Treatment of Malignant Pleural Mesothelioma

13th Perspectives in Lung Cancer
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Paul Baas, MD, PhD
The Netherlands Cancer Institute

Disclosure
Advisor for Merck Sharp Dohme
Advisor for Pfizer
Teaching courses Bayer
Asbestos

- Durable, fire and heat resistant fibrous mineral
- To strengthen materials or serve as insulation

Multistep carcinogenesis in MPM

- Accumulation of asbestos fibers and chronic tissue injury
- Persistent stimulation of tissue repair program leading to:
  - Epigenetic silencing or deletion of « caretaker » Ink4a locus (9p21)
  - Loss of « gatekeeper » NF2 function (22q12)
- Loss of contact-dependent growth inhibition and tumor progression
Epidemiology and tumorigenesis

• The incidence of mesothelioma in Europe will increase and peak between 2015 and 2020
• The median latency period from first exposure to clinical manifestation is over 40 years
• Asbestos continues to be used in many countries (developing world) without any laws on worker protection
• Genetic susceptibility:
  – frequent inactivation of tumor suppressor genes include p16\textsuperscript{INK4A}/p14\textsuperscript{ARF} and neurofibromatosis type 2 (NF2)

Which country does still export asbestos

1. Italy
2. The Netherlands
3. Canada
4. Tibet
5. Switzerland
6. Egypt
Cumulative incidence of MPM and asbestos use

Asbestos in the developing world
Cell Type

- Pleiomorphic
- Tubulopapillary
- Epithelioid
- Glandular
- Large Cell (giant cell)
- Small Cell
- Adenoid cystic
- Signet ring

- Epithelioid
- Mixed (Biphasic)
- Sarcomatous

MSKCC, Semin Thorac Cardiovasc Surg 2009; Courtesy, W. Travis

Differentiation from Lung Cancer

<table>
<thead>
<tr>
<th>Histology</th>
<th>Meso</th>
<th>Adeno</th>
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<tbody>
<tr>
<td>PAS stain</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>Mucicarmine</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>Immunostaining</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEA</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>TTF-1</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>LeuM-1 (CD 15)</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>Cytokeratin 5/6</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>Calretinin</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>EMA</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>WT1</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>HBMB1</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>D2-40</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>B72.3</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>MOC-31</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>Ber-Ep4</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>BG8</td>
<td>Neg</td>
<td>Pos</td>
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Epithelioid MPM

Calretinin

Biomarkers

- Blood, Serum, Effusion
  - Mesothelin (SMRP)
  - Osteopontin
  - CYFRA 21-1

CEA in serum must be normal!!!!

Staging Systems

- IMIG 2003 (update 2012?)
- AJJC (update 2010)
- many are based on surgical interventions

References:
<table>
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<tr>
<th>Stage</th>
<th>TA</th>
<th>TN</th>
<th>TM</th>
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<tbody>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1, T2</td>
<td>N1</td>
<td>M0</td>
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<tr>
<td></td>
<td>T1, T2, N2, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3, N0, N1, N2, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>Any</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N, M1</td>
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Conclusion:
clinical staging should be more simple

Surgery in MPM is still experimental

*J Thorac Cardiovasc Surg* 2009 135: 620
### Prognostic Factors

<table>
<thead>
<tr>
<th></th>
<th>CALGB 1998</th>
<th>EORTC 1998, 2005</th>
<th>Other</th>
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<tbody>
<tr>
<td>Age &gt; 75 y</td>
<td>Male</td>
<td>FDG-PET SUV(_{max}) &gt; 10</td>
<td></td>
</tr>
<tr>
<td>Chest Pain</td>
<td></td>
<td>↑COX-2 Expression</td>
<td></td>
</tr>
<tr>
<td>Poor Performance Status 1-2</td>
<td>Poor Performance Status 1-2</td>
<td>↑VEGF Expression ↑Glut-1 Expression</td>
<td></td>
</tr>
<tr>
<td>NonEpithelial Histology</td>
<td>NonEpithelial Histology</td>
<td>Hypermeth P16INK4α</td>
<td></td>
</tr>
<tr>
<td>Pleural Involvement</td>
<td>Certainty of Histological Diagnosis</td>
<td>↑Vascularity</td>
<td></td>
</tr>
<tr>
<td>LDH &gt; 500 IU</td>
<td>WBC &gt; 8.3</td>
<td>Evidence of SV40???</td>
<td></td>
</tr>
<tr>
<td>PLT &gt; 400 K</td>
<td>PLT &gt; 350 K</td>
<td>Tumor Bulk, ↑Nodes, ↑# Nodal Stations, Invasion EndoT Fascia, Positive Margins</td>
<td></td>
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### Chemotherapy
Systemic Therapy

- Chemotherapy provides symptom relief and increased OS
- Based on a landmark study of Vogelzang and Meerbeeck: the combination of cisplatin and anti-folate is standard
- Multimodality studies use neoadjuvant chemotherapy followed by extrapleural pneumonectomy or pleurectomy/decotication with or without RT
- Optimal second line chemotherapy is not defined
- Novel and targeting agents: so far no or very limited success

How to improve on platinum- pemetrexed?

- Do we need platinum-based combos?
- Variations in scheduling
  - Dose escalation
  - Maintenance pemetrexed
- Better cytostatic drugs
  - Other antifolates
  - Vinca alkaloids
  - Anthracyclins: amrubicin
  - New platins
  - Epothilones
- Better patient selection
  - In vitro drug resistance
  - Critical mutation (MTAP-deletion)
  - Predictive biomarkers: TS, ERCC1
- Targeted agents
  - Anti-mesothelin immunotoxin
  - Bevacizumab
  - HDAC-inhibitor
  - thalidomide
Maintenance Therapy
Thalidomide phase III study

P. Baas, presented at ASCO 2011, abstract 7006, Chicago

Thalidomide vs observation in non progressing patients after CT
Objectives

• Primary endpoint
  – To observe a > 50% increase in time to progression

• Secondary endpoints
  – Duration of response
  – Overall survival
  – Toxicity

• Statistics
  – Difference of 50% in median time to progression
  – 216 patients required
  – 80% power, 2-sided logrank test (α=0.05)
  – Stratification for histology and chemotherapy
  – IDSC test at 95 events

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Thalidomide</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>111</td>
<td>111</td>
</tr>
<tr>
<td>Age</td>
<td>64 (45-82)</td>
<td>64 (41-78)</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>83%</td>
<td>86%</td>
</tr>
<tr>
<td>WHO 0-1</td>
<td>96%</td>
<td>98%</td>
</tr>
<tr>
<td>WHO 2</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Epithelial Type</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>Post Study Treatment (%)</td>
<td>54/86 (63%)</td>
<td>46/74 (62%)</td>
</tr>
</tbody>
</table>

May 2004-December 2009: 222 patients

Participating centers: 8 Dutch (208 pts), 4 Australian (14 pts)
Results

**TTP**

- No further treatment: Transplantation and progression
- HR = 1.0 (0.7 - 1.2), p=0.71

**OS**

- No further treatment: Transplantation and progression
- HR = 1.2 (0.9 - 1.6), p=0.30

**Biologicals**
Anticancer activities of vorinostat

**VORINOSTAT**

HDAC1, 2, 3, 6

**Transcriptional effects**

- Histone acetylation
- Transcription factor acetylation
- Cortactin acetylation
- α-tubulin acetylation
- Hsp90 acetylation

**Non-transcriptional effects**

- Cell cycle
- Differentiation
- Apoptosis
- Angiogenesis
- Cell Motility
- Aggresome Formation
- Immune modulation

Hsp, heat shock protein


VANTAGE 014: study design

Patients with epithelial, sarcomatoid, or mixed histology malignant pleural mesothelioma which has progressed or relapsed following treatment with pemetrexed and either cisplatin or carboplatin

**Screen**

**Randomization 1:1**

**Vorinostat 300 mg bid + best supportive care**

<table>
<thead>
<tr>
<th>Days</th>
<th>3</th>
<th>7</th>
<th>10</th>
<th>14</th>
<th>17</th>
<th>21</th>
</tr>
</thead>
</table>

- ‘on’ treatment – 3 days
- ‘off’ treatment – 4 days

Objectives: overall survival, tumor response (RECIST), PFS, pulmonary function, patient-reported outcomes, safety

L. Krug, presented at ECCO, ESMO 2011, Stockholm
OS for the Intent to treat population

- Vorinostat median overall survival 31 weeks
- Placebo median overall survival 27 weeks

Hazard Ratio (V vs. P) 0.98, p-value 0.858

Conclusions

- VANTAGE 014 largest randomized trial in malignant pleural mesothelioma

- No statistically significant benefit in OS
  - Vorinostat 30.7 weeks vs. placebo 27.1 weeks, HR 0.98, p-value 0.858

- Statistically significant, but minor benefit in PFS
  - Vorinostat 6.3 weeks vs placebo 6.1 weeks, HR 0.75, p-value <0.001

- Planned analyses of tumor tissue to look for predictive biomarkers
Other systemic approaches

- Multi-targeted TKIs including VEGFR2 as target (vatalanib, sorafenib, sunitinib): few responses, not consistently active
  Janan, ASCO 06; Jänne ESMO 06; Nowak ASCO 2008,
- Bortezomib: preclinical data interesting, clinical studies ongoing
  Gordon, Cancer Chemothe Pharmacol 2008
- Combination therapies:
  - Phase 1 MEK inhibitor + erlotinib NKI-AVL
  - Phase II-III study with PI3Kinase inhibitor 2nd line

Conclusions

- First line chemotherapy
  - Requires a platinum-antifolate backbone
  - Likely equipoise between different combos
  - Tumors recur within 2 years
- Surgery as part of studies
- Second Line Chemotherapy
  - No standard yet
    - switch maintenance thalidomide negative
    - vorinostat negative
- Future lies in better patient selection
  - By a predictive baseline biomarker
  - By testing patient tumor cells for drug sensitivity
  - By use of molecular targeted drugs (combinations?)
  - Preferably via randomized phase 2 studies in 1st line with TR endpoint