Mesothelioma
Old drugs or new approaches

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Disclosures

• Grants from Pfizer and Roche
• Advisor for MSD and Verastem
A Never Ending Story

- Previously considered as a rare tumor
- Asbestos related
- BAP1 mutation
- Public health issue in developing world
- Many potential diagnostic pitfalls
- Treatment: no validated curative treatment so far
Asbestos production 2012

Top Five Producers (tonnes):
- Russia: 1,000,000
- China: 420,000
- Brazil: 306,500
- Kazakhstan: 241,200
- India: 20,000

Top Five Users (tonnes):
- China: 530,834
- India: 493,086
- Brazil: 167,602
- Indonesia: 161,824
- Russia: 155,476
Study and Treatment Issues
Key problems of studies

Studies take very long: 2-8 years!

Population: heterogeneous
  – Pretreated + untreated
  – Differences in stage and pathology
  – Measurable + non-measurable disease

Incomplete studies set-up
  – Unknown impact of post-study chemotherapy

Limited number of translational studies:
  – No tumor assessments pre-post-tx
## Studies before 2000

<table>
<thead>
<tr>
<th>Agent</th>
<th># Trials</th>
<th># Pts</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>1</td>
<td>51</td>
<td>14%</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>2</td>
<td>68</td>
<td>12%</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>2</td>
<td>62</td>
<td>5%</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
<td>3</td>
<td>109</td>
<td>5%</td>
</tr>
<tr>
<td>Liposomal daunorubicin</td>
<td>1</td>
<td>14</td>
<td>0%</td>
</tr>
<tr>
<td>Caelyx</td>
<td>1</td>
<td>24</td>
<td>21%</td>
</tr>
</tbody>
</table>
First line treatment

• Chemotherapy provides symptom relief and increased OS

• The combination of cisplatin and anti-folate is standard (2003)
  • 80% of tumors recur after 2 years
  • Median OS is 12-13 months

• Multimodality studies use:
  • neoadjuvant chemotherapy
  • extrapleural pneumonectomy or pleurectomy/decortication
  • with or without RT

• Novel and targeting agents: so far no or very limited success
## Second-line CT in MM

<table>
<thead>
<tr>
<th>Drug</th>
<th>#</th>
<th>RR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine/vinorelbine(^1)</td>
<td>30</td>
<td>10%</td>
<td>10.9 mo</td>
</tr>
<tr>
<td>Imatinib(^2)</td>
<td>17</td>
<td>0%</td>
<td>14.3 mo</td>
</tr>
<tr>
<td>Pemetrexed(^3)</td>
<td>123</td>
<td>19%</td>
<td>8.4 mo</td>
</tr>
<tr>
<td>Raltitrexed/oxaliplatin(^4)</td>
<td>15</td>
<td>20%</td>
<td>10.1 mo</td>
</tr>
<tr>
<td>Sorafenib(^5)</td>
<td>39</td>
<td>4%</td>
<td>14.3 mo</td>
</tr>
<tr>
<td>Sunitinib(^6,7)</td>
<td>23</td>
<td>1-18%</td>
<td>8.2 mo</td>
</tr>
<tr>
<td>Thalidomide(^8)</td>
<td>22</td>
<td>6%</td>
<td>11 mo</td>
</tr>
<tr>
<td>Vinorelbine(^9)</td>
<td>63</td>
<td>16%</td>
<td>9.6 mo</td>
</tr>
<tr>
<td>ZD0473(^10)</td>
<td>47</td>
<td>12%</td>
<td>6.7 mo</td>
</tr>
<tr>
<td>Ranpirnase(^11)</td>
<td>39</td>
<td>3%</td>
<td>7.3 mo</td>
</tr>
</tbody>
</table>

1. Zucali, Cancer 2008  
2. Villano Proc ASCO 2004  
4. Fizazi, JCO 2003;  
7. Laurie JTO 2011,  
8. Pavlakis, Proc IASLC 2003,  
9. Stebbing, Lung Ca 2008  
10. Giaccone BJC 2002  
11. Mikulski, JCO 2002
Other Agents

Recent studies
• Amituxamab (MORAb-9)/CDDP/Pem
  – ORR of 39% and median OS of 14.8 months
• Vinorelbine
  – No responses in 2\textsuperscript{nd}/3\textsuperscript{rd} line

Maintenance Studies
• Thalidomide
  – No differences in survival in Phase III trial maintenance setting vs observation (224 pts)
• Vorinostat
  – failed Phase III Trial in 2\textsuperscript{nd} line (660 pts, submitted)
New approaches

- Personalized treatment
  - Targeted agents
  - Immunotherapy
  - Old drugs; new chance?
Targeted therapy

• Better molecular pathway analysis

• Development of new targeted agents

• Combination therapy with targeted agents is possible
New Pathways

- PI3K-mTOR pathway
  - S0722* everolimus Phase II study negative
  - VS5584 + VS6063 phase I study ongoing

*OU et al JTO 2014 p 387
New Pathways

• Merlin pathway
  – Defactinib (VS6063) as inhibitory drug of cancer stem cells
  – Oral formulation
  – Phase 2 randomized double blind maintenance study
  – Stratification for Merlin high vs low
  – Recruitment until end 2015
Chaparone inhibition for mesothelioma

CR-UK MESO2

Confirmed mesothelioma
Chemonaive
Any histology
Consent for tissue

Randomized 1:1
110 pts

Pemetrexed/cisplatin

STA 9090/Ganetespib

Primary endpoint
PFS
HO: HR > 0.65 (5.7-8.8m)
2 year recruitment
1 year follow up

Pemetrexed/cisplatin

Courtesy: D Fennel UK
Immunotherapy

• Anecdotal reports of response of BCG

• MPM expresses PD-L1 in up to 40% of cases

• Different approaches
  – Anti-CTLA4 (Tremulimumab)
  – Dendritic cell reinfusion
  – CAR T-cell
  – Anti-PD1 (Nivolumab)
  – Anti mesothelin (SS1P)
Immunotherapy

- SS1P immunotoxin against mesothelolin
- 10 patients
- Pretreated
- 2/10 PR
- 1/10 SD
- Tox profile mild

*Science Translational Medicine 2013, Vol 5 Issue 208 208ra14*
Immunotherapy

• NivoMes study (NKI)
  – Recurrent MPM
  – Single arm study with Nivolumab (3 mg/kg q2 weeks)
  – RR at 12 weeks doubled
  
  – TR part
  – Thoracoscopy before start and after 6 weeks
    Tregs M1 M2 cells
  – Peripheral blood analysis

• ETOP study with pembrolizumab
Old drugs??

Dr. Batty's
For Your Health
Asthma Cigarettes
Since 1882
For the temporary relief of paroxysms of asthma
Effectively treats: Asthma, Hay Fever, Foul Breath, All Diseases of the Throat, Head Colds, Canker Sores, Bronchial Irritations
Not Recommended for Children under 6.

Stickney and Poor's
Pure Paregoric
U.S.P.
46% Alcohol
1 1/8 grains Opium to each fluid ounce

Guaranteed by Stickney & Poor Spice Co., Boston, Mass., under the Food and Drugs Act, June 30, 1906, Serial No. 47
PROOF study

• To identify the best s.a or combination for a patient.

• Testing of many drugs using a drug library

• Identifying (old) classes of drugs with positive results

• Stats: confirmation of prediction of success or failure. 51 patients required.
Primary culture testing
Cell morphology

Epithelial phenotype: 90%

Mixed phenotype: 10%

50% succes of PTC

Differentiation from reactive mesothelial cells
Chemosensitivity screens

- Responder 5
- Intermediate 23
- Non responder 9

Future:
RNA sequencing of samples from the 3 groups
## Library screen

<table>
<thead>
<tr>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depsipeptide</strong></td>
</tr>
<tr>
<td><strong>Bortezomib</strong></td>
</tr>
<tr>
<td><strong>Dactinomycin</strong></td>
</tr>
<tr>
<td><strong>Carfilzomib</strong></td>
</tr>
<tr>
<td><strong>Plicamycin</strong></td>
</tr>
<tr>
<td><strong>Doxorubicin</strong></td>
</tr>
<tr>
<td><strong>Daunorubicin</strong></td>
</tr>
<tr>
<td><strong>Dasatinib</strong></td>
</tr>
<tr>
<td><strong>Valrubicin</strong></td>
</tr>
<tr>
<td><strong>Mitoxantrone</strong></td>
</tr>
<tr>
<td><strong>Vorinostat</strong></td>
</tr>
<tr>
<td><strong>cladribine</strong></td>
</tr>
</tbody>
</table>

- HDAC-inhibitors
- Proteasome – inhibitors
- Anthracyclines
- Antineoplastic antibiotic
Conclusions

• Precision Medicine:
  – Immunotherapy is very promising, but hardly results yet
  – Targeted agents better used by increased knowledge of the molecular pathways
  – Old drugs aren’t that old… just used in a wrong way
Prevent undesired behaviour

Famous 1977 cartoon of Herblock in the NY Times
Thanks for your attention. Hubble telescope.