Unique Clinical and Biological Features of Pediatric Cancer: Impact on Further Treatment Advances – Turning Challenges into Opportunities

Gregory Reaman, M.D.
Associate Director, Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research
Disclosures and Disclaimer

- No financial relationships to disclose.
- Limited discussion of off label or investigational use of specific products/devices.
- The views expressed are those of the speaker and do not necessarily represent the opinion of the Food and Drug Administration.
Progress in Childhood Cancer

• Achieved through multi-center, multi-disciplinary, clinical and translational research
• Unique clinical practice/patient management model – highly integrated clinical care/clinical research
• Highly effective national clinical trials infrastructure
• Despite differences in biology, therapeutic product development has highly leveraged adult discovery/development
Childhood Cancer remains a problem

- Progress continues, but …
- Nearly 2000 children continue to die each year,
- Advances not seen for some diseases and stages of disease
- Some of those who survive have reduced QOL due to the effects of their cancer and its treatment

~ 2000 children and adolescents die of cancer each year in the US

Challenges to Therapeutic Research - Drug Development: Scientific and Pragmatic

- Low incidence disease (1% of U.S. Cancer diagnoses; 15,000/year)
- Small study populations for clinical trials
- Pharmacology considerations and effect of normal development/maturation: organ function and metabolic enzymes
- Formulation requirements for pediatric use
Challenges: (cont’d)

• Current industry R&D models not favorable to pediatric drug development
• Insufficient pre-clinical models and testing programs
• Long term availability of promising products
• Different perspectives on “clinical benefit” – prolonging survival vs. cure
• Approaching cancer as a “chronic disease” – not a pediatric perspective
Advances in Cancer Biology

• Unprecedented pace of discovery in genomic medicine and tumor biology → molecular pathogenesis of cancer
• Genetic mutations and amplifications involving key signaling pathways responsible for cell proliferation in specific cancers have emerged as validated targets for drug development
  – imatinib (Gleevec) in CML and Ph+ALL
  – crizotinib (Xalkori) in ALK+ NSCLC
  – vemurafenib (Zelboraf) in melanoma
  – vismodegib (Erivedge) in basal cell carcinoma
Cancer Biology

• Multiple molecularly targeted therapies (53 as of 2/19/2015) approved for advanced stage or recalcitrant adult cancers based on favorable benefit: risk considerations – none yet demonstrated to be curative

• Personalized or PRECISION Medicine has largely benefited adults with cancer
Cancer Biology (cont’d)

• Molecular drivers (validated targets) of cancers are not universal across specific histologic types of cancer – multiple “orphan” designations of what were once considered “common” adult cancers

• Genomic abnormalities are also not unique to specific histologic types and multiple biomarkers may exist for the same cancers “Master” (umbrella or basket) trials for genomically characterized tumors – Lung Cancer, Breast, NCI MATCH Trial
Progress in Childhood Cancer Genomics

- The vast majority of recurring genomic alterations for childhood cancers have been identified.
- This is the result of team science efforts led by groups such as the NCI TARGET Initiative, the St. Jude Children's Research Hospital - Washington University Pediatric Cancer Genome Project, and multiple others.
  - TARGET alone sequenced ~1,200 cases (primarily using WGS) and sequenced ~2,800 additional cases with frequency validation of 400 selected genes.
Genomics Lessons Learned

• Childhood cancers have fewer gene mutations than adult cancers
• Many childhood cancers are driven by mutations that are rare in adult cancers:
  – Histone mutations for DIPG and high-grade glioma
  – Distinctive fusion genes for pediatric sarcomas and some brain tumors
• Most childhood cancers at diagnosis lack mutations in genes that are relevant to approved molecularly targeted agents or those being developed for adult cancers
Challenges in Childhood Cancer Research

- The (fortunately) relatively small numbers of patients with any specific cancer creates challenges in conducting clinical trials to reliably identify more effective treatments:
  - Complicated by further subdividing of diagnoses based on their genomic characteristics
  - Example of medulloblastoma: now being divided into 4 subtypes, each potentially with its own therapeutic strategy
  - Example of high-grade glioma: only 5-10% have BRAF genomic alterations; evaluations of BRAF inhibitors challenging for this population
Medulloblastoma: From one disease to four distinctive subtypes
<table>
<thead>
<tr>
<th>Clinical features</th>
<th>WNT (~10%)</th>
<th>SHH (~30%)</th>
<th>Group 3 (~25%)</th>
<th>Group 4 (~35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender ratio (M/F)</td>
<td>~1/1</td>
<td>~1.5/1</td>
<td>~2/1</td>
<td>~3/1</td>
</tr>
<tr>
<td>Age distribution</td>
<td><img src="image1" alt="Incidence graph" /></td>
<td><img src="image2" alt="Incidence graph" /></td>
<td><img src="image3" alt="Incidence graph" /></td>
<td><img src="image4" alt="Incidence graph" /></td>
</tr>
<tr>
<td>Histology</td>
<td>Classic; very rare LCA</td>
<td>Classic &gt; desmoplastic/nodular &gt; LCA &gt; MBEN</td>
<td>Classic &gt; LCA</td>
<td>Classic; rarely LCA</td>
</tr>
<tr>
<td>Metastasis at diagnosis</td>
<td>~5–10%</td>
<td>~15–20%</td>
<td>~40–45%</td>
<td>~35–40%</td>
</tr>
<tr>
<td>Overall survival (5 years)</td>
<td>~95%</td>
<td>~75%</td>
<td>~50%</td>
<td>~75%</td>
</tr>
<tr>
<td>Proposed cell of origin</td>
<td>Lower rhombic lip progenitor cells</td>
<td>CGNPs of the EGL and cochlear nucleus; neural stem cells of the SVZ</td>
<td>Prominin 1+, lineage- neural stem cells; CGNPs of the EGL</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Genomic features**

**Cytogenetics**

- CTNNB1 (90.6%)
- DDX3X (50%)
- SMARCA4 (26.3%)
- MLL2 (12.5%)
- TP53 (12.5%)

- PTCH1 (28%)
- TP53 (13.6%)
- MLL2 (12.9%)
- DDX3X (11.7%)
- MYCN (8.2%)
- BGOR (3%)
- LDB1 (6.9%)
- TCF4 (5.5%)
- GLI2 (5.2%)

- MYC (16.7%)
- PVT1 (11.9%)
- SMARCA4 (10.5%)
- OTX2 (7.7%)
- CTDNEP1 (4.6%)
- LRP1B (4.6%)
- MLL2 (4%)

- KDM6A (13%)
- SNCAIP (10.4%)
- MYCN (6.3%)
- MLL3 (5.3%)
- CDK6 (4.7%)
- ZMYM3 (3.7%)
Challenges in Childhood Cancer Research

• No obvious opportunities for prevention and early detection

• Relatively few driver mutations present at diagnosis that are addressed by currently available targeted agents.

• Known driver mutations of pediatric tumors have little interest to pharmaceutical companies:
  – EWS-FLI1 (Ewing sarcoma)
  – Histone K27 mutations (high-grade gliomas)
  – PAX-FKHR (alveolar rhabdomyosarcoma)
Addressing “Re-purposing” of Targeted Therapy to Facilitate Pediatric Drug Development

• Maximizing regulatory authority provided by current legislative initiatives to address “indication-based” “waivers”

• Rational prioritization of products to be evaluated

• Re-design of early phase studies toxicity-dose selection-activity signals- expansion cohort for efficacy

• Early communication/collaboration – Investigators/Patients/Industry/Regulators
Addressing the Challenge of New Drug Development when No Adult Indication Exists

- No current legislative fix
- Substantial and early incentives to industry require expansion
- Continued success of current special initiatives (Pediatric Rare Disease Priority Review Vouchers) – subject to dilution of benefit and competing priority review mechanisms/”early” development incentive lacking
- Public/Private Partnerships – Role of NCI
  - Ch 14.18 (dinutuximab) in NBL
  - AMG479 in Ewing sarcoma
Opportunities for Precision Medicine in Pediatric Cancer

• ABL tyrosine kinase inhibitors in high risk ALL subpopulation (Ph+-like ALL)
• Pediatric MATCH (Molecular Analysis for Therapeutic Choice) Study
• Genomically-selected targeted agent approaches under development in neuroblastoma, medulloblastoma, and AML
Promising Approaches to Cancer Therapy: Role of Immunity

- Monoclonal Antibodies
  - BiTE (Bi-specific T-cell Engager)
- Immuno-conjugates (Brentuximab-vedotin, Adcetris)
- Enhancing host effector T-cell (anti-tumor cell) function
  - Check-point inhibitors – CTLA4 (ipilimumab, Yervoy)
  - PD1/PDL1 axis (pembrolizumab, Keytruda: nivolumab, Opdivo)
- Engineered cell therapy
  - CAR T-cells (CTL 019 and others)
Monoclonal Antibody (ch14.18) in Neuroblastoma

Improved Event-Free Survival (EFS) in children randomized to ImmRx vs CisRA alone
Event-free Survival

Years from Post-transplant Randomization

New Eng. J. Med. 335: 1324, 9/30/10
Blinatumomab has a Unique Mechanism of Action

- Murine, single-chain bispecific antibody construct directed against the pan-B-cell antigen CD19 and the CD3ε subunit of the T cell receptor complex
- Creates temporary synapse between CD19+ cell and T cell, inducing cytotoxic T cell response to kill tumor cell
Role of CTLA-4 vs PD-1 in suppressing antitumor immunity

**Activation** (cytokines, lysis, prolif., migration)

**Inhibition**

- PD-1
- PD-L1


**TCR Signal 1**

- CD28
- CTLA-4

**MHC-Ag**

**Tumor or Vaccine**

**APC**

**T cell**

**B7.1/2**
Chimeric Antigen Receptor (CAR)

CD19⁺ tumor

MHC-independent antigen engagement and induction of signalling

4-1BB (CD137)

CD3 zeta

Proliferation, cytokine production, CTL function, tumor lysis

Grupp, S. et. al. ASH 2014 Abstract 380
High Rates of Remission Induction in ALL with CTL019

Over 130 patients have been treated with CTL019 (CLL, ALL, NHL)

- Pediatric ALL phase 1/2a study (N = 39):
  - 36 of 39 in complete remission (92%)
  - 10 relapses, 5 CD19+ and 5 CD19(-)
  - Median follow-up 6 months, range 1.5-31 months
  - 15 patients out 1 year or more
  - No events after 12 months
  - 3 patients have gone to SCT

Grupp, S. et. al. ASH 2014 Abstract 380
Short-term/Long-term Safety (Toxicity) concerns: Continuing Challenges for Long-term Longitudinal Observation

• Targeted cancer agents are NOT non-toxic
• Unique effects on target tissues which depend on pathways being inhibited
• Heightened potential implications for children and developmental considerations
Acute and Potential Long-term Complications

- Diarrhea
- Fever, chills, asthenia
- Skin
- Cardiotoxicity, cerebrovascular, hypertension
- Pulmonary
- Ocular
- Musculoskeletal
- Neurologic
- Endocrine/reproductive
- Immunodeficiency/Autoimmunity

Dy GK and Adjei AA: CaCancer J Clin 2013
Short-term/Long-term Safety

• Insufficient long-term exposure data in adults
• Little combination toxicity data
• Organ/system targets and surveillance intervals needed
• A new paradigm for pediatric cancer LTFU
• Increased opportunities for industry collaboration to meet requirements for LT registry studies for toxicity
Patient-focused Drug Development

• A reality for children?
• Incorporating patient experience/perspective in changing benefit: risk assessment framework
• PROs/ObsROs: evidentiary standards to support treatment benefit claims
• Treatment Benefit: evidence of positive impact on a meaningful concept of interests: survival, disease-related symptoms, function in daily life
Challenges with Development of PRO Instruments in Children with Cancer

• Advice/input from ISPOR at PedODAC
  – Comprehension
  – Content validity/Domains of interest
  – Age appropriateness (8-11)
• Potential role for combined PRO and ObsRO data
• Limited early experience with qualification by SEALD team in plexiform neurofibromas
Challenges with Use of PRO/ObsRO endpoints in Pediatric Oncology

• Limited PRO labeling successes in oncology (symptoms/pain)
• Multi-domain concepts (QOL, Fatigue) – problematic
• Effect of concomitant meds
• Blinded and randomized trials required
• Objective and quantifiable measures
• More stakeholder input needed
Future Direction

• Pediatric Oncology – “Glass Half-full”
• Expand opportunities for evaluating Precision Medicine approaches early to improve outcomes
• Paradigm shifts in study design, initiation, conduct, and F/U
• Rational science-based strategy for prioritizing which/when new products to test in what diseases; successful integration with “standard” therapy
• Expanded collaboration. Patients/families - Investigators – Industry – Regulatory Agencies