Locally Advanced And/or Metastatic Thyroid Cancer: What New Options Are on the Horizon?

Steven P. Weitzman, MD, FACE, ECNU
The University of Texas MD Anderson Cancer Center
Department of Endocrine Neoplasia and Hormonal Disorders

Objectives

- Review the management of multi-kinase inhibitor side-effects
- Present patient cases
- Review:
  - BRAF inhibitors
  - MEK inhibitors
  - Redifferentiation therapy
  - Immunotherapy
  - Novel “druggable” targets

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

Toxicities

- VEGFRi: Common side effects & management
  - Hypertension: Aggressive monitoring and tx with beta blocker &/or ACEi
  - Proteinuria: ACEi or ARB
  - Fatigue:
    - Rule out / treat anemia, hypothyroidism, cardiomyopathy
    - Encourage the 2pm nap
    - Exercise
  - Hypothyroidism

GI toxicities

- Diarrhea
  - Loperamide, Lomotil first line therapy (alternate)
  - Tincture of opium second line therapy
  - Budesonide third line therapy
- Weight loss/anorexia
  - Megace
  - Marinol (also helps nausea)
- Nausea/vomiting
  - Anti-emetics
  - Dosing on a full stomach
- Mucositis/tongue sensitivity/dysgeusia
  - Non-mint toothpastes
  - Avoid spicy, hot foods or extremes of temperature

Skin toxicities

- Hand-foot skin reaction:
  - Depending on severity: hold drug
  - Prevention: avoid heat, excessive rubbing, use padded soles
  - Moisturizing creams
- Induration and hyperkeratotic areas on pressure points:
  - Prevention: use padded soles, pedicure prior to starting TKI
    - Podiatry consult (shaving)
    - Moisturizing creams
- Rash:
  - Depending on severity: hold drug
  - Topical emollients, topical steroids (avoid long-term use)
  - Folliculitis: topical clindamycin
  - Anti-histamines
  - Minocycline for EGFRi rash of vandetanib
- Photosensitivity:
  - Avoid sun exposure
  - Use and UVB sunblock
- Squamous cell carcinomas with BRAF inhibitors:
  - Regular dermatology visits for treatment
### Lab abnormalities
- Elevations in liver function tests
- QT prolongation
- Electrolyte abnormalities (can affect QT)
- Mild thrombocytopenia
- Anemia (common with vemurafenib)

### Serious AEs
- **Serious hemorrhagic events**
  - Look for CNS mets and treat with radiation
- **GI perforation and fistula formation**
  - High risk patients: h/o diverticulitis, ulcers, radiation, recent colonoscopy, recent GI surgery
- **Slow wound healing / necrosis**
  - Stop TKI at least 1 week before surgery. Reinitiate when wound has healed.
- **Cardiomyopathies (reversible)**
  - Non-invasive evaluation for LV dysfunction

### Tough cases

### Case 1 - DL
- **MRI lumbar spine** showed a lesion of the T11 vertebral body.
- **2 days later** she went to the ER via ambulance because she could not get out of bed. She received:
  - Pain medication
  - A muscle relaxant
  - A steroid taper
- **MRI thoracic spine** showed an expansile lesion involving the majority of the T11 vertebral body contacting the spinal cord and narrowing of the spinal canal. There was also a 6 mm nonenhancing lesion of the T2 vertebral body.
- She was admitted.

### Case 1 - DL
- Imaging during admission at outside hospital:
  - CXR negative.
  - CT CAP with contrast showed a soft tissue nodule in the left paratracheal region.
  - US thyroid showed a calcified 1 cm right thyroid mass and a 2.8 cm hypoechocic, avascular mass inferior to the left thyroid.
  - CT thoracic spine showed an osteolytic, expansile lesion in the T11 vertebra.
- She then underwent a T11 corpectomy (tumor resection and reconstruction). Tumor pathology showed metastatic thyroid cancer.
Case 1

- She comes to you now for recommendations.
- Her back pain improved after surgery but is still present. Prior imaging shows questionable finding in T2. There is a left iliac lesion also.
- CT shows a thyroid tumor invading into the esophagus. There is also a large anterior mediastinal mass which appears suspicious.
- CT also shows non-specific, sub-centimeter pulmonary nodules. Clinical correlation and surveillance are recommended.
- Thyroglobulin 12,838

11/2015, 30 Gy in 10 fractions to T10-T12.
12/2015, total thyroidectomy, central compartment dissection, left recurrent laryngeal nerve to left ansa cervicalis nerve anastomosis, resection of esophageal muscularis with primary closure of 1 cm segment of esophageal lumen, and reimplantation of the left inferior parathyroid gland. During this same procedure, thoracic surgery performed transcervical resection of the upper mediastinal mass.
Pathology showed a right-sided 1.2 cm PTC (conventional type) with no ETE or LVI and resection margin was negative.
The mediastinal mass showed metastatic PTC in 2/5 lymph nodes and soft tissue (largest focus 4 cm with extracapsular extension). The mediastinal mass showed necrosis.
Surgery was complicated by TE fistula requiring multiple CT scans with contrast.
- She was receiving denosumab.
- Thyroglobulin 9,693 (about 7 weeks post-op).
• Checked 24 hour urine 2 months later and it was normal. She followed a low iodine diet (via G-tube). There was no significant uptake on the diagnostic scan. Her stimulated thyroglobulin was 710 with negative thyroglobulin antibodies.
• Do you give RAI?
• She received an empiric dose of 147 mCi of I-131 via G-tube and the post therapy scan was negative.
• Does she have RAIR DTC?

• FDG PET/CT showed a right, deep suprasternal nodule adjacent to the trachea
• Ultrasound-guided FNA of the lymph node in the deep right suprasternal area which was FDG avid showed metastatic carcinoma (morphologically compatible with patients known thyroid primary).

What now?

• She underwent a revision right level VII neck dissection. The pathology showed PTC in 1/1 lymph node.
• Thyroglobulin 3.4
• What next?

3 months later FDG PET/CT unremarkable
CT chest 6 months later shows increase in the sub-centimeter pulmonary nodules. The largest increased from 4 mm to 7 mm in 3 months. The other nodules are <7mm in size. There are a few new sub-centimeter pulmonary nodules suspicious for metastases.
DL

- 10/2015 thyroglobulin 12,838
- Palliative XRT to T10-T12
- Surgery
- 01/2016 thyroglobulin 9693
- 02/2016 thyroglobulin 9015
- 04/2016 thyroglobulin 656
- 04/2016 thyroglobulin 710
- RAI (147 mCi) I-131
- 05/2016 thyroglobulin 278
- 06/2016 thyroglobulin 49.3

- Palliative XRT to the left hip
- 06/2016 thyroglobulin 20.4
- Revision right neck dissection
- 10/2016 thyroglobulin 3.4
- 12/2016 thyroglobulin 2.4
- 03/2017 thyroglobulin 3.8

DL

- Obtain molecular testing on the tumor
- Showed only mutated TP53 and SMAD4
- She has developed a few new skeletal mets
- Does she need systemics?
- Any questions about her?

Case 2 - MK

- 73 y.o. male who started to have back pain in 2011. It was located in his lower back and the pain radiated down his left leg. He saw his primary care provider and was treated with a steroid injection with improvement.
- A couple of years later he had pain in his left shoulder radiating down his arm. He was again treated with a steroid injection with improvement in his symptoms.
- Over the years, he had increasing difficulty with ambulation. He was able to get around using 1 crutch and one cane.
- May 2016, he experienced a severe worsening of his ability to ambulate.
- He went to the ER by ambulance and CT reveals a focal lytic lesion in the medullary cavity of the proximal third of the right femur.

Case 2 - MK

- He had multiple imaging studies at that hospital and was found to have other skeletal lesions as well as multiple liver lesions.
Case 2 - MK

• He underwent closed intramedullary rodding of the right femur due to an osteolytic diaphyseal bone lesion.
• At that hospital they performed CT guided core biopsy of lesions in the left clavicle and the right lobe of the liver.
• The specimen from the left clavicle showed carcinoma with papillary and Hürthle cell features. The specimen from the liver showed carcinoma with Hürthle cell and organoid features. The comment states that the overall morphology combined with the immunopanels favor thyroid origin.
• Thyroglobulin 38,641.
• Presented to Head & Neck Surgery. Staging scans performed before that appt showed multiple pulmonary emboli and he was sent to the Emergency Center and started on enoxaparin for anticoagulation.

Case 2 - MK

• Multiple, bilateral PEs were the only additional finding.

Case 2 - MK

• What next?
• Prophylactic treatment of the right femur (placement of 2 distal interlocking screws through existing right femur nail)
• He received 30 Gy of palliative radiation to the right femur in 10 fractions
• Started denosumab
• Short interval follow-up

Case 2 - MK

• He had a total thyroidectomy, left paratracheal and superior mediastinal dissection, left level 2-5 neck dissection. Concurrently, thoracic surgery performed resection of the left proximal clavicle with the left clavicular head.
• The pathology showed a unifocal, left sided follicular thyroid carcinoma with oncocytic features and poorly differentiated component (widely invasive). Measured 5.5 centimeters with extrathyroidal extension into fibroadipose. There was lymphovascular invasion present. The resection margin was positive. 12/55 lymph nodes contained metastatic thyroid cancer. The largest focus measured 2.2 centimeters. Some of the lymph nodes had extranodal extension. The head of the left clavicle showed carcinoma involving the bone. The bone margin was negative for tumor.

Case 2 - MK

• 2 months he returns and has an MRI of the abdomen/pelvis
• Hepatobiliary: Multiple liver metastases redemonstrated involving right and left liver and caudate process best seen on 20 minute delayed phase imaging. The lesions have increased in size compared to the prior contrast-enhanced CT. The dominant lesion centered on segment 6, measures 11.0 x 7.3 cm versus 9.2 x 5.8 cm on prior CT. Some of the lesion demonstrate areas of high signal intensity on T1-weighted images which may be related to small regions of hemorrhage.
• Bones: Lesions of high signal intensity and enhancement demonstrated in the left posterior 10th rib, and lower thoracic vertebral bodies, L5, sacrum, and right iliac bone, left ischial tuberosity. Dominant osseous metastasis arising from right iliac bone measuring 6.9 x 5.7 cm, is associated with a large soft tissue component extending into the gluteal musculature.
Case 2 - MK

- Negative for BRAF V600E by IHC.
- CMS 50 showed mutations in ATM, NF1, and SMAD4.
- Does he need systemic therapy?
- Any questions about him?

MK

- 56 yo female (lawyer) who was noted to have a very prominent thyroid several years ago but was never told she should have this evaluated
- No family history of thyroid cancer and no known radiation exposure
- Over the summer, she was traveling across the United States for vacation. During this time, she noticed a lesion on the posterior right side of her scalp which was growing in size.
- She completed her vacation and then presented for evaluation by her primary care physician. He referred her to a surgeon to have the mass removed.
- The pathology returned as thyroid cancer.

Case 3 - SR

- Path review showed PTC (follicular variant) with infiltration into bone with a positive surgical margin.
- FNA of a left thyroid nodule was AUS (reviewed at our institution as a follicular lesion).
- Staging identified a large thyroid mass, mediastinal and bilateral hilar necrotic lymph nodes, numerous bilateral pulmonary nodules (largest in the left lower lobe 1.5 cm), pleural metastases, rib metastases, vertebral metastases, calvarial metastases, and 2 brain metastases. FDG-avid lesions included the thyroid, hilar lymph nodes, pulmonary nodules, pleural nodules, and multiple skeletal mets.
- Thyroglobulin 203,759
Case 3 - SR

- Total thyroidectomy and bilateral central neck dissection.
- Pathology showed PTC with focal poorly differentiated component. It was multifocal with the largest focus measuring 6.2 cm on the left. There was ETE (into fibroadipose) and LVI. Resection margins were negative. There was PTC in 2/13 lymph nodes (largest focus 0.4 cm) without ENE.
- Molecular testing showed only NRAS mutation.

Case 3 - SR

- She received Gamma knife, XRT to the calvarial lesion and radiation to a vertebral lesion with epidural extension.
Case 3 - SR

- She received 252.9 mCi of I-131 as adjuvant therapy following dosimetry using thyrotropin alfa.
- The diagnostic scan showed uptake in bilateral lungs, mediastinum, hilar region, calvarium, left scapula, ribs, L2 vertebra, and possible left iliac bone.
- The post-therapy scan showed similar findings but also uptake in midline skull, pelvis, bilateral femurs and left tibia. There were some non-RAI avid lung lesions as well as mediastinal lymph nodes.

Case 3 - SR

- Staging 2 months later
  - Whole Body Bone Scan – activity in the calvarium, ribs, T11/T12, iliac bones, and scapulae.
  - MRI Brain – showed a slight decrease in the right lateral occipital lobe metastasis when compared to the pre-radiation imaging. The metastatic lesion in the left medial parietal lobe is no longer seen. There were no new parenchymal metastases. The right lateral occipital bone metastasis has decreased in size. There has been no significant change in the left lateral parietal bone lesion. A small metastasis in the frontal bone is stable.
  - CT Chest with Contrast – This shows stable disease of the lungs, pleura, mediastinum, hilum, and skeleton. Some lesions have slightly decreased in size.
- MRI of the brain showed 3 new metastatic brain metastases.
- FDG PET/CT showed overall stable or decrease in size of all lesions aside from a right upper lobe lung mass.
- What now?

Case 3 - SR

- Staging 2 months later
  - MRI of the brain was performed in preparation for gamma knife and there was interval development of at least 15 additional brain metastases.
- What now?
  - Whole brain radiation. She received 3250.00 cGy in 13 fractions.

Case 3 - SR

- She started MDACC protocol 2015-0003, A Randomized Double-Blind Phase 2 study of Radioactive Iodine (RAI) in Combination with Placebo or Selumetinib for the Treatment of RAI-Avid Recurrent/Metastatic Thyroid Cancers.
- After starting selumetinib/placebo she developed a Grade 2 acneiform rash on her face/upper chest/back.
- Following thyrotropin alfa stimulation and a low iodine diet, her stimulated thyroglobulin was 799,354 with negative thyroglobulin antibodies.
- The diagnostic radiiodine whole-body scan showed uptake in both lungs, nodal metastases in the chest, and skeletal metastases.
- She was treated with 154.7 mCi of I-131. The post-therapy scan showed a similar pattern but more extensive involvement of the axial and appendicular skeleton as well as bilateral pulmonary metastases and mediastinal adenopathy.
Case 3 - SR

Serum thyroglobulin level
- **10/2015** 203,759
- Gamma knife & XRT to spine and calvarial met
- **12/2015** 106,906
- **12/2015** 84,979
- **12/2015** 287 (hook effect)
- RAI (250 mCi)
- **02/2016** 38,423
- **04/2016** 28,493

Whole Brain Radiation (32.5 Gy)
- **09/2016** 97,485
- **10/2016** 799,354
- RAI (150 mCi)
- **11/2016** 74,625
- **01/2017** 34,611

Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer

- In mouse models, agents which inhibit MAPK pathway, increase expression of NIS
- 20 patients enrolled


Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer

- Any questions about her?
Other approaches

- 496 PTCs in the TCGA (The Cancer Genome Atlas) data
- Oncogenic driver found in 96.5%

BRAF inhibitors

- Vemurafenib
- Dabrafenib
- Sorafenib

Vemurafenib

- Open-label, non-randomized, phase 2 trial at 10 academic centers and hospitals worldwide
- 18 years or older with histologically confirmed recurrent or metastatic papillary thyroid cancer refractory to radioactive iodine and positive for the BRAF V600E mutation
- Evidence of progression by RECIST 1.1 within the preceding 14 months
  - Cohort 1 — no prior MKI
  - Cohort 2 — prior MKI
2 agents in human trials

• BLU-667
  - ClinicalTrials.gov Identifier: NCT03037385
  - Phase 1 Study of the Highly-selective RET Inhibitor, BLU-667, in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors

• LOXO-292
  - ClinicalTrials.gov Identifier: NCT03157128
  - Phase 1 Study of LOXO-292 in Patients With Advanced Solid Tumors, RET-Fusion Lung Cancer and Medullary Thyroid Cancer

PI3K inhibition

• Everolimus

• Temsirolimus

TRK

TRK Fusions Found in Diverse Cancer Histologies

- Solid tumors, including CNS tumors, with TRK fusion based on local or pre-existing testing
- Enrolling patients ≥ 12 yo; ECOG 0-3
- Dose: 100mg BID
- Primary endpoint: Best ORR
- Global study (20-30 sites)
- Patient concierge service for enrollment, including multiple patient protocols
- Hotline: 855-TRK-123
TRK

- Study of LOXO-101 (Larotrectinib) in Subjects With NTRK Fusion Positive Solid Tumors (NAVIGATE)
- ClinicalTrials.gov Identifier: NCT02576431

- Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions) (STARTTRK-2)
  - ClinicalTrials.gov Identifier: NCT02568267
  - Open-label, global, basket study of entrectinib (RXDX-101) for the treatment of patients with locally advanced or metastatic solid tumors that harbor NTRK1, NTRK2, NTRK3, ROS1, or ALK gene fusions.

Immunotherapy

- Figure 2: Schematic of immune checkpoint mechanisms. Tumors can express PD-L1, which interacts with PD-1 on T-cells, leading to suppression of the antitumor T-cell response. PD-L1 and PD-1 inhibitors prevent this interaction, unblocking the T-cell antitumor response. Anti-CTLA-4 antibodies bind to CTLA-4 to increase the ratio of effector T-cells to regulatory T-cells and achieve the same effect. PD-L1, programmed cell death-1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T lymphocyte-associated antigen 4.

The Three Es theory

- Elimination
- Equilibrium
- Escape

Abscopal effect

- Radiation Therapy
- Antigen-presenting cells
- Activates/potentiates immune response
### Immunotherapy

- Ipilimumab and Stereotactic Body Radiation Therapy (SBRT) in Advanced Solid Tumors  
  – ClinicalTrials.gov Identifier: NCT02239900
- Pembrolizumab and Lenvatinib in Treating Metastatic or Recurrent Differentiated Thyroid Cancer That Cannot Be Removed by Surgery  
  – ClinicalTrials.gov Identifier: NCT02973997

### Summary

- Discussed patient cases demonstrating use of  
  – MKI’s  
  – Redifferentiation therapy
- Discussed trials in progress for:  
  – BRAF inhibitors  
  – MEK inhibitors  
  – Novel “druggable” targets  
  – Immunotherapy
- Did not discuss ATC due to time constraints

### Questions?