344. Biology and treatment of malignant pleural effusions

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The second therapeutic intervention in malignant effusion trial (TIME2): A randomised controlled trial to assess the efficacy and safety of patient controlled malignant pleural effusion drainage by indwelling pleural catheter compared to chest drain and talc slurry pleurodesis

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Introduction: Malignant pleural effusions (MPEs) can be treated by indwelling pleural catheter (IPC) or chest drain and talc pleurodesis (usual care). This is the first direct, randomised comparison of these techniques as initial therapy assessing patient reported outcomes.
Methods: Randomised trial of IPC versus usual care (1:1) in patients with symptomatic MPE. IPCs were inserted as day cases, followed by patient education and home drainage. Usual care was admission for chest drain and talc pleurodesis in patients with good lung re-expansion. The primary outcomes were daily visual analogue scale (VAS) scores of breathlessness and chest pain over 42 days (100mm line, 0mm = no breathlessness/chest pain, 100mm = maximum breathlessness/pain).
Results: 106 patients were randomised. Dyspnoea improved in both arms, with no significant difference in intensity (mean VAS: IPC 24.7mm (SD 18.9), usual care 24.4mm (SD 17.0), difference 0.16mm, 95% CI -6.82 to 7.15, p=0.96). Dyspnoea decreased by mean 37mm (SD 27.1) IPC arm and 30.2mm (SD 27.7) usual care arm. Chest pain decreased from baseline in both arms (mean VAS: IPC 20.5mm (SD 18.2), usual care 17.6mm (SD 16.0), difference 5.4mm, 95% CI -3.0 to 13.8, p=0.21). Preliminary analysis demonstrated lower initial hospital stay in the IPC group (median days 0 (IQR 0-1) versus 4 (IQR 2-6)).
Discussion: IPC and usual care are comparably effective treatments for the relief of breathlessness in patients with MPE. The pain profile of IPC and usual care is similar over 6 weeks.

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Impact of indwelling pleural catheter on quality of life in management of malignant pleural effusion in patients with advanced malignancies

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Study objective: Malignant pleural effusion (MPE) is a common complication of some advanced malignancies with an important negative impact on symptoms and quality of life (QoL). Indwelling pleural catheter (IPC) is useful for controlling symptoms due to relapsed MPE. There are scarce data about its impact on QoL in patients with advanced malignancies.
We aimed to assess the QoL along time in patients with diagnosis of recurrent MPE and IPC.
Design and methods: A prospective multicentric observational study was performed in five university hospitals in Spain from September 2010 to September 2011. Patients included must have a histological-confirmed advanced malignancy and a diagnosis of MPE. QoL was assessed by the scale of the EORTC QLQ30. Three timing cut-off points were considered: previous insertion of pleural catheter (baseline), at 30 days and at 60 days after insertion.
Results: 52 patients with MPE (median age 66 years; 30 male) were included. Most frequent symptoms at study entrance were dyspnea(100%), chest pain(42%) and cough(44%). 52 patients completed baseline QoL questionnaire, 29 at 30 days and 16 at 60 days. At timing cut-off points of 30 days, QoL scales showed a significant improvement in symptoms severity and a non-significant trend to improve the global and functional scores.

Scale	Baseline (n=28)	30 days (n=28)	p value*
Global	33 (17–65)	50 (33–65)	0.09
Functional	48 (33–79)	66 (35–81)	0.07
Symptoms	39 (23–63)	32 (16–46)	0.02

Date are expressed as median (25th to 75th percentile); *t-Student for related samples.

Conclusions: IPC is a useful tool that increases QoL in the palliative management of advanced malignancies with MPE.

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Mesothelioma in Sunderland U.K 1998 -2011: Chemotherapy usage and impact on survival

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Background: UK and European guidelines on treatment of mesothelioma recommend combination chemotherapy with Cisplatin/Pemetrexed (CP) in patients with good performance status. In Sunderland CP chemotherapy has been the standard treatment for mesothelioma in selected patients since 2006. The aim of this study was to ascertain the usage of CP for mesothelioma and impact on survival.
Method: Study conducted at Sunderland Royal Hospital. Patients diagnosed with malignant mesothelioma between 1998-2011 were included. Data collected: demographics, performance status, comorbidity, histology, treatment. Patients were stratified by date of diagnosis: 1998-2005 and 2006-2011. Factors affecting survival were assessed by Cox's regression analysis.
Results: N=209, median (IQ range) age 69 (63-77) years, male 81.8%. Histology: Epithelioid 48%; Sarcomatoid 12.6%, Mixed 5.2%, Unspecified 34.2%. Proportion treated with chemotherapy 1998-2005 29.3%, 2006-2011 60.2%; OR 3.65 (2.03-6.5). Median (IQR) survival: 1998-2005 8.2 (3.7-19.3) months; 2006-2011 all patients 9.8 (3.7-15.8) months, patients given CP chemotherapy 12.7 (9.8-22.7) months $p > 0.05$. On regression analysis treatment with CP appeared to confer a survival benefit HR (95% CI) 0.30 (0.21-0.43). But overall survival was unchanged between 1998-2005 and 2006-2011 HR 0.98 (0.72-1.3).
Conclusion: Most patients with malignant mesothelioma are now treated with carboplatin/pemetrexed combination chemotherapy. However overall survival has not improved significantly and the apparent benefit of treatment may be due to patient selection.

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Efficacy and safety of autologous blood pleurodesis versus talc pleurodesis in patients with malignant pleural effusions: Preliminary results

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Autologous blood pleurodesis in clinical practice has not been evaluated in the treatment of malignant pleural effusions. The aim of this ongoing study is to determine the efficacy and safety of autologous blood pleurodesis versus talc pleurodesis in patients with malignant pleural effusions.
A prospective, randomized trial was carried out in a single centre. Our study has been conducted since March 2009 and by now comprised 21 patients with recurrent malignant pleural effusions. Patients were randomized to autologous blood and talc pleurodesis group. A blood sample of 3 ml/kg was obtained from the patient's brachial vein and immediately given into the intrapleural space. Four grams of talc mixed in 150 mL of normal saline was administered via tube thoracostomy. Patients were followed up with chest radiographs at 3 days and 1 month after pleurodesis.
Eight patients were randomly assigned to the autologous blood-treated group and 11 to the talc-treated group until January 2012. Two patients were ineligible due to rapid progression of systemic disease and death. The median age was 60,7 years. The success rate was 75% (6/8) in autologous blood group and 82% (9/11) in talc group. There was no statistically difference between the groups in regard to success rates ($p<0.574$). No severe or life-threatening adverse experiences were noted in the study. Chest pain is the most frequent minor complication in talc group.
According to these preliminary results, we have found that pleurodesis using both autologous blood and talc showed high efficacy for controlling malignant pleural effusions.

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Time to diagnosis and time to therapy in patients with malignant pleural mesothelioma (MPM) compared to patients with lung cancer in Denmark 2007 to 2011. A quality assurance analysis

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In Denmark patients with pleural diseases are usually first seen by departments taking care of patients with suspected lung cancer. When "diagnostic packages" was published in 2008 by the National Board of Health a 28 days maximal time to diagnosis and a 42 days maximal time to treatment were stated for lung cancer

as well as for MPM. We wanted to study how well these time frames are fulfilled for MPM. For the 5-year period 2007 to 2011, we have found 146 MPM patients in the pathology registry of Odense University Hospital. This is about 30% of all incident cases in Denmark in the period. MPM was confirmed by histology in 92% of the cases. Five patients died before the final diagnosis was known. Forty-two (30%) of 141 patients were treated by best supportive care. Two patients were lost for follow-up. In three patients therapy was initiated at progression, but in 94 patients therapy began as soon as possible after the diagnosis. Eighty-three had chemotherapy, 10 had radiotherapy, and one had resection as the first step of the treatment. For the 141 patients the median time to diagnosis was 38 days (range: 6-127 days). Only 30% of the patients were diagnosed within 28 days. The median time to therapy for the 94 patients was 58 days (range: 19 - 142 days) - 21% were treated within 42 days. Among the 77 MPM patients from our primary uptake area 42% were diagnosed within 28 days and 17 out of 54 (32%) were treated within 42 days. In the same period, 84% of patients with lung cancer from our primary uptake area were diagnosed within 28 days and 74% had started treatment within 42 days.

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Clinical role of pleural effusion MMP-3 levels in malignant pleural mesothelioma

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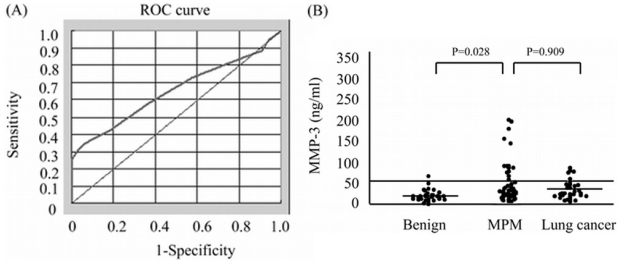
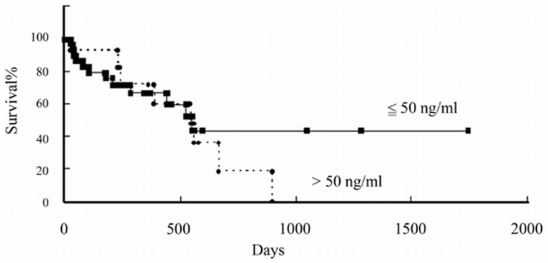
Malignant pleural mesothelioma (MPM) is an aggressive malignant tumor of mesothelial origin associated with asbestos exposure. MPM displays a limited response to conventional chemotherapy and radiotherapy, so early diagnosis of MPM is very important. Malignant tumor progression requires destruction of the basement membrane (BM), which is constructed from extracellular matrix (ECM) materials. Matrix metalloproteinase (MMP) are thought to be important due to their wide degrading function. We investigated the pleural effusion MMP-3 levels of patients with MPM and compared them to those of a population with non-malignant pleuritis or lung cancer involving malignant pleural effusion. The pleural effusion MMP-3 concentrations of 52 MPM patients and 67 non-MPM patients were measured. We demonstrated that the MPM patients had significantly higher pleural effusion MMP-3 levels than the population with non-malignant pleuritis.



The overall survival of the MPM patients with lower pleural effusion MMP-3 levels was longer than that of those with higher pleural effusion MMP-3levels.



Our data suggest clinical role of pleural effusion MMP-3 levels in malignant pleural mesothelioma.

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Inhibition of osteopontin modulates tumor-stimulated immune response and suppresses mesothelioma progression

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Rationale: Osteopontin (OPN) is overexpressed in mesothelioma tissue and has been associated with impaired patient survival. However, whether OPN is involved in mesothelioma growth and regulation of tumor-stimulated immune reaction is unknown.

Aim: To examine the functional importance of OPN in experimental malignant pleural mesothelioma.

Methods: AE17 murine mesothelioma cells which express high levels of OPN, engineered to stably express short hairpin RNAs (shRNAs) targeting the OPN transcript. To mimic pleural mesothelioma we intrapleurally injected syngeneic C57/Bl6 mice with AE17/OPNshRNA or AE17/vector cells. Tumor tissue and pleural fluid were harvested 15 days post-injection. The presence of pro-tumor cells including CD11b(+)/F4/80(+)/CD206(+) macrophages and CD11b(+)/Gr1(+) myeloid suppressor cells were evaluated using FACS.

Results: Pleural tumors in mice injected with AE17/shRNA were significantly smaller than those developed in mice injected with AE17/vector (mean tumor weight 428.3±41.2mg versus 107.2±25.6mg, $P<0.05$). In addition, animals bearing AE17/shRNA tumors had significantly less pleural fluid compared to those bearing control tumors (451.3±48.8μl versus 41.67±4.52μl, $P< 0.05$). Pleural fluid CD206(+) macrophages were significantly less in mice with AE17/shRNA tumors compared to those with AE17/vector. Similarly, pleural fluid CD11b(+)/Gr1(+) myeloid-suppressor cells were significantly reduced respectively.

Conclusion: OPN promotes experimental mesothelioma growth and formation of malignant pleural effusion. Importantly, OPN substantially contributes in pro-tumor inflammatory cell recruitment in the mesothelioma-affected pleural cavity.