Overview of Mesothelioma

Raffit Hassan, M.D.
Mesothelioma

• Is an aggressive tumor that arises from the serosal surfaces of body cavities

• In 1960, Wagner reported increased incidence of mesothelioma in asbestos miners of South Africa

• Asbestos is the primary cause of mesotheliomas

• Long latency from the time of asbestos exposure to onset of disease

• No history of asbestos exposure in 30-50% of cases of mesothelioma
Mesothelioma

• Endemic erionite exposure in Cappadocia, Turkey

• Simian virus 40 (SV40) has been implicated in the etiology of some mesotheliomas

• Some cases have been reported following therapeutic radiation

• Patients with Hodgkin’s disease may have an increased risk of developing mesothelioma

• Approx. 2200 new cases of mesothelioma are diagnosed each year in the United States
# Global Burden of Mesothelioma

<table>
<thead>
<tr>
<th>Country or Region</th>
<th>Incidence</th>
<th>Predicted Peak Year</th>
<th>Predicted No. of Deaths in Next 40 Yr</th>
<th>Predicted Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>15</td>
<td>2004</td>
<td>72,000</td>
<td>200</td>
</tr>
<tr>
<td>Europe</td>
<td>18§</td>
<td>2015–2020</td>
<td>250,000</td>
<td>80</td>
</tr>
<tr>
<td>Japan</td>
<td>7</td>
<td>2025</td>
<td>103,000</td>
<td>—</td>
</tr>
<tr>
<td>Australia</td>
<td>40</td>
<td>2015</td>
<td>30,000</td>
<td>5–10</td>
</tr>
</tbody>
</table>

*Table 1. Worldwide Trends in the Epidemiologic Features of Malignant Mesothelioma.*

1. Incidence: cases/million population
2. Predicted No. of Deaths in Next 40 Yr: billions of U.S. dollars
3. Predicted Cost: billions of U.S. dollars

§ Estimated values.
Asbestos Fibers

CHRYSOTILE (Serpentine)

AMPHIBOLES (Rod-like)
  Crocidolite
  Amosite
Asbestos Fibers

CHrysotile

Amosite
Occupations associated with asbestos exposure

• Miners (blue asbestos mine in Wittenoom, Australia)
• Family members of miners and others
• Asbestos insulators
• Plumbers
• Carpenters
• Defense personnel
Peritoneal Mesothelioma
Tunica Vaginalis Mesothelioma

Tolhurst et al. *Urologic Oncology*, 2006

Pericardial Mesothelioma

Sharaf El-Dean et al. *Arch Pathol Lab Med*, 2004
Histological Sub-types of Mesothelioma

Epithelial  
Sarcomatoid  
Biphasic
Pleural Mesothelioma
Pleural Mesothelioma
Presentation

- Pleural effusion *(cytology often negative)*
- Chest wall pain
- Constitutional symptoms
- Asymptomatic
- Distant metastasis uncommon at presentation
Staging

New international staging system for diffuse malignant pleural mesothelioma

T1  
T1a Tumor limited to the ipsilateral parietal including mediastinal and diaphragmatic pleura

No involvement of the visceral pleura

T1b Tumor involving the ipsilateral parietal including mediastinal and diaphragmatic pleura

Scattered nodules of tumor also involving the visceral pleura

T2  
Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features:

- involvement of diaphragmatic muscle
- contiguous visceral pleural tumor (including the fissures), or extension of tumor from visceral pleura into the adjacent lung parenchyma

T3  
Describes locally advanced but potentially resectable tumor

Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features:

- involvement of the endothoracic fascia
- extension into the mediastinal fat
- solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall
- non-transmural involvement of the pericardium

T4  
Describes locally advanced technically unresectable tumor

Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral) with at least one of the following features:

- diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction
- direct transthoracic extension of tumor to the pericardium
- direct extension of tumor to the contralateral pleura
- direct extension of tumor to one or more mediastinal organs
- direct extension of tumor to the spine
- tumor extending through to the internal surface of the pericardium with or without a pericardial effusion, or tumor involving the myocardium

N  
Lymph nodes

NX  Regional lymph nodes cannot be assessed

N0  No regional lymph node metastases

N1  Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes

N2  Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary nodes

N3  Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

M  
Metastases

MX  Presence of distant metastases cannot be assessed

M0  No distant metastasis

M1  Distant metastasis present
<table>
<thead>
<tr>
<th>Stage</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>$T_{1a} N_0 M_0$</td>
</tr>
<tr>
<td></td>
<td>$T_{1b} N_0 M_0$</td>
</tr>
<tr>
<td>II</td>
<td>$T_2 N_0 M_0$</td>
</tr>
<tr>
<td>III</td>
<td>Any $T_3 M_0$</td>
</tr>
<tr>
<td></td>
<td>Any $N_1 M_0$</td>
</tr>
<tr>
<td></td>
<td>Any $N_2 M_0$</td>
</tr>
<tr>
<td>IV</td>
<td>Any $T_4$</td>
</tr>
<tr>
<td></td>
<td>Any $N_3$</td>
</tr>
<tr>
<td></td>
<td>Any $M_1$</td>
</tr>
</tbody>
</table>
Overall Survival by Stage
Surgical Management

Has a role in patients with stage I and II mesothelioma

Pleurectomy / decortication

• Minimal bulk disease confined to parietal pleura

• Resection of the parietal and visceral pleura, pericardium + diaphragm

Extrapleural pneumonectomy (EPP)

• Bulky disease or disease that involves the fissures

• En bloc removal of lung, pleura, pericardium and diaphragm

• Post-operative XRT and Chemotherapy
Chemotherapy for mesothelioma

- Chemotherapy results in improved survival and quality of life
- Anti-folates are the most active agents
- Activity of anti-folates is markedly increased when given in combination with platinum compounds
## Phase III clinical trials of antifolates

<table>
<thead>
<tr>
<th>Author</th>
<th>Study arms</th>
<th>No. of patients</th>
<th>Response rate</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vogelzang et al</strong></td>
<td>Pemtrexed + Cisplatin</td>
<td>226</td>
<td>41%</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>222</td>
<td>17%</td>
<td>9.3</td>
</tr>
<tr>
<td><strong>Van Meerbeeck et al</strong></td>
<td>Raltitrexed + Ciplatin</td>
<td>110</td>
<td>24%</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>103</td>
<td>14%</td>
<td>8.8</td>
</tr>
</tbody>
</table>
Pemetrexed / Cisplatin Phase III Study

Vogelzang et al., JCO 2003
Second line agents for pleural mesothelioma

- Gemcitabine
- Gemcitabine plus carboplatin
- Navelbine
Peritoneal Mesothelioma
Median Overall Survival

Pleural mesothelioma 12 months

Peritoneal mesothelioma > 60 months
### Surgical debulking improves survival

<table>
<thead>
<tr>
<th>Study [reference]</th>
<th>No. of patients</th>
<th>CHPP agents</th>
<th>Residual disease status</th>
<th>Median survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington Cancer Institute, 2003 [58]</td>
<td>68</td>
<td>Cisplatin + doxorubicin</td>
<td>60% &lt;2.5 cm</td>
<td>67 mo</td>
<td>OS greater for women than men</td>
</tr>
<tr>
<td>National Cancer Institute, 2003 [62]</td>
<td>49</td>
<td>Cisplatin</td>
<td>88% &lt;1 cm</td>
<td>92 mo</td>
<td>OS better for patients ≤60 y Minimal residual disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>History of previous debulking</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>86% ascites palliated</td>
</tr>
<tr>
<td>Wake Forest University Baptist Medical Center, 2001 [61]</td>
<td>12</td>
<td>MMC</td>
<td>66% &lt;2 cm</td>
<td>34.2 mo</td>
<td></td>
</tr>
<tr>
<td>National Cancer Institute of Milan, 2003 [60]</td>
<td>19</td>
<td>Cisplatin + MMC or doxorubicin</td>
<td>75% &lt;2.5 mm</td>
<td>NR</td>
<td>94% ascites palliated</td>
</tr>
</tbody>
</table>

Abbreviations: MMC, mitomycin C; NR, not reported; OS, overall survival.
Pemetrexed for peritoneal mesothelioma

- Pemetrexed in combination with cisplatin or carboplatinum is now the first line treatment for patients who are not surgical candidates
- Neoadjuvant therapy, could make some patients resectable
- Adjuvant therapy after cytoreduction and intraperitoneal chemotherapy or use at time of recurrence
Novel Targets for Mesothelioma

- Mesothelin
- IGF-1R
Mesothelin

- Cell surface glycoprotein
- Normal expression in human tissues is limited to mesothelial cells of pleura, peritoneum & pericardium
- Mesothelin is highly expressed in many cancers

**Mesothelin processing**

*Mesothelioma*  *Ovarian Cancer*  *Pancreatic Cancer*  *Lung Cancer*

Mesothelin

• Biological function of mesothelin is not known

• Mesothelin is a novel CA125 binding protein and may play a role in tumor metastasis

• Shed into the serum and is elevated in patients with mesothelioma
Targeting mesothelin for cancer therapy

• The limited expression of mesothelin in normal tissues and high expression in many common cancers makes it a good target for antibody based therapies
Targeting mesothelin for cancer therapy

**Recombinant immunotoxin**

**SS1P**

**Anti-mesothelin Fv**

**Toxin**

**Chimeric mAb**

**MORAb-009**
SS1P, anti-mesothelin immunotoxin

- High affinity for mesothelin
- Cytotoxic to mesothelin expressing tumor cells obtained from patients
- Regression of mesothelin positive tumors in mice

Li et al. Anticancer Res., 2004
SS1P Phase I Study

- Patients with advanced mesothelin positive cancers
- SS1P given as IV infusion every other day x 3 doses
- Thirty four patients treated (20 mesothelioma, 12 ovarian and 2 pancreatic cancer)
- Maximum tolerated dose - 45 µg/kg
- Dose-limiting toxicity was self limited pleuritis
- Tumor response
  - Minor response 4
  - Stable disease 18
  - Progressive disease 11

SS1P in combination with chemotherapy results in increased anti-tumor activity

• Marked synergy between SS1P and chemotherapy in mice

• Synergy observed with several chemotherapeutic agents including taxol, cisplatin and gemcitabine

• Chemotherapy decreases mesothelin concentration in the tumor extracellular fluid leading to increased cell killing by SS1P

Zhang et al. PNAS, 2007
Phase I, dose-escalation study of SS1P plus Pemetrexed (P) and Cisplatin (C) for front line therapy of malignant pleural mesothelioma

Primary Objectives

• To determine MTD of SS1P that be safely given with P + C
• Anti-tumor activity of SS1P with chemotherapy
• SS1P toxicity and pharmacokinetics

Secondary Objective

• Serum mesothelin as a predictor of therapeutic response
SS1P plus Pemetrexed and Cisplatin Mesothelioma Study

Clinical trial design

SS1P C1D1, D3, D5

C1D1
Pemetrexed 500 mg/m²
Cisplatin 75 mg/m²

SS1P C2D1, D3, D5

C2D1
Pemetrexed 500 mg/m²
Cisplatin 75 mg/m²

*Restaging

C3D1
Pemetrexed 500 mg/m²
Cisplatin 75 mg/m²

Cycle 1

Cycle 2

Cycle 3-6
<table>
<thead>
<tr>
<th>Patient</th>
<th>SS1P dose level (µg/kg)</th>
<th>Response</th>
<th>PFS (months)</th>
<th>Overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>002</td>
<td>25</td>
<td>SD</td>
<td>35+</td>
<td>35+</td>
</tr>
<tr>
<td>004</td>
<td>25</td>
<td>PR</td>
<td>11</td>
<td>30+</td>
</tr>
<tr>
<td>005</td>
<td>25</td>
<td>PR</td>
<td>16</td>
<td>29+</td>
</tr>
<tr>
<td>006</td>
<td>35</td>
<td>PD</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>007</td>
<td>35</td>
<td>PD</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
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</tr>
<tr>
<td>016</td>
<td>45</td>
<td>SD</td>
<td>7+</td>
<td>7+</td>
</tr>
<tr>
<td>018</td>
<td>45</td>
<td>PR</td>
<td>6</td>
<td>6+</td>
</tr>
<tr>
<td>019</td>
<td>45</td>
<td>SD</td>
<td>4+</td>
<td>4+</td>
</tr>
<tr>
<td>012</td>
<td>55</td>
<td>PD</td>
<td>4</td>
<td>14</td>
</tr>
</tbody>
</table>

* + Response Ongoing*
Anti-tumor Response (all dose levels)

\[ n = 15 \]

<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>7</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>4</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>4</td>
</tr>
</tbody>
</table>
Anti-tumor Response (at MTD dose-level)

n = 8

Complete Response 0
Partial Response 5
Stable Disease 2
Progressive Disease 1
Patient 009 (45 µg/kg dose level)

Baseline  After Cycle 2  After Cycle 6

↓ 33%  ↓ 61%

Decrease in tumor area
Patient 009 (45 µg/kg dose level)

Baseline | After cycle 2 | After cycle 6
Patient 009 (45 µg/kg dose level)

Serum mesothelin

Time (weeks)

baseline progression

pre wk3 wk6 wk9 wk12 wk15 wk18 wk23
Tumor Response (Modified RECIST)*

Percentage change in modified RECIST tumor measurements

CT Grading of Response
- Progressive Disease
- Stable Disease
- Partial Response

30% decrease threshold

* Tumor response at end of 2 cycles or best response
SS1P plus Pemetrexed and Cisplatin Mesothelioma Study: Conclusions

- Chemotherapy plus SS1P well tolerated
- Dose expansion ongoing at 45 µg/kg dose level
- Out of 15 evaluable patients: 7 PRs and 4 SD
- Serum mesothelin levels may predict response
- If we continue to see this anti-tumor activity in the cohort expansion phase, will consider a randomized study of pemetrexed and cisplatin with and without SS1P
MORAb-009, anti-mesothelin monoclonal antibody

- Chimeric IgG1 antibody
- Same Fv as SS1P
- Kills mesothelin expressing cell lines by ADCC
- Inhibits mesothelin CA-125 interaction in vitro

Morphotek Inc.
Hassan et al., Cancer Immunity, 2007
Results of MORAb-009 Phase I study

• Dose-escalation study of MORAb-009 as weekly iv infusion to determine safety and maximum tolerated dose

• Twenty four pts. treated including 13 mesothelioma, 7 pancreatic and 4 ovarian cancer pts.

• Well tolerated with most common AE, infusion reaction

• Phase II dose established as 200 mg/m2

• Out of 20 evaluable patients 11 with stable disease and 9 with progressive disease
MORAb-009 with chemotherapy

Anti-tumor activity of MORAb-009 with gemcitabine

Hassan et al., Cancer Immunity, 2007
Phase II study of MORAb-009 plus pemetrexed and cisplatin for pleural mesothelioma

- Front line therapy in newly diagnosed patients
- Progression-free survival as primary end-point
- Translational endpoints - CA-125 kinetics
Phase II study of MORAb-009 plus pemetrexed and cisplatin for pleural mesothelioma

• Multi-institutional study with NCI as lead site
• 1st patient treated 2/11/09
• n = 89 patients treated (last patient treated 10/14/10)
• 49 patients still receiving treatment
• Data analysis planned for early 2011
Insulin Growth Factor 1 Receptor (IGF-1R) as Target for Mesothelioma Treatment
Insulin Growth Factors and IGF-1R

IGF and insulin signaling

IGF binding proteins

IGF-I
IGF-II
IGFBP-1
IGFBP-2
IGFBP-3
IGFBP-4
IGFBP-5
IGFBP-6
ALS

Ligands

IGF-I
IGF-II

Receptors

IGF-1R
IR

growth & differentiation
metabolic actions

Dupont & Holzenberger 2003 Birth Defects Res
IGF Pathway and Cancer

• The IGF pathway is a stimulatory signaling system that is integral to the growth of many tissues
• Stimulates cellular differentiation and proliferation
• Inhibits cancer cell apoptosis
• Associated with resistance to cytotoxic agents

Pollak et al. Nat Rev Cancer 2004
IGF Pathway and Mesothelioma

- IGF-1R is highly expressed in mesothelioma
- Activation of IGF-1R pathway may play a role in mesothelioma tumorigenesis
- In a hamster mesothelioma model an antisense plasmid to IGF-1R inhibited tumor growth
- IGF-1R inhibitors decrease viability of mesothelioma cell lines in vitro

Lee TC et al. Cancer Research, 1993
IMC-A12

- Fully human IgG1 high affinity monoclonal antibody that selectively binds IGF-1R
- Inhibits ligand binding to IGF-1R
- Induces rapid receptor internalization and degradation
- Anti-tumor activity against different tumor cell types in vitro as well as against tumor xenografts
- Phase I clinical trials using different scheduling regimens have been completed
Pre-clinical studies of IMC-A12 for treatment of mesothelioma

• Characterize IGF-1R expression in established mesothelioma cell lines as well as early passage tumor cells obtained from patients

• In vitro activity of IMC-A12 and correlation with IGF-1R expression

• In-vivo activity of IMC-A12 against mesothelioma tumor xenografts
IMC-A12: Growth Inhibition against established cell lines

% Cell Growth Inhibition

MCF7  NCI-H28  NCI-H226  YOU  H-MESO  NCI-H2452  M60  HAY  NCI-H2052

Growth Inhibition, IMC-A12

Pearson r = 0.9760
P < 0.0001
IMC-A12 : ADCC

NCI-H28 cell line

% Specific Lysis

-10% 0% 10% 20% 30% 40%

No antibody  human IgG  IMC-A12

* (* p<0.05)
Intraperitoneal Model to Evaluate Anti-tumor Activity of IMC-A12

• NCI-H226 cells were stably transfected with pFUGW-mPol2- fLuc2/eGFP vector containing both GFP and Luciferase genes

• $5 \times 10^6$ cells injected i.p. into athymic nude mice

• Mice were randomized into two groups and received either saline or IMC-A12 (5 mg/kg twice a week x 60 days)

• Analysis was done weekly and total luminescence flux was analyzed for each mouse
IMC-A12: Anti-tumor activity against NCI-H226 i.p. tumor model

*P < 0.05
IMC-A12 Preclinical Studies: Conclusions

• IGF-1R is expressed in mesothelioma cell lines and early passage tumor cells.

• However, IGF-1R sites per cell variable

• ADCC and inhibition of cell proliferation correlate with IGF-1R sites per cell

• Significant anti-tumor activity seen in mesothelioma i.p. tumor model
Phase II Clinical Trial of IMC-A12 in patients who have failed front line mesothelioma therapy

Primary Objective

• To determine the clinical response rate (PR + CR)

Secondary Objectives

• Progression free survival
• Overall survival

Exploratory Objectives

• Tumor expression of IGF-1R
• Serum mesothelin as a marker of tumor response
IMC-A12 : Phase II Mesothelioma trial

- Patients who have failed front line therapy
- IMC-A12 dose of 20mg/kg every 3 weeks
- Tumor restaging after every 2 cycles
- Separate cohort of pleural and peritoneal mesothelioma patients
- Trial opened in July 2010 and 20 pts. enrolled thus far
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Martin Phillips
Susan Weil
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Luigi Grasso

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Helen Chen
Kevin Conlon
Maria Merino