doses of zoledronic acid every 3-4 weeks, then received 8 doses every 3 months, followed by 5 doses every 6 months, a much more intensive dosing schedule of zoledronic acid compared to that of ABCSG-12. Unfortunately, in results first presented last year at the San Antonio Breast Cancer Symposium, there was no difference between those receiving zoledronic acid and those receiving only standard therapy in terms of DFS events, AZURE's primary endpoint, nor was there a

difference in invasive DFS events, one of the study's secondary endpoints.

However, Dr. Coleman and his colleagues were struck by an intriguing finding from a pre-planned subgroup analysis that evaluated patients by their menopausal status: while there were no statistically significant differences, in terms of invasive DFS events, between zoledronic acid-treated subjects and controls in a younger group of patients who were premenopausal, peri-menopausal or whose menopausal status was unknown, there was such a statistically significant difference in postmenopausal patients; in the latter group, there was a 25% reduction in invasive DFS events. Furthermore, though the AZURE investigators, when they looked at the effects of adding zoledronic acid on bone recurrences according to menopausal status, could find no difference between groups (a similarly consistent, weak effect of zoledronic acid on first bone recurrence was observed in both groups), a different picture emerged when they examined the effects on first recurrence outside bone. Indeed, now postmenopausal patients exhibited a 30% reduction in extraskeletal recurrences, while the group of those who were pre- or peri-menopausal or whose menopausal status was unknown actually exhibited an increased risk of extra-skeletal recurrences. This difference in recurrences outside bone according to menopausal status also translated into a survival benefit, with postmenopausal patients showing a statistically significant 29% decrease in the risk of dying, a mitigation of risk that began to appear at just 1 or 2 years of follow-up. (Despite their increased risk of extra-skeletal recurrence, the premenopausal, postmenopausal and unknown status group did not have an increased risk of dying, though Dr. Coleman noted this must be monitored closely. In addition, panelist Peyman Hadji, a professor at Philipps-University of Marburg in Germany, raised the issue of whether a trend towards harm concerning extraskeletal recurrence was also seen in ABCSG-12. Dr. Gnant noted that such a trend has not been seen in that study; in fact, patients in ABCSG-12 experienced fewer events in all event categories, including fewer extraskeletal events).

These clear differences documented in AZURE between subgroups classified according to menopausal status have certainly caught the attention of the webinar panelists. “The heterogeneity within AZURE is quite striking,” said Dr. Gnant, a professor of surgery at the Medical University of Vienna in Austria. “I've never seen something like this before in any other clinical trial of such size that excludes any numerical or statistical bias,” he said, also noting that forthcoming data from ABCSG-12 are in line with the interpretation of AZURE results offered by Dr. Coleman during the webinar.

The striking subgroup findings from AZURE lead to a view that challenges the conventional wisdom in the cancer and bone field. “I think we have to re-debate the clinical relevance of the vicious cycle,” Dr. Coleman said. “Is inhibiting it always beneficial?” he asked. Indeed, because of the potential for harm – a greater number of visceral metastases and locoregional recurrences – observed in the younger subgroup of patients in AZURE, Dr. Coleman stressed that the cancer and bone field needs to think even more deeply about the role of reproductive hormones in the bone microenvironment, and specifically about what happens when bone remodeling becomes a process driven less by estradiol and inhibins and more by activins and BMP tone, as is the case in the postmenopausal situation, and how these changes may affect cancer cells in that microenvironment and their likelihood of spreading and establishing metastases elsewhere in the body.

The panelists agreed both that this potential for harm documented in AZURE needs to be substantiated with additional evidence, and furthermore, that the field must find a compelling explanation to account for why the effect of zoledronic acid seems to depend so heavily on the hormonal environment. In addition, Dr. Clézardin also reminded webinar attendees that despite the disconcerting findings from the AZURE subgroup analysis, there is nonetheless still

good reason to believe in possible positive effects of interrupting the vicious cycle. “There is potential for zoledronic acid to inhibit bone resorption and because of that to inhibit the release of growth factors that could promote or help the formation of pre-metastatic lesions in soft tissues – there is indeed some evidence for this at the preclinical level [see recent BoneKEy article here] – so we could still observe a positive effect in terms of blocking the occurrence of micrometastases in different tissues,” Dr. Clézardin said.

Conclusion

Only additional studies will clarify the role of the vicious cycle in the clinical setting of breast and other cancers. For now, though, Dr. Coleman stressed that results from AZURE and from ABCSG-12 suggest that adjuvant bisphosphonate therapy in breast cancer should be considered only in an environment of low reproductive hormones. “I would certainly be very cautious about giving zoledronic acid to a young patient in the absence of effective ovarian suppression,” Dr. Coleman said, a sentiment with which the panelists wholeheartedly agreed. On the positive side, despite the disappointing lack of an effect of zoledronic acid on AZURE's primary endpoint that investigators were hoping to see, results from the pre-planned subgroup analysis in AZURE suggest that bisphosphonates may be quite helpful for patients with postmenopausal status, and findings from other studies like ABCSG-12 are consistent with this interpretation of results. Future studies that are able to delineate the mechanistic basis behind this intriguing result will help push the bone and cancer field toward a better understanding of the role of bisphosphonates as anti-tumor agents for patients with cancer.