812 POSTER

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.

813 POSTER

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.

814 POSTER

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.

815 POSTER

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