Proffered Papers

Lung cancer

1027 ORAL

Distinct patterns of chromosomal imbalances in adenocarcinoma and squamous cell carcinoma of the lung

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Purpose: To detect chromosomal imbalances that are associated with tumor differentiation in non-small cell lung carcinomas.

Methods: Comparative Genomic Hybridization (CGH) was used to screen 25 adenocarcinomas and 25 squamous cell carcinomas (SCC). For the first time, the differences between both tumor groups was visualized by a histogram and evaluated for statistical significance by Chi square test.

Results: DNA copy number decreases common to both entities and detectable in more than 50% of cases were observed on chromosomes 1p, 3p, 4q, 5q, 6q, 8p, 9p, 13q, 18q and 21q. Similarly, DNA gains were observed for chromosomes 5p, 8q, 11q13, 16p, 17q and 19q. Adenocarcinomas showed more frequently overrepresentations of chromosome 1q and DNA losses on chromosomes 3q, 9q, 10p and 19 whereas SCC were characterized by increased overrepresentations of chromosome 3q and 12p as well as deletions of 2q. The difference histogram of both entities and the statistical analysis indicated that the overrepresentation of the chromosomal band 1q23 and the deletions at 3q27–28, 9q22, 9q32–33, 9q34, 10p13, 19p13.3 and 19q13.2 were significantly associated with adenoid differentiation. Accordingly, the DNA loss of chromosomal band 2q36–37 and the overrepresentations at 3q21–22, 3q24-qter were statistically significant markers for the squamous cell type.

Conclusion: The study strengthen the notion that distinct patterns of chromosomal changes are prevalent in different tumor subtypes which will help in the development of a genetic grading and classification system of lung carcinomas.

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Lung cancer – Prognosis and classification

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Purpose: In lung cancer anatomical tumor spreading is an important prognostic factor and is classified by the worldwide uniform TNM classification. The data of 5,155 patients were analysed prospectively to examine the prognostic impact of the new 5th edition (1997).

Methods: These 5,155 patients entered the Thoraxklinik Heidelberg between January 1, 1988 and December 31, 1994 (date of last follow-up: December 31, 1996).

Results: The new substages IA and IB of the 5th edition could be validated referring to the clinical and the pathological staging ($p = 0.003$), $p = 0.001$), but no significant difference revealed after comparing the new stages IB and IIA. The prognosis of the new substages IIA and IIB was of significant difference in the clinical ($p = 0.049$), but not in the pathological classification ($p = 0.114$). All other comparisons of the new stages (IIB vs. IIIA, IIIA vs. IIIB and IIIB vs. IVB) were significant.

Conclusions: The the new 5th edition did satisfy most but not all requirements for an optimal prognosis-relevant classification. Some proposals for improvements are made.

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Detection of disseminated tumor cells in bone marrow of patients with resectable non-small cell lung cancer (NSCLC) – Long term results after 5 years of follow-up

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Introduction: By using immunocytochemical analysis an early dissemination of tumor cells into the bone marrow has been described in patients with apparently resectable NSCLC. However, the significance of this finding for the long term prognosis of patients with NSCLC is not known.

Methods: At primary surgery disseminated tumor cells in the bone marrow were detected immunocytochemically in 139 patients with NSCLC using a monoclonal antibody against the cytokeratin No. 18. After a median follow up of 60 months the influence of disseminated tumor cells in the bone marrow on disease-free and overall survival was analyzed.

Results: Cytokeratin positive cells were detected in 83 of 139 (59.7%) patients with no significant differences with respect to standard clinico-pathological parameters. In contrast to patients with lymph node involvement, in patients with early tumor stages (pN0) the detection of disseminated tumor cells in bone marrow was a strong and independent predictor of a shortened disease free ($p = 0.005$) and overall survival ($p = 0.018$).

Conclusions: In patients with apparently localized NSCLC the detection of disseminated tumor cells in bone marrow might be a useful indicator for the requirement of an adjuvant therapy.

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Possible negative impact on survival of too short an interval between surgery and postoperative radiotherapy in NSCLC

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Purpose: To evaluate the influence of prognostic factors in postoperative radiotherapy of NSCLC with special emphasis on the time interval between surgery (SX) and start of radiotherapy (RT).

Methods: A retrospective analysis of 340 cases with a median time interval between SX and RT of 36 days was performed. 230 patients (68%) had N2-disease; 228 patients were completely resected (R0).

Results: Patients with a long interval (37 to 84 days) had higher 5 year survival rates (26%) and median survival time (MST: 21.9 months, 95% C.I. 17.2 to 28.6 mo.) than patients with a short interval (18 to 36 days: 15%; 14.9 mo., 13 to 19.9 mo.; $p = 0.013$). A subgroup analysis revealed significant higher survival rates in patients with a long interval in N0/1 disease ($p = 0.011$) and incompletely resected NSCLC ($p = 0.012$). In multivariate analysis, time interval had a P-value of 0.009 (nodal disease: $p = 0.0083$; KPI: $p = 0.0037$; gender: $p = 0.035$).

Conclusion: Shortening the time interval between SX and RT to less than 6 weeks is not necessary and might even be deleterious.

1031 ORAL

Long-term survival after complete response to chemotherapy in small cell lung cancer depends on cytokine secretion capacity at diagnosis

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Purpose: Suppression of Interleukin-2 (IL-2) secretion is mediated by Transforming growth factor (TGF) β1 secreted by small cell lung cancer

(SCLC) tumor cells. In patients with SCLC, IL-2 secretion is significantly impaired at the time of diagnosis. Reconstitution of cytokine secretion correlated with reduction of tumor load. Thus, the immune system was suppressed by the tumor.

Methods: Using the Kaplan-Meier method, the log-rank test and the cox-regression model, we analysed the relation of IL-2 secretion in whole blood cell cultures from 52 patients with SCLC at diagnosis to established prognostic factors and survival.

Results: Impairment of IL-2 secretion influences survival in SCLC ($p = 0.004$). This prognostic factor is independent from stage of disease, NSE, LDH, age, and sex. The prognostic value of IL-2 secretion is comparable to the most predominant prognostic factors identified for SCLC. In the final model of cox regression, p-value for IL-2 and stage of disease was 0.012 and 0.019, respectively. High level of IL-2 predicts for improved survival after complete response (CR) to chemotherapy. With 45/52 failures at the last follow up, median survival was 1290 days (d) in CR/IL-2 > 1550 pg/ml (high), 330 d in CR/IL-2 < 1550 pg/ml (low), 390 d in PR/high IL-2, 300 in PR/low IL-2 ($p = 0.00005$).

Conclusion: Prognosis in SCLC may be predicted from IL-2 level at diagnosis. Long term survival seems to be partly characterized by CR to chemotherapy and high IL-2 level at diagnosis. As IL-2 secretion is suppressed by SCLC-derived TGF β1, immunobiological interactions may influence the clinical course of this disease.

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Preliminary results of a randomised comparative phase III trial of topotecan versus CAV as second-line therapy of small cell lung cancer

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Purpose: To compare single agent topotecan (T) with the commonly used regimen CAV for the second-line therapy of small cell lung cancer (SCLC) in an ongoing international randomised trial.

Methods: Eligible patients (pts) with measurable disease, who responded to first-line chemotherapy & were off-treatment ≥60 days before relapse receive either T (1.5 mg/m^2/d iv. d1–5 q 21 d) or CAV (cyclophosphamide 1000 mg/m^2, doxorubicin 45 mg/m^2 & vincristine 2 mg, iv., d 1 q 21d). At interim analysis 161 pts received ≥1 treatment; 125 pts are evaluable for efficacy with up to ≥20 weeks follow-up. 64 pts were treated with T (total 239 courses [crs], median 3.5/pt); 61 pts were treated with CAV (total 195 crs, median 3/pt).

Results: Partial responses were seen in 16/64 (25%) T pts & 9/61 (15%) CAV pts (confirmed by independent radiological review). Median time to progression for T pts is 11.1 wk & 11.9 wk for CAV pts. Median survival for T pts is 21.7 wk & for CAV pts is 23.1 wk. Grade 3/4 haematological toxicities: neutropenia in 63% of T crs & in 67% CAV crs; anaemia in 18% of T crs & 6% of CAV crs; thrombocytopenia in 32% of T crs & 9% of CAV crs. Neutropenic fever, infection with neutropenia, or sepsis have been associated with 7.5% of T crs & 9.7% of CAV crs. Grade 3/4 non-haematological toxicities related to study drug occurred in 19 (30%) T pts & in 20 (33%) CAV pts. Related adverse events caused 11 pts to withdraw from the study, (5 T[8%] & 6 CAV[10%] pts).

Conclusion: Preliminary results suggest that single agent T has similar efficacy, with manageable toxicity, to CAV in pts with SCLC who responded to first-line therapy.

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Preliminary results of a randomised phase III trial of an established chemotherapy (CT) regimen with or without lenograstim (rHuG-CSF) in small cell lung cancer (SCLC): Impact on survival

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Purpose: to investigate the potential survival benefit of the CT optimisation due to lenograstim support in previously untreated SCLC patients (pts).

Methods: up to 6 cycles of ACE (Doxo 45 mg/m^2, day 1 (d1), Cyclo 1000 mg/m^2, d1 and VP16 100 mg/m^2 iv d1 and 240 mg/m^2 po or 100 mg/m^2 iv d2–d3) with (lenograstim arm: L) or without (control arm: C) rHuG-CSF, were planned to be administered every 3 weeks Lenograstim was administered at a daily dose of 50 μg/m^2 sc, starting on d4.

Results: 280 pts were randomised. (L arm: 141; C arm: 139), 276 were treated. An intent-to-treat analysis was performed. A total of 859 cycles was administered. Twenty seven percent of pts in both arms completed 6 CT cycles. The number of pts with CT delay was lower in the L arm (39% vs 47%). The recovery of ANC > 1.5 × 10^9/l at d14 was significantly higher in the L arm over cycles. Non haematological toxicity was identical in both groups as well as infections. The assessment of tumoural response was stratified according to the tumour status at baseline (limited [LD] or extensive [ED] disease). The objective response (CR + PR) and complete response rate in the 268 evaluated pts were not different.

With a median follow-up of 25 months, the median survival was 11 months in the L arm and 9 months in the C arm (not significant).

Conclusion: in this chemotherapy optimisation trial, the survival improvement did not reach statistical significance. However, considering the good neutrophil recovery at d14 in the L arm, CT intensification seems feasible as was demonstrated by Thatcher et al (EJC, 1995) and could lead to further survival benefits as was proposed by Woll et al (JCO, 1995). This is being explored in further studies.

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Randomized trials evaluating radiotherapy adjuvant to chemotherapy for small cell lung carcinoma (SCLC): Qualitative evaluation before meta-analysis

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The role of adjuvant radiotherapy for limited disease SCLC remains controversial. In 2 recent meta-analyses, survival was significantly prolonged when radiotherapy was added to chemotherapy. Chalmers et al have elaborated qualitative criteria evaluating publications methodology and Marino et al tested that scale in a meta-analysis in non small cell lung cancer. Our group elaborated a more complete qualitative scale, including 51 criteria. The quality score of the article was expressed in percentage of a maximal theoretical score. We compared the results obtained by our method with these of Chalmers-Marino. A quantitative meta-analysis, based on the available published data (8 studies) was performed. Chest radiotherapy combined to chemotherapy was associated to a non significant advantage (odd ratio = 0.82; 95%CI 0.63–1.07). The qualitative ELCWP score of the 14 eligible articles ranged from 29.5% to 73%. A good correlation could be established between our score and that of Chalmers-Marino ($r = 0.87$, $p < 0.001$). No significant difference in quality score was observed between the studies according to eligibility for quantitative meta-analysis, date of publication, date of the first patient inclusion and reported radiotherapy efficacy. Few studies mentioned important criteria like definition of the primary endpoint (14.2%) and β error (0%). In conclusion, quality scores should be taken into account when publishing quantitative meta-analyses in order to reduce heterogeneity in the studies quality.