Precision Medicine for Children with Cancer

Lessons from The Dana-Farber/Boston Children’s Experience

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Dana-Farber Boston Children’s Perspective on Precision Cancer Medicine (PCM)

- **Goal:** Provide just enough of the right therapy for the individual patient in order to decrease side effects and increase success
  - Tumor profiling tests (molecular diagnostics) based on NGS assess all genes or a large set of genes of interest with one test using clinical samples
    - Gene variants known to alter behavior in a manner that results in cancer progression and / or spread
  - Targeted therapy: a treatment with a known, specific mechanism of action
  - Precision cancer medicine: **targeted therapy** selected based on identifying **key gene variants**
Dana-Farber Boston Children’s Perspective on Precision Cancer Medicine (PCM)

2½ year old with metastatic inflammatory myofibroblastic tumor with ALK rearrangement

One month of Crizotinib (COG ADVL 1212)

We are interested in determining whether we can extend the success of precision cancer medicine to pediatric cancers where the key variants are not yet known or poorly understood.
Dana-Farber Boston Children’s Perspective on Precision Cancer Medicine (PCM)

PRECISION CANCER MEDICINE

The goal of precision medicine is to treat patients with drugs that target the specific genetic mutations in their tumors, regardless of where the tumors are found. This approach may improve the success of treatment and reduce side effects.

"I’m here about the details."
Bringing Genomics to the Clinic: PROFILE

- DFCI, BCH and BWH enterprise level research project
- All children with cancer or suspected cancer seen at Boston Children’s or Dana-Farber are offered the opportunity to participate

  - Participation allows
    - Sequencing of clinically acquired specimens
      - With a targeted gene panel test (OncoPanel)
    - Clinically acquired leftover specimens and derivatives placed in tumor bank
    - Genomic data linked to clinical data

- Sequencing performed in a clinical lab and results with potential to impact clinical care returned to primary oncologist and patient

- After 2 ½ years approximately 500 pediatric cancers sequenced
The First Multi-Institution PCM Study in Pediatric Oncology: the iCat1 Study

- Goal: to determine whether it is feasible to identify key gene mutations and make an individualized cancer therapy or iCat recommendation using currently available clinical gene tests

Eligibility: High risk solid tumors

Expert Panel
The iCat1 Study, Results

- High degree of physician and patient engagement
- Conducting a multi-institution study is feasible
  - 40% patients enrolled from 3 collaborating Institutions
- 30% of patients received an iCat recommendation
- 40% had a result with implications for care
- >90% would participate again (Marron J., PBC, in press)

Harris M et al., JAMA Oncology 2016
Putting the puzzle pieces together

“Potentially” clinically-relevant tumor mutations (many not currently targetable) in 25%

Inherited cancer mutations in 10%

Combined tumor and germline exome results

n=121 cases

Lesson 3: Germline cancer predisposition is more common than previously appreciated

Slide Credit: Will Parsons
Parsons et al, JAMA Oncology
Pilot study of 9 selected samples RNA Sequencing

- Undifferentiated sarcomas or translocation associated sarcomas
- 2 patients expected translocation was identified
- 3 patients translocations were identified that clarified diagnosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Clinical Presentation</th>
<th>Initial Diagnosis</th>
<th>Molecular Testing at Initial Diagnosis</th>
<th>Identified Translocation</th>
<th>Diagnosis Suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Lung mass and femur lesion</td>
<td>Ewing sarcoma</td>
<td>CD99 IHC</td>
<td>EWSR1-CREB1</td>
<td>Primary pulmonary myxoid sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EWSR1 break-apart FISH</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>Occipital mass, adenopathy</td>
<td>Stage III melanoma</td>
<td>S100 IHC</td>
<td>EWSR1-ATF1</td>
<td>Cutaneous clear-cell sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Melan-A IHC</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>Forearm mass, recurrence lung</td>
<td>Intermediate-grade spindle-cell sarcoma</td>
<td>ETV6 break-apart FISH</td>
<td>EML4-NTRK3</td>
<td>Infantile fibrosarcoma</td>
</tr>
</tbody>
</table>

Lesson 4: Not known which tumor profiling assays optimally balance the competing factors of minimal tissue requirements, comprehensive genomic assessment and rapid data analysis and results reporting
The iCat1 Study, Results

- 3 of 31 received targeted therapy matched to the iCat recommendation
  - Reasons matched therapy (MTT) not received assessed by survey
    - Clinical trial not available: completed accrual or patient ineligible
    - Clinical status: patient in second remission or disease too advanced or deceased
- Similar results in Mody et al., *JAMA*, 2015
Lesson 5: A limited number of patients receive MTT

### Selected Molecular Profiling Initiatives and Genotype-Matching to Clinical Trials

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample Size</th>
<th>Platform</th>
<th>Fresh Biopsy vs FFPE</th>
<th>Germ-line Control</th>
<th>Number and % of Patients in Genotype-Matched Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustave Roussy</td>
<td>708</td>
<td>30-75 gene panels (Life) + CGH (Agilent)</td>
<td>Fresh biopsy</td>
<td>Yes</td>
<td>140/708 = 19%</td>
</tr>
<tr>
<td>Institut Curie</td>
<td>741</td>
<td>46 gene panel (Life) + CNA (Affymetrix) + IHC</td>
<td>Fresh biopsy</td>
<td>No</td>
<td>195 randomized/741 = 26%</td>
</tr>
<tr>
<td>BCCA</td>
<td>100</td>
<td>Whole genome</td>
<td>Fresh biopsy</td>
<td>Yes</td>
<td>1/100 = 1%</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>2,000</td>
<td>11-50 gene panels (Life)</td>
<td>FFPE</td>
<td>No</td>
<td>83/2000 = 4%</td>
</tr>
<tr>
<td>Princess Margaret</td>
<td>1,640</td>
<td>23-48 gene panels (Illumina, Life)</td>
<td>FFPE</td>
<td>Yes</td>
<td>92/1640 = 5.6%</td>
</tr>
</tbody>
</table>

CNA = Copy number alterations; IHC = Immunohistochemistry

From Lillian L. Siu, MD, FRCPC, Implementing Personalized Cancer Genomics in Clinical Trials
ASCO Annual Meeting, 2016
Lesson 5a: Pre-clinical models essential

Lesson 5b: PCM studies should assess reasons for failure to receive MTT
12 institutions collaborate on the design and conduct of clinical genomic or tumor profiling protocols investigating the clinical impact of a precision cancer medicine approach in recurrent/refractory pediatric cancers.
Cohort Study To Evaluate Outcomes after Receipt of Targeted Therapy Matched to an iCat recommendation in Children and Young Adults: The GAIN Consortium/iCat2 Study

High risk, Relapsed Refractory extracranial solid tumor
825 patients, 3 years

• Eligibility

All: T+N targeted NGS panel
Rare: WES
Selected: RNA Sequencing

• Tumor Profiling

Clinical Impact Matrix
iCat Recommendation:
Tier based on evidence
Classify drug availability

• Curation, clinical interpretation

Vital Status
Treatment
Response

• Follow-up data

iCatalog: Pedi PCM knowledge base
U. Chicago

Derive low passage cell lines
Create patient derived xenograft models

1) Describe OS, PFS in each group
2) Identify factors associated with outcome
3) Determine factors associated with iCat recommendation and receipt MTT
4) For subset with measurable disease, ORR and PFS by group

Evaluable n=617
No iCat n=401
iCat, Unmatched therapy n=148
iCat, Matched therapy n=68
Extraordinary responder
# PCM Trial Designs

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Summary</th>
<th>Pediatric Oncology Examples (USA)</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies of Molecular Profiling Clinical Utility</td>
<td>-Frequency of alterations&lt;br&gt;-Assess feasibility sequencing</td>
<td>-iCat1&lt;br&gt;-BASIC3&lt;br&gt;-MiOncoSeq</td>
<td>Foundation for subsequent studies</td>
<td>Does not assess impact on outcome</td>
</tr>
<tr>
<td>Longitudinal Cohort</td>
<td>-Collaborative&lt;br&gt;-Prospective collection genomic, treatment and outcome data</td>
<td>-PROFILE&lt;br&gt;-GAIN consortium/ iCat2 Study&lt;br&gt;-G4K (Genomes for Kids)</td>
<td>-Provide access to profiling&lt;br&gt;-Supplement pediatric sequencing databanks (recurrent samples)&lt;br&gt;-Facilitate basket trial design&lt;br&gt;-Assess impact MTT on outcome</td>
<td>Doesn’t address access to MTT</td>
</tr>
<tr>
<td>Basket Trial</td>
<td>-Histology independent&lt;br&gt;-Treatment arms defined by genotype&lt;br&gt;-Typically phase II</td>
<td>Pediatric MATCH</td>
<td>Identifies histology-specific signals of activity $\rightarrow$ phase II/III</td>
<td>Significantly different activity by histology $\rightarrow$ risk missed signal of activity</td>
</tr>
<tr>
<td>Master-Protocol</td>
<td>-Single disease&lt;br&gt;-Multiple treatment arms by genotype&lt;br&gt;-Typically phase II</td>
<td>NEPENTHE</td>
<td>Increased likelihood patient receiving tailored therapy</td>
<td>Requires understanding genomic subtypes of disease</td>
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Adapted from Martine J. Piccart-Gebhart, D. Zardavas “Clinical Trials of Precision Medicine through Molecular Profiling”, ASCO Ed Session, 2015
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