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

T 45 mgr/m2/iv weekly during the 7 weeks of treatment; Gr-2 received only radiation therapy (60-65 Gys, 200 cGy/day over 6 weeks). 4 p could not be evaluables, 55 p were evaluables for response and 56 p for toxicity.

Results: Upon TCG induction chemotherapy: 1 CR and 37 PR (RR 69.1%;CI95%:56-80), 10 SD (18.1%) and 7 PD (12.8%).7 p went to surgery: 2 pCR, 2 pPR and 3 pSD. 17 p in Gr-1 completed the consolidation treatment with 4 CR, 9 PR, 1 SD and 3 PD (RR 76.5%) and 14 p in Gr-2 with 5 CR, 7 PR and 2 PD (RR 85.7%). At a median follow-up of 9.3 months, the median survival were 16.5 mo (Gr-1 13.7 mo and Gr-2 14.5 mo) and 1-year survival rate of 65% (Gr-1 69% and Gr-2 62%). A total of 168 cycles of TCG were administered (3 per p), with the hematologic toxicity (NCI-CTC) per p Grade 1-2/3-4 (%) as follows: neutropenia 30.3/42.8; anemia 59/12.5; thrombopenia 28.5/25; there was 1 death from toxicity and 10 hospitalisations for complications. The main toxicities (RTOG) in consolidation treatment were: in Gr-1: g1/2 esophagitis in 5/6 p, g 1/2 pneumonitis in 3/3 p, g1/2 neurophathy in 2/5 p; in Gr-2: g1/2 esophagitis in 2/2 p and g1 pneumonitis in 2 p.

Conclusions: The TCG scheme of induction chemotherapy is active against stage III NSCLC with moderate toxicity. A larger number of patients and a longer follow-up will be required to allow final conclusions to be drawn as to the posible difference between the consolidation treatment groups.

195 POSTER

UFT plus cisplatin with concurrent radiotherapy for locally advanced non small-cell lung cancer: a multiinstitutional phase II trial. Cis-UFT-RT Study Group

A. Gemma[1], Y. Ichinose[2], Y. Nakai[3], H. Semba[4], M. Shibuya[1], S. Kudoh[1]. *[1] Nippon Medical School, 4th Dept of Internal Med, Tokyo, Japan; [2] National Kyushu Cancer Center, Dept. of Chest Surgery, Fukuoka, Japan; [3] Sendai Kohsei Hospital, Dept. of Internal Medicine, Sendai, Japan; [4] Kumamoto Regional Medical Center, Respiratory Disease Unit, Kumamoto, Japan*

Purpose: A multiinstitutional phase II study of combined-modality treatment consisting of uraciland tegafur (in a molar ratio of 4:1 [UFT]) plus cisplatin (Platinol) and concurrent radiotherapy was conducted to conclude the high activity of this regimen in patients with locally advanced non small-cell lung cancer.

Methods: Eligible patients with cytologically or histologically confirmed, unresectable stage III non-small-cell lung cancer received UFT (400 mg/m2 orally on days 1 - 14, 29- 42) and cisplatin (80 mg/m2 intravenously on days 8, and 29). Radiotherapy, with a total dose of 60 Gy, was delivered in 30 fractions on days through 40.

Results: Among the 58 patients entered(Stage IIIA 12; Stage IIIB 46), 46 experienced good responses (CR 1; PR 45)(79.3%; 95% confidence interval, 67.2% to 87.7%). Hematologic toxicity was moderate. Grade 3 leukopenia occurred in 11 patients (19%), but grade 4 hematologic toxicity was observed in 1 patient. Grades 3 or 4 nonhematologic toxicities were reported in 1 patient with esophagitis.

Conclusion: These observations suggest that oral UFT plus cisplatin with concurrent radiotherapy can be safely administered to patients with locally advanced non-small-cell lung cancer with mild toxities. The demonstrated antitumor activity is high, making this combined-modality treatment worthy of further investigation in comparison with other cisplatin-based regimens in a prospective randomized trial.

196 POSTER

Preventive epoetin a (EPO) use in the treatment of advanced nsclc: an AIPO oncology study group multicenter trial

L. Portalone[1], A.M. Altieri[1], A. Antilli[1], S. Barbera[2], R. Bernardini[3], A. Lombardi[1], L.G. Monaco[4], C. Seebacher[5], M. Signora[1]. *[1] C. Forlanini H., 6 Pneumo Oncology, Rome, Italy; [2] M. Santo H., 2 Pneumology Unit, Cosenza, Italy; [3] A. & C. Cartoni H., Pneumology Unit, Rocca Priora (Rome), Italy; [4] S. Giovanni H., Pneumology Unit, Rome, Italy; [5] Bolzano H., Pneumology Unit, Bolzano, Italy*

Purpose: Anemy is an important problem which we meet in the treatment of neoplasms. Meanly it reduces drug dose intensity and influences patient quality of life. Epoetin a can improve hemoglobin level but its use, until now, is reserved to correct anemy. Now we try to use Epoetin a to prevent anemy and improve drugs tolerance and quality of life in patients in chemotherapy for advanced NSCLC.

Methods: We have randomised, until now, 64 patients in chemotherapy for advanced NSCLC in two arms when hemoglobin level is 12 g/dl. or less: the group in arm A was treated with Epo a 150 u.i./kg. every other day for three months. Arm B is the control group without Epo a: but, if the hemoglobin level becomes less than 10 g/dl. patient comes out from the trial and will be treated with Epo a. We have evaluated hemoglobin levels, chemotherapy dose intensity and quality of life at 0 time, after one and three months. QoL was measured by patient completion of two scale, FACT-G and FACT-An, which was translated and adapted by us to Italian people.

Results: At this moment only 36 patients, 18 for arm, are evaluable. In arm A the differences between the hemoglobin level of baseline and third month control show an increasing of values ($P<0,093$); the same control in arm B shows a decrease in hemoglobin level, statistically significant ($P<0,0004$). Dose intensity in arm A reaches 95%, in arm B 65%. Scores of the evaluation scale in arm A are uniform in the time; in arm B scores show statistically significant increasing between first and following evaluations.

Conclusions: At this moment our findings show that preventive use of Epoetin a is able to improve tolerance of NSCLC patients to chemotherapy, measured by hemoglobin levels and dose intensity. QoL appeares to be better during the time of treatment too.

197 POSTER

Phase i/ii study of docetaxel(DOC) and carboplatin(CBDCA) with concurrent radiotherapy in patients with stage III unresectable non-small cell lung cancer(NSCLC), preliminary results

S. Kato[1], M. Sakura[1], T. Kazumoto[1], H. Sakai[2], S. Yoneda[2], Y. Noguchi[2], K. Kobayashi[2], S. Honda[2], S. Kosaihira[2]. *[1] Saitama Cancer Center, Radiation Oncology, Saitama, Japan; [2] Saitama Cancer Center, Respiratory Disease, Saitama, Japan*

Purpose: Concurrent chemoradiotherapy plays an important role in the treatment of stage III NSCLC. Both DOC and CBDCA have demonstrated activity as radiation sensitizers in preclinical studies. We conducted a phase I/II study to determine the maximum tolerated dose (MTD) and recommended dose (RD) of DOC and CBDCA when administered with concurrent thoracic radiotherapy (Phase I), and subsequently, to evaluate the efficacy and toxicity of the treatment regimen at the RD (Phase II).

Methods: Twenty three patients with stage III unresectable NSCLC were enrolled in the phase I study. DOC and CBDCA were administered bi-weekly (D1, 15, 29, 43, 57, 71) at the following DOC (mg/m2)/CBDCA (AUC) dose levels: 20/2.5, 20/3.0, 30/2.5, 30/3.0, and 40/3.0. Concurrent thoracic radiotherapy was performed in 2Gy daily fractions to a total dose of 60Gy. DLT was defined as grade 4 hematological toxicity, or grade 3 or 4 nonhematological toxicity. Three to six patients were entered at each dose level. Dose escalation continued until greater than one half of patients developed DLT. After determing the MTD and RD, the phase II study was initiated to evaluate the efficacy and toxicity at the RD.

Results: The MTD was DOC 40mg/m2 and CBDCA AUC 3. To date, 19 patients have been treated in the phase II study. An overall response rate of 83%(95% C.I.: 56-96%) was observed in 18 evaluable patients (15 PR, 2 NC, 1 PD).

Conclusions: Combined chemotherapy of bi-weekly DOC and CBDCA with concurrent radiotherapy in stage III NSCLC was well tolerated. The preliminary efficacy data are promising. Updated results will be presented.

198 POSTER

Neoadjuvant chemo-radiation with paclitaxel/carboplatin in stage III non small cell lung [NSCLC] patients

W. Budach[1], G. Friedel[2], T. Hehr[1], S. Sepe[1], D. Hruschka[3], L. Kanz[4], H. Toomes[2], R. Dierkesmann[3], M. Bamberg[1]. *[1] University of Tuebingen, Radiooncology, Tuebingen, Germany; [2] Klinik Schillerhohe, Thoracic Surgery, Gerlingen, Germany; [3] Klinik Schillerhohe, Oncological Pneumology, Gerlingen, Germany; [4] University of Tuebingen, Medical Oncology, Tuebingen, Germany*

Background: Neoadjuvant chemo-radiation has been shown to induce significant down staging and improved resectability in stage III NSCLC. The reported high response rates of paclitaxel/carboplatin were rationale to test the efficacy of these drugs in combination with radiotherapy in the neoadjuvant setting in a phase II trial.

Methods: Patients (>17 to <70 years, KPS >70%) in stage III NSCLC (staging included CT-thorax/abdomen/cranium, PET, and mediastinoscopy) without supraclavicular lymph node involvment qualified for the study. Paclitaxel 100 mg/m* and carboplatin AUC 2 were administered at day 1, 8, 15, and 22 followed by hyperfractionated/accelerated radiotherapy starting at day 43 (2x1.5 Gy/day, 5x/week to 45 Gy) with simultaneous paclitaxel (50 mg/m*) and carboplatin (AUC 2) at day 44, 51, and 58. Erythropoetin (3x 150 I.E./kg/week) was given at a Hb $\leq$10.5 g/100 ml. After complete restag-