MANAGEMENT OF REFRACTORY THYROID CANCER

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CONFLICTS OF INTEREST

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The planners and speakers have no relevant relationships to disclose.

I will be discussing off-label use of medications.
THROID CANCER- OVERVIEW

Estimated New Cases in 2015: 62,450
% of All New Cancer Cases: 3.8%

Estimated Deaths in 2015: 1,950
% of All Cancer Deaths: 0.3%

Percent Surviving 5 Years: 97.9%
2005-2011

SEER Stat Fact Sheets: Thyroid Cancer
INCIDENCE IN CHILDREN

Figure. Trends in age-standardized incidence rates of differentiated thyroid carcinoma in children, adolescents, and young adults (SEER 9, 1984-2010).

David A. Siegel et al. Pediatrics 2014;134:e945-e955
INCIDENCE VERSUS MORTALITY

Ahn et al. NEJM 2014
CLINICAL SITUATIONS

• Development of thyroid nodules/cancer in childhood cancer survivors
• Consult for patients with refractory thyroid cancer
HODGKIN LYMPHOMA AND DTC

28 cases in 1981 patients after a median follow-up of 14 years

9.2 fold increase in thyroid cancer risk

Age< 20 years and female sex were the significant risk factors
MIBG THERAPY AND DTC

Survivors
N=16

No Thyroid abnormalities
N=3

Thyroid Abnormalities
N=13

TE
N=4

TE & Thyroid Nodule
N=4

Thyroid Nodule
N=5

Thyroid Carcinoma
N=2

MEDIAN FOLLOW-UP 15.5 YEARS

# PTEN AND THYROID NODULES

Table 1  Clinical findings and youngest age of diagnosis in 34 children with molecularly diagnosed PTEN hamartoma tumour syndrome (PHTS)

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>Proportion* (%)</th>
<th>Youngest documented age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrocephaly</td>
<td>27/27 (100)</td>
<td>13 months</td>
</tr>
<tr>
<td>ASD</td>
<td>7/7 (100)</td>
<td>2 years 2 months</td>
</tr>
<tr>
<td>DDMD</td>
<td>23/25 (92)</td>
<td>UNK</td>
</tr>
<tr>
<td>Pigmented penile macules (males)</td>
<td>19/19 (100)</td>
<td>2 years 5 months</td>
</tr>
<tr>
<td>Gastrointestinal polyps</td>
<td>9/12 (75)</td>
<td>2 years 10 months</td>
</tr>
<tr>
<td><strong>Vascular anomaly†</strong></td>
<td>16/34 (47)</td>
<td>Birth</td>
</tr>
<tr>
<td>Cutaneous lipoma(s)</td>
<td>12/31 (39)</td>
<td>Birth</td>
</tr>
<tr>
<td><strong>Thyroid nodule(s)</strong></td>
<td>10/18 (56)</td>
<td>5 years</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>4/34 (12)</td>
<td>7 years</td>
</tr>
<tr>
<td><strong>All tumours‡</strong></td>
<td>7/34 (21)</td>
<td>7 years</td>
</tr>
</tbody>
</table>

### DICER 1 AND DTC

#### Table 1. Summary of Cases of Thyroid Carcinoma Arising in Patients With PPB and/or a Germline DICER1 Mutation

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Germline DICER1 Status</th>
<th>Somatic DICER1 Status in Thyroid Carcinoma</th>
<th>Other DICER1-Associated Lesions</th>
<th>Family History of Thyroid Disease</th>
<th>HDC</th>
<th>Bone Marrow Transplantation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Follicular variant papillary thyroid carcinoma</td>
<td>Positive: c.3505dupT</td>
<td>Positive: c.5439G→T</td>
<td>PPB, PPB metastasis</td>
<td>Mother: hypothyroidism</td>
<td>Yes</td>
<td>Autologous peripheral blood stem cell transplantation</td>
<td>Case 1 (this report); Shin et al (13)</td>
</tr>
<tr>
<td>2</td>
<td>Follicular variant papillary thyroid carcinoma</td>
<td>Positive: c.3579_3580delCA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Positive: c.5438A→G</td>
<td>PPB, CBME</td>
<td>Unknown</td>
<td>Yes</td>
<td>No</td>
<td>Case 2 (this report); Slade et al (4)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Bilateral papillary thyroid carcinoma</td>
<td>Positive: c.2379T→G</td>
<td>Positive: c.5113G→A</td>
<td>PPB, CN</td>
<td>Unconfirmed</td>
<td>Yes</td>
<td>No</td>
<td>Case 3 (this report)</td>
</tr>
<tr>
<td>4</td>
<td>Follicular thyroid carcinoma</td>
<td>Unknown</td>
<td>Unknown</td>
<td>PPB</td>
<td>Mother: thyroid adenoma</td>
<td>Yes</td>
<td>Double Auto-BMT</td>
<td>Que et al (17)</td>
</tr>
<tr>
<td>5</td>
<td>Follicular thyroid carcinoma</td>
<td>Unknown</td>
<td>Unknown</td>
<td>PPB, cERMS, bladder RMS, MNG</td>
<td>Unknown</td>
<td>Yes</td>
<td>Autologous peripheral blood stem cell transplantation</td>
<td>Rome et al (21)</td>
</tr>
</tbody>
</table>

MOLECULAR PATHOGENESIS OF THYROID CANCER

## BRAF V600E MUTATION PEDIATRIC STUDIES

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Method</th>
<th>% of BRAF</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henke 2014</td>
<td>27</td>
<td>RFLP</td>
<td>63%</td>
<td>No correlation with outcome</td>
</tr>
<tr>
<td>Givens 2014</td>
<td>19</td>
<td>Pyrosequencing</td>
<td>37%</td>
<td>No correlation with aggressive behavior</td>
</tr>
<tr>
<td>Ballester 2015</td>
<td>27</td>
<td>NGS mutation panel</td>
<td>37%</td>
<td>RET fusions- 22% CTNNB1- 3%</td>
</tr>
<tr>
<td>Picarsic 2015</td>
<td>18</td>
<td>7-gene mutation panel, NGS ThyroSeq V2</td>
<td>17%</td>
<td>ETV6/NTRK3 fusion-3 TPR/NTRK1 fusion -1 RET fusions-3 PAXC8/PPARg -1</td>
</tr>
</tbody>
</table>

TARGETED THERAPIES FOR THYROID CANCER
FDA APPROVED MEDICATIONS

• Chemotherapy:
  – Doxorubicin (not used)

• Oral Tyrosine Kinase Inhibitors:
  – DTC
    • Sorafenib (2013)
    • Lenvatinib (2015)
  – MTC
    • Vandetanib (2011)
    • Cabozantinib (2012)
COMPLETED PHASE II TRIALS - DTC

- Axitinib
- Geftinib
- Motesanib
- Pazopanib
- Selumetinib
- Sunitinib
- Vandetanib
- Vemurafenib (currently in phase III)
INDICATIONS FOR MEDICAL THERAPY

• Radiorefractory differentiated thyroid cancer with evidence of clinically significant disease progression

DECISION TRIAL - SORAFENIB

Brose et al. The Lancet 2014; 384: 319-328

PR- 12%
SD – 42%
Tumor shrinkage – 88%
LENVATINIB MECHANISM OF ACTION

http://dx.doi.org/10.2147/BTT.S39381
SELECT TRIAL - LENVATINIB

PR - 63%
SD – 15%
Tumor shrinkage – 98.6%

SORAFENIB IN A 14 YEAR OLD WITH PTC

Waguespack et al, Thyroid 2009: 19; 407-411
SORAFENIB IN A 8-YEAR OLD WITH PTC

BASELINE

AFTER 52 DAYS

Iyer et al. THYROID Volume 24, Number 1, 2014
SORAFENIB IN A 14 YEAR OLD WITH PTC
PRE-SORAFENIB

POST-SORAFENIB
THYROGLOBULIN TREND

5 MONTHS ON SORAFENIB
CONCLUSION

• The MAP kinase pathway and PI3K-AKT pathway play a key role in the development of thyroid cancer.

• Majority of patients have excellent outcomes with surgery and RAI treatment

• In the few patients refractory to radio-iodine and progressive disease, tyrosine kinase inhibitors may be indicated.

• TKI inhibitors in children should ideally be administered as part of a clinical trial, and in consultation with our adult colleagues.
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