PEDiatric perspective on cancer control

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No child should die of cancer
Disclosures

• None
SIOP Mission

- **By advocating** globally on behalf of patients and families to ensure that every child and adolescent with cancer **has access to state of the art diagnosis, treatment and care**

- By providing training opportunities for all childhood and adolescent cancer care providers worldwide on the latest clinical and scientific advances through meetings, networking, and educational outreach for continuing professional development
SIOP Mission

- By promoting and advancing basic, clinical, and other research, and by supporting collaborative opportunities and translating scientific discovery to improve the outcomes for children and adolescents with cancer
- By supporting those caring for children and adolescents with cancer and to provide them with the best curative and palliative therapies
- By advocating appropriate long-term follow-up for survivors
Objectives

- To describe specific issues of the cancer control continuum for children and adolescents
- Advocate for a national / international cancer control strategy that contains a separate section relevant to this age cohort
Estimated numbers of cancer cases and deaths (thousands) in ages 0-14 years, 2010s

Data from IARC
Image: © Petr Vaclavek/Shutterstock.com
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Cancer Control Continuum is different from adults

Growth & Development

- Prevention
- Epidemiology
- Biology
- Therapy
- Supportive care (Nutrition)
- Toxicity
- Psychology/Distress
- Survivorship/Delayed effects
- Palliative care
Case-control studies of childhood cancer are indicating that folate during early pregnancy may be important in mitigating risk

- Fruits and vegetables ↓ risk (n=5)
- Prenatal vitamin supplementation ↓ risk (n=3)
- Folic acid ↓ risk 9n=2)
Epidemiology-prenatal multivitamins with folic acid

- Meta Analysis-seven studies
  - 47% protective effect for neuroblastoma
  - 39% for leukemia
  - 27% for CNS tumors

Goh YI Clinical Pharmacology & Therapeutics 81, 2007
Mechanisms

- Evidence indicates that aberrant methylation patterns are involved in cancer.

- Disturbances during early development in methylation of imprinted genes can predispose individuals to cancer.

- Folate is a necessary nutrient in the DNA methylation process.
Epigenetics & Molecular Epidemiology

- “you are what you eat”
- “You are what your mother ate”

- Genetic polymorphisms (SNPs)
- Epigenetic regulation of genes
Diet could potentially compensate for or accentuate effects of genetic polymorphisms.

The consequences of a diet are dependent on the balance of health and disease states and on an individual’s genetic background.
Prevention begins in Childhood

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Prevention begins in Childhood

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# Biology: Most Common Pediatric & Adolescent Cancers:

<table>
<thead>
<tr>
<th>Age 0-14</th>
<th>Age 15-19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leukemia</strong></td>
<td><strong>Lymphoma</strong></td>
</tr>
<tr>
<td>32%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td><strong>Germ-cell</strong></td>
</tr>
<tr>
<td>20%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Lymphoma</strong></td>
<td><strong>Leukemia</strong></td>
</tr>
<tr>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Neuroblastoma</strong></td>
<td><strong>CNS</strong></td>
</tr>
<tr>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Rhabdo/STS</strong></td>
<td><strong>Soft-tissue Sarcoma</strong></td>
</tr>
<tr>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td><strong>Bone</strong></td>
</tr>
<tr>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Bone</strong></td>
<td><strong>Thyroid carcinoma</strong></td>
</tr>
<tr>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Germ-cell</strong></td>
<td><strong>Melanoma</strong></td>
</tr>
<tr>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Retinoblastoma</strong></td>
<td></td>
</tr>
</tbody>
</table>
Treatment, Supportive Care & Outcomes

Figure 1. Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009.
Influence of Site of Treatment and Use of Research Protocol*

Treatment of Patient:  

... in a pediatric cancer center on protocol  58 %

... outside pediatric cancer center on protocol  40 %

... outside pediatric cancer center off protocol  19 %

*Murphy SM: Med Pediat Oncol 24:279, 1995
EFS of children with ALL

Survival gap - Unavoidable

High-income countries

Survival gap - Preventable

Low-income countries

Years:
What comprises the survival gap?

• Access to diagnosis
• Access to treatment & supportive care
• Availability of drugs
• Availability of pediatric trained HCP
• Abandonment
• Co-Morbidities
• Toxic death
• Excess relapse
• Low priority for resources
International Society of Pediatric Oncology (SIOP)
Committee for Pediatric Oncology in Developing Countries (PODC)

- Pediatric oncology professionals from all continents

- Special committee (PODC) to help with low- and middle-income countries

- Working Groups of PODC with specific activities
Countries represented in PODC and/or its Working Groups and Task Forces

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SIOP-PODC 10 Working Groups 2016

Patient, Family & Stakeholder Engagement
Palliative Care
Supportive Care
Nutrition
Twinning, Collaboration and Support
Adapted Therapy Regimen
Nursing
Abandonment of Therapy
Essential Drugs
Education and Training

Africa/PODC Collaborative Wilms Tumour Project
Hospital Detention
T&CM Integrative Medicine
Psycho-social

PODC TASK FORCES

SOCIÉTÉ INTERNATIONALE D'ONCOLOGIE PÉDIATRIQUE
INTERNATIONAL SOCIETY OF PEDIATRIC ONCOLOGY

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Adapted protocols

- Adjust protocols to suit resources available
- Essential Drugs- WHO list
- Supportive care
- Cultural Sensitive
ALL Stepwise regimen

Pediatr Blood Cancer

REVIEW

Treatment Strategies and Regimens of Graduated Intensity for Childhood Acute Lymphoblastic Leukemia in Low-Income Countries: A Proposal

Stephen P. Hunger, MD, Lillian Sung, MD, PhD, and Scott C. Howard, MD, MSc

Cure rates for children with acute lymphoblastic leukemia (ALL) are 80–85% in high-income countries (HICs) in North America and Western Europe. However, cure rates are much lower in many low-income countries (LICs), where most cases of ALL occur. Over the past several decades partnerships (“twinning”) between HIC and LIC pediatric oncology programs have led to major improvements in outcome for children with ALL in some LICs, often by developing time and resource intensive relationships that allow LIC centers to treat children with regimens similar or identical to those used in HICs. However, the resources are not available in most LICs to allow immediate introduction of intensive ALL treatment regimens similar to those used in HICs. With these thoughts in mind, we present a proposal for a systematic and graduated approach to ALL diagnosis, risk classification, and treatment in LICs. We have based the strategy and the proposed regimens on those developed by the Children’s Cancer Group (CCG) and Children’s Oncology Group (COG) over the past several decades, beginning with a first level regimen similar to CCG therapy of the early 1980s and then layering on successive treatment intensifications proven effective in randomized clinical trials. Simple monitoring rules are included to help centers decide when they are ready to add new treatment components. This proposal provides a framework that LIC centers can use to provide effective ALL therapy, particularly in regions of the world where few children are currently being cured. Pediatr Blood Cancer © 2008 Wiley-Liss, Inc.

Key words: ALL, developing countries, leukemia
Principles-Wilms Africa Project

- Keep it feasible, affordable and as simple as possible
- Improve step by step
- Local clinicians in the lead
- Long term strategy
- Give priority to interventions with most impact

Collaborative Wilms Tumour Africa Project

Adaption of treatment guidelines for Wilms tumour

- No radiotherapy
- Surgical staging to stratify postop chemotherapy
- Nutritional support
- Strategies to enable parents to complete treatment
- Reduced dosage doxorubicin
- Optional prolongation preop chemotherapy
- Postop chemo: omit single vincristine – chance to go home

Collaborative Wilms Tumour Africa Project
No child should die of cancer

## Baseline – AIMS – Preliminary results

<table>
<thead>
<tr>
<th>End of treatment:</th>
<th>Baseline (%)</th>
<th>Preliminary (%)</th>
<th>AIMS (%)</th>
<th>Malawi - post (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive - NED</td>
<td>39%</td>
<td>60%</td>
<td>(65%)</td>
<td>46%</td>
</tr>
<tr>
<td>Estimated OS</td>
<td>25%</td>
<td>45%</td>
<td>50%</td>
<td>6%</td>
</tr>
<tr>
<td>Incomplete</td>
<td>31%</td>
<td>14%</td>
<td>&lt; 10%</td>
<td>6%</td>
</tr>
<tr>
<td>Treatment related</td>
<td>26%</td>
<td>14%</td>
<td>&lt; 10%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Preliminary results:
N = 110
N = 10 misdiagnosis

**Collaborative Wilms Tumour Africa Project**

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*SOP: Société Internationale d'Oncologie Pédiatrique*

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Nutritional Deficiencies / Insufficiencies Cause Pathology

- Growth- stunting
- Cognitive impairment
- Impaired physiology
- Organ dysfunction
- Immunity- Increased risk of infections
- Micronutrients- specific pathologies
- Exacerbated by cancer & its treatment
## Distribution of children by category of nutritional status using 3 (TSFT, MUAC, Albumin) indicators and outcome

<table>
<thead>
<tr>
<th>Nutritional Status by classification disease</th>
<th>First event N (%)</th>
<th>N. of patients</th>
<th>% 2-year EFS (SE) Log-rank test p-value</th>
<th>HR (Cl95%) Log-likelihood test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death</td>
<td>Relapse</td>
<td>Abandonment</td>
<td></td>
</tr>
<tr>
<td>TOTAL Adequate</td>
<td>48 (14.0)</td>
<td>45 (13.1)</td>
<td>21 (6.1)</td>
<td>344 (22.7)</td>
</tr>
<tr>
<td>Moderately depleted</td>
<td>46 (16.8)</td>
<td>36 (13.2)</td>
<td>34 (12.5)</td>
<td>273 (18.1)</td>
</tr>
<tr>
<td>Severely depleted</td>
<td>184 (20.5)</td>
<td>132 (14.7)</td>
<td>125 (14.0)</td>
<td>896 (59.2)</td>
</tr>
<tr>
<td>Total</td>
<td>278 (18.4)</td>
<td>213 (14.1)</td>
<td>180 (11.9)</td>
<td>1513</td>
</tr>
<tr>
<td>Trend test</td>
<td>P=0.006</td>
<td>P=0.407</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
“For patients who remained either obese or underweight for > half of pre-maintenance therapy, the risk of eventual relapse or death was up to double that of patients remaining at normal weight throughout treatment. Conversely, for patients who began treatment obese or underweight and subsequently attained normal/overweight status, this risk was reduced to be equivalent to having normal weight throughout”.

Nutritional status should be a standard component of care in pediatric oncology.

“The effect of BMI on outcome in pediatric AML is not a trivial problem: the reduced survival in underweight and overweight patients is roughly equal to the improved survival accomplished by 10 years of progress in pediatric AML.”
Summary of the Literature

- Nutritional status **reduces** survival, most apparent in children with ALL and AML.
  - Support for this in both HIC and LMIC
- The association of nutritional status and toxicity is less known but increased risk of infection.
- **Remediation** of undernutrition removes the risk of poor nutrition and outcome in children with cancer.
- Obesity is a clear risk factor for the **development of certain cancers**
- The effect of obesity on survival and relapse may be **underestimated**.
- The effect of lifestyle variables (diet, exercise) on the development of obesity during treatment is **virtually unknown**.
A Framework for Adapted Nutritional Therapy for Children With Cancer in Low- and Middle-Income Countries: A Report From the SIOP PODC Nutrition Working Group

Elena J. Ladas, PhD, RD, 1,2* Brijesh Arora, MD, DM, 3 Scott C. Howard, MD, 4 Paul C. Rogers, MD, 5 Terezie T. Mosby, EdD, RD, 6 and Ronald D. Barr, MB ChB, MD 7

The utilization of adapted regimens for the treatment of pediatric malignancies has greatly improved clinical outcomes for children receiving treatment in low- and middle-income countries (LMIC). Nutritional depletion has been associated with poorer outcomes, increased abandonment of therapy, and treatment-related toxicities. Surveys have found that nutritional intervention is not incorporated routinely into supportive care regimens. Establishing nutritional programs based upon institutional resources may facilitate the incorporation of nutritional therapy into clinical care in a way that is feasible in all settings. We present a framework for establishing and monitoring of nutritional care based on the infrastructure of institutions in LMIC. Pediatr Blood Cancer 0000;00:000–000. © 2016 Wiley Periodicals, Inc.

Key words: adapted guidelines; international outreach; low- and middle-income countries; nutrition; nutritional status

INTRODUCTION

The treatment of cancer in childhood is often described as a success story. In a little over four decades, cure rates have risen to approximately 80% for children and adolescents who live in high-income countries (HIC).[1] Unfortunately, this figure is not reflective of regions where most children with cancer reside. At least 80% of children diagnosed with a malignancy live in low- or middle-income countries (LMIC) where limited access to treatment, essential medications, and trained clinicians are barriers to receiving optimal therapy.[2] Despite these challenges, a considerable number of children who live in LMIC are surviving cancer. For example, in some parts of Central America, survival rates range from 30% to 90% in children with leukemia.[3] It is clear that efforts are needed to reduce the high rates of abandonment of therapy.[11] Subsequent studies have reported that remediation of poor nutritional status mitigates the negative association with survival.[12,13]

Oncologists practicing in LMIC often have a higher volume of patients compared to their colleagues in HIC; therefore, nutritional therapy is often delayed or ignored due to allocation of time directed toward life-saving cancer treatment.

Additional supporting information can be found in the supporting information tab for this article.

Abbreviations: BMI, body mass index; EN, enteral nutrition; GT, gastric tube; HIC, high-income countries; LMIC, low- and middle-income countries; MTX, methotrexate; SIOP, International Society of Paediatric Oncology; PODC, Pediatric Oncology Dietetic Council; TPN, total parenteral nutrition.
Survivors
No child should die of cancer
Steps To Implementation Of A National Pediatric Oncology Program In Low-Income Countries

PART I: CONTEXT, STAKEHOLDERS & RESOURCES

CONCLUSION

“The principle asserts that in all circumstances, we ought to produce the greatest possible balance of value over disvalue for persons affected.”

Bentham: Common Good
The opportunity cost of any activity is the loss of the opportunity to pursue the most attractive alternative given the same time and resources.

“Productive life years saved”
Conclusions

- Childhood and Adolescent Cancer is different
- Cancer Control Programs need to identify this difference and develop appropriate strategies relevant to this cohort
- Priority within the Cancer Control continuum should be on Diagnosis, Treatment, supportive care and palliative care
Conclusions

- Treatment should be adapted to the resources available
- Advocacy and training to build capacity
- Clinical Trials & Evaluation process
- Childhood health is identified as a WHO priority and should include cancer
- COLLABORATION at all levels
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