Results: With the initial study design of 2D XRT, dose limiting toxicity (DLT) of grade 3 esophagitis occurred in 3/6 pts at G 150 mg/m2/wk and 2/3 pts at G 125 mg/m2/wk. The protocol was thus amended to 3D conformal XRT. Using 3-D XRT, 0/3 pts who received G 125 mg/m2/wk and 0/3 at a G dose of 150 mg/m2/wk experienced DLT. At a G dose of 190 mg/m2/wk with concurrent 3D XRT, 2/6 pts had DLT of grade 3 esophagitis. There was a strong relationship between volume of esophagus in the XRT port and grade of esophagitis. Percent esophageal exposure at 60 Gy averaged 71% for the 2D cohort vs only 11% in the 3D cohort. With a median follow-up of 40 weeks, estimated median survival is 55 weeks and estimated 1-year survival is 53% [95% CI: 33%, 85%].

Conclusions: The MTD of G given weekly concurrent with conventional 2D XRT was less than or equal to 125 mg/m2/wk x 7wks. However, with 3D chest XRT the MTD was 190 mg/m2/wk x 7wks. DLT was grade 3 esophagitis. G given concurrently with 3D XRT is better tolerated than with 2D XRT, presumably due to decreased volumes of esophagus exposed using 3D approach.

187 POSTER

Weekly docetaxel as second line chemotherapy in advanced non small cell lung cancer (NSCLC): Final results and survival analysis

M. Serke, D. Argiropolus, N. Schönfeld, R. Loddenkemper. *Zentralklinik Emil von Behring, Dep. Lungenklinik Heckeshorn, 14109 Berlin, Germany*

The activity and toxicity of weekly docetaxel (D) after platin-based first-line therapy for advanced NSCLC were investigated in a prospective phase II study. A final analysis of 36 patients is presented.

Patients and Method: 36 patients were enrolled between 1/99 and 4/00. Most pts. (n = 26) showed progressive disease under first-line therapy. One third (n = 11) of pts. had a "sensitive relaps". Pts were treated with 6 cycles of weekly D (35 mg/m^2) each interrupted by a 14 days break. In total 3 courses were administered. A total of 222 infusions of docetaxel were administered (median 6 weekly infusions).

Results. *Toxicity:* Severe (grade III/grade IV) hematotoxicity was not seen. Other than one grade IV diarrhea, grade III non-hematologic toxicities included nausea (1), asthenia (1), spontaneous pneumothorax (2), fluid retention (1), arrythmia (1), and nail toxicity (1). Mild cutaneous and nail toxicity occurred in 29 pts, neutropenia grade II in 2 cases, and mild asthenia (grade I and II) in 48 courses. *Response:* 35 patients were evaluable for response. Partial response (PR) was observed in 4/35 (11%), stable disease or minor response (SD/MR) in 14/35 (40%), and progressive disease (PD) in 17/35 (49%). Three pts are still alive (censored 8.3%). Median survival was 160 days (115–205, 95% CI., Kaplan-Meier-analysis, 3 cases censored).

Conclusion: Weekly docetaxel (35 mg/m^2) as second line therapy is a well tolerated and safe regimen without occurrence of grade III/IV hematotocicity.

188 POSTER

Gemcitabine (GEM) and docetaxel (DTX) salvage regimen in non-small cell lung cancer (NSCLC) failing prior paclitaxel platinum-based chemotherapy

C. Kosmas[1], N. Tsavaris[2], M. Vadiaka[2], N. Stavroyianni[2], A. Koutras[3], N. Malamos[1], A. Onyenadum[3], H. Kalofonos[3]. *[1]Helena-Venizelou Hospital, Medical Oncology Unit, Athens, Greece; [2]Laikon General Hospital, Medical Oncology Unit, Athens, Greece; [3]Patras University Hospital, Department of Medicine-Oncology, Rio-Patras, Greece*

Purpose: Treatment options in patients with recurrent NSCLC remain limited as a result of poor activity of older agents after platinum-based therapy. In the present phase II study we evaluated the combination of GEM DTX in relapsed NSCLC.

Methods: Patients with advanced NSCLC (stages IIIB/IV), WHO-PS-2, prior paclitaxel platinum-based chemotherapy, unimpaired hematopoietic and organ function were eligible. Chemotherapy was administered as follows: GEM 1000mg/m2 on days 1 8 followed by DTX 100mg/m2 on day 8, recycled every 21 days. Prophylactic G-CSF was administered from day 10-14 or until WBC 5.000/Zl.

Results: 43 patiens have entered; 41 were evaluable for response and all for toxicity: median age=63 (47-70), PS=1 (0-2), gender=38 males/5 females, stages IIIA=4, IIIB=17, IV=22. Metastatic sites included; lymph nodes: 28, bone: 6, liver: 5, brain: 5, lung nodules: 8, adrenals: 7, other: 3. All patients had prior paclitaxel platinum-based treatment; 28 patiens had prior paclitaxel-ifosfamide-cisplatin. Objective responses were; PR: 14/43 [33%; 95% confidence interval (CI)=18.5-46.6%], SD: 16/43 (37%; 95% CI=22.8-51.6%) and PD: 13/43 (30%; 95% CI=16.3-43.7%). The median time-to-progression (TTP) was 6mo (1-20) and median survival 8mo (1.5-20). 1-year survival was 28%. Grade 3/4 neutropenia was seen in 53% of patients (30% grade 4) and 14% incidence of febrile neutropenia. Grade 3 thrombocytopenia was seen in 7% of cases (no grade 4), while other grade 3 non-hematologic toxicities were never encountered.

Conclusion: The combination of GEM DTX is active and well tolerated in patients with advanced NSCLC failing prior taxane/platinum. It represents an effective combination to apply in the palliative treatment of relapsed NSCLC.

189 POSTER

Neoadjuvant chemotherapy followed by surgery in stage IIIa/IIIb non-small cell lung cancer

I. Spasova[1], J. Petera[2], V. Hytych[3], M. Marel[4]. *[1]Department of Pulmonary Medicine, [2]Department of Radiology and Clinical Oncology, University Hospital, Hradec Kralove, Czech Republic; [3]Central Military Hospital, Department of Thoracic and Abdominal Surgery, Prague, Czech Republic; [4]University Hospital Motol, Department of Pulmonary Medicine, Prague, Czech Republic*

Purpose: The study was undertaken to test whether marginally resectable or unresectable stage IIIa-IIIb non-small cell lung cancer (NSCLC) patients (pts) could reach a complete resectability after induction chemotherapy. The response to chemotherapy, surgical results and survival analysis were evaluated.

Methods: 56 pts were included into the study of Group A, vinorelbine 35mg/m2 day 1 and cisplatin 75 mg/m2 day 1; and Group B, vinorelbine 30mg/m2 day 1 and 8 and cisplatin 80 mg/m2 day 1. Cycles were repeated every 21 days. At the completion of induction therapy pts assessed to be resectable underwent thoracotomy. Radiation therapy was applicated in nonresected pts. The minimal follow up was 24 months.

Results: In our previous study, cisplatin and vinorelbine in the both dose intensity regimens proved to have a comparable toxicity and efficacy regarding response and survival. We report here the results of treatment for the entire group of 56 eligible pts. A total of 161 cycles were delivered. No complete response was observed. 30 pts (54%) had partial response, 15 pts (27%) had stable and 11 pts (19%) had progressive disease; 29 pts (52%) were surgically explored and 18 pts (32%) underwent a complete resection (pT0-3 N0-1). Complete pathological response was observed in 3 pts. In 6 pts lobectomy and in 6 pts pneumonectomy was done. 10 pts required intrapericardial pneumonectomy, with one tracheal, one esophageal and one chest wall resection. There were no lethal complications of surgery. The median survival of the whole group was 61 weeks. The cumulative survival was 59% at 1 year and 27% at 2 years. The median survival was 75 weeks in stage IIIa and 60 weeks in IIIb, the difference was not statistically significant. Responders survived significantly longer (93 weeks) comparing to pts with stable disease and progression (39 weeks, $p<0,001$). The completely resected pts survived significantly longer (122 weeks) as compared with the incompletely plus nonresected pts (50 weeks, $p<0,001$).

Conclusions: 32% of pts with marginally resectable or unresectable stage IIIa-IIIb NSCLC could reach a complete resectability after induction chemotherapy. Survival of pts stage IIIa was comparable to stage IIIb. Responders and resected pts survived significantly longer comparing to the pts with stable disease and progression, respectively to the incompletely resected plus nonresected pts. There were no treatment-related deaths in our study.

190 POSTER

A phase II trial of preoperative chemoradiotherapy using uft in clinical stage IIIb non-small cell lung cancer

Y. Ichinose, Y. Fukuyama, H. Asoh, C. Ushijima, M. Yamaguchi, T. Teruya, J. Ikeda. *National Kyushu Cancer Center, Department of Chest Surgery, Fukuoka, Japan*

Purpose: Since our prior phase II trial showed the oral administration of UFT (Uracil + Tegafur) plus cisplatin with concurrent radiotherapy (60 Gy) in locally advanced non-small cell lung cancer patients to be effective (a response rate of 91%) and safe, we performed a phase II trial of preoperative treatment using this regimen.

Methods: From Sept., 1995 to Oct., 2000, 23 clinical stage IIIB patients were entered into this trial. Nineteen patients demonstrated T4N0-2M0 while 4 showed T1-2N3M0. UFT (400 mg/m2, p.o., d1-14, 29-42) plus cisplatin (80 mg/m2, i.v., d8, 36) were administered with concurrent radiotherapy (2 G/f. total 40 Gy).

Results: Preoperative concurrent radiochemotherapy showed a partial response in 18 (78%) patients and no change in 5. The main adverse reaction was leukopenia of grade 3 or 4 which was observed in 30%. No severe pulmonary toxicity or esophagitis was observed. An operation was performed in 21 (91%) of the 23 patients consisting of an extrapleural pneumonectomy in 6 patients, a resection of the superior vena cava or vertebral body in 4 each, a carinal resection in 2, and other surgical modalities. Nineteen patients underwent a complete resection. The median survival time of all patients was 27 months and the 1- and 3-year survival rates were 88% and 43%, respectively. There was no mortality related to either the preoperative treatment or operation.

Conclusions: The oral administration of UFT plus cisplatin with concurrent radiotherapy was found to be a safe and effective preoperative treatment. A complete resection was also feasible in highly selected stage IIIB patients.

191 POSTER

Combined analysis of apoptotic index and growth fraction in non-small cell lung carcinomas

F. Puglisi[1], A.M. Minisini[1], G. Aprile[1], P. Cataldi[2], M. Pandolfi[2], C. Di Loreto[2]. [1] *Medical Oncology, University of Udine, Udine, Italy;* [2] *Anatomic Pathology, University of Udine, Udine, Italy*

Purpose: To investigate the significance of apoptotic index (AI) and growth fraction in predicting survival of completely resected non-small cell lung carcinomas (NSCLC).

Methods: Sections of 89 NSCLC (27 adenocarcinomas and 62 squamous cell carcinomas) served for TUNEL staining to detect apoptotic cells and immunohistochemical staining to detect MIB-1 expression (i.e. growth fraction). The AI was defined as the number of apoptotic cells per 1,000 tumor cells. To evaluate the percentage of MIB-1 positive nuclei, 1,000 tumor cells were scored for each case. The postoperative survival rate according to AI and MIB-1 immunoreactivity was analyzed by the Kaplan-Meier method. Patients were excluded from survival calculations if death occurred within 30 days from surgery.

Results: The median AI was 11 (33rd-66th percentiles, 8-17). AI was significantly lower in adenocarcinomas (median 8) than in squamous cell carcinomas (median 13.5) (p=0.02). MIB-1 immunopattern was nuclear and the median value of MIB-1 staining was 30.4% (33rd-66th percentiles, 21.52-34.02%). Among histotypes, no significant difference in MIB-1 expression was observed (p=0.7).

Interestingly, when AI and growth fraction were analyzed separately no association with clinical outcomes was observed. On the contrary, combining together AI and MIB-1, the cases with low AI (<33rd percentile) and high MIB-1 (> 66th percentile) identified a group with a significantly poor prognosis (log-rank test, p=0.0007).

Conclusions: The balance between apoptosis and growth fraction seems to be prognostic in patients with NSCLC.

192 POSTER

Front line chemotherapy with four different schedules of gemcitabine and carboplatin in stage IV non-small cell lung cancer (NSCLC)

S.C. Stani[1], E. Bajetta[1], D. De Candis[1], P. Pozzi[1], E. Ferrario[1], D. Cortinovis[1], L. Mariani[2], P. Bidoli[1]. [1] *Medical Oncology Unit B;* [2] *Opertive Unit of Medical Statistics and Biometry, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy*

Purpose: We designed a phase II study in order to evaluate the activity and the tolerability of the combination of Gemcitabine (G) + Carboplatin (C) as first line chemotherapy for metastatic NSCLC. Gemcitabine and Cisplatin (CDDP) exhibit synergist cytotoxicity against NSCLC. Carboplatin appears to be equally efficacious with a better toxicity profile. According to our lab's preclinical data on SCLC cell lines, we explored four different schedules of administration of G + C.

Methods: From September 1998 to December 2000, 88 chemo-naive stage IV NSCLC pts were randomized to receive the same dose of G (1000 mg/m2) and C (AUC5), but with different sequences. Pts were randomly assigned to arm A: G on days 1 and 8 with C on day 1, given 4 hours before G; arm B: same schedule but with C given 4 hours after G; arm C: G on days 1 and 8 with C on day 2; arm D: G on days 2 and 9 with C on day 1. Courses were repeated every 21 days. All of the pts had ECOG PS 0–1; 58% were adenocarcinomas; 77% males; median age was 64 years (33–75); the four arms were balanced for pts' characteristics.

Results: At present all of the pts are valuable for toxicity, 73 pts for response. According to standard analysis the overall response rate (RR) was 40% (29/73, 95% CI: 28.5–50.9%). Response rate arm by arm was: 55% in arm A, 25% in arm B, 30% in arm C, 37% in arm D. Toxicity was generally mild without significant difference in the four arm. Grade 3–4 neutropenia and thrombocitopenia occurred in 11% in 14% of pts, respectively. No pts required hospitalization for toxicity. Overall median duration of response was 6 mos (range 3–11). Overall median survival was 13 mos (range 7–26). One-year and 2-year survival is 54% and 17%, respectively.

Conclusion: G + C is an active and safe combination in stage IV NSCLC. Our data seem to indicate that C given before G produces better results. In view of its activity and tolerability this schedule could become the first line standard regimen for metastatic NSCLC.

193 POSTER

Correlation between C-ERBB-4 receptor expression and response to gemcitabine-cisplatin chemotherapy in non-small cell lung cancer

O. Merimsky[1], J. Greif[2], Y. Schwartz[2], N. Wigler[1], A. Staroselsky[2], A. Mann[2], S. Marmor[3], E. Shmueli[1], M. Inbar[1]. [1] *Tel-Aviv Medical Center, Oncology, Tel-Aviv, Israel;* [2] *Tel-Aviv Medical Center, Pulmonology, Tel-Aviv, Israel;* [3] *Tel-Aviv Medical Center, Pathology, Tel-Aviv, Israel*

Background: While the overexpression of c-erbB gene family in several malignancies is associated with poorer prognosis, the association between the expression of the cellular markers and the response to chemotherapy is not yet clear. In this study we investigated the expression of c-erbB-4 receptor in NSCLC and correlated it with the response to gemcitabine-cisplatin combination chemotherapy.

Patients and Methods: Forty-three NSCLC patients with histologically or cytologically proven disease were treated with gemcitabine-cisplatin combination chemotherapy. Immunohistochemical stains for c-erbB-4 receptor were performed in 20 cases on paraffin sections using the avidin-biotin-peroxidase method.

Results: Two patients achieved complete response (5%), and 16 achieved partial response (37%) yielding an overall objective response rate of 42%. Minimal response was observed in 7 patients (16%) and disease stabilization in 7%. Immunohistochemical stain was positive for the presence of c-erbB-4 receptor in 25% of patients, and negative in 75%. No response was documented in c-erbB-4 positive patients (0/5) while an objective response (complete, partial or minimal) was seen in 11/15 (73%) c-erbB-4 negative patients. Negative stain for c-erbB-4 significantly favored response to gemcitabine-cisplatin combination (p<0.01).

Conclusion: C-erbB-4 expression status showed no correlation with survival and cannot be accepted at this time as a guiding factor for therapeutic management. These interesting results deserve further evaluation in a large-scale prospective trial before treatment recommendations on the basis of c-erbB-4 presence can be finally made.

194 POSTER

Induction chemotherapy with taxol (T), cisplatin (C) and gemcitabine (G) and subsequent radiation therapy with or without concomitant taxol for stage III non small cell lung cancer (nsclc). a galician lung cancer group (GLGC) study

J. Casal[1], J. Firvida[2], M. Lázaro[3], S. Vázquez[4], F. Barón[5], G. Huidobro[1], R. Rodriguez[2], J. Carrasco[3], G. Quintela[4], M. Caeiro[1]. [1] *Hospital Meixoeiro, Oncología Médica Y Radioterapia, Vigo, Spain;* [2] *Hospital Santa Maria Nai, Oncología Médica, Ourense, Spain;* [3] *Hospital Xeral-Cies, Oncología Médica, Vigo, Spain;* [4] *Hospital Xeral-Calde, Oncología Médica, Lugo, Spain;* [5] *Hospital Clínico Universitario, Oncología Médica, Santiago, Spain*

Introduction: Combined thoracic radiation and chemotherapy has become the treatment of choice for unresectable stage III NSCLC. The GLCG commenced a phase II study for these patients (p), with a scheme of induction chemotherapy of TCG combination and if not surgery, followed by consolidation thoracic radiation therapy with (Group-1) or without (Gr-2) taxol, according to avaible capacity to administer the concomitant treatment.

Material and Methods: A total of 60 p with stage III NSCLC (except for pleural T4) were included: age 58.2 years (range 36-72); 4 F/56 M; ECOG 0/1 in 7/53 p; squamous/adeno/large cell carcinoma: 63.3%/18.3%/18.3%; 12 p (20%) stage IIIA and 48 p (80%) stage IIIB. The common TCG induction scheme is: T 125 mgr/m2/iv, C 50 mgr/m2/iv and G 1000 mgr/m2/iv on days 1 and 8 every 3 weeks through 3 cycles. If no surgery, consolidation treatment in Gr-1 consisted of radiation therapy (60Gys, 180 cGy/day) with