Malignant Mesothelioma
State of the Art

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Summary

- Diagnosis; epithelial type subdivided
  - Pleiomorphic vs other

- Staging:
  - IASLC-IMIG initiative
  - Clinical vs. surgical staging

- Treatment issues
  - Chemotherapy: maintenance and 2\textsuperscript{nd} line Rx
  - Surgery: EPP vs. P/D
  - Radiation: IMRT and hybrid techniques

- Future plans......
Etiology of MPM

- Asbestos- “Blue” and “White” Fibers- 70-80% found in tissues
- Persistent stimulation of tissue repair program
- Familial occurrence in Turkey

Epidemiology

- Europe: incidence will increase and peak between 2015 and 2020
- Median latency period to clinical manifestation is over 40 years
- Asbestos production and use is still increasing (developing world)
- Genetic susceptibility:
  - frequent inactivation of tumor suppressor genes include \( p16^{\text{INK4A}} / p14^{\text{ARF}} \) and NF2
Diagnosis

• Cytology vs Histology
  ▫ Thoracentesis
    Confirmatory in 35-40%
  ▫ Abrams Needle biopsy
    confirmatory in 40-50%
  ▫ Thoracoscopy 94-98%
    1-2 x 5mm ports-
    NO FROZEN SECTION
    DIAGNOSIS

Pathology

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

- Mixed Epithelial-Sarcomatous (Biphasic)

- Sarcomatoid (Fibrous, Sarcomatous, Mesenchymal)

- Transitional

- Desmoplastic

- Localized Fibrous Mesothelioma

Slide from W. Travis, MSKCC

Semin Thorac Cardiovasc Surg 2009
Staging

• IMIG 2003 staging system

• AJJC staging system 2010

• Staging involves
  • thoracoscopy
  • often mediastinoscopy

• ~2012 planned new staging system IMIG/IASLC
White light vs PpIX fluorescence
The Evolution of Therapy for MPM

- Biopsy and palliative care
- Biopsy and some sort of surgery
- Biopsy and more radical surgery
- Biopsy and chemotherapy without surgery
- Biopsy and novel intraoperative therapies
- Biopsy and “better” chemotherapies
- Biopsy, radical surgery, and radiotherapy
- Biopsy, induction therapy, surgery and postoperative radiation therapy

“stolen” from H. Pass, ILCC Kona 2009
Chemotherapy
## Phase III studies in 1\textsuperscript{st} line

<table>
<thead>
<tr>
<th>Therapy</th>
<th># patients</th>
<th>MST</th>
<th>1 yr surv</th>
<th>(P)</th>
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</thead>
<tbody>
<tr>
<td>MS01 ASC</td>
<td>136</td>
<td>7.6</td>
<td></td>
<td>0.32</td>
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<tr>
<td>MVP/Vinorelbine</td>
<td>273</td>
<td>8.5</td>
<td></td>
<td></td>
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<tr>
<td>Vogelzang</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cisplatin</td>
<td>222</td>
<td>9.3</td>
<td>38%</td>
<td>&lt; 0.001</td>
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<tr>
<td>Pemetrexed/Cis</td>
<td>226</td>
<td>12.3</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>EORTC</td>
<td></td>
<td></td>
<td></td>
<td>0.046</td>
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<tr>
<td>Cisplatin</td>
<td>124</td>
<td>8.8</td>
<td>39.4%</td>
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<tr>
<td>Raltitrexed/Cis</td>
<td>125</td>
<td>11.2</td>
<td>45.5%</td>
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</tbody>
</table>

*M. Muers Lancet 2008; Vogelzang JCO 2003; van Meerbeeck JCO 2005*
Maintenance therapy

- Maintenance therapy with Thalidomide: negative

TTP

HR = 1.0 (0.7 - 1.2), p=0.71

OS

HR = 1.2 (0.9 - 1.6), p=0.30

P. Baas, abstract 7006, pASCO 2011
Second line therapy

- Retreatment with 1\textsuperscript{th} line regimen (ERS/ESTS 2010)
- Phase III study Vorinostat vs. Placebo (ESMO 2011)

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

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

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

n=660, inclusion closed, data expected Sept 2011
Surgery
Surgical treatment: which to choose?

Extra pleural pneumonectomy

Pleurectomy/Decortication
EPP treatment

- Is a R1 resection
- Mortality rate <5%
- Morbidity rate ~65%

Choice of
- neo-adjuvant chemotherapy
- postoperative RT
- trimodality
P/D treatment

- Tumor reduction R1-2
- Mortality <3%
- Morbidity ~40%
- Palliative treatment

3 Institutions MSKCC, Karmanos, NYU
1990-2006, 663 pts
Retrospective analysis

![Survival by Procedure](image)

**TABLE 2. Site of first recurrence after extrapleural pneumonectomy versus pleurectomy/decortication**

<table>
<thead>
<tr>
<th>Site of Recurrence</th>
<th>EPP (n = 219) n (%)</th>
<th>P/D (n = 133) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrences</td>
<td></td>
<td></td>
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<tr>
<td>Ipsilateral chest</td>
<td>73 (33%)</td>
<td>86 (65%)</td>
</tr>
<tr>
<td>Pericardium</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Distant recurrences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral lung/pleura</td>
<td>146 (66%)</td>
<td>47 (35%)</td>
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<tr>
<td>Peritoneum</td>
<td>49 (22%)</td>
<td>14 (11%)</td>
</tr>
<tr>
<td>Peritoneum + chest</td>
<td>57 (26%)</td>
<td>24 (18%)</td>
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<tr>
<td>Abdominal viscera</td>
<td>17 (8%)</td>
<td>1</td>
</tr>
<tr>
<td>Bone</td>
<td>12 (5%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Brain</td>
<td>7 (3%)</td>
<td>-</td>
</tr>
<tr>
<td>Cutaneous (distant)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

*EPP,* Extrapleural pneumonectomy; *P/D,* pleurectomy/decortication.
MARS study

257 patients screened

- **Patients Registered**
  - N = 112
  - (57 Registered Patients Screened Prior to Therapy)

- **Randomisation**
  - N = 50

- **Allocated to EPP Surgery (With Radical Radiotherapy)**
  - N = 24

- **Allocated to No EPP Surgery**
  - N = 26

- **Registration Phase Not Completed**
  - 55
  - Disease Progression = 27
  - Patient Withdrawal = 18
  - Inoperable = 5
  - Other = 4
  - Died = 1

- **Reviewed by MDT**
  - 57
  - Excluded: Disease Progression / Deemed Inoperable = 6
  - Patient Withdrawal = 1

19 treated with EPP

*T. Treasure, Lancet Oncology July 2011, WCLC, 2011*
MARS: conclusions


group died perioperatively after receiving EPP off trial in a non-MARS centre. The hazard ratio [HR] for overall survival between the EPP and no EPP groups was 1.90 (95% CI 0.92–3.93; exact p=0.082), and after adjustment for sex, histological subtype, stage, and age at randomisation the HR was 2.75 (1.21–6.26; p=0.016). Median survival was 14.4 months (5.3–18.7) for the EPP group and 19.5 months (13.4 to time not yet reached) for the no EPP group.

**Interpretation** In view of the high morbidity associated with EPP in this trial and in other non-randomised studies a larger study is not feasible. These data, although limited, suggest that radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients.

But:

Induction treatment: not well defined, some patients were removed from the study for unclear reasons

Surgery: 19 procedures in 12 centers….

Statistics: incomplete # of patients; conclusions made are not supported
Radiation therapy
Radiotherapy in MPM

- **Conventional RT**
  - Prophylactic to entry ports
  - Palliative for pain
  - As part of MMT
  - No real proof of efficacy
  - Good indication
  - Difficult because of dose constraints

- **Intensity Modulated RT**
  - As part of MMT after EPP
  - As part of MMT after P/D
  - Chance of grade 5 toxicity
  - Promising approach

O’Rourke 2005; Allen 2008; Zauderer WCLC 2011
IMRT

Conventional
Future plans in MPM

• To improve staging and pathology by building DB

• To perform small phase II studies with TR

• Emphasis on epigenetic/targeted drugs
  ▫ In 1th line together with CT
  ▫ In 2nd line alone or in combination

• To design studies with P/D in MMT
Thank you for your attention!