Medullary Thyroid Carcinoma: New Therapies and Trials

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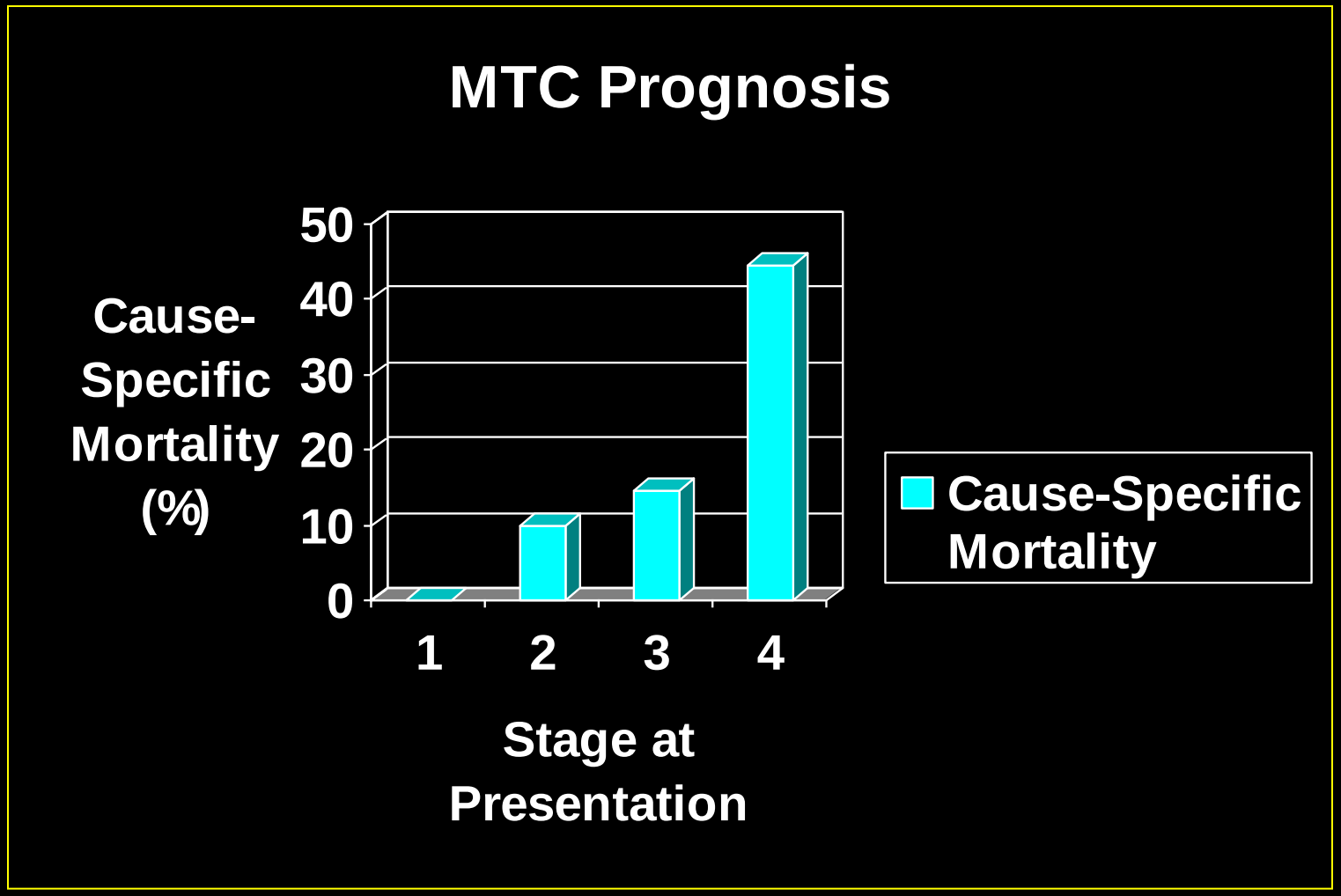
Medullary Thyroid Carcinoma: Demographics

- 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



Kebebew, et al Cancer 2000;88: 11139-1148

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.

Barbet, et al J Clin Endocrinol Metab. 2005 90:6077-6084

Medullary Thyroid Carcinoma: Calcitonin Doubling Time

	5-yr survival	10-yr survival
Calcitonin DT (all time points)		
>2 yrs	100%	100%
0.5-2.0 yrs	94%	64%
<0.5 yrs	23%	15%

Barbet, et al J Clin Endocrinol Metab. 2005 90:6077-6084

Calcitonin and CEA Doubling Time MetaAnalysis

- Meijer, et al (Clin Endocrinol 2010;72:534-42)
  - 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

- Hajje, et al (2013, Eur J Endocrinol. 168:113-118)
  - 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 Overal 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

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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)

1. De Souza ,et al J. Clin Oncol; 2010; 2. Carr LL Clin Cancer Res 2010; 3. Lam et al. J Clin Oncol:2010; 4. Cohen EE, et al J Clin Oncol 2010.

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; Nintedenib
  - **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.

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 diseae
  - Induce Partial response in a minority of patients
  - Are Associated with Side effects
  - Require further studies to clarify best dosing strategies and predictors of respnse for long-term therapy are ongoing
- Preclinical studies for New Treatments for Treatment Refractory disease are ongoing