MALIGNANT PLEURAL MESOTHELIOMA

New insights in treatment

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MALIGNANT PLEURAL MESOTHELIOMA

Outline

Asbestos
Pathophysiology
Current treatment options
New insights in treatment
MESOTHELIOMA
An asbestos-related disease

Asbestos: is a set of six naturally occurring silicate minerals, which all have in common their asbestiform habit: i.e., long (roughly 1:20 aspect ratio), thin fibrous crystals, with each visible fiber composed of millions of microscopic "fibrils"
ASBESTOS

Widely used, but despite legislation still everywhere in the environment
MESOTHELIOMA
Pathophysiology
MESOTHELIOMA
Pathophysiology

MESOTHELIOMA

Incidence

MESOTHELIOMA
Life expectancy

Mesothelioma cancer (C45): 2009–2013
Five-year net survival by age, England

MESOTHELIOMA

Histology

Mesothelial tumours
Diffuse malignant mesothelioma
  - Epithelioid mesothelioma
  - Sarcomatoid mesothelioma
    - Desmoplastic mesothelioma
Localised malignant mesothelioma
  - Epithelioid mesothelioma
  - Sarcomatoid mesothelioma
  - Biphasic mesothelioma
Well-differentiated papillary mesothelioma
Adenomatoid tumour

**Mesothelioma Staging**

**T – Primary Tumour**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tbody>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2, T3</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>II</td>
<td>T1, T2</td>
<td>N1</td>
<td>M0</td>
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<td>T3</td>
<td>N1</td>
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<td>IIIB</td>
<td>T1, T2, T3</td>
<td>N2</td>
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<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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**N – Regional Lymph Nodes**

<table>
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<tr>
<th>Stage</th>
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<tr>
<td>N0</td>
<td>No regional lymph nodes/metastases</td>
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<tr>
<td>N1</td>
<td>Metastases to ipsilateral infrathoracic lymph nodes (includes ipsilateral bronchopulmonary hilar, subcarinal, paratracheal, supradiaphragmatic, paraaortic, pericardial, intercostal and internal mammary nodes)</td>
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<tr>
<td>N2</td>
<td>Metastases to contralateral infrathoracic lymph nodes</td>
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**M – Distant Metastasis**

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<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
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<tr>
<td>M1</td>
<td>Distant metastasis present</td>
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- Stage T2 describes locally advanced, but potentially resectable tumour.
- Stage T4 describes locally advanced, technically unresectable tumour.

SYMPTOM MANAGEMENT IN MESOTHELIOMA

Dyspnea due to pleural effusion

- Drainage with pleurodesis
- Permanent pleural catheter
- Thoracoscopy
CURRENT TREATMENTS IN MESOTHELIOMA

Used in clinical practice

Surgery in limited disease patients
- Extrapleural pneumonectomy
- Extended pleurectomy decortication

Palliative chemotherapy as first-line treatment
- Pemetrexed - platinum combination
CURRENT TREATMENTS IN MESOTHELIOMA

Surgery

No randomised data supporting the use of surgery
Most data support tri-modality treatment
Can be considered in selected patients
Needs shared decision making
SURGERY IN MESOTHELIOMA
Developments

Pleurectomy decortication vs. EPP
(neo)adjuvant radiotherapy

Treasure T, et al. Lancet 2011:12(8):763-772. Reproduced under the terms of the Creative Commons Attribution License (CC BY 4.0). https://creativecommons.org/licenses/by/4.0/, accessed June 2019
RADIOTHERAPY IN MESOTHELIOMA

Palliative
- Symptom management
- Prophylactic radiotherapy on pleural drainage track (?)

Radiotherapy in multimodality treatment
- Under debate
- New radiotherapy techniques (IMRT)
CURRENT TREATMENTS IN MESOTHELIOMA

Pemetrexed-platinum

CURRENT TREATMENTS IN MESOTHELIOMA

Clinical debate

Role of surgery
Role of maintenance pemetrexed treatment
Second-line treatment
Role of anti-angiogenesis agents
CURRENT TREATMENTS IN MESOTHELIOMA

Clinical debate

Role of surgery

Role of maintenance pemetrexed treatment

Second-line treatment

Role of anti-angiogenesis agents
MAINTENANCE TREATMENT

The Rotterdam Experience

MAINTENANCE TREATMENT
Dutch Pulmonology Society Trial

NVALT 19: Switch maintenance with gemcitabine, Phase II

Pemetrexed
Cisplatin
OR
Carboplatin
x ≥4 cycles

Primary endpoint
- Progression free survival

Secondary endpoints
- Response rate
- Overall survival
- Toxicity
- Biomarkers

Gemcitabine 1250 mg/m²
IV d1, d8
Observation
CURRENT TREATMENTS IN MESOTHELIOMA

Clinical debate

Role of surgery
Role of maintenance pemetrexed treatment

Second-line treatment
Role of anti-angiogenesis agents
SECOND LINE TREATMENT

No randomised controlled trials supporting the use after pemetrexed first line

Single agent chemotherapy
- Vinorelbine/gemcitabine
- Response rates <10%, QoL effect?

Retreatment with pemetrexed (mono or combination)
- Depending on response and interval?
CURRENT TREATMENTS IN MESOTHELIOMA

Clinical debate

Role of surgery
Role of maintenance pemetrexed treatment
Second-line treatment

Role of anti-angiogenesis agents
ANTI-ANGIOGENESIS AGENTS

Bevacizumab

**ANTI-ANGIOGENESIS AGENTS**

**Nintedanib**

- Patients with histologically confirmed, unresected MPM
  - Life expectancy of ≥3 months
  - No previous systemic chemotherapy for malignant pleural mesothelioma

**R 1:1**

**Nintedanib 200 mg bid* + pemetrexed†/cisplatin‡**

- Non-PD patients
- Nintedanib maintenance
- Progressive disease§

**Placebo 200 mg bid* + pemetrexed†/cisplatin‡**

- Non-PD patients
- Placebo maintenance
- Progressive disease§

Total
N=87 (Phase II) + 310–450 (Phase III)

*On days 2–21.
†Pemetrexed 500 mg/m² intravenous over 10 minutes on Day 1 of each 21-day cycle.
‡Cisplatin 75 mg/m² intravenous over 2 hours on Day 1 of each 21-day cycle.
§Treatment beyond progression is allowed if clinical benefit is perceived.

Scagliotti GV, IASLC 19th World Conference on Lung Cancer 2018 (Abstract PL02.09)
MALIGNANT PLEURAL MESOTHELIOMA

Outline

Asbestos
Pathophysiology
Current treatment options

New insights in treatment
MOLECULAR ALTERATIONS

NEW INSIGHTS IN TREATMENT

Nf2 mutation

NEW INSIGHTS IN TREATMENT

Arginine deprivation in ASS1 deficient mesothelioma

**Alive and progression free**

Median survival, mo
- BSC: 2.0
- ADI-PEG20 + BSC: 3.2

Hazard ratio: 0.56 (95% CI: 0.33-0.96)
Log rank $P = .03$ (1-sided $P = .02$)

**Alive**

Median survival, mo
- BSC: 11.1
- ADI-PEG20 + BSC: 11.5

Hazard ratio: 0.68 (95% CI: 0.39-1.16)
Log rank $P = .15$ (1-sided $P = .08$)

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NEW INSIGHTS IN TREATMENT

Disease progression

Tumour profiling

- ASS1 loss
- BAP1 loss
- CDKN2A mutation
- PDL1 positive
- Mesothelin overexpression
- PI3K–AKT aberration
- NF2 mutation or Merlin loss
- No actionable aberrations

Arginine deprivation
- EZH2 inhibitor or PARP inhibitor
- CDK4/6 inhibitor or PRMT5 inhibitor
- PD1 or PDL1 inhibitor
- Mesothelin directed therapy
- PI3K–AKT inhibitor
- FAK inhibitor or NEDD8 inhibitor
- Platinum-based chemotherapy with or without anti-angiogenic agent (or other immunotherapies and vaccine therapies)

Monitoring on therapy
- Clinical
- Radiological
  - Conventional imaging
  - Functional imaging
- Molecular
  - Blood
  - Pleural fluid
  - Tumour biopsy

NEW INSIGHTS IN TREATMENT

Immunotherapy

IMMUNOTHERAPY

Clinical results

Checkpoint-inhibitors
- Monotherapy
- Combination

Cell-based therapy

LARGEST RANDOMISED TRIAL

Tremilimumab as second- or third-line treatment

Reprinted from the Lancet Oncol 18(9), Maio M, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial, 1261-1273, Copyright 2017, with permission from Elsevier.
## Checkpoint blockade in lung cancer and mesothelioma

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COMBINATION PD-(L)1 RESULTS

Chemotherapy
- The Australian experience

Combination IO/IO
- Combination PD-1/CTLA-4

Cell based therapy
- CAR T-cell results
- Dendritic cell therapy
Single-arm, multicentre phase II trial, N=54 (31 in this Stage 1 analysis)

**Population**
- 1st line MPM
- Non-surgical
- ECOG PS 0-1
- No PD-L1 selection

**Induction**
- Cisplatin 75 mg/m² + pemetrexed 500 mg/m² + durvalumab 1125 mg q3w

**Maintenance**
- Durvalumab 1125 mg q3w x 52 w (until PD or toxicity)

**Exclusions**
- AID, steroids, prior IO agent

**Outcomes**
- PFS*
- OTRR (CR + PR)*
- Toxicity
- PFS*
- OS

* mRECIST for MPM, mirRC
**THE AUSTRALIAN EXPERIENCE: PEM/PLATINUM/DURVA**

**Study schema**

Single-arm, multicentre phase II trial, N=54 (31 in this Stage 1 analysis)

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### Outcomes
- PFS*
- OTRR (CR + PR)*
- Toxicity
- PFS*
- OS

### Exclusions
- AID, steroids, prior IO agent

### DREAM: Durvalumab + chemotherapy as first-line therapy for MPM
- Phase 2 with 54 patients
- 6-mo PFS: 57%
- mPFS: 6.2 mo
- Objective tumour response by iRECIST: 54%
- mDOR: 6.5 mo
- Grade 3 to 5 in 36 patients (66%)
  - 5 deaths; none attributed to durvalumab
  - Included neutropenia, fatigue, peripheral neuropathy, nausea

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COMBINATION IO/IO
Second line results

COMBINATION IO/IO

Upcoming results, Checkmate 743

Phase 3, randomised, open-label trial with nivolumab + ipilimumab for unresectable MPM

N=600

Key eligibility criteria
- Unresectable pleural mesothelioma
- Available tumour sample
- ECOG PS 0-1
- No prior chemotherapy for plural mesothelioma

Study start date: October 2016
Estimated completion date: September 2021
Estimated primary completion date: October 2020
Status: Active, not recruiting

Primary outcome measures: OS, PFS
Secondary outcome measures: ORR, DCR, association between PD-L1 expression and efficacy measures

CAR T-CELLS IN MESOTHELIOMA


MESOTHELIN-TARGETED CAR T-CELL THERAPY

8 patients treated
Additional 4 patients treated systemically (NCT 02792114)
No adverse events noted

Personal communication with Dr Adusumilli, as off 2018.
DENDRITIC CELL IMMUNOTHERAPY

Most potent antigen-presenting cells
Activate total immune system (innate and adaptive)
  - Activate naive T-cells
  - NK cells
  - B-cells
  - Memory T-cells
Activate the immune system in a natural way
  - Costimulatory molecules
Multiple antigen loading
DENDRITIC CELL IMMUNOTHERAPY
THE ROTTERDAM EXPERIENCE

Slide Courtesy of Prof Aerts et al.

AUTOLOGOUS DENDRITIC CELLS PULSED WITH ALLOGENIC TUMOUR CELL LYSATE IN MESOTHELIOMA

From mouse to human

OVERALL SURVIVAL AND RECIST RESPONSES AFTER FIRST VACCINATION

DENDRITIC CELL IMMUNOTHERAPY
Randomised Phase III study ongoing

Histologically confirmed MPM
SD, CR or PR after first-line treatment
ECOG performance status 0–1

Dendritic cell therapy + BSC
BSC alone

R 1:1
Phase III
n=230

Primary endpoint: OS
Secondary endpoints: OS at 12 and 18 months, progression free survival, overall response rate, quality of life

MALIGNANT MESOTHELIOMA TAKE HOME MESSAGES

New insights in treatment

Chemotherapy remains standard of care
Surgery is an option in selected cases
New molecular treatments are upcoming
Immunotherapy will have a role in mesothelioma treatment
THANK YOU!