iSBTc Mini-symposium: Biologics Effects of Targeted Therapeutics

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Evolution of Cancer Therapy

- **1800s** - Surgery
- **1920s** - Radiation Therapy
- **1970s** - Cytotoxic chemotheraphy
- **1985** - Immunotherapy
CANCER BREAKTHROUGH

INTERLEUKIN-2, HUMAN
(des-alanyl, serine-125)

Preparation
Lyophilized Preparations
Store 2-8°C — For single
use only — Reconstitute with
sterile Water for Injection

Cetus Corp.'s tumor-zapping
Interleukin-2
COMPACT DISCS: A SONIC BOOM

Newsweek

CANCER AND INTERLEUKIN-2

The Search for a Cure

Dr. Steven Rosenberg
at the National Cancer Institute
Evolution of Cancer Therapy

- 1880 - Surgery
- 1920 - Radiation Therapy
- 1970s - Cytotoxic chemotherapy
- 1985 - Immunotherapy
- 2000 - Targeted Therapy
Essential Alterations in Cell Physiology in Malignancy

Limitless potential for replication

Self-sufficiency in growth signals

Evading apoptosis

Insensitivity to anti-growth signals

Sustained angiogenesis

Tissue invasion & metastasis

Hanahan & Weinberg, Cell 100:57 (2000)
Targets and Tools

Receptor Tyrosine Kinase

Growth Factor Mutation, Translocation, Amplification

Ras  mutation - active

Raf

MEK

PI3K

Akt  mutation - inactive

mTOR

PTEN

CCI-779

Cell Proliferation

Survival

 Migration

Angiogenesis

Antibody to Receptor
e.g. Herceptin(R)
EGFR antibody

FTI
e.g. R115777

Raf Inhibitor
e.g. sorafenib

MEK Inhibitor
e.g. CI-1040

RTK Inhibitor
e.g. ZD1839

CDK Inhibitor
e.g. Flavopiridol

BCL-2 Inhibitor
e.g. G3139

MET Inhibitor

Src Inhibitor
e.g. Bevacizumab

VEGF Inhibitor
Targeted Therapy: Promise and Progress

♦ Antibodies
  • transtuzimab, bevacizumab, rituximab, cetuximab

♦ Small molecules
  • C-Kit- imatinib
  • VEGFR: sunitinib, sorafenib
  • EGFR: gefitinib, erlotinib
  • mTOR: Temsirolimus

♦ Demethylating agents
  • decitabene
"Bummer of a birthmark, Hal"
Targeted Therapy: Issues (1)

- Pathways are relevant to more than just tumor cells
  - Endothelium
  - Pericytes
  - Immune cells- DCs, Tcells, Tregs

- Small molecule RTK inhibitors are less selective than originally anticipated
  - Sorafenib, sunitinib
  - Herceptin- VEGF

- Blocking some targets may produce pro-survival effects
  - GSK3β activation
  - Compensatory increases in upstream molecules -
    - HIF related proteins with VEGFR inhibition
    - AKT with mTOR blockade

- Cell death may trigger distinct biologic pathways
Targeted Therapy: Issues

Off target biologic effects of targeted therapies may influence the tolerability, activity duration of benefit, and ability to combine these agents.
Targeted Therapy: Issues (2)

- Treatments are largely non-curative
- Durable complete responses will likely require tumor specific immune activation
- Push for combination targeted therapy and biologic therapy
Mini-Symposium: Goals

- Describe the current knowledge regarding various off-target effects of current therapies
- Identify most relevant issues and current gaps in knowledge base
- Discuss optimal means of obtaining necessary information

- Use above information to:
  - Inform and influence basic science efforts and discussions
  - Rationally design combination treatment regimens
  - Optimally design most relevant correlative studies in the context of current and future treatments
Save the Date
21st Annual Meeting
October 26-29, 2006
Hyatt Regency Century Plaza
Century City, Los Angeles, California

International Society for Biological Therapy of Cancer
22nd Annual Meeting
November 1-4, 2007 • Boston, Massachusetts
Seaport World Trade Center

International Society for Biological Therapy of Cancer

iSBTc
Save the Date
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