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PRESS RELEASE

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Promising Developments in Early Diagnosis and Treatment of Mesothelioma

Presentations at the 3rd European Lung Cancer Conference

Lugano-CH/Aurora-US-CO/Geneva-CH, 18 April 2012 -- New results presented at 3rd European Lung Cancer Conference in Geneva, Switzerland show important steps being made to improve the diagnosis and treatment of malignant pleural mesothelioma, an aggressive cancer of the outer lining of the lungs caused by asbestos exposure.

Micro RNAs speed diagnosis

Australian researchers have identified a small molecule that is more abundant in the blood of people with the deadly lung disease mesothelioma than in healthy people. Their findings bring scientists a step closer to being able to diagnose mesothelioma earlier than is currently possible.

At present diagnosing mesothelioma depends on the availability of a lung biopsy that contains enough tumor tissue. However suitable biopsies are not always available, which can leave doctors uncertain about the patient's diagnosis, sometimes resulting in a delay to the start of treatment. "If doctors could use a diagnostic marker based on a simple blood test to help with diagnosis, it could circumvent the problem of availability of tumor tissue and help to accelerate the diagnostic process," says Dr. Michaela Kirschner from the Asbestos Diseases Research (Concord Hospital Campus) in Sydney, who reported the new findings.

So far a number of proteins have been proposed as blood-based markers for malignant pleural mesothelioma; however none of these has so far reached the accuracy required for routine clinical use.

In the new study, Kirschner and colleagues explored whether molecules known as microRNAs in blood could serve as a diagnostic marker for the disease. Studying 5 patients with malignant pleural mesothelioma and 3 healthy controls, they identified 17 microRNAs with significantly

differential abundance in the two groups. They then validated these miRNAs in a series of blood samples from 15 patients and 13 controls. These studies revealed that the level of a particular microRNA known as miR-625-3p was four-fold higher in the blood of mesothelioma patients. Measuring levels of that molecule in blood samples allowed the researchers to discriminate between MPM patients and controls with an accuracy of 82.4 percent.

“Detailed analyses of our two independent sample series have shown that miR-625-3p performs as well as any previously proposed protein marker for detecting mesothelioma,” Kirschner said. “However, like most diagnostic markers, miR-625-3p is not 100 percent accurate, and therefore there is a chance the assay will produce both false positives as well as false negatives. Further studies on larger sample sizes are needed to see whether the accuracy of miR-625-3p can be confirmed or even turn out to be better than currently observed.”

“Should further studies prove that microRNAs in plasma are accurate enough for the diagnosis of malignant pleural mesothelioma, this will lead to the development of a diagnostic test for routine clinical use,” Kirschner said. “This test would then represent a relatively simple way to circumvent the problems associated with obtaining a tissue biopsy. For a patient this would mean that appropriate treatment could be instituted at an earlier stage.”

High-dose radiotherapy gives good response rates

Despite a widespread belief that mesothelioma does not respond to radiotherapy, Australian researchers have found that it may have the best response rates of any single treatment for patients with disease largely confined to one side of the chest.

Between 2003 and 2011, Dr. Malcolm Feigen and colleagues from Austin Health Radiation Oncology Center in Melbourne gave radiotherapy to 45[1] patients aged 45 to 74 with doses of between 45 and 60 Gy to one side of the chest over six weeks. The radiation was administered using 3D-conformal or intensity-modulated radiotherapy. None had surgery to remove their affected lung. At the beginning of treatment more than 80 percent of patients had the more advanced stage III or IV disease, and all had prior chemotherapy and/or surgery, except for two.

The median survival for the patients was 12.4 months from starting radiotherapy, ranging from 2 to 87 months, the researchers say. There were no life-threatening or fatal toxicities from treatment.

“Many believe mesothelioma to be radioresistant and that toxicity is prohibitive if high doses are given with the affected lung *in situ*,” Feigen and colleagues say.

“Our experience provides clear evidence that radiation is arguably the most effective single agent for mesothelioma and new technologies including intensity-modulated radiotherapy allow high

doses to be delivered safely."

Blood markers identified

Swiss, Italian and US researchers report that they have tested another group of potentially useful blood markers for mesothelioma.

Dr. Ferdinando Cerciello from the Swiss Federal Institute of Technology and the University Hospital Zurich and colleagues studied 56 candidate biomarker peptides that they isolated from laboratory samples of mesothelioma and tested in the blood of patients with mesothelioma, healthy donors and non-small-cell lung cancer patients.

The study "revealed potential candidate biomarkers in serum, accessible simultaneously by mass spectrometry," the authors report. At the meeting, they will report the strategy for the selection and measurement of their 56 peptides in serum as well as the results of an evaluation in 75 blood samples.

Sorafenib well tolerated

The drug sorafenib is well tolerated in patients with mesothelioma after completion of platinum containing chemotherapy, British investigators report.

In a phase II trial of sorafenib following first-line chemotherapy in 53 patients with malignant mesothelioma, 34 percent of patients were progression-free after six months.

Dr. Sophie Papa and Dr. James Spicer from Kings College London and colleagues say that the drug was well tolerated and offered a length of progression-free survival that "compares favorably" to other targeted agents in this disease.

"Mesothelioma, one of the most important occupational diseases, is attracting more and more attention nowadays," noted Prof Paul Baas from the Department of Thoracic Oncology at The Netherlands Cancer Institute, member of the ESMO Chest Tumors Faculty Group. "New developments in the diagnostics and treatment of this disease are really important, including those presented during the ELCC 2012 meeting: improvements in the diagnosis by simply measuring biomarkers in peripheral blood samples will identify patients who may be candidates for new studies or financial reimbursement by their employers. The developments in molecular biology allow us now to detect circulating fragments of (micro)RNA and peptides that may play an important role. Furthermore the understanding that radiation therapy and targeted agents can be given to these patients will lead to new, promising, studies."

-END-

Notes to Editors

[1] The authors have updated data with respect to figures included in the original abstract appended to this press release. Final figures will be presented during the session.

Disclaimer

Information contained in this press release was provided by the abstract's authors and reflects the content of the studies. It does not necessarily express ESMO's or IASLC's point of view.

About the European Lung Cancer Conference (ELCC) 2012

The European Lung Cancer Conference (ELCC) has become the reference event in Europe for professionals treating lung cancers. From surgical resection to complex treatment options with novel agents and novel targets; from lung cancer in non-smokers to issues surrounding gender; from various forms of lung cancer, the big killer, to rare forms of chest tumors: the third edition of the ELCC will provide a comprehensive multidisciplinary overview of the latest as well as of the state-of-the-art knowledge in thoracic malignancies, covering different aspects such as prevention, screening, diagnosis, treatment modalities and the results of basic, clinical and translational research, presented by top international academic experts. More than 1,500 attendees are expected from throughout Europe and the rest of the world.

About the European Society for Medical Oncology (ESMO)

The European Society for Medical Oncology (ESMO) is the leading European professional organization committed to advancing the specialty of medical oncology and promoting a multidisciplinary approach to cancer treatment and care.
ESMO's mission is to advance cancer care and cure through fostering and disseminating good science that leads to better medicine and determines best practice.
As a trusted organization with 35 years of experience, ESMO serves its members and the oncology community through: a brand of excellence in post-graduate oncology education and training; leadership in transforming evidence-based research into standards of cancer care in Europe; dedicated efforts to foster a more favorable environment for scientific research; innovative international platforms to share expertise, best practices and disseminate the most up-to-date scientific research to as wide an audience as possible.
ESMO's scientific journal, Annals of Oncology, ranks among the top clinical oncology journals worldwide. ESMO events are the meeting place in Europe for medical oncologists to update their knowledge, to network and to exchange ideas.
To find out more about ESMO, please visit: www.esmo.org

About the International Association for the Study of Lung Cancer (IASLC)

The International Association for the Study of Lung Cancer (IASLC) is the only global organization dedicated to the study of lung cancer. Founded in 1974, the association's membership includes more than 3,500 lung cancer specialists in 80 countries. To learn more about IASLC please visit www.iaslc.org.

Abstract 230O
Mesothelioma
Proffered Paper session: Friday, 20 April, 16:20-17:40, Room E

Assessment of circulating miRNAs as potential biomarkers for Malignant Pleural Mesothelioma (MPM)

The definitive diagnosis MPM often depends on the availability of a biopsy of sufficient size. The identification of a biomarker that can be easily measured in blood with a potential use in the early detection setting would represent an important step forward. Recently it has been shown that microRNAs (miRNAs) detectable in serum or plasma represent a class of potential new biomarkers. In this study we investigated the ability of certain miRNAs in plasma and serum to serve as a diagnostic marker for MPM.
Using Agilent 8x15k miRNA microarrays we profiled miRNA expression in plasma samples from healthy volunteers and patients with MPM. Candidate miRNAs identified in the arrays were validated by TaqMan assay-based quantitative real-time PCR or using the OpenArray real-time PCR platform.
Microarray-based expression profiling of plasma from 5 MPM patients and 3 healthy controls identified 17 miRNAs with significantly differential abundance in the two sample groups. Validation of these miRNAs in a series of plasma samples from 15 MPM patients and 13 controls (healthy controls and patients with coronary artery disease) revealed that levels of miR-625* are not only significantly elevated in plasma of MPM patients (4-fold higher, p=0.004), but are also able to discriminate between MPM patients and controls with an accuracy of 82.4 %. Furthermore, levels of two miRNAs previously reported to be associated with MPM, miR-29c* and miR-92a, were also elevated in our MPM series however without reaching statistical significance. Assessing levels of miR-625* in serum of another series of MPM (N= 30) and asbestosis (n=10) confirmed that miR-625* was significantly (p=0.023) elevated only in serum of MPM patients and was able to discriminate between cases and controls with an accuracy of 79.3 %. Finally, miR-625* was also found to be present at significantly higher levels (2-fold higher, p= 0.006) in tumour specimen from 18 MPM patients who underwent extrapleural pneumonectomy than in normal mesothelium (pericardial tissue).
Taken together these data provide evidence that miR-625* has the potential to serve as a novel blood-based biomarker for MPM.

Author Block
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Abstract 228O
Mesothelioma
Proffered Paper session: Friday, 20 April, 16:20-17:40, Room E

Prolonged survival of patients with localised malignant pleural mesothelioma after high dose hemithoracic radiotherapy to an intact lung

Introduction
Mesothelioma patients will obtain best palliation with treatment that controls their enlarging tumour masses, which originate in the pleura of one hemithorax and spread into surrounding organs, producing distressing local symptoms of pain and respiratory impairment. As most are unsuitable for extrapleural pneumonectomy and chemotherapy provides poor local control, we postulated that high doses of radiotherapy to large volumes would provide the best and most durable symptom relief.
Methods
In 2003 our institution began a prospective program of high dose radiotherapy for mesothelioma patients using new technological advances and precision targeting of all viable tumour with ^{18}F-FDG PET scans. We believed that radiation toxicity could be limited by advanced techniques with 3-D treatment planning and delivery.
All patients had histologically confirmed malignant pleural mesothelioma of any subtype, confined to one hemithorax with normal lung, liver and renal function. None had undergone a pneumonectomy.
Results
From 2003 to 2011, 44 patients aged 37-76 received doses of 45-60 Gy to part or all of one complete hemithorax over 6 weeks, using 3D-conformal or, in 27 cases, intensity-modulated radiotherapy (IMRT). 84% had advanced stage III-IV disease on planning PET scans. 21 had a pleurectomy/decortication, 16 a pleurodesis and 5 only a biopsy. 19 were chemotherapy-naive and 22 had progressed after palliative chemotherapy.
Median survival of all patients was 22 mths from diagnosis (range 7-91). Survival is 80%, 39% and 7% at 1, 2 and 5 years, and 15 are still living. 26 deaths were from progressive disease (in 25 outside the irradiated volume), mostly in the contralateral lung or the ipsilateral lung that had been excluded from radiotherapy in our early patients while we established our normal tissue tolerance constraints. Apart from one debatable death from pneumonitis, there were no grade 4 or 5 toxicities.
Conclusions
Many believe mesothelioma to be radioresistant and that toxicity is prohibitive if high doses are given with the affected lung in situ. Our experience provides clear evidence that radiation is arguably the most effective single targeting agent for mesothelioma and new technologies including IMRT allow high doses to be delivered safely to large volumes. Survival is not compromised.

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Abstract 229O
Mesothelioma
Proffered Paper session: Friday, 20 April, 16:20-17:40, Room E

Glycopeptide Serum Markers for Malignant Pleural Mesothelioma Diagnostics

Background: Malignant pleural mesothelioma (MPM) is an aggressive cancer of the pleura caused by asbestos exposure. Recent therapeutic advances have raised growing interest in the identification of serum accessible diagnostic markers for MPM. Here, we used mass-spectrometry (MS) based technologies for the identification and clinical verification of glycopeptide MPM candidate biomarkers in serum. Glycopeptide MPM candidate biomarkers were selected from a pool of glycopeptides discovered through comparison of the surfaceome of MPM with control cell lines. The clinical significance of the selected glycopeptides was verified by using Selected Reaction Monitoring (SRM) in serum from cohorts of MPM patients and controls.

Methods: The surfaceome of four MPM (epithelioid and biphasic) and four control (pleura and lung adenocarcinoma) cell lines was investigated by using Cell Surface Capturing (CSC) technology and label free quantitative mass spectrometry. Glycopeptides detected in higher abundance in the MPM surfaceome were selected for SRM-based quantitative analysis in patient sera enriched for N-glycopeptides.

Results: Surfaceome analysis revealed 500 N-glycopeptides, corresponding to more than 300 cell surface N-glycoproteins from MPM-derived cell lines. 56 candidate biomarker peptides were selected for initial SRM quantification and verification in serum of patient cohorts. The cohorts consisted of 25 MPM patients (13 epithelioid and 12 biphasic, stage I-IV), 25 healthy donors and 25 non-small-cell lung cancer patients (16 adenocarcinoma and 9 squamous, stage III-IV) matched per sex and age. We verified the robustness of our approach based on serum analysis of the mesothelioma marker soluble mesothelin–related protein (SMRP).

Conclusion: The relative quantitative investigation of the MPM surfaceome revealed serum accessible potential MPM candidate biomarkers. SRM technology enables now the parallel verification of glycopeptide candidate biomarkers in serum samples of selected patient cohorts. A multiplexed 56 peptides SRM-assay for MPM was established and evaluated in 75 serum samples.

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Abstract 233P
Poster display: as of Thursday, 19 April, 8:00-19:30, Poster area

A phase 2 study of sorafenib after first line platinum containing combination chemotherapy in malignant mesothelioma.
Background: The incidence of mesothelioma is rising, with a predicted peak in the UK expected in 2020. Cisplatin and pemetrexed first line confers a survival benefit, but with a median progression-free survival of only 5.7 months. Sorafenib inhibits the raf/MEK/ERK signalling pathway, as well as tyrosine kinases including receptors for VEGF which are present at particularly high circulating levels in mesothelioma patients. Antibodies to VEGF, VEGFR1 & VEGFR2 inhibit mesothelioma growth.
Methods: Sorafenib at 400mg BD was assessed in a single arm multi-centre phase 2 study. A Simon 2-stage design was used. Eligible patients had received prior platinum combination chemotherapy. The primary endpoint was progression-free survival (PFS) at 6 months assessed by CT using modified RECIST. Published reference values for PFS in mesothelioma (Francart et al. 2006 J Clin Oncol) provide a benchmark of 28% progression-free at 6 months.
Results: A total of 53 patients have been treated, 41 male and 12 female. Primary histology was epithelioid (37), sarcomatoid (2), mixed (7). No histological sub-group was recorded in 7 patients. 96% of patients had a performance status of 0 or 1. The most frequent adverse events were fatigue, hand-foot syndrome, diarrhoea and hypertension. Overall treatment was well tolerated with few grade 3 and no grade 4 toxicities. At 6 months 34% of patients were progression free, despite all patients having already received prior chemotherapy. A total of 5 patients remained on study beyond one year.
Conclusions: Sorafenib is well tolerated in patients with mesothelioma after completion of platinum containing chemotherapy. PFS compares favourably to that reported for other targeted agents in this disease.

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