metastasis. Local control rates were 62% and 54.9% in 2 and 5 years. Two and 5 years disease free survival rates were 46%, 21% and actuarial survival rates were 62% and 19.9% respectively. In univariate analysis; pneumonectomy, tumor of the left upper lobe and negative thorax wall invasion had significant better rates for local control. Patients with grade 3 tumors had worse disease free survival rates and patients with left lower lobe tumors and grade 3, N3 tumors had worse actuarial survival rates. In multivariate analysis; thorax wall invasion was the only significant factor for local control and grade was the significant prognostic factor for disease free survival. Grade, nodal status and mediastinal lymph node localisation were independent prognostic factors for actuarial survival.

Conclusions: In this retrospective analysis, local control and survival rates seem to be lower than the literature rates. This may be related to the incomplete preoperative evaluation of the patients and high close or positive surgical margins.

819 POSTER

Induction carboplatin-paclitaxel-gemcitabine (CPG) followed by concurrent weekly carboplatin-paclitaxel (CP) and radiation therapy in unresectable stage iii non-small cell lung cancer (NSCLC). A phase II study.

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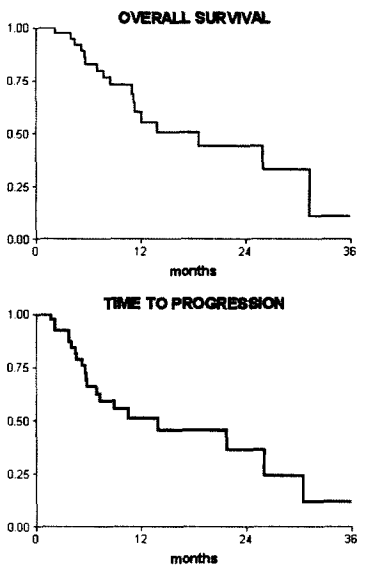
Background: Preliminary results from a phase III trial in advanced NSCLC comparing CP vs. CPG suggest an advantage in RR and TTP with a superior but acceptable toxicity for CPG. Therefore we used CPG as induction regimen in stage III pts. CT concurrent to RT was employed because paclitaxel with platinum compounds potentiates the effects of ionizing radiation.

Eligibility Criteria: ECOG 0-1, unresectable stage III (including supraclavicular lymph node methastases but excluding pleural effusion), measurable disease, no prior chemotherapy, informed consent.

Treatment: induction CT: 2 cycles of Carboplatin AUC 6, Paclitaxel 200 mg/m^2 day 1, and Gemcitabine 1000 mg/m^2 days 1-8 q 21 days. Concurrent CT: Carboplatin AUC 2 and Paclitaxel 45 mg/m^2 weekly with concomitant standard-dose radiotherapy (60 Gy). After 40 Gy pts were revaluated for surgery, if yet inoperable they received definitive chemo-radiotherapy.

Results: From April 1998 to November 2002, 40 consecutive patients were entered. Patient characteristics were: ECOG PS 0/1: 26/14(65/35%); clinical stage IIIA/IIIB: 17/23(43/57%); median age 62 (41-77); male/female 33/7(83/17%); histology: 25(62.5%) squamous cell carcinoma, 8(20%) adeno, 3(7.5%) large cell and 4(10%) undifferentiated. All 40 pts completed induction CPG chemotherapy and are evaluable for toxicity and activity. 3 pts have not yet completed the concurrent treatment. The induction treatment was well tolerated with 4% hypersensitivity reaction to taxol infusion, 15%/25% grade 3/4 neutropenia and 15%/5% grade 3/4 thrombocytopenia and 2 cases of febrile neutropenia. The most severe toxicities occurred in the last part of concurrent treatment: 27% grade 3 esophagitis that required dose reduction and in 1 case treatment interruption were observed. 4,5% had reversible grade 3 neuropathy. 1 patient died with pneumonitis 2 months after the end of the concurrent treatment. RR to induction CPG was 43% (2.7% cCR). After induction chemotherapy 4 pts developed distant methastases, one suffered rapid deterioration of PS and another underwent surgery. All six pts were not submitted to the subsequent CT/RT. Overall 31 pts. completed the planned treatment. The intention to treat RR at the end of the sequential treatment was 21/37 (56.7%, with 16.2% cRC). Median survival was 18,6 mo, with 1 yr and 2 yr survival of 61% and 46% respectively. Median time to progression was 13,9 mo.

Conclusions: This sequential/concurrent treatment seems promising with a manegeable toxicity and a promising median and 2 years survival.



820 POSTER

TGF-beta1 suppression by the antisense oligonucleotide AP 11014 as treatment strategy for non-small cell lung cancer and colorectal cancer

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Transforming growth factor-beta (TGF-beta) is a unique cancer target by triggering the transition from localized tumors to a metastatic generalized disease. Reduction of TGF-beta has already been proven as a successful strategy for tumor therapy: AP 12009, a TGF-beta2 antisense oligonucleotide, has shown efficacy by prolonging overall median survival time in clinical phase I/II trials for the treatment of malignant gliomas. Whereas in malignant gliomas TGF-beta2 is the predominant isoform, in non-small cell lung cancer (NSCLC) and colon cancer in particular the TGF-beta1 isoform is correlated with malignant progression and poor clinical prognosis. Significantly elevated TGF-beta1 plasma levels to threefold in colon cancer and eightfold in NSCLC as compared to healthy control persons further support the role of TGF-beta1 as a key tumor promoter. Thus, a treatment strategy based on the inhibition of TGF-beta1 synthesis by antisense oligonucleotides has been developed. AP 11014 is a phosphorothioate antisense oligonucleotide specific for the mRNA encoding human TGF-beta1. AP 11014 significantly reduces TGF-beta1 secretion in different NSCLC cell lines (A549, NCI-H661, SW 900) by 62 - 100% compared to the control and thus abrogates TGF-beta dependent effects on malignant progression: Tumor cell proliferation was inhibited in a dose-dependent manner. Similar results have been obtained with AP 11014 in a colon cancer cell line (HCT-116). Animal toxicological studies with AP 11014 have been started. So far, AP 11014 shows the same toxicology profile as the TGF-beta2 antisense oligonucleotide AP 12009 that has already successfully been employed in clinical studies. Our data clearly indicate TGF-beta1 suppression by AP 11014 as a highly promising approach for the therapy of non-small cell lung cancer and colorectal cancer.

821 POSTER

MRP functional activity is revealed in most non-small cell lung cancer (NSCLC)

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Background: One of the mechanisms of tumor multidrug resistance (MDR) is related to cytostatic efflux out of cells by energy dependent ABC-transporters. Polymerase chain reaction, immunoblotting and immunohistochemistry analysis are methods widely used for determination of tumor MDR-phenotype. But the presence of m-RNA encoding a transporter protein and even the protein expression in tumor cells do not mean the ABC-transporter activity and false-positive results may be obtained. So, the best informative approach for analyzing MDR-phenotype of solid tumors can be determination of ABC-transporters functional activity. Purpose of the study is to answer question how often MRP gene or protein expression had been revealed in NSCLC is associated with expression of MRP functional activity.

Material and methods: MRP functional activity was determined by a new flow cytometry approach which was developed in our laboratory for detecting function of different ABC-transporters. The index is determined as the change in doxorubicin intracellular accumulation after preincubation of tumor cell suspension with ABC-transporter(s)' inhibitors. In this study genistein (specific inhibitor of MRP) was used. Thirty biopsy samples of lung cancer were examined.

Results: Increase in doxorubicin intracellular accumulation as well as doxorubicin binding to DNA under genistein action was detected in most tumor samples investigated.

Conclusions: 1) Functional activity of MRP is an index of most NSCLC. 2) Taking into account high frequency of MRP gene or protein expression and high functional activity of MRP revealed in most lung tumors we answer the question proposed above: polymerase chain reaction, immunoblotting and immunohistochemistry analysis should be admitted as adequate methods to determine MRP-phenotype for multidrug resistance prediction in NSCLC patients. Supported by Russian Foundation for Basic Research (No. 01-04-49213)

822 POSTER

Correlation between tumor necrosis factor-alpha and D-dimer levels in non-small cell lung cancer patients

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Background: Recent studies have shown that activation of fibrinolysis occurs in non-small cell lung cancer (NSCLC), although the origin of this activation could not be related to consistent changes in plasminogen activator and inhibitor levels. Neutralization of endogenous tumor necrosis factor-alpha (TNF) in endotoxemia completely prevents fibrinolysis, suggesting a direct role of this cytokine in the activation pathway of the fibrinolytic system. Increased serum TNF levels can be found in lung cancer. Thus the present study was designed to investigate whether a correlation exists between TNF and coagulation (thrombin-antithrombin III, TAT) or fibrinolysis (D-dimer) activation in patients with NSCLC.

Methods: 130 patients with NSCLC (n=65, 53 males, mean age 65±8) or chronic obstructive pulmonary disease (COPD)(n=65, 51 males, mean age 67±9), treated at our Institutions, were enrolled. As control group 65 healthy donors (51 males, mean age 61±14) were studied. NSCLC was histologically diagnosed as adenocarcinoma (n=32) or squamous cancer (n=33), and staged according to the TNM classification: Stage I 29%, Stage II 9%, Stage III 36%, and Stage IV 26%. Plasma TNF (R&D) and TAT (Dade-Behring) levels were determined by ELISA kits. D-dimer levels were measured by an automated analyzer (Roche).

Results: The results obtained showed that median D-dimer levels were higher in NSCLC patients (2.95 ug/ml) compared either to COPD patients (1.07 ug/ml, $p<0.0001$) or controls (0.34 ug/ml, $p<0.0001$). Positive TNF levels (>10 pg/ml) were found in 26% of NSCLC compared to 3% of COPD and 4% of controls ($p<0.0001$). Median TAT levels were elevated in both NSCLC (6.9 ug/L) and COPD (5.7 ug/L) patients compared to controls (1.8 ug/L, $p<0.001$). Correlation analysis showed that D-dimer strongly correlated with TNF (rho=0.35, $p<0.005$), but not TAT levels, in NSCLC patients. Thus, to further analyze the relationship between D-dimer and clinical and laboratory variables of NSCLC, a multiple regression analysis including age, sex, stage, diagnosis, D-dimer, TAT and TNF levels was performed. Final model by stepwise analysis showed that TNF levels (regression coefficient= 0.38, $p<0.03$) were independently related to VEGF, but only in the subset of patients with adenocarcinoma.

Conclusions: These results suggest that increased levels of TNF might be responsible for an activation of fibrinolysis in patients with lung adenocarcinoma. *Partially supported by Grant PF Ministero della Sanità.*

823 POSTER

A full Navelbine Oral (NVB oral) treatment in combination with Cisplatin (P) followed by NVB oral single agent as consolidation therapy in advanced non small-cell lung cancer (NSCLC)

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Background: The combination of alternating NVB iv/oral with P has demonstrated similar activity as a reference regimen NVB iv + P in the treatment of advanced NSCLC (Jassem et al, Ann Oncol 2002). A multinational phase II trial was performed to investigate a new schedule of a full NVB oral treatment in combination with P followed by consolidation therapy with NVB oral as single agent in advanced NSCLC. Patients and methods: chemonaive stage III/IV NSCLC patients (pts) were eligible to be treated with 4 cycles on a 3 weekly schedule combining P: 80 mg/m2 on d1 with NVB oral: 60 mg/m2 on d1 & d8 for the first cycle with dose escalation of NVB oral at 80 mg/m2 on d1 & d8 for the following cycles in absence of grade 3-4 neutropenia. Pts with objective response (OR) or stable disease (SD) received consolidation therapy with weekly NVB oral.

Results: between 04/01 and 04/02, fifty six pts were included (M/F 40/16), median age was 60 years (40-70), median KPS 90% (80%-100%), squamous (43%)/adenocarcinoma (45%), stage IV (70%), IIIB (22%). Fifty-five pts were evaluable for safety and 49 pts for efficacy. A total of 180 cycles of combination therapy were administered with a median of 4 cycles (1-5), the RDI was 86% for NVB oral and 96% for P. As consolidation therapy, 25 pts received a total of 281 administrations of NVB oral with a median of 9 (6-24). Thirteen pts achieved partial response (OR: 26.5%) and 22 pts (44.9%) had stable disease. Median progression free survival and overall survival were 3.8 and 10 months respectively. The main grade 3-4 toxicities (NCI-CTC) were neutropenia 34,5% pts, nausea 5.4% pts, vomiting 8.9% pts, fatigue 12.5% pts, one pt experienced grade 3 neuropathy while another one had grade 3 constipation and two pts developed neutropenic infection.

Conclusion: this schedule of NVB oral + P provides comparable activity as standard regimen with iv form with a better convenience. The consolidation therapy with NVB oral single agent maintained the therapeutic benefit and improved the patient acceptance and comfort.

824 POSTER

Role of gross tumour volume and dose parameters on outcome and toxicity of patients undergoing concurrent chemo-radiotherapy for locally advanced non-small cell lung cancer

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Background. Concurrent chemo-radiotherapy (CRT) is a recommended treatment for locally advanced NSCLC. However, CRT is generally associated with higher frequency of toxicity when compared to radiotherapy alone, and the prognosis still remains poor. The aim of this study was to evaluate the prognostic role of gross tumour volume (GTV) on clinical outcome, regardless of T and N status. In addition, we analysed variables important for the development of lung toxicity.

Materials and methods. We analysed retrospectively data from 25 patients (pts) with locally advanced NSCLC treated at our institution between 1999 and 2001. Pts characteristics were as follows: mean age 59.9 years (range 44-76), PS 0-1, stage IIIA/N2 (6 pts) and IIIB (19 pts), M/F ratio = 16/9. Pts received concurrent CRT, according to the following schedule: weekly paclitaxel 100 mg/m^2 plus carboplatin AUC 2 for 3 weeks, followed by weekly paclitaxel 60 mg/m^2 plus carboplatin AUC 2 for 6 weeks with concomitant conventional thoracic radiotherapy, 2 Gy per fraction, 5 fractions per week up to 60 Gy. Dose volume histograms were collected from the 3-D treatment plans. GTVs were recalculated for all pts and correlated with time to progression (TTP) and overall survival (OS). In correlation with the development of radiation pneumonitis (RP) WHO grade 2 or higher, the following variables were examined: GTV, planning target volume, mean lung dose, V20 and V30 (volume of lung receiving more than 20 and 30 Gy respectively). Lung parameters were considered both for two lungs taken as a paired organ, as for each lung separately.