Personalized Medicine in Oncology

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Agenda

- Evolution of precision medicine in oncology
- Technologies/tests used in precision medicine
- Recent Advances and successes
The Evolution In Our Understanding Of Cancers And Treatment Options
CANCER IS A DISEASE OF THE GENOME

- DNA is exposed to carcinogenic events every day; this causes gene alterations to occur
- Exposure to cancer risk factors increases the chances of gene alterations
HOW GENOMIC ALTERATIONS CAN CAUSE CANCER

ALTED GENES

ALTED PROTEINS

CDKN2a
PTEN
RAS
RAF
mTOR
MAPK
AKT

ALTED PATHWAYS

RAS
RAF
MAPK

Code for

Resulting in

CANCER
TYPES OF ALTERATIONS AND TESTS

Normal, Germline

- BRCA1
- BRCA2
- TP53
- PTEN
- ATM
- CHEK2
- BRIP1
- PALB2
- Other genes familial risk factors
- 79 common SNPs

Contribution of known genes to familial aggregation of breast cancer

- SNVs

Pharmacogenomics

Tumor, Somatic

- Number of alterations per tumor
- Prognostic
- SOC companion Dx

- Predictive, Therapy response

Predisposition testing

SNVs

<table>
<thead>
<tr>
<th>Drug (toxicity)</th>
<th>FDA label</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belinostat (neutropenia)</td>
<td>&quot;Reduce starting dose in patients known to be homozygous for UGT1A1*28 allele&quot;</td>
<td>None (too early)</td>
</tr>
<tr>
<td>Azathioprine, Thioguanine, Mercaptopurine (myelosuppression)</td>
<td>&quot;It is recommended that consideration be given to either genotype or phenotype patients for TPMT&quot;</td>
<td>AHRQ: no benefit over monitoring</td>
</tr>
<tr>
<td>Capetibinib, Tegafur, Fluorouracil (neutropenia)</td>
<td>&quot;Capetibine is contraindicated in patients with known DPG deficiency&quot;</td>
<td>No guidelines; Dosing rec from CPIC and DPWG</td>
</tr>
<tr>
<td>Irinotecan (neutropenia)</td>
<td>&quot;Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following treatment&quot;</td>
<td>EGAPP: not recommended</td>
</tr>
</tbody>
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CHANGING THE TREATMENT PARADIGM

Traditional medicine

- Unique Biology
- Same Treatment

Considered ‘standard of care’, but often toxic and may not provide benefit

Personalized medicine

- Unique Biology
- Molecular Profiling
- Targeted Therapies

Unlike chemotherapy, often less toxic and may have a cost benefit, especially if standard treatment likely won’t be efficacious or previously failed
LUNG CANCER: POSTER CHILD FOR PRECISION MEDICINE

MOLECULAR PROFILING HAS CHANGED THE CLASSIFICATION OF LUNG CANCER

Lung Adenocarcinoma

- Vemurafenib, Dabrafenib
- Trastuzumab, Afatinib
- Crizotinib, Ceritinib
- Erlotinib, Afatinib
- Cabozantinib
- Crizotinib
- Trametinib

2003

2016

NCCN GUIDELINES IN NSCLC

“Strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials.”
NUMBER OF TARGETED THERAPEUTICS RISING

KNOWING WHICH TESTS TO ORDER FOR A TUMOR TYPE IS INCREASINGLY CHALLENGING

Target Markers

- FBXW7
- VEGF/VEGFR
- AURKA
- CCND1
- DDR2
- DNMT3A
- GNAQ
- ERBB3
- BRCA1
- BRAF
- CDK4
- KRAS
- RET
- VEGF/VEGFR
- AURKA
- CDK4
- CCND1
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Extrapolated from BioCentury Online Intelligence Database
PERSONALIZED APPROACH IMPROVES CANCER TREATMENT OUTCOMES

Genomics-matched targeted therapy = BEST OUTCOME

Targeted therapy w/o mutation matching = Worst outcome

(Ref: Schwaederle et al., JCO 2015)
BARRIERS TO PRECISION MEDICINE
CLINICAL, TECHNOLOGIC AND ACCESS CHALLENGES

1. **Cancer Genome Complexity**
   - Hundreds of genes, millions of alterations driving tumor growth
   - Every patient’s tumor genomic profile is unique

2. **Limitations of Current Panels**
   - Most of the “tumor type” and “hot spot” panels only look at frequently altered genes and only at commonly altered areas of the gene

3. **Limitations of Real World Samples**
   - Low tumor purity frequent in metastatic/recurrent/post-treatment samples
   - Less invasive sampling leads to smaller specimen sizes from work-ups

4. **Lack of Access to Therapies**
   - Few approved targeted therapies in many tumor types
   - Extremely difficult to access off-label therapies
   - Difficulty to access and enroll in clinical trials
Technologies Advances are Overcoming Challenges in Precision Medicine
FOUR TYPES OF GENOMIC ALTERATIONS

Base Substitutions
- BRAF V600E
- vemurafenib

Insertions and Deletions
- EGFR Exon 19 Deletion-
erlotinib

Copy Number Alterations
- HER2 amplification-
trastuzumab

Rearrangements
- ALK Fusion-
crizotinib
TRADITIONAL TESTING

Limitations

- Only a limited number of alterations screened at once
- Misses some types of alterations
- Often depletes limited tissue sample
- Results are specific for the test used; need to know ahead of time what questions to ask

<table>
<thead>
<tr>
<th>DNA Alterations Detected or Missed by Traditional Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
</tr>
<tr>
<td>IHC</td>
</tr>
<tr>
<td>FISH</td>
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<tr>
<td>Sequencing; Hot Spot Panels</td>
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</table>

Comprehensive Genomic Profiling: Covers all alterations
Test differences

1. TECHNICAL
   - No. of genes, association with drugs
   - Coverage (Breadth of coverage, exons, introns, promoters)
   - Sequencing depth
   - No. of genomic alterations detected (SNV, indels, SVs, CNVs)
   - Turn-around-time (TAT)

2. ANALYTICS
   - Analytical, clinical validity
   - Clinical utility

3. LABORATORY QUALITY CONTROL
   - CLIA
   - CAP

4. FINANCIAL
   - Cost
   - Reimbursement

5. INTERPRETIVE
   - FDA-approved drugs
   - Clinical trials
   - Physician support

MOLECULAR CHARACTERIZATION BY NEXT GENERATION SEQUENCING

- TARGETED PANEL
  - Smallest Content
  - High Sequencing Depth
  - Shorter TAT

- WHOLE EXOME SEQUENCING
  - Medium Content
  - High Sequencing Depth
  - Medium TAT

- WHOLE GENOME SEQUENCING
  - Largest Content
  - Lowest Sequencing Depth
  - Medium TAT

PLUS Cost, Complexity, Confusion

Sensitivity, Throughput
Solution: Comprehensive Genomic Profiling to Identify Personalized Treatment Options
“HOT SPOT” VS COMPREHENSIVE GENOMIC PROFILING

Comprehensive approach
Sequences coding regions of genes
In their entirety

Hot Spot approach
Only sequences select
regions of a gene

Select base substitutions,
short indels, limited copy number
alterations, no rearrangements

ALL base substitutions, indels,
copy number alterations,
rearrangements

Gene 1
Exon 1 Exon 2 Exon 3 Exon 4

= Clinically Relevant Alteration

* = FoundationOne® test
DELETIONS MISSED BY STANDARD TESTING DETECTED USING COMPREHENSIVE GENOMIC PROFILING

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)® Acknowledge the Utility of Broad Molecular Profiling in NSCLC

1. Establish histologic subtype with adequate tissue for molecular testing for metastatic disease.
2. Recommend EGFR mutation testing (Category 1) and ALK testing (Category 1).
3. Strongly endorse broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials.

Single gene testing misses up to 35% of ALK and 17% of EGFR alterations

Hot Spot NGS
50% of targetable alterations can be missed without supplemental FISH

Comprehensive Genomic Profiling FoundationOne
Detects all classes of NSCLC clinically relevant alterations

Conventional hot spot tests found to miss key alterations in NSCLC

Frequency of selected drivers across 6,632 cases of NSCLC

ALK: 4.1%  EGFR: 20.0%  BRAF: 5.7%  ERBB2: 6.0%  RET: 2.4%  MET: 5.6%  ROS1: 1.5%  KRAS: 32.0%

Recommended agents for ALK and EGFR:
Emerging targeted agents for genetic alterations (BRAF V600E, ERBB2, RET, MET, ROS1).

ALK Rearrangement: Crizotinib*
Certinib**
Alectinib
EGFR Mutation: Erlotinib**
Gefitinib**
Afatinib**
BRAF V600E Mutation: Vemurafenib
Dabrafenib +/– Trametinib
ERBB2 Mutation: Trastuzumab/Herceptin®
RET Rearrangement: Cabozantinib
MET/METex14 Amplification: Mutations: Crizotinib
ROS1 Rearrangement: Crizotinib
KRAS Mutation: No Tx available today; MEK inhibitors in clinical trials*
EXPERIENCE: ~6000 LUNG ADENOCARCINOMAS

Diagram showing mutations and targeted therapies for lung adenocarcinomas. The chart details the percentage of patients with specific mutations and the drugs that can target these mutations. Key mutations and targeted therapies include:

- KRAS, EGFR, ERBB2, BRAF, PIK3CA, MET, ALK, DNMT3A, PTEN, RET, ROS1, KIT, FGFR1, JAK2, PTCH1, SRC, RARA, GNA11, GNAQ

Therapies approved in this tumor type:
- Afatinib, Erlotinib, Lapatinib, Cetuximab

Therapies approved in another tumor type:
- Trametinib, Cobimetinib

Key mutations include:
- KRAS mutations
- EGFR mutations
- BRAF V600E
- Other point mutations
- MAP2K1 mutations
- AKT1 mutations
- PIK3CA mutations
- ERBB2 KD mutations
- ALK fusions
- RET fusions
- ROS1 mutations
- NRAS mutations

Graphs and charts show the distribution of patients with mutations and the effectiveness of targeted therapies.
NOVEL RET FUSIONS TRANSLATED TO CLINIC, NSCLC

*KIF5B*-RET (exons 1-15)  *RET* (exons 12-20)

Baseline CT scan showing paramediastinal and pleural-based nodularities in left upper lobe.

Repeat CT scan after 28 days of anti-RET therapy: disappearance of paramediastinal and near complete resolution of pleural disease.

Multiple patients with RET fusions now known to have responded to RET inhibitor
TARGETED THERAPIES HIT COMMON DRIVER PATHWAYS
ERBB2 AND ERBB3 MUTATIONS PREDICT RESPONSE TO AFATINIB IN BLADDER CARCINOMA

GENOMIC PROFILING EVIDENCE IS GROWING

Additional publications in the areas of clinical utility, investigator-led evaluations, and case study reports (to name a few):

- Schrock et al (2016)
- Schwaederle et al (2015)
- Gatalica et al (2014)
- Kris et al (2014)

Molecularly matched clinical trials (not exhaustive)

- SU2Cs Signature
- MATCH My Pathway
- MPACT IMPACT2
- FOCUS4 Lung-MAP
- TAPUR
Recent Advances in Precision Medicine

Immunotherapy
Tumor burden
Liquid Biopsies
COMPLEX LANDSCAPE FOR IMMUNOTHERAPIES

Batlevi et al., Nature Reviews Clinical Oncology, 2015
TUMOR MUTATIONAL BURDEN (TMB)

TMB is a measurement of the total number of coding somatic base substitution and indel mutations occurring in a tumor specimen, per megabase of coding genome assessed.

Tumors with more alterations are more likely to respond to immunotherapies, because of the increased likelihood that they will have neoantigens that can be targeted by the immune system. **TMB IS NOW CONSIDERED A BIOMARKER FOR RESPONSE TO IMMUNOTHERAPY.**

![Graphs showing TMB in different tumor types](image)

Similar results seen in melanoma and bladder cancer

MICROSATELLITE INSTABILITY (MSI)

Microsatellite instability is caused by defects in DNA mismatch repair genes and results in greatly increased insertion/deletion mutation rate in microsatellite repeat genome regions. MSI is associated with positive prognosis and increased likelihood of response to immunotherapy.

Microsatellite instability and BRAF mutation testing in colorectal cancer prognostication.
Lockhead et al, J Natl Cancer Inst; 2013
NCCN Guidelines for Bladder Carcinoma
Invoke Genomic Profiling

Bladder Cancer

Clinical Staging

Metastatic

- Bone scan clinical suspicion or symptoms of bone metastases
- Chest CT
- Consider CNS imaging
- 24-hr urine creatinine clearance, if calculated GFR < 60 mL/min

Additional Workup

Node only
- Consider biopsy of nodes (See BL-6)

Primary Treatment

Disseminated
- Chemotherapy (See Treatment of Recurrent or Persistent Disease (BL-8))

Consider molecular testing in a CLIA-approved laboratory. See Discussion.

Cisplatin


Atezolizumab
WHEN BIOPSY IS NOT AN OPTION

Blood based tumor detection is extremely challenging
Requires a highly sensitive and specific assay

Compared to ≥20% tumor content from the tissue, tumor content in blood may be less than 1%
LIQUID BIOPSY CASES

• 66 yo man with mixed papillary/clear RCC progressed on cabozantinib
  • Liquid biopsy results identified an EML4-ALK fusion
  • ALK fusions in RCC associated with PRCC (Kim et al and Sukov et al)
  • Patient now on alectinib

• 60 yo man with lung adenocarcinoma
  • Liquid biopsy results identified an EML4-ALK fusion

• 65 yo man with lung adenocarcinoma
  • Liquid biopsy results identified an EGFR L858R mutation and FGFR3-TACC3 fusion

• 56 yo woman with breast invasive ductal carcinoma
  • Liquid biopsy results identified EGFR E749K and PIK3CA H1047R mutations
CONCLUSIONS

• Personalized medicine is improving care...in rare, refractory, aggressive cancer patients... and in some early cancers (NSCLC)

• Limitations exist and the field is ever changing

• Despite limitations, evidence indicates positive impact to patients

• Concerted efforts to educate and create personalized medicine environment will move the evidence into clinical practice
ACKNOWLEDGEMENTS

The patients and their families

THANK YOU!