Biomarkers of Acquired Resistance: Detecting EGFR T790M in Tissue and in Plasma

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The Growing Family of EGFR Inhibitors

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Disclosures for Howard (Jack) West, MD

• Consulting:
  Clovis, Genentech/Roche, Novartis,
  Celgene, Merck
Case Discussion

• 11/2012 Never-smoker 72 yo Burmese F presented w/st IV NSCLC
  • Escalating dyspnea x 2-3 mo, large left pleural effusion
  • ER visit (outside hosp) U/S-guided large volume thoracentesis
    • Cytology: lung adenocarcinoma (pos for TTF-1, napsin A)
  • Visited interventional pulmonologist at Swedish – more fluid
  • EGFR and ALK testing – negative; also neg for KRAS

• CT chest/abd showed near complete consol of LLL, LLL bronchus narrowing, diffuse L pleural & fissural nodular thickening, loculated pleural effusion, bilat nodules, hilar & med LAN, L supraclav LAN, L axilla, liver met, intraperit & retroperit LAN
Continued Workup, Starting Therapy

- PET/CT not covered
- Brain MRI shows multifocal small (under 8 mm) mets
- ECOG performance status 2
- 12/2012 WBRT initiated
- 1/2013 starts chemo with carbo/pemetrexed, tolerates well
Chemotherapy, then erlotinib for EGFR/ALK wild type advanced lung adenocarcinoma

- 2/2013  Mild shrinkage; continues chemo
- 4/2013  Further mild shrinkage; continues chemo
- 6/2013  Further gradual response, transition to pemetrexed
- 9/2013  Multifocal progression; considering treatment options
  - consideration of clinical trial, not eligible
  - consideration of off protocol options
  - favor docetaxel > erlotinib based on TAILOR trial
- 10/2013 Drop in performance status → started erlotinib due to not having PS sufficient for chemo
- 11/2013 Marked improvement in performance status
- 12/2013 Repeat chest CT demonstrates excellent PR
Ups and Downs in 2014

- 3/14  Ongoing PR; severe rash, dose lowered to 100 mg/d
- 6/14  Marked progression of multifocal disease
  - perit carcinomatosis, ascites → diminished POs, wt loss
- 6/14  Started on weekly docetaxel, continued on erlotinib
  - clinical improvement weekly
- 8/14  CT demonstrates good PR again, clinically markedly better
- 9/14  Asymptomatic, patient strongly advocates break
- 11/14 Repeat scan shows very slight progression, clinically well
  - rec resuming chemo & repeating biopsy
- 12/14 Right pleural effusion tapped → Φ
What Next?

• Initial driver mutation testing negative

• Excellent but transient response to EGFR TKI therapy in never-smoker with adenocarcinoma

• Suspect false negative on EGFR mutation testing
  • No further access to further EGFR TKI-based Rx, but what if she’s actually got activating EGFR mutation & T790M??

• How should we proceed?
Targeting a Targeted Therapy

- 12/15 Imaging reviewed w/interventional radiology & thoracic surgery
  - IR: Nothing accessible on imaging
  - Thoracic: OK, thoracoscopy and biopsy
- 1/15 VATS biopsy
  - lung adenocarcinoma
    - EGFR del 19 mutation, T790M mutation
    - Worse ascites; Performance status worsening
    - Unable to pursue rociletinib trial
- 1/15 Restarts weekly docetaxel
- 2/15 Clinical slow further decline → hospice
- 4/1/15 Dies at home
What went wrong?

- Original testing was false negative
  - tissue sampled was neg, other areas of cancer were not
  - tissue was truly EGFR del 19 positive, but it was missed by poor testing
    (or, remarkably unlikely, great response in truly EGFR wt, then developed EGFR mutations)

- Tissue was not readily accessible
- Patient was reluctant for aggressive tissue collection

- Clinical decline faster than workup could be completed
  - missed opportunity for potentially very effective therapy
Tumor Heterogeneity: You can MISS the mutation, even when it’s there!


Also explains why response rate to targeted therapies for driver mutations is 60-80%, not 99-100%
Early Reports of Tumor Heterogeneity and EGFR Mutation Discordance

Tissue Heterogeneity of EGFR Mutation in Lung Adenocarcinoma

JTO 2008;5:527-9

Akira Sakurada, MD,* Humberto Lara-Guerra, MD,* Ni Liu, MSc,* Frances A. Shepherd, MD,† and Ming-Sound Tsao, MD‡

Discordance of Molecular Biomarkers Associated with Epidermal Growth Factor Receptor Pathway between Primary Tumors and Lymph Node Metastasis in Non-small Cell Lung Cancer

JTO 2009;4:809-15

Sarah Park, MD,* Alison J. Holmes-Tisch, MD, PhD,‡ Eun Yoon Cho, MD, PhD,‡ Young Mog Shim, MD, PhD,§ Jinkook Kim, MD, PhD,§ Hyo Song Kim, MD, Jeeyun Lee, MD, PhD,‖ Yeon Hee Park, MD, PhD,‖ Jin Seok Ahn, MD, PhD,‖ Keunchil Park, MD, PhD,‖ Pasi A. Jänne, MD, PhD,† and Myung-Ju Ahn, MD, PhD‖
Variability in detection of EGFR mutation: Spatial Tumor Heterogeneity

- 67 EGFR TKI-naïve pts w/paired primary & metastatic tumors
- Direct sequencing of EGFR exons 18-21
- 9/18 (50%) of pts w/EGFR mut+ primary cancer EGFR wt in mets
- 17/26 (65%) of pts w/EGFR mut+ metastases were EGFR wt in primary tumor
- Overall discordance rate 27%

EGFR Mutation Heterogeneity & “Mixed Response” to EGFR TKIs

- 180 matched pairs of tumor biopsies tested for EGFR mutation

- Overall discordance rate 14% (25/180)

Concordance of Genomic Alterations Within Primary Tumor and Between Primary and Metastatic Lesions


- NGS testing of paired samples of primary tumor sampled from different blocks (N = 4), lung tumors of different histology in same patient (N = 3), or primary lung tumor & metastasis (N= 4)

- 45% of total breakpoints shared between areas of adjacent tumor

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Marked Discordance Between Primary Tumor and Metastatic Lesion

- 8-75% concordance of genetic alterations between primary tumor and metastatic focus

Remarkable spatial tumor heterogeneity revealed

Liquid Biopsies: Circulating Tumor Cells and Cell-Free DNA

- Physical Properties
  - Size
  - Deformability
  - Density
  - Electrical charge

- Biological properties
  - EpCAM
  - CD45
  - HER2
  - EGFR

CTC Chip to detect EGFR Mutations

- Detected CTCs, matched EGFR mut in 11/12 cases (94%)


Lim E, Tay A, Nicholson AG. JTO 2012;7:e42-3
Circulating Free DNA for Plasma Biopsies

- 100x more DNA material
- Very short half-life (2 hrs)
  - Reflective of the immediate situation
- Potentially useful alternative means to detecting activating mutations, acquired resistance mutations
- However, need to detect very small signal amidst DNA from far more non-tumor DNA

Detecting EGFR Mutations in Circulating Free DNA (cfDNA) : EURTAC Trial

- Serum collected prospectively in EURTAC trial looking for mut’ns
- N = 173 patients, 97 w/serum available for testing
- EGFR mutation detected from cfDNA in plasma of 76/97 (78%)
- Same trends for PFS and OS as seen in tissue-based detection
- Significantly superior OS in pts w/exon 19 del > L858R mutation
Even More Accessible Testing: ctDNA in Urine

- Testing of urine for T790M in 22 patients with activating mutation on EGFR TKI
- Droplet digital PCR on ctDNA
- T790M detected from cfDNA in urine of 15/22 pts (68%); in urine of 10/10 pts w/tissue T790M
- Detected in urine up to 3 months before radiographic progression
- Significantly superior OS in pts w/exon 19 del > L858R mutation

Husain H, et al. ELCC 2015, abstract 360
Two methods of detection, each with limitations: What’s the Real Gold Standard?

- Tissue has historically defined mutation testing, but we KNOW it’s not perfect
  - Marked spatial tumor heterogeneity
  - Response rates 60-75%
  - Tumor tissue testing can have false negatives

- Both CTC and circulating free DNA detection methods are still in development, but clear proof of principle
  - Sensitivity still a barrier
  - Can overcome spatial tumor heterogeneity
  - Recent sensitivities in same ballpark as concordance numbers for tissue testing

- Each approach has potential merit; liquid biopsies an emerging tool
Conclusions: New Value for Repeat Biopsies

- With the availability of merelitinib (AZD9291) and rociletinib (CO-1686) in global trials and hopefully commercially soon, there is a value to obtaining a repeat biopsy for guiding management decisions in EGFR acquired resistance TODAY.

- Tumor tissue, while the historical “gold standard”, suffers from tumor heterogeneity and sometimes difficult safe access.

- Liquid biopsies using CTCs or circulating tumor DNA are emerging as a potentially valuable tool, though sensitivity needs clarification.

- This field is rapidly progressing as demand for accurate mutation data increases. Stay tuned for more soon.