Precision Medicine: a Primer for the Practicing Internist

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Ripped from the Headlines
Carcinogenesis
AGENTs BINDING TO DNA
(Stop DNA synthesis)
alkylating agents, anti-
tumour antibiotics,
platinum compounds,
miscellaneous others

S phase
DNA synthesis

7 hours

G1 phase
Synthesis of components of DNA

3 hours

M phase
Cell division

1 hour

G2 phase
Synthesis of components for cell division

5 hours

MICROTUBULE INHIBITORS
(Stop cells making components needed to separate)
Vinca alkaloids (vinblastine, vincristine, vinorelbine),
docetaxol, paclitaxel

ANTI-METABOLITES
(Stop cells making the building blocks of DNA)
methotrexate, azathioprine, 6-MP, 6-TG, 5-FU

Resting cells
Carcinogenesis – The Vogelgram

NORMAL COLON  MUCOSA AT RISK  ADENOMAS  CARCINOMA

Mucosa  Submucosa  Muscularis propria

Germ-line (inherited) or somatic (acquired) mutations of cancer suppressor genes ("first hit")

Methylation abnormalities inactivation of normal alleles ("second hit")

Protooncogene mutations

Homozygous loss of additional cancer suppressor genes
Overexpression of COX-2

Additional mutations
Gross chromosomal alterations

APC at 5q21  APC β-catenin  K-RAS at 12p12  p53 at 17p13
LOH at 18q21 (SMAD 2 and 4)

Telomerase, Many genes

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Carcinogenesis –
The Hallmarks of Cancer
Self-Sufficiency in Growth Signals

• Normal cells require mitogenic signals to proliferate
• Tumor cells generate their own signals
# Oncogenes for Self-Sufficiency

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Cancer</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td><strong>ERB B2</strong></td>
<td>Breast cancer</td>
<td>Gene amplification</td>
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<tr>
<td><strong>BCR-ABL</strong></td>
<td>Chronic myelogenous leukemia</td>
<td>t(9;22)</td>
</tr>
<tr>
<td><strong>Ras</strong></td>
<td>Multiple types</td>
<td>Gene mutation</td>
</tr>
<tr>
<td><strong>c-myc</strong></td>
<td>Burkitt lymphoma</td>
<td>t(8;14)</td>
</tr>
</tbody>
</table>
Oncogenes for Self-Sufficiency

1. ERB B2
2. Ras
3. Myc
Gene Chip Technology

- Isolate mRNA
- Convert to cDNA and label with fluorescent molecules
- Mix
- Hybridize to gene chip
- Scan red and green wavelengths

<table>
<thead>
<tr>
<th>Genes</th>
<th>Fluorescence Intensity</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>+++</td>
<td>Up-regulated in neoplastic tissue</td>
</tr>
<tr>
<td>B</td>
<td>++</td>
<td>Unchanged in neoplastic tissue</td>
</tr>
<tr>
<td>C</td>
<td>+</td>
<td>Down-regulated in neoplastic tissue</td>
</tr>
<tr>
<td>D</td>
<td>–</td>
<td>Not expressed in either tissue</td>
</tr>
</tbody>
</table>
Diffuse Large B-Cell Lymphoma

- Most common type of aggressive lymphoma
- Standard therapy cures some of the DLBCL patients
- Remaining patients have a high probability of death within 5 years
- Clinical factors are somewhat predictive of treatment outcome

Key Question: What is the biology underlying the disparate treatment outcome?
Gene Expression Profiling of DLBCL

- 240 patients with Diffuse Large B-cell Lymphoma
- Specimens collected at the time of diagnosis
- All patients received adriamycin-based chemotherapy
- Gene expression was compared to patient outcome

Alizadeh et al., Nature, 2000
Gene Expression Profiling & DLBCL

1) Identified DLBCL subtypes
2) Subtypes reflect the tumor biology
3) Subtypes add to the predictive power of the clinical features
A Clinical Example: Chronic Myelogenous Leukemia
Chronic Myelogenous Leukemia
BCR-ABL in Chronic Myeloid Leukemia

- ABL is a non-receptor tyrosine kinase
- The t(9;22) in CML generates novel fusion proteins, designated BCR-ABL
- The fusion proteins have constitutive tyrosine kinase activity (i.e., normal regulation is lost)
- Imatinib mesylate (Gleevec) was developed to target BCR-ABL
Gleevec in the Treatment of CML

- Its development was the start of molecularly targeted therapies for cancer
- Alternate names: ST1571, imatinib mesylate and imatinib
- Recognizes the ATP binding site of ABL
- Inhibits the constitutive tyrosine kinase activity

Brian Druker, M.D.
Gleevec - Phase III Clinical Trial Results

- Newly diagnosed patients with chronic-phase CML

- Randomly assigned:
  - interferon alpha plus low dose cytarabine (553 patients)
  - imatinib (553 patients)

- 318 of the combination therapy patients eventually crossed over to imatinib

Gleevec - Phase III Clinical Trial Results

### Gleevec Clinical Trial – Adverse Events*

<table>
<thead>
<tr>
<th></th>
<th>Combination Therapy</th>
<th>Gleevec</th>
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</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>4.3%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25.0%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16.5 %</td>
<td>7.8%</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>24.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Depression</td>
<td>12.8%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

*Numbers indicate the percent of patients with the adverse event, Grade 3 or 4*
Precision Medicine in Cancer

Tailoring of the treatment to the individual characteristics of the patient
Personalized Medicine

The good physician treats the disease; the great physician treats the patient who has the disease.

-Sir William Osler
Personalized approaches consider:

- Different personal needs
- Different shared decision-making needs
- Different genetic characteristics
- Different lifestyle factors that may impact manifestation of genomics
Epigenetic Changes

• Alterations in DNA, other than in the primary sequence or in the number of gene loci

• Includes DNA methylation and histone acetylation

• Result in a differences in gene transcription and can contribute to carcinogenesis
Altered Gene Expression
With Epigenetic Changes

Maternal Supplements
(vitamin B12, folic acid, choline)

HDACS: histone deacetylases
Challenges to precision oncology

- Cancer is heterogeneous
  - No one single mutations
- Cancer evolves
  - Testing today may not be the same tomorrow
Research Shift

• Research shift
  – One cancer/multiple mutations: target each mutation
  – One mutation/multiple cancers: target mutation in multiple cancers
Molecular Tumor Boards

• Identify actionable mutation
  – Better outcomes
  – Lower costs
Patient focused interventions

• Basch et al JAMA 2017
  – Monitoring of patient reported outcomes: better outcome
  – Improved survival (p=0.03)
Vision for the Transformation of Medicine in the 21st Century

"I predict that comprehensive, genomics-based health care will become the norm with individualized preventive medicine and early detection of illnesses."

- Elias A. Zerhouni, 2006
How do we think this through?

• Is there a clinical benefit to the person?
  – What is the likelihood of adverse impact? That is, what is the likelihood that the mutation will impair health (PPV: BRCA1/2-60-80% lifetime risk)
  – Is there an intervention?
  – Will the intervention have a health benefit?

• Is there an impact on life decisions?

• Is it impactful for others?
  – What are the probabilities?
Beyond monogenic

• Testing of panels of genes
• Developing polygenic risk models
• Goal: risk profiles with tailored interventions
Whose job is precision medicine?

• Public health: National screening programs
• Clinical geneticist: screening
• Oncologist: cancer risk
• Pathologist: for specific testing
• Primary care physician: to identify risk, educate/counsel, and screen
  – The team!
Barriers to thoughtful guidance

• Lack of knowledge
• Lack of best practices/guidelines
• Increased prevalence of direct to consumer testing
• Rapidly changing landscape
Resources

• Gen-Equip: Equipping European Primary Care Health Professionals to Deal with Genetics

• Genetic education for primary care physicians

https://www.primarycaregenetics.org/?page_id=109&lang=en
Thank you!

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