Recent Advances in the Management of Malignant Pleural Mesothelioma

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Pleural plaques

Asbestosis

Pleural mesothelioma
Occupational and environmental asbestos exposure causes malignant mesothelioma

- 1943 Wedler, Germany: Suggestion of asbestos as cause for mesothelioma
- 1960 Wagner, South Africa: 33 cases of mesothelioma in neighborhood of crocidolite mines in West Cap Province
- 1979 Baris, Turkey: High mortality from mesothelioma in villages in central Turkey located in volcanic tuff (fibrous erionite)
- 1985 Langer, Greece: Association of Metsovo lung and pleural mesothelioma (tremolite-containing whitewash)
- 2006 Dogan, Cancer Research: Genetic predisposition to fiber carcinogenesis causes mesothelioma epidemic in Turkey
Mesothelioma in Europe

**Peto, BJC 1999:**
Peak incidence around 2020

- British mesothelioma register and male death rates for cancer of the pleura from 6 European countries
- Statistical modeling taking into account asbestos legislation and long latency period

**Perlucchi, BJC 2004; Hodgson BJC 2005:**
Peak leveling off between 2010 and 2015
Continued Exposure in the Third World
**Chromosomal Alterations and Tumor Suppressor Genes in Mesothelioma**

- Numerical changes and structural changes identified in all chromosomes

- Chromosomal loss often at 1p21-22, 3p21, 6q15-21, 9p21-22, and 22q12
  - CDKN2A at locus 9p21 is deleted in about 70% of mesothelioma (Prins, IJC 1998; Xiao, Oncogene 1995)
  - Neurofibromatosis type 2 gene at 22q12 locus is mutated/inactivated in a proportion mesotheliomas (Sekido, Cancer Research 1995)

- P53: Absence of p53 mutations (Mor 1997)

- RB1 (retinoblastoma gene): Absence of mutations or deletions (van der Meeren, Eur Resp Rev 1993)
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, contribution to tumor development not yet elucidated (Sekido, Cancer Res 1995)

• NF2 gene product merlin inhibits cell proliferation, decreases the expression of cyclin D1 and arrest cells at G1 (Xiao, Mol Cell Biol 2005)

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

• Re-expression of merlin inhibits invasiveness in mesothelioma cells and negatively regulates FAK (Poulakis, Oncogene 2006)
Deletion of 9p21 loci in mesothelioma

9p21 locus

CDKN2B

CDKN2A

MTAP

(Methylthioadenosine phosphorylase)

9p21 locus

p15INK4B

p16INK4A

p14ARF

MTAP

MTA

Adenine +
MTR-1-P

L-alanosine

AMP synthesis

Cyclin D-CDK4/6

MDM2

pRb

p53

Loss of cell cycle control

Loss of p53 DNA damage checkpoint??

Loss of salvage pathway of AMP biosynthesis

MTA

telomere

centromere
P16/CDKN2A Deletion is an Adverse Prognostic Factor

Expression profiling of 99 resected mesothelioma:

Significant adverse prognostic factors (multivartiate analysis):

- Advanced stage
- Sarcomatous histology
- P16/CDKN2A homozygous deletion (59/80 cases)

Lopez-Rios, Cancer Res 2006
Targeting survivin in MPM with antisense oligonucleotides sensitizes cells to cisplatin-induced apoptosis

Survivin AS 4003 is specific for nucleotides 232-251

Hopkins-Donaldson, Neoplasia 2006
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 antracycline: RR 14-22%

Tiong and Vogelzang, JCO 1997
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 in Mesothelioma

- Pemetrexed + cisplatin I
- Pemetrexed + carboplatin I
- Pemetrexed single-agent II
- Pemetrexed + cisplatin vs. cisplatin III
- Pemetrexed + BSC (2nd line) versus BSC III
- Pemetrexed + carboplatin II
- Pemetrexed + cisplatin neoadjuvant II
Pemetrexed Phase II in Advanced Mesothelioma

- Median age: 65 years (range 39-80)
- Epi/mixed/sarc/unspecified histology: 70%/14%/13%/3%; Stage III/IV: 34%/52%
- Overall Response Rate: 9/64 PRs (14%)
  - 7/43 (16%) fully vitamin supplemented
  - 2/21 (9.5%) non-vitamin supplemented
- Activity maintained and 3/4 toxicity improved with the addition of vitamin supplementation
- Median TTP: 4.7 months; median survival: 10.7 months; 1-year survival: 48%

Scagliotti, JCO 2003
Pemetrexed + Cisplatin vs Cisplatin: in Malignant Pleural Mesothelioma

- Randomized, single-blind, controlled, multicenter
- FA and B₁₂ supplementation initiated during study
- **Primary Objective:** To compare survival (HR=0.67)
- **Secondary Objectives:**
  - Other time to events
  - Tumor response rate
  - Clinical benefit and LCSS
  - Change in PFT and Lung Density
  - Toxicity assessment

Vogelzang, JCO 2003
Pemetrexed + Cisplatin vs Cisplatin: Study Design

Primary endpoint: survival

- 80% power to detect hazard ratio of 0.67 in FA/B₁₂ group
- 92% power to detect hazard ratio of 0.67 in entire study

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

**Tumor Response Rates**

- All Eligible:
  - Pemetrexed/Cis: 41% (CI 42-34) vs Cis: 17% (CI 22-72)
  - P < 0.001

- FA/BB:
  - Pemetrexed/Cis: 46% (CI 53-39) vs Cis: 20% (CI 27-14)
  - P < 0.001

- Partially and no FA/BB:
  - Pemetrexed/Cis: 29% (CI 43-19) vs Cis: 8% (CI 19-3)
  - P = 0.005

**Survival: All Eligible Patients**

- MST = 9.3 mos for Pemetrexed+Cisplatin (n=228)
- MST = 12.1 mos for Cisplatin (n=222)

- HR: 0.77
- Logrank p-value: 0.020

**Vogelzang, JCO 2003**
# Pemetrexed + Cisplatin vs Cisplatin: Selected grade 3/4 toxicity (%)

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>No FA/B$_{12}$</th>
<th>FA/B$_{12}$</th>
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<tbody>
<tr>
<td></td>
<td>ALIMTA + Cis</td>
<td>ALIMTA + Cis</td>
<td>ALIMTA + Cis</td>
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<tr>
<td></td>
<td>n=226</td>
<td>n=58</td>
<td>n=168</td>
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<tr>
<td></td>
<td>Cis n=222</td>
<td>Cis n=59</td>
<td>Cis n=163</td>
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<tr>
<td>Possible DRD</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>28</td>
<td>41</td>
<td>23</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>2</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Vomiting</td>
<td>13</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

DRD = Drug related death

Vogelzang, JCO 2003
Lung Function (Vital Capacity) by Treatment Arm

- **Pent/Cis**
  - Cycle 0: 2.45
  - Cycle 2: 2.55
  - Cycle 4: 2.60
  - Cycle 6: 2.70

- **Cis**
  - Cycle 0: 2.50
  - Cycle 2: 2.55
  - Cycle 4: 2.65
  - Cycle 6: 2.70

**p-values:**
- Pent/Cis vs. Cis:
  - Cycle 2: p = 0.034
  - Cycle 4: p = 0.006
  - Cycle 6: n.s.

Lung Cancer Symptom Scale: Dyspnea

- **Pent/Cis**
  - Cycle 0: n.s.
  - Cycle 2: 35
  - Cycle 4: 35
  - Cycle 6: 40

- **Cis**
  - Cycle 0: 30
  - Cycle 2: 30
  - Cycle 4: 35
  - Cycle 6: 40

**p-values:**
- Pent/Cis vs. Cis:
  - Cycle 0: p = 0.476
  - Cycle 2: p = 0.344
  - Cycle 4: n.s.
  - Cycle 6: p = 0.004

Lung Cancer Symptom Scale: Pain

- **Pent/Cis**
  - Cycle 0: n.s.
  - Cycle 2: 25
  - Cycle 4: 30
  - Cycle 6: 35

- **Cis**
  - Cycle 0: 20
  - Cycle 2: 25
  - Cycle 4: 30
  - Cycle 6: 35

**p-values:**
- Pent/Cis vs. Cis:
  - Cycle 0: n.s.
  - Cycle 2: p = 0.064
  - Cycle 4: p = 0.017
  - Cycle 6: p = 0.017

**Note:** The diagram shows the changes in vital capacity and symptom scales over cycles for two treatment arms, Pent/Cis and Cis.
Pemetrexed + Cisplatin vs Cisplatin: Patients Receiving Post-Study Therapy

Manegold, Ann Oncol 2005
# Pemetrexed + Cisplatin vs Cisplatin

## Updated Survival: 2005

<table>
<thead>
<tr>
<th>Survival Time</th>
<th>% Patients Alive</th>
<th>Difference</th>
<th>p-value</th>
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<tbody>
<tr>
<td>ALIMTA + Cisplatin</td>
<td>Cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>76.8</td>
<td>70.3</td>
<td>6.5</td>
</tr>
<tr>
<td>9 months</td>
<td>62.7</td>
<td>49.9</td>
<td>12.8</td>
</tr>
<tr>
<td>12 months</td>
<td>51.8</td>
<td>37.8</td>
<td>13.9</td>
</tr>
<tr>
<td>15 months</td>
<td>39.6</td>
<td>27.1</td>
<td>12.5</td>
</tr>
<tr>
<td>18 months</td>
<td>32.7</td>
<td>23.4</td>
<td>9.3</td>
</tr>
<tr>
<td>21 months</td>
<td>26.2</td>
<td>21.1</td>
<td>5.1</td>
</tr>
<tr>
<td>24 months</td>
<td>22.1</td>
<td>17.2</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Vogelzang, WCLC 2005
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 and Carboplatin: Phase II Trial within Expanded Access Program

102 patients with measurable disease, no prior chemotherapy, treated with pemetrexed 500 mg/m² and carboplatin AUC 5

RR: 19%
Median time to progression: 6.5 mo
MST: 12.7 mo

Ceresoli, JCO 2006
# Pemetrexed and Carboplatin: Phase II Toxicity by patient Grade 3/4

<table>
<thead>
<tr>
<th></th>
<th>3 (no.)</th>
<th>4 (no.)</th>
<th>3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>9</td>
<td>11*</td>
<td>19.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>2</td>
<td>7.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>11</td>
<td>1</td>
<td>11.7</td>
</tr>
<tr>
<td>N/V</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

*Febrile Neutropenia reported in 2 patients

Ceresoli, JCO 2006
Early vs Delayed Chemotherapy

- 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
Early vs Delayed Chemotherapy

O’Brien, Ann Oncol 2005

**Freedom from Symptom Progression**
- Early (n=21)
- Delayed (n=17)

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

p=0.03
p=0.1
PET Response over Time

Baseline  |  3 Cycles  |  6 Cycles  |  9 Cycles
Feasibility and efficacy of pemetrexed maintenance was assessed in 13 of 27 pts with no progression after 6 cycles of pemetrexed or pemetrexed/carboplatin.

- Median 4 (range 2-14) cycles
- Toxicity: G 3/4 toxicity: neutropenia (15%), anemia, leucopenia (8% each); fatigue (15%)
- Response: in 3/13 pts (23%) further improvement from SD to PR was achieved
- Pemetrexed maintenance feasible and further study warranted

Van den Bogaert, JTO 2006
Extrapleural Pneumonectomy for Malignant Pleural Mesothelioma

- Extrapleural pneumonectomy (EPP) is the only approach with the potential for long-term survival and cure in selected patients.
- EPP with adjuvant chemotherapy and radiotherapy:
  - Sugarbaker, JTCVS 1999; Baldini, ATS 1997
    176/183 pts: MST 19 months, periop. mortality 3.8%, 35% local failure.
- EPP with high dose hemithoracic radiotherapy may increase local tumor control. Toxicity?
  - Rusch, JTCVS 2001:
    13% local only failure vs 55% distal only failure, 61/88 EPP: MST 17 mo, periop. mortality 11%
The discovery of effective chemotherapy in MPM has sparked interest in studying combined modality therapy for fit patients prior to extrapleural pneumonectomy and radiotherapy in an effort to improve success.

Pilot trials have shown promise with treatment with gemcitabine + cisplatin followed by EPP and hemithoracic RT.

Studies on neoadjuvant chemotherapy with pemetrexed and cisplatin have been initiated.

Stahel, ASCO 2004 and Lung Cancer 2005;
Flores, ASCO 2004; Weider, J CO 2004; Krug, Lung Cancer 2005
**SAKK 17/00: Neoadjuvant Gem/Cis followed by Extrapleural Pneumonectomy**

**Patient characteristics:**

- **61 patients (57 male)**
- **Age:** median age 59 years, range 44-72 years
- **WHO Performance status:** 0: 37; 1: 23; 2: 1

**T-stage:**

- cT1 17
- cT2 34
- cT3 10

**N-stage:**

- pN0-1 53
  - (mediastinoscopy)
- pN2 7
- Nx 1

**Distant metastases:** none
SAKK 17/00: Neoadjuvant Gem/Cis followed by Extrapleural Pneumonectomy

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 17/04: Multicenter randomized phase II trial (initiated Q4 2005)

Part 1
- Registration after staging
- Chemotherapy*
- Restaging
- Surgery
- Reassessment
- Follow-up if not operable

Part 2
- Randomisation
  - R0 or R1
  - R2
  - Follow-up

Arm A: No Radiotherapy
Arm B: Hemithoracic Radiotherapy

*3 cycles of pemetrexed/cisplatin
Targeted Therapy in Mesothelioma

- VEGF signalling: SU5416, bevacizumab
- EGFR signalling: Gefitinib, erlotinib
- Multiple targets, including PDGF: Imatinib, PTK787, sorafenib
- Thalidomide
- Tetrathiomolybdate (TM) after cytoreductive surgery
- L-alanosin
- Bortezomib
- Deacetylase inhibitors: SAHA (Suberoylanilide hydroxamic acid): 2/13 unconfirmed responses in phase I study (Kelly, JCO 2005), randomized phase II initiated
Malignant Pleural Mesothelioma
Conclusions 1

- Doubling of incidence in Europe over the next 10 years
- The therapeutic nihilism must end
- Pemetrexed + cisplatin are now the standard front-line therapy for patients with malignant pleural mesothelioma
- 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 phase III trial: results are awaited

The combination of pemetrexed and cisplatin has been chosen as neoadjuvant chemotherapy in at least three phase II studies

A beneficial effect of molecular therapies based on known biological properties remains to be proven

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