CHEMOTHERAPY FOR BONE SARCOMAS

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Incidence of Bone Sarcomas, SEER 1975-2000
Proportion of Newly Diagnosed Patients Accrued to National Trials, 1997-2003

Bleyer 2007

BLEYER 2006
“The Lost Tribe”

NEWSFOCUS

Survival in young adults with cancer shows little change across decades. Why is that, and how can the disease be pushed back?

In Their Prime, And Dying of Cancer
In Canada, each year…

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Cases</th>
<th>Bone Sarcoma</th>
<th>Age</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>25,000</td>
<td></td>
<td>Age 0-14</td>
<td>35</td>
</tr>
<tr>
<td>Lung</td>
<td>24,000</td>
<td></td>
<td>Age 20-44</td>
<td>75</td>
</tr>
<tr>
<td>Breast</td>
<td>23,000</td>
<td>Bone Sarcoma</td>
<td>Age 15-19</td>
<td>?</td>
</tr>
<tr>
<td>Colon</td>
<td>21,000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ewing’s Sarcoma

del(11)(q23)
der(11)(11;22)
Therapeutic Strategy:
Increasing Drugs
Addition of IE to VDC Improves Survival in Localized Ewing’s Sarcoma

5 yr EFS: 54% vs. 69%, p=0.005

N=398, localized

Grier 2003
‘Pediatric’ Therapy

- 5 cycles of VDC
- 8 cycles of IE
- 4 cycles of VC
- \( ADR = 375 \text{ mg/m}^2 \)

- 13% > age 18

Unclear benefit of IE in adults
Therapeutic Strategy:
Increasing dose Intensity
Randomized Comparison of q2 week vs. q3 week Chemotherapy

VDC, IE q 3 weeks x 2

LOCAL CONTROL

VDC, IE q 3 weeks x 5

VDC, IE q 2 weeks x 3

LOCAL CONTROL

VDC, IE q 2 weeks x 4

14 cycles

Womer, ASCO 2008. COG
25% ↑ dose intensity; no increase toxicity. Improved EFS.

n = 568

3 yr EFS: 65% vs. 76%

Womer, ASCO 2008. COG
Small numbers Limit Power in Adults “…should give them benefit of the doubt”

13% > age 17

Womer, ASCO 2008. COG
Ewing’s Sarcoma in Toronto

- 10 cycles of VDC alternating with IE
- ADR = 375 mg/m²

- 17 cycles of VDC alternating with IE
- ADR = 375 mg/m²
Localized EWS in Toronto

EFS

PEDIATRIC

ADULT

years
Multivariable Analysis of Prognostic Features for EFS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>95% C.I.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Dose</td>
<td>0.97</td>
<td>(0.95, 0.98)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic Primary</td>
<td>2.12</td>
<td>(1.1, 4.26)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total Dose</td>
<td>0.56</td>
<td>(0.33, 0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Is Age an Independent Prognostic Factor in Ewing’s Sarcoma?

**Yes**
- Craft  JCO 1998
- Cotterill  JCO 2000
- Bacci  JCO 2000
- Grier  NEJM 2003

**No**
- Oberlin  Proc ASCO 1996
- Verrill  JCO 1997
- Fizazi  JCO 1998
- Paulussen  JCO 2001
Ewing’s in First Relapse

Irinotecan 20 mg/m² x 5 OR = 30%
Temozolomide 100 mg/m² x 5
Wagner 2004, 2007

CPM 250 mg/m² x 5 OR = 33 – 57%
Topotecan 0.75 mg/m² x 5

Upfront therapy
Osteosarcoma
Active Agents in Osteosarcoma

- Doxorubicin
- Cisplatin
- Methotrexate
- [Ifosfamide]

Despite various doses, combinations, pre-op, post-op, North America, Europe…
...survival of localized osteosarcoma has not changed in >20 years

Winkler JCO 1984 EFS 68%
- COSS-80

Meyers JCO 2005 EFS 71%
- POG-9351
Add Ifosfamide: no difference

Median age = 13

Ifosfamide 9 g/m²

Meyers 2005
Therapeutic Strategy: Improve % Necrosis

chemotherapy → Surgical resection → chemotherapy
After induction chemotherapy, necrosis in primary tumour at definitive surgical resection is correlated with event-free survival > 95% necrosis

Meyers 2008
Changing % Necrosis: no difference

- Patients randomized to MA vs. MIE pre-op
  - Ifosfamide = 12 g/m²
  - Proportion of patients with favorable necrosis increased from 39% to 56%
  - No effect on survival

Le Deley EJC 2007
Therapeutic Strategy: Dose Intensity
Increasing dose intensity from q3w to q2w: no difference

- AP x 6
- Surgery at week 6
- Proportion of patients with favorable (>90%) necrosis increased from 36 to 50%
- No impact on EFS or OS
Therapeutic Strategy: Immunotherapy
Immunotherapy in Osteosarcoma

- Wound infection improves survival
  Liptak Vet Surgery 2006
MTP-PE - synthetic analog of BCG cell: no difference

P = 0.08

N = 662

Meyers 2008
Interferon-α as the only adjuvant treatment in high-grade osteosarcoma

Muller 2005

Historical control

N=89

39%
Therapeutic Strategy: Altering Therapy in Response to % Necrosis + Immunotherapy
A randomized trial of the European and American Osteosarcoma Study Group to optimize treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy.

Clinical trial protocol
Version: 1.2
Date: 30 March 2007
A Randomized Trial to Optimize Treatment Strategies Based on Histological Response to Pre-Operative Chemotherapy

- **MAP**
- **SURGERY**
- **RANDMOIZE**
- **MAP + IFN**
- **MAP**
- **MAP + IE**

- >90% necrosis
- <90% necrosis
EURAMOS – current status
Novel Therapeutics
Bone tumours and IGF-IR

- Peak incidence of bone tumours in adolescence/young adults
- IGF pathway important in bone growth
- High circulating levels of IGF
Special Story: Ewing’s and IGF-IR

- IGF receptors are expressed in sarcoma
  Andrulis 1995

- IGF-IR is required for EWS-FLI1 mediated transformation of fibroblasts
  Hellman 1997

- EWS-FLI1 represses transcription of IGFBP3 - leading to constitutive activation of IGF pathway
  Delattre 2004
Monoclonal Antibody Against IGF-IR Receptor in Mouse Tumour Xenografts

Ewing’s Sarcoma

0.5 mg/mouse twice weekly x 4 weeks

Kolb 2008
Small Molecule Inhibitor of IGF-IR in Ewing’s Sarcoma

Clin Cancer Res 2007
Phase II Trials IGF-IR Antibody

- Coming soon
mTOR Inhibition

Rapamycin induces the fusion-type independent downregulation of the EWS/FLI-1 proteins and inhibits Ewing’s sarcoma cell Proliferation

Mateo-Lozano 2003

ARIAD - A Pivotal Trial to Determine the Efficacy and Safety of AP23573 When Administered as Maintenance Therapy to Patients With Metastatic Soft Tissue or Bone Sarcomas
mTOR + IGF-RI

The IGF-IR signaling pathway

Nucleus
Cell growth, proliferation, survival, transformation, metastasis, angiogenesis, protein synthesis, cell size, glucose transport

Picci 2008
Relapsed Disease

- Novel agents on the horizon
- Combination therapy
- Maintenance therapy
Currently, there are no clinical trials available in Canada for newly diagnosed patients > 18 yrs of age with Ewing’s or Osteosarcoma.

Unclear whether data obtained from pediatric studies are directly applicable to young adult patients.