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The Significance of the Serum Leptin, Ghreline, Tumour Necrosis Factor Alpha and Interleukine-1 Levels in Patients With Non-Small Cell Lung Cancer

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Introduction and Purpose: Many studies suggested that these increases may be responsible from development of NSCLC, and also may result in cachexia decrased and survival. This study examines the relations between serum leptin, ghreline, TNFα and IL1B levels, and survival, cachexia and resectability.
Materials and Methods: Seventy-one recently diagnosed NSCLC patients between 43 to 80 years old and without comorbidities are enrolled the study. Fasting serum samples of the patients are collected and leptin, ghrelin, TNFα and IL1B levels are measured by enzyme-linked immunosorbent assay. Decreases in body weight, histopathologic types, median survivals, resectabilities of the patients are compared by the levels of serum leptin, ghreline, TNFα, and IL1B.
Findings: Mean age of the enrolled patients was 63.3±8.22 years, and 81% of them were males. Fifty-two percent of the patients.were resectable. The sqamous cell, adenocarcinoma and other histologies were found in 60.5%, 32% and 7.2% of the patients, respectively. There was body weight loss in 9.8% of the patients in cachexia level. Mean measured levels were as follows: Ghrelin 35.89±16.7 pg/mL, leptin 12.90±38.49 pmol/mL, TNFα 9.50±2.43 pg/mL, and IL1B 196±147 pg/mL. Decrease in body weight was significantly higher in unresectable patients (35.5% vs 20%, $p = 0.001$). Mean body weight decrease rate was significantly lower in resectable patients when compared to unresectable group (3.8% vs. 8.94%, $p = 0.001$). Unresectable patients have significantly lower serum ghreline levels (27.77±2.4 pg/mL vs. 39.05±1.21 pg/mL, $p = 0.018$). There was no significant relation between body weight loss or cachexia and serum levels of leptin, ghrelin, TNFα and IL1B. But, mean serum leptin levels were significantly higher in patients with adenocarcinoma, compared to sqamous cell histology (26.99±6.2 pmol/mL vs. 5.10±9.1 pmol/mL, $p = 0.004$). There was no significant relation between serum TNFα, leptin, IL1B levels and survival. But survival was shorter in patients with leukocytosis [10 months vs. 29 months, $p = 0.014$].
Conclusion: Although we could not show prognostic significance of leptin and gherilin in NSCLC patients, serum leptin levels may help in detecting adenocarcinoma subtype and/or follow-up of the patients. We need further studies with higher number of patients to clarify this issue.

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The Relationship Between Oxysterol Binding Protein Like 5 and Calumenin During Lymph Node Metastasis

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Background: Tumour metastasis to lymph nodes represents a vitally important prognostic factor. Therefore, development of diagnostic techniques and methods to prevent tumour metastasis is urgently needed. Indeed, significant research effort is currently focused on identifying proteins that constitute new diagnostic or therapeutic targets. In this respect, we have established “antibody proteomics technology” which accelerates the discovery of proteins that are useful diagnostic markers or molecular targets. Here, we applied this technology to two kinds of lung cancer cells with different metastatic properties and searched for lymph node metastasis-related proteins.
Materials and Methods: *Two dimensional differential in-gel electrophoresis (2D-DIGE) analysis*: Cell lysates prepared from high-metastatic LERF-LC-KJ cells and low-metastatic LERF-LC-MS cells were labeled with Cy3 or Cy5 and analyzed by 2D-DIGE. Non-labeled samples were also loaded in a normal gel for mass spectrometry (MS) analysis and a modified gel that can be solubilized for antibody isolation. Proteins of interest were extracted from the gel and subjected to MS analysis.
Isolation of monoclonal antibodies: Protein samples extracted from the solubilized gel pieces derived from 2D-DIGE analysis were immobilized on a nitrocellulose membrane. Using these proteins as targets, phages displaying single chain fragment variable (scFv) antibodies with affinity to the relevant targets were enriched and selected.
Tissue microarray (TMA) analysis: Expression profiles of candidate proteins identified by 2D-DIGE were analyzed by immunostaining of TMAs with the isolated scFv-phages.
Results: The protein expressing level was compared between two cell lines using 2D-DIGE analysis. In all, 16 candidate proteins were identified from high metastatic tumour cells as being expressed at elevated levels. Using an *in vitro* scFv-phage affinity selection procedure, monoclonal scFvs binding to each of these candidate proteins were successfully isolated within a few weeks. The TMA analysis showed oxysterol binding protein like 5 and calumenin were highly expressed in clinical lung cancer tissues and significantly correlated with lymph node metastasis.
Conclusions: Our data demonstrate the utility of the antibody proteomics technology for discovering and validating tumour-related proteins. We are currently analyzing the functions of the identified proteins as potential diagnostic markers or therapeutic targets.

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Randomized Phase II Study of Maintenance Enzastaurin Following Whole Brain Radiation Therapy in the Treatment of Brain Metastases From Lung Cancer – the MENZA Study

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Background: Enzastaurin (E) is a novel protein kinase C inhibitor with anti-angiogenic activity and has demonstrated clinical activity in lung cancer (LC). The MENZA study (NCT 00415363, sponsor Eli Lilly) was designed to determine if maintenance enzastaurin (E) improves the outcome of whole brain radiation therapy (WBRT) in LC patients (pts) with brain metastases (BM).
Material and Methods: In this multicenter, randomized, double-blind Phase II study, pts who had received WBRT (20 or 30 Gy) for BM from LC (any histology) received oral maintenance E (1125 mg on Day 1 followed by 500 mg daily) or an equivalent number of placebo (P) tablets until progression. The primary endpoint was time to progression (TTP) of BMs; secondary objectives included progression-free survival (PFS), overall survival (OS), health-related quality of life (HRQoL) as reported on the EORTC QLQ C30+BN20, and safety.
Results: From December 2006 to April 2010, 109 pts were enrolled at 11 hospitals (E: 55; P: 54). ECOG PS 0–1/2 was (%) E: 71/29; P: 70/30. Small cell lung cancer (SCLC)/non-small cell lung cancer (NSCLC) was (%) E: 29/71; P: 24/76. WBRT 30 Gy/20 Gy was (%) E, 53/47; P, 57/43. Median TTP of BM was (months) E: 6.9 (95% confidence interval [CI]: 3.4–11.9) and P: 4.9 (95% CI: 3.6-N/A); $p = 0.8234$. The overall response rate (ORR) for BM was (%) E: 9; P: 7 ($p = 0.7133$) and for extracranial metastases was (%) E: 0; P: 5 ($p = 0.4947$). Median OS was (months) E: 3.8 (95% CI: 2.6–5.6) and P: 5.1 (95% CI: 3.7–5.7; $p = 0.4649$). Median PFS was (months) E: 2.2 (95% CI: 1.1–2.3) and P: 2.0 (95% CI: 1.3–2.3); $p = 0.7478$. There was no difference in TTP of BM hazard ratio (HR) for WBRT 30 vs. 20 Gy (HR = 0.76 [95% CI: 0.40–1.41]; $p = 0.3814$). SCLC patients had a shorter TTP of BM than NSCLC patients (HR = 3.56 [95% CI: 1.80–7.05]; $p = 0.0003$). Grade 3/4/-5 TEAEs (⩾5% of pts) were (%) thrombosis (E: 13; P: 19), fatigue (E: 17; P: 9), lung infection (E: 13; P: 17), nausea (E: 13; P: 6), dyspnea (E: 7; P: 8), motor neuropathy (E: 7; P: 2), vomiting (E: 6; P: 4), thrombocytopenia (E: 6; P: 2), and neutropenia (E: 6; P: 0). Study drug-related hospitalizations were (pts) E: 6; P: 1. There was 1 treatment-related death in each arm (E: unknown cause; P: pulmonary embolism). No significant differences in HRQoL were observed (all tests $p > 0.05$).
Conclusions: Enzastaurin was well tolerated but did not improve ORR, TTP, OS, PFS, or HRQoL after WBRT in LC patients with BM.