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POSTER DISCUSSION

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

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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

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POSTER

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

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Background: Globotriasylceramide (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 (NSCLC) 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.

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POSTER

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

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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 P31 than 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.

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POSTER

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

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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.