



Medical Management of Medullary Thyroid Carcinoma

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER



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Medullary thyroid carcinoma (MTC) represents 5-10% of all new cases of thyroid cancer in a given year in the United States. Of the new cases, 70-75% are sporadic and 25% are hereditary. In 1993-1994, germline point mutations of the *RET* (*RE*arranged during *Tr*ansfection) proto-oncogene, were found to be responsible for the autosomal-dominantly inherited syndromes of Multiple Endocrine Neoplasia Type 2A (MEN2A), MEN2B, and Familial MTC. More than 95% of MEN2 families have germline *RET* mutations, with C634R (cysteine to arginine) being the most common mutation in MEN2A and M918T (methionine to threonine), the most common in MEN2B. Twenty-five percent of sporadic MTC cases are associated with somatic *RET* mutations. These findings indicate the importance of this genetic mutation in the development of both sporadic and hereditary MTC.

Surgical resection remains to this day the most definitive curative modality available, with the adequacy of the initial operation being the most important determinant of outcome [see Dr. Evan's article in this newsletter]. Biochemical cure of MTC varies depending upon the extent of lymph node involvement at the time of surgery (75%–90% in patients without lymph node involvement and 20%–30% in those with lymph node involvement). Distant metastatic disease represents a therapeutic challenge, as there are no curative options available at this time. The available treatments (chemotherapy and external radiation) for unresectable or metastatic MTC are nonspecific for the disease process and have variable outcomes without demonstration of improved long-term survival. Symptoms from

metastatic disease can be treated selectively, such as with embolization of large hepatic metastases or radiation for skeletal metastases, and aggressive therapy for diarrhea is often necessary. Treatments used for the differentiated forms of thyroid cancer, radioiodine and TSH-suppressive thyroid hormone therapy, are ineffective and not used for MTC. However, this article will review new strategies for targeted management of MTC demonstrating promising outcomes in clinical trials.

RET as a Therapeutic Target

As a result of the success of tyrosine kinase inhibitors (TKIs) in the treatment of other cancers (e.g., imatinib for gastrointestinal stromal tumors and chronic myelogenous leukemia; erlotinib for certain non-small cell lung carcinomas), *RET*, a tyrosine kinase receptor, has become an important potential therapeutic target for MTC. A TKI is a small molecule that competes with the ATP-binding site of the catalytic domain of a tyrosine kinase. The occupation of this site inhibits the autophosphorylation and activation of the tyrosine kinase and prevents further activation of intracellular signaling pathways. A TKI can be specific to one or many homologous tyrosine kinases (e.g., vascular epidermal growth factor receptor – VEGFR, epidermal growth factor receptor – EGFR, platelet derived growth factor receptor – PDGFR). Over the last few years, a substantial amount of research has focused on the effectiveness of tyrosine kinase inhibitors in *RET*-associated tumors, specifically differentiated thyroid carcinomas and MTCs. A tyrosine kinase inhibitor selective only for *RET* is currently not available for clinical use, but many other tyrosine kinase inhibitors are being evaluated in the treatment of MTC. (Hu, Page 2)



(Hu, continued from Page 1)

Motesanib diphosphate (AMG-706, Amgen, Inc., Thousand Oaks, California), a multi-kinase inhibitor targeting VEGF, PDGF, and Kit receptors, leads to anti-angiogenic and direct anti-tumor activity. Data from a phase I study of motesanib diphosphate in a subset of thyroid cancer patients were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2006 by M. D. Anderson investigators working within the Phase I Clinical Trials Program. These results showed objective evidence of partial response according to RECIST in 3 patients (one each of medullary, papillary, and follicular subtypes). Adverse events included diarrhea, hypertension, fatigue, dizziness, nausea, vomiting, and headache. A larger phase II trial was subsequently led by faculty in the Department of Endocrine Neoplasia and Hormonal Disorders. This international, multicenter study, that evaluated motesanib diphosphate in patients with differentiated thyroid carcinoma (n=93) and MTC (n=91), completed enrollment months ahead of schedule. After a median follow-up of 32 weeks, most patients experienced some decline in tumor growth with 80% of cases showing stable disease by RECIST criteria. Data regarding extended follow-up were presented at national meetings last June, demonstrating a more substantial benefit in DTC patients than MTC patients. Publication of the results from the two separate cohorts of patients is expected this year.

Sunitinib (Sutent®, SU11248, Pfizer, Inc., New York, New York), a TKI that targets PDGFR, VEGFR, and fms-related tyrosine kinase 3 (FLT3), has recently been approved in the United States and Europe for use in renal cell carcinoma and gastrointestinal stromal tumors. Additionally, it inhibits the tyrosine kinase activity of RET/PTC in vitro. Currently, a multi-center, phase II clinical trial is evaluating the use of sunitinib in unresectable differentiated thyroid carcinoma and MTC.

Sorafenib (Nexavar®, BAY 43-9006, Bayer Pharmaceuticals Corp., West Haven, Connecticut) is a biaryl urea compound that was developed to inhibit BRAF kinase but was subsequently found to be a more effective inhibitor of the activity of tyrosine kinases (RET, VEGFR-2, VEGFR-3, PDGFR-beta, c-kit, and FLT-3). Carlomagno and colleagues recently published data on the ability of sorafenib to inhibit RET function and oncogenic activity in vitro in RET/

PTC1 and TT carcinoma cell lines, representing papillary and medullary carcinomas, respectively. Their results showed inhibition of RET activity and decreased growth progression, even in cells carrying the *RET* V804L mutation, which may confer inherent resistance to other tyrosine kinase inhibitors. A small cohort of 5 patients with symptomatic, metastatic MTC treated with sorafenib was reported at ASCO last year. All patients had marked improvement of their symptoms due to tumor secretions such as diarrhea, and 2 patients experienced significant tumor reductions. A single-institution phase II clinical trial of sorafenib in patients with metastatic, locally advanced, or recurrent MTC is currently ongoing.

Vandetanib (Zactima™, ZD6474, Astra-Zeneca Pharmaceuticals LP, Wilmington, Delaware) is a selective inhibitor of RET, VEGFR-2, and, to a lesser extent, EGFR. Vandetanib inhibits VEGF-mediated endothelial cell migration and proliferation. Due to the anti-angiogenic effects of this inhibitor, there is a risk of bleeding. Three clinical phase II trials are evaluating the use of vandetanib in hereditary and/or sporadic MTC: one trial using a 100-mg daily dose, and the others using a starting dose of 300 mg daily. The open-label trial of vandetanib (300 mg daily) in patients with hereditary MTC has demonstrated promising initial data. As of November 2005, 16 patients had been treated orally with 300 mg vandetanib daily. Fifteen patients could be evaluated for tumor response and for calcitonin and carcinoembryonic antigen (CEA) levels. Objective partial tumor responses were seen in 3 patients, stabilized disease in 10 patients (duration of 8 to >24 weeks), and progressive disease in 2 patients. Calcitonin levels dropped by >50% for at least 4 weeks in 12 patients, and a similar magnitude of decline in CEA was seen in 6 patients. Side effects included diarrhea, nausea, rash, fatigue, hypertension, and asymptomatic QTc prolongation. A large, international, randomized trial of vandetanib is now underway in patients with both sporadic and inherited metastatic MTC, to determine whether treatment with the drug improves progression-free survival compared with placebo treatment along with best supportive care.

XL184 (Exelixis, Inc., San Francisco, California) is a selective inhibitor of MET (another tyrosine kinase receptor), RET, and VEGFR-2. (Hu, page 3)

Upcoming Events

AACE 17th Annual Meeting & Clinical Congress: The Art & Science of Endocrinology: Focusing on Best Patient Outcomes. May 14-18, 2008. Walt Disney World Dolphin Resort, Orlando FL. <http://www.aace.com/meetings/ams/2008/>

ASCO 44th Annual Meeting, May 30-June 3, 2008. Chicago, IL. <http://www.asco.org/ASCO/Meetings/ASCO+Annual+Meeting>

The Endocrine Society (ENDO) Meeting 2008. June 15-18, 2008. San Francisco, CA. <http://www.endo-society.org/educationevents/annual/>

ATA 78th Annual Meeting, Oct 1-5, 2008. New York, NY. http://www.thyroid.org/ann_mtg/2007_78th/index.html

World Congress on Thyroid Cancer, May 27-31, 2009. Toronto, Canada. <http://www.thyroid2009.ca/>

Third Annual Thyroid Neoplasms Conference, Oct. 21-24, 2009. El Dorado Hotel, Sante Fe, NM (Additional information to be announced later)



(Hu, continued from page 2)

In a current phase I trial (see Dr. Kurzrock's article in this newsletter), more than 20 patients with MTC have been enrolled primarily at M. D. Anderson, and enrollment continues at this time. A more complete set of data will be presented at ASCO later this spring, but partial responses were seen in 3 of the first 7 patients treated, with tumor shrinkage seen as early as the first month of treatment. Side effects from the drug have been relatively mild and generally tolerable. The study has identified the appropriate dose of the drug to use in subsequent trials, and an international, phase III trial of XL184 is being planned to begin later this summer or fall based on the impressive results being seen in this phase I study.

Conclusion

Therapeutic options other than primary surgical resec-

tion have had extremely limited effectiveness until recently. The RET receptor offers a variety of biosynthetic and activation sites for therapeutic targeting for the treatment of MTC. Results from extension studies of the above agents and future trials evaluating the long-term efficacy of tyrosine kinase inhibitors, alone or in combination with other systemic regimens, are eagerly anticipated.

Dr. Mimi Hu is currently participating in the randomized trial of vandetanib, and will be the lead investigator at M. D. Anderson for the much anticipated XL 184 phase III trial. She has also initiated a novel study of teriparatide (recombinant PTH, Forteo (Lilly)) in patients with postsurgical hypocalcemia immediately after neck surgery. To refer patients to see Dr. Hu or for possible participation in her studies, please contact the Endocrine Center at (713) 563-7600.

Introducing: Atlas of Endocrine Neoplasia

By Mouhammed Amir Habra, M.D., and Rena Vassilopoulou-Sellin, M.D.

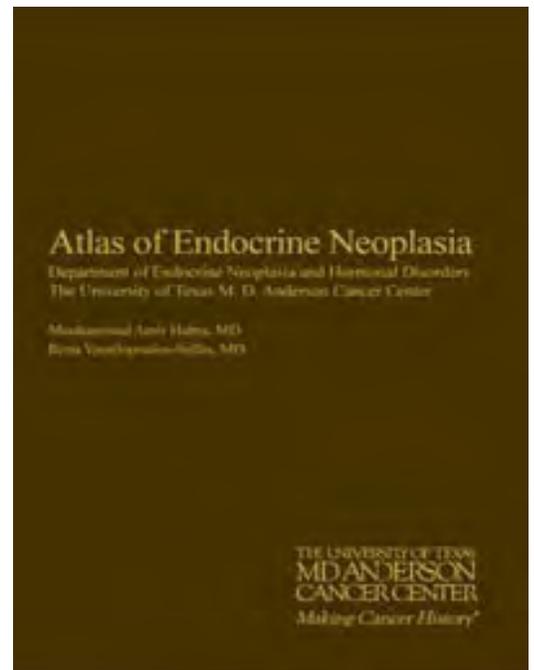
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This atlas provides a detailed coverage of endocrine neoplasms including the epidemiology, clinical features, diagnostic procedures and treatment. This classical compilation is intended to serve as a reference for physicians as well as medical students 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.

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Multiple Endocrine Neoplasia Type 2: Review of Genetics

Theresa A. Rich, MS, CGC, Certified Genetic Counselor, Dept of Surgical Oncology and Endocrine Center

Medullary thyroid carcinoma (MTC) is a rare cancer that develops from the calcitonin-producing cells of the thyroid (C-cells). Approximately 25% of all cases of MTC are associated with multiple endocrine neoplasia type 2 (MEN2), an autosomal dominant condition caused by activating germline mutations of the *RET* proto-oncogene. MEN2 is characterized by a very high lifetime risk of developing MTC (>95%) in untreated patients. MEN2-associated MTC typically occurs at a younger age than sporadic MTC and is more often associated with C-cell hyperplasia (the precursor lesion of hereditary MTC) and multifocality or bilaterality.¹ Three clinical subtypes, MEN2A, MEN2B, and familial MTC (FMTC), have been defined based on whether there is an additional risk of pheochromocytoma or hyperparathyroidism, or the presence or absence of characteristic physical features.

MEN2A is the most common subtype of MEN2 and is associated with MTC and risk of developing pheochromocytoma (approximately 50% of patients) and primary hyperparathyroidism (20-30% of patients).² A small number of families with MEN2A have also been reported to have pruritic cutaneous lichen amyloidosis or Hirschsprung disease. MEN2B is the rarest subtype of MEN2 and is associated with MTC, pheochromocytoma (50% of patients), and a characteristic physical appearance which includes enlarged lips, a "bumpy" tongue, and eversion of the eyelids resulting from mucosal neuroma development, and marfanoid body habitus.³ Corneal nerve thickening and ganglioneuromatosis of the gastrointestinal tract are also commonly observed. The physical traits are usually evident in early childhood. Finally, FMTC is characterized by risk to develop MTC but not other tumors. MTC in FMTC families tends to be the least aggressive MTC seen among all the MEN2 subtypes and tends to have the oldest age at onset, although age at onset varies considerably even among family members with the same mutation.^{4,6} The classification of FMTC is clinical and must be strict: only families in which four or more cases of MTC exist with documented absence of pheochromocytoma and hyperparathyroidism should be considered to have FMTC.⁷

The most definitive method of diagnosis of MEN2 is by *RET* genetic testing. In fact, offering *RET* genetic testing is considered by many to be the standard of care for newly identified MTC patients. Approximately 7% of individuals presenting with apparently sporadic MTC have a germline mutation of the *RET* proto-oncogene,⁸ therefore, *RET* genetic testing should be offered to MTC patients regardless of age at diagnosis or family history. *RET* genetic testing is highly accurate. Over 95% of patients with MEN2 have an identifiable mutation in exon 10, 11, 13, 14, 15, or 16. Sequencing of these exons is currently the most common method of *RET* genetic test-

ing and is widely available. Rarely, mutations in other exons have been reported in MEN2 families.^{9,10} Genetic testing of exons other than 10, 11, 13-16 is not widely available and is generally reserved for patients with a strong clinical suspicion of MEN2 who have previously tested negative for a mutation in the common exons.

The presence or absence of a mutation provides essential risk information for the patient and his or her family members. Due to the presence of strong genotype-phenotype correlations, identification of a specific *RET* mutation can help predict clinical subtype (i.e. risk for pheochromocytoma and hyperparathyroidism) and age at onset and aggressiveness of MTC, which can help direct management. In addition, the children of individuals found to have a *RET* mutation each have a 50% risk to inherit the mutation, whereas the children of individuals who have apparently sporadic MTC and do not have a *RET* mutation have a very low likelihood to develop MTC and do not need additional medical management. Children at risk of inheriting a *RET* mutation are recommended to undergo predictive genetic testing and mutation carriers are generally recommended to undergo prophylactic thyroidectomy during childhood, given the high lifetime risk, difficulty in early detection, and limited treatment options for advanced MTC. The age at which prophylactic thyroidectomy should occur also depends on the specific mutation found.

Management guidelines for individuals with the most commonly observed *RET* codon mutations were made by an international consensus conference of experts in MEN syndromes in 1999.¹¹ Mutations were classified into one of three levels to define recommended age at prophylactic thyroidectomy. Level 1 mutations are associated with the least aggressive MTC. There was no consensus about the age at which level 1 mutation carriers should undergo prophylactic thyroidectomy given the significant variability in the age at onset of MTC associated with different level 1 mutations, though several panel members recommended age 5 or 10 years. Level 2 mutations are associated with moderately aggressive MTC and carriers of level 2 mutations should undergo prophylactic thyroidectomy by age 5 years. Level 3 mutations are associated with the most aggressive MTC and include the codon mutations associated with MEN2B (codons 918, 883, and 922). Individuals with level 3 mutations should undergo prophylactic thyroidectomy by 6 months of age, with some experts advocating even for earlier surgery.

Table 1 provides a summary of the most commonly observed *RET* codon mutations according to the level of risk for development of MTC as described above as well as association with clinical subtype 11, 12. Notably, there is a broad overlap in the spectrum of *RET* mutations seen in FMTC and MEN2A, (Rich, page 5)

(Rich, page 4)

so genetic testing alone cannot always distinguish between these MEN2 subtypes. In addition, mutations in codons once classified as associated with FMTC have since been found in families with MEN2A. Thus, the designation of FMTC must be used cautiously. Families with fewer than four affected members or young families without pheochromocytoma or hyperparathyroidism should be considered to have “unclassified MEN2” and screened as MEN2A patients until they meet criteria for MEN2A or FMTC.

It is often very helpful to consult with a genetic counseling clinic when considering ordering genetic testing for a patient. Coordination of genetic testing is not always a simple process. The testing methodology, necessary paperwork, specimen and shipping requirements, turnaround time, results reporting process, and the cost and billing options vary considerably between laboratories. In addition, informed consent is necessary in order to provide accurate and complete information about the benefits, risks, limitations, and alternatives of genetic testing. Informed consent involves a discussion of the general features associated with the syndrome in consideration, accuracy of testing, likeli-

hood of a positive genetic test result, impact of result on management, impact on family members’ management, the possibility that one could receive an uninterpretable result, cost of the testing, and potential risks of testing including psychological sequelae and insurance discrimination. In addition to coordinating genetic testing, genetic counselors help to educate patients about hereditary cancer and genetic testing so that they can better make decisions regarding their health care, communicate risk information effectively to their relatives, and anticipate how their condition could impact various aspects of their personal life.

Thereasa Rich is a genetics counselor in the Endocrine Center who has specialized in assessing and helping patients with endocrine cancers. In addition to genetic counseling for patients with inherited medullary thyroid cancers, she also shares her expertise with patients with familial non-medullary thyroid cancers, multiple paraganglioma syndromes, Cowden’s disease, MEN I and its variants, and other familial disorders affecting thyroid, parathyroid, and adrenal glands. To refer patients for genetic counselling, please contact the Endocrine Center at (713) 563-7600.

Table 1 - Genotype-Phenotype Correlations in MEN2^{11,12}

Level	RET codon	Age of Prophylactic Thyroidectomy	Associated Clinical Subtypes	Relative Risk for Pheochromocytoma	Relative Risk of Hyperparathyroidism
1	768	No consensus (5-10 years?)	MEN2A or FMTC	Low	Low
	790 791 804		MEN2A or FMTC	Moderate	Moderate
	891		MEN2A or FMTC	Low	Low
2	609 611	< 5 years	MEN2A or FMTC	Low	Moderate
	618 620 630		MEN2A or FMTC	Moderate	Moderate
	634		MEN2A	High	High
3	883 918 922	< 6 months	MEN2B	High	No Increased risk

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Douglas B Evans, M.D., Professor, Department of Surgical Oncology



Medullary thyroid cancer (MTC) can develop as a sporadic event or as part of a variant of the multiple endocrine neoplasia type 2 (MEN 2) syndromes due to inherited mutations in the *RET* gene [see Thereasa Rich's article, "Multiple Endocrine Neoplasia Type 2: Review of Genetics"). In sporadic MTC, more than 25% of the tumors develop with a mutation in the same *RET* gene, but this mutation is

not inherited and is only found in the tumor cells. Strong genotype-phenotype correlations exist for specific *RET* codon mutations which have important implications for surgical treatment. For example, the *RET* mutation predicts the clinical subtype of MEN 2 which is phenotypically expressed, and the age of onset and aggressiveness of MTC. Although some overlap exists between *RET* mutations and the resulting clinical subtype of MEN 2 that results, 85% of patients with MEN 2A have a codon 634 mutation in exon 11, hyperparathyroidism in MEN 2A is most often associated with the codon 634 mutation, a codon 918 mutation in exon 16 is exclusively associated with MEN 2B (and is usually produced as a spontaneous new mutation following conception [i.e., the "de novo" mutation is not carried by either parent]). *RET* mutations have been stratified into 3 risk levels (level 1: high risk, level 2: higher risk, level 3: highest risk). Patients with level 3 mutations include those with MEN 2B (codons 883 and 918) and have the highest risk for the early development and aggressive growth of MTC. Patients with level 2 mutations, including codons 611, 618, 620, 634, have an intermediate risk for the early development and growth of MTC. Patients with level 2 mutations may have evidence of MTC or its precursor C-cell hyperplasia by age 5 years and perhaps earlier. And finally, patients with level 1 mutations, including codons 609, 768, 790, 791, 804, 891, have, in general, the most indolent form of MTC.

At present, knowledge of the *RET* mutation status and disease extent is required to determine the correct operation for any patient with MTC (refer to Table) because the aggressiveness of the disease and the management of devascularized parathyroids is mutation specific. However, in general, a total thyroidectomy is preferred for all patients with MTC

and a central compartment neck dissection is performed when MTC is grossly evident as a thyroid nodule (palpable or seen on US or CT) or if the serum calcitonin level is elevated (> 40-50 pg/ml). The recommendation for removal of the lymph nodes in the central neck compartment, predominantly those in the tracheo-esophageal groove and para-esophageal space, is due to the common finding of node-positive disease in patients with established MTC. Dissection of the lateral neck compartments is generally only performed when there is image positive disease. It is critically important that surgeons avoid iatrogenic injury to the recurrent laryngeal nerves and minimize the complication of permanent hypoparathyroidism. The later complication can be avoided by careful preservation of the superior parathyroid glands in-situ, and by identification and auto-transplantation of the inferior parathyroid glands when necessary.

Dr. Douglas Evans is a well known surgical endocrinologist with expertise in surgery for tumors of the thyroid, parathyroid, adrenals, and pancreas. He has published widely, especially noted for his contributions to research-driven surgical care for medullary thyroid carcinoma. To refer patients to see Dr. Evans and his surgical colleagues, please contact the Endocrine Center at (713) 563-7600.

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Patient Classification	Management of the Neck	Management of Parathyroid Glands that are devascularized/removed
Prophylactic thyroidectomy in MEN 2A/FMTC	Performance of central (level VI) neck dissection based on <i>RET</i> mutation, age of the patient, serum calcitonin level, and cervical US findings	-Autograft in neck if <i>RET</i> mutation consistent with FMTC -Cryopreserve/autograft in forearm for <i>RET</i> mutations consistent with MEN 2A
Prophylactic thyroidectomy in MEN 2B	-Central (level VI) neck dissection -Lateral neck (levels IIA, III, IV, V) dissection based on age of the patient, serum calcitonin level, and cervical US findings	Autograft in the neck as the parathyroid glands are normal in MEN 2B
Therapeutic thyroidectomy in MEN 2A/FMTC; patients with a malignant thyroid nodule(s) and a normal lateral neck by US	-Level 1 or 2 <i>RET</i> mutation: Central (level VI) neck dissection -Level 3 <i>RET</i> mutation: level VI and bilateral levels IIA-V neck dissection are generally performed	-Autograft in neck if <i>RET</i> mutation consistent with FMTC or MEN 2B -Cryopreserve/autograft in forearm for <i>RET</i> mutations consistent with MEN 2A
Therapeutic thyroidectomy in sporadic MTC (no <i>RET</i> mutation) with a malignant thyroid nodule and a normal lateral neck by US	Central (level VI) neck dissection should be performed in all patients; the lateral neck is dissected if abnormal lymph nodes are seen on imaging (US/CT)	Autograft in neck

Collaborative efforts drive forward Phase I trials for thyroid cancer patients



Razelle Kurzrock, M.D., Chair, Department of Investigational Cancer Therapeutics

Thyroid cancer is a complex malignancy that has not been adequately emphasized in previous clinical trials. Recently, however, more is being learned about the molecular basis of these tumors. For instance, medullary thyroid cancer is known to have a hereditary and non-hereditary form and both can have mutations in the *RET* gene. The Phase I Clinical Trials Program (now Department of Investigational Cancer Therapeutics) has worked closely with the faculty of the Department of Endocrine Neoplasia, led by Dr. Sherman, to place patients on new drugs that target RET. Two trials are being conducted that include such drugs: XL184, and a combination of tipifarnib and sorafenib. Dr. Razelle Kurzrock, who is the Chair of the Department of Investigational Cancer Therapeutics and is the principal investigator of the XL184 trial noted that, "The majority of patients with medullary thyroid cancer who have entered these trials have shown a response, without a lot of side effects." Dr. David Hong, who is the PI on the tipifarnib combined with sorafenib trial notes that sorafenib is the drug that specifically inhib-

its the RET kinase, and that clinical testing in medullary thyroid cancer patients is now being performed, even though sorafenib is already FDA approved for kidney cancer. This illustrates one of the hidden benefits of Phase I trials, regardless of whether they involve new first-in-human drugs (such as XL184) or combinations that include approved drugs (such as tipifarnib and sorafenib), that is the ability to search for response signals that can then be quickly transitioned to larger Phase II and III efficacy studies as is already in the works for XL184. Another example involves a Phase I, first-in-human study with RTA402, a drug that modulates several cancer-related signaling pathways. Unexpectedly, Dr. Hong, who chairs this study, noted an impressive response in a patient with anaplastic thyroid cancer, a tumor that grows rapidly and is notoriously hard to treat. Additional patients with this cancer are now being enrolled in this study, and if more responses are seen, then a Phase II study, which would be conducted in the Dept. of Endocrine Neoplasia, could be quickly developed. These studies suggest that the collaborative efforts described above are rapidly yielding important new information about targeted therapies that have a beneficial impact on patients with thyroid cancer.

From the Department Chair



Steven I. Sherman, M.D., Chair, Department of Endocrine Neoplasia and Hormonal Disorders

The past 7 years have seen an unprecedented growth of clinical trials testing novel therapies for patients with advanced thyroid cancers, including papillary, follicular, medullary and anaplastic diseases. Of central interest has been the recognition that more than 90% of papillary carcinomas are initiated by an activating mutation in one of three related genes, *RET/PTC*, *RAS*, or *BRAF* and virtually all inherited medullary carcinomas are triggered by germline mutations of *RET*. These etiologic mutations appear to remain critical to the further growth and development of these cancers, and thus therapies to counteract these mutations have been under intense investigation. One strategy that has been particularly effective at the M. D. Anderson Cancer Center has been a multidisciplinary collaborative effort involving endocrinologists, surgeons, medical oncologists, and genetics counselors to focus on the optimal evaluation of patients with medullary carcinoma. For those patients in whom potentially curative treatment is fea-

sible, primary surgical therapy is directed by imaging studies integrated with knowledge of an individual patient's genetic risk for regional disease. On the other end of the spectrum, patients with advanced, metastatic, and symptomatic disease are benefitting from multimodality therapy administered by our multidisciplinary team, including identification of appropriate patients to be treated in phase I and phase II clinical trials. Faculty members at M. D. Anderson have been leading the international efforts to pursue clinical trials for patients with all varieties of advanced thyroid cancers, and more than 10 phase II studies have already been pursued at our institution. With our extensive collaborations with experts in phase I clinical trials, led by Dr. Razelle Kurzrock and her faculty in the Department of Investigational Cancer Therapeutics, we have extended the spectrum of novel agents available to treat patients with advanced thyroid cancers for whom standard therapies prove ineffective. Through our clinical investigations, laboratory-based research, sophisticated genetics assessment, and talented surgical interventions, we are Making Cancer History for patients with thyroid cancer.

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

M. D. Anderson has created a new online referral process, *myMDAnderson*, to help you get your patient into M. D. Anderson as quickly as possible. Once approved, 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 get started on the referral through *myMDAnderson* please access this portal: <https://my.mdanderson.org/public/physicians/user/>

To refer a patient to one of the physicians in the Department of Endocrine Neoplasia and Hormonal Disorders, please call 713-563-4400.

Clinical Trials

Phase II study of Bortezomib (Velcade) in Metastatic Papillary Thyroid Carcinoma or Follicular Thyroid Carcinoma (M. D. Anderson Protocol #2004-0059)

The Velcade study is for patients with metastatic differentiated thyroid carcinoma who have a tumor that is at least 1cm in size. The tumor mass can not have been radiated at any time in the past. In addition, the patient must be 4 weeks away from another oncologic-type treatment, and have no concurrent serious disease. Velcade is administered intravenously on days 1,4,8 and 11 with a rest from days 12 to 21. The tumor size will be evaluated every 6 weeks

Phase II study of Decitabine in Patients with Metastatic Papillary Thyroid Cancer or Follicular Thyroid Cancer Unresponsive to Radioiodine (NCI Protocol #5964)

This study (2003-0308) uses the drug Decitabine in order to increase the radioactive iodine (RAI) uptake in patients. RAI is the gold standard of care for care for this type of population. Patients may not have a RAI-avid tumor or tumor less than 1cm in size within 4 weeks of starting trial. They will need to have a low

level of urinary iodine so that the lack of iodine uptake is not caused by iodine in the system. Decitabine is given daily x5 in a week period (Mon to Fri) that is repeated the next week. The third week, the patient undergoes radioactive scans for three days. With increased uptake, the patient goes home off thyroid replacement drugs and returns for another 2 weeks of treatment before treating with RAI.

Both trials are NCI sponsored trials and cannot be administered outside of a NCI designated cancer center.

For more information, please contact Mary Jean Klein, Manager, Clinical Protocol Administration, at 1-713-792-2840 for further information.

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/>

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