MALIGNANT MESOTHELIOMA

What you need to know...

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MALIGNANT MESOTHELIOMA

Highly aggressive neoplasms that arise primarily from the surface serosal cells of the pleural, peritoneal and pericardial cavities.

Primary cause: exposure to asbestos fibers
- Other implications: simian virus 40, genetic predisposition, possibly carbon nanotubes

Long latency from exposure to malignancy \( \rightarrow \) multiple somatic genetic events required for tumorigenic conversion of normal mesothelial cell
HISTOLOGY OF MALIGNANT MESOTHELIOMA

Epithelial morphology
- Most common, 50-60%
- Well differentiated variants, “prolonged” survival, up to 2 years

Fibrous morphology, or sarcomatoid type
- Only 10%
- Resistant to therapy with median survival < 1 year

Mixed type or biphasic
- 30 – 40%
- Differential includes: metastatic carcinosarcomas & biphasic synovial sarcoma

Poorly differentiated malignant mesothelioma
- Cannot be subcategorized histologically
PATHOLOGY

Need well trained pathologist
- Can be confused with carcinoma vs. mesothelial in origin

Immunohistochemistry
- Diffusely positive: pankeratin, keratin 5/6, calretinin, WT-1
- Negative for epithelial markers: CEA, CD15, Ber-EP4, Moc-31, TTF-1, B72.3

Gold standard: EM showing classic long-branching microvilli of human mesothelial, compared to short nonbranching microvilli of carcinomas

New methods: microRNAs
Death rates parallel consumption of asbestosis by individual countries
- Highest in: Australia, UK, New Zealand, Canada, Western Europe & US

Estimated 400,000 deaths in these countries from 2000 – 2049

US: 2,500 deaths/year since 1999
- Highest risk: Industrial exposures in construction & ship building
- Also at risk: plumbers, piper fitters & steamers

Generally seen in men in 50s, 60s & 70s
- Due to 25-40 year latency period from occupational asbestos exposure
- Male to female ratio: 5:3
SYMPTOMS

Median time to diagnosis: 2 months

Right side affected > left side (60% vs. 40%)
  • Greater volume

Nonpleuritic chest pain classically located posterolaterally and low in the thorax

Dyspnea

Pleural effusion
  • 95% of patients will have at some point during their disease
PHYSICAL EXAM

Decreased BS, dullness to percussion, decreased motion of involved chest wall

“Trapped” lung after thoracentesis – no improvement in dyspnea

Late stages: dramatic cachexia, marked contraction of involved chest wall with narrowed interspaces & hypertrophy of contralateral hemithorax

Chest wall mass: 25% patients (10 – 40%)
  - Often at site of prior thoracentesis, thoracotomy or thoracoscopy wounds
LABORATORY EXAM

Generally non-specific
- Hypergammaglobulinemia
- Eosinophilia
- Anemia of chronic disease

Vitamin deficiencies
- Elevated homocysteine level, folic acid deficiency (~ 15%)
- Biochemical evidence of B12 deficiency (17%)
- Biochemical signs of B6 deficiency (32%)

Thrombocytosis (60 – 90%)
- 15% of patients with plt counts > 1 million
CHEST X-RAY

Pleural effusion, diffuse pleural thickening & nodularity

Smooth, lobular pleural masses that infiltrate pleural space & fissures → contraction & fixation of the chest (46 – 60%)

Lung becomes encased, mediastinal shift due to volume loss

The Merck Manuals
CT SCAN

Pleural changes of pleural plaques, diffuse pleural thickening, pleural effusion

Lobulated pleural encasement causing lower lobe collapse

Intrapulmonary nodules & infiltration along fissures

Enlarged hilar & mediastinal LNs

Evaluation of pericardium & diaphragmatic surfaces
MRI/PET

MRI w/ contrast: improves staging, surgical resectability
  ▪ Diaphragm and endothoracic fascia invasion

PET: may have false-positive LN
  ▪ If extrapleural pneumonectomy is considered, should biopsy FDG-avid nodes
  ▪ 25% of patients found to have metastatic disease at time of initial diagnosis
  ▪ May have prognostic implications when used in early assessment of response to chemotherapy
    ▪ When looking for early metabolic response – trend towards longer time to progression & survival
DIAGNOSIS

Thoracentesis or closed pleural biopsy
- Generally need a cell block from thoracentesis

VATs indicated for patients at risk for mesothelioma if:
- Develop large effusion with negative thoracentesis/pleural biopsy
- Recur with effusion after initial thoracentesis

Thoracoscopy able to estimate extent of disease involvement with diaphragm, pericardium, chest wall & nodes

Risk of chest wall masses from seeding complication from any diagnostic procedure (~ 10%) – avoid with RT to scar
Most patients, treated or not, will die from complications of local disease

- Increasing tumor bulk causes progressive respiratory compromise, pneumonia or myocardial dysfunction with arrhythmias
- Unrelenting chest wall pain, requiring narcotics
- Dysphagia from tumor compression of the esophagus

Extrathoracic mets generally occur later in course & not direct cause of death

- Liver, adrenal gland, kidney & contralateral lung
- Intracranial mets seen only 3%, predominately from sarcomatous type
PROGNOSIS

Median survival from 337 patients treated in 10 CALGB trials: 7 mo
- PS 0: 13-14 months median survival

EORTC & CALGB clinical prognostic scoring systems
- Poor prognostic indicators: Poor PS, nonepithelioid histology, male gender, low Hgb, high plts, high WBC, high LDH
- No validated gene sets for prognostication

Staging:
- Stage IA: exclusive involvement of diaphragmatic pleura & parietal pleura, median OS: 31.2 months
- Stage IB: if visceral pleura invasion median OS: 6.75 months

Quantification of SUV + histology
- Low SUV: 24 months
- High SUV: 14 months
## Staging — AJCC, 1995

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
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<tbody>
<tr>
<td>Ia: T1aN0M0</td>
<td>T2N0M0</td>
<td>Any T3 M0</td>
<td>Any T4</td>
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<tr>
<td>Ib: T1bN0M0</td>
<td></td>
<td>Any N1 M0</td>
<td>Any N3</td>
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<tr>
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<td></td>
<td>Any N2 M0</td>
<td>Any M1</td>
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- **T1a**: tumor is limited to ipsilateral parietal +/- mediastinal +/- diaphragmatic pleura; no involvement of visceral pleura
- **T1b**: tumor involving to ipsilateral parietal +/- mediastinal +/- diaphragmatic pleura, also involving visceral pleura

- **T2**: tumor involves each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following: involvement of diaphragmatic muscle or extension of tumor from visceral pleura into the underlying pulmonary parenchyma

- **T3**: Locally advanced, but potentially resectable
- **T4**: Locally advanced, technically unresectable tumor
TREATMENT

ESMO recommendations published in 2009 – otherwise no published standard of care

Evolving understanding of surgery with/without intra-op or post-op adjuvant therapies

For patients with unresectable disease, who are candidates for chemo: cis + pem
- 3-4 month survival advantage for doublet vs. cis alone
SUPPORTIVE CARE

Median survival for supportive care alone: 4 – 13 months

Control of pleural effusions: repeated thoracenteses, talc pleurodesis, pleuro-peritoneal shunting, tunneled catheters

Pain management

Local RT for chest wall pain, nodules
1) Primary effusion control

2) Cytoreduction before multimodal therapy
   - Done only if microscopic disease alone is left (no gross disease at completion)

3) Deliver and monitor intrapleural therapies

Role of surgery & type of surgery remains controversial
   - Extrapleural pneumonectomy vs. pleurectomy

Transverse section of an extrapleural pneumonectomy surgical specimen with the entire right lung, parietal and visceral pleurae, portions of pericardium and the majority of the right hemidiaphragm. Thick rind of tumor along the pleural surface encasing the lung, interlobar fissures, and invading the diaphragm.
“Curative” RT as single modality

- Limitation is treatment of large volume of disease with curative radiation dose (> 60 Gy) risks severe damage to normal tissue

- Rotational technique
  - Survival: 3 – 10 months, one patient 4 years

- 50 Gy to entire hemithorax
  - Median survival: 17 months, vs. 7 months
  - Selection bias due to fitness

- Other studies with survival < 10 months

Generally XRT as single agent, reserved for palliation
PREVENTION OF SCAR RECURRENCES

Prophylactic RT as prevention of tumor seeding at site of diagnostic or therapeutic intervention
  • Prophylactic radiation: 21 Gy in 3 fractions

Conflicting results & no standard of care regarding prophylactic radiation
  • Discrepancy in rate of chest wall recurrence in trials
  • On going phase III in UK now
ADJUVANT THERAPY

Generally, surgery + postop adjuvant therapy has better outcome than palliative treatment alone

- Seen in consecutively treated patients at single institutions
- No phase III data (nor will there ever be likely…)
- May be selection bias

Possible that surgery + adjuvant therapy changes course of disease

Strong consideration should be given to treating patients with post-op chemo or RT or both
CHEMOTHERAPY

Regimens:

- Mitomycin C, vinblastine, cisplating
- Single agent vinorelbine
- Gemcitabine, carboplatin, cisplatin – all modest single agent activity
- Cisplatin + gemcitabine
  - Supportive phase 2 data, no phase 3 studies

Meta-analysis of 59 published trials has confirmed greater response rates for platinum-containing regimens versus nonplatinum-containing regimens

- 23.2% vs. 11.6%, p <.001
PEMETREXED

Antifolate compound which inhibits enzymes involved in purine + pyrimidine synthesis
- Dihydrofolate reductase, thymidylate synthase, glycinamide ribonucleotide formyltransferase

Enters cell primarily through reduced folate carrier and undergoes extensive intracellular polyglutamation by folylpoly-gamma-glutamate synthetase
- Polyglutamated forms are retained in cell longer & have > 100-fold greater affinity for thymidylate synthase and glycinamide ribonucleotide formyltransferase than parent drug

Evidence that malignant mesothelioma cells overexpress the α-folate receptor & may make cells more susceptible to antifolate drugs
Phase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients With Malignant Pleural Mesothelioma

By Nicholas J. Vogelzang, James J. Rusthoven, James Symanowski, Claude Denham, E. Kaukel, Pierre Ruffie, Ulrich Gatzemeier, Michael Boyer, Salih Emri, Christian Manegold, Clet Niyikiza, and Paolo Paoletti

**Purpose:** Patients with malignant pleural mesothelioma, a rapidly progressing malignancy with a median survival time of 6 to 9 months, have previously responded poorly to chemotherapy. We conducted a phase III trial to determine whether treatment with pemetrexed and cisplatin results in survival time superior to that achieved with cisplatin alone.

**Patients and Methods:** Chemotherapy-naive patients who were not eligible for curative surgery were randomly assigned to receive pemetrexed 500 mg/m² and cisplatin 75 mg/m² on day 1, or cisplatin 75 mg/m² on day 1. Both regimens were given intravenously every 21 days.

**Results:** A total of 456 patients were assigned: 226 received pemetrexed and cisplatin, 222 received cisplatin alone, and eight never received therapy. Median survival time in the pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the control arm ($P = 0.020$, two-sided log-rank test). The hazard ratio for death of patients in the pemetrexed/cisplatin arm versus those in the control arm was 0.77. Median time to progression was significantly longer in the pemetrexed/cisplatin arm: 5.7 months versus 3.9 months ($P = 0.001$). Response rates were 41.3% in the pemetrexed/cisplatin arm versus 16.7% in the control arm ($P < 0.001$). After 117 patients had enrolled, folic acid and vitamin $B_{12}$ were added to reduce toxicity, resulting in a significant reduction in toxicities in the pemetrexed/cisplatin arm.

**Conclusion:** Treatment with pemetrexed plus cisplatin and vitamin supplementation resulted in superior survival time, time to progression, and response rates compared with treatment with cisplatin alone in patients with malignant pleural mesothelioma. Addition of folic acid and vitamin $B_{12}$ significantly reduced toxicity without adversely affecting survival time.

PEMETREXED + CISPLATIN VS. CISPLATIN ALONE

EMPHACIS Trial

457 patients randomized, phase III, blinded study
- 226: cis + pem
- 222: cis alone

Measurable, histologically proven, life expectancy at least 12 weeks, KPS > 70, not candidate for curative surgery

Pem 500 mg/m2 IV D1 + Cis 75 mg/m2 IV D1
- No maintenance arm...
PEMETREXED + CISPLATIN VS. CISPLATIN ALONE

Median survival: 12.1 vs. 9.3 months (p = 0.20)

Hazard ratio for death in pem/cis arm was 0.77.

Median time to progression: 5.7 vs. 3.9 months

Response rates: 41.3% vs. 16.7% (P<.0001)
Fig 1. Kaplan-Meier estimates of overall survival time for all patients (A) and for fully supplemented patients (B). Overall survival was significantly longer for the pemetrexed/cisplatin-treated patients (Pem/Cis) in the group of all patients (P = .020) and approached significance for the group of fully supplemented patients (P = .051). MS, median survival; Cis, cisplatin alone.
PEMETREXED + CISPLATIN VS. CISPLATIN ALONE

Fig 2. Kaplan-Meier estimates of time to progressive disease (PD) for all patients (Pt.) (A) and for fully supplemented patients (B). Time to progressive disease was significantly longer for pemetrexed/cisplatin-treated patients (Pem/Cis) in the group of all patients ($P = .001$) and in the group of fully supplemented patients ($P = .008$). TTP, time to progression; Cis, cisplatin alone.
RALTITREXED + CISPLATIN VS. CISPLATIN ALONE

EORTC trial, 250 patients

Raltitrexed: pure, specific thymidylate synthase inhibitor, less expensive than pemetrexed

Results showed combo produced nonsignificant improvement in RR, median survival and 1 year survival...

- Significant improvements were seen in disease-related symptoms (pain & dyspnea)
- No significant serious additional toxicity

Modern chemotherapy improves symptoms and has no deleterious effect on quality of life.
ADDITION OF BEV TO CIS + PEM?

MAPS trial
- Lead to Bev approval in France
- NCCN lists it as front line option
  - Not FDA approved

Patients should have no contraindications to bevacizumab therapy: poorly controlled hypertension, deep venous thrombosis, proximity to surgery, or viscous perforation) with good PS. Use with caution in patients over the age of 75.

448 patients randomly assigned, not eligible for radical surgery
- Cis 75 mg/m2 + Pem 500 mg/m2 + Bev 15 mg/kg D1
  - Bev maintenance every 3 weeks following completion of 6 cycles
Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial

Gérard Zalcman, Julien Mazieres, Jacques Margery, Laurent Grellier, Clarisse Audigier-Valette, Denis Moro-Sibilot, Olivier Molinier, Romain Corre, Isabelle Monnet, Valérie Gounant, Frédéric Rivière, Henri Janicot, Radj Gervais, Chrystèle Locher, Bernard Milleron, Quan Tran, Marie-Paule Leblatisy, Franck Morin, Christian Creveuil, Jean-Jacques Parienti, Arnaud Scherpereel, on behalf of the French Cooperative Thoracic Intergroup (IFCT)

PFS improved with Bev: 9.2 vs. 7.3 months

OS significantly increased with combo: 18.8 vs. 16.1 months

No OS difference seen in 3 prior phase III studies...

Bev vs. pem maintenance?
**CHEMOTHERAPY**

Pemetrexed + cisplatin should be considered first choice

- If contraindications to cisplatin: consider carboplatin
  - Phase 2 data showing response rates of 25%, median survival of 14 months

Other options:

- Single agent pemetrexed (data from extended access program)
- Cis + raltitrexed
- Cis or carbo + gemcitabine
- Single agent weekly vinorelbine
  - Vinorelbine + oxaliplatin → increase toxicity & not more effective than vinorelbine alone

If NO platinum at all: pemetrexed + gemcitabine
SECOND LINE THERAPY

No standard of care for previously treated malignant mesothelioma patients

If disease recurs in setting of prolonged treatment break from platinum-pemetrexed-based regimen, can consider re-challenge
SECOND LINE THERAPY

Clinical trials
- HDAC inhibitors (vorinostat): no clinically significant PFS or OS of single agent
- Thalidomide
- TKI’s: sorafenib, sunitinib, imatinib, vatalinb, cediranib

New agents targeting mesothelin
- Prelim efficacy and randomized trials are ongoing
IMMUNOTHERAPY

Pembrolizumab
- 25 patients, 88% with previous systemic therapy → 6 partial responses, 13 stable disease. Overall control rate: 76%

Tremelimumab
- CTLA-4 inhibitor, studied in large phase II trial DETERMINE → no survival benefit beyond placebo

Older immunotherapeutic approaches, alone or with chemo, do not offer any substantial benefit
- Interferons, IL-2
QUESTIONS???