Experience of a Pediatric Oncology Clinical Research Center in Brazil

Antonio Sergio Petrilli, MD, PhD
Children and adolescents

- Heterogeneous in many aspects
- 38% of Brazilian population (IBGE, 2000)
- 11,530 new cases of cancer/year (<20 years) (INCA, 2012)
Too few kids

Unlicensed and off label drug use
- over 50% of the medicines used for children had not been tested for use in this age group
- since 2008: more than 600 pediatric investigation plans have been approved

PROGRESS REPORT ON THE PAEDIATRIC MEDICINE REGULATION 2007 (2013)

Develop cooperative groups
Training human resources
Funding
Improve regulatory environment
- Average time to approval (IOP-GRAACC/UNIFESP, Brazil): 8-16m

Boklan, Mol Cancer Ther, 2006
Conroy, Annals of Oncology, 2003
Promote collaboration between industry, academia and government

- Academy: fostering research, publications
- Industry: reduce drug lag, strengthen pipelines, generates spill over effect
- Government: economic benefit, setting of global level standard

Only 10% of 15-to-19 year old adolescent cancer patients are entered into trials, compared to 60% of those under the age of 15 (NCI, 2008)
### Mortality Rate Reduction – U.S.A 1990-1998

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Median Annual %</th>
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<tbody>
<tr>
<td>0-4</td>
<td>2.8%</td>
</tr>
<tr>
<td>5-9</td>
<td>2.6%</td>
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<tr>
<td>10-14</td>
<td>1.8%</td>
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<tr>
<td>15-19</td>
<td>1.5%</td>
</tr>
<tr>
<td>20-24</td>
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<td>25-29</td>
<td>0.9%</td>
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<td>30-34</td>
<td>1.1%</td>
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<tr>
<td>35-39</td>
<td>1.5%</td>
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</table>

**Why?**

Enrollment in NCI-Sponsored Trials (1990-1998)

Epidemiology

Epidemiology

Rate of participation in U.S. clinical trials and mortality (1990-1998)

Clinical Research in Pediatric Oncology - Successes

- 5 year survival ~ 80% (SEER 2010)

- Parents supported by medical staff are highly motivated to enroll their kids on CT

- Response assessment easier in kids

- Development of Clinical Trials in a Cooperative Group Setting

Boklan, Mol Cancer Ther, 2006
Well-trained infrastructure:

- Dedicated medical personnel
- Study coordinators, nurse and pharmacist
- Data manager, statistical support
- Electronic data capture for institutional protocols
- Full regulatory support
- Archiving facilities
### IOP-GRAACC/UNIFESP - Studies

<table>
<thead>
<tr>
<th>Year</th>
<th># Institutional</th>
<th># Sponsored</th>
<th># Participants</th>
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<tbody>
<tr>
<td>2009</td>
<td>5</td>
<td>3</td>
<td>238</td>
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<tr>
<td>2010</td>
<td>4</td>
<td>2</td>
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<tr>
<td>2011</td>
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<tr>
<td>2012</td>
<td>1</td>
<td>4</td>
<td>152</td>
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<tr>
<td>2013</td>
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<td>2</td>
<td>89</td>
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<tr>
<td>Total</td>
<td>18</td>
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<td>1129</td>
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<tr>
<td></td>
<td>Average</td>
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<td>3.6 2.8</td>
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</table>

#### Accrual – studies ongoing

![Accrual Chart](chart.png)

#### Feasibilities

- **2011**: 7/13 (53%)
- **2012**: 5/11 (45%)
- **2013**: 1/9 (11%)
COG clinical trials:
- adrenocortical carcinoma, hepatoblastoma, retinoblastoma

Drug development industry sponsored clinical trials (II-IV)

Global Databases:
- Center for International Blood and Marrow Transplant Research (CIBMTR)
- Paediatric Fungal Network (PFN)

Investigator Initiated Trials (IITs):
- CNS and bone tumors, infectology
Genetic and Molecular Biology Laboratory

Investigation of tumor markers and therapeutic targets

- Tissue Bank Consortium
- Tests in OS cell lines

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<th>Tumor</th>
<th>Patients</th>
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<td>2272</td>
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<tr>
<td>CNS</td>
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<tr>
<td>Leukemia</td>
<td>261</td>
<td>573</td>
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<tr>
<td>Neuroblastic</td>
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<tr>
<td>Wilms</td>
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<td>Langerhans</td>
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<td><strong>6071</strong></td>
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</table>
Cutting edge research

Clinical Research

Genetics and Genomics

Clinical data

Adams, J.U, Building the bridge from bench to bedside, Nature Reviews Drug Discovery, June 2008
Brazilian Osteosarcoma Treatment Group (BOTG)

- Created in 1980’s
- 5 consecutive studies completed
- Beginning:
  - small number of patients enrolled
  - few specialized institutions in a single city (SP)
- Study V:
  - 25 institutions from 9 states and 15 different cities
  - 368 patients enrolled
Results of the Brazilian Osteosarcoma Treatment Group Studies III and IV: Prognostic Factors and Impact on Survival

A. Sérgio Petrilli, Beatriz de Camargo, Vicente Odone Filho, Paula Bruniera, Algemir L. Brunetto, Reymaldo Jesus-Garcia, Olavo P. Camargo, Walter Pena, Pedro Péricles, Alexandre Davi, José D. Prospero, Maria Teresa S. Alves, Claudia R. Oliveira, Carla R.D. Macedo, Wellington L. Mendes, Maria Teresa A. Almeida, Maria L. Borsato, Telma M. dos Santos, Jorge Ortega, and Elio Consentino

Cardioprotective Effect of Dexrazoxane During Treatment With Doxorubicin: A Study Using Low-Dose Dobutamine Stress Echocardiography

Marcelo G. Paiva, MD,1* Antonio S. Petrilli, MD,2 Valdir A. Moisés, MD,1 Carla Renata Donato Macedo, MD,2 Cristiana Tanaka, BSN, MSN,2 and Orlando Campos, MD3

Use of Amifostine in the Therapy of Osteosarcoma in Children and Adolescents

Antonio Sergio Petrilli, M.D., Ph.D., Delma Tostes Oliveira, M.D., Valeria Cortez Ginani, M.D., Rita Kechichian, M.D., Andrea Dishchkhenian, M.S., Werthon de Medeiros Roque Filho, M.D., Cristiana Tanaka, R.N., Carla Gonçalves Dias, R.N., Maria do Rosário Dias de Oliveira Latore, Ph.D., Algernon Lunardi Brunetto, M.D., Ph.D., Hedilene Cardoso, M.D., Maria Teresa Almeida, M.D., and Beatriz de Camargo, M.D., Ph.D.

Activity of Intraarterial Carboplatin as a Single Agent in the Treatment of Newly Diagnosed Extremity Osteosarcoma

A.S. Petrilli, MD,1* R. Kechichian, MD,1 A. Broniscer, MD,1 R.J. Garcia, MD,2 C. Tanaka, RN,1 J. Francisco, MD,2 H. Lederman, MD,2 V. Odone Filho, MD,4 O.P. Camargo, MD,2 P. Bruniera, MD,4 P. Pericles, MD,7 E. Consentino, MD,7 and J.A. Ortega, MD9
At present

**Latin American Group of Osteosarcoma Treatment**

Multicentric, randomized study with data collection over 32 sites in Latin America

Self-maintained
Generate information on lower cost treatments
Objectives:

- Evaluate if HD-MTX, CDDP and Doxorubin will improve EFS of patients with resectable osteosarcoma

- Investigate the impact of metronomic treatment on EFS of non-metastatic and metastatic osteosarcoma patients
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**SURGERY**

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**RANDOMIZATION**

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**CIS**= Cisplatina IV 60mg/m²/dia (D1-D2)

**DOX**= Doxorubicina IV 37,5mg/m²/dia (D1-D2)

**MTX**= Metotrexato IV 12g/m²/dia (D1)

**dex**= Dexrazoxane IV 375mg/m²/dia (D1-D2)

**ciclo**= Ciclofosfamida VO 25mg/m²/dia (Todos os dias)

**mtx**= Metotrexato VO 1,5mg/m²/2x dia (segunda/quinta)
Osteosarcoma 2006 Protocol – Non Metastatic

CICLO = ciclofosfamida VO 25mg/m²/dia (todos os dias)
MTX = metotrexato VO 1,5mg/m²/2xdia (segunda/quinta-feira)

CIS= Cisplatina IV 60mg/m²/dia (D1-D2)
DOX= Doxorubicina IV 37,5mg/m²/dia (D1-D2)
MTX= Metotrexato IV 12g/m²/dia (D1)
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ciclo= Ciclofosfamida VO 25mg/m²/dia (Todos os dias)
mtx= Metotrexato VO 1,5mg/m²/2x dia (segunda/quinta)
CIS = Cisplatina IV 60mg/m²/dia (D1-D2)
DOX = Doxorrubicina IV 37,5mg/m²/dia (D1-D2)
MTX = Metotrexato IV 12g/m²/dia (D1)
ciclo = Ciclofosfamida VO 25mg/m²/dia (Todos os dias)
mtx = Metotrexato VO 1,5mg/m²/2x dia (segunda/quinta)
dex = Dexrazoxane IV 375mg/m²/dia (D1-D2)
Overall survival

N=655

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<td>87.5</td>
<td>67.7</td>
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<tr>
<td>B</td>
<td>84.8</td>
<td>75.6</td>
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<td>49.1</td>
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<tr>
<td>E</td>
<td>46.3</td>
<td>23.1</td>
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Value of a shared protocol

OS outcomes in 2 centers

Center 1

Relapse
Progression
Refusal
Toxic death

Center 2

Relapse
Progression
Refusal
Toxic death
High-income vs. low middle-income countries

Childhood Cancer Survival

High-income countries

Low middle-income countries

Survival gap
Survival gap closing in GRAACC, Brazil

High-income countries

Low middle-income countries

IOP/GRAACC-UNIFESP
Our contacts

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