Cancer genes to drugs

Linda Lowe-Krentz
September 11, 2015
Traditional Chemotherapy

• The earliest of these (before 1970) led to a Nobel Prize in Physiology and Medicine in 1988.
  – (James Black, Gertrude Elion and George Hitchings)

• The first outcomes of the War on Cancer
  – Started with funding legislation in 1971

• Aimed at killing rapidly growing cells

• Toxic to normal cells that need to proliferate

• For solid tumors, these drugs remain in use and have had spectacular success in a few cancers.

• Tumor removal (when possible) is still preferred.
Early Chemotherapy

- Targets – rapidly growing cells.

Small molecules → ATP, etc.
NTP → dNTP
dNTPs → DNA
A purine analog

6-Mercaptopurine. The molecule inhibits several purine synthesis steps.

With allopurinol (above, to block degradation) 6-mercaptopurine stays in the body long enough to be effective.
Drugs targeted to gene defects?

- Types of genes – reminder
- Accelerators – often Kinase enzymes
  - Add a phosphate to other proteins or molecules
- Receptors (exposed on the cell surface)
  - Recognize growth signals from outside
- Factors that alter gene expression
  - Bind to specific regions of the DNA
- Brakes (tumor suppressors)
  - DNA repair and damage recognition
  - Enzymes that turn off signals
Small molecule drugs

- Small molecule inhibitors.
- These are often termed “ib”.
- They are usually specific.
- Some of these small molecule drugs are initially effective, but cancer cells can sometimes acquire mutations that make them less effective over time.
Gleevec

Instead of blocking ATP binding, it stabilizes an inactive conformation

Chronic myelogenous leukemia chromosome rearrangement between chromosomes 9 and 22.
Lots of accelerators are enzymes

- Tarceva. This drug blocks ATP from binding to specific kinase enzymes.
Blocking protein-protein interactions

- Other driver (oncogene and tumor suppressor) mutations alter protein-protein interactions. Generally these are considered harder to block with small drugs.
Some cancer cells make pumps to dump the drugs back out.
Drug Antibodies

- Antibodies against growth factor receptors or mutated overactive forms of the receptors.

- Antibodies might recruit the immune system
- Antibodies might block ligand binding to remaining receptors
- Antibodies might block receptor function
Blocking blood vessels

- Avastin – an antibody based blocking agent, survival for one to several months longer.

(F) pericytes provide survival functions to endothelial cells

endothelial cells are partially resistant to VEGF-R inhibition and are less sensitive to chemotherapy

targeting pericytes e.g., via PDGF receptor inhibitors

impaired support or protection by pericytes

endothelial cells are very sensitive to VEGF-R inhibition and chemotherapy

Figure 13.46 The Biology of Cancer (© Garland Science 2014)
65 or more breast cancer drugs

- Trastuzumab – Herceptin – induces cell death after binding to the overexpressed receptor
- Triple negative (progesterone, estrogen, Her2)

Biology of Cancer, Weinberg

http://www.cancer.gov/about-cancer/treatment/drugs/breast#2
Let’s talk

• Based on what I just said – what do you think someone might want to know about their tumor before getting treatment?

• Who should have access to genetic and protein expression information?

• Does that differ from access to genetic information generally?
Long term goals

• Ultimately, targeting the stem cells that are cancerous rather than only the most rapidly growing cells will be important.
• Development of specific drugs based on specific cancer situations is also continuing (personalized medicine).
• http://www.cancer.gov/