Precision Oncology & Pediatric Clinical Trials

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Overview

• Pediatric (&AYA) precision oncology in Canada

• A shifting paradigm: Molecularly targeted clinical trials in pediatrics

• One patient’s story
TREATMENT OF LEUKEMIAS

Acute leukemias run their course, uninfluenced by any treatment. Transfusion may be of benefit, but the improvement is very transitory. Most cases succumb in the course of a few weeks, either to hemorrhage, circulatory failure or an intercurrent infection.

Chronic forms of leukemia with marked increase in the leukocytes are more susceptible to treatment. Although the fatal outcome cannot be prevented it can sometimes be put off for several years. The chronic myeloid leukemias show the most favorable response. Radium or x-ray treatment will cause the white cells to diminish, with an accompanying diminution in the size of the spleen and lymph nodes and relief from symptoms. The leukocytes may continue to fall for some
Pediatric Cancers: Survival at Relapse

Dr. Stefan Pfister, DKFZ, Heidelberg
Question 1

Over the past decade, what has been true for MOST pediatric oncology early phase clinical trials?

A. Include a specific tumour type, aim to identify maximum tolerated dose and have objective response rates (ORR) >20%
B. Include many tumour types, aim to identify biologically effective dose, have ORR >10%
C. Include many tumour types, aim to identify maximum tolerated dose and have ORR <10%
D. Include a specific tumour type, aim to identify biologically effective dose and have ORR >20%
E. Include many tumour types with a specific genomic target, aim to identify maximum tolerated dose and have RR ~80%
More recent meta-analysis of pediatric phase IIs (2004-2015) shows similar ORR ~10% - ONLY 3% in solid tumours*

Populations within a type of cancer
Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer
## Precision Oncogenomics

<table>
<thead>
<tr>
<th>Informed consent</th>
<th>Sample acquisition</th>
<th>WGS / WTS sequencing</th>
<th>Targeted alignment analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology consult &amp; consent</td>
<td>Biopsy (Metastatic site) Pathology review Sample preparation</td>
<td>Tumour (80x) Normal (40x) RNA (200M)</td>
<td>‘In silico panel’ report</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genomic data generation</th>
<th>Integrative analysis</th>
<th>Tumour board discussion</th>
<th>Clinical action</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNV, CNV, SV Expression Other analyses</td>
<td>Genomic events of potential biological and therapeutic relevance (in context to patient disease)</td>
<td>Review of genomic findings Discussion of potential for clinical action</td>
<td>Follow up consult &amp; clinical decision</td>
</tr>
</tbody>
</table>
Models of CAYA Cancers

Biospecimen

Molecular Profiling & Precision Medicine Clinical Trials

Efficacy of Precision Medicine

Canadian CAYA Cancer Biobank & Data Repository

- Discover New Targets
- Develop Therapies
- Understand Biology

IMPROVE OUTCOMES FOR HARD-TO-TREAT CAYA CANCERS

- Biomarkers of Response
- New Profiling Tools
- Fuel Future Discoveries
Question 2

Precision Oncogenomics in Pediatrics

Which of the following best reflects our current understanding of the genomics of pediatric cancers?

a) Pediatric cancers have a higher mutation burden overall compared to adult cancers
b) Transcriptome data is routinely used in pediatrics to guide targeted therapy
c) Pediatric cancers frequently have oncogenic fusions
d) Germline analysis contributes little to our understanding of pediatric cancers
Challenges in pediatric cancer

- Relatively rare, many with genome data n=1
- Few aberrations in the genome
- Hard to target driver events

38 types of cancer from 72 pediatric POG patients

PROFYLE CLINICAL NODE

Quality Assurance and Ethics Oversight

Identify, screen, consent / assent
Tissue collection, pathology review, Biobanking
Molecular Tumour Profiling, Data Analysis
Molecular Tumour Board

Actionable Genomic Finding(s)
No actionable Genomic Finding

CAPTUR clinical trial
Pediatric phase I/II trials
Compassionate / SAP access
Health Canada Open Label Individualized Patient Protocols
Can-Pediatric basket trial & International Collaborations

≥12y
CAPTUR adult cohort
CAPTUR pediatric cohort

CAPTUR drugs

ALK inhibitor
PDGFR inhibitor
mTOR inhibitor
BRAF inhibitor
PARP inhibitor
SMO inhibitor

PR, CR, SD → Continue therapy
PD

Can
CAPTUR – Canadian Profiling & Targeted Agent Utilization Trial

≥12y

CAPTUR adult cohort

<12y

CAPTUR pediatric cohort

CAPTUR drugs

ALK inhibitor
PDGFR inhibitor
mTOR inhibitor
BRAF inhibitor
PARP inhibitor
SMO inhibitor
Pan-Canadian trial to leverage national genomic profiling efforts and CCTG clinical trial capabilities

Pharma partners: Committed to provide drug and funding

Design modeled on, and linked to, US-TAPUR and Netherlands DRUP trials

CAPTUR

8 Patients

≥1x response? → + 16 Patients

<1x response?

≥5x response? → Further investigation

<5x response? → Stop cohort

Stop cohort
NCI Pediatric MATCH (APEC 1621)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular Target</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larotrectinib</td>
<td>NTRK1/2/3</td>
<td>Prior Peds phase I</td>
</tr>
<tr>
<td>Erdafitinib</td>
<td>FGFR1/2/3/4</td>
<td>No peds phase I*</td>
</tr>
<tr>
<td>Tazemetostat</td>
<td>EZH2, SMARCB1, SMARCA4</td>
<td>Peds phase I ongoing</td>
</tr>
<tr>
<td>LY3023414</td>
<td>TSC1/2, PI3K/mTOR</td>
<td>No peds data; Limited dose-finding phase (n=12)**</td>
</tr>
<tr>
<td>Selumetinib</td>
<td>MEK</td>
<td>Prior peds phase I</td>
</tr>
<tr>
<td>Ensartinib</td>
<td>ALK, ROS1</td>
<td>No prior peds phase I*</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF</td>
<td>Ongoing pediatric study</td>
</tr>
<tr>
<td>Olaparib</td>
<td>ATM, BRCA1/2, RAD51C/D</td>
<td>No peds data; limited dose-finding phase**</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>CDK4/6, CCND1/2/3</td>
<td>Ongoing pediatric phase Is</td>
</tr>
<tr>
<td>Ulixertinib</td>
<td>NRAS, HRAS, KRAS, ARAF, BRAF, MAP2K1,GNAQ, MAPK1</td>
<td>No peds data; limited dose-finding phase**</td>
</tr>
</tbody>
</table>
NCI Pediatric MATCH (APEC 1621)

- Phase II Basket; marker-specific, histology-agnostic
- DNA/RNA **panel** approach
- Some non-commercially available drugs
- Some drugs without established pediatric phase I studies
- No combinations
ESMART
(European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed/Refractory Tumours)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
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<tbody>
<tr>
<td>Ribociclib &amp; Topotecan/Temozolomide</td>
</tr>
<tr>
<td>Ribociclib &amp; Everolimus</td>
</tr>
<tr>
<td>AZD1775 &amp; Carboplatin</td>
</tr>
<tr>
<td>Olaparib &amp; Irinotecan</td>
</tr>
<tr>
<td>Enasidenib</td>
</tr>
<tr>
<td>Lirilumab &amp; Nivolumab</td>
</tr>
</tbody>
</table>

- (Phase I)/Phase II – ORR
- R/R solid, CNS or leukemia
- Opened in 2016 (ongoing)
CONSISTENCY
It's Only a Virtue if You're Not a Screwup.

www.despair.com
A Case from BC

• 13 year-old male
• Diagnosis: Papillary Thyroid Carcinoma
  – 11 years
  – TNM Stage: T4aN1bM0
  – Papillary Thyroid Carcinoma of right lobe, with extensive microscopic involvement of left lobe and isthmus, positive margins, extensive soft tissue invasion & positive nodes

• Treatment:
  – Initially received 100 millicuries of radioactive iodine (I$^{131}$ RAI)

• Family history non-contributory; no prior radiation exposure
Relapse

• 12 months later
  – Thyrogblobulin levels rising
  – Relapse in neck, thyroid bed, paratracheal LNs and new bilateral pulmonary nodules

• Repeated OR for cervical debulking surgery and second 150mCi of I\textsuperscript{131}-RAI.

• Repeat CT chest / neck 2 months later: rapid progression of innumerable pulmonary metastatic nodules.
Case Presentation

• At the time of POG (2015)
  – TNM Stage: TXN1bM1
  – Biopsy sites: Bilateral and central neck compartments
  – Biopsy again showed Papillary Thyroid Carcinoma
POG results: Large structural variants

TPM3-NTRK1 fusion

Pediatric PTC

- More likely advanced / metastatic in children
- Recurrence rate is high – multiple ORs and RAI
- PTC – mutations and fusions in NTRK, RET, RAS and BRAF
- Children more often have fusion proto-oncogenes
  - NTRK1/3 fusions in up to 26% of pediatric PTC\(^1\)

- At the time of POG presentation (2015) – no available NTRK inhibitor
- 2016 – Learned of preliminary adult phase I data for larotrectinib; open pediatric phase I study (in the US only)

\(^1\) Prasad et al. Cancer 122:1097-1107.
The “Trek” to Loxo101

• Lestaurtinib...

• The Endocrinologists

• Tumour Board

• Access to pediatric phase I studies out of country
  – BC Medical Services Plan

• Loxo Oncology and Seattle Children’s Hospital
Case Conclusion

• Patient enrolled on Loxo101 (Pediatric Phase I of larotrectinib) in Seattle in Sept 2016

• Repeat CT chest/neck (post cycles 2, 4 & 6) showed resolution of almost all pulmonary nodules

• Excellent functional status, no therapy-related toxicity

• Still on study (cycle 28!)

• Larotrectinib pediatric phase I: **93% ORR** among pediatric patients with TRK fusion cancers*
  
  – 0% ORR among 7 patients without TRK fusions

Summary

• Changing paradigm of pediatric phase I/II trials in era of molecular targets

• Era of genomics = desperate need to translate targetable findings into clinical trials / new therapies

• Strategies to overcome challenges in our Canadian context
Questions?

Elliot

Robert
Clinical Trials Innovation In An Age of Precision Medicine
Challenges with Clinical Trials

“What do you think?”
Examples of Patient Roles In Addressing Challenges

Proposal to the Federal Minister of Health
• Priority setting key part of building proposal
• Ac2orn secured meeting with the Federal Minister of Health, the Honourable Ginette Petitpas Taylor for April 2018
• Support from numerous cancer organizations and about 30 individual Oncologists from across North America
• Follow up meeting with Health Canada in August and additional meeting planned for December

Pan Canadian Research Ethics Board
Feedback on Trial Design
Back To Clinical Trials

• Phase I: Dose finding studies
  – Primary Objectives:
    • Determine the **Maximum Tolerated Dose** and the **Recommended Phase II dose**
    • Describe the toxicity profile
    • Primary endpoint: **Dose limiting toxicity**
  
  – Secondary Objectives:
    • Characterize pharmacokinetics (PK) and pharmacodynamic studies
    • **Preliminary data** on anti-tumour activity (efficacy)
    • Correlative biology aims
Definitions: Phase 2

• Phase II: First **EFFICACY** studies
  – Primary Objective:
    • Determine anti-tumour activity of novel agent(s)
  – Primary Endpoint: **Objective response rate**
    – Based on disease re-evaluations (Imaging, marrows, tumour markers)
    – Need MEASURABLE or EVALUABLE disease at study entry*

  – Secondary Objectives:
    • Impact of therapy on **survival outcomes** (EFS, OS)
    • Further investigate pharmacokinetics and toxicity outcomes
Looking Backwards To Change A Paradigm
Finn
My Perspective on Clinical Trials
To Change A Paradigm, We Have To Stop Confusing How We Do Clinical Trials With Why We Do Clinical Trials
Confusing How With Why Leads to Compartmentalization
Confusing How With Why Creates Challenges and Impedes Solutions
We Have A Golden Opportunity To Shift A Paradigm
We Need to Design With Challenges In Mind

- Time consuming, complicated, and expensive

- Historically getting pharmaceutical companies interested has been a challenge

- Funding, contracts, Health Canada, REBs, compliance, audits, paperwork

- Access – small studies, small networks, international collaboration
We Need to Design With Why In Mind