Department of Endocrine Neoplasia and Hormonal Disorders
NEWSLETTER
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ENDOPERSPECTIVES®

Bone Health in Patients With Cancer

THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER
Making Cancer History™

Robert F. Gagel, M.D., Professor, Department of Endocrine Neoplasia and Hormonal Disorders; Division Head, Division of Internal Medicine, Co-Director, Rolanette & Berdon Lawrence Bone Disease Program of Texas

Dr. Mimi Hu sighed as she completed her second consult in a week for aromatase inhibitor-induced bone loss. As she walked back to her office, she couldn't help but reflect on the growing number of women who face difficult decisions when they are considering aromatase inhibitor treatment for their breast cancer; although the treatment provides the potential for a better cancer outcome, it is associated with side effects that include bone loss and joint pain. There is little question that aromatase inhibitors are an effective therapy for treatment of estrogen receptor positive breast cancer. Recent clinical studies have shown that this class of therapy, which works by lowering conversion of androgens to estrogen, is more effective in preventing recurrence of estrogen receptor positive breast cancer than the previous therapies and is routinely used. Lowering the plasma estrogen concentration leads to an acceleration of bone loss in these women. In addition, many patients have muscle and joint aches and pains that range from very mild to severe. Some patients consider discontinuation of the aromatase inhibitor therapy because of these side effects. Patients treated with one of the three major aromatase inhibitors, Anastrozole, Letrozol, or Exemestane have bone loss rates of 2-to-3 percent per year over the 3-to-5 year studies. While this amount of bone loss does not sound like a large number, if one considers the fact that a normal individual is considered to have osteoporosis when he or she has lost approximately 30% of bone mass, changes of this magnitude become highly significant. In one 2-year clinical trial there was more than a 2% greater incidence of fractures in patients treated with an aromatase inhibitor than in the control group.

Seeing women confronted with these daunting choices on a regular basis stimulated Dr. Hu of the Department of Endocrine Neoplasia and Hormonal Disorders and her colleagues in Medical Breast Oncology and the Bone Disease Program of Texas to develop a program to identify at-risk women and initiate treatment. Dr. P.K. Morrow in Medical Breast Oncology, Dr. Terry Bevers, Clinical Cancer Prevention, and Dr. Hu worked with other colleagues to develop specific criteria for evaluation and treatment of bone loss in women treated with aromatase inhibitors and breast cancer survivors. The good news is that there are effective therapies to prevent bone loss in this context. For example, intravenous bisphosphonates are highly effective and it is likely that a new therapy, a monoclonal anti¬body that targets RANK ligand, will be available later this year or early 2010.

The Rolanette and Berdon Lawrence Bone Disease Program of Texas

Drs. Morrow, Bevers, and Hu's work dovetails with a larger effort by the Division of Internal

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Medicine and the Rolanette and Berdon Lawrence Bone Disease Program of Texas to develop clinical and research efforts focused on prevention and treatment of osteoporosis and other bone diseases. The Bone Disease Program of Texas is a collaborative program with Baylor College of Medicine focused on improving bone health in the greater Houston area and Texas. The M. D. Anderson component of this program is led by Dr. Robert Gagel, Head, Division of Internal Medicine.

The MDACC Bone Health Clinic

The Division of Internal Medicine has created a Division-wide Bone Health Clinic to strengthen the Institution's focus on bone health. The initial goals for this new clinic will be to provide a single center location for bone health within the Institution. As a part of this Center, participants have developed a multidisciplinary monthly conference focused on bone health. In addition to faculty participation by Drs. Camilo Jimenez, Hu & Gagel of the Department of Endocrine Neoplasia and Hormonal Disorders and Dr. Linda Lu of the Section of Rheumatology, there is participation by Dr. William Murphy in the Division of Radiology and Dr. Beth Chasen in the Department of Nuclear Medicine. In addition, an Education Center for Bone Health in the context of cancer is being developed and will incorporate digital learning aides, informative articles, and classes on bone health. The importance of nutrition and calcium intake will be addressed by a collaborative effort with the Department of Nutrition.

In addition to bone loss and osteoporosis associated with estrogen deficiency in the context of breast cancer, other patient groups at particular risk for development of osteoporosis and fractures include older men with prostrate cancer treated with androgen blocking agents, men or women with leukemia, lymphoma, myeloma and patients receiving immunosuppressive therapy for bone marrow transplantation. Dr. Linda Lu has been working closely with Dr. Richard Champlin to improve bone health in stem cell transplant patients. She developed a study to assess the efficacy of bisphosphonate therapy in the prevention of bone loss in patients undergoing bone marrow transplant. Others are working to improve outcomes in patients with myeloma and other lympho-proliferative disorders.

Prevention of Fractures in Cancer Survivors

Another focus area of the Bone Program is survivorship. Although a broad spectrum of therapies has increased survival in many cancers in recent years,, many of these survivors may experience disability related to long-term complications of cancer or its therapy. Bone health is high on the list of concerns for cancer survivors and the Bone Program has addressed these issues in special ways. First, there are specific clinical protocols to determine the effects of therapeutic agents to prevent osteoporosis in the context of acute lymphoblastic leukemia (Dr. Maria Ca-

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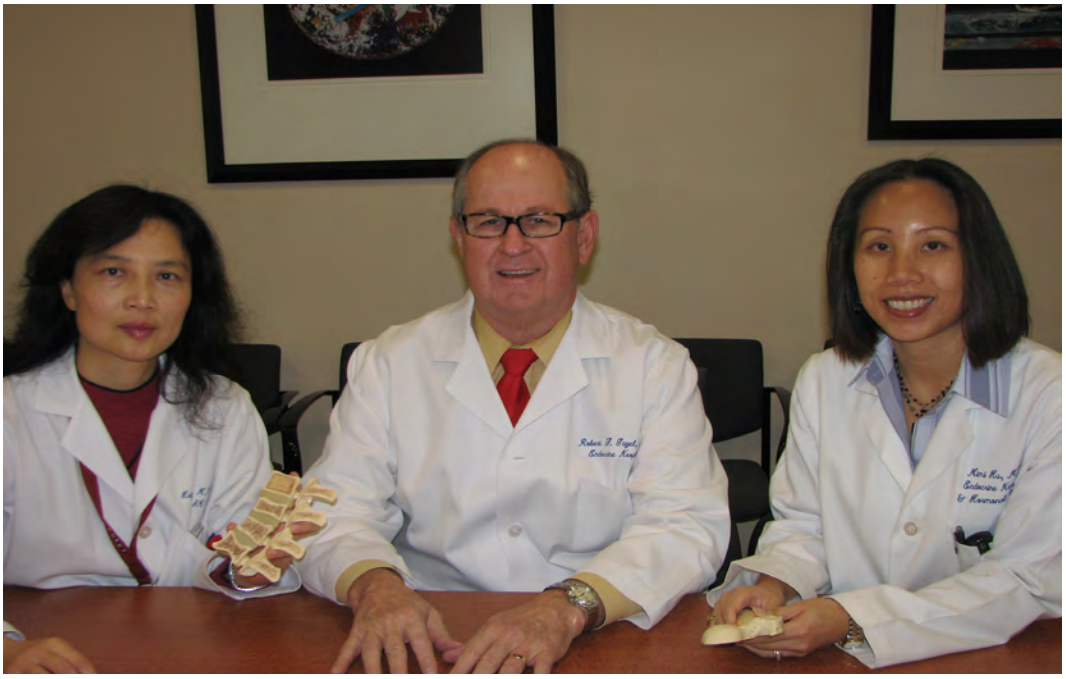


Huifang Linda Lu, MD, Robert Gagel, MD, and Mimi Hu, MD

Upcoming Events

AACE 19th Annual Meeting and Clinical Congress
April 21-25, 2010
Sheraton Boston Hotel and the John B. Hynes Veterans Memorial Convention Center
Boston, MA (http://www.aace.com/meetings/calendar/calendar.php)

AAES 2010 Annual Meeting
April 18-20, 2010 Pittsburgh, PA (www.endocrinesurgery.org)

LWPES 2010 Annual Meeting May 1-3, 2010. Vancouver, Canada. (http://www.lwpes.org/meetingsEvents/pdf/2010LWPESschedule.pdf)

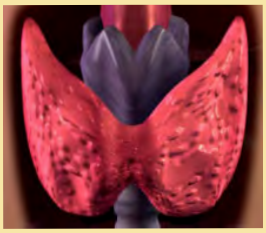
ATA Spring Meeting of the American Thyroid Association May 13-16, 2010. Minneapolis, MN (www.thyroid.org)

The Endocrine Society ENDO 2010, June 19-22, 2010. San Diego, CA. (www.endo-society.org)

14th International Thyroid Congress Sept. 11-16, 2010 Paris, France. (www.itc2010.com)

North American Neuro-Endocrine Tumor Society Annual Conference
October 29-30, 2010
Santa Fe, New Mexico
(www.nanets.net)

14th Asia-Oceania Congress of Endocrinology
December 2-5, 2010
Kuala Lumpur, Malaysia
(www.aoce2010.com)



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banillas, Department of Endocrine Neoplasia and Hormonal Disorders) and bone marrow transplant (Dr. Linda Lu, Rheumatology). Other studies are under consideration to address bone loss in the context of breast cancer. The long-term goal of the Department of Endocrine Neoplasia and Hormonal Disorders and the Bone Disease Program is to provide a safety net for patients undergoing active treatment and to safeguard the long-term bone health of cancer survivors.


Camilo Jimenez, MD

Dr. Lu, a rheumatologist, is also working to address joint aches and bone pains associated with aromatase inhibitor use. The goal is to develop therapies to reduce symptomatology while maintaining effective therapy for breast cancer.

The Rolanette and Berdon Lawrence Bone Disease Program of Texas, a philanthropic program established jointly by the University of Texas M. D. Anderson Cancer Center and Baylor College of Medicine, was established to tackle problems of this type. The goal of this program is to develop better therapies to stimu¬late bone formation in patients with and without cancer as a therapy for osteoporosis and to prevent bone metastasis in the context of cancer. This cutting edge program has been in existence for approximately seven years. During this period, the program has sought to develop both research and clinical components of the program that will enable researchers and clinicians from across the medical center to develop new therapies for treatment of bone disease in patients with or without cancer. This program has had a notable number of successes including the identification of one of the major regulators of bone cell function and development, RUNX2 (Gerard Karsenty, Baylor College of Medicine), another major regulator of bone formation, Osterix (Dr. Benoit deCrombrugghe), and numerous other firsts in bone biology. The support received by the Bone Program has enabled it to develop bone histology and immunohistochemical laboratories, microcomputerized tomography techniques for microscopic evaluation of bone, and unique animal models of several types of bone disease. Basic researchers in the program work alongside clinicians to focus research on osteoporosis and other bone-related problems seen in patients with or without cancer.

This support also has enabled the Department of Endocrine Neoplasia to develop a Section of Bone and Mineral Metabolism, a group of physicians focused on bone health. Current members include Drs. Robert Gagel, Section Head, Mimi Hu, Camilo Jimenez, and Sara Peleg. Each has a research and clinical focus on bone disease.

Dr. Hu's development of practice guidelines for prevention and treatment of osteoporosis in the context of breast cancer is one example of how this program has already improved bone health in our patient population. She and Dr. P.K. Morrow of Medical Breast Oncology worked over a period of six months to develop guidelines for identification and treatment of patients with bone-related problems.

"Dr Mini Hu to Lead Study Addressing the Effectiveness of Denosumab, a new agent, in the treatment of cancer-related hypercalcemia"

Denosumab is a humanized monoclonal antibody directed against a protein, RANK ligand, and necessary for the development of the bone resorbing osteoclasts. Treatment with this monoclonal antibody results in rapid and continuous reduction of the formation of osteoclasts for a period in excess of six months. Since most hypercalcemia (high blood calcium) seen in the context of cancer is caused by tumor products stimulating osteoclast-mediated bone resorption, there is good reason to believe that treatment with denosumab will be effective for rapidly lowering the serum calcium concentration. This therapy offers patients who have become refractory to other approved therapies for hypercalcemia a new therapeutic option. Physicians who are seeking information regarding this study should call Dr. Mimi Hu at 713.792.2841.

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If interested, please send submissions to Charles Stava, cstava@mdanderson.org. We reserve the right to edit for length, content, and style.

Department of Endocrine Neoplasia and HD website: http://www.mdanderson.org/departments/endocrinology/

The Rolanette and Berdon Lawrence Bone Disease Program of Texas

The Rolanette and Berdon Lawrence Bone Disease Program of Texas

BCM Baylor College of Medicine

The University of Texas MD Anderson Cancer Center Making Cancer History

The Rolanette and Berdon Lawrence Bone Disease Program of Texas is a collaborative research and clinical program of Baylor College of Medicine and the University of Texas M. D. Anderson Cancer Center.

The mission of the Bone Disease Program of Texas include:

- Develop bone-forming treatments for all degenerative bone diseases
- Improve prevention and treatment of bone cancer metasasis
- Foster bi-institutional collaboration in bone disease research and treatment.

In the United States today, 10 million individuals are suffering from various bone diseases, including osteoporosis and bone metasasis. Almost 34 million more are estimated to be at increased risk for osteoporisis.

For more information, please contact Lea Tatar, Program Director, at 713-792-1345, or visit: www.bonediseaseprogram.com

The Thyroid Cancer Survivorship Program

The Department of Endocrine Neoplasia and Hormonal Disorders is proud to feature the new Thyroid Cancer Survivorship Clinic at The University of Texas M. D. Anderson Cancer Center. The mission of the Thyroid Cancer Survivorship Program is to address the outcomes of thyroid cancer and its therapy, and improve survivors' health and quality of life through integrated programs in patient care, research, prevention and education.

A Specialty-trained dedicated nurse practitioner and Endocrinologist are here to monitor cancer survivors for recurrence of thyroid cancer. Additionally, our team works closely with other specialized physicians and nurses to look for and manage late effects related to thyroid cancer and its therapies. We are uniquely able to coordinate care related to speech and swallowing problems, bone and heart health, dry mouth, tearing, and dental complications, as well as fatigue.

Finally, an important mission of our Thyroid Cancer Survivorship Program is to ensure that all of our patients are receiving adequate cancer prevention screening for all malignancies, whether at M. D. Anderson or in the community.

To refer a patient, please call our New Patient Referral Coordinators at 713-563-4400.
For physician to physician referrals, please call 713-792-2841.

Wish to refer a patient to M. D. Anderson?

my MDAnderson

Online Referrals:
M. D. Anderson has created an online referral process, myMDAnderson, to help you get your patient into M. D. Anderson as quickly as possible. You can use myMDAnderson to follow the treatment your patients receive by viewing transcribed reports and accessing your patients' schedules. To qualify for this free service, you must be a licensed, practicing physician. To start a referral through myMDAnderson, please access this portal:
https://my.mdanderson.org/public/physicians/user/

Telephone Referrals:
Physician to Physician referrals to the Dept. of Endocrine Neoplasia and H.D., please call 713-792-2841.
To speak to a New Patient Referral Coordinator, please call 713-563-4400.
For Pediatric Referrals (patients less than 18 years of age), please call 713-792-5410

Notes from the Endocrine Faculty Team

Congratulations to Drs. Robert Gagel, Victor Lavis, Rena-Vassilopoulou-Sellin, Steven Sherman and Steven Waguespack for making the 2009-2010 list of the "Best Doctors in America." Best Doctors was founded in 1989 by two Harvard Medical School physicians. A peer-review by thousands of doctors determines the physicians included in the database. Only those who earn the consensus support of their peers, as well as meet additional qualification criteria, are included.

We are proud to introduce two new additions, Rozita Bagheri-Yarmand, Ph.D., and Maria E. Cabanillas, M.D., to the Department of Endocrine Neoplasia and HD's faculty team.

Rozita Bagheri-Yarmand, Ph.D., Assistant Professor

Dr. Bagheri-Yarmand is a biochemist and cell biologist who is a graduate of the University of Paris XIII. Her research interest focuses on the mechanism by which misregulation of oncogene (cyclin E) and tumor suppressor (ATF4) leads to chromosomal instability, tumorigenesis and metastatic phenotype in breast cancer. She is also interested in studying the impact of RET mutation on metastatic phenotype of medullary thyroid cancer. After working in the Department of Experimental of Radiology Oncology since June of 2005, she joined the Dept of Endocrine Neoplasia and Hormonal Disorders on October of 2009. Her primary goal in her current capacity is to validate the significance of these proteins as a prognostic marker and their use as a target in breast or thyroid cancer.

Maria E. Cabanillas, M.D., Assistant Professor

After finishing residency training in Internal Medicine, Dr. Cabanillas joined the faculty at M. D. Anderson Cancer Center as a hospitalist for the Leukemia Department in 2001. She had the unique opportunity to conduct clinical research in the area of supportive care and was the principal investigator on two investigator-initiated clinical trials. One of these trials is related to bone metabolism and health, which led to her interest in Endocrinology. After nearly 6 years at M. D. Anderson, she made the decision to pursue a career in Endocrinology and joined the joint Baylor/M. D. Anderson fellowship program in 2007. All it took was a month at M. D. Anderson for her to decide that she wanted to work in the area of advanced thyroid cancer. She formally joined the Dept. of Endocrine Neoplasia and Hormonal Disorders department team in August 2009 and was awarded a K-12 grant in order to dedicate most of her time to thyroid cancer research. She is also the co-principal investigator of the multi-center E7080 trial for advanced thyroid cancer. Her hope is that we will always have something to offer patients who need treatment for thyroid cancer and make significant contributions to the field.

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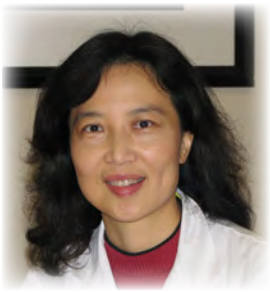
Glucocorticoids-Induced Osteoporosis



Huifang Linda Lu, MD PhD Assistant Professor, Section of Rheumatology, Department of General Internal Medicine, AT and EC

Glucocorticoids (GC) are widely used in treating inflammatory conditions. GC-induced osteoporosis (GIOP) is the most common cause of secondary osteoporosis, which leads to an increased risk of fracture. The normal bone homeostasis is the balance of constant remodeling with resorption and formation as functions of osteoclasts and osteoblasts. GCs can cause a rapid bone loss, by decreasing bone formation via GC-induced apoptosis of both osteoblasts and osteocytes, and increasing bone resorption due to the increased life-span of pre-existing osteoclasts. Anti-resorptive agents such as bisphosphonates are effective in treating GIOP. Recent studies show promising roles of anabolic therapeutic reagent, the active (1–34) parathyroid hormone (PTH) molecule, teriparatide, in treating GIOP. Teriparatide has been demonstrated in several clinical studies to significantly increase the bone mass and decrease the incidence of fractures in patients affected by GIOP. With the available screening and treatment options, GC induced bone loss continue to be under-diagnosed and under-treated.

Introduction

Pharmacological use of synthetic glucocorticoids (GCs) is the most frequent second form of clinical hypercortisolism. GCs are commonly used in the treatment of autoimmune, allergic, demyelinating, pulmonary, gastrointestinal diseases, and for the immunosuppression after organ and stem cell transplant. GCs are also fundamental drugs used in the treatment of lymphoid malignancies with apoptotic cell death as the proposed mechanism of action. Recent studies show that dexamethasone induces autophagy in lymphoid leukemia cells, a prerequisite for the efficient killing of the leukemic cells by dexamethasone [1]. The wide use of GCs is associated with a host of potential side effects. The unwanted effects on bone tissue, named GC-induced osteoporosis (GIOP), is a metabolic bone disease characterized by decreased skeletal strength with an increased fracture risk [2]. Fracture can occur in 30-50% of patient on long-term treatment of GCs [3]. Vertebral fractures occur early and often remain asymptomatic after GC exposure, when there is rapid bone loss. GC induced fracture also tends to occur at the bone mineral density (BMD) level higher than women with postmenopausal osteoporosis. Although it was known that the GC-induced bone loss is dose-dependent, current studies show that long term treatment with low dose GCs, as low as 2.5-7.5 mg daily, can lead to significant bone loss and increased risk for fracture. [2] [4] [5].

Mechanisms of GIOP and Fractures

Prior and current exposure to GCs increases the risk of fracture beyond that explained by levels of BMD. Bone loss, predominantly found in bones high in trabecular contents, occurs rapidly after the exposure to GCs, as high as 12% the first year, although the rate of bone loss decreases to about 3% annually later on. The rapid bone loss leads to a greater risk of fractures. The risk of fractures of the hip and spine increases 7- and 17-fold after being treated with prednisone 10 mg for 3 months [6]. The negative impact of GCs on the bone is due to both direct effect on bone cells and indirect effect on extraskeletal tissues. GCs increase osteoblast apoptosis and death of osteocytes. Strikingly, the loss of vertebral compression strength observed in GC-treated wild mice was prevented in the transgenic mice where the GC was inactivated, despite equivalent bone loss in both wild-type and transgenic mice [7]. These results suggest that GC-induced loss of bone strength results in part from increased death of osteocytes, independent of bone loss. Dying osteocytes in turn become the beacons for osteoclast recruitment to the vicinity, which results in the increase of bone resorption and bone loss. Gene expression analysis in human osteoblasts exposed to GC identifies coordinated alteration of members of the WNT signaling pathway, including frizzled-2, frizzled-7, DKK1 and WNT5B [8]. The WNT pathway is a key regulator of skeletogenesis as well as differentiation of bone cells. Modulation of DKK1, members of the WNT pathway in animal studies attenuates GC induced osteoblast apoptosis, adipocytic differentiation, and the loss of bone mass [9]. The pro-apoptotic effects of GCs on osteoblasts and osteocytes are due to the activation of caspase 3, a common effecter of several apoptotic signaling pathways [10] [7]. Osteocytes play an important role in the repair of bone microdamage as mechanosensors [11]. Loss of osteocytes disrupts the osteo-canalicular network, by modifying the elastic modulus surrounding osteocytic lacunae, which can lead to the failure of detecting stimulating signals to initiate the repair of damaged bone. [12]. GCs affect bone resorption by acting directly on osteoclasts, prolonging the life-span of existing osteoclast [13] [14] and by promoting osteoclastogenesis via the inhibition of osteoprotegerin through multiple levels [15].

GCs also influence bone cells by regulating the growth factors in bone microenvironment. GCs decrease the expression of insulin-like growth factor (IGF)- I and the IGF binding proteins (IGFBP). IGF-I increases bone formation and the synthesis of type I collagen, decreases bone collagen degradation and osteoblast apoptosis [16]. The effects of GCs on IGF-I expression by osteoblasts are reversed by PTH, which may partially explain the efficacy of PTH in the treatment of GIOP [17] [18].

GC indirectly regulates bone metabolism via its action on extraskeletal tissues. GCs inhibit calcium absorption from the gastrointestinal tract, by opposing vitamin D actions and decreasing the expression of specific calcium channels in the duodenum [19]. Renal tubular calcium reabsorption is also inhibited by GCs. In addition to the direct effect on the growth factors in the skeletal microenvironment, GCs alter the growth hormone (GH)/IGF-1 axis by blunting the secretion of GH [20] and by inhibiting the gonadal axis which result in the decreased secretion of testosterone and estrogen.

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These systemic effects may contribute to the pathogenesis of GIOP [21].

Therapeutic Perspectives

Due to the direct effects of GCs on bone cells, therapeutic agents aimed at restoring balanced bone cell activity by increasing apoptosis rate of osteoclasts (e.g., bisphosphonates) or by directly decreasing apoptosis rate of osteoblasts (e.g., cyclical PTH, Teriparatide) are preferred to protect patients from bone loss and reduce fracture risk. Bisphosphonates have been widely used as the standard treatment of GIOP; recent studies show that intermittent administration of human PTH (1–34) stimulates bone formation by increasing osteoblast number. In addition, human PTH (1–34) regulates the level and activity of locally produced growth factors, such as IGF-1, that are important for bone metabolism. Calcitonin may be indicated where bisphosphonates are contraindicated and in the management of acute pain due to vertebral fracture. Based on currently available evidence, fluoride, androgens and estrogens cannot be recommended for the sole purpose of prevention and treatment of GIOP. However, supplementation of sex hormones may be indicated if GC-induced hypogonadism is present and leads to clinical symptoms.

Management of GIOP

Guidelines for the primary and secondary prevention of GIOP are proposed by the Royal College of Physicians and the American College of Rheumatology (ACR). For primary prevention, both recommended the use of a bisphosphonate at the initiation of GCs at the dose of more than 5 mg of prednisone equivalent daily for at least 3 months, with the UK guideline also including the additional risk factors of age > 65 and/or prior fracture [22]. For secondary prevention, ACR recommended bisphosphonates to be started at T-score ≤ - 1.0, whereas UK guideline recommended T-score ≤ - 1.5 or with a reduction of BMD of ≥ 4% after 1 year of observation. Sex hormones can be considered in postmenopausal women and men with hypogonadism, who are exposed to GCs. Calcium and vitamin D should be a systematic adjunctive measure to optimize drug treatment for GIOP. Kyphoplasty for selected patients with painful vertebral fractures related to GC use is a useful addition to medical treatment. Life style changes should also be consulted on smoking cessation, reduction of alcohol consumption, and a weight-bearing exercise program.

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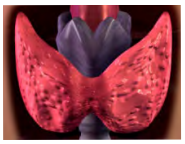

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Atlas of Endocrine Neoplasia

By Mouhammed Amir Habra, MD, and Rena Vassilopoulou-Sellin, MD

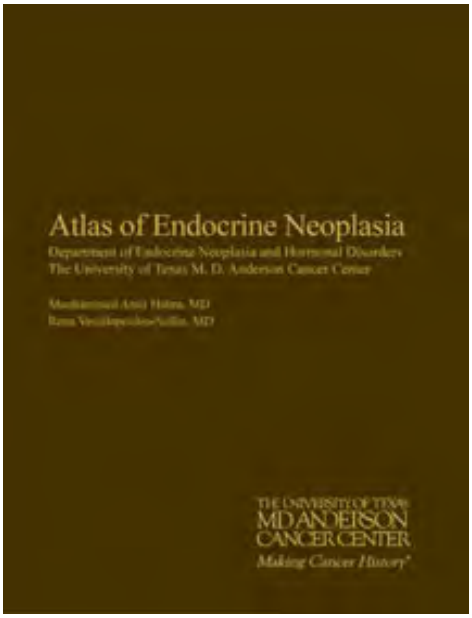
With many endocrine tumors being relatively uncommon, it is exceedingly hard to find clear documentation of the natural course of these tumors and their clinical presentation. This book has documented four decades of very unique clinical data gathering combined with the most recently used tests and diagnostic procedures to make it an unparalleled resource for physicians in practice as well as those in training.

It comes in a leather bound cover with 167 pages containing approximately 700 pictures and colored illustrations. In addition, this atlas provides relevant text, tables and algorithms to make it a comprehensive, yet concise, reference for endocrine neoplasia.

This atlas provides a detailed coverage of endocrine neoplasms including the epidemiology, clinical features, diagnostic procedures and treatment. This classical compilation is intended to serve as a reference for physicians as well as medical students and trainees who can see the natural course of various clinical syndromes and endocrine tumors. In addition, it summarizes the diagnostic work up and the interpretation of wide variety of endocrine tests currently in clinical use.

To Order:

Please visit: http://www.mdanderson.org/publications/atlas-of-endocrine-neoplasia/index.html for an order form, or call 713-792-2841.



Clinical Trials

Phase II, Multicenter, Open-label, Single Arm Trial to Evaluate the Safety and Efficacy of Oral E7080 in Medullary and Iodine-131 Refractory, Unresectable Differentiated Thyroid Cancers, Stratified by Histology.

The goal of this clinical research study is to learn if E7080 can help control metastatic thyroid cancer. The trial will determine the effect of E7080 on the objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) by independent imaging review (IIR) and determine the pharmacokinetic (PK) profile and the pharmacokinetic/pharmacodynamic (PK/PD) relationships of E7080.

The trial is open to patients with a confirmed diagnosis of differentiated thyroid cancer or medullary thyroid cancer, with a measurable lesion of at least 1.5cm in diameter, who show evidence of disease progression, and have unresectable 131I refractory resistant disease.

For more information, please contact Cheryl Mize, RN, Research Nurse, at: 1-713-792-9851.

Phase II trial of Sunitinib (SU11248) in Iodine-131 refractory, Unresectable differentiated thyroid cancers and medullary thyroid cancers.

The goal of this clinical research study is to learn if sunitinib can help control thyroid cancer that has spread outside the thyroid. The safety of this drug will also be studied.

The trial is open to patients who have histologically or cytologically confirmed papillary, follicular, or Hurthle cell carcinoma (cohort A) or medullary thyroid carcinoma (cohort B). Their disease must have progressed despite treatment with iodine-131 therapy or they are not candidates for iodine-131 therapy and their disease cannot be completely removed by surgery. All patients with WDTC are expected to be on thyroxine suppression therapy, and cannot have received prior receptor tyrosine kinase inhibitors, or cannot have received more than one prior chemotherapy regimen for metastatic disease.

For more information, please contact Cheryl Mize, RN, Research Nurse, at: 713-792-9851

For information on other clinical trials conducted at M. D. Anderson Cancer Center, please visit: http://www.mdanderson.org/Cancer_Pro/CS_Resources/display.cfm?id=562561A1-751F-11D4-AEBD00508BDCCE3A&method=displayFull. For information on other clinical trials conducted at other institutions, please visit: http://www.clinicaltrials.gov/

Building Bone Health in Cancer Patients

Mimi I. Hu, M.D., Assistant Professor, Department of Endocrine Neoplasia and Hormonal Disorders

Nearly 4% of the United States population has been diagnosed with cancer with the number of cancer survivors growing to more than 10.8 million. Although advancements in targeted therapies have positively influenced progression-free survival, long-term undesirable effects are recognized and require multidisciplinary evaluation and management. One of the most prevalent long-term health effects in cancer survivors is bone loss or osteoporosis. Osteoporosis is a systemic skeletal disorder defined by low bone mineral density and deterioration of the bone tissue microarchitecture, which may result in an increased propensity to fracture. It has been recognized as a major health threat for an estimated 44 million Americans, or 55% of people 50 years of age and older. In the United States, at least 10 million people have osteoporosis, and an additional 34 million are estimated to have low bone mass, placing them at increased risk for osteoporosis.

Several groups of cancer survivors are recognized to be at particularly high risk for developing osteoporosis. Women with breast cancer treated with cytotoxic chemotherapy frequently experience early menopause and consequently bone loss. Adjuvant therapy with an aromatase inhibitor can further increase bone turnover and worsen bone loss. Men with prostate cancer treated with surgical orchiectomy or antiandrogenic therapy are at equivalent risk for developing osteoporosis. A third group at risk for bone loss is patients with lymphoma, myeloma, or leukemia (*see article by Dr. Lu on page 6*). Common mechanisms shared by these groups include exposure to osteoclast-activating cytokines secreted by neoplastic cells and to high-dose glucocorticoids. Accelerated loss of bone mineral density, with consequential complications of compression fractures and pain, becomes more important with increased duration of survival. Disease-related skeletal complications are associated with shorter overall survival and a decreased quality of life.

The health effects reported by cancer survivors are numerous, but medical research and published literature on the topic are scarce, especially for adult survivors. Published literature on the risk, incidence, and detection of cancer treatment-induced bone loss in survivors of cancers other than breast or prostate cancer remains limited. Most studies of cancer treatment-induced bone loss focused on survivors of childhood cancers. Those studies show varied and occasionally conflicting results, making it challenging for researchers to reach explicit conclusions. Developing strategies to monitor, prevent, and treat significant bone loss, which can lead to osteoporosis and insufficiency fractures, has become a prominent focus of clinical research in survivors of cancer.

Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women. An estimated 194,000 new cases of breast cancer are expected to occur in the United States in 2009. From 1973 until 1997, the incidence of breast cancer increased worldwide, particularly in women older than 50; however, mortality has stabilized or decreased in most countries. Early detection through implementation of large-scale screening programs and improved treatment modalities are key factors influencing survival rates. Unfortunately, the significant benefits imparted by more efficacious therapies, particularly aromatase inhibitors, are associated with adverse effects on bone health. Significant bone loss can be seen in women within a year of developing chemotherapy-induced menopause. Overall, bone loss with various breast cancer therapies can range from 2.6 – 7.7% in the lumbar spine within the first year of treatment, greater than that seen with natural menopause (average of 2% per year for 5 – 10 years). Even more importantly, the annual incidence of vertebral insufficiency fractures is higher in patients with early-stage breast cancer than in the general population. Results from the large observational study in the Women's Health Initiative showed that breast cancer survivors had a 15% higher rate of all fractures, regardless of the treatment they received, than women without any cancer history.

Prostate Cancer

Prostate cancer is the most frequently diagnosed cancer in men. An estimated 192,280 new cases of prostate cancer are expected to occur in the United States in 2009. With 27,360 deaths projected to occur during the same period, prostate cancer is a leading cause of cancer death in men. However, prostate cancer death rates have declined since the early 1990s. This trend is explained by widespread prostate cancer screening and by improvements in hormone therapy for this condition. Taking advantage of the tumor's dependence on testosterone, androgen-deprivation therapy (ADT) is indicated for men with metastatic or locally advanced non-metastatic prostate carcinoma. Despite significant therapeutic benefits, ADT (bilateral orchiectomy, leuprolide and other GnRH analogues), either alone or in combination with an antiandrogen (e.g., flutamide, bicalutamide) causes severe hypogonadism characterized by loss of libido, impotence, gynecomastia, muscle mass reduction, and bone loss. Significant bone loss can be seen in men within a year of castration or 6 months after initiating treatment with a gonadotropin-releasing hormone (GnRH) analogue.

The annual incidence of osteoporotic fractures is higher in prostate cancer patients treated with surgical or medical castration than in those who receive other treatment or in healthy men. In retrospective reviews, fractures start to occur within 2 years of beginning treatment and increase in frequency with longer durations of ADT. More importantly, skeletal fractures in patients with prostate cancer may be associated with shorter survival, independent of the pathological stage of the cancer.

Factors Mediating Bone Loss and Fractures

Breast and prostate cancer patients may develop osteoporosis as a consequence of therapeutic hypogonadism. Therapeutic hypogonadism is an important strategy in controlling hormone-dependent tumors such as most breast and prostate cancers. Unfortunately, estrogen and testosterone deficiencies are associated with abnormally increased bone production of

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interleukins-1 and -6 and tumor necrosis factor alpha, as well as reduced bone synthesis of transforming growth factor-beta 1. Moreover, estrogen-deficient bone marrow is associated with reduced expression of RunX2 and osterix in osteoblast precursors. Patients treated with estrogen- or androgen-deprivation therapy against breast or prostate cancer, respectively, may later exhibit an abnormally increased RANKL/OPG ratio, leading to increased osteoclastogenesis. In hypogonadal individuals without cancer, estrogen and testosterone deficiencies translate into severe abnormalities in bone microarchitecture. Because estrogen- and androgen-deprivation therapies can dramatically and severely decrease hormone levels, similar or even worse microarchitectural abnormalities are expected in survivors of breast or prostate cancer, manifesting clinically as osteoporosis and/or fractures.

Selective Estrogen Receptor Modulators and Aromatase Inhibitors

In patients with breast cancer expressing estrogen or progesterone receptors, adjuvant endocrine treatment (i.e., selective estrogen receptor modulators [SERMs], aromatase inhibitors [AIs], or ovarian ablation or suppression), which blocks estrogen action on target organs or suppresses estrogen levels, results in significant improvement in disease-free and overall survival rates.

The SERMs, tamoxifen and raloxifene, have differential effects on various organs; their antagonist properties in breast tissue support their roles as adjuvant therapy for patients at high risk for recurrence and preventive therapy for healthy women at risk of developing breast cancer. Both SERMs have antagonist and agonist effects on the bone depending on menopausal status. Premenopausal women taking a SERM can experience loss in bone mineral density (BMD) attributed to antagonism of the effects of endogenous estrogen on bone. In contrast, postmenopausal women, who have extremely low levels of bioavailable estrogen, typically exhibit increased bone density, as the estrogen-like effect of a SERM is sufficient to positively influence bone density. Moreover, postmenopausal women who cease taking tamoxifen experience rapid bone loss within 12 months.

For years, tamoxifen was the standard hormonal treatment in both premenopausal and postmenopausal women. Aromatase inhibitors (AIs), introduced in the mid-1990s, have changed the paradigm of management of breast cancer. Three third-generation AIs have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of estrogen-dependent breast cancer in postmenopausal women: two reversible nonsteroidal agents (anastrozole, letrozole) and one irreversible steroidal agent (exemestane). Aromatase activity mediates the peripheral conversion of androgenic precursors (testosterone and androstenedione) of adrenal origin to estradiol and estrone within the ovaries, adipose tissue, liver, muscle, and brain. After menopause, the proportion of estrogens synthesized by nonovarian tissues increases. Thus, already low levels of estrogen in postmenopausal breast cancer patients can be diminished further by use of agents that inhibit aromatase. Treatment with an AI, rather than tamoxifen, has become the preferred adjuvant therapy for postmenopausal women with hormone receptor–positive breast cancer.

As the AIs markedly reduce circulating levels of bioavailable estrogens, it is expected that they will exacerbate bone loss and increase fracture risk in postmenopausal patients. Several studies have found that each AI is associated with statistically significant losses in BMD when compared to placebo or tamoxifen (see Table). Increased fracture rates have been reported in some of these studies, as well.

Gonadotropin-releasing hormone agonists

For premenopausal women, complete estrogen suppression via ovarian ablation is required for the treatment of hormone-sensitive breast cancer. This can be accomplished by bilateral oophorectomy, radiation-induced ovarian ablation, or administration of an agonist of GnRH, or luteinizing hormone–releasing hormone (LHRH). Goserelin, the only LHRH-agonist approved for use in breast cancer in the U.S., is safe, reversible, and does not cause permanent ovarian dysfunction. Combination therapy with tamoxifen and ovarian suppression is preferred over either treatment alone in premenopausal women with hormone-sensitive breast cancer. BMD can decrease substantially with treatment; however, it can recover partially within one year after cessation of goserelin.

In patients with prostate cancer, significant losses in bone mineral density can be seen with leuprolide or goserelin, in ranges higher than that observed with normal male aging. These findings correlate with abnormally increased bone turnover in which bone destruction is predominant over bone formation. Accelerated bone loss in prostate cancer survivors is similar to that observed in women who have undergone bilateral oophorectomy and is greater than that observed in healthy postmenopausal women.

Chemotherapy

Adjuvant systemic chemotherapy can induce ovarian failure in premenopausal patients with early stage breast cancer and exacerbate the expected bone loss in postmenopausal patients. Chemotherapy-induced amenorrhea is dependent on age, dose, and medication type. Ovarian failure develops within 1 year of initiating adjuvant chemotherapy treatment in 63-96% of premenopausal women. Cyclophosphamide-based regimens are strongly associated with premature menopause in a cumulative dose-dependent manner. After chemotherapy, women over the age of 40 years demonstrate a higher frequency of ovarian failure and lower rate of resumed when compared to younger women. There is a strong correlation between development of ovarian failure and bone loss.

Other Contributing Factors

Radiation therapy after surgical resection for breast, prostate or gynecologic cancers can lead to a higher incidence rib or pelvic insufficiency fractures. Exposure to high-dose corticosteroids give with systemic chemotherapy may exacerbate bone loss acutely by prolonging osteoclast lifespan and inducing osteoblast apoptosis. Other conditions, such as decreased physical activity during and after cancer therapy or vitamin D deficiency, may potentiate bone loss in this population of patients. Further studies are needed to clarify these as the influence of these risks upon bone health.

Prevention and Management of Bone Loss in Cancer Patients

A critical element in the prevention of bone loss in cancer patients is to increase awareness of the potential adverse effect of treatments upon bone health within the medical community and amongst our patients, as osteoporosis is a silent disease until a symptomatic fracture occurs. Appropriate surveillance for bone loss must be implemented. According to 2003 guidelines from the American Society of Clinical Oncology (ASCO), a BMD study is recommended in women with breast cancer at high risk for osteoporosis: those older than 65 years old; those aged 60-64 years with a family history of osteoporosis, low body weight, prior nontraumatic fracture, or other risk factors; postmenopausal

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women receiving AI treatment, and premenopausal women with treatment-induced ovarian failure, Serial testing with dual X-ray absorptiometry (DXA) scan is important in identifying active bone loss over time. ASCO has not yet provided guidelines for screening of bone health in prostate cancer patients. However, the accepted practice is to assess bone mass by DXA scan in male patients with high risk for developing osteoporosis (e.g., ADT).

Prevention and treatment of bone loss in cancer patients has been best studied in breast cancer survivors. Multiple studies have been conducted evaluating the efficacy of bisphosphonates (clodronate, alendronate, risedronate, pamidronate, zoledronic acid) for the prevention of bone loss related to chemotherapy, tamoxifen, and AIs. These trials suggest that early initiation of bisphosphonate therapy in patients with hormone-responsive breast cancer who are at high risk for severe bone loss (i.e., treatment with an AI or LHRH-agonist) may be beneficial in preventing or delaying bone loss. The clinical value of this practice will need to be validated, however, by demonstration of diminished fracture rates in longer follow-up studies of these patients. It has been shown in several studies that patients with normal BMDs at baseline did not become osteoporotic; in comparison, osteopenic patients experienced greater decreases in BMD after treatment with an AI. Correlation between rates of bone loss over time and fracture risk may help identify patients who would most benefit from preventive medications. Analyses of on-going studies [Zometa-Femara Adjuvant Synergy Trial (Z-FAST), Anastrozole Bisphosphonate Study in Postmenopausal Women with Hormone-Receptor-Positive Early Breast Cancer (SABRE), and SWOG-S0307] likely will offer more insight into appropriate intervention strategies for the prevention of bone loss secondary to AIs for postmenopausal women with early stage breast cancer.

Very few trials have evaluated the effect of antiresorptives in prostate cancer patients treated with ADT. Additionally, these studies were not powered to examine fracture reduction as an outcome and included observations over very short periods of time. Consequently, no definitive studies have determined the rate of fracture prevention in prostate cancer survivors with medical therapy. Surrogate markers of osteoporosis (e.g., BMD, markers of bone resorption) are positively affected by either an oral or IV bisphosphonate. Estrogens play an important role in regulating normal bone metabolism in men. The efficacy of estrogens in preventing bone loss has been evaluated in patients undergoing ADT. Besides significantly reducing bone markers in patients treated with ADT, treatment with estrogen or a SERM has been shown to preserve BMD. However, estrogen-based therapies have been associated with higher rates of cardiovascular events in males.

There are currently no reports on the bone-protective effects of calcium and vitamin D in cancer patients. However, supplementation with vitamin D has been shown to reduce the risk of hip fractures in healthy ambulatory women. It is recommended that any evaluation of low bone mass include an assessment of vitamin D status.

Conclusions

Although cancer survivors are living longer with advances in surveillance and treatment of cancer, long-term adverse effects upon other body systems are known to occur, which can lead to clinically significant and highly morbid outcomes. The preservation of bone health and fracture prevention in high-risk patients should be considered a goal by both medical professionals and the patients themselves. Patients should be educated and included in their treatment plan. They can take an active role in their care by implementing management strategies such as diet modification, calcium and vitamin D supplementation, exercise, and other lifestyle changes.

At The University of Texas M. D. Anderson Cancer Center, we identify survivorship as an important phase in the continuum of cancer management. Within our survivorship programs, we have implemented bone health surveillance and management algorithms specific to our patients. We have developed a multidisciplinary bone health clinic that includes a wide range of clinical providers including: endocrinology, rheumatology, oncology, radiology, orthopedic surgery, pain management, nutrition, and rehabilitative medicine. Through collaborative efforts in clinical management and research programs, we hope to strengthen the bone health of our cancer survivors.

As awareness of the problem of bone loss in cancer increases and further research is conducted, we can expect improved surveillance protocols and treatment modalities for clinically relevant bone loss in cancer patients, thus leading to improvement in quality of life for our patients.

Table. Bone mineral density changes and fracture rates in response to aromatase inhibitors

Trial	Treatment Arms	Change in BMD from Baseline AI vs. comparator	Follow-Up (years) (n = patients in bone study)	Clinical Fracture Rate AI vs. comparator (median follow-up interval)
ATAC	Anastrozole vs. Tamoxifen*	Spine: -6.1% vs. +2.8% (P<0.0001) Hip: -7.2% vs. +0.7% (P<0.0001)	5 (n=308)	11% vs. 8% (P<0.0001) (n=6286) (68 mos)
MA.17	Letrozole vs. Placebo	Spine: -5.35% vs. -0.7% (P=0.008) Hip: -3.6% vs. -0.71% (P=0.044)	2 (n=226)	5.3% vs. 4.6% (P=0.25) (n=226) (30.6 mos)
IES	Exemestane vs. Tamoxifen†	Spine: -2.97% vs. -0.02% (P<0.0001) Hip: -1.57% vs. -0.5% (P<0.0001) Spine: -4% vs. -0.6% (P value not available)	1 2 (n=206)	7% vs. 5% (P=0.003) (n=4724) (58 mos)

*Analysis of monotherapy arms with a total of 167 patients evaluable at 5 years.
†Exemestane compared to continued tamoxifen after all patients treated with tamoxifen for 2-3 years.
ATAC – Arimidex, Tamoxifen, Alone or in Combination; MA.17 – National Cancer Institute of Canada Clinical Trials Group MA.17; IES – Intergroup Exemestane Study; AI – aromatase inhibitor

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Thyroid Nodule Clinic

Do you need a Resource for a Suspicious Thyroid Nodule?

Thyroid nodules are fairly common, representing the most common endocrine problem in the United States, but effective evaluation is extremely important to rule out thyroid cancer.

Dr.. Naifa Busaidy, Director of the Thyroid Nodule Clinic now open at M. D. Anderson Cancer Center says, "The clinic serves as a resource for our physicians and all patients with thyroid nodules. We want to be a part of your team in providing an exceptional experience for the community physician and their adult and pediatric patients.

Getting a rapid and accurate diagnosis in one place at one time for a patient anxious about whether or not they might have cancer, improves the experience for all those involved. The experienced multidisciplinary team of endocrinologists, surgeons, mid-levels, cytopathologists radiologists and ultrasonographers at M. D. Anderson are here to help you. We also have two pediatric endocrinologists who can evaluate pediatric patients of all ages.

All patients receive within one day:
- Consultation with a thyroid specialist
- Thyroid ultrasound
- Thyroid biopsy, if needed
- Multidisciplinary conference to discuss treatment options, if needed.

The Thyroid Nodule Clinic is located inside the Endocrine Center at M. D. Anderson Cancer Center at 1515 Holcombe in Houston, Texas.

For more information or to refer a patient for an appointment:

New Patient Referral Coordinators: 713-563-4400, and 713-792-5410 for patients under 18 years of age.

Physician to Physician Referrals: 713-792-2841 Online Referrals: https://my.mdanderson.org/

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