8th PMH Conference: New developments in cancer management

Contributions of EORTC trials to the management of sarcoma

Ole Steen Nielsen
on behalf of the EORTC STBSG

STBSG PMH/OSN
Not 50 years but 20 years since I was at PHM!
Molecular biological knowledge in sarcomas increases:

- Genetic involvement
- Many genes are affected:
  - p53, Rb, ras, myc
  - MDM2, CDK4, GLI
- Genetic changes (cytogenetic aberrations):
  - t(X;18) (p11;q11) - SSX1&2 SYT: Synovial sarcomas
  - t(12;22) (q13;q12) - ATF1, EWS: Clear Cell sarcomas
  - t(12;16) (q13;p11) - CHOP, TLS: Myxoid liposarcomas
  - t(2;13)(q37;q14) - PAX3 FKHR: Rhabdomyosarcomas
  - t(11;22) (q24;q12) - FLI-1, EWS: Ewing family (EFT)
- Others (lipomas, fibrosis, schwannomas, chondros. etc.)
- Etc…….

• New subtypes?
• New treatment targets?
SARCOMAS
Treatment and research problems

• A rare disease
• Too few patients locally!
• Many subtypes!
• Molecular biological knowledge!
• Nationally: Centralisation!
• Internationally: Collaboration!
An example of International Cooperation: EORTC STBSG

- To develop, stimulate and coordinate studies on all aspects of sarcomas within the framework of the EORTC.
- To organize congresses, conferences and symposia to promote these studies.
EORTC Soft Tissue and Bone Sarcoma Group

- 52 member institutions from 13 countries
- > 500 patients / year in clinical trials
- > 3000 patients in the central database
- 58 clinical trials conducted so far
- Strict quality control programs
  - Strict membership policy (site visits, recruitment, data quality)
  - Review of pathology and response
  - On site visits
Patient recruitment

- Phase I
- Phase II
- Phase III - Advanc.dis.
- Phase III - Adjuvant
(Neo)-adjuvant phase III trials in STS

• The STBSG has conducted the largest adjuvant trials:

  – CYVADIC vs observation after surgery +/- radiotherapy (77-88: 468 pts)
    Advantage of CYVADIC only in delaying local recurrences for pts with localizations other than limbs
    No proof of effect!

  – DOXO-IFOS-GCSF vs observation after surgery (95-03: 351 pts)
    No advantage in survival

  – Neo-adjuvant VP16-IFOS-DOXO±hyperthermia (97-06: 341 / 340 pts)
    Advantage in disease free survival for the hyperthermia arm

  – Imatinib vs observation after surgery in GIST (05-ongoing: 879 / 900 pts)
    with ISG, FSG, GEIS, AGITG
Projects based on the STBSG database of adjuvant studies

| Data originating from centers with a large recruitment (> 5 pts in a study) is of better quality |
| Validation of the Trojani grading system |
| Development of a prognostic index based on mitotic count, necrosis and tumor size |
| Inclusion of the results of the CYVADIC study in the Sarcoma Meta-Analysis Collaborative group project |
| Patients with marginal resection, males, and patients older than 40 years benefit more from chemotherapy than others; tumor size and histological grade have no predictive value. |
EORTC STBSG STUDY STRATEGY
ADVANCED/METASTATIC STS

- Standard is doxorubicin
- Only multicenter studies.
- Study strategy:
  - Phase 1: Selected centres
  - Phase 2: 2nd line chemotherapy
  - Phase 2: 1st line chemotherapy
  - Phase 3: New drug vs standard
### Phase I-II trials in STS (1977-2008)

**Examples 1st and 2nd line chemotherapy**

<table>
<thead>
<tr>
<th>1st line chemotherapy</th>
<th>2nd line chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>ACNU</td>
</tr>
<tr>
<td>Chlorozotocin</td>
<td>Fotemustine</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Miltefosine</td>
</tr>
<tr>
<td>PALA</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Ellipticineum</td>
<td>Lipo. doxorubicin</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>Temozolomide</td>
</tr>
<tr>
<td>Etoposide (iv/oral)</td>
<td>Raltitrexed</td>
</tr>
<tr>
<td>DTIC (high dose)</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>TGU</td>
<td>Ecteinascidin-743</td>
</tr>
<tr>
<td>MDS</td>
<td>Brostallicin</td>
</tr>
<tr>
<td>MT-PPE</td>
<td>Exatecan</td>
</tr>
<tr>
<td>Mitozolomide</td>
<td>Gefitinib</td>
</tr>
<tr>
<td>MZPES</td>
<td>Razopanib</td>
</tr>
<tr>
<td></td>
<td>Eribulin mesylate</td>
</tr>
<tr>
<td></td>
<td>And more …</td>
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</tbody>
</table>

NEW DRUGS STILL NEEDED!
Phase III trials in advanced STS

Examples 1st line chemotherapy

- CYVADIC (comparison of 2 schedules)
  Oct 76 - Mar 80 (312 pts)

- DOXORUBICIN (75 mg/m²) vs EPIRUBICIN (75 mg/m²)

NO SUPERIORITY IN SURVIVAL

COMpared to single agent

DOXORUBICIN

- DOX (50) vs IFOS (5) vs DOX (75) vs IFOS (5) - GM-CSF
  Mar 92 - Jan 95 (296 pts)

- IFOS (5 g/m²/24 h) vs IFOS (3 x 3 g/m²/4h)
  Mar 92 - Jul 96 (182 pts)

- DOX (75) vs DOX (75) - IFOS (9 g/m²/72h)
  Feb 98 – Oct 01 (326 pts)

- DOX (75) vs IFOS (3 x 3 g/m²/4h) vs IFOS (9 g/m²/72h)
  Mar 03 – ongoing
Summary
Advanced STS - 1st line therapy

• Systematic evaluation in phase II and phase III trials of:
  – CYVADIC (Doxo, CPH, DTIC)
  – Doxorubicin, 75 mg/m2
  – Epirubicin, 75 mg/m2 and 150 mg/m2
  – Ifosfamide, 5 g/m2, 9 g/m2, 12 g/m2
  – Doxorubicin – Ifosfamide combinations
  – Docetaxel
  – Liposomal doxorubicin

• Doxorubicin, 75 mg/m2, q 3 weeks remains the “golden standard”

• On-going phase III trial
  – Doxo 75 mg/m2 vs Doxo 75 mg/m2 + Ifos 9 g/m2 + GCSF

• Accumulation of a database of > 3000 cases
Projects based on the STBSG database of 1st line studies

A potentially curable disease…

(EJC 39, 2003, p.64)

5 years survival: 8%

- Long terms survivors observed in all prognostic groups
Summary
Advanced STS 2\textsuperscript{nd} and 3\textsuperscript{rd} line therapy

- 28 phase II trials on various drugs
- Accumulation of a database of 380 patients treated with active and inactive drugs
- Reference values for phase II trials using PFR as the primary end-point (i.e. for cytostatic drugs or targeted therapies)
Progression free rate observed in STBSG 2\textsuperscript{nd}/3\textsuperscript{rd} line phase II studies in STS

<table>
<thead>
<tr>
<th>Agents</th>
<th>3 mon.</th>
<th>6 mon.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estim.</td>
<td>s.e.</td>
</tr>
<tr>
<td>Active (4 trials)</td>
<td>39 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Inactive (9 trials)</td>
<td>21 %</td>
<td>3 %</td>
</tr>
</tbody>
</table>

Number of patients at risk:

Inactive agents: O 221234 N 47 16 5 1
Active agents: O 136146 N 55 18 14 11
Imatinib and GIST!
The Garden of Delights

Hieronymus Bosch (1450-1516)
Dose response?

*Imatinib 400 mg vs 800 mg*

- No response difference
- Longer PFS after 800 mg
- No survival difference
- Toxicity 800 > 400 mg

Verweij et al., Lancet 2004
Discontinuation of Imatinib Increases Risk of GIST Progression

- Continuous therapy (n = 23)
  - Median PFS: 6 months
  - Patients, %
  - Months After Randomization

- Stop therapy (n = 25)
  - Median PFS: 6 months

P = 0.0001
Response rate in GIST according to mutational status for c-KIT mutational status.

| Exon 11 | 85 | 74 | 53 | 2 |
| Exon 9  | 23 | 11 | 6  | 0 |
| No Mutation | 9 | 2 | 1 | 0 |

Graph showing event-free survival (%) over days for different mutation statuses.

- Green line: Exon 11
- Red line: Exon 9
- Blue line: No Mutation

Event-Free Survival (%) vs Days with treatment days: 0, 250, 500, 750.
Progression-free survival advantage for 800 mg dose in GISTs with KIT exon 9 mutations

P = 0.0013

Debiec-Rychter et al Eur J Cancer 2007
Adjuvant Imatinib?
Phase III EORTC Trial Study Design

- Complete resection of GIST
- No treatment
- Follow for 5 years
- Glivec (400 mg/d for 2 years)
- Discontinued treatment*

2005 - ongoing: 879/900 pts with ISG, FSG, GEIS, AGITG
Interactive risk calculator for predicting imatinib toxicities in GIST patients

<table>
<thead>
<tr>
<th>Patient's characteristics</th>
<th>Probability of</th>
</tr>
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<tbody>
<tr>
<td>Imatinib dose (/day) 400</td>
<td>Edema (g2+) 18 %</td>
</tr>
<tr>
<td>Age (years) 60</td>
<td>Lethargy (g2+) 24 %</td>
</tr>
<tr>
<td>Sex (1=M, 2=F) 1</td>
<td>Rash (g2+) 9 %</td>
</tr>
<tr>
<td>PS (WHO) 1</td>
<td>Nausea (g2+) 9 %</td>
</tr>
<tr>
<td>Pr.chem. (0=N, 1=Y) 0</td>
<td>Diarrhea (g2+) 14 %</td>
</tr>
<tr>
<td>Largest diam.(mm) 80</td>
<td>Anemia (g3+) 6 %</td>
</tr>
<tr>
<td>Gl origin (0=N, 1=Y) 1</td>
<td>Neutrop.(g3+) 2 %</td>
</tr>
<tr>
<td>HGB (mmol/l) 8</td>
<td></td>
</tr>
<tr>
<td>ANC (10**9/l) 9</td>
<td></td>
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</tbody>
</table>

Van Glabbeke et al
Phase III trials in other tumor types

- **EOI osteosarcoma phase III trial**
  
  _Aug 93 – Sep 02_

  _In cooperation with MRC, UKCCSG, CSG, SIOP_

- **Euro-EWING phase III trial**
  
  _Jun 01 – on-going_

  _In cooperation with GPOH, UKCCSG, SFOP, SIAK_

- **Phase II trial of moderate dose radiotherapy for inoperable aggressive fibromatosis**
  
  _Nov 01 – Mar 08_

  _In cooperation with the EORTC Radiotherapy group_
New concept in Soft Tissue Sarcomas
EORTC STBSG

Selected drugs for selected sarcomas
and/or
specific agent for specific tumour targets
## Disease specific studies

<table>
<thead>
<tr>
<th>Before:</th>
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<tbody>
<tr>
<td>Ewing/PNET, osteosarcomas</td>
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<table>
<thead>
<tr>
<th>Now:</th>
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<tr>
<td>Agressive fibromatosis, GIST, Synovial sarcomas, Angiosarcomas, DFSP</td>
</tr>
</tbody>
</table>

and in the near future...

Chondrosarcomas, uterine sarcomas and …
Conclusions

- In **soft tissue sarcoma**, relevant clinical trials can only be conducted by **cooperative groups**

- Studies conducted in **specific histological subtypes** may require the **collaboration of several groups**

- The **complexity of the disease** requires **strict quality control procedures**, that should preferably be **centrally managed**

- **Centralization** of the database and **standardization** of the collected data set enable to conduct **retrospective research projects** leading to a better understanding of this (these) disease(s)
From EORTC STBSG (and me)

Thank you and congratulations with 50th PMH/OCI Anniversary