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Medullary Thyroid Cancer: Monitoring and Therapy

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Abstract

This review summarizes clinical features and molecular pathogenesis of medullary thyroid cancer (MTC), and then focuses on current use of molecular, biochemical, and imaging disease markers as a basis for selection of appropriate therapy. Clinicians treating MTC patients face a series of challenges: 1) distinguishing MTC as early as possible from benign nodular disease and differentiated thyroid cancer (DTC) in order to choose appropriate initial surgery; 2) managing low-level residual cancer in otherwise asymptomatic individuals; and 3) treating progressive metastatic disease. Early clinical trials employing small molecules targeting Ret and/or VEGF receptors suggest that such approaches could be effective and well-tolerated. This review highlights early progress in targeted therapy of MTC, along with significant challenges in disease monitoring to appropriately select and evaluate patients being treated with these therapies.

Overview of Clinical Features and Natural History

MTC accounts for 2-5% of cases of thyroid cancer. In the United States, there were an estimated 30,180 new cases of thyroid cancer in 2006 with 1500 deaths.1 Whereas a marked increase has been observed in thyroid cancer incidence in the U.S., this increase has been almost entirely accounted for by DTC, especially papillary cancer. No comparable increase has been detected in MTC.2 In SEER data from 1973-2002, U.S. MTC patients had a median age of 50 at diagnosis and a slight female preponderance.[3] Approximately 25% of MTC cases are inherited, in one of the three disorders comprising MEN 2, all stemming from activating mutations in the ret proto-oncogene. The most common form of MEN 2 is MEN 2A, comprising MTC as the cardinal feature, pheochromocytoma in ~50%, and hyperparathyroidism in ~ 20%, depending on the ret mutation. FMTC (familial medullary thyroid cancer) is operationally defined as MTC without other hereditary endocrine tumor. Some families initially classified as FMTC eventually develop cases of pheochromocytoma, making this classification tentative, especially in families with fewer than eight affected members. MEN2B comprises MTC as the cardinal feature, plus pheochromocytoma, plus enteric ganglioneuromas, enlarged corneal nerves and a marfanoid body habitus. A minority of MEN 2A patients develop characteristic cutaneous lichen amyloidosis or a limited form of Hirschsprung's syndrome.

At presentation, patients with sporadic MTC most commonly present with an isolated thyroid nodule, or a palpable cervical lymph node. Diagnosis is then made through a combination of fine needle aspiration cytology and serum calcitonin. Increasingly, MTC patients are also being

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identified through detection of incidental thyroid nodules or lymph nodes, discovered in the course of carotid ultrasound or neck or chest CT or FDG-PET, performed for another indication. A minority of MTC patients present with systemic manifestations of their cancer, including diarrhea, flushing, symptoms related to hypercortisolism due to ectopic ACTH production, or painful bone metastases.

Cervical lymphadenopathy is a common manifestation which occurs early in the clinical course of MTC. Moley and colleagues found that >75% of MTC patients with palpable primary tumors had associated lymph node metastases.4 Machens, Dralle and colleagues reported a significantly higher rate of nodal metastasis for MTC than PTC, with a trend toward more frequent involvement of the contralateral cervical and mediastinal compartments in MTC.5 Cervical nodal involvement involves central and ipsilateral nodes more frequently than contralateral nodes -- Scollo et al. found that both central and ipsilateral node involvement occurred in approximately 50% of patients, whereas contralateral nodes had a 25-30% prevalence.6 Contralateral and mediastinal involvement becomes common (50-60%) when the primary tumor is locally invasive (pT4).[5] Furthermore, Machens and Dralle noted the very strong correlation between contralateral and mediastinal nodal disease and distant metastases, arguing that the presence of adenopathy at these sites is an important marker of systemic (therefore surgically non-curable) disease.7

MTC distant metastases typically occur in the mediastinum, lung, liver, abdominal lymph nodes and bone. Clinically-occult liver metastases are a leading cause of failure to achieve biochemical cure with surgery. Early in their course, these liver metastases have a miliary pattern that makes radiographic detection difficult. Even macroscopic liver metastases may be mis-diagnosed as hepatic cysts, based on the low-attenuation signal of these lesions as seen in typical venous phase contrast CT. The estimated prevalence of MTC liver metastases varies depending on the technique, but may be as high as 90% in some patient populations, using hepatic arteriography.[8] For bone involvement, MRI has proved more sensitive than conventional technetium bone scintigraphy and indicates a prevalence of approximately 75% in a population of patients with known distant metastases at any site (vs. 57% for conventional scintigraphy).[9]

Survival in MTC is intermediate between well-differentiated and poorly differentiated or anaplastic thyroid cancers. IN U.S. SEER data (1973-2002) reviewed by Sosa and colleagues, patients with tumors classified as confined to the thyroid gland had a 10 year survival greater than 95%, whereas patients with regional disease had an overall survival of 75%. Patients with distant metastases had a 40% 10 year survival. No significant survival improvements were detectable across this 30 year time interval.[3] Among the entire cohort of Swedish MTC patients, overall relative survival for sporadic cases was 63% at 10 years and 50% at 20 years. Initial clinical stage remains highly predictive of future mortality even up to 20 years after diagnosis. 10 The application of two relatively new markers, calcitonin doubling time and somatic ret mutation status, to assess prognosis and select patients for clinical trials, is discussed below.

Molecular Pathogenesis and Markers

Activating germline mutations in the ret proto-oncogene occur in virtually all patients with inherited MEN 2 whereas somatic (tumor-specific) ret mutations are detectable in a significant fraction of sporadic MTC cases. Ret is a single-pass transmembrane receptor belonging to the tyrosine kinase superfamily. Closest neighbors in this family are FGF receptors and VEGF receptors. Ret binds to a set of circulating ligands including GDNF (glial derived neurotrophic factor), in the presence of accessory proteins referred to as GDNF receptor alpha 1-4. Ligand binding leads to ret dimerization, and auto-phosphorylation of key tyrosine residues in the intracellular domain of ret, especially Tyr1062. Phosphorylated Tyr1062 and additional sites

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become docking residues for the adaptor molecules including Shc, IRS1 and 2, and others, leading to activation of downstream signaling pathways such as P-I3K-AKT, and Ras-Raf-Mek-Erk. Several research groups have provided comprehensive reviews of ret signaling.[11, 12]

The ret gene is normally expressed in a narrow range of neural crest-derived tissues in the adult, including basal ganglia, autonomic neurons, enteric ganglia, thyroid calcitonin-producing parafollicular cells, and adrenal medullary chromaffin cells. Germline inactivating mutations of ret are responsible for approximately 50% of cases of familial Hirschsprung's disease.13 The key role of Tyr1062 phosphorylation in ret signaling and development is illustrated by “knock-in” transgenic mice in which the Tyr1062 residue of the endogenous ret alleles was replaced by phenylalanine (which is not phosphorylatable). These knock-in mice showed marked growth retardation and had defects in enteric neurons and renal development, although this phenotype is less severe than complete ret knockout.14 Ret is classified as a proto-oncogene because naturally-occurring or experimental mutations that activate the receptor can lead to neoplastic transformation of a variety of cell types. A reasonable assumption is that activated forms of ret can transform many tissue types, and that the restricted tumor and hyperplasia syndromes seen in MEN 2 reflect the limited range of tissues in which the ret promoter is normally active. A slightly different paradigm is observed in ~20% of cases of papillary thyroid cancer. Here, a truncated, active form of ret is genetically rearranged as a RET-PTC oncogene, so that a variety of different promoters inappropriately transcribe the mutant ret gene in thyroid epithelial cells (see 15 for review).

There is experimental evidence suggesting that ret mutations play a critical role in initiating MTC tumorigenesis. Transgenic mice bearing the M918T ret mutation characteristic of MEN2B develop diffuse and nodular C cell hyperplasia, but, somewhat surprisingly, no frank MTC by 12 months of age. In addition, these experimental mice develop pheochromocytomas and enteric ganglioneuromas.[16] In contrast to these “knock-in” results, transgenic over-expression of MEN 2A and MEN 2B forms of ret under the control of a tissue-specific calcitonin promoter does lead to frank MTC.[17, 18]

In human familial MTC, there is now an extensive literature correlating specific germline ret mutations with age-specific penetrance of cancer development and nodal metastases.19 For the most common mutation in MEN 2A (codon 634, accounting for 68% of MEN 2 families), 50% of affected children develop at least microscopic MTC by age 10. 40% develop nodal metastases by age 20, with the earliest reported nodal disease at age 5.19, 20 The codon 634 mutation has been assigned a risk category level 2, with a consensus for prophylactic thyroidectomy by age 5.21 The codon 918 mutation associated with the vast majority of cases of MEN 2B confers a high risk of metastatic MTC, beginning even in the first years of life. This mutation (along with codons 883 and 912) has been assigned a risk category level 3, indicating highest risk, and a need for prophylactic thyroidectomy in the first year of life, if possible. In contrast, patients with several other intracellular domain codon mutations including 768, 790, 791 804, and 891 have variably reduced penetrance, and are assigned risk category 1.21

In sporadic MTC, a limited literature suggests that the presence of somatic ret mutations, especially M918T, may confer an adverse prognosis. Somatic ret mutations have a quite variable prevalance in different series, ranging from 20-50%.22, 23 The discovery that mutation-positive and mutation-negative regions may co-exist in the same sporadic MTC tumor24 suggests that such genetically heterogeneous MTC's may not be clonally-derived from a ret mutant initiating tumor cell. Data from Schilling and colleagues indicate that in spite of genetic heterogeneity within primary tumors, 76% of patients have concordant ret mutation results in all lymph nodes tested (43% all-positive, 33% all negative).[25] Furthermore, the

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presence of an M918T mutation (in any specimen) was a strong negative prognostic indicator for metastasis-free survival and, by trend, for overall survival. 10 year survival was approximately 45% in M918T- positive patients versus 90% when the mutation was absent. 25 Larger scale studies are needed to further explore this provocative finding and to validate somatic M918T mutations as a marker of high-risk disease, and potentially, of susceptibility to ret-targeted therapies.

Integrated MTC Monitoring: Genetic and Biochemical Markers and Imaging

Pre-operative

Germline testing for ret proto-oncogene mutations is now accepted as standard-of-care as part of the initial diagnostic work-up of MTC, even in the absence of a family history of MTC or MEN 2. Approximately 4-6% of family history-negative individuals are found to harbor germline mutations.[26] These mutations tend to be disproportionately clustered amongst the class 1 mutations listed above, with reduced clinical penetrance compared to classic extracellular mutations such as codon 634. Patients found to harbor cryptic germline mutations clearly require testing for pheochromocytoma and hyperparathyroidism, as well as family screening. In addition, surgical decision-making may be altered, based on a higher risk of bi-lobar tumors and contralateral nodal metastasis. In our institution, patients with newly diagnosed MTC are evaluated with ret protooncogene testing, 24 hour urine metanephrines or fractionated plasma metanephrines, serum calcium, calcitonin and CEA.

Calcitonin is a specific and highly sensitive biomarker for MTC and C cell disease. Although calcitonin values in early occult MTC may merge with the upper limit of normal, the vast majority of MTC patients exhibit significant calcitonin elevations. European data have shown that pre-operative calcitonin levels correlate with tumor size and disease stage. Calcitonin levels < 100 pg/ml were associated with a median tumor size of 3 mm, with 98% < 1 cm. Calcitonin levels >1000 pg/ml correlated with a median tumor diameter of 2.5 cm.[27] Nodal metastasis first could be observed at basal calcitonin levels of 10-40 pg/ml (normal range, <10 pg/ml). Distant metastasis and extrathyroidal growth began appearing in patients with calcitonin levels of 150-400 pg/ml. Node-positive patients did not achieve biochemical remission when their preoperative basal calcitonin levels exceeded 3000 pg/ml in the population reported by Machens, Dralle and colleagues.[28]

In parallel with calcitonin, CEA levels may provide valuable information for risk stratification in patients with MTC. Machens and Dralle have recently reported that pre-operative serum CEA levels > 30 ng/ml in their series were incompatible with surgical remission.[7] The rate of central and lateral lymph node involvement in these patients was 70%; this rate increased to 90% if the CEA were greater than 100. CEA levels greater than 100 were also associated with high rates of contralateral nodal disease and distant metastases.

The choice of pre-operative imaging for MTC patients varies depending on hereditary status, age, and calcitonin and CEA level. Thyroid and neck ultrasound, coupled with FNA, allows detection of multifocal thyroid involvement and metastasis to central and jugular chain nodes. However, the pre-operative sensitivity of cervical ultrasound is only moderate, with 32% of patients having false negative central neck examinations and 14% false negatives in the ipsilateral neck.[29] Ultrasound is also highly operator-dependent, with many facilities unfortunately lacking experience in performing nodal surveillance in thyroid cancer. Additional imaging is guided by the degree of calcitonin elevation. Neck, chest, and abdominal CT scanning are most commonly performed in pre-operative staging of patients with significant calcitonin elevations. The use of an arterial phase contrast abdominal CT has proven useful in other neuroendocrine tumors[30] and may improve detection of macroscopic MTC liver

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metastases. Hepatic arteriography, though more sensitive than CT for small lesions, has not been employed widely.

Post-operative

In the post-operative setting, repeat calcitonin testing is typically deferred approximately 6 weeks to allow for a post-operative nadir. Levels of CEA, elevated in approximately 30% of MTC patients, may reach their nadir even later. A hallmark of surgical remission is an undetectable basal and pentagastrin-stimulated calcitonin. Overall, the majority of sporadic patients have persistent calcitonin elevations post-operatively, indicating residual cancer. After comprehensive lymphatic clearance along with thyroidectomy, those patients found to be node negative have a 95% chance of an undetectable basal calcitonin level. However, the presence of any lymphadenopathy reduces the chance of calcitonin normalization to approximately 30%.[6] Recent data from the French MTC consortium show that serial post-operative calcitonin measurement can provide valuable prognostic information. At least 4 measurements of calcitonin over a 2-3 year period could provide an accurate estimate of the calcitonin doubling time in most patients, which remained relatively stable over the natural history of the disease. A calcitonin doubling time shorter than 6 months was associated with a significant risk of death in a 5 year follow-up interval (75%), whereas none of the patients with a doubling time greater than 2 years had disease-specific mortality in follow-up. Calcitonin doubling time was a strong prognostic indicator in multivariate analyses, even when adjusted for clinical stage.[31] CEA doubling time, in general, was comparably informative to calcitonin doubling time in patients who had both markers elevated. These findings of Barbet and colleagues are promising, in that they allow detection of some high risk individuals even at a relatively early point in their disease course, potentially prior to the detection of extensive stage IV disease on imaging studies. Rapid calcitonin doubling time certainly is an indicator of progressive disease, and may prompt more intensive imaging, or in some circumstances, referral of patients for clinical trials of systemic therapy.

Clinicians and patients may be frustrated with calcitonin testing because of chaotically variable swings from test to test. It is well-documented, although poorly explained, that some patients have widely variable readings, whereas other patients conform more closely to a trendline.[31] Intrinsic biologic variability in calcitonin secretion is certainly a contributing factor. However calcitonin measurement may also be hampered by the high dose hook effect, seen with some immunoradiometric assays.[32] The hook effect may be suspected when rising CEA or changing imaging findings are not accompanied by rising calcitonin. A hook effect may be confirmed by showing that the observed calcitonin reading remains similar despite serial dilution of the sample. Perhaps more insidious than the hook effect is non-linearity of calcitonin assays at higher levels. Consistent use of a reputable calcitonin assay with concurrent CEA testing is probably the best current approach to this problem.

Germline ret mutational analysis has now become an accepted standard-of-care in the initial work-up following diagnosis of MTC, as discussed above. One can anticipate two other potential uses of ret testing in monitoring patients with established MTC. An emerging class of small molecule inhibitors, described below, inhibit the tyrosine kinase activity of ret. Two critical issues have yet to be resolved regarding ret as a biomarker. First, do sporadic patients bearing the common M918T (or other) ret mutations in their tumors respond differently to small molecule inhibitors of ret? Already there is precedent that tumors bearing a specific ret mutation at codon 804 are markedly resistant to the kinase inhibitor zactima.[33] One might speculate that tumors bearing M918T mutations could exhibit oncogene dependence and initial sensitivity, although further mutations conferring resistance could emerge. To date, commercial laboratories do not yet offer somatic ret mutation analysis, and this remains a research test. A further application of ret analysis is to measure the effectiveness of therapy

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targeting ret. Clinical trials are using immunohistochemical analysis of active, phosphorylated ret in post-treatment biopsy specimens as a key biomarker to indicate whether ret is actually being inhibited or not. It is not yet clear whether post-treatment FNA's to measure ret inhibition could have a role in clinical practice.

The choice of post-operative imaging depends on prior imaging results, calcitonin and CEA levels, presence of any symptoms, and the rationale for potential treatment. Patients with undetectable or very low calcitonin levels are unlikely to have any identifiable disease on imaging. In our institution, we frequently consider periodic imaging with neck ultrasound in patients with modest calcitonin elevations (> 20 pg/ml) and more extensive imaging with higher calcitonin levels (>100-200 pg/ml). Neck ultrasound has the potential to detect recurrent or persistent lymph nodes < 1 cm, and allows efficient selection of nodes for FNA. Neck CT and MRI, exhibiting somewhat less resolution, have the capacity to image deeper structures in the neck, as does FDG-PET.[34] Mediastinal and lung metastases are sensitively detected with chest CT. As noted above, detection of hepatic metastases remains a major challenge in MTC, with a trade-off between highly sensitive/highly invasive techniques (laparoscopic biopsy and hepatic arteriography) versus a moderately sensitive/non-invasive technique (arterial phase contrast abdominal CT). Detection of bone metastases is effective with an axial MRI including cervical, thoracic, lumbar and pelvic sequences.9 As an alternative, FDG-PET appears to have utility for whole body bone imaging.34 Conventional technetium bone scintigraphy has proven disappointing in MTC.9

Two special imaging indications deserve mention. The first indication is selection of patients for systemic therapy clinical trials. Most MTC trials to date have utilized Recist criteria, requiring measurable disease such as lesions > 1cm on spiral CT.[35] Bone lesions or other lesions without quantifiable three dimensional measurements are not applicable. Patients with progressive Stage IV disease on imaging should be actively considered for clinical trials. The presence of moderate cervical lymphadenopathy, as well as distant metastases, could be considered advantageous in targeted therapy trials, allowing for a post-treatment biopsy to assess the degree of target inhibition. A more traditional indication of imaging is the selection of patients for potentially curative re-operation. Here the importance of imaging is more in a negative sense, to effectively rule out inoperable disease. On the other hand, the use of new imaging techniques to detect operable disease and promote curative resection has been generally ineffective.[34, 36] This lack of effectiveness has frequently been attributed to the high frequency of occult liver metastases in patients with longstanding MTC.[8, 37] A more realistic surgical strategy for re-operation is described below, reserving this procedure for patients with incomplete or inadequate primary surgery or a clearcut intent for palliation or forestalling likely complications.

Evolving Therapy of MTC

Surgery

Surgical treatment of MTC has been extensively studied and reviewed; several excellent summaries are published.[38-40] For patients with established, palpable sporadic MTC, the recommended procedure is total thyroidectomy with central compartment and ipsilateral modified radical neck dissection, encompassing levels II-VI. Some centers also routinely perform an initial contralateral neck dissection, while others select contralateral nodal dissection at a second stage, based on the predictive value of a positive contralateral central neck specimen,[6] combined with postop calcitonin measurement and other indicators.

In the U.S., a surprisingly high percentage of MTC patients have undergone incomplete surgery as their initial operation. In SEER data (1973-2002), more patients underwent thyroidectomy without lymph node dissection (37%), than total thyroidectomy with modified radical or radical

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neck dissection (26%) as their initial procedure.[3] Potential explanations for this clinical practice include the initial misdiagnosis of MTC by FNA in some cases, and the relatively high percentage of initial operations performed by surgeons with very limited experience with the disorder. Certainly a strong case can be made for centralized referral of MTC patients to centers of excellence. Intra-operative assessment of lymph nodes by palpation and observation is not an adequate method of assessing nodal involvement, with less than 70% sensitivity and specificity.41 The performance of the central lymph node dissection is of critical importance, because of the predilection of MTC to sites in the tracheo-esophageal groove, which may be difficult to access. An appropriate central nodal dissection entails removal of all lymphatic tissue from the level of the hyoid bone to the innominate vessels and laterally to the carotid arteries.41 Finally, it is important to emphasize the importance of local control of MTC, even in patients with relatively advanced stage IV disease. Since even widespread MTC may be associated with long symptom-free intervals, it is critical to obtain local control to forestall complications such as vocal cord paralysis, airway obstruction, and hemoptysis.

The role of re-operative neck surgery in MTC remains controversial. Re-operation with a curative intent is most feasible in patients who have had an inadequate initial operation. A second indication is imageable recurrent cervical metastasis. If the intent of re-operation is curative, i.e. reducing the post-operative calcitonin to undetectable levels, then there is an onus on the clinician to extensively rule-out distant, inoperable disease, including sensitive examinations of the liver. Moley and colleagues have shown a 25% prevalence of occult liver metastases by laparoscopic biopsy and even higher rates have been detected by hepatic arteriography.[8, 42] Palliative re-operation may be indicated if there is risk for future compression or invasion of the trachea or major vessels, for example.

Radiation

External beam radiation therapy has a limited role in MTC that has been well-summarized elsewhere.[43] Four non-randomized studies support the use of adjuvant external beam radiotherapy in post-operative patients at high risk for local recurrence, for example in patients with locally-invasive tumor, grossly positive surgical margins, or extensive adenopathy with extra-nodal extension. In this setting, adjuvant XRT may reduce the 10 year local recurrence rate by 30-50%.[44] External beam radiotherapy is also useful in a palliative fashion in bone metastases. There is of course no role for radioiodine therapy in MTC. Targeted radiotherapy, using either anti-CEA monoclonal antibodies or radiolabeled somastatin receptor ligands, is also under investigation.

Systemic Therapy

Experience to date with single agent or combination chemotherapy for MTC has been largely unsatisfactory, with no large scale or phase III studies performed to date. Nocera *et. al*. reported a partial response rate of 15% in MTC patients treated with a combination of doxorubicin, streptozotocin, 5-FU and dacarbazine.[45] Approximately 28% of advanced MTC patients had partial responses in a small-scale trial of cyclophosphamide, vincristine, and dacarbazine.[46] Based on the significant mortality of Stage IV MTC and the absence of effective conventional chemotherapy, a number of groups have sought targeted therapy of the disease, using the ret tyrosine kinase, angiogenic growth factors, somatatostatin receptors, CEA, the proteasome, and heat shock proteins as principal targets.

Ret as a therapeutic target

Proof-of-principal that ret inhibition can provide useful treatment for MTC stems from several experimental studies. A dominant negative ret molecule, preserving the extracellular and transmembrane domains of the receptor but lacking the intracellular tyrosine kinase domain, was capable of inducing growth arrest and programmed cell death when over-expressed in

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MTC cells that expressed a native ret activating mutation at codon 634, but had no effect in heterologous tumor cells lacking a mutant ret.[47] Neutralizing antibodies directed at activated ret (including phosphporylated Tyr1062) also inhibited growth.[48] Based on such encouraging proof-of-principal studies, and the remarkable initial responses of such small molecule inhibitors as imatinib in CML and gastrointestinal stromal tumor, a growing list of candidate inhibitors of ret now have been identified and tested.

Small molecule tyrosine kinase inhibitors (TKI's) with activity against ret include the following: RPI-1, sunitinib (SU11248), PP1 and PP2, CEP-701 and CEP-751, zactima (ZD6474), sorafenib (BAY 43-9006), XL-880, and XL-184 (see 12 and 49 for recent summaries). Other small molecule inhibitors of ret are expected to emerge soon. Most of these agents bind to the ATP-binding pocket of ret which is highly conserved compared to other receptor tyrosine kinases, creating the potential for multiple inhibitory targets, and potentially, greater side effects. Sunitinib, zactima, sorafenib, XL-880 and XL-184 all target KDR/VEGFR2, a second highly important target in MTC. In fact, it is a challenge for clinical trials to distinguish anti-Ret efficacy from activity stemming from inhibition of VEGF receptors and other targets.

Early clinical trials employing TKI's targeting ret suggest that this strategy could be well-tolerated and relatively effective, at least in a cytostatic fashion. Wells and colleagues reported preliminary data on a phase II trial of zactima, a multifunction TKI targeting ret (IC_{50} 100 nM), VEGFR2/KDR (IC_{50} 40 nM), and EGFR.[50] Of fifteen patients with hereditary MTC, three showed partial tumor responses, ten stable disease and two progressive disease. Median duration of treatment was 136 days. Twelve of fifteen patients had a greater than 50% decrease in calcitonin; some patients had >90% declines. Approximately half of the patients also had significant declines in CEA. Side effects for this oral drug included diarrhea, nausea, skin rash and fatigue, often necessitating dose reductions. Although this trial was not powered to distinguish responses to different ret mutations, independent *in vitro* work has indicated marked differences in sensitivity to this agent, with one common mutation at codon 804 highly resistant to zactima but relatively sensitive to sorafenib.[33, 51] An international phase III trial is currently beginning, in order to evaluate the efficacy across a broader population of MTC patients.

In addition to zactima, MTC clinical trials are currently planned or underway for sorafenib and sunitinib. Agents earlier in the developmental pipeline have the potential to inhibit ret at subnanomolar concentrations, and significant promise for hereditary and at least some cases of sporadic MTC.

The strategy of combining targeted therapy with cytotoxic chemotherapy has had some notable successes, for example trastuzamab plus chemotherapy in breast cancer. However targeted and cytotoxic agent pairings need to be carefully designed. Preclinical studies are just beginning to examine ret inhibition in combination with cytotoxic drugs. As a single agent in MTC xenograft studies in mice, irinotecan had excellent activity with median progression-free survival of 95 days and all mice progression-free at 75 days.[52] The combination of irinotecan plus the TKI CEP-751 did not reach median progression-free survival at 135 days, with 100% of mice progression-free at 110 days, after a treatment course lasting 30 days. CEP-751 has an IC_{50} for RET of 100nM in the presence of serum and additional activity against VEGFR2 and TrkA.[52] While the mechanism for the additive activity of CEP-751 and irinotecan is uncertain, the TKI in this experiment appeared to abrogate the mid-S phase arrest associated with the DNA damage response to irinotecan. Other TKI's targeting ret shared this property, although the specificity of this interaction needs further investigation.[52]

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Angiogenesis inhibitors

Two phase II clinical trials recently have been completed for single agent TKI's targeting VEGF receptors 1-3 in thyroid cancer including significant populations with MTC. Axitinib (AG-013736) was associated with an overall partial response rate of 20% in thyroid cancer patients in preliminary results. Two of twelve MTC patients had radiographic partial responses and six stable disease with four patients progressing on treatment.53 Interestingly, follicular thyroid cancer exhibited the strongest response to date (33% PR, 87% PR or SD). Reported side effects of this oral agent were moderate, including fatigue, hypertension and proteinuria. The best overall response rate to Axitinib as a single agent is in renal cell carcinoma (46%), a VHL and VEGF-dependent tumor.54 A Phase II study of the VEGFR inhibitor AMG-706 (Amgen, Thousand Oaks) in MTC has also reached completion. It will be interesting to see if combinations of angiogenesis inhibitors and chemotherapy or other targeted agents show greater efficacy in MTC, as has been observed in colorectal cancer, for example. Multifunction TKI's have the potential to target both ret and VEGFR's, combining these two excellent targets in MTC.

Other target targeted therapies

A number of other therapeutic targets are under investigation in MTC. These investigational approaches include targeting somatostatin receptors with high energy-emitting ligands,[55] radio-immunotherapy using monoclonal antibodies to CEA,[56] and the use of proteasome inhibitors such as bortezomib, potentially targeting the AKT-Nf kappa B pathway.[57] Heat shock protein inhibitors, such as 17-AAG and other geldanomycin derivatives, can lead to impaired protein folding and potentially to destabilization of mutant proteins such as activated ret.[58]

Future Prospects for Monitoring and Therapy

Activated Ret is the outstanding target for therapy in MTC, based on the relatively high prevalence of this mutated oncogene (~50% of tumors overall), a relatively specific expression pattern, and emerging proof-of-principal studies. There is an immediate need to correlate biomarkers relating to ret mutational status and ret inhibition at the tumor level, with clinical response to TKI's. There are several critical monitoring issues for MTC patients who fail ret inhibitor treatment: 1) do they exhibit a “sensitive” ret mutation; 2) is heterogeneity of ret mutations within their tumors a problem; 3) has ret kinase activity been effectively inhibited by the drug? Furthermore, conventional Recist criteria may provide inadequate imaging guidelines for response to therapies such as ret inhibitors which appear primarily cytostatic. The role of functional imaging such as FDG-PET or DCI-MRI has not been studied in this setting.

A further challenge will be to devise effective drug combinations that overcome the resistance associated with effective kinase inhibitors in other disorders, such as imatinib in CML and GIST, for example, which may stem from second site mutations or more complex adaptive mechanisms.[59, 60] Clearly, understanding the tumor adaptation to ret inhibition may be helpful in developing combination strategies. It is encouraging to both patients and clinicians that a variety of promising avenues is now emerging for MTC.

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References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin Mar-Apr;2006 56(2):106–130. [PubMed: 16514137]
2. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. Jama May 10;2006 295(18):2164–2167. [PubMed: 16684987]
3. Roman S, Lin R, Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. Cancer Nov 1;2006 107(9):2134–2142. [PubMed: 17019736]
4. Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. Ann Surg Jun;1999 229(6):880–887. discussion 887-888. [PubMed: 10363903]
5. Machens A, Hinze R, Thomusch O, Dralle H. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg Jan;2002 26(1):22–28. [PubMed: 11898029]
6. Scollo C, Baudin E, Travagli JP, et al. Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer. J Clin Endocrinol Metab May;2003 88(5):2070–2075. [PubMed: 12727956]
7. Machens A, Holzhausen HJ, Dralle H. Contralateral cervical and mediastinal lymph node metastasis in medullary thyroid cancer: systemic disease? Surgery Jan;2006 139(1):28–32. [PubMed: 16364714]
8. Szavcsur P, Godeny M, Bajzik G, et al. Angiography-proven liver metastases explain low efficacy of lymph node dissections in medullary thyroid cancer patients. Eur J Surg Oncol Mar;2005 31(2):183–190. [PubMed: 15698736]
9. Mirallie E, Vuillez JP, Bardet S, et al. High frequency of bone/bone marrow involvement in advanced medullary thyroid cancer. J Clin Endocrinol Metab Feb;2005 90(2):779–788. [PubMed: 15572422]
10. Bergholm U, Bergstrom R, Ekbom A. Long-term follow-up of patients with medullary carcinoma of the thyroid. Cancer Jan 1;1997 79(1):132–138. [PubMed: 8988737]
11. Ichihara M, Murakumo Y, Takahashi M. RET and neuroendocrine tumors. Cancer Lett Feb 20;2004 204(2):197–211. [PubMed: 15013219]
12. de Groot JW, Links TP, Plukker JT, Lips CJ, Hofstra RM. RET as a diagnostic and therapeutic target in sporadic and hereditary endocrine tumors. Endocr Rev Aug;2006 27(5):535–560. [PubMed: 16849421]
13. Attie T, Pelet A, Edery P, et al. Diversity of RET proto-oncogene mutations in familial and sporadic Hirschsprung disease. Hum Mol Genet Aug;1995 4(8):1381–1386. [PubMed: 7581377]
14. Jijiwa M, Fukuda T, Kawai K, et al. A targeting mutation of tyrosine 1062 in Ret causes a marked decrease of enteric neurons and renal hypoplasia. Mol Cell Biol Sep;2004 24(18):8026–8036. [PubMed: 15340065]
15. Santoro M, Melillo RM, Carlomagno F, Fusco A, Vecchio G. Molecular mechanisms of RET activation in human cancer. Ann N Y Acad Sci Jun;2002 963:116–121. [PubMed: 12095936]
16. Smith-Hicks CL, Sizer KC, Powers JF, Tischler AS, Costantini F. C-cell hyperplasia, pheochromocytoma and sympathoadrenal malformation in a mouse model of multiple endocrine neoplasia type 2B. Embo J Feb 15;2000 19(4):612–622. [PubMed: 10675330]
17. Michiels FM, Chappuis S, Caillou B, et al. Development of medullary thyroid carcinoma in transgenic mice expressing the RET protooncogene altered by a multiple endocrine neoplasia type 2A mutation. Proc Natl Acad Sci U S A Apr 1;1997 94(7):3330–3335. [PubMed: 9096393]
18. Acton DS, Velthuyzen D, Lips CJ, Hoppener JW. Multiple endocrine neoplasia type 2B mutation in human RET oncogene induces medullary thyroid carcinoma in transgenic mice. Oncogene Jun 22;2000 19(27):3121–3125. [PubMed: 10871866]
19. Machens A, Niccoli-Sire P, Hoegel J, et al. Early malignant progression of hereditary medullary thyroid cancer. N Engl J Med Oct 16;2003 349(16):1517–1525. [PubMed: 14561794]
20. Gill JR, Reyes-Mugica M, Iyengar S, et al. Early presentation of metastatic medullary carcinoma in multiple endocrine neoplasia, type IIA: implications for therapy. J Pediatr Sep;1996 129(3):459–464. [PubMed: 8804341]
21. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab Dec;2001 86(12):5658–5671. [PubMed: 11739416]

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22. Hofstra RM, Landsvater RM, Ceccherini I, et al. A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. Nature Jan 27;1994 367(6461):375–376. [PubMed: 7906866]
23. Blaugrund JE, Johns MM Jr. Eby YJ, et al. RET proto-oncogene mutations in inherited and sporadic medullary thyroid cancer. Hum Mol Genet Oct;1994 3(10):1895–1897. [PubMed: 7849720]
24. Eng C, Mulligan LM, Healey CS, et al. Heterogeneous mutation of the RET proto-oncogene in subpopulations of medullary thyroid carcinoma. Cancer Res May 1;1996 56(9):2167–2170. [PubMed: 8616867]
25. Schilling T, Burck J, Sinn HP, et al. Prognostic value of codon 918 (ATG-->ACG) RET proto-oncogene mutations in sporadic medullary thyroid carcinoma. Int J Cancer Jan 20;2001 95(1):62–66. [PubMed: 11241313]
26. Wohllk N, Cote GJ, Bugalho MM, et al. Relevance of RET proto-oncogene mutations in sporadic medullary thyroid carcinoma. J Clin Endocrinol Metab Oct;1996 81(10):3740–3745. [PubMed: 8855832]
27. Cohen R, Campos JM, Salaun C, et al. Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma. Groupe d'Etudes des Tumeurs a Calcitonine (GETC). J Clin Endocrinol Metab Feb;2000 85(2):919–922. [PubMed: 10690910]
28. Machens A, Schneyer U, Holzhausen HJ, Dralle H. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. J Clin Endocrinol Metab Apr;2005 90(4):2029–2034. [PubMed: 15634717]
29. Kouvaraki MA, Shapiro SE, Fornage BD, et al. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. Surgery Dec;2003 134(6):946–954. discussion 954-945. [PubMed: 14668727]
30. Paulson EK, McDermott VG, Keogan MT, DeLong DM, Frederick MG, Nelson RC. Carcinoid metastases to the liver: role of triple-phase helical CT. Radiology Jan;1998 206(1):143–150. [PubMed: 9423664]
31. Barbet J, Campion L, Kraeber-Bodere F, Chatal JF. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab Nov;2005 90(11):6077–6084. [PubMed: 16091497]
32. Leboeuf R, Langlois MF, Martin M, Ahnadi CE, Fink GD. "Hook effect" in calcitonin immunoradiometric assay in patients with metastatic medullary thyroid carcinoma: case report and review of the literature. J Clin Endocrinol Metab Feb;2006 91(2):361–364. [PubMed: 16278263]
33. Carlomagno F, Guida T, Anaganti S, et al. Disease associated mutations at valine 804 in the RET receptor tyrosine kinase confer resistance to selective kinase inhibitors. Oncogene Aug 12;2004 23 (36):6056–6063. [PubMed: 15184865]
34. de Groot JW, Links TP, Jager PL, Kahraman T, Plukker JT. Impact of 18F-fluoro-2-deoxyD-glucose positron emission tomography (FDG-PET) in patients with biochemical evidence of recurrent or residual medullary thyroid cancer. Ann Surg Oncol Aug;2004 11(8):786–794. [PubMed: 15289241]
35. Therasse P, Arbuck SG, Eisenhauer EA, et al. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst Feb 2;2000 92 (3):205–216. [PubMed: 10655437]
36. Udelsman R, Ball D, Baylin SB, Wong CY, Osterman FA Jr. Sostre S. Preoperative localization of occult medullary carcinoma of the thyroid gland with single-photon emission tomography dimercaptosuccinic acid. Surgery Dec;1993 114(6):1083–1089. [PubMed: 8256211]
37. Machens A, Dralle H. Angiography-proven liver metastases explain low efficacy of lymph node dissections in medullary thyroid cancer patients. Eur J Surg Oncol Nov;2005 31(9):1051–1052. [PubMed: 15908165]
38. You YN, Lakhani V, Wells SA Jr. Moley JF. Medullary thyroid cancer. Surg Oncol Clin N Am Jul; 2006 15(3):639–660. [PubMed: 16882502]
39. Fleming JB, Lee JE, Bouvet M, et al. Surgical strategy for the treatment of medullary thyroid carcinoma. Ann Surg Nov;1999 230(5):697–707. [PubMed: 10561095]

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40. Machens A, Ukkat J, Brauckhoff M, Gimm O, Dralle H. Advances in the management of hereditary medullary thyroid cancer. J Intern Med Jan;2005 257(1):50–59. [PubMed: 15606376]
41. Fialkowski EA, Moley JF. Current approaches to medullary thyroid carcinoma, sporadic and familial. J Surg Oncol Dec 15;2006 94(8):737–747. [PubMed: 17131404]
42. Tung WS, Vesely TM, Moley JF. Laparoscopic detection of hepatic metastases in patients with residual or recurrent medullary thyroid cancer. Surgery Dec;1995 118(6):1024–1029. discussion 1029-1030. [PubMed: 7491518]
43. Brierly, JD.; Tsang, RW. External Radiation Therapy of Medullary Thyroid Cancer. In: Wartofsky, L.; Van Nostrand, D., editors. Thyroid Cancer: A Comprehensive Guide to Clinical Management. Humana; Totowa, N.J.: 2006. p. 605-607.
44. Brierley J, Tsang R, Simpson WJ, Gospodarowicz M, Sutcliffe S, Panzarella T. Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. Thyroid Aug;1996 6(4):305–310. [PubMed: 8875751]
45. Nocera M, Baudin E, Pellegriti G, Cailleux AF, Mechelany-Corone C, Schlumberger M. Treatment of advanced medullary thyroid cancer with an alternating combination of doxorubicin-streptozocin and 5 FU-dacarbazine. Groupe d'Etude des Tumeurs a Calcitonine (GETC). Br J Cancer Sep;2000 83(6):715–718. [PubMed: 10952773]
46. Wu LT, Averbuch SD, Ball DW, de Bustros A, Baylin SB, McGuire WP 3rd. Treatment of advanced medullary thyroid carcinoma with a combination of cyclophosphamide, vincristine, and dacarbazine. Cancer Jan 15;1994 73(2):432–436. [PubMed: 8293411]
47. Drosten M, Hilken G, Bockmann M, et al. Role of MEN2A-derived RET in maintenance and proliferation of medullary thyroid carcinoma. J Natl Cancer Inst Aug 18;2004 96(16):1231–1239. [PubMed: 15316058]
48. Salvatore D, Barone MV, Salvatore G, et al. Tyrosines 1015 and 1062 are in vivo autophosphorylation sites in ret and ret-derived oncoproteins. J Clin Endocrinol Metab Oct;2000 85(10):3898–3907. [PubMed: 11061555]
49. Santoro M, Carlomagno F. Drug insight: Small-molecule inhibitors of protein kinases in the treatment of thyroid cancer. Nat Clin Pract Endocrinol Metab Jan;2006 2(1):42–52. [PubMed: 16932252]
50. Wells S YY, Lakhani V, Hou J. A phase II trial of ZD6474 in patients with hereditary metastatic medullary thyroid cancer. Journal of Clinical Oncology 2006;24(18S):5553.
51. Carlomagno F, Anaganti S, Guida T, et al. BAY 43-9006 inhibition of oncogenic RET mutants. J Natl Cancer Inst Mar 1;2006 98(5):326–334. [PubMed: 16507829]
52. Strock CJ, Park JI, Rosen DM, et al. Activity of irinotecan and the tyrosine kinase inhibitor CEP-751 in medullary thyroid cancer. J Clin Endocrinol Metab Jan;2006 91(1):79–84. [PubMed: 16263812]
53. Kim S RL, Cohen EE, Cohen RB. A Phase II study of axitinib (AG-013736), a potent inhibitor of VEGFRs, in patients with advanced thyroid cancer. Journal of Clinical Oncology 2006;24(8S) Abstract 5529.
54. Larkin JM, Eisen T. Kinase inhibitors in the treatment of renal cell carcinoma. Crit Rev Oncol Hematol Dec;2006 60(3):216–226. [PubMed: 16860997]
55. Bodei L, Handkiewicz-Junak D, Grana C, et al. Receptor radionuclide therapy with 90YDOTATOC in patients with medullary thyroid carcinomas. Cancer Biother Radiopharm Feb;2004 19(1):65–71. [PubMed: 15068613]
56. Chatal JF, Campion L, Kraeber-Bodere F, et al. Survival improvement in patients with medullary thyroid carcinoma who undergo pretargeted anti-carcinoembryonic-antigen radioimmunotherapy: a collaborative study with the French Endocrine Tumor Group. J Clin Oncol Apr 10;2006 24(11):1705–1711. [PubMed: 16549819]
57. Mitsiades CS, McMillin D, Kotoula V, et al. Anti-tumor effects of the proteasome inhibitor bortezomib in medullary and anaplastic thyroid carcinoma cells in vitro. J Clin Endocrinol Metab. Jul 18;2006
58. Cohen MS, Hussain HB, Moley JF. Inhibition of medullary thyroid carcinoma cell proliferation and RET phosphorylation by tyrosine kinase inhibitors. Surgery Dec;2002 132(6):960–966. discussion 966-967. [PubMed: 12490842]

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59. Agaram NP, Besmer P, Wong GC, et al. Pathologic and molecular heterogeneity in imatinib-stable or imatinib-responsive gastrointestinal stromal tumors. Clin Cancer Res Jan 1;2007 13(1):170–181. [PubMed: 17200352]

60. Ritchie E, Nichols G. Mechanisms of resistance to imatinib in CML patients: a paradigm for the advantages and pitfalls of molecularly targeted therapy. Curr Cancer Drug Targets Dec;2006 6(8): 645–657. [PubMed: 17168670]