Recent Advances in Diagnosis and Treatment of ARD

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Outline

• None
• Advances and current status of biomonitoring and imaging (including CT) in diagnosis and surveillance of asbestos exposed populations.

• Recent innovations in the treatment of mesothelioma: current clinical trials of promising agents.
Mesotheiloma

- Tumor of serosal surfaces of pleura, peritoneum, pericardium, tunica vaginalis
- Median survival is poor
  - 8-14 months
- Morbidity and mortality related to local invasion of vital structures
- Treatment options suboptimal
The Challenge of Early Detection

• Long period where disease is present without symptoms
• Better outcomes with treatment when early stage
• “Common” disease
  – 2000 cases
  – 10 million exposed
• Good tools for early diagnosis
  – Imaging (e.g. CXRs and Chest CT scans)
  – Blood tests
SMRP

Serum mesothelin (nM)

Non-exposed Healthy
Cardiac Disease
Kidney Disease
Lung Disease
Pleural Disease
Exposed Healthy
Asbestosis
Asbestosis & Plaques
Plaques
Lung Cancer
Ovarian Cancer
Other Cancer
MM
PE exudate
PE transudate
Osteopontin (OPN)

• Elevated in MM
• Less specific than mesothelin

Pass H, et al. NEJM 2005
<table>
<thead>
<tr>
<th>Sensitivities of biomarkers</th>
<th>90% specificity (threshold value)</th>
<th>95% specificity (threshold value)</th>
</tr>
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<tbody>
<tr>
<td>MPF</td>
<td>68 (12.66)</td>
<td>92 (12.66)</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>53 (12)</td>
<td>47 (18)</td>
</tr>
<tr>
<td>SM</td>
<td>78 (1.4)</td>
<td>73 (1.6)</td>
</tr>
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MPF, megakaryocyte potentiating factor; SMRP, serum mesothelin-related proteins.
FBLN3 after Cytoreductive Surgery

Pass H, et al. NEJM 2012
SMRP and Screening

- Wittenoom Cohort
  - ~ 7000 workers Blue Asbestos Company
  - ~ 5000 residents of township
- Lifetime MM risk of 17%
- Subset of population took part in cancer prevention program since 1991
Serum Mesothelin

- 6 months before Mesothelioma Diagnosis

Blood collection and SMRP measurement (n=538)

- SMRP normal (<2.5nM)
  - No clinical indication for investigation. Review in 12 months

- SMRP abnormal (≥2.5nM, n=15; incl 1 renal failure)
  - Perform chest CT scan (n=15), one lung cancer successfully resected
    - Perform FDG-PET/CT imaging (n=14), 3 hilar lymphadenopathy and 1 increased uptake in the heart
    - Other investigations / treatment as clinically indicated

Park, et al AJRCCM 2008
Dust Disease Board Cohort Study

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Other investigations / treatment as clinically indicated

<table>
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<tr>
<th>Outcome</th>
<th>N (%)</th>
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<tr>
<td>Positive SMRP</td>
<td>15 (3%)</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>1</td>
</tr>
<tr>
<td>MM</td>
<td>0</td>
</tr>
</tbody>
</table>

Park, et al AJRCCM 2008
Imaging - Ultra low dose CT

Schaal, et al. PLOS ONE; Dec 2016
Mesothelioma Treatment

Surgery

Extrapleural pneumonectomy

Radical pleurectomy & decortication

Parietal pleura

Visceral pleura
# EPP vs Pleurectomy

<table>
<thead>
<tr>
<th></th>
<th>EPP N=385</th>
<th>P/D N=278</th>
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</thead>
<tbody>
<tr>
<td>Operative mortality</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>33%</td>
<td>65%</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>66%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Overall Survival (both groups)</strong></td>
<td>14 months</td>
<td>5 year survival 12%</td>
</tr>
<tr>
<td>Stage I</td>
<td>38 months</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>19 months</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>11 months</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>7 months</td>
<td></td>
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Chemotherapy

Folate antimetabolite that inhibits three enzymes used in purine/pyrimidine synthesis.
IFCT-GFPC-0701 trial: MAPS
Mesothelioma Avastin cisplatin Pemetrexed Study

- MPM proved by pleural biopsies (thoracoscopy...)
- Written informed consent
- Age ≥18 - <75 years
- PS 0 - 2
- Chemonaïve patients
- not candidate to curative intent surgery according to Multidisciplinary Board
- At least 1 evaluable or measurable lesion by CT
- Weight loss <10% within 3 months prior to enrolment
- No significant cardiovascular comorbidity and/or other usual chemo or beva contra-indications (HTA, GI perforation...)
- Prophylactic radiotherapy (3 x 7 Gy) before chemo

IFCT-sponsored, open-label, multi-centre randomized phase II-III trial
(bevacizumab supplied by Roche)

A
Pemetrexed 500 mg/m² D1
+ Cisplatin 75mg/m² D1
x 6 cycles, Q21D

Surveillance

PD: No cross-over allowed

B
Pemetrexed 500 mg/m² D1
+ Cisplatin 75mg/m² D1
+ Bevacizumab 15 mg/kg D1
x 6 cycles, Q21D

Maintenance Bevacizumab
15 mg/kg D1, Q21D until PD

CT-scan Q 3 cycles in both arms; Response assessed with modified RECIST criteria for MPM

Phase 3 primary goal = OS; Secondary goals: PFS, QoL, ancillary studies

Stratification: center, histology (epithelioid vs sarcomatoid/mixed), PS (0-1 vs 2), smoking status
Efficacy: ITT median Progression-free Survival (PFS)

median follow-up = 39.4 months [11.0-83.05]

Arm A (PC): 7.48 mo, 95%CI [6.79-8.13]
Arm B (PCB): 9.59 mo, 95%CI [8.49-10.59]

Stratified HR=0.61; 95%CI [0.50-0.75]
$p<0.0001$

IFCT 0701 ‘MAPS’ randomized phase 3 trial
Efficacy: ITT median Overall Survival (OS)

median follow-up = 39.4 months [11.0-83.05]

Arm A (PC): 16.07 mo, 95%CI: [14.00-17.93]
Arm B (PCB): 18.82 mo, 95%CI: [15.90-22.62]

Stratified HR=0.76; 95%CI [0.61-0.94]  
p=0.015

IFCT 0701 ‘MAPS’ randomized phase 3 trial
IMRT After Chemotherapy

(A) P/D patients

Median OS: 26 months
(95%CI: 8 - NR)

(B) Non-resected patients

Median OS: 17 months
(95%CI: 11 - 24)

Paradigm of Multimodality Therapy

- EPP -> XRT -> Chemo
- 183 pts through 1999
- Overall Median Survival ~19 mos.
- 5-year survival ~15%
- Highly selected
- Non-randomized
- Non-controlled

Sugarbaker, et al., JTCVS, 1999
The Cancer Immunity Cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

Adapted from Chen and Mellman (2013) Immunity

Chemo / XRT

Anti-CTLA-4

Anti-VEGF

Anti-PD1/PD-L1

Vaccines
Scientific Rationale

MESOTHELIOMA

Tumor infiltrating lymphocytes

Tumor reactive TILs

Functional tumor reactive TILs

Tumor reactive TILs hypofunctional from PD1
Blockade of T cell Checkpoints

**Without immune therapy**
- T-cell
- PD-1 receptor
- Antigen
- Tumor cell

**With immune therapy**
- T-cell
- PD-1 inhibitor
- PD-L1 inhibitor
- Tumor cell
Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial

Evan W Alley, Juanita Lopez, Armando Santoro, Anne Morosky, Sanatan Saraf, Bilal Piperdi, Emilie van Brummelen
Methods to Increase T-cells

- Isolate tumor infiltrating lymphocytes (TILs) and grow to them to large numbers outside the patient before injecting them back in
- Has worked for certain tumors (e.g. melanoma, renal cancer)
- Difficult strategy for many tumors
  - Low numbers of TILs
  - Even lower numbers of TILs that bear reactivity to the tumor (i.e. many “bystander” TILs)
  - Methods to break apart tough tumors to release the T cells can be harsh on them
Methods to Increase T-cells

- Engineering T cells isolated from the bloodstream can overcome many of these hurdles
  - No need to expose T cells to harsh digestion methods to isolate them
  - Non-reactive T cells can be made reactive by engineering them to express receptors that recognize proteins (aka “antigens”) expressed on the tumor surface
  - Has achieved remarkable cures in lymphoma and leukemia
Mesothelin-specific Chimeric Antigen Receptor mRNA-Engineered T cells Induce Anti-Tumor Activity in Solid Malignancies

No major toxicities

CAR T cells detected transiently in the blood (mRNA)

One patient with a dramatic response

Pre-Rx

3 months post-Rx

50% reduction in volume
DANGER
ASBESTOS HAZARD