9022 POSTER DISCUSSION

Long-term Excess Mortality for Survivors of Non-small Cell Lung Cancer in the Netherlands

M. Janssen-Heijnen[1], L. van Steenbergen[2], E. Steyerberg[3], O. Visser[4], D. De Ruysscher[5], H. Groen[6]. *[1]VieCuri Medical Centre, Clinical Epidemiology, Venlo, [2]Eindhoven Cancer Registry, Research, Eindhoven, [3]Erasmus University Medical Centre, Public Health, Rotterdam, [4]Comprehensive Cancer Centre Netherlands, Registration and Research, Amsterdam, [5]Maastricht University Medical Center, Radiation Oncology (Maastro Clinic), Maastricht, [6]University Medical Center Groningen, Pulmonary Diseases, Groningen, The Netherlands*

Background: Most patients diagnosed with non-small cell lung cancer (NSCLC) die within the first few years after diagnosis. However, only little is known about those who have survived these first years. Conditional 5-year relative survival may serve as the most suitable information about the long-term prognosis of cancer survivors.
Material and Methods: All 12,148 patients aged 45−74 years diagnosed with stage I-III NSCLC between 1989 and 2008 in the Netherlands were derived from the Netherlands Cancer Registry. Conditional 5-year relative survival was calculated for every additional year survived up to 15 years.
Results: Conditional 5-year relative survival rapidly improved with every year survived up to 4−5 years after diagnosis. However, a significant excess mortality of 20−40% remained. Conditional 5-year relative survival for those aged 45−59 years did not exceed 80% for survivors with stage I or II disease and remained just over 70% for those with stage III disease. For those aged 60−74 years these proportions were 70%, 65% and 60%, respectively.
Conclusion: Since lung cancer is very lethal, most studies only focus on the first 5 years after diagnosis, whereas little attention is given to the relatively few (but absolutely many) patients who survive the first 5 years. We have shown that a significant excess mortality remains, which is probably largely explained by death due to smoking-related co-morbidity. Caregivers can use this information for planning optimal cancer surveillance and informing cancer survivors about their actual prognosis.

Poster Presentations (Mon, 26 Sep, 14:00−16:30)
Lung Cancer − Localised/Local Regional

9023 POSTER

Co-expression of Globotriasosylceramide (Gb3) With MDR1 in Cisplatin-resistant Pleural Mesothelioma and Non-small Cell Lung Cancer Cell May Lead to a New Tumour Resistance Treatment Approach

P. Behnam-Motlagh[1], A. Tyler[1], A. Johansson[2], T. Brännström[1], K. Grankvist[1]. *[1]Umeå University, Medical Biosciences Clinical Chemistry, Umeå, [2]Umeå University, Odontology Periodontology, Umeå, Sweden*

Background: Globotriasosylceramide (Gb3) consist of a trisaccharide linked to a lipid based in the plasma membrane and is expressed by several tumours. MDR1/PgP acts as a glycolipid translocase involved in the biosynthesis of glycolipids such as Gb3, and elevated levels of Gb3 have also been seen in drug-resistant cancers, and functional interplay between membrane Gb3 and MDR1/PgP has been suggested. We have demonstrated an increased cell surface expression of Gb3 in induced cisplatin-resistant mesothelioma (MPM) and non-small lung cancer (NSCLC) cells. We therefore studied the co-expression and effect of specific inhibitors of intracellular and extracellular Gb3, MDR1 and MRP1 in MPM and NSCLC cells with and without induced cisplatin resistance.
Materials and Methods: Intracellular and extracellular Gb3-, MDR1/PgP- and MRP1-coexpression were determined by flow cytometry and immunohistochemistry (IHC) in cultured P31 (MPM) and H1299 (NCSLC) cells with corresponding cisplatin-resistant sub-lines (P31res/H1299res).
Results: Cells from the resistant sub-lines had elevated extracellular Gb3 expression, MDR1 expression and MRP1 expression compared to the parental cell-lines. There was a correlation between Gb3 and MDR1 extracellular expression in P31 res MPM cells but not the other cell sub-lines. The intracellular expression levels of Gb3 was significantly increased in all cell sub-lines except for P31 cells, intracellular MDR1/PGP expression was high and MRP1 low in all cell sub-lines. Pre-treatment with the Gb3-synthesis inhibitor PPMP (15 μmol/L) for 72 h inhibited extracellular Gb3 expression in all cell sub-lines except P31 cells but intracellular Gb3 expression only in P31res cells. The MDR1/PgP and MRP1 inhibitor cyclosporine A (10 μmol/L) for 72 h did not affect intracellular or extracellular Gb3, MDR1/PgP, nor MRP1 expression in any cell sub-line. IHC similarly showed increased Gb3 expression in all cell sub-lines except P31 cells. Pre-treatment with PPMP resulted in a reduction of Gb3 intracellular expression in all cells sub-lines except P31 cells.
Conclusions: Extracellular Gb3 and MDR1 were co-expressed in the cisplatin-resistant MPM cell sub-line but no other correlation was noted for extracellular or intracellular expression of Gb3 and MDR1 or MRP1. PPMP pre-treatment affected only Gb3 expression but none of the resistance proteins. A relation of Gb3 to multidrug resistance protein expression encourages the idea that Gb3-targeted therapy could be a possible treatment approach.

9024 POSTER

Effect of BH3-mimetics GX15–070 and ABT-737 on Cisplatin Resistance in Malignant Pleural Mesothelioma Cells

A. Tyler[1], V. Janson[1], P. Behnam-Motlagh[1], A. Johansson[2], K. Grankvist[1]. *[1]University Hospital Umeå, Medical Biosciences Clinical Chemistry, Umeå, [2]University Hospital Umeå, Odontology Periodontology, Umeå, Sweden*

Background: Platinum-based drugs, such as cisplatin, is the standard treatment for malignant pleural mesothelioma (MPM), but resistance development is a major problem with the treatment. One of the mechanisms of cisplatin is that it activates the mitochondrial pathway of apoptosis, which is regulated by the Bcl-2 family of proteins. By targeting Bcl-2-proteins with BH3-mimetics, it is possible to sensitize cancer cells to cisplatin.
In this study we have examined the effect of combining two BH3-mimetics; ABT-737 and GX15–070, with cisplatin in the MPM cell line P31 and its resistant sub-line P31res.
Materials and Methods: P31 cells subjected to combinations of cisplatin, ABT-737 and GX15–070 for 6h were analyzed for apoptosis through TUNEL assay and viability and proliferation through FMCA. Changes in protein expression were analyzed through western blotting and proteome profiler arrays.
Results: TUNEL results show a significant synergy effect on apoptosis when cisplatin is combined with GX15–070 in P31res, and an additive effect in P31. ABT-737 had no additive effect on either cisplatin or GX15–070. The apoptosis inducing effect of GX15–070 alone was greater in P31than in P31res cells. Western blot results show that 6h exposure of cisplatin increased most of the relevant BH3-only proteins in the sensitive cell line, whereas expression levels remained unchanged or decreased in the resistant sub-line.
Conclusions: The apoptosis inducing effect of GX15–070 alone was pronounced in the sensitive cell line, indicating that cisplatin-resistant cells are more resistant to GX15–070. GX15–070 enhances the apoptotic effect of cisplatin in both P31wt and P31res. Cisplatin therapy combined with GX15–070 might therefore be a possible future treatment of MPM.

9025 POSTER

Clinicopathologic Significance of Cytokeratin 8/18 Expression in Non-small Cell Lung Carcinoma

L. Min Ki[1], L. Chang Hun[2]. *[1]Pusan National University Hospital, Internal Medicine, Busan, [2]Pusan National University Hospital, Pathology, Busan, South Korea*

Background: Cytokeratins(CKs) constitute the largest family of intermediate filament proteins. A balanced co-expression of type II cytokeratin (CK) 8 and type I CK18 which are found in simple epithelia is necessary for formation of cytoskeletal filaments in an epithelial cell-type preferential manner, and their abnormal expression has been linked to human diseases. In this study, we evaluated the clinicopathologic significance of CK8/18 expression in operable non-small cell lung carcinoma (NSCLC).
Materials and Methods: Immunohistochemical staining was performed on 90 cases of operable NSCLC (45 squamous cell carcinomas and 45 adenocarcinomas) using tissue microarray blocks. Primary antibodies applied were as follows: CK8/18 (1:100, Dako), CK19 (1:100, Dako), p63(1:100, Dako), deltaNp63 (1:200, BioLegend), p53 (1:50, Lab Vision), E-cadherin (1:200, Zymed), cyclin D1 (1:100, Neomarkers), PCNA (1:2000, Sigma). Following incubation of primary antibodies, immunohistochemical staining was performed with two-step Envision plus kit (Zymed Co.) with chromogen DAB. The immunohistochemical expression of cytokeratins 8/18 and 19 were correlated with the clinicopathologic parameters such as demography (age, gender), TNM stage, and histologic factors (type, differentiation, p63, deltaNp63, p53, E-cadherin, cyclin D1 and PCNA index).
Results: The expression of CK8/18 protein in tumour cells was noted in cytoplasmic and/or membranous locations. Lowered CK8/18 expression was correlated with squamous cell carcinoma, and higher levels of p63, deltaNp63, p53, and PCNA index. In sex, male patients was correlated with lowered CK8/18. Otherwise, other clinicopathologic factors (E-cadherin, beta catenin, cyclin D1, age, TNM stage, and patients' survival) were not related with the degree of CK8/18 expression.