CLINICAL CASE

55 YEAR OLD WOMAN
PAINLESS RIGHT ANTERIOR CERVICAL ADENOPATHY

PHYSICAL EXAM

3 RIGHT ANTERIOR CERVICAL LYMPH NODES AND 1 PALPABLE NODULE IN THE UPPERPOLE OF THE RIGHT THYROID LOBE
NECK ULTRASOUND

THYROID NODULE

BILATERAL NECK LYMPH NODES

VERY SUSPICIOUS !!!!!!!
FINE NEEDLE ASPIRATION

MTC CELLS FEATURES:
Binuclear cells, abundant cytoplasm, eccentric nucleus

Definitive diagnosis
THYROID GLAND: 2 CELLULAR TYPES

1% THYROID CELLS DIFFERENT EMBRYOGENESIS

C CELL or PARAFOLLICULAR CELLS

NEURAL CREST

4° e 5° TASCHE FARINGEE
Medullary thyroid carcinoma ≠ Papillary and follicular thyroid carcinoma

- CHROMOGRAFIN +
- CALCITONIN +
- THYROGLOBULIN -

Survival %

PTC
FTC
MTC
ATC

Years
0 2 5 10 15 20
0 50 100
MEDULLARY THYROID CANCER (N=554)
PREVALENCE AMONG THYROID CANCERS (N=7382)
(Department of Endocrinology, Pisa, 1969-2007)

% of all thyroid tumors

- Papillary: 80%
- Follicular: 20%
- Medullary: 7.5%
- Anaplastic: 0%
- Lymphomas: 0%
- Unknown: 0%

7.5%
PREVALENCE OF DIFFERENT FORMS OF MEDULLARY THYROID CARCINOMA

MTC

SPORADIC 75%

FAMILIAL 25%

MEN 2A
MEN 2B
FMTC
Neoplasie endocrine multiple di tipo 2

- Thyroid
- Parathyroid
- Adrenal Glands
- feocromocitoma
- carcinoma midollare
- adenomatosi multipla

- PHEO
- MTC
- ICC
50% of descendants can inherit the tumoral disease
MEDICAL HISTORY

NON-SMOKER

FAMILY HISTORY NEGATIVE FOR:

THYROID CANCER
PHEOCROMOCYTOMA
HYPERPARATHYROIDISM
SPECIFIC LABORATORY TESTS IN MTC PATIENTS

**BLOOD**
- Calcitonin 450 pg/ml (VN < 10 pg/ml)
- CEA 10 ng/ml (VN non-smoker <2.5 ng/ml)
- Calcium, PTH and VitD: WNL
- Fractionated plasma metanephrine: WNL

**URINE**
- 24 hours urine for catecholamines and total methanephrines WNL
METASTATIC EVALUATION: STAGING

NECK: BILATERAL CERVICAL ADENOPATHY

CHEST AND ABDOMEN: NEGATIVE
SURGICAL TREATMENT: pathology report

TOTAL THYROIDECTOMY + BILATERAL CERVICAL LYMPHADENECTOMY

MTC 2.2 x1.9 cm in the right lobe
No extracapsular invasion
4/13 right and 1/9 left cervical lymph nodes with MTC metastases
T2N1M0
CLINICAL COURSE

FIRST CONTROL:
6 WEEKS AFTER TT+LNC: serum Ct and CEA WNL

FURTHER CONTROLS EVERY 3 MONTHS

1° CONTROL (4.5 MONTHS AFTER TT+LNC):
serum Ct and CEA WNL

2° CONTROL (7.5 MONTHS AFTER TT+LNC):
serum Ct: 125 pg/ml and CEA: 6 ng/ml
RESTAGING: TOTAL BODY CT SCAN

NEGATIVE FOR METASTATIC LESIONS
QUESTIONS

1. CONTINUED WATCHFUL WAITING WITHOUT FURTHER EVALUATION OR THERAPY

2. SURGICAL EVALUATION FOR POSSIBLE LOCOREGIONAL RECURRENTNESS: IF POSITIVE, CONSIDER EXTERNAL BEAM IRRADIATION

3. CONSIDER A TRIAL OF “SYSTEMIC THERAPY” USING SERUM CALCITONIN AND CEA LEVEL TO ASSESS RESPONSE
BEFORE ANSWERING

TAKE INTO ACCOUNT...
LYMPH NODES METASTASES AT DIAGNOSIS IS THE MOST IMPORTANT NEGATIVE PROGNOSTIC FACTOR (MAYO CLINIC SERIES)

Prognostic Impact of Serum CT and CEA Doubling-Times in Patients with Medullary Thyroid Carcinoma
Barbet J, Campion L, Kraeber-Bodéré F, Chatal J and the GTE Study Group

Prognostic Factors in the Follow Up

J Clin Endoc Metab, 2005
SURVIVAL CURVE IN MTC PATIENTS WITH AND WITHOUT RET SOMATIC MUTATIONS
n= 100, mean follow-up 10 years

Log rank
p=0.006

Elisei R et al, J Clin Endocrinol Metab. 2008, 93:6827
ATA-ETA GUIDELINES: we are here

Status post-thyroidectomy, including those with incidental MTC

Basal calcitonin + CEA

Calcitonin detectable:<150 pg/mL
- Neck US
- Additional imaging listed to the right may be considered

Calcitonin ≥150 pg/mL
- Get imaging listed to the right

Calcitonin undetectable

Systemic metastasis localization and baseline imaging:
- Neck US
- Chest CT
- Neck CT
- 3-phase contrast-enhanced multidetector liver CT, or contrast-enhanced MRI
- Bone MRI of the spine and pelvis
- Bone scan

M₀ or minimal M₁

Extensive M₁

Palliative neck operation if needed for trachea compromise or local pain.¹,²

Consider clinical trials, and palliative therapies including surgery, EBRT, percutaneous interventions, and hepatic embolization.

¹,² Compartmental dissection of image or biopsy positive compartments.¹,²,³
- Consider empiric level VI compartmental dissection if not previously done¹ (controversial).
- In the presence of M₁ disease or advanced local features, consider less aggressive neck surgery to preserve speech and swallowing, and maintain locoregional disease control to prevent central neck morbidity.
- Consider EBRT for high risk patients (controversial).
CLINICAL COURSE our MTC CASE

No evidence of locoregional recurrence and or distant metastases

Thus...

Waiting and see program
14 months after TT+LNC...

*Serum Ct:* 800 pg/ml  
(it was 125 pg/ml 6.5 months before)

*TB CT scan:*
1) mediastinal adenopathy in the upper retrosternal area, with no evidence of superior vena caval obstruction but persistent retrosternal pain

2) multiple pulmonary nodules (biggest: 1.5 cm)

3) no liver metastases
QUESTION

WHAT DO YOU RECOMMEND FOR THIS SYMPTOMATIC PATIENT WITH AN ECOG PERFORMANCE STATUS OF 1?

1. EBRT
2. CHEMOTHERAPY
3. TKI TARGETED THERAPY
BEFORE ANSWERING

TAKE INTO ACCOUNT...
Update on External Beam Radiation Therapy in Thyroid Cancer

James D. Brierley

Department of Radiation Oncology, University of Toronto, Princess Margaret Hospital, Toronto, Ontario, Canada M5G 2M9

(J Clin Endocrinol Metab 96: 2289–2295, 2011)

Summary

Further single institutional data supports the use of EBRT in improving local control in highly selected patients with MTC. However, given the natural history of the disease, survival is not improved; therefore, EBRT should be reserved only in patients at high risk of devastating cervical recurrence requiring extensive ablative surgery.
Pain control in patients with cancer represents a significant aspect of radiation therapy practice. Radiation therapy is one of the most effective, and often the only, therapeutic option to relieve pain caused by nerve compression or infiltration by malignant tumor, pain from liver and bony metastases and it provides also successful palliation of dysphagia caused by oesophageal carcinoma and of pain due to pancreatic cancer.
## CONVENTIONAL CHEMOTHERAPY IN MTC

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>REFERENCES</th>
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<td>etoposide</td>
<td>Fiore 1984</td>
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<td>methotrexate</td>
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<td>dacarbaz+5FU</td>
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<td>5FU+decarbaz/s treptoz.</td>
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</table>
TYROSINE-KINASE INHIBITORS: RATIONALE

MUTATED RET

ACTION
- Stop Phosphorylation
- Stop signal transmission
- Inhibition cellular growth

Cell membrane

ras pathway

p110

PI3K

p110

p05

DAG

PKC's

Pi4,5P

Ca

PLCγ

Dynamin

Gαi2

Sos

Raf-1

p21ras GDP

p21ras GTP

p21ras GDP

MEK

MAPK

Transcription

Nucleus

c-Fos
c-Myc
c-Jun
RATIONALE TKI THERAPY: COSTITUTIVE ACTIVATION OF RET!

✓ 98% of familial cases show a germinal RET mutation

✓ 40-45% of sporadic cases show a somatic RET mutation

✓ RET mutation is correlated with an advanced stage at diagnosis and a lower survival
TYROSINE KINASE INHIBITORS (TKI)

The majority of TKI inhibit several receptors with different degree of inhibition

<table>
<thead>
<tr>
<th>DRUG</th>
<th>IC$_{50}$(nm)</th>
<th>VEGFR1</th>
<th>VEGFR2</th>
<th>VEGFR3</th>
<th>RET</th>
<th>MET</th>
<th>KIT</th>
<th>BRAF</th>
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<td>130</td>
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<td>EGFR (500)</td>
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<td>MOTESANIB</td>
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<td>-</td>
<td>FGFR1 (25)</td>
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<td>CABOZANTINIB (XL-184)</td>
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<td>-</td>
<td>4.5</td>
<td>1.8</td>
<td>-</td>
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</tbody>
</table>
Microvessels, expression of neo-angiogenesis, are more represented in MTC than in other thyroid tumors (Fontanini G et al, Mod Pathol, 1996)

VEGFR-1, and VEGFR-2 are overexpressed in MTC (Capp C, et al, Thyroid, 2010)

MET is overexpressed in a subgroup of MTC (Papotti M et al, Endoc Pathol 2000, Trovato M et al, Thyroid 1998)

EGFR is overexpressed in MTC (Wang W et al, Acta Oncol, 1997) and in particular in its metastasis (Rodriguez-Antona C et al, Endoc Rel Cancer 2010)
ZETA Study Design

Patients with unresectable locally advanced or metastatic MTC (N=331)

2:1 randomization

Vandetanib 300 mg/day
N=231
Follow for progression

Placebo
N=100
Follow for progression

Discontinue blinded treatment at progression: cross over placebo vs drug

Follow for survival
Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial (ZETA)

Samuel A Wells, Bruce G Robinson, Robert F Gagel, Henning Dralle, James A Fagin, Massimo Santoro, Eric Baudin, Rossella Elisei, Barbara Jarzab, James Vasselli, Jessica Read, Peter Langmuir, Anderson J Ryan and Martin Schlumberger, for the ZETA investigators*

Significant increase of progression free survival

RET negative MTC are responsive to Vandetanib BUT Ret positive cases are more responsive

*J Clin Oncol, 2012
Vanetanib already commercially available in USA: approved by EMA in February 2012
Phase 3 Study Design (EXAM)

Treatment until progression or unacceptable toxicity

Locally advanced or metastatic MTC with documented RECIST progression

2:1 Randomization

Cabozantinib 140 mg

Placebo

PROGRESSION

No Cross-Over
No Unblinding

Survival follow-up

330 subjects randomized across 90 sites in 23 countries:

55.8% in Europe
30.9% in North America
13.3% in the rest of the world
Progression Free Survival by IRC (Primary Endpoint)

<table>
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<tr>
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<td>Median PFS (months)</td>
<td>11.2</td>
<td>4.0</td>
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<tr>
<td>1 year PFS</td>
<td>47.3%</td>
<td>7.2%</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.28 (0.19, 0.40)</td>
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p < 0.0001
What we did???

We first explored the possibility of a surgical excision of mediastinal lymph nodes.

Yes and complete:
- CT scan and Ct measurement 3-4 months later
- Vandetanib
- If new disease and/or lung progression

Yes, big debulking but not complete, + adjuvant EBRT

Not possible
She is still «on» vandetanib: stable disease, stable Ct and CEA.
THANK YOU FOR YOUR ATTENTION!!!