New Developments in the Treatment of Colorectal Cancer

Jonathan Loree, MD, MS, FRCPC
Department of Medical Oncology
BC Cancer – Vancouver Centre
Personalized Medicine

- Currently already part of oncology:
  - What are the risks and benefits for taking chemotherapy based on pathology and the patient’s health
  - Modify doses based on side effects
  - Modify treatment based on the response
Precision Medicine

• Predictive markers – who will or will NOT respond to treatment
• Spare patients side effects/cost
• Examples: KRAS for EGFR therapy
  • A mutation in KRAS determines that the cancer would not respond to treatment
The Changing Face of Oncology

- Clinical Oncology
  - Clinical/disease specific treatment

- Pathologic Oncology
  - Specific therapies for different tumor types

- Molecular Oncology
  - Molecular analysis and targeted agents
Sequencing Costs are Dropping Dramatically!
Current Biomarkers in Colorectal Cancer

- **Trastuzumab + Lapatinib?**
- **Trastuzumab + Pertuzumab?**
- **FOLFOXIRI + Bev?**
- **EGFRi, BRAFi, MEKi?**
- **Cetuximab / Panitumumab**
- **RAS**
  - MT 56%
  - WT 44%
- **HER2**
  - Amplified 4%
  - Normal 96%
- **BRAF**
  - MT 9%
  - WT 91%
- **PIK3CA**
  - MT 23%
  - WT 77%
- **MSI Status**
  - MSI 4%
  - MSS 96%

Loree et al., *Journal of Gastrointestinal Oncology.* (2017)
<table>
<thead>
<tr>
<th>Genes</th>
<th>ERBB2</th>
<th>MSI-H</th>
<th>ERBB3</th>
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<tbody>
<tr>
<td>BRAF</td>
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<td>KRAS</td>
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Personalized OncoGenomics (POG) Program
Personalized oncogenomics: “POG”

• Patients with metastatic (incurable) cancers
• Look at the genome of each person’s cancer
• Identify aberrant pathways that drive that cancer
• Identify drugs that might block those pathways
# Genomic Alterations in Cancer

<table>
<thead>
<tr>
<th>Structural variants</th>
<th>Copy number alterations</th>
<th>Point mutations &amp; indels</th>
<th>Gene expression</th>
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<td>Translocations</td>
<td>Amplifications</td>
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<td>Inversion</td>
<td>LOH</td>
<td>Splice site</td>
<td>Pathways &amp; signatures</td>
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Wild type: AGTGA
Mutant: AGAGA

Adapted from: Roychowdhury et al. Sci Transl Med; 2012
What does this entail?

- Whole genome sequencing = 6 billion bits of information
- Compare cancer to normal cells
- Patterns of RNA expression
- Analyze abnormalities and search for their function in databases
- Sift through scientific literature for evidence to link pathways to specific drugs
1. SDC4::NRG1 fusion uncovered from whole genome and transcriptome data

SDC4::NRG1 fusion

Canonical SDC4::NRG1 structure found

Exon 1 and 2 of SDC4 fused to exon 6-12 of NRG1 (Transcript NRG1-004 ENST00000287842)

2. Fusion highly expressed in the tumour based on mRNA expression

3. Activation of ERBB pathways expected from literature evidence, and supported by pathway analysis based on expression data

4. Afatinib was suggested for ERBB-family targeted inhibition based on integrative analysis and literature evidence

5. Patient responded to recommended therapy

52 yo M with lung cancer

SDC4

NRG1

ERBB2

ERBB3

EGFR

MAPK Pathway

AKT Pathway

Proliferation

(NRG1 EGF domain)
Baseline prior to therapy

+8 weeks with Afatinib
“Liquid Biopsies”

Metastasis/relapse in different organs → Tumor microenvironment → Shedding of CTCs, ctDNAs, cmiRNAs and exosomes from primary tumor site → Cancer patient blood sample to analyze biomarkers

Genomic Landscape of Cell-Free DNA in Patients with Colorectal Cancer

What does this mean for patients?

• Opportunity to participate in world class research that can directly affect patient care
• Opens the door to possibilities beyond “standard of care”
• Gain a better understanding of what causes and drives cancers
Immuno-Oncology
Evolution of Cancer Therapy: Treatment Modalities

- Surgery: 1846
- Chemotherapy: 1946
- Targeted Therapy: 1997
- Radiation Therapy: 1901
- Immuno-Oncology: 2011
Hallmarks of cancer

For Immuno-Oncology therapies (I-O therapies) to work, they generally incorporate an understanding of the mechanisms of tumor escape.\(^2,3\)

I-O therapies seek to modulate the immune system to promote antitumor activity, and counteract this hallmark.\(^4\)

Introduction to the immune system

In order to protect an individual, the immune system:

1. detects the presence of an infection or malignant cells,\(^1\)
2. carries out effector functions to contain or to eliminate the affected cells,\(^1\)
3. performs self-regulation to minimize collateral damage to healthy cells in the body,\(^1\) and
4. generates immunological memory so that subsequent exposures to the same antigen are dealt with efficiently.\(^1\)
T-Cell Checkpoint Regulation

- T-cell responses are regulated through a complex balance of inhibitory (“checkpoint”) and activating signals.
- Tumors can dysregulate checkpoint and activating pathways, and consequently the immune response.
- Targeting checkpoint and activating pathways is an evolving approach to cancer therapy, designed to promote an immune response.

Inhibitory receptors
- CTLA-4
- PD-1

Activating receptors
- CD28
- OX40
- CD137

Agonistic antibodies
- CD28
- OX40
- CD137

Antagonistic (blocking) antibodies
- CTLA-4
- PD-1
- TIM-3
- LAG-3

Who should we treat with immunotherapy?
How is a trial created?

• Idea!
• Pharmaceutical compound
• Develop a protocol
• Obtain funding
• Approval from Health Canada
• Approval from Research Ethics Board
• Trial is offered to patients
Who funds these?

• Little or no institutional or government support
• Investigator Initiated Trials
• Non-profit groups
  • National Cancer Institute of Canada
  • Easter Cooperative Oncology Group
  • South Western Oncology Group, etc.
• Pharmaceutical company
  • Funds for staffing the study (nurses, data collection) and provide the drug
Where does the money go?

• Not a money-making venture

• Costs:
  • Nurse
  • Clerks
  • Booking
  • Data collection
  • No physician compensation

• Biological or special testing – expensive and complex
How to decide whether to participate?

• Opportunity
• Always voluntary
• Detailed discussion with doctor, nurses, friends and family
• It takes time to decide
• Advantages and disadvantages
Metastatic Colorectal Cancer

FOLFOX/FOLFIRI + bevacizumab

Alternate Doublet + biologic*

RAS Wild Type

regorafenib, or clinical trial

anti-EGFR

2014
Precision Medicine is Here!

Metastatic Colorectal Cancer

- **RAS Mutant**
  - Right
  - Side?
  - Left
- **RAS Wild Type**
- **BRAF Mutant**

**2nd Line**

- **FOLFOX/FOLFIRI + bevacizumab**
- **Alternate Doublet + biologic**
- **FOLFOX/FOLFIRI + anti-EGFR**
- **2nd Line**
- **≥ 3rd Line**

- **2nd Line**
- **≥ 3rd Line**

- **Consider FOLFOXIRI + bevacizumab**
- **Consider anti-EGFR +/- cytotoxic**
- **regorafenib, TAS-102, or clinical trial**

*BC Cancer Provincial Health Services Authority*
2018

Precision Medicine is Here!

FOLFOX/FOLFIRI + bevacizumab

RAS Mutant

RAS Wild Type

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Alternate Doublet + biologic*

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Metastatic Colorectal Cancer

Consider FOLFOXIRI + bevacizumab

FOLFOX/FOLFIRI + anti-EGFR

BRAF Mutant

RAS Mutant

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FOLFOX/FOLFIRI + anti-EGFR

regorafenib, TAS-102, or clinical trial

Consider BRAFi + EGFRi +/- MEKi + chemo

2nd Line

≥3rd Line

Immunotherapy

MSI

2nd Line

≥3rd Line

2nd Line

≥3rd Line

2nd Line

≥3rd Line