Systemic Therapy for Thyroid Cancer: Who, When, and Why?

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Objectives

- Briefly review
  - Epidemiology of thyroid cancer
  - TSH suppressive therapy
  - RAI use
- Discuss supportive treatment options which are not “chemotherapy”
- Describe the rationale behind use of multi-kinase inhibitors
- Present the data supporting treatment with FDA approved agents

Disclosures

- I have no relevant financial or nonfinancial relationship(s) with the products or services described, reviewed, evaluated or compared in this presentation.
- This presentation includes discussion of investigational agents not approved by the US Food and Drug Administration (FDA) for use in the United States or off label use of FDA approved drugs.

Thyroid cancer epidemiology - 2017

- Estimated new cases – 56,800
- Estimated deaths – 2,010
- Lifetime risk of developing cancer: Approximately 1.2% of men and women will be diagnosed with thyroid cancer at some point during their lifetime
- Prevalence:
  In 2014, there were an estimated 726,646 people living with thyroid cancer in the United States

This audience knows what is common

- All races, 2010-2014
- Differentiated thyroid cancer (DTC)
  - Papillary thyroid cancer (PTC) 89.4%
  - Follicular thyroid cancer (FTC) 4.6%
  - Hürthle cell thyroid cancer (HCC) 2.0%
  - Poorly differentiated thyroid cancer
- Medullary thyroid cancer (MTC) 1.7%
- Anaplastic thyroid cancer (ATC) 0.8%
- NOS 1.3%
- DTC makes up ~ 97% of all thyroid cancers

Standard therapies for DTC

Radioiodine
- Used since the 1940s
- Takes advantage of the NIS

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TSH Suppressive therapy

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TSH Suppressive therapy
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Surgery (select pts)

Surgery (select pts)

Levotyroxine Sodium Tablets, USP
300 mcg (0.3 mg)

Levotyroxine Sodium Tablets, USP
300 mcg (0.3 mg)

Radioiodine
• I-131 causes cell death by emission of short path-length (1 to 2 mm) beta particles
• The uptake of I-131 by thyroid tissue can be detected by scanning for the gamma radiation that is also emitted by the isotope

How radioiodine works

How radioiodine works

RAI - Uses
• Remnant ablation
• Reduce risk of recurrence
• Treat microscopic disease
• Treat distant disease
• Reduce risk of death
• Does not definitively treat bulky disease
• Does not definitively treat skeletal metastases

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When is RAI no longer an option?

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RAI refractory disease
• Disease does not take up radioiodine at known sites of disease
• Continued growth within 12-16 months after RAI
• Total cumulative dose ≥ 600 mCi

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**RAI refractory disease**
- Disease does not take up radioiodine at known sites of disease
- Continued growth within 12-16 months after RAI
- Total cumulative dose ≥ 600 mCi

**RAIR disease… What's next?**

- Watchful waiting
- Localized therapies
- Systemic or targeted therapies

**Watchful waiting**

[C37] Which patients with metastatic thyroid cancer can be followed without additional therapy?

- **RECOMMENDATION 92**
  (A) Patients with ¹³¹I-refractory metastatic DTC that is asymptomatic, stable, or minimally progressive who are not likely to develop rapidly progressive, clinically significant complications and do not have indications for directed therapy can be monitored on TSH-suppressive thyroid hormone therapy with serial radiographic imaging every 3–12 months.

  (Weak recommendation, Low-quality evidence)

[TC1] What is the role of systemic therapy (kispeptide, other selective therapies, conventional chemotherapy, biophosphonate, denosumab) in treating metastatic DTC?

  Systemic therapeutics of several types in selected clinical scenarios appear to provide clinical benefit in treating metastatic DTC (C103). Benefits have been demonstrated in the form of improved progression-free survival (objective criteria, evidence level B1), and survival (B1). Benefits have also been demonstrated in the form of reduced durable tumor regression (B105–B107).

  However, randomized clinical trial data are not yet available to address many additional critical questions, including: effectiveness of systemic therapies of various types on survival and quality of life; on ability to identify tumors of optimal patient selection/inclusion/exclusion criteria for therapy and duration of therapy.

  To date, no clinical trial has demonstrated an overall survival advantage or improved quality of life from use of any therapy in RAI-refractory, DTC (B103, B104).
Distant disease or locally advanced disease


Stage at diagnosis and survival rates


1-4% at the time of diagnosis
7-23% develop distant metastases during their disease course
Sites of metastasis: Lung > Bone

When are distant mets discovered in DTC?

< 45 yo
≥ 45 yo

Localized treatments

• Surgery
• Radiation
• ETOH ablation
• Cryoablation
• Embolization

Zolendronic acid - DTC


Table 2. Skeletal-related Events in Patients with Bone Metastasis from Differentiated Thyroid Carcinoma

<table>
<thead>
<tr>
<th>Event</th>
<th>Group 1: No bisphosphonate therapy (n = 28)</th>
<th>Group 2: Zoledronic acid therapy (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone fracture</td>
<td>2 (7%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>4 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>13 (46%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Total SREs</td>
<td>14 (50%)</td>
<td>3 (14%)</td>
</tr>
</tbody>
</table>

Zolendronic acid - DTC

Anti-resorptive therapy - MTC

- Fewer patients in the AR+ group developed ≥1 SREs when compared with patients in the AR- group (25% vs 42%, P=0.026)
- The beneficial effect of ARs on SREs development remained significant after adjusting for age, gender, and distant non-bone metastases (P=0.047)
- In addition, fewer patients in the AR+ group developed a subsequent BM compared with the AR-group (59% vs 84%, P=0.005)

### Criteria for starting systemic therapy

**All other options have been exhausted and good PS**

- Clinically significant rapidly progressive disease
- Disease threatening critical structures
- Symptomatic disease which cannot be managed with local therapies

**You have assessed:**

- Cross sectional imaging (CT/MRI/PET)
- Rate of progression
- Risks versus benefits of systemic therapy

### Considering systemic therapy?

**Is it rapidly progressing?**

**CRITERIA**

<table>
<thead>
<tr>
<th>Measurable lesions</th>
<th>Non-Measurable lesions</th>
<th>Target lesions</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions able to be accurately measured at least one dimension ≥5 mm and suitable for repeated measurements</td>
<td>All other lesions</td>
<td>Minimum of 5 lesions, 2 per organ</td>
<td>Sum of the longest diameter of target lesions</td>
</tr>
</tbody>
</table>

**Is it rapidly progressing?**

**Table 16: Factors to Review When Considering Knee Inhibitor Therapy**

<table>
<thead>
<tr>
<th>Factors influencing kinase inhibitor therapy</th>
<th>Factors discouraging kinase inhibitor therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute or repeat past disease (e.g., diabetes, HIV, inflammatory bowel disease, recent bowel resection)</td>
<td>• Bone disease (e.g., distant metastases, radiation therapy)</td>
</tr>
<tr>
<td>• Prior radiation therapy (e.g., CVA, MD)</td>
<td>• Recent cardiovascular events (e.g., MI, AHD)</td>
</tr>
<tr>
<td>• Prior treatment for bone pain (e.g., bisphosphonates)</td>
<td>• Active or repeat past disease (e.g., diabetes, HIV, inflammatory bowel disease, recent bowel resection)</td>
</tr>
<tr>
<td>• Flare or radiation therapy (e.g., CVA, MD)</td>
<td>• Bone disease (e.g., distant metastases, radiation therapy)</td>
</tr>
<tr>
<td>• Recent cardiovascular events (e.g., MI, AHD)</td>
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<td>• Prior treatment for bone pain (e.g., bisphosphonates)</td>
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<td>• Flare or radiation therapy (e.g., CVA, MD)</td>
<td>• Bone disease (e.g., distant metastases, radiation therapy)</td>
</tr>
</tbody>
</table>

**Quality Improvement & Patient Education**

1. Reduce the risk of bone metastases with anti-resorptive therapy
2. Monitor bone health with regular assessments
3. Consider the benefits and risks of systemic therapy

**References**

### Development of thyroid cancer

![Diagram of thyroid cancer development](Image)

- **MAPK pathway**: MAPK pathway activation in PTC (medullary thyroid cancer).
- **PTK-akt**: PTK-akt activation in thyroid cancer.
- **Fibrosis (FB)**: Fibrosis development in thyroid cancer.
- **RAS**/MEK/ERK pathway: Inhibitors targeting this pathway include tipifarnib, vemurafenib, and sorafenib.
- **BRAF** inhibitors: Dabrafenib and trametinib are used in thyroid cancer.
- **MEK inhibitors**: Selumetinib and cobimetinib are also used.
- **mTOR inhibitors**: Everolimus and temsirolimus are used.

**Anti-angiogenic kinase inhibitors**

- **Formation of new blood vessels**: Inhibitors targeting angiogenesis.
- **Vascular Endothelial Growth Factor (VEGF)**: Inhibitors targeting VEGF signaling.

**Multi-kinase inhibitors**

- The specific kinase targets vary.
- The drug IC$_{50}$ varies between drugs and between different kinases.

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC$_{50}$ (nM)</th>
<th>BET</th>
<th>VEGFR2</th>
<th>VEGFR3</th>
<th>EGFR</th>
<th>FGFR</th>
<th>BRAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>1.2</td>
<td>11.2</td>
<td>0.98</td>
<td>4</td>
<td>1,3</td>
<td>14.4</td>
<td>48</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>6.4</td>
<td>4.7</td>
<td>2</td>
<td>1.3</td>
<td>89</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Tipifarnib</td>
<td>0.7</td>
<td>3</td>
<td>10</td>
<td>37</td>
<td>47</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>2.9</td>
<td>50</td>
<td>19</td>
<td>20</td>
<td>45</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

### RECIST v 1.1

**Target lesion response**

- **Complete response (CR)**: Disappearance of all target lesions.
- **Partial response (PR)**: ≥30% decrease in the sum of the longest diameters of target lesions compared with baseline.
- **Progressive disease (PD)**: ≥20% increase in the sum of the longest diameters of target lesions compared with the smallest sum of longest diameters recorded (within a 28-day period).
- **Stable disease (SD)**: Neither PR or PD.

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*“Angiogenesis”, nd. Retrieved from [http://www2.nau.edu/~bio372-class/cancer/angiogen.htm](http://www2.nau.edu/~bio372-class/cancer/angiogen.htm)*
2 approved drugs for RAIR DTC

- Sorafenib
- Lenvatinib

Sorafenib

- Approved by the FDA in 2013 for the treatment of locally recurrent or metastatic, progressive DTC that no longer responds to radioactive iodine treatment

The recommended daily dose is 800 mg:
400 mg taken twice daily
without food
(at least 1 hour before or 2 hours after a meal)

DECISION trial (sorafenib versus placebo)

- DECISION (stuDy of sorafEnib in loCally advanced or metastatic patientS with radioactive iodine refractory thyrOid caNcer)
- Multicenter, randomized, double-blind, placebo-controlled phase 3 trial
- RAIR DTC with progression in 14 months
- Placebo pts could cross over if progress


Enrolled and randomized 419 pts (2 randomized twice and excluded)

Sorafenib

- NO difference in OS (overall survival)
- Complicated by cross-over

- Objective response rate – all PRs
  - 12.2% vs 0.5% (p<0.0001)

- Disease control rate – PR + SD x ≥ 6 mo
  - 54.1% vs 33.8% (p<0.0001)
Sorafenib

- Serious AEs
  - 37.2% sorafenib
  - 26.3% placebo

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Lenvatinib

- Approved by the FDA in 2015 for the treatment of locally recurrent or metastatic, progressive DTC that no longer responds to radioactive iodine treatment

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SELECT trial (lenvatinib versus placebo)

- Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid
- Multicenter, international, randomized, double-blind, placebo-controlled phase 3 trial
- RAIR DTC with progression in 12 months
  - Allowed 1 prior TKI
- Placebo pts could cross over if progressed

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Lenvatinib

- 392 pts were randomized and all included in intention to treat analysis

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Lenvatinib

- NO difference in OS (overall survival)
- Complicated by cross-over

---
Lenvatinib

<table>
<thead>
<tr>
<th>Effect</th>
<th>Lenvatinib (N = 316)</th>
<th>Placebo (N = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67.8</td>
<td>36.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>58.4</td>
<td>34.3</td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>59.0</td>
<td>31.3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>56.2</td>
<td>31.3</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>41.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>38.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>31.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Pulmonary embolism or thrombosis</td>
<td>31.0</td>
<td>19.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Headache</td>
<td>27.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>24.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

There were 118 deaths (about 75% due to progression in both arms)

In the lenvatinib arm, there were 20 pts (7.7%) who died as a result of drug AE – 6 deaths (2.3%) were thought to be drug related.

In placebo arm there were 6 pts (4.6%) who died as a result of drug AE. None were considered treatment related.


2 approved drugs for MTC

- Vandetanib
- Cabozantinib

Vandetanib

- Approved by the FDA in 2011 for the treatment of locally recurrent or metastatic, progressive DTC that no longer responds to radioactive iodine treatment

Thursday, 7 April 2011

AstraZeneca today announced that the US Food and Drug Administration (FDA) approved the orphan drug vandetanib for the treatment of medullary thyroid cancer that cannot be removed by surgery or that has spread to other parts of the body.
Vandetanib

• Approved by the FDA in 2013 for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable, locally advanced, or metastatic disease.
• Only prescribers and pharmacies certified through the Vandetanib Risk Evaluation Mitigation Strategy Program, a restricted distribution program, are able to prescribe and dispense vandetanib.

Vandetanib (ZD6474)
• Zactima Efficacy in Thyroid Cancer Assessment
• Multicenter, international, randomized, double-blind, placebo-controlled phase 3 trial
• Measurable, unresectable locally advanced or metastatic, hereditary or sporadic MTC
• Placebo pts could cross over if progressed

ZETA study

• Median PFS
  • Vandetanib
    Weibull model predicted **30.5 months**
    HR 0.46; p<0.001
  • Placebo = **19.3 months**

### Table 4: Common Adverse Events (safety population)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Vandetanib 300 mg No. = 221</th>
<th>Placebo No. = 200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade occurring with an incidence ≥ 10% overall</td>
<td>130 59 26 29</td>
<td>130 50 18 18</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>104 45 11 11</td>
<td>105 49 18 18</td>
</tr>
<tr>
<td>Nausea</td>
<td>77 35 18 18</td>
<td>78 35 18 18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73 32 5 5</td>
<td>73 32 5 5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55 24 23 23</td>
<td>55 24 23 23</td>
</tr>
<tr>
<td>Headache</td>
<td>90 26 9 9</td>
<td>90 26 9 9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>40 14 12 12</td>
<td>40 14 12 12</td>
</tr>
<tr>
<td>Acne</td>
<td>46 20 5 5</td>
<td>46 20 5 5</td>
</tr>
<tr>
<td>Anemia</td>
<td>34 14 11 11</td>
<td>34 14 11 11</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34 14 7 7</td>
<td>34 14 7 7</td>
</tr>
<tr>
<td>Back pain</td>
<td>21 9 20 20</td>
<td>21 9 20 20</td>
</tr>
<tr>
<td>Dry skin</td>
<td>23 10 5 5</td>
<td>23 10 5 5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>30 13 10 10</td>
<td>30 13 10 10</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>33 14 5 5</td>
<td>33 14 5 5</td>
</tr>
<tr>
<td>Dermatitis acriform</td>
<td>35 15 2 2</td>
<td>35 15 2 2</td>
</tr>
<tr>
<td>Cough</td>
<td>26 13 10 10</td>
<td>26 13 10 10</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>26 11 9 9</td>
<td>26 11 9 9</td>
</tr>
<tr>
<td>ECG QT prolongation</td>
<td>33 14 1 1</td>
<td>33 14 1 1</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>34 13 9 9</td>
<td>34 13 9 9</td>
</tr>
</tbody>
</table>

Cabozantinib

• Approved by the FDA in 2012 for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).
EXAM trial

- Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer
- Multicenter, international, randomized, double-blind, placebo-controlled phase 3 trial
- Unresectable, locally advanced, or metastatic MTC
- Patients were required to have radiographic disease progression per modified Response Evaluation Criteria in Solid Tumors (mRECIST) within the prior 14 months.
- Placebo pts could NOT cross over if progressed

Cabozantinib

- Compared to Vandetanib 30.5 months and Placebo 19.3 months

<table>
<thead>
<tr>
<th>AE</th>
<th>Cabozantinib (n = 214)</th>
<th>Placebo (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>135 63.1 15.9</td>
<td>36 33.0 2.1 1.8</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>107 50.0 12.6</td>
<td>2 1.8 0</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>94 47.7 10 4.7</td>
<td>11 10.1 0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>96 45.6 10 4.7</td>
<td>17 15.6 1 0.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>52 43.0 3 1.4</td>
<td>23 21.1 0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>67 40.7 20 9.3</td>
<td>31 28.4 3 2.9</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>73 34.1 1 0.5</td>
<td>6 5.5 0</td>
</tr>
<tr>
<td>Hair color change</td>
<td>72 33.6 1 0.5</td>
<td>1 0.9 0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70 32.7 18 8.4</td>
<td>5 4.6 1 0.9</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>62 29.0 4 1.9</td>
<td>3 2.8 0</td>
</tr>
<tr>
<td>Constipation</td>
<td>57 26.6 6</td>
<td>5.5 0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>54 25.2 7 3.3</td>
<td>17 15.6 1 0.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52 24.3 8 3.3</td>
<td>2 1.8 1 0.9</td>
</tr>
</tbody>
</table>

Systemic Therapy for Thyroid Cancer

- Summary
  - Reviewed the epidemiology of thyroid cancer
  - Discussed use of RAI and TSH suppressive therapy
  - Clarified the role of localized therapies
  - Explained the use of systemic therapies
    - 4 FDA approved drugs
    - Data supporting their use
    - Side-effect profile
  - If you cannot use one of the approved treatments, it is recommended to refer the patient to a clinical trial
- In a separate talk I will present:
  - Patient cases
  - Alternative therapies
  - Off label and novel therapies

Thank you