conducted with the oral formulation of NVB aiming to evaluate equal efficacy/tolerability.

Material and methods: Pts to be recruited were *70y with unresectable localised or metastatic NSCLC. Oral NVB was given weekly 60mg/m2x3 (1 cycle/cy) and then escalated to 80mg/m2 if no gr 4 neutropenia/no more than 1 gr 3 during first cy. At 80mg/m2, if 1 gr 4/2 consecutive gr 3 neutropenia occurred, dose was reduced to 60mg/m2. All pts had anti-emetic prophylaxis. Primary endpoint was response rate (OR) with secondary endpoints being response duration (MDR), progression-free survival (PFS), median survival (MS), tolerance and pharmacokinetics (PK).

Results: 56 pts were recruited from April 2001 to March 2002 in 6 European countries. Median age was 74 (range: 70-82), 75% were male with a KPS of 80 in 48%, 90 in 34% and 100 in 18%. 43 pts (76.8%) had metastatic disease at inclusion with 1/2 organs involved in 64.3% and * 3 in 35.7%. Co-morbidities were present in 87.5% of pts: 39 (69.6%) had 1 or 2 and 10 (17.9%) had * 3 co-morbidities. Cardiovascular morbidity was present in 36 (64.3%). 200 cy were given (median 3cy/pt, range:1-10), median dose intensity (DI): 47.2mg/m2/w with RDI of 66%. 472 doses were administered (median=7). Out of 45 pts receiving 2d cy, 29 (64%) were escalated to 80mg/m2. 13 pts received *6cy. Considering the intent-to-treat population (ITT): 6 PR (10.7%, 95% CI [2.6-18.8]) and 25 NC (disease control/DC=55.4%) were reported. MDR was 5.2 months (95% CI [4.3-9.1]), PFS 3.7 months (95% CI [2.5-4.5]) and MS 8.2 months (95% CI [6.2-11.3]). In the evaluable population (47pts/56), OR was 12.8% (DC=66%). A total of 125 doses (20.9%) were cancelled, 91 (72.8%) due to haematological toxicity. Grade 3/4 neutropenia was present in 61cy (30.8%), infection with neutropenia in 5cy (2.5%), leucopenia in 43cy (21.5%) and anemia in 2cy (1%). Grade 3 non-haematological toxicities were only fatigue (4%cy), nausea (2.5%cy), diarrhoea (1.5%cy). 1 pt had a grade 4 thrombosis (0.5%). PK performed in 52/56 pts reported similar bio-availability and blood profiles when compared to a large adult database.

Conclusion: Oral NVB given as weekly monotherapy was easy to administer and well tolerated, offering an optimal disease control in such elderly population leading to a favourable activity /toxicity ratio.

816 POSTER

Malignant pleural mesothelioma (MPM): analysis of consecutive 65 patients (pts)

A. Santo, M. Giovannini, A. Terzi, R. Pedersini, A. Tommasini, G. Festi, A. Cipriani, G. Falezza, G.A. Soardi, G. Cesaro, P. Manno, M. Pavarana, F. Maluta, F. Calabrò, G.L. Cetto. *University of Verona-GIVOP (on behalf ofthe Gruppo Interdisciplinare Veronese Oncologia Polmonare)*

Introduction: MPM is a rare but raising neoplasia characterized by poor prognosis in the majority of cases. Surgery plays a pivotal role in the treatment of this disease in early stages; the role of chemotherapy (CT) and local irradiation (RT) is controversial, even if the introduction of new drugs is very promising.

Patients and methods: We analyzed 65 cases of MPM collected by the Department of Medical Oncology and of Thoracic Surgery of the Civic Hospital of Verona from 1983 to 2003. We considered 3 groups of pts: pts with early MPM treated only with surgery(#49); pts treated with surgery plus adjuvant CT/RT(#11) and pts with advanced MPM treated only with CT(#5).

Results: The characteristics of pts were: median age 56.7 years; M/F 52/13; histology: epithelial 50, biphasic 13, sarcomatous 2. Stage I #28, II #23, III #12, IV #2 (Brigham's stadiation). Asbestos exposure was registered in 35 cases (53%); 22 of these (33%) were related to smoke and asbestos. 60 pts (pts) with good PS (ECOG 0-1) underwent pleuropneumonectomy; 49 pts underwent only radical surgery, with macroscopic residual of disease in 4 pts; 9 pts had adjuvant CT-RT, 2 adjuvant RT and 5 palliative CT. Intraoperative mortality was 7.5%; surgical accidents occurred in 39% of pts. In adjuvant setting 3 pts were treated with CAP schedule (CTX 600 mg/m2; ADM 50 mg/m2; CDDP 70 mg/m2) and 6 pts with CBDCA (AUC 6) and TXL (200 mg/m2) followed by RT (50 Gy); 5 pts were treated with palliative CT (CDDP and GEM). In the group of pts treated with CAP scheme only 1 patient completed adjuvant treatment (4 cycles of CT followed by sequential RT). Neutropenia G3-4 occurred in 2 pts Nausea and vomiting G3 and alopecia G3 occurred in all pts. In the group of pts treated with CBDCA and TXL timing of CT was respected in all cases. Asymptomatic neutropenia occurred in 3 pts (G4 in 2 cases and G3 in 1 case); 1 febrile neutropenia was observed; Alopecia G2-3 occurred in all pts; arthromialgies were referred by 2 pts. No cases of nausea or vomiting were registered. OS at 1, 3 and 5 years for pts treated only with surgery was respectively 49%, 23 and 14%; OS at 1, 3 and 5 years for epithelial subtype was 61%, 30 and 18%; for biphasic and sarcomatous histotype it was 8% at 1 year, 0% at 3 years. Median Survival for pts treated with adjuvant CT + RT was 22 months; for pts with advanced disease treated only with CT it was 10 months.

Conclusions: In our experience surgery maintains a pivotal role in the treatment of early MPM; about adjuvant CT the association of CBDCA and TXL seems to be better tolerated than CAP and can be considered the standard therapy in the adjuvant setting in association with sequential RT. Prognosis of pts with MPM relapsed after surgery remains very poor, above all for non epithelial histotypes.

817 POSTER

Optimized schedule of gemcitabine (G), paclitaxel (T) and cisplatin (P) in the treatment of stage IIIB/IV non-small cell lung cancer (NSCLC): results of a phase II study

F. Nelli[1], F. De Marinis[2], G. D'Auria[1], A. De Pasquale Ceratti[1], M.R. Migliorino[2], G. Metro[1], M. Di Molfetta[2], M.L. Evangelista[1], E. Cortesi[1]. *[1] University of Rome "La Sapienza", Medical Oncology, Rome, Italy; [2] Forlanini Hospital, Fifth Pulmonary Oncology Unit, Rome, Italy*

Background: The combination of G, T and P has been proposed as one of the most active regimen in advanced NSCLC (Frasci et al, J Clin Oncol 1999;17:2316-25). However, the best schedule and sequence have not been yet determined. Preclinical and clinical evidences show that G should be administered at least 4 hours before P, whereas T is well known to have a better toxicity profile when administered before P. Moreover, no drug-interaction has been observed between G and T. With the aim to optimize the schedule proposed by Frasci et al., we undertook this phase II trial to evaluate the activity and toxicity of the following schedule: G 1000 mg/m2 days 1-8, T 125 mg/m2 days 1-8, P 50 mg/m2 days 1-8, every 21 days.

Patients and Methods: From 06/01 to 10/02, 43 untreated patients (pts) with stage IIIB/IV NSCLC were enrolled. Pts characteristics were: M/F ratio 28/15; PS 0/1/2 = 15/18/10; histology: adenocarcinoma 19, squamous-cell 10, undifferentiated/large cell 14; stage IIIB/IV 28/15.

Results: all pts were evaluable for toxicity and 41 for response. PR were observed in 27 pts. for a RR of 62.8%; SD was reported in 7 (16.3%), whereas 5 (11.6%) pts progressed. Hematological toxicity was moderate with WHO grade (Gr) 3-4 neutropenia, thrombocytopenia and anemia occurring in only 16 (37.2%), 5 (11.6%), and 4 (9.3%), respectively. Febrile neutropenia occurred in 2 pts and RBC transfusion was required in 2 cases. Non-hematological toxicity was mild with only asthenia (9.3%) and emesis (4.6%) reaching Gr 3. To date, 19 pts progressed with a median time-to-progression of 5 months. Data on 1-year and median survival are still premature.

Conclusion: In comparison with the original schedule, the modification of drug sequence, based on pharmacokinetic evidences, led to a reduction of hematological toxicity without reducing the activity of the treatment. Data on survival, after longer follow-up, will confirm these findings.

818 POSTER

Results of postoperative radiotherapy for pathological stage III and surgical margin close or positive T3N0 NSCLC

F. Oner Dincbas[1], B. Ceylaner[1], M. Sar[2], B. Eren[2], B. Oz[2], S. Koca[1]. *[1] Istabul University Cerrahpasa Medical Faculty, Radiation Oncology, Istanbul, Turkey; [2] Istabul University Cerrahpasa Medical Faculty, Pathology, Istanbul, Turkey*

Background: A retrospective analysis is performed in order to evaluate the local control, survival outcomes, relapse patterns and prognostic factors in patients with NSCLC who had postoperative radiotherapy.

Methods and Materials: We evaluated 85 patients; 64 patients with p stage 3 and 21 with surgical margin close or positive T3N0 patients with NSCLC and had postoperative radiotherapy between 1978-2000 in Cerrahpasa Medical Faculty, Department of Radiation Oncology. All of the pathological specimens were reviewed in Department of Pathology of our faculty. Female male ratio was as 4/81. Histology was squamous in 56 and nonsquamous in 29 patients. Operation types were lobectomy in 38, pneumonectomy in 38, bilobectomy in 6, wedge resection in 3 patients. There were 4 T1, 23 T2, 50 T3, 8 T4, 25 No, 18 N1, 40 N2, 2 N3 patients. Radiotherapy dose differed between 46-66 Gy. Dose was increased after 45-50 Gy when there were close or positive margins. Age, type of operation, histology, grade, primary tumor size, T stage, N stage, perinodal invasion, number and level of nodal lymph node invasion, lymphatic invasion, surgical margins, thorax wall invasion, pleural invasion, interval between surgery-radiotherapy, radiotherapy dose were the factors used for univariate and multivariate analysis.

Results: Median follow-up time was 42 months (3-102months) in alive patients. Twenty-eight patients locally recurred and 38 patients had distant

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*

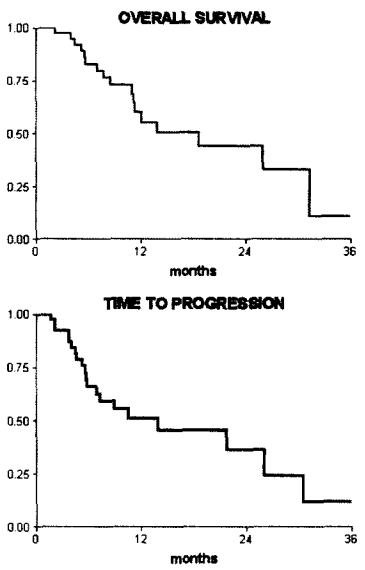
Background: Preliminary results from a phase III trial in advanced NSCLC comparing CP vs. CPG suggest an advantage in RR and TTP with a superior but acceptable toxicity for CPG. Therefore we used CPG as induction regimen in stage III pts. CT concurrent to RT was employed because paclitaxel with platinum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