9022 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

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

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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

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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 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

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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.

Conclusions: These results lead to presumption that the downregulation of CK8/18 expression in NSCLC could play a significant role on the disordered proliferation of tumour cells during neoplastic progression, while the expressionof CK19 might be not influential during the progression of the tumour. However, the prognostic significance of CK8/18 expression is required to keep further speculation.

9026 POSTER

The Risk of Lifelong DNA Damage Caused by Lung Cancer Among Rural Male Smokers Who Begin at Teenage

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Background: It is an established fact that tobacco is the major risk factor for lung cancer incidence. However, it affects more people in developing countries resulting to DNA damage.
Goals: To examine the effect of smoking on lung cancer risk and entire DNA damage in a relative large number of rural men, many of whom are poor and started smoking as teenagers.
Methods: We followed 50,232 men, ages 25 to 50 years, through a community-based tobacco control outreach program with questionnaires both in English and the local language to the North western and North eastern Nigerian Cohort Study in 2002/2003, through December 2007. We estimated relative risk (RR) of lung cancer associated with different measures of smoking initiation, duration, and intensity adjusting for confounding variables. We conducted analyses on the entire study population, among men who had smoked for at least 15 years, among non drinkers, and separately for each geo-political zone.
Results: Altogether, 10,240 men were diagnosed with lung cancer. Compared with never smokers, men who smoked for at least 15 years and who smoked 10 cigarettes or more daily had a higher RR. In contrast, men who had smoked for at least 15 years, but started after their 19th birthday, did not experience an increased lung cancer risk. The increased RR associated with smoking was observed among nondrinkers of alcohol, men with and without a family history of lung cancer in both geo-political zones in Nigeria.
Conclusion: Our results support the notion that men who start smoking as teenagers and continue to smoke for at least 15 years may increase their lung cancer risk with dramatic and lifelong DNA damage.
Tobacco killed one hundred million people in the 20th century, if nothing urgent is done to reduce tobacco use, it will kill 1 billion people this 21st century. There is need for countries who are already parties to the Framework Convention on Tobacco Control-FCTC to domesticate the laws in their respective countries.

9027 POSTER

Does the Timing of Additional Chemotherapy Affect the Outcome of Radical Surgery for Malignant Epithelioid Mesothelioma?

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Background: There is lack of evidence regarding the optimal timing of chemotherapy as part of multimodality treatment for malignant pleural mesothelioma (MPM). We aimed to examine whether timing of additional chemotherapy affects oncological outcome of radical surgery for MPM.
Material and Methods: From a prospective database we identified 154 patients with complete follow-up, referred from 40 hospitals, who underwent radical surgery as part of multi-modality treatment for epithelioid MPM in our centre in 11 years. No clear protocol existed for additional chemotherapy and the indication to start was left to the oncologist of the referring centre.

Chemotherapy	N	Survival [months] (excl 30 d mort)	Median FU [mo]	Median age [y]	% Male	% Stage III/IV	% EPP
Pre-operative	40	25 mo [15.4–34.6] (1 × 30 d mort)	20	59	83%	80%	70%
Early (<90d)	19	23 mo [19.9–26.1]	14	59	79%	79%	37%
Delayed	26	26 mo [14.2–37.8]	24	57	89%	76%	42%
None	69	14 mo [9.4–19.7] (7 × 30 d mort)	10	60	84%	89%	65%
Chemo vs no chemo p		**0.011**	NS	NS	NS	NS	**0.02**

Results: Out of 154 patients, 129 were Male, median age was 59 [14−75], 91 had extra pleural pneumonectomy (EPP) and 63 had lung sparing pleurectomy decortication (LSPD). The majority of the patients had stage IMIG III (58%) and IV (22%) disease.
40 Patients received preoperative chemotherapy, 19 early (<90d) and 26 delayed; 69 did not receive any chemotherapy. 85% Received platinum based therapy, in 50% in combination with Pemetrexed. Thirty-day mortality was 5.2%. Median follow up was 18 months [range 1−93]. Group characteristics are shown in the table. EPP represented the majority in the pre-operative and in the no-chemotherapy groups. LSPD patients received post-operative chemotherapy more often. Other characteristics did not differ significantly.
Significant survival benefit was found for patients who received additional chemotherapy compared to surgery alone ($p = 0.011$). Timing of this chemotherapy did not seem to influence this outcome ($p = 0.16$).
Out of 114 patients who did not receive pre-operative chemotherapy, only 45 (39%) have received chemotherapy post-operatively. A poor post-operative performance state or local treatment preferences in the referring centres are possible explanations for this finding.
Conclusions: Receiving chemotherapy is of significant influence on survival after surgery for MPM. Timing of this chemotherapy does not seem to affect the results. Administering chemotherapy pre-operatively might help to achieve a higher rate of completed chemotherapy courses.

9028 POSTER

Gemcitabine and Cisplatin Followed by Concurrent Gemcitabine and Radiotherapy or Sequential Radiotherapy Alone in Unresectable Stage III Non-small Cell Lung Cancer (NSCLC)

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Background: Gemcitabine is a radiosensitizer. It has been used to a limited extent in combination with radiotherapy in stage III NSCLC due to toxicity from full-dose gemcitabine with radiotherapy and due to high radiation volumes. A phase I study led to an optimal combination threshold (van Putten et al, Clin Cancer Res, 9:2003). The aim is to evaluate the outcome of concurrent and sequential chemoradiotherapy.
Methods: Patients with unresectable stage III NSCLC and a performance status WHO of 0- 2 were selected. Concurrent chemoradiotherapy consisted of 2 cycles of gemcitabine 1125 mg/m^2 on day 1 and 8 and cisplatin 80 mg/m^2 on day 1 of each 21-day cycle followed by weekly gemcitabine 300 mg/m^2 during 5 weeks of thoracic radiation (60 Gy). When the radiation field was considered too large or patients were too fragile, patients received sequential chemotherapy which consisted of 2−4 cycles of the same chemotherapy followed by 5 weeks of thoracic radiation alone (60 Gy).
Results: Between March 1999 and August 2008 283 consecutive patients were treated, 135 patients received concurrent chemoradiation and 148 received sequential chemoradiation. For the concurrent group median age was 63 (range 35−86); male/female ratio was 73%/27%; WHO performance status 0/1/2/missing was 46%/51%/3%. Median progression-free survival (PFS) was 13 months (95% CI, 10−16) and median overall survival was 23 months (95% CI, 17−29). For the sequential group median PFS was 11 months (95% CI, 8−14) and median overall survival was 16 months (95% CI, 13−19).
Conclusion: Concurrent chemoradiotherapy with gemcitabine as radiosensitizer gives comparable results as reported for high-dose chemoradiotherapy regimens. Nearly half of patients were not fit enough to be treated with concurrent chemoradiotherapy schedules.

9029 POSTER

Where Do We Stand in the Multidisciplinary Approach to Non-small Cell Lung Cancer (NSCLC) − a Retrospective Single Institution Experience From Rural India

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Background: Lung cancer is the leading cause of cancer-related death in men and women in the world. Numerous validated prognostic factors have been established which relate to survival outcomes in non small cell lung (NSCLC) cancer. However, in regions with limited resources there are other factors besides conventional ones which prognosticate the treatment. To better understand the demographic profile, treatment parameters and tumour response in such constrained environment like ours, we conducted this retrospective study.
Materials & Methods: From June 2009 through April 2011, 73 diagnosed NSCLC patients were included in this study. The patient, tumour-related and treatment related factors were analyzed. Median overall survival (OS), Kaplan–Meier survival plots, T-test, Cox Proportional Hazards models were