A View to the Future: The Development of Targeted Therapy for Melanoma

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How Do We Treat Melanoma?

Localized Disease (Skin)
- Surgery

Regional Disease (Lymph Nodes)
- Surgery
  +/- Systemic Therapy

Distant Disease (Lung, Liver, CNS)
- Systemic Therapy
  - Immunotherapy
  - Chemotherapy
  - NEW: Targeted Therapy
A Brief History of Chemotherapy

• 1920s: Soldiers exposed to nitrogen mustards in WWI developed infections due to loss of their white blood cells (immune system)
  – Concept: Can we treat cancer of white blood cells with similar agents?
• 1946 First published trial of successful treatment of cancer with chemotherapy
• 1950s-1980s Development of most standard chemotherapy drugs
• 1977 Discovery of the First Oncogene
  – Oncogene: Normal gene that becomes mutated \(\rightarrow\) converts normal cell to cancer
  – Beginning of research that identifies the molecules that cause cancer
• 1977 – 2009 Identification of mutations that occur in most types of cancer

‘Targeted Therapy’: Treat cancer by targeting the genes that are activated in cancer cells
Successful Targeted Therapy: CML

- CML: Biology to Therapy
  - 1960s Philadelphia chromosome
  - 1980s BCR/ABL fusion protein
  - 1990s Imatinib (Gleevec) characterized as BCR/ABL inhibitor
  - 2001 Imatinib = standard of care
    - > 90% response rate

Key: Understanding and Inhibiting a Genetic Event Present in ~All CML Patients

Philadelphia Chromosome t(9;22)

Imatinib (Gleevec) for CML

Targeted Therapy for Breast Cancer

• **Hormone Receptor (+)**
  – Treatment: **Hormonal Therapy**

• **Hormone Receptor (-)**
  – Treatment: **Chemotherapy**

• **HER2/Neu Breast Cancer**
  – Growth factor receptor
  – Amplified/Overexpressed in some breast cancers
  – More aggressive disease, less responsive to therapy

• **Trastuzumab (Herceptin)**
  – monoclonal antibody against HER2/Neu
  – Increases efficacy of chemotherapy in the metastatic and adjuvant settings
    • **BUT** Only effective in patients with HER2/neu amplification

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**Adjuvant Trastuzumab +/- Chemotherapy In HER2/Neu Breast Cancer**

[Graph showing survival rates with and without Trastuzumab]

Romond, NEJM 353: 1673, 2005

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**Breast Cancer: Key**
Choosing the Right Treatment for the Right Patient
The Development of Successful Targeted Therapy for Cancer

Success will depend upon
- Identifying the right targets to inhibit
- Selecting patients who will benefit
- Determining how to select an effective dose for each patient
- Developing combinations that increase efficacy while minimizing toxicity

Using this information to identify the best treatment for each patient, i.e. Personalized Therapy for Cancer
Melanoma: Targets for Therapy

• >80% of melanomas have activating mutations in kinase signaling pathways
  – BRAF
  – NRAS
  – PI3K
  – AKT
  – PTEN
  – C-KIT
  – GNAQ

2009: Targeted Therapy Trials for Patients with Specific Mutations

Mutations by Sites

- Cutaneous Melanoma (Skin)
  - 60% BRAF Mutations
  - 20% NRAS Mutations

- Acral Melanoma (palms, soles)
  - 20% NRAS Mutations

- Mucosal Melanoma (intestines, vaginal)
  - <10% BRAF
  - <10% NRAS
  - Up to 40% c-KIT

- Chronic-sun damaged skin (face)
  - Up to 40% c-KIT

- Uveal (Eye)
  - 50% GNAQ
Targeting BRAF-Mutant Melanoma

PLX4032

- Oral small molecule inhibitor of mutant BRAF
  - BRAF Mutations: ~60% cutaneous melanomas
- Side Effects
  - Fatigue, rash
- Preliminary Results: Active in BRAF-Mutant Melanoma

Before Treatment

Day 0

Day + 15

PET Scan

Flaherty, ASCO Ann Meeting, 2009

Phase I (n=16)
80% Patients with a BRAF Mutation Achieved Tumor Shrinkage
Targeting C-KIT Mutant Melanoma

- **C-KIT Mutations**
  - Very rare in cutaneous
  - Up to 40% of mucosal, acral, and CSD skin

- **Imatinib (Gleevec)**
  - C-KIT Inhibitor
  - FDA-Approved for CML, GIST
  - Previous Trials in Melanoma: ~1% Response
    - **BUT: Did not select for patients with C-KIT Mutation**

- **2009 ASCO Annual Meeting**
  40% Response Rate in Melanoma Patients with C-KIT Mutation or Amplification

Hodi, J Clin Oncol, 2008
Targeted Therapy: Conclusions and Future Directions
Targeted Therapy for Melanoma: Future Directions

• Can we identify more/better targets?

• How Can We Increase the Rate and Duration of Clinical Responses?
  – Picking the right patient for the right inhibitor
  – Combining agents together
    • Targeted Therapies, Chemotherapy, Immunotherapy

• How Do We Overcome Resistance?
  – Clinic: Biopsies from Patients Who Develop Resistance
A View to the Future…

Today

Clinical Research

Laboratory Research

The (Near) Future…

Treatment 1

Treatment 2

Treatment 3

Treatment 4

Treatment 5
Thank you for your attention!

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