Mesothelioma update

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Pleural plaques

Asbestosis

Pleural mesothelioma
New alternatives in malignant pleural mesothelioma

- Molecular alterations
- Chemotherapy
  - Situation before randomized phase III studies
  - Randomized phase III studies
  - When to treat and maintenance therapy?
- Multimodality therapy including extrapleural pneumonectomy
- Targeting therapy and new drugs
22q12 locus in mesothelioma

- NF2 at 22q12 locus (neurofibromatosis type 2 gene): Mutated/inactivated in a proportion of cell lines and smaller proportion of tumors (Sekido, Cancer Res 1995)

- NF2 gene product merlin inhibits cell proliferation, decreases expression of cyclin D1 and leads to G1 arrest (Xiao, Mol Cell Biol 2005)

- NF2 (+/-) knockout mice exposed to asbestos develop mesothelioma more frequently than wt mice. The tumors demonstrate a homologous deletion of CDKN2A and CDKN2B (Altomare, Cancer Res 2005)

- Re-expression of merlin inhibits invasiveness in mesothelioma cells (Poulidakos, Oncogene 2006)
Deletion of 9p21 loci in mesothelioma

9p21 locus (Methylthioadenosine phosphorylase)

CDKN2B  CDKN2A  MTAP

$p15^{INK4B}$  $p16^{INK4A}$  $p14^{ARF}$  MTAP

Cyclin D-CDK4/6  MDM2

$pRb$  $p53$

Loss of cell cycle control  Loss of p53 DNA damage checkpoint??

MTA  Adenine + MTR-1-P

L-alanosine  AMP synthesis

Loss of salvage pathway of AMP biosynthesis
Chemotherapy in Mesothelioma: The Past

Small phase II studies, generally less than 40 pts
- Doxorubicine and epirubicine: RR 5%-15%
- Cisplatin and carboplatin: RR 7%-16%
- Antifolates (methotrexate, edatrexate, trimetrexate): RR 12-37%
- Combination chemotherapy
  - Alkylating agents and anthracyclins: RR 11-30%
  - Cisplatin and anthracycline: RR 14-22%

Tiong and Vogelzang, JCO 1997
## Chemotherapy in mesothelioma: activity of newer agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>RR</th>
<th>MST</th>
</tr>
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<tbody>
<tr>
<td><strong>Vinorelbinene</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Steele, JCO 2000</td>
<td>21%</td>
<td>10.6 months</td>
</tr>
<tr>
<td>(symptom improvement)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gemcitabine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bischoff, PASCO 1998</td>
<td>31%</td>
<td>n/a</td>
</tr>
<tr>
<td>- v. Meerbeck, Cancer 1999</td>
<td>7%</td>
<td>8.0 months</td>
</tr>
<tr>
<td>- Kinder, Lung Cancer 2001</td>
<td>0%</td>
<td>4.1 months</td>
</tr>
<tr>
<td><strong>Raltitrexed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Baas, EJC 2003</td>
<td>21%</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Pemetrexed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Scagliotti, JCO 2003</td>
<td>14%</td>
<td>10.7 months</td>
</tr>
</tbody>
</table>

Inactive agents: taxanes, camphothecins, temozolamide
## Chemotherapy in mesothelioma: Platin and gemcitabine combinations

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>21</td>
<td>53</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1000 d1,8,15</td>
<td>1000 d1,8,15</td>
<td>1250 d1,8</td>
<td>1000 d1,8,15</td>
</tr>
<tr>
<td>Platin</td>
<td>Cis 100</td>
<td>Cis 100</td>
<td>Cis 80</td>
<td>Carbo AUC 5</td>
</tr>
<tr>
<td>Response</td>
<td>48%</td>
<td>33%</td>
<td>16%</td>
<td>26%</td>
</tr>
<tr>
<td>Survival (median)</td>
<td>9.5 ms</td>
<td>11.2 ms</td>
<td>9.6 ms</td>
<td>15 ms</td>
</tr>
</tbody>
</table>
MVP in Mesothelioma Provides Symptom Relief

- 150 patients
- RR 15% (95% CI 9%-21%)
- Symptom improvement 69%
  - Dyspnea 50%
  - Cough 62%
  - Pain 71%
  - Malaise 39%
- Median survival 7 months
- 1-year and 2-year survival: 31% and 11%

Pemetrexed + Cisplatin vs Cisplatin: Study Design

Primary endpoint: survival

- 80% power to detect hazard ratio of .67 in FA/B_{12} group
- 92% power to detect hazard ratio of .67 in entire study

Vogelzang, JCO 2003
Pemetrexed + Cisplatin vs Cisplatin: Tumor Response Rates and Survival

**Tumor Response Rates**

- **All Eligible**
  - Pemetrexed + Cisplatin: 41% (CI 38-44), Cisplatin: 17% (CI 12-22)
  - p < 0.001

- **FA/B<sub>12</sub>**
  - Pemetrexed + Cisplatin: 46% (CI 53-38), Cisplatin: 28% (CI 27-14)
  - p < 0.001

- **Partially and no FA/B<sub>12</sub>**
  - Pemetrexed + Cisplatin: 29% (CI 43-18), Cisplatin: 9% (CI 19-3)
  - p = 0.005

**Survival: All Eligible Patients**

- **MST**
  - Pemetrexed + Cisplatin: 9.3 months
  - Cisplatin: 12.1 months

- **HR**: 0.77
- **Logrank p-value**: 0.020

-Vogelzang, JCO 2003
Pemetrexed + Cisplatin vs Cisplatin: Symptomatic improvement

**Lung Cancer Symptom Scale: Pain**

- **Cycle 0**: n.s., p = 0.064
- **Cycle 2**: p = 0.017
- **Cycle 4**: n.s.
- **Cycle 6**: p = 0.017

**Lung Cancer Symptom Scale: Dyspnea**

- **Cycle 0**: n.s., p = 0.476
- **Cycle 2**: p = 0.344
- **Cycle 4**: p = 0.004
Cisplatin vs Cisplatin and Raltitrexed in Malignant Pleural Mesothelioma

PS WHO 0-2, adequate hematological and organ function

Response rate:
P 13.6%
PR 23.6%

Median survival:
P 8.8 mo
PR 11.4 mo

Global quality of life: no difference

Van Meerbeeck, JCO 2005
Pemetrexed in 2nd line for MPM: Study design and results

- **2nd line**
- **PS 0 - 2**

**Primary objective:** Overall Survival

- **ALIMTA 500 + BSC**
  - RR 19%
  - PFS 3.8 months*
  - OAS 8.6 months

- **BSC**
  - RR 2%
  - PFS 1.5 months*
  - OAS 9.8 months

N = 240 Patients

Data locked; Nov. 2005

Jassem, ESMO 2006
## Pemetrexed in 2nd line for MPM: Post-Discontinuation Chemotherapies*

<table>
<thead>
<tr>
<th>Chemotherapy type, n (%)</th>
<th>P-BSC (N=123)</th>
<th>BSC (N=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients receiving at least one chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum salts</td>
<td>14 (11)</td>
<td>23 (19)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>16 (13)</td>
<td>12 (10)</td>
</tr>
<tr>
<td><strong>Pemetrexed</strong></td>
<td>4 (3)</td>
<td>22 (18)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>7 (6)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>6 (5)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Other agents</td>
<td>2 (2)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Raltitrexed</td>
<td>3 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Mitomycin-C</td>
<td>0 (0)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Median time to initiation of post-discontinuation chemotherapy: P-BSC arm 15.2 months versus BSC arm 4.3 months, p<0.0001
Early vs Delayed Chemotherapy

Patients randomized to receive Early (ET) or Delayed (DT) chemotherapy (MVP; cis or carbo) q 3 wks up to 4 courses:

- **Freedom from symptom progression**
  - Early (n=21)
  - Delayed (n=17)

- **Overall survival**
  - Delayed (n=22)
  - Early (n=21)

O’Brien, Ann Oncol 2005
PET Response over Time

- Baseline
- 3 Cycles
- 6 Cycles
- 9 Cycles
Extrapleural pneumonectomy (EPP) for malignant pleural mesothelioma

- EPP has the potential for long-term survival and maybe cure in selected patients

- EPP with adjuvant chemotherapy and radiotherapy:
  - Brigham: 176/183 pts: MST 19 months, periop. mortality 3.8%, 35% local failure (Sugarbaker JTCVS 1999; Baldini, ATS 1997)

- EPP with high dose hemithoracic radiotherapy: Increase of local tumor control, more toxicity?
  - 13% local only failure vs 55% distal only failure, 61/88 EPP: MST 17 mo, periop. mortality 11% (Rusch, JTCVS 2001)
Why investigate neoadjuvant chemotherapy followed by EPP?

- Inability to provide adjuvant therapy after EPP as planned and poor outcome of pilot trial in Zürich (Taverna, ESMO 2000)
- Experience in neoadjuvant therapy of stage III non-small cell lung cancer
- Report on high response rate with the combination of cisplatin and gemcitabine (Byrne JCO 1999)
- Results of a pilot study at the University Hospital Zürich: 19 pts, 16 EPP, MST 23 months (Weder, JCO 2004)
SAKK 17/00: Patients and methods

• Patients selection:
  ◦ PS 0-2
  ◦ T1-3, N0-2, M0 disease considered resectable
  ◦ Estimated postoperative FEV1 over 40%

• Chemotherapy:
  ◦ Cisplatin 80 mg/m² d1 and gemcitabine 1000 mg/m² d1, d8, d15 x3 cycles

• Surgery:
  ◦ EPP

• Radiotherapy:
  ◦ Recommended to areas of obvious incomplete resection (60 Gy in 2 Gy fractions) or to high-risk areas as defined by the surgeon (50 Gy in 2-Gy fractions)
SAKK 17/00: Surgery

• 45 of 58 patients completing 3 cycles of chemotherapy were considered resectable by EPP:
  Operability rate 78% (95% CI: 66%-88%) [74%]

• 37 of 45 patients were completely resected by EPP:
  Resectability rate: 64% [61%]

• Postoperative hospitalization: median 14 (range 3-84) days

• Postoperative complications: 21 patients

• Postoperative death: 1 patient
SAKK 17/00: Overall survival

One-year survival: 69%
Median survival: 19.8 mo
[95% CI: 14.6-24.5]

*Complete resection 35 pts (61%)

One-year survival: 78%
Median survival: 23.0 mo
[95% CI: 16.6-32.9]

Stahel and Weder, submitted
SAKK 17/00: Quality of life change

Psychological score

Physical score

Activity level

Overall quality of life

Stahel and Weder, submitted
SAKK 17/04: Multicenter randomized phase II trial (initiated Q4 2005)

Part 1
- Registration after staging
- Chemo-therapy*
- Restaging
- Surgery
- Reassessment

Part 2
- Randomisation
- Arm A: No Radiotherapy
- Arm B: Hemithoracic Radiotherapy

*Follow-up if not operable
*R0 or R1
*R2
*3 cycles of pemetrexed/cisplatin
Clinical trial with anti-mesothelin antibodies

- **SS1P** (recombinant immunotoxin):
  - Phase I: IV qdx6, MTD 45 ug/kg, DLT reversible pleuritis but no pericarditis, 34 pts, including 21 with mesothelioma: MR 4, SD 19, some resolution of ascites
  - Phase II: in combination with gemcitabine initiated

- **MORAb-009** (humanized antibody):
  - Elicits ADCC, inhibits mesothelin binding to MU16
  - Phase I: ongoing

Hassan, Lung Cancer 2006
Double-blind, placebo-controlled randomized phase II trial of bevacizumab

Median overall survival: 15.7 months [95% CI 11.7, 20.9]

Kindler, ASCO 2005
Phase II trials with VEGFR2 (KDR) TKIs

Trials completed and communicated:

- **SU5416** (primarily KDR): RR 10%, abandoned because of toxicity
  (Kindler, ASCO 2004)

- **Vatalanib** (VEGFR1, KDR, PDGF, c-kit): 44 pts, RR 9%, median PFS 4 months
  (Jahan, ASCO 2006)

- **Sorafenib** (KDR, PDGF, raf): 51 pts, RR 5%, median FFS 4.1 months
  (Jänne, ESMO 2006)
Trials completed and communicated:

- **EGFR TKIs:**
  - Gefitinib: 43 pts, RR 2%, median FFS 3.6 months (Givindan, CCR 2005)
  - Erlotinib: 64 pts, RR 0% (Garland, ASCO 2004)

- **Imatinib:**
  - 25 pts, RR 0%, median PFS 2 months (Mathy, Lung Cancer 2005)
  - 11 pts, RR 0%, median PFS 2.5 months (Pora, Cancer Chemther Pharmacol 2006)
The therapeutic nihilism should end

The addition of an antifolate to cisplatin is well tolerated and leads to a survival advantage

Pemetrexed + cisplatin not only improves survival as compared to cisplatin alone, but is also associated with a better quality of life

Pemetrexed + BSC vs BSC demonstrates improved progression-free survival and a response rate of 19% in the pemetrexed arm
The results of a small trial suggest better symptom control with less deterioration in QoL by the early use of chemotherapy.

The tolerability of pemetrexed and clinical observations suggest further investigation into its role in maintenance therapy.

Results from multimodality approaches with neoadjuvant chemotherapy and extrapleural pneumonectomy are encouraging.

Targeted therapies and new cytotoxic agents (vorinostat, bortezomib) are under investigation.
SAHA (Vorinostat) Phase III Trial

Unresectable MPM
One or two prior chemo regimens (most recent must include pemetrexed)
Stratify by:
  - Histology
  - KPS
  - # prior regimens

Vorinostat (initially 300mg BID x 14 days q 21, changed to 300mg BID for 3 days q 7)

Placebo

Primary endpoint: Overall survival, N=660 patients
1st interim analysis after 50 pts enrolled for response
2nd interim analysis after 220 pts enrolled for secondary endpoints

Correlative studies: tissue collection for genotyping, volumetrics, serial PFTs, symptom and QOL assessment
## Pemetrexed + Cisplatin vs Cisplatin: Selected grade 3/4 toxicity (%)

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>No FA/B&lt;sub&gt;12&lt;/sub&gt;</th>
<th>FA/B&lt;sub&gt;12&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALIMTA + Cis</td>
<td>ALIMTA + Cis</td>
<td>ALIMTA + Cis</td>
</tr>
<tr>
<td></td>
<td>ALIMTA</td>
<td>Cis</td>
<td>ALIMTA</td>
</tr>
<tr>
<td></td>
<td>n=226</td>
<td>n=222</td>
<td>n=58</td>
</tr>
<tr>
<td>Possible DRD</td>
<td>4</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>28</td>
<td>2</td>
<td>41</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>0</td>
<td>7</td>
</tr>
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</table>

DRD = Drug related death

Vogelzang, JCO 2003
Early vs Delayed Chemotherapy in MPM

- Patients randomized to receive Early (ET) or Delayed (DT) chemotherapy (MVP; cis or carbo) q 3 wks up to 4 courses
  - 21 ET vs 22 DT
  - Med time to symptomatic progressing 25 wks ET vs 22 wks DT (p=0.08)
  - Med Survival 14 mo ET vs 10 mo DT (=0.04)
  - QoL: ET marginal worsening fatigue and alopecia; no significant differences in functional scales
  - DT: physical functioning significantly worse (p=0.008), dyspnea significantly worse (p=0.02)

- Symptom control with less deterioration in QoL and small survival advantage by early use of chemotherapy in this small trial

O’Brien, Ann Oncol 2005
Double-blind, placebo-controlled randomized phase II trial of gemcitabine/cisplatin ± bevacizumab

Both arms combined (106pts):

Median progression-free survival:
- 6.4 months [95% CI 5.5, 7.3]

Median overall survival:
- 15.7 months [95% CI 11.7, 20.9]

1-year survival:
- 60.1% [95% CI 49.3, 70.8]

Kindler, ASCO 2005
Pemetrexed in 2nd line for MPM:
Survival when post-discontinuation pemetrexed is counted as P-BSC Arm (exploratory analysis)

\[ P = 0.07 \]

Jassem, ESMO 2006
**Chromosomal Alterations and Tumor Suppressor Genes in Mesothelioma**

<table>
<thead>
<tr>
<th>Numerical changes and structural changes identified in all chromosomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal loss often at 1p21-22, 3p21, 6q15-21, 9p21-22 and 22q12</td>
</tr>
<tr>
<td>- CDKN2A at locus 9p21 is deleted in about 70% of mesothelioma (Prins, IJC 1998; Xiao, Oncogene 1995)</td>
</tr>
<tr>
<td>- Neurofibromatosis type 2 gene at 22q12 locus is mutated/inactivated in a large proportion of mesothelioma (Sekido, Cancer Research 1995)</td>
</tr>
<tr>
<td>P53: Absence of p53 mutations (Mor 1997)</td>
</tr>
<tr>
<td>RB1 (retinoblastoma gene): Absence of mutations or deletions (van der Meeren, Eur Resp Rev 1993)</td>
</tr>
</tbody>
</table>