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CD90 is a diagnostic marker to differentiate between malignant pleural mesothelioma and lung carcinoma with immunohistochemistry.

Authors: Kawamura, K., et al.

Reference: Am J Clin Pathol. 2013;140:544-9.

URL: <http://ajcp.ascpjournals.org/content/140/4/544.long>

Comment: The differential diagnosis between epithelioid mesothelioma and lung adenocarcinoma is often difficult in terms of the surgical pathology, but is important from the standpoint of therapeutic procedures. This study conducted immunohistochemical analyses on clinical specimens, including 26 cases of mesothelioma, 28 cases of lung adenocarcinoma and 33 cases of lung squamous cell carcinoma to pathologically distinguish mesothelioma from lung carcinoma, particularly adenocarcinoma. The CD90 expression was useful for making a differential diagnosis between epithelioid mesothelioma and lung adenocarcinoma, whereas sarcomatoid mesothelioma and lung carcinoma specimens, irrespective of the histologic types, were negative in general. The sensitivity and specificity of CD90 expression in epithelioid mesothelioma and lung adenocarcinoma were comparable to those of well-established markers used for a differential diagnosis. These data indicate that CD90 is a novel diagnostic marker that contributes to a diagnosis of epithelioid mesothelioma.

Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial.

Authors: Calabrò, L., et al.

Reference: Lancet Oncol. 2013;14:1104-11.

URL: [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(13\)70381-4/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(13)70381-4/fulltext)

Comment: A new immunotherapeutic strategy involves the targeting of regulatory molecules expressed on immune cells to enhance the anti-tumor activity of T cells. Monoclonal antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA4) have been demonstrated to have therapeutic activity against different tumor types. The efficacy, safety and immunological activity of an anti-CTLA4 monoclonal antibody, tremelimumab, was investigated in patients with advanced malignant mesothelioma. The study was an open-label, single-arm phase 2 clinical trial. Patients aged 18 years or older with measurable, unresectable malignant mesothelioma and progressive disease after a first-line platinum-based regimen were enrolled. Patients were given tremelimumab intravenously at 15 mg/kg once every 90 days until progressive disease or severe toxicity developed. The primary endpoint was the proportion of patients who achieved an objective response, with a target response rate of 17%, according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) for pleural malignant mesothelioma or the standard RECIST 1.0 for peritoneal malignant mesothelioma. A total of 29 patients were enrolled in this study. No patients had a complete response and two patients (7%) had a durable partial response. Although this study did not reach its primary endpoint, there was disease control in nine (31%) patients and a median progression-free survival of 6.2 months (95% CI 1.3-11.1),

and a median overall survival of 10.7 months (0.0-21.9), which were fairly good. Twenty-seven patients (93%) had at least one grade 1-2 treatment-related adverse event, and four patients (14%) had at least one grade 3-4 treatment-related adverse event (two gastrointestinal, two hepatic, one neurological and one pancreatic). Even though this study did not meet the primary endpoint, tremelimumab seemed to have encouraging clinical activity and an acceptable safety and tolerability profile in previously treated patients with advanced malignant mesothelioma.

Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma.

Authors: Ceresoli, G.L., et al.

Reference: Br J Cancer. 2013;109:552-8.

URL: <http://www.nature.com/bjc/journal/v109/n3/full/bjc2013368a.html>

Comment: Since preclinical studies suggested that angiogenesis has a key role in the progression of malignant mesothelioma (MPM), the authors conducted an open-label phase II study (NCT00407459) to assess the activity of bevacizumab, an anti-vascular endothelial cell growth factor (VEGF) antibody, combined with pemetrexed and carboplatin in patients with previously untreated, unresectable malignant pleural mesothelioma (MPM). Eligible patients received pemetrexed at 500 mg/m², carboplatin with an area under the plasma concentration-time curve (AUC) 5 mg/ml per minute and bevacizumab at 15 mg/kg, administered intravenously every 21 days for six cycles, followed by maintenance bevacizumab. The primary endpoint of the study was the progression-free survival (PFS). Seventy-six patients were evaluable for the analysis. A partial response was achieved in 26 cases (34.2%, 95% CI 23.7-46.0%). Forty-four patients (57.9%, 95% CI 46.0-69.1%) had stable disease. The median PFS and overall survival were 6.9 and 15.3 months, respectively. The hematological and non-hematological toxicities were generally mild; however, some severe adverse events were reported, including grade 3-4 fatigue in 8% and bowel perforation in 4% of patients. Three toxic deaths occurred. The primary endpoint of the trial was not reached. Although this study had negative results, the acquisition of further data seems to be necessary before drawing conclusions on the role of bevacizumab in MPM because of the limitations of this non-randomized phase II design.

New Impact factor and ranking for Respiriology released June 2013



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microRNA-1 induces growth arrest and apoptosis in malignant mesothelioma

Authors: Xu, Y., et al.

Reference: Chest. 2013. doi: 10.1378/chest.12-2770.

URL: <http://journal.publications.chestnet.org/article.aspx?articleid=1705707>

Comment: MicroRNAs (miRNA) are a family of short, noncoding regulatory RNA molecules expressed in a tissue-specific, developmentally regulated manner. Although a growing number of reports indicate that there is dysregulation of miRNA expression in human cancers, including malignant pleural mesothelioma (MPM), key MPM-associated miRNA(s) have not yet been identified. Therefore, the authors investigated the miRNA expression profiles of MPM specimens to identify novel miRNAs that are potentially involved in the oncogenic transformation of human pleural cells. miRNA microarray transcriptional profiling studies of 25 MPM primary tumors were performed. Normal pleural tissue from an unmatched patient cohort was used for comparison. Representative cell lines, H513 and H2052, were used in the functional analyses of miRNA-1. In addition to several novel MPM-associated miRNAs, the authors observed that the expression level of miRNA-1 was significantly lower in the tumors compared to the normal pleural specimens. Subsequently, a pre-mir of miRNA-1 was introduced into MPM cell lines to induce them to overexpress this miRNA. The cellular proliferation rate was significantly decreased after the overexpression of microRNA-1. Early and late apoptosis were increased markedly in these miRNA-1-transfected cell lines. Taken together, these data suggested that the overexpression of miRNA-1 induced apoptosis in these MPM cell lines, acting as a tumor suppressor. This study identified miRNA-1 as a MPM-associated miRNA, and indicated that it has potential pathogenic and therapeutic significance.

Hyaluronic acid in the pleural fluid of patients with malignant pleural mesothelioma

Authors: Fujimoto, N., et al.

Reference: Respir Investig. 2013;51:92-7.

URL: [http://www.respiratoryinvestigation.com/article/S2212-5345\(13\)00008-7/abstract](http://www.respiratoryinvestigation.com/article/S2212-5345(13)00008-7/abstract)

Comment: Hyaluronic acid (HA) is a glycosaminoglycan, which is involved in embryogenesis, angiogenesis, cell growth and migration. Although numerous studies have investigated the diagnostic importance of HA in malignant pleural mesothelioma (MPM), no large study has been conducted to clarify the clinical utility of HA as a diagnostic marker. Therefore, the authors retrospectively analyzed the HA concentrations in the pleural fluid and evaluated its utility for the differential diagnosis of MPM. The pleural fluid HA concentrations were measured in 334 patients, including patients with MPM, benign asbestos pleurisy (BAP), lung cancer (LC), other malignant conditions (OMCs), infectious pleuritis (IP), collagen disease (CD) and other non-neoplastic conditions. The median (range) HA concentrations in the pleural fluid were 78,700 (7920-2,630,000) ng/ml in the MPM group, 35,950 (900-152,000) ng/ml in the BAP group, 19,500 (2270-120,000) ng/ml in the LC group, 14,200 (900-101,000) ng/ml in the OMC group, 23,000 (900-230,000) ng/ml in the IP group, 24,600 (9550-80,800) ng/ml in the CD group and 8140

(900-67,800) ng/ml in the other diseases group. The HA levels were significantly higher in the MPM group than in the other groups. A receiver operating characteristic (ROC) analysis revealed an area under the ROC curve value of 0.832 (95% confidence interval, 0.765-0.898) for the differential diagnosis of MPM. When a cut-off value of 100,000 ng/ml was used, the sensitivity and specificity were 44.0 and 96.5%, respectively. In the MPM group, the HA values were significantly higher for the epithelioid subtype than for the sarcomatous subtype ($p=0.007$), and higher in earlier stages (I and II) than in advanced stages (III and IV) ($p=0.007$). The authors concluded that a diagnosis of MPM should be strongly considered in patients with pleural fluid HA concentrations exceeding 100,000 ng/ml. This is a first large scale study showing the clinical utility of the measurement of the HA levels in pleural effusion as a diagnostic marker for MPM.

Phase II study of first-line bortezomib and cisplatin in malignant pleural mesothelioma and prospective validation of progression free survival rate as a primary end-point for mesothelioma clinical trials (European Organisation for Research and Treatment of Cancer 08052).

Authors: O'Brien, M.E., et al.

Reference: Eur J Cancer. 2013;49:2815-22.

URL: [http://www.ejca.com/article/S0959-8049\(13\)00405-X/abstract](http://www.ejca.com/article/S0959-8049(13)00405-X/abstract)

Comment: Bortezomib is a small molecule proteasome 20S inhibitor developed as a novel agent to treat human malignancies. The treatment of mesothelioma cell lines with bortezomib induced cell arrest in the G2M phase, while it increased the expression of the cyclin-dependent kinase inhibitor, p21, and Bax. Bortezomib exhibited limited activity as a single agent in the second line treatment of patients with malignant pleural mesothelioma (MPM). This prospective phase II study of the combination of cisplatin and bortezomib in the first-line treatment of MPM was conducted to validate the progression-free survival rate at 18 weeks (PFSR-18) as the primary end-point. Chemotherapy-naïve patients with histologically-proven MPM were treated with cisplatin at 75 mg/m² on day 1 and bortezomib 1.3 mg/m² on days 1, 4, 8 and 11 every three weeks. The primary end-point validation utilized the landmark method. Eighty-two patients were entered into the study. The PFSR-18 was 53% (80% confidence interval, CI, 42-64%). The overall survival (OS) was 13.5 months (95% CI 10.5-15) with 56% (95% CI 44-66%) of the patients alive at one year. The median PFS was 5.1 months (95% CI 3.3-6.5), and the response rate was 28.4% (95% CI 18.9-39.5%). The most frequent grade 3-4 toxicities were hyponatremia (46%), hypokalemia (17%), fatigue (12.2%), thrombocytopenia (11%), neutropenia (9.7%) and neurotoxicity (motor, sensory, other: 1.2%, 8.5%, 2.4%). There were two toxic deaths (32 and 74 days) due to acute pneumonitis and cardiac arrest. The end-point validation showed that patients with no progression/progression at 18 weeks had a median OS of 16.9/11.9 months, respectively. The hazard ratio was 0.46 (CI 0.32-0.67), the results of the log-rank test and C-index were 0.007 and 0.60. The 50% PFSR-18 for Bortezomib was contained within the 80% CI for (42-64%). Therefore, the null hypothesis could not be rejected. Accordingly, this combination does not warrant further investigation. The PFSR-18 was confirmed as a strong predictor of survival.

Combination of mesothelin and CEA significantly improves the differentiation between malignant pleural mesothelioma, benign asbestos disease, and lung cancer.

Authors: Muley, T., et al.

Reference: J Thorac Oncol. 2013;8: 947-51.

URL: <http://journals.lww.com/jto/pages/articleviewer.aspx?year=2013&issue=07000&article=00015&type=abstract>

Comment: Although soluble mesothelin-related peptides (SMRP) have been reported as potential markers for the diagnosis of malignant pleural mesothelioma (MPM), its accuracy is not sufficient. Therefore, the authors investigated whether a combination of SMRP with a carcinoembryonic antigen (CEA) test might improve the relatively low diagnostic yield of the SMRP test. In a retrospective study, the SMRP (mesothelin) and CEA serum concentrations were measured in 93 previously untreated MPM patients, 75 patients with benign asbestos disease and 139 patients suffering from lung cancer (LC). The differentiation between MPM, LC and benign asbestos disease could be improved by applying the ratio of mesothelin/CEA. The area under the receiver operator characteristics curve (AUC) for mesothelin alone was found to be only 0.708. However, for the mesothelin/CEA ratio, the AUC of the receiver operator characteristics curve increased to 0.978. The sensitivity was 93% (69%), with 95% (100%) specificity for the differentiation between MPM and LC. A comparison of MPM and benign asbestos disease showed that the AUC was 0.887 and the sensitivity 56% (47%) at 95% (100%) specificity. An average increase in sensitivity of 38% (range, 16%-63%) could be achieved by using the quotient mesothelin/CEA compared with the sensitivity of mesothelin alone. The diagnostic yield of the mesothelin test can be considerably improved when combined with a CEA test with regard to the differential diagnosis between MPM and LC and between MPM and benign asbestos disease.

Radical pleurectomy and chemoradiation for malignant pleural mesothelioma: the outcome of incomplete resections.

Authors: Bölükbas, S., et al.

Reference: Lung Cancer, 2013;81:241-6

URL: [http://www.lungcancerjournal.info/article/S0169-5002\(13\)00169-4/abstract](http://www.lungcancerjournal.info/article/S0169-5002(13)00169-4/abstract)

Comment: The role of curative surgery in the treatment of malignant pleural mesothelioma has been the subject of debate after the MARS (Mesothelioma and Radical Surgery) trial in 2011. Macroscopic complete resection (MCR) is the goal of surgery and a key prognostic factor. This clinical study demonstrated the outcomes of incomplete resections (R2) within multimodality treatment protocols. Eighty-eight patients underwent radical pleurectomy (RP), followed by chemoradiation within a prospective study. A MCR could be achieved in 64.8% (57/88) of the cases. Compared to MCR patients, the R2-patients (n = 31) had an inferior overall survival (MS 13 vs. 33 months, P < .0001), shorter progression-free-survival (MS 9 vs. 16 months, P

< .0001) and inferior survival after disease progression (MS 4 vs. 11 months; $P < .0001$), respectively. R2 was associated with an advanced p-T-Status ($P < .0001$), p-N-Status ($P = 0.046$) and p-IMIG stage ($P < .0001$). No difference could be observed with regard to the age, histology, laterality, surgical morbidity or mortality. Unresectable T4-disease and an impaired cardiopulmonary reserve were the main reasons for ineligibility for EPP in 35.5% (11/31) and 48.4% (15/31) of cases, respectively. These findings suggest that R2 in patients undergoing RP is associated with inferior outcomes, and that only very selected cases would have qualified for EPP to achieve MCR. There is a need to further investigate effective intrapleural additive treatment options for patients undergoing R2 surgeries.

Prognostic significance of metabolic response by positron emission tomography after neoadjuvant chemotherapy for resectable malignant pleural mesothelioma.

Authors: Tsutai, Y., et al.

Reference: Ann Oncol. 2013;24:1005-10

URL: <http://annonc.oxfordjournals.org/content/24/4/1005.long>

Comment: The factors influencing the outcome after the resection of malignant pleural mesothelioma (MPM) are controversial. In this study, the investigators retrospectively evaluated the usefulness of the metabolic response assessed by fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) after neoadjuvant chemotherapy to predict the prognosis of patients with resectable malignant pleural mesothelioma (MPM) who underwent extrapleural pneumonectomy (EPP) ± postoperative hemithoracic radiotherapy in a multicenter study. Patients with a decrease of $\geq 30\%$ in the tumor maximum standardized uptake value (SUVmax) after neoadjuvant platinum-based chemotherapy were defined as metabolic responders. The radiological response using the modified RECIST or metabolic response and surgical results were analyzed in 50 patients. The median overall survival (OS) from diagnosis was 20.5 months. A metabolic response significantly correlated with the OS, with the median OS for metabolic responders not reached versus an OS of 18.7 months for non-responders. No correlation was observed between the OS and radiological response with the median OS for radiological responders and non-responders. Based on the multivariate Cox analyses, a decreased SUVmax and epithelioid subtype were significant independent factors predicting the OS. These results suggest that a metabolic response after neoadjuvant chemotherapy is an independent prognostic factor for patients with resectable MPM. Patients with a metabolic response or epithelioid subtype may be good candidates for EPP.

Clinical characteristics of patients with malignant pleural mesothelioma harboring somatic BAP1 mutations.

Authors: Zauderer, M.G., et al.

Reference: J Thorac Oncol. 2013;8:1430-3

URL: <http://journals.lww.com/jto/pages/articleviewer.aspx?year=2013&issue=11000&article=00014&type=abstract>

Comment: BRCA1-associated protein 1 (*BAP1*) is a tumor suppressor gene. Somatic *BAP1* mutations are common in malignant pleural mesothelioma (MPM), as well as cutaneous and uveal melanoma. *BAP1* is involved in various biological processes, including the DNA damage response and regulation of cell growth. In uveal melanoma and clear cell renal cell carcinoma, *BAP1* mutations are associated with poor outcomes, but their clinical significance in MPM is unknown. In this study, the characteristics of MPM patients whose tumors harbor somatic *BAP1* mutations were investigated. The percentage of current or former smokers among the cases with *BAP1* mutations was significantly higher than in *BAP1* wild-type cases, (75% versus 42%; $p = 0.006$). However, the types of nucleotide substitutions in *BAP1* did not suggest that there was a causative association with smoking. No other clinical features, i.e., the age at diagnosis, sex, histology, stage, asbestos exposure and family or personal history of malignancy, were significantly different among those with and without *BAP1* mutations in their MPM. There was also no difference in survival according to the somatic *BAP1* mutation status. Their conclusion was that there is no apparent distinct clinical phenotype for MPM with a somatic *BAP1* mutation. Extensive clinicopathological studies are required to clarify the roles of *BAP1* mutations in MPM.

See you all very soon at the 18th APSR Congress in Yokohama!



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