316. Treatment of lung cancer

P2912

Synergistic therapy for NSCLC: Additive preclinical efficacy of interleukin-6 inhibitor madindoline A with crizotinib

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Backgrounds and aims: Crizotinib has also demonstrated the development of acquired drug resistance. Despite secondary mutation, resistance of crizotinib may also be influenced by tumor microenvironment. Senescent cells display a senescence-associated secretory phenotype (SASP) involving the production of inflammatory cytokines that alter tumor microenvironment. Here, we analyzed the level of IL-6 and its signaling pathway in NSCLC cells and assessed the efficacy of IL-6 inhibitor madindoline A in combination with crizotinib in vivo.
Methods: We detected senescence, SASP, IL-6/STAT3 and PI3K/AKT/mTOR signaling after crizotinib treatment in the presence or absence of madindoline A in NSCLC cell lines. The in vivo effect of the combination of crizotinib and madindoline A was assessed by tumor growth experiments using xenograft tumors.
Results: Crizotinib induced tumor cellular senescence with senescent characteristics including increased senescence-associated β-galactosidase activity and higher expression SASPs. Depletion of the key IL-6R signaling component STAT3 by RNA interences markedly increased crizotinib-induced NSCLCs apoptosis in the addition of IL-6. When madindoline A and crizotinib were used in combination, they inhibited all the tested kinases in the IL-6/STAT3 and PI3K/AKT/mTOR pathways. Combined treatment with madindolin A and crizotinib exhibited significant inhibition of tumor growth in NSCLC cell xenografts in nude mice.
Conclusions: We show that IL-6 is essential for the survival of premature senescence NSCLC cells treated with crizotinib. Study of the syngeneic model demonstrated the superior potency of the crizotinib combined with madindoline A.

P2913

Bevacizumab shows survival benefit for non-small lung cancer patients who received subsequent pemetrexed treatment but not had a therapeutic effect in clinical practice

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Backgound: Bevacizumab (BEV), a humanized monoclonal antibody against vascular endothelial growth factor, is one of molecular targeting agents for non-small lung cancer (NSCLC). The aim of this study is to evaluate the efficacy of BEV in clinical practice.
Methods: We retrospectively investigated the clinicopathological characteristics of 26 NSCLC patietnts who had undergone BEV therapy in Saitama Medical University International Medical Center and Saitama Medical University Hospital.
Results: The patients had a median age of 64 years (range, 33 to 75 years), and 19 males and current smokers. Epidermal growth factor receptor gene mutations were found in 6 patients (23%). Combined with BEV, each half of 26 patients received the chemotherapeutic regimen of either carboplatin/paclitaxel or carboplatin/pemetrexed. Objective response rate was 54% and disease control rate was 96%, and median progression free survival and overall survival were 100 days and 202 days, respectively. Adverse events included 4% of arrhythmia, 27% of hypertension, 8% of lower gastrointestinal bleeding, 19% of nasal bleeding, and 23% of proteinuria. Using Kaplan-Meier survival curves and logrank tests, therapeutic response influenced neither progression free survival nor overall survival, whereas longer overall survival was observed in NSCLC patients treated with pemetrexed-containing chemotherapy after failure of BEV.
Conclusion: Therapeutic response to BEV does not predict survival benefit of BEV-treated NSCLC patients. Meanwhile, pemetrexed may be a novel therapeutic option for NSCLC patients who have failed BEV treatment.

P2914

Improved results after preoperative concurrent chemotherapy and high dose radiation therapy in selected cases with stage III N2 lung cancer?

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Objective: Optimal management of stage IIIA-N2 non–small cell lung cancer remains controversial. The use of neoadjuvant chemoradiotherapy can present challenges in the perioperative management of patients undergoing lung resection for non-small cell lung cancer. Preoperative chemoradiotherapy may reduce pulmonary function, and can result in significant fibrosis around key anatomic structures, making dissection difficult and hazardous.
Methods: This is a retrospective study of 40 consecutive patients with T1-3 N2 M0 lung cancer who underwent induction chemoradiation before surgical intervention from January 2005 through December 2011. Induction chemotherapy consisted of cisplatin, and etoposide; and concurrent radiotherapy to a mean of 59.3 Gy. Lung resection was performed within 6 weeks of completion of chemoradiation.
Results: Twenty-five patients were submitted to pneumonectomy, simple or intrapericardial one, 10 to lobectomies and 5 either to segmentectomies or atypical resection. R0 resection was achieved in all cases. The overall operative mortality rate was 2.5% (one died in the lobectomy group). No important morbidity was noted and the overall hospital stay ranged from 7 to 14 days.
Conclusion: Chemoradiation before pulmonary resection in carefully selected patients with surgically resectable stage IIIA (N2) non–small cell lung cancer can be performed with low mortality and morbidity and might lead to improved overall and disease-free survival.

P2915

Pemetrexed in the first line treatment in non-small cell lung cancer (NSCLC): A multicentre prospective analysis of data from clinical practise of Czech Republic

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Background: Pemetrexed is a novel multi-targeted antifolate that is used in the treatment of NSCLC. This analysis presented examines data from Czech Republic obtained from 166 pts who were treated with pemetrexed in the 1st line treatment.
Methods: Pts with advanced NSCLC were treated between 12/2008 and 12/2011 in 10 institutions with pemerexed 500mg/m^2 and cisplatin 80 mg/m^2 on day 1 every 3 weeks. We evaluated efficacy and toxicity.
Results: From 166 pts were 47% men and 53% women, median age 62 years. Non-smokers were 32,5%, stop-smokers 26,5% and current smokers 41,0% pts. PS 0 was in 18,1%, PS 1 in 76,5% and PS 2 in 5,4%. Stage IV had 86,2% pts. Adenocarcinoma was confirmed in 84,9%. CR was confirmed in 1,5%, PR in 26,3%, SD 41,6%, 21,9% progressed and 8,8% pts were not evaluated. Major toxicities (grade 3-4) were neutropenia in 10,8%, leucopenia in 4,8%, anemia

in 6,0% and thrombocytopenia in 1,2% pts, but the therapy was finished due to toxicity only in 6 (4,4%) patients. Median OS (95% CI) was 12,5 months (7,5; 17,5). Probability of one-year survival was 52,2%. PFS (95% CI) was 3,9 (3,4; 4,5) and probability of 6-months PFS was 38,9%. The best OS survival (13,5 months) was in pts with adenocarcinoma. We don't find the differences between groups of pts according smoking (p=0,532), sex (p = 0,696) and PS (p = 0,131).
Conclusions: Pemetrexed with cisplatin as the 1st line treatment was well tolerated (only 4,4% of pts finished therapy due to toxicity), with evidence of antitumour activity in adenocarcinomas. The results from clinical practise of Czech Republic are comparable with the results of registration study.

P2916
Non-small cell lung carcinoma–advanced disease (NSCLC-AD): Effectiveness of subsequent therapeutic lines and predictive factors of poor outcome
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Five years observational study (2006-2010) of a cohort of patients with NSCLC-AD (1st line monotherapy excluded). Epidemiology, histology, *performance status* (PS), therapy, response – disease control (DC) or progression (n-DC), progression free survival (PFS) and overall survival (OS) after each therapy were evaluated. We also tried to assess predictors for DC and OS.
Results: We included 276 patients, 77.9% men, mean age 63.1 years (±10.9), most of them smokers (36.6%) with PS 1 (89.1%). The most frequent histology was adenocarcinoma (59.8%). Metastasis in 1, 2 or 3 organs was found in 65.2%, 31.2% and 3.6% of the patients. All patients were initially treated with a platinum-based duplet; Pemetrexed or Erlotinib were the most used in 2nd-line setting (53,9% of the patients) and Erlotinib in 3rd (15.6% of the patients). There was a progressive reduction of the DC rate along the 3 lines- 71.7%, 67.1% and 51.2%. The median PFS and OS for each line were: 1st- 4.53M ± 0.22 and 10.12M ± 0.55, 2nd- 4.17M ± 0.21 and 9.1M ± 0.66, 3rd- 4.47M ± 0.68 and 10.42M ± 3.35. Prognostic factors were: smoking status (*HR* 1.54, *p-value 0.016*), the presence of metastasis> 1 organ (*HR* 1.50, *p-value* 0.003), PS2 (*HR* 3.62, *p-value*<0.001) and n-DC after 1st line (*HR* 2.71, *p-value*<0.001). The presence of DC after each line did not predict subsequent DC (*p-value*> 0.05), but the PFS after 1st line correlates with the following PFS (*p-value* 0.001).
Conclusions: There is an increase in OS and PFS in the 3rd line, probably reflecting the influence of new biological treatments. Strong predictors for a poor outcome were PS 2 and n-DC after 1st line.

P2917
Prevalence and effectiveness of third-line therapy for advanced non-small cell lung cancer (A-NSCLC)
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Background: Systemic chemotherapy is the main option for A-NSCLC. Few patients receive third-line therapy and in this setting little is known about outcomes.
Objectives: Evaluate demographics, histology, performance status (PS), sites of metastases, response, toxicity, progression-free survival (PFS) and overall survival (OS) in patients with A-NSCLC treated with third-line therapy.
Methods: We reviewed 5 years of clinical practice (Jan. 2006 - Dec. 2010): 676 patients with A-NSCLC were diagnosed and 330 received systemic chemotherapy. Of these, 44 completed 3 lines.
Results: 73% male, mean age 61.8Y (± 9.4). Smoking status: 36% non-smokers, 36% former-smokers and 28% active smokers. Histology: 66% adenocarcinomas, 27% squamous cell carcinomas, 5% large cell carcinomas and 2% NSCLC-NOS. Initially all patients had PS 0-1. Main sites of metastases: lung (80%) and bone (43%), with 34% of patients with ≥ 2 metastatic foci. First-line platinum-based duplet: 50% achieved an objective response, 30% had stable disease, PFS 6.4M. Second-line setting (docetaxel/pemetrexed/erlotinib): partial response (PR) 30%, stable disease (SD) 52%, PFS 5.4M. Third-line (erlotinib/pemetrexed): PR 14%, SD 36%, PFS 4.2M. Hematological toxicity: 18% in 1st-line, 16% in 2nd-line and 7% in 3rd-line. Non-hematological toxicity: 16% in 1st-line, 20% in 2nd-line and 14% in 3rd-line. OS was 24.05M.
Conclusions: Third-line therapy was used in 6.5% of the patients. 1st-line platin-based chemotherapy with new-generation agents like pemetrexed and erlotinib in the subsequent lines had good efficacy with less toxicity and strongly contributed to the 24 months in overall survival in our patients.

P2918
A study on chemotherapy induced interstitial lung disease in patients with unresectable non-small cell lung cancer complicated by combined pulmonary fibrosis and emphysema
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Background: Combined pulmonary fibrosis and emphysema (CPFE) frequently complicates lung cancer. Chemotherapy induced interstitial lung disease (ILD) is frequently occurs in these patients and chemotherapy is hard to undertake in such case.
Objective: The purpose of this research was to clarify the risk and prognosis of ILD in cases of unresectable non-small cell lung cancer (NSCLC) with CPFE treated by chemotherapy.
Method: We conducted a retrospective investigation of 14 patients with stage IIIB or IV NSCLC with emphysema and interstitial pneumonia detected by chest computed tomography, who were treated by chemotherapy at our hospital between April 1, 2004 and August 31, 2010.
Results: Six of the 14 patients developed ILD. High values of KL-6 (P = 0.028) measured before chemotherapy were identified as a predictor of the development of ILD.Median survival in ILD group and non ILD group was respectively 237 and 820 days.
Conclusion: Unresectable NSCLC patients with CPFE receiving chemotherapy show a high predisposition for developing ILD, especially in cases with high KL-6 values, and tend to have a poor prognosis.

P2919
Management of chemotherapy-induced anemia in patients with lung cancer (LC): A comparative study of erythropoietic agents
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Chemotherapy-induced anemia is a frequent complication of LC.Platinum-based chemotherapies (CT) particularly impair erythropoietin production.One option for the management of this anemia is the administration of recombinant human erythropoietin (RHE) which stimulates red blood cell (RBC) formation.
We compared the efficacy and safety of two types of RHE: epoetin alpha (Eprex) and epoetin beta (NeoRecormon) in anemic patients with LC.Thirty eight patients (mean age 62 years) receiving CT for a LC (stage III and IV) with anemia (hemoglobin level≤11g/dl) were included: 19 patients in group 1 treated by Eprex 40000UI/week and 19 patients in group 2 treated by NeoRecormon 30000UI/week for 6 weeks. A hematopoietic response was defined as an increase in hemoglobin concentration ≥2g/dl or hemoglobin (Hb) concentration ≥12g/dl in the absence of a RBC transfusion.The mean Hb levels at baseline were identical: 10 g/dl in group 1 and 9.8 g/dl in group 2. Each group was divided into two subgroups (transfused and non-transfused). 15.8% of patients in the first group required a RBC transfusion versus 36.8% in the second group (p=0.26). The mean changes in hemoglobin level during treatment in non-transfused patients were 0.83 g/dl for group 1 (p=0.003) and 0.31 g/dl for group 2 (p=0.13) without statistical difference among groups (p=0.08). While 12.5% patients in group 1 had a significant hematopoietic response, none was observed in group 2. Two patients in group 2 developed thrombotic events.
The tested erythropoietic agents increased the Hb level in anemic patients with LC. In our study epoetin alpha was better in terms of efficacy and safety than epoetin beta.

P2920
Docetaxel-related peripheral neuropathy is a dose-dependent event; a retrospective study in a Greek population with NSCLC
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Introduction: Neurotoxicity is the most important non-hematologic toxicity of taxanes. It presents as peripheral neuropathy with tingling, numbness and pain with a "glove and stocking" distribution and influences the daily activities of patients treated with taxanes.
Aim: To record peripheral neuropathy in relation with the dosage of docetaxel in NSCLC.
Method: We retrospectively studied 700 consecutive files of patients from the archive of the oncology unit of our institution in treatment from December 2006 until May 2008. Election criteria includes patients with NSCLC, PS 0-2, any stage, treated with docetaxel in any combination. We evaluated peripheral neuropathy with CTCAEv3.0
Results: We found 105 patients,84 males(80%),21 females(20%), median age 62.94±9.29, smokers 95(90,5%), median dose of docetaxel 74,42±7,88mg/m^2, median aggregate dose 427,17±282,9mg, dose intensity 32,63±5,88mg/m^2/week, median treatment duration 12,6±7,99weeks. Peripheral neuropathy presented in 28 (26,7%) patients, mild or moderate gravity, mainly sensory neuropathy in 75%, after 2,64±1,68 cycles. The group of patients who received docetaxel ≥ 80mg/m^2 presented neuropathy at 37,5% versus 21,9%(P=0,09). The group with dose intensity ≥37,5mg/m^2/week presented neuropathy at 47,1% versus 16,9%(P=0,001). In the group of aggregate load dose ≥600 mg, 51,6% presented neuropathy versus 16,4% with <600 mg(P=0,0001). Neuropathy was a reversible adverse event in 25 of 28 patients.
Conclusion: Peripheral neuropathy is a dose-dependent adverse event that increases with the accumulation and the dose intensity of docetaxel. Symptoms usually resolve after treatment or by decreasing the dosage.

P2921

Is skin toxicity a predictive or prognostic factor in EGFR-inhibition as treatment of advanced NSCLC?

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Targeted therapy addressing the Epidermal Growth Factor Receptor (EGFR) is available for the treatment of advanced NSCLC in our clinic with the Tyrosine Kinase Inhibitors Gefitinib and Erlotinib as well as the Monoclonal Antibody Cetuximab within the Gemtax Trial. We analysed clinical markers especially skin toxicity to find predictive and prognostic factors in this therapeutic setting.
Between March 2003 and December 2008 we began TKI therapy in 81 patients and between August 2006 and April 2011 cetuximab therapy in 51 patients (induction chemotherapy and cetuximab maintenance after four cycles). Median age was 66 years and median treatment duration 3 month, patients with treatment less than six weeks were not considered. We found a median Time to Progression (TTP) of 3.5 month and Overall Survival (OS) from start of therapy of 7.5 month. In the subgroup of patients who developed no or mild skin toxicity TTP was 2.0 month, whereas patients who developed a skin toxicity above grade I had a TTP of 4.5 month ($p = 0.0002$, HR = 0.48). Difference in OS in these two subgroups was 6.0 and 14.9 month respectively ($p = 0.025$, HR = 0.64). Age, gender, histology and smoking status showed less strong correlations.
Patients who develop skin toxicity during EGFR inhibiting therapy show a prolonged TTP and OS. To what extend skin toxicity is rather a prognostic factor is yet unclear. Further prospective studies should differentiate the predictive and prognostic value of skin toxicity. There is also a need to identify biomarkers that correlate with the development of skin toxicity and thus could predict a favourable therapeutic course of these costly targeted agents.

P2922

Anti-cancer therapy and monitoring plasma concentration of carboplatin in lung cancer patients receiving hemodialysis

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To investigate the pharmacokinetics of carboplatin (CBDCA) in lung cancer who were receiving hemodialysis (HD), we measured plasma concentrations of platinum by inductively coupled plasma mass spectrometer. We sampled bloods from two patients at the starting of HD one hour after the finishing administration of CBDCA, and at the end of it. Patient 1, a 78 year-old man with SCLC, was treated with CBDCA(250mg/m^2) and etoposide(50mg/m^2)and received HD at day 1, 3, 8. Patients 2, 71 year-old man with NSCLC, was treated with CBDCA (200mg/m^2, day1) and paclitaxel (180mg/m^2, day1), received HD at day 1, 2, 3, 4, 5, 8, and he was treated with same doses of the drugs at day 28 as the second course and received HD at s.c. day 1(day 28), 2, 3, 5, 8. Plasma concentrations of platinum before HD were 6.76 to 8.16 μg/ml. Mean reduction rate of plasma platinum concentrations (after hemodialysis/before hemodialysis) was 16.4±6.1%, suggesting highly effective clearance of CBDCA by hemodialysis. From 3 days after the administration of CBDCA, plasma concentrations of platinum at the end of HD were higher than those at the starting of the next HD. Thus, we speculated that CBDCA is stored in the tissues and then backflow to blood depending on the plasma concentration of platinum. In Patient 1, partial response and adverse events of grade 3 neutropenia and grade 4 thrombocytopenia were observed. In Patient 2, progressive disease and grade 4 neutropenia was observed. We conclude that in patients with lung cancer receiving HD, monitoring of plasma concentrations of platinum is valuable to get effective plasma concentrations of CBDCA or CDDP and to avoid severe adverse effects.

P2923

XAGE-1b and p53: Potential targets for immunotherapy of non-small cell lung cancer (NSCLC)

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Induction of immune responses specifically against tumor-associated antigens by vaccination is a promising approach for cancer immunotherapy. XAGE-1b is a cancer-testis antigen that is aberrantly expressed in lung adenocarcinoma. p53 is a tumor suppressor protein that is over-expressed in NSCLC. We investigated local (primary tumor, tumor draining lymph node (TDLN)) and systemic (peripheral blood) immune responses against XAGE-1b and p53 in lung adenocarcinoma.
Tissue and blood samples from 6 lung adenocarcinoma patients were obtained. Tumor-infiltrating lymphocytes (TIL) were isolated from tumor tissue by culturing for 3 weeks. Lymph node mononuclear cells (LNMC) were obtained from TDLN and cultured in 3 ways: medium alone (LN neg), stimulated once by XAGE-1b (LN XAGE) or p53 overlapping peptides (LN p53). Peripheral blood mononuclear cells (PBMC), TIL and the 3 LNMC cultures were analyzed for antigen-specificity by a 4-day proliferation assay and in supernatants taken at day 2 cytokine release was determined.
In 1 out of 6 patients, XAGE-1b induced proliferation in LN XAGE and IFNγ release in LN XAGE and TIL. In another patient, XAGE-1b induced proliferation in PBMC and LN neg, but no IFN-γ release. In 3 out of 6 patients, a p53-induced proliferation was observed in LN p53, which was accompanied by IFN-γ release in 2 patients. In one patient, p53 induced TNF-α release in TIL.
These preliminary data show T-cell immunity to XAGE-1b and p53 in lung adenocarcinoma indicating that these antigens are potential targets for immunotherapy. More patients are needed to define strength, breadth and phenotype of this antigen-specific response and its relation with antigen expression in the primary tumor.

P2924

Do elderly lung cancer patients profit from radical mediastinal lymphadenectomy?

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Objective: The therapeutic impact of a radical mediastinal lymphadenectomy (RLA) associated with a pulmonary resection for *lung cancer* remains controversial. Our objective is to investigate the impact of radical lymphadenectomy compared to the sampling on the overall survival for *elderly lung cancer* patients and assess whether the non-performance of an RLA could be justified in the surgical treatment for this group.
Material: We analysed the records of 60 patients aged 75 years and older (41 males, 19 females) who underwent surgery for non-small-cell *lung cancer*. They were divided into two groups, according to the type of intra-operative mediastinal lymphadenectomy, the radical systematic lymphadenectomy (RLA Group, n=36) and the Sampling (SLN group, n=24) groups. A Cox proportional hazards model and the Kaplan-Meier method were used for the survival analyses.
Results: RLAs had no protective effect on mortality; the hazard ratio for the RLA group in comparison to the SLN group was 0.93 in the multivariate analysis. The 3-year survival for the SLN group, was marginally better than that of the RLA group. There was no significant difference in the overall survival between the two groups ($p>0.05$).
Conclusions: There was no survival benefit for the Radical Lymphadenectomy. Although in some reports a systematic mediastinal lymphadenectomy is recommended for correct staging, a pulmonary resection with non-performance of radical lymphadenectomy could be an acceptable surgical treatment for the increasing number of *elderly lung cancer* patients.

P2925

Lung cancer in Berlin – Therapeutic concepts and their impact on survival in patients with NSCLC stage II/III from 2000 to 2008

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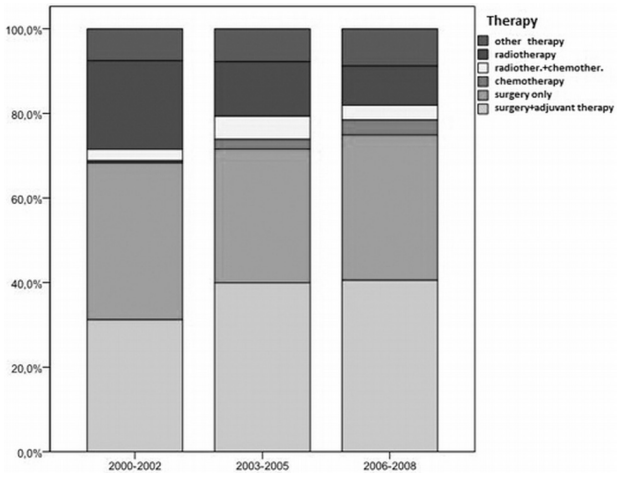
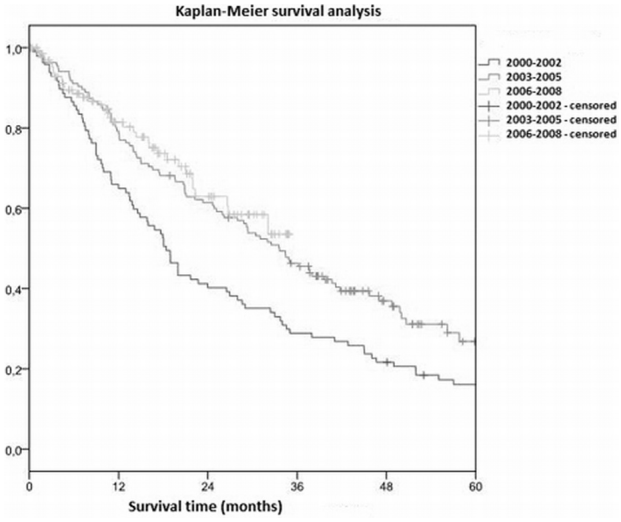
Backgroud: The Tumorzentrum Berlin (TZB) amalgamates the clinical data of lung cancer pts. in order to improve pt. care by means of joint quality assurance.
Aims: To evaluate the effect of changing therapeutic concepts on survival times in pts. with newly diagnosed NSCLC stage II/III from 2000 to 2008.
Methods: In this retrospective case study, the pooled data of the TZB of pts. with newly diagnosed lung cancer during 2000 and 2008 were analyzed. Pts. were divided into three 3-year groups (G1: 2000-2, G2: 2003-5 and G3: 2006-8).
Results: The total cohort comprised 14,302 pts.
For pts. with NSCLC stage II/III, the proportions of pts. with surgery and adjuv. therapy increased in G2 and G3 (Figure 1, see p. 536s).
Kaplan-Meier survival analysis could not demonstrate significant differences between G1 and G2/3 in general, but for pts. with NSCLC stage II and III (Figure 2, see p. 536s).
Conclusions: According to the pooled data of the TZB, the analysis of therapeutic concepts spotted an increase of surgery and adjuv. therapy among pts. with NSCLC stage II/III over time corresponding with an improvement in survival in these groups.



Abstract P2925 – Figure 1



Abstract P2925 – Figure 2

P2926

Treatment modalities in lung cancer patients with brain metastasis

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Forty lung cancer patients with diagnosed brain metastasis were evaluated at the Institute of Lung diseases at Sremska Kamenica in the period of three years. Duration of survival in such patients was evaluated and compared according to the treatment employed as well as to the histology, number of metastasis and presence/absence of synchronous other visceral metastasis. Treatment modalities included: irradiation, surgery, and chemotherapy for chest tumor, and for the brain metastasis, and symptomatic treatment. There were 34 male (85%) and 6 female (15%). 72.5% have had solitary metastases, while 27.5% presented with multiple metastasis. Mean survival was 3.2 months from the diagnosis of brain metastasis (range 0-14 months). Irradiation of thorax underwent 57.5%, chest operation 15% and chemotherapy 22.5%. Irradiation of brain metastasis underwent 42.5% of patients, chemotherapy 7.5% patients, while 12.5% were operated for brain metastasis. 37.5% were treated only symptomatically. Sixty percent were without other visceral metastasis. Statistical significance in terms of longer survival was found in patients who had solitary compared to multiple metastasis $p<0.026$, in patients with irradiated brain metastasis $p<0.015$ and in patients operated for brain metastasis $p<0.003$.

Although prognosis of patients with lung cancer and brain metastasis is gloomy, our investigation suggests longer survival with employed brain surgery or brain irradiation.

P2927

Prodromal face of a study: High dose rate endobronchial brachytherapy (HDERB) as a first step introductory treatment of a multimodality therapy approach in non operable NSCLC with endobronchial obstruction

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Introduction: Lung cancer patients frequently present with advanced stage. HDREB has always been used as a palliative treatment option in end-stage disease, and has not yet been thought of as a first-step therapeutic approach of a multimodality treatment strategy. We strongly feel that HDERB could be the method of choice in carefully selected patients with endobronchial obstruction, prior to other treatments.

Aim: HDERB could be used as a first-step, introductory treatment in selected patients with inoperable obstructive endobronchial carcinoma of the lungs.

Methods: A catheter is placed through bronchoscopy in the obstructed lumen. HDREB is delivered in two sessions separated by one week. Bronchoscopy is performed 3 weeks later. Pulmonary function tests are preformed before and after HDREB monthly. Evaluation of quality of life is assessed with Saint Georges Respiratory Questionaire. Obstruction score is also evaluated before and after treatment.

Results: Six patients with previously untreated, inoperable NSCLC associated with endobronchial obstruction, were treated with HDREB as an introductory treatment of a multimodality therapeutic approach. We found significant improvement on symptoms (cough, dyspnoea, hemoptysis) and intraluminal reduction of the obstruction.

Conclusions: HDREB is a low-cost, semi-invasive, and well-tolerated method that has been applied with a limited palliative purpose, whilst it could provide an improved performance status and partial disease regression early enough, giving the patient the opportunity of a better outcome of treatment, overall.

P2928

Non-small cell lung cancer – Advanced disease: Barriers to inclusion in clinical trials and its impact on survival

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Introduction: Inclusion in clinical trials allows patients to submit to innovative therapies and a meta-analysis showed that this may be associated with increased rates of survival.

Aims: Identify reasons that hindered the inclusion of patients in clinical trials of first-line therapy; Compare overall survival (OS) and progression-free survival (PFS) between groups of included and excluded patients.

Methods: This study was conducted over 36 months in a central hospital. Patients with well defined histology and candidates to chemotherapy were considered eligible for clinical trials. Reasons for non inclusion have been detailed. OS and PFS were compared.

Results: We identified 199 eligible patients, mean age 64.9±10.7 years, 75.9% males, 61.8% with non-squamous cell carcinoma. From these 22.1% were included in trials. Among those not included 18.7% had performance status (Zubrod) 2 and 66.5% had other exclusion criteria, mainly heart disease (22.3%), respiratory disease (21.4%), brain metastases (15, 5%) or second malignancy (15.5%). About 15% of patients refused to be involved in trials. Of patients who had performance status 0/1 (N = 170), there was no statistically significant difference in analysis of OS or PFS between those included in trials and the excluded, whether by criteria (Cox Regression: OS p=0.705/PFS p=0.807) or by refusal (Cox Regression: OS p=0.465; PFS=0.900).

Conclusion: Liberalization of exclusion criteria and recognition of causes that lead to refusal are possible determinants of increased participation in clinical trials.

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P2929

Intratumoral injection of plasmid-encoded flagellin inhibits growth of NSCLC-cells in murine lung cancer model

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Lack of progress in the treatment of NSCLC urges to look for experimental therapeutic methods, such as gene therapy. Currently used therapeutic vectors can cause adverse effects, or have a limited potential to transduce cells. The aim of this work was 1) to construct a vector suited for gene therapy allowing for selective transduction of only tumor cells 2) to assess therapeutic potential of *Salmonella* flagellin (FliC).

Engineered plasmid vector was obtained by PCR synthesis. For the purpose of tumor-specific transcriptional activity it was necessary to design a two-step promoter unit system based on telomerase minimal promoter.

Influence of FliC on NSCLC cells was assessed by measuring proliferation of tansfected cells and by phenotyping of maturation markers on DCs incubated with

A549 cells. NSCLC tumors in mice were injected with empty or FliC-coding vector. Tumor growth and survival of the mice were analyzed.

FliC-transfected A549 cells had significantly lower proliferative potential. Such cells enhanced maturation of MoDC as suggested by higher expression of CD80 and CD83. NSCLC-inoculated mice administered with a vector containing FliC gene had a significantly longer survival time ($p<0.002$) and slower tumor growth ($p<0.01$) comparing to the control group.

Designed two-step promoter unit allows for efficient and tumor-selective expression of therapeutic gene. Results suggest that NSCLC transduction with FliC gene may inhibit its proliferation *in vitro* and tumor growth *in vivo* and increase survival rate. Due to ambiguous results obtained in co-culture of transfected A549 and DC antitumor properties of FliC other than induction of DC maturation need to be considered.