TARGETED THERAPY FOR CHILDHOOD CANCERS

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Introduction

• The area of molecularly targeted cancer therapeutics is generating tremendous interest.

• Most clinical research in this field to date has focused on adult patients.

• Some molecularly-targeted therapies with promise for treatment of pediatric malignancies are now in clinical trials.
What is Targeted Cancer Therapy?

- Targeted cancer therapy can be defined as therapy designed to interfere with a specific molecular pathway important in the genesis and/or maintenance of the malignant phenotype.
How does it differ from Chemotherapy?

• Traditional cancer chemotherapy agents interfere with some aspect of the global cellular machinery that is shared by malignant and non-malignant cells.

• The promise of targeted therapy is that it will more efficiently eradicate malignant cells while leaving host cells largely unaffected.

• Translating that promise into reality is however a very challenging task!
Why is the Development of Targeted Therapy so Important in Pediatric Oncology?
Childhood Cancer Mortality

Despite dramatic improvement in outcome, cancer still remains the leading cause of death in children and adolescents.
Childhood ALL

Survival has increased from 5% to > 80%
However, Not All Cancers are being Cured!

- Cancers with current 5 year survival rates $\leq 50$
  - AML
  - Relapsed ALL
  - ALL with specific structural abnormalities
    - $t(9;22)$, $t(4;11)$, MLL gene rearrangements
  - Biologically unfavorable sub-groups of neuroblastoma
    - Age $> 1$ year, chromosome 1p deletions, amplified N-MYC
  - Supratentorial high grade and brain stem gliomas
  - Metastatic sarcomas of the bone and soft tissue
There are Challenges to Improving Cure Rate

- A subset of pediatric tumors still have a poor outcome

- Incomplete understanding of the mechanisms of intrinsic or acquired resistance of certain tumors to therapy

- Widely variable host differences in distribution, metabolic rate and clearance of pharmacological agents

- Acute and long term toxicity associated with conventional, cytotoxic chemotherapy
We believe Development of Targeted Therapy is Important in Pediatric Oncology

• Improving overall survival and reducing morbidity are major goals of childhood cancer research
• Increased survival in childhood cancer could be achieved by inhibiting specific cancer targets
• Many leukemias, lymphomas and solid tumors of childhood contain tumor-specific chromosomal translocations that lead to stably expressed ‘fusion proteins’
  • These *fusion proteins* modulate the pathogenesis and maintenance of the tumor phenotype
• They make ideal tumor-specific therapeutic targets
What is an ideal Tumor Antigen Target?

• A molecular therapeutic target for a given cancer

1. Must be present in all cases of the disease under consideration for targeted therapy
2. Must be differentially expressed on the tumor versus normal cells
3. Must be required for critical cell biological function and/or survival
4. Patient tumor tissue must express the target at sufficient levels to be biologically meaningful
5. Inhibition of the tumor phenotype must be shown by mutation or inactivation of the molecular target
The Cancer Model

• Cancer is defined as an uncontrolled proliferation of cells
  – Results from the transformation of a normal cell to a cancer cell

• Cancer is not the result of a single random event

• Series of steps that lead to the development of a primary tumor, its growth, progression and spread to distant parts of the body

• These steps are genetic and epigenetic
  – Occur in the tumor cell
  – Also in normal cells located in the microenvironment of the tumor
Pathological Basis of Disease
Early Steps of Tumor Formation

- Alteration in the genes that control cell growth and death and cell cycle control

- 2 classes of genes contribute to tumor development and progression
  - Oncogenes - activation
  - Tumor suppressor genes – loss of function
Characteristics of Cancer Cells

1. MANIPULATION OF GROWTH SIGNALING

   • Cells can become independent of external signals
   • Amplify available growth signals
   • Produce both the signal and receptor for a growth factor
   • Both mechanisms result in tumor growth and progression

   • Insulin-like growth factors (IGF’s) and their receptor (IGF-R) represent a signaling pathway that tumor cells can use to become self sufficient

   • Targeted therapy being developed based on blockade of growth factor receptor signaling
Cell Signaling
Characteristics of Cancer Cells

2. HAVE THE ABILITY TO RESIST THE MECHANISMS THAT CONTROL OR SUPPRESS CELL PROLIFERATION

• These controls lie within the regulation of the cell cycle

• Movement of cells through the cell cycle is regulated at control check points
  – RB gene controls movement from G1 to S phase
  – Mutations in RB gene are very common in cancer

• Transition through phases of the cell cycle occurs through interactions between cyclins and cyclin dependant kinases
  – Mutations in cyclins, cdk’s and inhibitors
Genes for CDK-molecules and cyclins can function as oncogenes. CDK-molecules and cyclins collaborate with products of tumor suppressor genes e.g. RB and p53.
3. CANCER CELLS EVADE APOPTOSIS

- Caspases are proteolytic enzymes that are responsible for cell death
- Normal apoptotic pathway function is required to detect DNA damage
  • Defects in detection of DNA damage – p53
- Defects in apoptosis initiation – Bcl-2 family proteins
- Defects in apoptosis execution – caspases
- Defective apoptosis initiation due to Bcl-2 overexpression is thought to be a mechanism of chemotherapy resistance

• Therapeutic targeted therapy in development for anti-apoptotic cancers
Apoptosis

Programmed cell death

Intrinsic and Extrinsic pathways leading to apoptosis
Mutations in P53 and bcl-2
Characteristics of Cancer Cells

4. FAILURE TO FOLLOW APPROPRIATE SIGNALS OF AGING (SENESCEENCE)

• Telomeres regulate the number of divisions an individual cell will undergo during its life
  – At a critical length, senescence followed by apoptosis
  – Tumor cells evade cell death by increased telomerase activity and become immortal

• Telomerase is a potential therapeutic target because of its specificity to malignant cells
Senescence

Diagram showing the process of senescence:
- Short capped telomere
- At DNA replication
- Extended telomere
- G4 ligand
- DNA replication
- Critically shortened telomere
- Senescence/apoptosis
Characteristics of Cancer Cells

5. METASTASES IS THE MOST SIGNIFICANT PROBLEM ASSOCIATED WITH CANCER

• Key factor for metastases
  – is the creation of new blood vessels – angiogenesis
  – Subversion of existing blood vessels to the cancer

• Normally, there is controlled endothelial cell proliferation maintained by the proteins that activate or antagonize endothelial cell

• Endothelial cells or endothelial progenitors are activated by tumor-derived growth factors
  – Survival, motility, invasion, differentiation and organization of endothelial cells
  – New capillaries at tumor site are formed
Angiogenesis

• Evidence that angiogenesis is important in the biology of metastases
  – Vascularity of a primary tumor has been correlated with metastatic behavior
  – MRI and other imaging studies have correlated vascularity with poor outcome
  – Expression of angiogenesis associated growth factors and their receptors (VEGF-R, FGF-R, PDGF-R) in serum and tumors have been correlated with outcome

• Anti-angiogenesis agents are attractive targeted therapeutic agents
## Current COG / NCI Sponsored Clinical Trials in Pediatrics

<table>
<thead>
<tr>
<th>Type of Target</th>
<th>Specific target</th>
<th>Agent name</th>
<th>Type of agent</th>
<th>Proposed mechanism</th>
<th>Tumor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosine kinases</td>
<td>BCR/ABL c-KIT HER2</td>
<td>Imatinib (Gleevec) Trastuzumab (Herceptin)</td>
<td>Small molecule Small molecule mAb</td>
<td>Inhibits oncogenic kinase Blocks ligand binding</td>
<td>CML, Ph+ ALL Sarcoma Osteosarcoma</td>
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<tr>
<td>Surface markers</td>
<td>CD20 CD20 CD33 GD2</td>
<td>Rituximab Y-Ibritumomab Gemtuzumab Anti-GD2 (ch14.18)</td>
<td>mAb mAb-conjugate mAb-conjugate mAb</td>
<td>Opsonizes tumor cells (1,4) Delivers toxin (2,3)</td>
<td>NHL, HD, PTLD (1,2) AML Neuroblastoma</td>
</tr>
<tr>
<td>Anti-apoptotic proteins</td>
<td>Bcl-2 PML-RARα EWS-FLI-1 PAX-FK-HR</td>
<td>G3139 ATRA Peptide pulsed APC’s (3,4)</td>
<td>mRNA antisense Retinoid Cellular Cellular</td>
<td>Apoptosis Differentiation Immuno-therapy (3,4)</td>
<td>Solid tumors APL Ewings tumors Rhabdomyosar</td>
</tr>
<tr>
<td>Farnesyl transferase inhibitors</td>
<td>RAS</td>
<td>R115777 (Tipifarnib)</td>
<td>Small molecule</td>
<td>Prevents RAS activation</td>
<td>Leukemia, solid tumors</td>
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Agents with a proven track record of efficacy in pediatric patients

- All *trans*-retinoic acid (ATRA) in APL
  - Randomized controlled trial
- 3F8 – monoclonal antibody in refractory neuroblastoma
  - Phase II trial with GM-CSF for MRD in bone marrow

Currently in trials:
- Imatinib (Gleevec) in Ph + CML and ALL
  - Preliminary results look promising
- Gemtuzumab (Mylotarg) for AML
  - Phase III trial with chemotherapy
- Rituximab (Rituxan) for NHL, PTLD
  - Phase III trial
Cancer Stem-Cells

- It is becoming clear that many malignancies arise from a rare population of cells that can self-renew and sustain the tumor.

- These ‘cancer stem cells’ are often biologically different from the bulk of the differentiated cancer cells that characterize the disease.

- Eradication of this stem-cell compartment of the tumor also, may be essential to achieve long lasting remissions and even cure.
Cancer Stem-Cells

• Stem cells have 3 unique properties
  – Capacity for self renewal
  – Capability to develop into multiple lineages
  – Potential to develop into any cell in the tumor population

• Proliferative ability to drive continued expansion of the population of malignant cells

• Biologically distinct ‘tumor initiating’ cells have been identified in cancers of the hematopoietic system, brain and breast
Figure 1. Examples of Stem Cells Found in Adult Somatic Tissues.

Neural stem cells generate cells in the central nervous system (Panel A). Hematopoietic stem cells generate mature blood cells (Panel B). Mammary stem cells generate breast tissue (Panel C).
Stem-Cell Systems
Scenarios involving Cancer Stem-cells
Cancer Stem-Cells in the Hematopoietic System

- Malignancies that appear to arise from cancer stem-cells include
  - Chronic Myeloid Leukemia
  - Acute Myeloid Leukemia
  - Acute Lymphoblastic Leukemia
  - Myelodysplastic Syndrome
Targeted therapy in Ph + Leukemia
CML and ALL

- CML accounts for 2-3% of childhood leukemias
- Characterized by the presence of the Philadelphia (Ph) chromosome
- Ph chromosome results from a balanced t(9;22) translocation that leads to the expression of the BCR-ABL fusion protein
- BCR-ABL encodes a 210 kilodalton dysregulated tyrosinase kinase domain seen in > 90% childhood and adult CML
- Ph chromosome may also encode a 190 kilodalton dysregulated tyrosinase kinase seen in 2-5% of childhood ALL
Philadelphia Chromosome

The translocated \textit{abl} gene inserts into the \textit{bcr} gene. The two genes fuse. The altered \textit{abl} gene functions improperly, resulting in CML.
Imatinib mesylate (Gleevec)

• Imatinib mesylate (Gleevec) is the first FDA approved drug developed to treat cancer by inhibition of a chimeric tyrosinase kinase
• Single drug therapy in Ph+ CML
• With intensive chemotherapy in Ph+ ALL
• Dosage 260 – 570 mg/m2 is safe and effective
• Minimal side effects
• PROBLEM – RESISTANCE TO IMATINIB
Remission and Relapse

• Initial response rate 60-70%
• Cytogenetic and RT-PCR remission achieved by 287 days (224-366 days)
• Relapses can occur due to BCR-ABL mutations by 2.2 months
• Allogeneic bone marrow transplant is still the most promising strategy for Ph+ ALL
• Dasatinib is a bcr-abl inhibitor used for imatinib resistant CML
• Nilotinib has a favorable safety profile as well
• Future??
  – BCR-ABL inhibitor + conventional chemotherapy?
Fig. 1. Schematic of targets for small molecule drugs in myeloid leukemias. RTK: receptor tyrosine kinases; NRTK: non-receptor tyrosine kinases.
Targeted therapy in Acute Promelocytic Leukemia (APL)

- t (15;17) and t(11;17) are the most common translocations in APL
- Fusion protein
  - retinoic acid receptor – α chain
  - to
  - the PML gene (PML – RAR α)
  - APL zinc finger protein (PLZF/RARα)
- ATRA is a retinoic acid receptor ligand that causes differentiation
- 80% survival in patients achieved in PML/RARα
- Minimal complications including bleeding
- PLZF/RARα insensitive to ATRA
- ATRA resistant patients may receive Arsenic trioxide, an apoptosis inducing agent
Acute Promyelocytic Leukemia

\[ t(15;17)(q22;q12) \]

↑

ATRA, Arsenic Trioxide
Role of Monoclonal Antibodies in the Treatment of B-Cell NHL in Children

- B-cell lymphomas make up 6% of all NHL in children and adolescents
- 2/3 have Burkitt or Burkitt-like histology
- 1/3 have a diffuse large B-cell lymphoma (DLBCL)
- 25% patients have localized disease
- 75% have advanced disease
- 5 year EFS for limited disease is 90 -99%
- 4 year EFS for advanced disease is 60 -90%
- Mediastinal B-cell lymphoma and combined BM and CNS disease have a 4 year EFS of 60%
- Recurrent B-cell lymphoma has a 10 -30% EFS
Which B-cell lymphoma patients will benefit from targeted therapy?

- Patients with limited disease
  - Reduce toxicity from chemotherapy
  - Maintain high survival rate of 90-99%
  - Decrease morbidity and days of hospitalization

- Patients with advanced, recurrent disease or mediastinal lymphoma
  - Add targeted monoclonal antibody therapy to improve survival
Monoclonal Antibody therapy for B-cell lymphoma

- **Rituximab (anti CD20)**
  - Naked chimeric antibody to CD20
  - Improved survival in adults with CHOP – R
  - Currently in COG trials for newly diagnosed and recurrent B-NHL
- **Ibritumomab –tiuxetan Y$_{90}$ (anti CD20)**
  - Radioimmunoconjugate antibody to CD20
  - Recently approved in adults with refractory/recurrent B-NHL
  - Currently in Phase I trials in children with refractory/recurrent B-NHL
- **Epratuzumab (anti CD22)**
  - > 98% B-NHL and 95% precursor-B ALL in children express CD22
  - Phase I trial with re-induction therapy for children with Precursor-B ALL
- **Alemtuzumab (CD52)**
  - 80% childhood Burkitt’s lymphoma and 93% DLBCL express CD52
  - Phase II study as a single agent and in combination with 6MP/MTX
Summary

• Targeted therapy has the potential to enhance the efficacy of conventional therapy while reducing toxicity
• The application of targeted therapy is beginning to occur in pediatric malignancies in the context of clinical trials
• The success of any individual therapy will depend on its specificity, its ability to be combined with other therapies and the expression of its target in the cancer stem cell