Medullary Thyroid Cancer: Review & Update

Jessica E. Gosnell MD
Assistant Professor in Residence
Department of Surgery
November 9, 2012

Nothing to disclose.

Medullary Thyroid Cancer:

- MTC has distinct embryology, genetic association and clinical features
- All patients with MTC need genetic testing
- ATA guidelines 2009
- Many patients develop recurrent/persistent disease
- New FDA-approved drug (Vandetanib)

Medullary Thyroid Cancer

- Unpredictable, often aggressive, rare tumor
- Parafollicular, not follicular cell origin
- Sensitive tumor marker: calcitonin
- Known genetic RET mutation
- Requires rigorous strategy
  - Work-up
  - Operative technique
- Many patients with persistent/recurrent disease
  - Clinical/biochemical surveillance
  - Novel treatments
Medullary Thyroid Cancer: History and Incidence

- Original description by Jaquet- “malignant goiter with amyloid”
- Hazard, Hawk and Cline- histologic description in 1959
- Williams- para-follicular “C-cells”, derived from the neural crest
- Accounts for 3-9% of thyroid cancer cases

Medullary Thyroid Cancer: Histology

- Para-follicular C cells
- Amyloid
- Calcitonin

Medullary Thyroid Cancer: Clinical Presentation

- Familial: 25%
- Sporadic: 75%
Medullary Thyroid Cancer: Clinical Presentation

**Clinical Features:**

<table>
<thead>
<tr>
<th>Disease</th>
<th>MTC features</th>
<th>Assoc. abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>Unifocal</td>
<td>None</td>
</tr>
<tr>
<td>MEN-2A</td>
<td>Multifocal, bilateral</td>
<td>Pheochromocytoma, Hyperparathyroidism</td>
</tr>
<tr>
<td>MEN-2B</td>
<td>Multifocal, bilateral</td>
<td>Pheochromocytoma, marfanoid habitus, mucal neuromas, mega-colon, skeletal</td>
</tr>
<tr>
<td>FMTC</td>
<td>Multifocal, bilateral</td>
<td>None</td>
</tr>
</tbody>
</table>

**Sporadic-75%**

- Third to fifth decade
- Solitary thyroid nodule (45 – 94%)
- Palpable lymph nodes in 50%
- Distant metastases in 12-25% (lung, liver, bone)
- Diarrhea 20%

(Marlon A. Guerrero, Sheila Lindsay, Insoo Suh, Menno R. Vriens, Elham Khanafshar, Wen T. Shen, Jessica Gosnell, Electron Kebebew, Quan-Yang Duh, Orlo H. Clark)

Journal of Cancer 2011;2:200

- 11/50 patients with MTC presented with neck pain vs 3/50 with PTC (p=0.041)
- Of those with neck pain, 82% had lymph node involvement, as compared to 36% without neck pain
Medullary Thyroid Cancer: Clinical Presentation

Hereditary-25%

- Can be suggested by family history
- Increasingly identified by genetic testing
- Age-related disease

(Bargholm et al. Cancer 1989;63:1196)
(Kalinoski et al. Surgery 1993;114:491)

RET proto-oncogene

Medullary Thyroid Cancer: Genetic testing

- Autosomal dominant, chromosome 10
- Point mutations in the RET gene (1993-1994)
- Genotype-phenotype correlations
  - codon 918 MEN2B
  - codon 634 MEN2A
- Up to 10% of apparent “sporadic” cases of MTC will be found to have RET mutation
- Essentially all pts with RET mutation will develop MTC


Medullary Thyroid Cancer: Genetic testing

- May “tailor” operative approach (adrenal & parathyroid glands)
- Identifies at-risk kindred
- Obviates the need for lifelong surveillance for gene-negative kindred
- Allows prophylactic thyroidectomy
  - age 6 yr: FMTC, MEN 2A
  - age 1 yr: MEN 2B


RET mutations: ATA guidelines

(Thyroid, 2009)
Medullary Thyroid Cancer

Prognosis:
- 10-year overall survival of 75%, but 40% with locally advanced or metastatic disease
- Often a systemic disease when diagnosed
- High incidence of associated lymph node disease (pT1 33%, pT2 53%, pT3 100%, pT4 100%)
  - Gimm et al., WJS 1998

Medullary Thyroid Cancer: Work-up & treatment

- History & physical exam
  - Family hx, symptoms, abnormal phenotype, fixed tumor, adenopathy
- Serum calcitonin, CEA, calcium, iPTH
- Urinary catecholamines, plasma metanephrines
- Neck ultrasound
- Laryngoscopy
- RET testing for genetic mutations

Medullary thyroid cancer: Work-up & treatment

- calcitonin < 400 pg/ml
- calcitonin > 400 pg/ml
Medullary Thyroid Cancer: Surgical treatment

- Total thyroidectomy - preservation vs autotransplantation of parathyroids
- Central lymph node dissection - between carotid sheaths, from hyoid bone to innominate vein, head of clavicle
- Lateral lymph node dissection - "selective approach" (clinical or radiographic evidence of disease)

TOTAL THYROIDECTOMY, BILATERAL CENTRAL LYMPH NODE DISSECTION (Kebebew, Curr Treat Options Oncol 2000)

MTC: Poor biochemical cure rates

- Although about 70% of pts who present with MTC and nodal metastases are alive at 10yrs, very few are calcitonin negative
- No patients with extrathyroidal tumor involvement or distant metastases was biochemically cured
  - Gimm et al, WJS 1998

"Overall, the rate of persistent hypercalcitoninemia is nearly 50% for patients with nonpalpable macroscopic disease and greater than 80% for patients presenting with a palpable MTC” (van Heerden, Ann Surg 2000)

Medullary Thyroid Cancer: Recurrent/Persistent

Presentation:

- Asymptomatic elevated serum calcitonin
- Palpable disease in the neck
- Symptoms from local disease
  - stridor, dyspnea, hoarseness
- Symptoms from metastatic disease
  - bone pain
- Symptoms from secretion of vasoactive substances
  - diarrhea, flushing
Medullary Thyroid Cancer: Recurrent/Persistent

**Work-up:**
- Exam
- Serum calcitonin, CEA
- Neck ultrasound, CT scan, MRI, octreotide scintigraphy
- R/o mets (mediastinum, hilar nodes, liver, lungs)
- Laryngoscopy
- Diagnostic laparoscopy

Medullary Thyroid Cancer: Adjuvant therapy

**Thyroid hormone suppression**

**Chemotherapy**

**Radioiodine ablation**

**XRT**

SUCCESS

Medullary Thyroid Cancer: Recurrent/Persistent

**Treatment:**
- Re-operation
  - completion thyroidectomy, LND
  - debulking
- Chemotherapy/XRT of limited value
- Medications (Loperamide, somatostatin analogs, histamine blockers)
- Local, palliative treatment (RFA of liver tumors, peripheral XRT)
- Novel agents/clinical trials

Explosion of targeted therapies!

(Time magazine, May 28, 2001)
Multi-kinase interaction

(Gomez et al, Journal of Thyroid Research; vol 2011)

Recurrent/Persistent MTC

Treatment:
- Tyrosine kinase inhibitors
  - Vandetanib (Caprelsa)
  - XL 184 (cabozantinib)
- Approved for other solid cancers
  - Sorafenib (Nexavar)
  - Sunitinib (Sutent)
  - Pazopanib (Votrient)
- Clinical trials
  - E7080 (lenvatinib)
- Monoclonal antibodies
  - bevacizumab
- Radio-labeled molecules
  - 90 Yttrium DOTA

Vandetanib for the Treatment of Patients With Locally Advanced or Metastatic Hereditary Medullary Thyroid Cancer

Samuel A. Wells Jr, Jessica E. Gosnell, Robert F. Gagel, Jeffrey Moley, David Pfister, Julie A. Sosa, Michael Skinner, Annette Krebs, James Vasselli, and Martin Schlumberger

Journal of Clinical Oncology 2010;28(5):767

- Open label, phase II study
- Once daily dosing of 300mg
- 30 patients worldwide
- Inclusion criteria included:
  - RET mutation
  - measurable metastatic lesion per RECIST
  - WHO performance status of 0-2
**Vandetanib for the Treatment of Patients With Locally Advanced or Metastatic Hereditary Medullary Thyroid Cancer**

Samuel A. Wells Jr, Jessica E. Gosnell, Robert F. Gagel, Jeffrey Moley, David Pfister, Julie A. Sosa, Michael Skinner, Annette Krebs, James Vasselli, and Martin Schlumberger

*Journal of Clinical Oncology* 2010;28(5):767

- 20% partial response
- 50% stable disease

**RESULTS**

**Vandetanib in patients with locally advanced or metastatic Medullary thyroid cancer: a randomized, double-blind Phase III trial.**


- Randomized prospective trial
- 2:1 vandetanib 300mg: placebo
- 331 patients worldwide
- Inclusion criteria included:
  - measurable metastatic lesion per RECIST
  - WHO performance status of 0-2

**RESULTS**

- Progression free survival (PFS) with vandetanib vs placebo
  - HR 0.46, 95% CI, 0.31 to 0.69 (P<0.001)
  - PFS for placebo 19.3, median for vandetanib group not reached, estimated at 30.5 months by statistical model
- Statistically significant advantages for:
  - Objective response rate, disease control rate and biochemical response
- Survival data still immature (when >50% pts have died)

**Vandetanib: adverse events**

- Diarrhea
- Rash
- Nausea
- Hypertension
- Fatigue
- QTc prolongation

12% patients stopped due to side effects
Medullary Thyroid Cancer:

**Conclusions:**

- MTC has distinct embryology, genetic association and clinical features
- All patients with MTC need genetic testing
- ATA guidelines 2009: Total thyroidectomy, bilateral central lymph node dissection
- Many patients develop recurrent/persistent disease
- There are several promising targeted therapies (TKIs), including vandetanib, recently approved by the FDA