Medullary Thyroid Carcinoma: New Therapies and Trials

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Medullary Thyroid Carcinoma: Demographics

- Hundahl, et. al., studied ~53,856 patients with thyroid cancer in the US from the National Cancer Data Base:
- MTC accounted for 3.6% of all thyroid cancer cases. Similar frequency in males and females.
- Survival was predicted by tumor stage and patient age at diagnosis.
- Options for treating metastatic disease are not curative.
Medullary Thyroid Carcinoma: Prognosis & TNM Stage

<table>
<thead>
<tr>
<th>Stage at Presentation</th>
<th>Cause-Specific Mortality (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
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<tr>
<td>3</td>
<td>30</td>
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<td>4</td>
<td>50</td>
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Medullary Thyroid Carcinoma: Distant Metastases

• Key Issues in Patients with Metastatic MTC
  – Who should be treated in the absence of symptoms?
  – Can we predict who will have aggressive disease before it “takes off?”
  – Are there effective systemic or local therapies?
Medullary Thyroid Carcinoma: Calcitonin and CEA Doubling Time

- Calcitonin and CEA Doubling Time
  - Barbet, et al evaluated 65 patients retrospectively (2.9-25 yrs of follow-up)
  - Calcitonin and CEA doubling times (DT) were calculated and stratified
    - >2 yrs
    - 0.5-2 yrs
    - <0.5 yrs
  - The prediction of death from MTC was compared to TNM and EORTC Staging.

## Medullary Thyroid Carcinoma: Calcitonin Doubling Time

<table>
<thead>
<tr>
<th>Calcitonin DT (all time points)</th>
<th>5-yr survival</th>
<th>10-yr survival</th>
</tr>
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<tbody>
<tr>
<td>&gt;2 yrs</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>0.5-2.0 yrs</td>
<td>94%</td>
<td>64%</td>
</tr>
<tr>
<td>&lt;0.5 yrs</td>
<td>23%</td>
<td>15%</td>
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Calcitonin and CEA Doubling Time MetaAnalysis

  – 10 studies that have post-op calcitonin
  – Enough samples for doubling time
  – Includes survival as an endpoint

• Evaluated multiple cut point of doubling times. Many were significant but 12 months seemed to be the greatest discriminator for survival for both calcitonin and CEA
CEA Doubling Time as a Marker of Lack of Response to Therapy

  - Retrospective Study of 28 patients with metastases treated with cytotoxic chemotherapy from 2001-2010 from one institution
  - Changes in calcitonin levels over the first three months did not statistically correlate with PFS
  - CEA levels did correlate with PFS and a rise in CEA was highly associated with shorter Progression free survival.
Does FDG Uptake Predict Aggressive Disease in MTC?

• Verbeek, et al. (J Nucl Med 2012;53:1863-1871) compared FDG PET and DOPA PET with calcitonin and CEA doubling times in 47 patients with residual calcitonin levels.

• DOPA PET was slightly more sensitive than FDG PET (44% vs 34%)

• However, only FDG PET correlated with calcitonin doubling time <12 months and higher calcitonin levels
Medullary Thyroid Carcinoma: Multikinase Inhibitors

• Multi-Kinase Inhibitors
  – Compounds that inhibit receptor tyrosine kinase signaling
  – Some inhibit RET signaling in addition to other receptors such as VEGFR, EGFR, PDFGR and others

• Two FDA-approved for metastatic progressive or symptomatic MTC
  • Vandetinib: RET/VEGFR/EGFR
  • Cabozantinib: RET/VEGFR/MET
Vandetanib Phase III Study

• Phase 3 study (Wells SA, J Clin Oncol. 2012;30:134-41
  – 331 patients from 23 centers (12/06-11/07)
  – 2:1 vandetanib:placebo randomization with open
    label extension; 24 month follow up
  – 231 pts received Vandetanib; 100 received Place

• Patients with metastatic MTC with RECIST
  measurable disease. Progression was not
  required. Calcitonin >500 pg/ml

• Duration of Progression Free Survival was
  primary Endpoint
Vandetanib Phase III Study: Toxicity and Tolerability

• 52 % (120/231) discontinued treatment
  – 17% either died or voluntarily withdrew
  – Diarrhea: 56% vs 26%
  – Rash: 45% vs 11%
  – Hypertension: 32% vs 5%
  – Fatigue: 24% vs 23%
  – Acneiform Rash: 15% vs 2%
  – QTc Prolongation: 14% vs 1%
Vandetanib and Body Composition

- Massicotte, et al (J Clin Endocrinol Metab; 2103:2401-08)
  - 33 patients retrospective review: 23 with vandetanib; 10 placebo from Phase III study
  - Compared with placebo group
    - Vandetanib had increased Body Weight (p=0.02); skeletal muscle mass (p=0.009) and Adiposity (p=0.004)
    - Patients with dose limiting toxicity had higher serum concentration of the compound and had less skeletal muscle mass
Vandetanib and Rash

• Rosen AC, et al (J Clin Endocrinol Metab 2012 1125-1133) retrospectively reviewed the literature between 2006 and 2011 for data regarding rash and Vandetanib (1751 treated vs 1210 controls)
  – All Grades: 46.1% (54.3 % in MTC)
  – High Grade: 3.5% (3.4% in MTC)
• Presumed due to EGFR effects
Cabozantinib Phase III study

- Phase 3 study (Ellisei, et al, J Clin Oncol. 2013;31:3639)
  - 330 patients from 23 countries
  - 2:1 cabozantinib:placebo randomization with no crossover; 219 vs 111 in each group

- Progression by RECIST was required over 14 months prior to enrollment

- Primary Endpoint was Progression Free Survival; Overall Response Rate and Overall Survival were Secondary Endpoints

- Dose holds and two dose level reductions allowed
Cabozantinib Phase III Study: Toxicity and Tolerability

- 219 Patients on Treatment Arm
  - 45% Continued Treatment
  - 55% Discontinued Treatment
    - Progressive Disease: 26%
    - Adverse Events: 16%
    - Death: 5%
- Diarrhea 63% vs 33%; Hand-Foot Syndrome: 50%
- Weight Loss: 48%
- Hypertension: 33% and Hemorrhage 25%
- No QTc prolongation
Comparison of Vandetanib and Cabozantinib

• **Efficacy:**
  – Study Entrance Requirements Differed
  – Duration of Responses
  – Vandetanib: 30.5 months vs 19 months (placebo)
  – Cabozantinib: 11.2 months vs 4 months

• **Side Effects**
  – Vandetanib: QTc, Hypertension, Acneiform Rash, Diarrhea, Headache: Requires REMS Training
  – Cabozantinib: Diarrhea, Weight Loss, Nausea, Hand-Foot Syndrome
Phase II Studies in MTC

• Not FDA-approved for MTC
  – **Sunitinib**: 2 studies including 30 patients
    • PR: 35-50%; SD: 57% (1,2)
  – **Sorafenib**: 16 patients:
    • PR: 6.3%; SD: 87.5% (3)
  – **Axitinib**: 27 patients
    • PR: 18%; SD: 27% (4)

MTC Clinical Trials: An International Effort (10/19/13)

• Current or Soon to Start Studies
  – **USA:** Pasireotide/Everolimus; CEA Antibody; Cabozantinib (2 doses); Vandetinib (children/adolescents; Ponatinib
  – **Europe:** Pasireotide/Everolimus; iTEP: anti-CEA/HSG with imaging; Nintedanib
  – **Asia:** Anlotinib
What Patients Should Be Considered for a Kinase Inhibitor

- Patients with **Progressive Distant Metastases** based on Anatomic Imaging Criteria (CT or MRI---RECIST) in whom you are concerned about mortality from MTC
- Patients without contraindications such as cardiac arrhythmias
- Patients in whom non-durable partial responses are expected to increase life expectancy.

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Matthew Ringel)
What Patients Should Not Be Placed on a Kinase Inhibitor

• Patients with stable metastatic MTC on anatomic imaging, particularly if the calcitonin or CEA doubling time are slow
• Patients with multiple co-morbidities
• Individuals with contraindications for treatment such as cardiac disease, arrhythmias, or uncontrolled hypertension
Summary

- Patients with Progressive, Metastatic MTC have systemic therapeutic options that:
  - Prolong Progression Free Survival and can stabilize progressive disease.
  - Induce Partial response in a minority of patients.
  - Are Associated with Side effects.
  - Require further studies to clarify best dosing strategies and predictors of response for long-term therapy are ongoing.

- Preclinical studies for New Treatments for Treatment Refractory disease are ongoing.