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The impact of gender on outcomes in limited stage small cell lung cancer treated with concurrent chemoradiation

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Background: Female sex is considered a positive prognostic factor when it comes to small cell lung cancer (SCLC) survival. To explore the basis for this finding, a retrospective review was carried out to determine whether the sex of patients (pts) receiving concurrent chemotherapy (ChT) and radiotherapy (RT) for limited stage SCLC (LSCLC) is associated with differences in treatment-related toxicity rates, failure patterns and survival.

Materials and Methods: From 1989 to 1999, 215 LSLC pts received 6 cycles of alternating cyclophosphamide/adriamycin/vincristine and etoposide/cisplatin (EP), as per an NCI-Canada randomized trial best arm. Thoracic RT stared with EP only (cycle 2 or 3) and was: 40 Gy/15 fractions/3weeks or 50 Gy/25 fractions/5 weeks. RT fields encompassed gross and microscopic disease with 2-cm margins. Prophylactic cranial irradiation was administered to complete responders following re-staging and at the discretion of the clinician. RT interruptions during concurrent ChT+RT were recorded as number of days and used as the marker for treatment toxicity. Smoking status at treatment start was recorded for all known smokers.

Results: At the time of analysis, 23 pts (10.7%) were alive and 192 (89.3%), dead. Overall survival (OS) for all pts at 2 and 5 years was 22.7% and 7.2%, respectively, with median survival of 14.7 months. 126 pts were men (58.6%) and 89 (48.4%), women. Smoking status at treatment start was recorded for 186 pts (86.5%): 107 not smoking (58%) of which 76 (71%) male and 31 (29%) female; and 79 continuing smoking (42%) of which 36 male (46%) and 43 female (54%) [male vs. female, p=0.0005]. There were otherwise no significant differences between the 2 cohorts over a range of pt- and treatment-related variables. 56 pts (26%) had treatment breaks for toxicity, for a median length of 5 days (range 1-18). The incidence of RT breaks was not related to gender (p=0.95). OS at 2- and 5-years were greater for women than men [30%; 12.5% vs. 18%; 2.5%, respectively (p=0.07)]. The table below provides survival results according to sex, use of RT breaks and smoking status during treatment. Looking at sex and treatment interruptions: women without treatment breaks do the best, men with breaks the worst (p=0.002). A woman with a treatment break does as well as a man without a break. Looking at smoking status and sex: continued smoking decreases a woman's survival (p=0.01). Overall, women survive longer than men irrespective of their smoking status. Males continuing to smoke on treatment did the poorest (p=0.005). Sites of first relapse were recorded in 132 cases (61%). Chest failures were greater in men than in women (45% vs. 35%), but brain failure rates were equivalent. Multivariable analysis of prognostic factors including smoking revealed positive benefit to female sex (HR=0.66; 95%CI (048,0.92); p=0.014).

	FEMALE				MALE			
	No break	RT break	Not smoking	Smoking	No break	RT break	Not smoking	Smoking
N	66	23	31	43	93	33	76	36
Median(mths)	15.6	14.5	19.6	13.6	15.7	13.4	17.7	13.7
2-year(%)	32.4	23.6	38.7	21.6	23.0	3.8	22.9	9.1

Conclusions: Female LSCLC pts treated with concurrent ChT+RT tolerated treatment as well as men but overall had better survival. Whether or not a woman smoked or experienced treatment interruptions, she survived longer than her male counterpart. Failure patterns suggested poorer control in the chest in men than women. The results suggest an intrinsic biological basis for the improved survival of women with LSCLC.

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Preoperative concurrent chemoradiotherapy in non-small-cell lung cancer. Feasibility, toxicity and long-term results of a phase II study.

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Purpose: We carried out a phase II trial to evaluate the feasibility, toxicity and effect on survival of polychemotherapy delivered concurrently with accelerated modified hyperfracctionated radiotherapy (AMHR) in non-small-cell lung cancer stage III patients.

Methods: Thirty four patients with locally advanced stage III NSCLC received neoadjuvant therapy consisting of AMHR 40.2 Gy in 3 weeks concurrent with the second cycle of chemotherapy using cisplatin 80 ml/m2 on day 1, ifosfamide 1.5 gr/m2 on day 1 and VP-16 100 mg/m2 for 3 days.

Results: From October 1997 to October 2001, 34 patients were entered into the study. The most frequent cell type was squamous cell carcinoma, 16 (47.06%), and adenocarcinoma 9, (26.47%). PS was 0 in 3 patients (8.57%), PS 1: 27 (80%) and PS 2: 4 (11.43%). The prominent grade 3-4 side-effect was leucopenia 21%, trombopenia 12% and anemia 9%. Other toxicity grade 3-4 was esophagitis in 4%. There was 1 surgically related death. The response rate was 47% (1 CR, 15 PR), 29.41% with stable disease and 23.53% with progressive disease. Surgical-pathological staging showed downstaging in 18 patients including complete sterilization of the tumor in 8 patients (30%) and necrosis >90% in 54%. The median survival for all 34 patients was 18.4 months with 25% 5-years survivors. Final chemoradiation mean Hb values were positive correlated with radiological response (p= 0.026).

Conclusions: This neoadjuvant chemoradiotherapy treatment has a tolerable and survival-enhancing multimodality approach to stage III NSCLC.

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Quantitative analysis of LUN expression, trans-activator of e-cadherin gene

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Background: We isolated cDNAs encoding a novel RING finger protein (LUN), the mRNAs of which were expressed at high level in the lung. And lun gene locus was assigned to chromosome 9p21. *In situ* hybridization revealed that lun mRNAs were expressed in the alveolar epithelium of the lung. Lun gene consists of three exons. And two types of splicing valiant to contain exon2 or not were identified. Furthermore, we identified a novel palindromic binding consensus (5'-TCCCAGCACTTTGGGA-3') for LUN protein. Interestingly, one of LUN binding sequences is found in the upstream transcriptional regulatory region of the e-cadherin gene. And we showed that LUN *trans*-activated the promoter activity of e-cadherin 5' regulatory regions *in vitro*. In the present study, we examined quantitative analysis of lun expression in cell lines and surgical specimens of lung cancer patients.

Material and methods: Real-time RT-PCR assay was performed in 13 lung cancer cell lines (A549, PC14, H522, H441, H23, H520, H1299, H460, Lu99, H69, H128, H146, H209), normal human lung fibroblasts (NHLF) and surgical specimens of lung cancer patients (n=51).

Results: The analysis of cell lines did not reveal any characteristic tendency of lun expression among cell types. On the other hand, in the patients, the levels of lun mRNA expression were significantly reduced in the tumor tissues compared to in the normal lung tissues. The ratio of them in tumor tissue / normal tissue of each patient was 0.45 on average. In addition the lun mRNA expression was negatively correlated to the pathological stage, especially LN metastasis. And lun mRNA expression in normal lung of the smokers was lower than non-smokers.

Conclusions: We showed that lun mRNA expression was reduced in the advanced lung cancer tissue. Our results suggested that LUN might play a role of tumor suppressor with *trans* -activating e-cadherin expression.

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Elderly patients (pts) with unresectable localised or metastatic non-small-cell-lung-cancer (NSCLC): results of a phase II study with oral navelbineâ (nvb) given as a weekly monotherapy and first line treatment

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Background: Intravenous NVB as monotherapy has proven to be effective in elderly NSCLC population with reduced toxicity. This phase II was

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.

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

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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.

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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

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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.

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

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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