



## Complications to the Hypothalamic-Pituitary Axis (HP axis) in Pediatric Cancer Patients



**Anita K Ying, MD**  
**Assistant Professor**  
**Department of Endocrine Neoplasia and Hormonal Disorders**

Evaluation for hormone deficiencies in pediatric cancer patients is primarily focused on the childhood cancer survivor. Because these late effects can occur anywhere from 2 to 25 years after therapy, adult and pediatric endocrinologists need to be aware of these issues.

Disorders of the HP axis are generally due to injuries to the hypothalamus and/or pituitary from surgery or radiotherapy. Although surgery or tumoral expansion in the area can cause an immediate effect, complications from radiotherapy can take years to manifest.

### **Growth hormone deficiency (GHD)**

GHD is the most common anterior pituitary deficit after cranial irradiation. The higher the dose of radiation and the longer the time from treatment, the greater the risk of GHD. For radiation exceeding 30Gy, GHD can present within 5 years and cumulative incidence is approximately 90%. For doses ranging from 18-24Gy, GHD can manifest in 10 or more years. Other high risk factors include TBI given in a single fraction or pretransplant cranial radiation.

The Children's Oncology Group Long Term Follow Up Guidelines (LTFU) recommend monitoring growth velocity every 6 months until growth is complete, and then annually for onset of adult growth hormone deficiency. For those patients with GHD during childhood, some authors recommend retesting after linear growth is complete. Using IGF-1 and IGFBP3 levels as screening tools are not reliable after cranial radiation because they can be in the normal range despite the presence of GHD.

GH therapy can improve final height in childhood cancer survivors, especially if treated at a younger bone age. However, children who have received > 20Gy to the spine do not respond as well. And

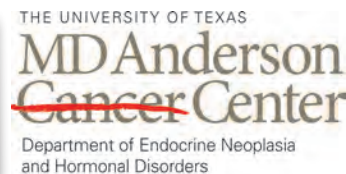
younger patients receiving spinal radiation have a higher risk for skeletal dysplasia, characterized by a shorter seating height than standing height. Long term cohort studies have not shown increased risk of recurrence or death from GH replacement therapy. However, there is an increased relative risk of 2.15 for developing a second neoplasm, with meningiomas being the most common.

### **LH/FSH Disorders**

Radiotherapy in doses  $\geq$  18Gy and younger age at treatment increase the risk of developing precocious puberty. Physicians should be alerted if there is sustained breast development before the age of 8 or menarche before the age of 10 years in girls. For boys, testicular volume is not an accurate indicator of puberty because many therapies can damage the seminiferous tubules. Thus, early onset of secondary sexual characteristics or growth spurt should raise suspicion in a male patient. Development of precocious puberty can also mask the growth failure of a GHD patient because of seemingly normal growth velocity due to inappropriate sex steroid secretion.

LTFU guidelines recommend monitoring yearly until the child is sexually mature. Treatment with GnRH agonist, with or without GH replacement depending on GH status, does positively impact final adult height.

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Radiation to the hypothalamic-pituitary region  $\geq 40\text{Gy}$  can lead to gonadotropin deficiency. The incidence is less than GHD. More recent reports suggest that there may be some subtle defects from doses in the 18-24Gy range. Hormonal replacement therapy is recommended, and some survivors may need reproductive endocrinology referrals for infertility evaluation. Bone density testing can also be considered in patients who are hypogonadal.

#### Central adrenal insufficiency (ACTH deficiency)

For patients receiving  $\geq 40\text{Gy}$  radiation to the hypothalamic-pituitary region, central adrenal insufficiency can occur in over 35% within 4 years. It is generally associated with other HPA deficiencies. Some authors recommend annual screening by checking 8:00am cortisol levels for at least 15 years after treatment. There have also been reports that AM cortisol levels can appear normal despite abnormal stimulation testing, suggesting that AM levels should not be used as a screen.

#### Central hypothyroidism (TSH deficiency)

After irradiation of the HP area, central hypothyroidism occurs less often than GHD and central precocious puberty. The incidence in patients treated with  $\geq 40\text{Gy}$  radiation has been reported at 23% within 4 years. LFTU guidelines recommend annual TSH, free T4 levels.

#### Hyperprolactinemia

High-dose irradiation ( $\geq 50\text{Gy}$ ) to the hypothalamic area can cause hyperprolactinemia due to loss of dopamine from the hypothalamus, which normally inhibits prolactin secretion from the pituitary gland. It is most frequently seen in young women and is usually subclinical. In patients with decreased libido, galactorrhea

or women with amenorrhea, a prolactin level should be checked.

#### Hypothalamic Obesity

Insult to the hypothalamus has been hypothesized to cause hyperphagia by altering satiety centers. It has also been suggested that increased parasympathetic tone causes hyperinsulinemia, which leads to fat storage and may be a contributing factor to obesity. Patients with this disorder are quite challenging to treat. Octreotide has been tried in a small, randomized trial with encouraging results. Dextroamphetamine has also had some success to control weight gain. Gastric bypass surgery is now being explored as a potential intervention for patients that have completed their pubertal development.

#### Autoimmune Hypophysitis

Acute adverse effects to the HP axis during treatment are rare in children. Novel therapies, such as Anti-CTLA-4, are associated with hypophysitis causing hypopituitarism, pituitary enlargement, and associated symptoms. ACTH, TSH, and gonadotropin deficiency often occur. While TSH and gonadotropin function usually return, reports thus far show persistence of ACTH deficiency. If these agents become a part of pediatric cancer protocols, then pediatric endocrinologists and oncologists will need to monitor for these consequences.

As the population of childhood cancer survivors grows, adult and pediatric endocrinologists can expect to care for patients at risk for pituitary hormone deficiencies. At UT MD Anderson Cancer Center, Endocrinology works closely with our medical and radiation oncology colleagues to establish protocols to monitor patients at risk for HP axis dysfunction.

## Upcoming Events

**Pediatric Endocrine Society 2011 Annual Meeting.** April 30-May3, 2011. Denver, Colorado. ([www.lwpes.org](http://www.lwpes.org))

**13th European Congress of Endocrinology's ECE 2011.** April 30- May 4, 2011. Rotterdam, Netherlands ([www.ece2011.com/](http://www.ece2011.com/))

**Endocrine Society's Endo 2011, 93rd Annual Meeting & Expo.** June 4-7, 2011. Boston, MA. ([www.sherago.com/endocrine/AnnualMeeting.htm](http://www.sherago.com/endocrine/AnnualMeeting.htm))

**American Society of Clinical Oncologists (ASCO) 2011 Annual Meeting** June 4-8, 2011. Chicago, IL. ([www.asco.org/portal/site/ASCOv2](http://www.asco.org/portal/site/ASCOv2))

**American Society for Bone and Mineral Research (ASBMR) 2011 Annual Meeting** Sept 16-20, 2011. San Deigo, CA. (<http://www.asbmr.org/Meetings/AnnualMeeting.aspx>)

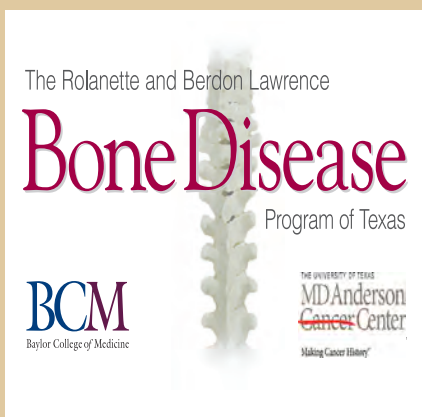
**4th Current Concepts in the Management of Thyroid and Parathyroid Neoplasms.** Oct 20-23, 2011. Sante Fe, New Mexico. (<http://www.mdanderson.org/education-and-research/education-and-training/schools-and-programs/cme-conference-management/conferences/index.html>)

**American Thyroid Association ATA's 81st Annual Meeting** October 26-30, 2011. Indian Wells, CA. ([http://www.thyroid.org/ann\\_mtg/2010\\_81st/index.html](http://www.thyroid.org/ann_mtg/2010_81st/index.html))

**15th International Congress of Endocrinology.** May 5-9, 2012. Florence, Italy. ([www.endosociety.com](http://www.endosociety.com))



## The Rolanette and Berdon Lawrence Bone Disease Program of Texas



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 MD Anderson Cancer Center.

The mission of the Bone Disease Program of Texas includes:

- Developing bone-forming treatments for all degenerative bone diseases
- Improving prevention and treatment of bone cancer metastasis
- Fostering 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 metastasis. Almost 34 mil-

lion more are estimated to be at increased risk for osteoporosis.

For more information, please contact Lea Tatar, Administrative Program Director, at 713-792-1345, or visit: [www.bonediseaseprogram.com](http://www.bonediseaseprogram.com)

# Hyperglycemia in Patients Being Treated for Cancer



**Victor R. Lavis, MD, Professor**  
**Department of Endocrine Neoplasia and Hormonal Disorders**

Hyperglycemia is very common among people with cancer. For example, at MD Anderson in 2006, 20% of inpatients had documented circulating glucose levels at least 200 mg/dL on more than one day. Hyperglycemia and cancer are interrelated in multiple ways.

People with diabetes mellitus are at increased risk of developing several types of cancer.

Those with type 2 diabetes, the most common diabetes phenotype in the United States and worldwide, experience elevated incidence of and death from cancer, particularly malignancies arising in the liver, pancreas, endometrium, colon, breast and bladder. In part, this may be because many of the factors that predispose to type 2 diabetes, including obesity, insulin resistance, hyperinsulinemia, oxidative stress and chronic inflammation, also predispose to development of cancer. Growth hormone and IGF-1 signaling promote both insulin resistance and susceptibility to cancer. A recent survey of individuals with the Laron syndrome, a loss-of-function mutation in the growth hormone receptor gene, showed very low incidences of both diabetes and cancer, again suggesting that these conditions may have common origins.

Also, it has been suggested that hyperglycemia itself may provide a favorable environment for the growth of malignant cells, which rely on anaerobic glycolysis rather than respiration for energy and, therefore, have a high demand for glucose. If hyperglycemia, per se, is important for tumor growth or survival, one would expect type 1 diabetes to be associated with progression of cancer; to date, there are no good epidemiologic data pertinent to this question.

Various oncogenes and tumor suppressor genes have turned out to be linked to intermediary metabolism. For example, the key tumor suppressor gene p53 is an important regulator of both mitochondrial and pentose phosphate cycle activity. The clinical importance of these relationships is not yet known.

#### **Various treatments for cancer can produce hyperglycemia.**

Perhaps the most important drivers of hyperglycemia among cancer treatments are high-dose glucocorticoids, used primarily for four reasons: (a) mitigation of tumor development in patients with lymphoma, lymphoid leukemia and myeloma; (b) amelioration of side effects of chemotherapy, e.g. nausea; (c) reduction

of edema surrounding tumor masses, particularly as related to neurological symptoms and; (d) suppression of manifestations of graft-versus-host disease in patients with stem cell transplants. High-dose glucocorticoids are very commonly prescribed for patients with cancer; at M.D. Anderson in 2006, they were administered during 52% of all admissions. Glucocorticoids augment insulin resistance in the short term; in animal models, long-term treatment may be toxic to pancreatic beta cells. The hyperglycemic response to glucocorticoids appears to be greatest in those individuals whose beta cells fail to compensate for acute increases of insulin resistance. In humans, glucocorticoids seem especially to evoke postprandial hyperglycemia. In a cell culture model, exendin-4 protected beta cells from apoptosis produced by dexamethasone, and a recent clinical study showed that exenatide ameliorated steroid-induced hyperglycemia in healthy humans. It remains to be seen whether GLP 1 agonists will be clinically useful for treatment of glucocorticoid-induced hyperglycemia.

There has recently been great interest in the roles of insulin and IGF 1 signaling in the pathogenesis of cancer, and in development of anti-cancer therapies that target those pathways. Not surprisingly, hyperglycemia is a common response to those therapies. Marked hyperglycemia can have a number of immediate adverse effects, including volume depletion, catabolism with loss of nutrients in the urine, and impaired host defense against infection. One of the critical questions facing oncologists is to determine whether treatment of hyperglycemia with insulin or beta-cell secretagogues will vitiate the anti-tumor effects of these targeted therapies.

Patients being treated for cancer often have impaired nutrition, owing to the effects of surgery, radiation therapy or chemotherapy. All forms of nutritional supplementation, including oral supplements, tube feedings and parenteral nutrition, include concentrated nutrients that present a major challenge to pancreatic beta cells. In general hospital settings, hyperglycemia in response to nutritional supplementation predicts adverse outcomes.

#### **No one really knows how best to manage hyperglycemia in patients undergoing treatment with cancer.**

There are two major concerns related to treatment of hyperglycemia in patients with cancer: (1) how aggressively to treat, and (2) what medication to use.

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Website: <http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/endocrine-neoplasia-and-hormonal-disorders/index.html>

(Lavis, continued from Page 3)

There are almost no data to support informed decision-making for either of them.

The usual treatment goals for hyperglycemia are, in the short term, to eliminate nocturia, polydipsia, urinary loss of calories and excessive catabolism, and to restore host defense against infection. Most of these goals can be met by keeping circulating glucose below about 180 mg/dL (10 mM), corresponding to HbA1c of about 7.9%. The longer-term goal of diabetes treatment is prevention of microvascular and macrovascular events, including retinopathy, nephropathy, coronary artery disease and stroke. Both observational studies and controlled trials have shown that more strict control of hyperglycemia, particularly early in the course of diabetes, delays or prevents microvascular disease in both type 1 and type 2 diabetes. The relation of glycemic control to macrovascular events is less clear, particularly for people with type 2 diabetes, who tend to be afflicted with multiple cardiovascular risk factors prior to development of hyperglycemia.

Observational studies have shown hyperglycemia to be associated with less favorable cancer outcomes. A recent retrospective analysis noted increased toxicity of chemotherapy for non-Hodgkin's lymphoma in patients who were hyperglycemic at baseline. An important question for clinicians, as well as for patients with life-threatening types of cancer, is whether strict control of glycemia – i.e. maintenance of glucose levels below the symptom threshold of about 180 mg/dL - will influence therapeutic or toxic responses to treatment for cancer. At MD Anderson there was a randomized trial of strict glycemic control vs. conventional therapy in hyperglycemic patients being treated for acute lymphoid leukemia. The results, which have been presented at an oncology meeting but not yet published in a peer-reviewed journal, showed no benefit of strict control, although it is not clear whether the intervention group met its glycemic target. Additionally, there was no documentation that glycemic separation of the treatment groups was maintained between hospitalizations for chemotherapy. I am not aware of any published evidence that aggressive treatment of hyperglycemia improves outcome in any type of malignancy. Observational studies have consistently shown that diabetic patients treated with metformin experience less incident cancer and better outcomes of treatment for cancer than those treated with other medications. These findings are of great interest in light of the evidence that metformin inhibits the growth of malignant cells *in vitro*<sup>17</sup>, an effect that may in part be related to activation of AMP kinase. However, the results should be interpreted with great caution, because metformin tends to be prescribed for patients who are younger, have shorter duration of diabetes and have better renal function than those who receive other drugs, particularly insulin. There are ongoing trials of treatment with metformin in patients with cancer<sup>17</sup>, and one of these has shown promising improvement in a surrogate end point.

In general insulin promotes cell growth and survival, however, there are concerns that treatment with insulin, particularly insulin analogs, may increase cancer-related mortality. While treatment with insulin may be associated with higher mortality from cancer, the data are difficult to interpret because people taking insulin for type 2 diabetes tend to be older and to have longer duration of diabetes, higher glycemia and greater prevalence of renal disease than those taking oral medications. Accordingly, treatment with insulin may be a surrogate for impaired homeostatic mechanisms and general debility. Insulin glargine has come under particular suspicion because of its relatively strong signaling

through the IGF-1 receptor, compared to human insulin. About two years ago there appeared some observational studies that linked insulin glargine to increased cancer-related mortality, but the validity of these inferences has been challenged.

**One of the residua of successful treatment for cancer can be a predisposition to diabetes.**

Followup studies have shown a high prevalence of adiposity and insulin resistance in cancer survivors, particularly in survivors of treatment of childhood leukemia. These components of the "metabolic syndrome" predispose to development of type 2 diabetes and to atherosclerotic disease. Indeed, one recent report described markedly increased mortality from circulatory disorders in survivors of childhood cancer. The mechanisms responsible for this situation are speculative, although deficiency of growth hormone, hypogonadism and physical inactivity have been postulated to play roles.

#### **Summary**

There are common pathways in both the inherited and acquired components of the pathogenesis of cancer and diabetes, thus, causing hyperglycemia in patients, causing them to be predisposed to developing several kinds of cancer. Treatments for cancer, especially the promiscuous use of high-dose glucocorticoids, tend to promote and exacerbate hyperglycemia. There is a profound lack of evidence regarding the optimal glycemic targets and the best medications for hyperglycemia while people are being treated for cancer. Finally, one of the long-term sequelae of treatment for cancer seems to be the "metabolic syndrome," known to predispose to future development of diabetes mellitus.

For a complete list of references, please email the editor at [cstava@mdanderson.org](mailto:cstava@mdanderson.org).

### **MD Anderson Ranks Among Houston's Best Hospitals**

MD Anderson Cancer Center was recently ranked as No. 2 in U.S. News & World Report's first-ever list of the Best Hospitals in Houston, Texas. Its Diabetes and Endocrinology specialty has been ranked as number one in the state of Texas and the 21st in the country.

The data was based on the U.S. News & World Report's 2010-2011 Best Hospitals Survey.

U.S. News states that the new metro rankings are aimed at consumers who may not require the special expertise found only at a nationally-ranked hospital. To be ranked, a hospital had to score in the top 25% among medical institutions and hospitals, and have at least one of 16 medical specialties

## 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 at MD 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 MD 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 MD 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/>

## The Thyroid Cancer Survivorship Clinic



The Department of Endocrine Neoplasia and Hormonal Disorders is proud to feature the Thyroid Cancer Survivorship Clinic at The University of Texas MD 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 MD Anderson or in the community.



To refer a patient, please call our New Patient Referral Coordinators at 713-563-4400.

## The New Bone Healthcare Program



The Bone Healthcare Program provides treatment for cancer patients with metabolic bone disorders or bone loss caused by cancer treatments. The Program helps streamline referral and triage processes for MD Anderson patients by bringing together consulting physicians from endocrinology, rheumatology and pediatric endocrinology. In addition to treatment, supportive care is provided by experts from radiology, pain management, rehabilitation and nutrition.

The Bone Healthcare Program provides evaluation and treatment of:

- \* Osteoporosis
- \* Low bone mass
- \* Fractures
- \* Height loss
- \* Vitamin D deficiency

The Program offers increased availability of appointments and same-day consults, particularly for out-of-town patients. Additionally, the Program offers treatments at 3 convenient locations at MD Anderson Cancer Center in Houston, Texas. Patients are referred to the Program by their MD Anderson physician. Ask your doctor to contact the Internal Medicine Center at 713-563-7100, and ask to speak with a Bone Healthcare Program employee.

## Recent News from the Endocrine Faculty Team

- Congratulations to Drs. **Robert Gagel**, **Victor Lavis**, **Rena-Vassilopoulos-Sellin**, **Steven Sherman** and **Steven Waguespack** once again, for making the 2011-2012 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.

- In addition to Dr. **Lavis's** recognition, he was also named the local Physician of the Year by the Houston chapter of American Diabetes Association.

- Dr. Erika Alford, a fellow with the Dept. of Endocrine Neoplasia & HD, presented an abstract on Thyroxine Autoantibody in a Patient with Hashimoto's Thyroiditis and Cryoglobulinemia which won a 2011 Endo Society Outstanding Abstract Award, and was nominated for the Presidential Poster Competition. Her mentor is Dr **Mimi I. Hu**.

- Dr. Montserra Ayala-Ramirez, a fellow who is a mentee of Dr **Camilo Jimenez**, has also had two of her abstracts, Experience with the Tyrosine Kinase Inhibitor Sunitinib in Metastatic Pheochromocytomas and Paragangliomas, and Benefits of Chemotherapy in Patients with Metastatic Pheochromocytomas and Sympathetic Paragangliomas: Review of the Largest Single-Institution Experience, nominated for the Endo Society Presidential Poster Competition.

### Publications:

- Moreno MA, Agarwal G, deLuna R, Siegel ER, **Sherman SI**, Edeiken-Monrose BS, Clayman GL. Preoperative Lateral Neck Ultrasonography as a Long-term Outcome Predictor in Papillary Thyroid Cancer. Arch Otolaryngol Head Neck Surg. 2011 Feb; 137(2):157-62

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**Waguespack SG**, Hernandez M, El Naggar AK, Bidyasar S, Wright J, **Sherman SI**, Kuzrock R. Inhibition of the Ras/Raf/MEK/ERK and RET Kinase Pathways with the Combination of the Multikinase Inhibitor Sorafenib and the Farnesyltransferase Inhibitor Tipifarnib in Medullary and Differentiated Thyroid Malignancies. J Clin Endocrinol Metab. 2011 Feb 2 [Epub ahead of print]

- Chintharlapalli S, Papineni S, Lee SO, Lei P, Jin UH, **Sherman SI**, Santarpia L, Safe S. Inhibition of pituitary tumor-transforming gene-1 in thyroid cancer cells by drugs that decrease specificity proteins. Mol Carcinog. 2011 Jan 25 [Epub ahead of print]

Hoff AO, Toth B, **Hu M**, Hortobagyi GN, **Gagel RF**. Epidemiology and risk factors for osteonecrosis of the jaw in cancer patients. Ann NY Acad Sci. 2011 Feb;1218:47-54.

- Ayala-Ramirez M, Feng L, Johnson MM, Ejaz S, **Habra MA**, Rich T, **Busaidy N**, **Cote GJ**, Perrier N, Phan A, Patel A, **Waguespack S**, **Jimenez C**. Clinical risk factors for malignancy and overall survival in patients with pheochromocytomas and sympathetic paragangliomas: primary tumor size and primary tumor location as prognostic indicators. J Clin Endocrinol Metab. 2011 Mar;96(3):717-25

- Jasim S, **Ying AK**, **Waguespack SG**, Rich TA, Grubbs EG, **Jimenez C**, **Hu MI**, **Cote GJ**, **Habra MA**. Multiple endocrine neoplasia type 2B with a RET proto-oncogene A883F mutation displays a more indolent form of medullary thyroid carcinoma compared with a RET M918T mutation. Thyroid. 2011 Feb;21(2):189-92.

- Shahani S, Ahmad A, Barakat FH, Chuang HH, Fowler NH, Myers JN, Stava C, **Habra MA**. F-18 FDG PET/CT Detecting Thyroid Plasmacytoma After the Successful Treatment of Gastric Large B-Cell Lymphoma. Clin Nucl Med. 2011 Apr;36(4):317-9.

## Announcements

The Department of Endocrine Neoplasia and Hormonal Disorders presented an exhibition booth at the AACE conference from April 13-17, 2011 at the San Diego Convention Center in San Diego, CA. If you would like to receive an electronic copy of the hand-outs that were distributed at the booth, please feel free to email the editor at [cstava@mdanderson.org](mailto:cstava@mdanderson.org).

## New Clinical Trials

### A Double-Blind, Randomized Phase III Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo in Locally Advanced/Metastatic RAI-Refractory Differentiated Thyroid Cancer (2009-0600)

This phase III study is focused on subjects with differentiated thyroid cancer (papillary, follicular, Hurthle cell carcinoma) who are refractory to radioactive iodine treatment. The objective of this study is to compare the treatment groups in terms of progression free survival evaluated by the Response Evaluation Criteria. For more information, please contact Madonna Pool, RN, at 713-792-9851.

### A Phase I Drug-Drug Interaction Study of the Effects of XL 184 on the Pharmacokinetics of a Single Oral Dose of Rosiglitazone in Subjects with Solid Tumors (2010-0031)

The purpose of this study is to evaluate the effect of multiple daily doses of XL184 on single dose PK of rosiglitazone in patients with solid tumors (including DTC and RCC), and to evaluate the safety and tolerability of daily oral administration of XL184 and two single doses of rosiglitazone in subjects with solid tumors (including DTC and RCC). The study will also evaluate the plasma PK of XL184 after a single dose of rosiglitazone in patients with solid tumors, and assess the antitumor activity of XL184 in patients with solid tumors. For more information, please contact Debra

Nichols, Research Nurse, at 713-792-0839.

### A Phase II trial using RAD001 for patients with radioiodine refractory thyroid cancer (2010-0049)

The purpose of this study is to measure progression free survival in patients with progressive thyroid cancer and to measure objective response rate (complete and partial responses modified by RECIST criteria); provide symptom improvement in a cohort of patients with medullary thyroid cancer; and determine genetic expression of AKT, PTEN, P13K, and analysis of mutations such as B-raf on tumor tissue. For more information, please contact Pat Degen, Research Nurse Supervisor, at 713-792-2396.

### A Single-arm, Multicenter, Proof-of-concept Study of Denosumab in the Treatment of Hypercalcemia of Malignancy in Subjects with Elevated Serum Calcium Despite Recent Treatment with IV Bisphosphonates (2009-0595)

This proof-of-concept study is designed to evaluate the potential for denosumab to treat hypercalcemia of malignancy that does not respond to recent treatment with intravenous bisphosphonates by lowering corrected serum calcium  $\leq 11.5$  mg/dL (2.9 mmol/L) by study day 10. For more information, please contact Madonna Pool, RN, at 713-792-9851.

# Disorders of the Thyroid Gland

**Charles J. Stava, MHSA, Program Manager, and Rena Vassilopoulou-Sellin, MD, Professor, Department of Endocrine Neoplasia and Hormonal Disorders**

The following article is an excerpt of the publication, Endocrine sequelae of cancer and cancer treatments, by C. Stava, C Jimenez, MD, and Rena Vassilopoulou-Sellin, MD. *J Cancer Surviv.* 2007 Dec;1(4):261-74

Exposure to systemic chemotherapy and radiotherapy, although improving survival rates in cancer patients, can carry several unwanted and persistent health effects long after therapy is completed. These long-term effects are varied, and can include neurologic, cardiovascular, musculoskeletal, gastrointestinal, genitourinary, integumentary, pulmonary, and endocrinologic problems.

## **Hypothyroidism**

The effects of chemotherapy and endocrine treatment on thyroid function are still being debated. Young age and the addition of chemotherapy to treatment regimens were reported to be associated with a higher incidence of hypothyroidism. Primary hypothyroidism is seen more frequently than central hypothyroidism.

Treatment with cytokines has been linked with primary hypothyroidism. In a study of low-dose interleukin-2 for melanoma, 14 of 55 patients (25%) experienced thyroid dysfunction, attributed to autoimmune thyroiditis. A French study reported that interferon alfa may induce thyroid autoimmune disease, and an earlier published report demonstrated that the frequency of thyroid dysfunction from interleukin-based immunotherapy ranged from 15 to 91%.

Primary hypothyroidism is a frequent complication of sunitinib, a novel tyrosine kinase inhibitor used for malignancies such as renal cell carcinoma and gastrointestinal stromal tumors. Studies have revealed incidences of hypothyroidism resulting from sunitinib use of 30 to 85%. This complication has been attributed to sunitinib's effect on the thyroid endothelium, which results in thyroid dysfunction. Another tyrosine kinase inhibitor, sorafenib, has also been associated with hypothyroidism. However, two University of Chicago researchers stated that to their knowledge, no prospective studies of thyroid function in patients being treated with sorafenib were under way as of 2006.

Bexarotene is a retinoid-X receptor-selective ligand used to treat patients with cutaneous T-cell lymphoma. Central hypothyroidism (low serum thyrotropin and T4 concentrations) is a frequent complication of bexarotene. To date, this is the only form of selective central hypothyroidism induced by pharmacologic agents in humans. The most common adverse effect from irradiation to the thyroid gland is primary hypothyroidism, in both its overt form (with a low T4 level and elevated thyroid-stimulating level) and compensated form (with a normal T4 level and elevated thyroid-stimulating hormone level).

Cranial and spinal irradiation, alone or in combination, can also compromise thyroid function, leading to hypothyroidism and increased risk of malignant thyroid nodules.

Radiotherapy alone and combined with chemotherapy is associated with a higher risk of thyroid dysfunction than is chemotherapy alone. Craniospinal irradiation, compared with total body irradiation (TBI) or direct thyroid irradiation was found to

be less harmful to the thyroids. Female patients were more sensitive than male patients.

Radiation-induced thyroid dysfunction may include primary or central hypothyroidism, Graves' disease, thyroiditis, euthyroid Graves' ophthalmology, benign adenomas, multinodular goiter, and radiation-induced thyroid malignancies. The most common radiation-induced thyroid late effect, primary hypothyroidism, affects 20 to 30% of patients treated with radiotherapy to the neck area.

The association between radiotherapy and thyroid dysfunction in cancer survivors has been outlined in other publications. A study conducted in Japan reported progressive thyroid dysfunction in a subset of patients treated with bone marrow transplantation during childhood and concluded that thyroid dysfunction is contingent on age at transplantation with greater risk in younger patients.

## **Hyperthyroidism, including Graves' disease**

Several studies have reported the development of hyperthyroidism in adult cancer survivors who had undergone radiotherapy to the neck area, especially those treated for Hodgkin's disease; the prevalence of hyperthyroidism exceeded that seen in the general population.

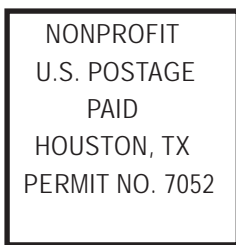
A team of Saudi Arabian researchers described a patient who developed reversible Graves' disease after an induction course of chemotherapy with cytarabine and daunorubicin for acute leukemia. Recent studies have summarized cases of hyperthyroidism and Graves' disease induced by interferon alfa therapy. Another study also reported that 13 of 55 patients who were treated with interleukin-2 for melanoma developed hyperthyroidism, this condition was reversed in most patients after treatment was discontinued.

The symptoms of hyperthyroidism experienced by survivors who have received radiotherapy to the neck area are similar to those of Graves' disease: diffusely enlarged thyroid gland, elevated level of thyroid hormone, suppressed level of thyroid-stimulating hormone, increased thyroidal uptake of radioactive iodine, and development of auto antibodies to the thyroid. An analysis on data from a childhood cancer survivor study reported that the overall incidence of hyperthyroidism in survivors of Hodgkin's disease was eight times greater than that reported in sibling controls and the risk of hyperthyroidism was dose-dependent.

## **Serum thyroid hormone-binding protein abnormalities**

L-Asparaginase appears to inhibit the biosynthesis of thyroxine (T4)-binding globulin, at least in vitro. Increased levels of T4-binding globulin found in patients taking estrogens and tamoxifen, mitotane, and fluorouracil led to elevated levels of total T4. Small decreases in T4-binding globulin were observed in a cohort of patients treated with alkylating agents and podophyllin. The chemotherapeutic effects on thyroid hormone-binding proteins have not been extensively studied in recent years.

For a complete list of references, please email the editor at [cstava@mdanderson.org](mailto:cstava@mdanderson.org).



## Wish to make a donation to Endocrine Research?

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## Department of Endocrine Neoplasia and Hormonal Disorders Faculty

Steven I. Sherman, M.D., Chair and Professor  
and Center Medical Director, Endocrine Center  
Naifa L. Busaidy, M.D., Assistant Professor  
Rozita Bagheri-Yarmand, Ph.D., Assistant Professor  
Maria E. Cabanillas, M.D., Assistant Professor  
Gilbert J. Cote, Ph.D., Professor  
Robert F. Gagel, M.D., Professor  
Mouhammed A. Habra, M.D., Assistant Professor

Mimi I. Hu, M.D., Assistant Professor  
Camilo Jimenez, M.D., Assistant Professor  
Victor R. Lavis, M.D., Professor  
Sara Peleg, Ph.D., Associate Professor  
Rena Vassilopoulou-Sellin, M.D., Clinical Professor  
Steven G. Waguespack, M.D., Associate Professor  
Sai Ching Jim Yeung, M.D., Ph.D., Associate Professor  
Anita K. Ying, M.D., Assistant Professor