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.

O. Francesco[1], A. Paccagnella[1], S. Fasan[2], S. Ardit[3], C. Gatti[1], R. Biason[1], M. Medici[1], P. d'Amanzo[1], M.G. Ghi[1], O. Nascimben[1].
[1] *Ospedale Umberto I Mestre, Medical Oncology, Mestre (Ve), Italy;* [2] *Ospedale Umberto I Mestre, Radiotherapy, Mestre (Ve), Italy;* [3] *Ospedale Umberto I Mestre, Surgery, Mestre (Ve), Italy*

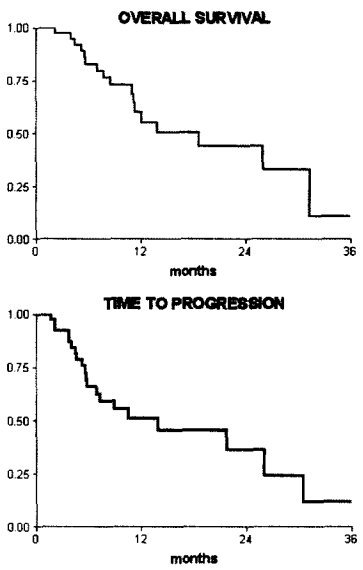
Background: Preliminary results from a phase III trial in advanced NSCLC comparing CP vs. CPG suggest an advantage in RR and TTP with a superior but acceptable toxicity for CPG. Therefore we used CPG as induction regimen in stage III pts. CT concurrent to RT was employed because paclitaxel with platinum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

P. Jachimczak, K.-H. Schlingensiepen, R. Schlingensiepen, A. Bischof, K. Graf, M. Hafner, M. Kielmanowicz, M. Szyrach, G. Stauder. *Antisense Pharma GmbH, Regensburg, Germany*

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)

T.A. Bogush, A. Ravcheeva, E. Bogush, Y. Shishkin, T. Zabotina, Z. Kadagidze, K. Laktionov, B. Polotskiy, A. Barishnikov. *Russian Blokhin Cancer Research Centre, Medical Chemistry, Moscow, Russian Federation*

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.