Malignant Mesothelioma
Recent Advances

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DM Seminar

Malignant mesothelioma

- A tumour of serosal surfaces
- Pleura, peritoneum
- Increasing incidence worldwide
- Association with asbestos exposure
- Compensation costs over 40 yrs
- $200 billion US
- $80 billion Europe
India
- 100,000 tonnes used annually
- 1/5th mined in India.
- AP, Rajasthan, Bihar
- 9th largest producer
- 6th largest user
- 13 large scale/ 673 small scale industries
- 6000 workers in direct contact

Advances
- Diagnosis
- Management
- Reviews
  - Advances in Malignant mesothelioma
  - Malignant mesothelioma
    - *Lancet* 2005; 366;397-408
Clinical Features

- Pleura
  - 80% male
  - Effusion
  - Chest wall pain
  - Wt loss and fatigue

- Peritoneum
  - Ascites
  - Abdominal pain
  - Bowel obstruction

- Extensive at presentation (closed cavity)

- Local invasion
  - LN enlargement
  - SVCO
  - Cardiac tamponade
  - SC extensions
  - Cord compression

- Miliary spread
Signs

- Effusion/ascites
- Clubbing <1%
- Fixed chest wall
- SC masses (tracks, surg sites)
- Cancer syndrome
  - Wt loss, cachexia
  - Fever, night sweats
  - Fatigue, ESR, anaemia
  - IL-6
Causes

- Asbestos
- Amphiboles: long thin fibres/blue asbestos
- Chrysotile: feathery/white asbestos
- Parietal surface
- Repeated trauma, inflammation, repair

Simian virus 40

- Potent oncogene
- SV 40 DNA (bone/ lung tumours)
- Role unproven
- Sabin polio vaccine

- Radiation
- Zeolite (Erionite) Turkey
Epidemiology

- Rising incidence
- Peak yet to come
- 2000/year USA
- Need for controls on asbestos
- 3 cohorts:
  - Miners
  - Plumbers/carpenters/defence personnel
  - Unknown

Pathogenesis

- 2 billion cells
- Facilitate free movement; enmesh glycoproteins
- Asbestos induces mutations
- 4 mechanisms postulated
Mechanisms of Injury

- Irritate pleura (plaques, malignancy)
- Disruption of mitotic spindle
- Reactive Oxygen species (DNA damage)
- Phosphorylation of kinases; increase expression of proto-oncogenes

Cytogenetic abnormalities

- Loss of chromosome 22
- Rearrangement of 1p, 3p, 9p, 6q
- Animal models
  - Murine useful; respond to asbestos exposure
  - Hamsters SV-40
  - Pre clinical testing of therapies
Six characteristic features

- Increased dysregulated growth
- Immortalization (telomerase expression)
- Tumor supp genes absent (p16, p14, NF-2merlin)
- Anti-apoptosis
- Increased angiogenesis
- Matrix interactions

Biological Features

![Diagram showing biological features of tumor cells]
Diagnosis

- Accurate and rapid
- Therapeutic and medicolegal
- Differentiation from disseminated adenocarcinoma

Cytologic

- Fluid 33-84%
- FNAC tumour (no effusion)
- Immunohistochemistry
  - Calretinin
  - Wilm’s tumour 1 antigen
  - Epithelial membrane antigen
HP Analysis

- Closed Biopsy <<< Thoracoscopic biopsy
- Cytokeratin
- EMA, calretinin, WT1,cytokeratin 5/6,HBME-1,mesothelin
- Absence of CEA,TTF-1,BG8
- EM microscopy

Imaging

- CXR
  - Pleural mass +effusion
  - Encircling rind
  - Lobulated masses
  - Plaques ( sign of exposure)

- CT
  - Effusion 74%
  - PI masses 92% +/- Inter lob septal thickening 86%
  - Chest wall invasion (18%)
MRI & PET

- Bony invasion
- Planning spinal RT
- Benign vs malignant
- LN involvement
- Staging and extent
- Tumor vs fibrosis

Serum markers

- Serum mesothelin related protein
  - 84% vs 2%
  - Adjunct to cyto/histopath
  - Monitoring therapy
  - Screening
- Other markers
  - CA125/CA15-3/hyaluronic acid/Osteopontin
  - Role in paired analyses (inc in sp/sens)
Other non sp tests

- Hb
- Platelets
- ESR
- Gamma globulin
- LFT
- Albumin

PFT

- Restrictive pattern
- Increased max exp flow rates
- Change in FVC reflects prog/regression provided pleural fluid constant
Prognosis & Staging

- Median survival 12 months
- Worse prognosis for:
  - Male, ext disease, perf status
  - Leucocytosis, anaemia, thrombocytosis
  - Sarcomatoid histology
  - Exp of COX 2 and VEGF
  - Vascularity
  - SV-40

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Table 1: New International TNM Staging System for Diffuse SCLC According to the IASLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic angles.</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic angles.</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor involving all of the ipsilateral pleural surfaces (mediastinal, diaphragmatic, and external) with or without the following features:</td>
</tr>
<tr>
<td></td>
<td>- Sarcomatoid histology</td>
</tr>
<tr>
<td></td>
<td>- Expression of COX 2 and VEGF</td>
</tr>
<tr>
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<td>- Vascularity</td>
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<td>- SV-40</td>
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M0: No distant metastases identified
M1: Distant metastases present

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From the IASLC, with permission.
Surgery
- Useful for diagnosis (VATS, open Bx)
- Palliation (debulking, pleurodesis)
- Potentially curative (Radical resection)
- Extrapleural pneumonectomy
- Best with adjuvant chemo/radio/immuno/other treatment
- Periop mort 6%. Median surv 2 yrs

Chemotherapy
- Poor response rates till recently
- Decrease tumor burden
- Improve pain, breathlessness, chest wall masses
Pemetrexed+cisplatin vs cisplatin
(12.1m vs 9.3 m) 448 pts
Inhibitor of thymidylate synthase + platinum compound
Objective response of 41%

Gemcitabine + cisplatin
False nucleotide
Objective response of 48% / 33%

Imatinib/geftinib no response
(PDGF/EGF)
Pemetrexed + cisplatin

Radiotherapy

- Resistant to traditional RT
- Diffuse nature of tumour (pneumonitis)
- Intensity modulated
- Relief of pain
- Prevention of seeding of surgical sites
- Brachytherapy logical but disappointing

Immunotherapy

- To bolster intrinsic weak immune response
- BCG
- IFN-alpha
- IL-2
- Intratumoural GMCSF

- No results justifying widespread use.
Gene Therapy
- Intratumoral injection of vaccinia vector with IL-2 transgene.
- No major regression despite lymphocytic infiltration.
- “Suicide gene” therapy
  - (Thymidine kinase + ganciclovir)
  - Some response

Other therapies
- Photodynamic therapy
  - Light acts on drug
  - Produces reactive O₂ species
  - Cellular necrosis
- Cytoreduction achieved
- No long term response
Antiangiogenic agents

- Target vascular VEGF pathway
- Bevacizumab, thalidomide, BAY43-9006, PTK787
- Antimesothelin monoclonal antibodies labeled with toxins
- Apoptosis inducing agent + immune therapy against APC

Palliation

- Pleurodesis (talc, surgery)
- Pain
  - Chest wall/ic nerve/organ invasion
  - NSAID/anticonvulsants/nerve block
- Dyspnea
  - Fluid/anaemia
  - Opiates
- Psychosocial factors
  - Anger, fear, worsened by MLC process
Prevention

- Vitamin A
- Vaccines directed at mesothelial proteins (risk of autoimmunity)
- Prophylactic bilateral pleurectomies!!

Conclusions

- The worst is yet to come
- Need for urgent focused research
- Enormous compensation costs may provide an economic incentive.