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Cisplatin and etoposide (EP-regimen) is superior to cyclophosphamide, epirubicin, and vincristin (CEV-regimen) in small cell lung cancer: results from a randomized phase III trial with 5 years follow-up

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Purpose: To investigate whether chemotherapy with etoposide and cisplatin (EP) is superior to cyclophosphamide, epirubicin, vincristine (CEV) in the treatment of patients with small cell lung cancer (SCLC).

Methods: 436 eligible patient were randomized to chemotherapy with EP (N=218) or CEV (N=218). The patients were stratified according to extent of disease [218 limited disease (LD); 214 extensive disease (ED)]. The EP group received 5 courses of etoposide 100 mg/m2 IV and cisplatin 75 mg/m2 IV on day one, followed by oral etoposide 200 mg/m2 daily on day 2-4. The CEV group received 5 courses of epirubicin 50 mg/m2, cyclophosphamide 1000 mg/m2, and vincristine 2 mg, all IV on day one. In addition, LD patients received thoracic radiotherapy concurrent with chemotherapy cycle 3, and those achieving complete remission during the treatment period received prophylactic cranial irradiation.

Results: The treatment groups were well balanced with regard to age, gender, and prognostic factors such as weight loss, performance status, and biochemical markers. For all patients, the 2- and 5-year survival in the EP arm (14% and 5%, P=0.0004) were significantly higher as compared to the CEV arm (6% and 2%). Among LD patients, the median survival time was 14.5 months versus 9.7 months in the EP and CEV arm, respectively (P=0.001). The 2- and 5-year survival of 25% and 10% in the EP arm compared to 8% and 3% in the CEV arm (P=0.0001). For ED patients there was no significant survival difference between the treatment arms. The quality of life (QoL) assessments revealed no major differences between the randomized groups.

Conclusion: The EP-regimen is superior to the CEV-regimen in LD-SCLC patients. In ED-SCLC patients, the benefits of EP and CEV chemotherapy appear equivalent with similar survival time and QoL.

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First - line chemotherapy in SCLC: a phase III study of taxol, etoposide phosphate and carboplatin (TEC) versus carboplatin, etoposide phosphate and vincristin (CEV)

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Introduction: Paclitaxel, Carboplatin and Etoposide has shown great activity combined with a very moderate toxicity profile in first-line treatment of SCLC. We now established a Phase III trial to compare efficiacy and toxicity of TEC with the standard regimen Carboplatin, Etoposide and Vincristin (CEV).

Methods: From 2/1998 to 11/1999 we enrolled 615 chemonaive patients with SCLC. 306 patients (group A) were randomized to receive Paclitaxel 175 mg/m2 IV (3h) day 4, Etoposide Phosphate 125 mg/m2 IV day 1-3 and Carboplatin AUC 5 IV day 4. 309 patients (group B) were randomized to receive Carboplatin AUC 5 IV day 1, Etoposide phosphate 159 mg/m2 IV day 1-3 and Vincristin 2 mg IV day 1 and 8. Patients with Stage IV disease received a lower dose of Etoposide Phosphate because of safety reasons (group A: 102,2 mg/m2, group B: 125 mg/m2). Treatment courses were repeated every 21 days up to 6 cycles. Eligibility criteria included chemonaive SCLC (stage I-IV), an adequate renal, hepatic and hematologic function and a performance status according to ECOG 0-2.

Results: Both groups were well balanced with 50% stage I-IIIb patients and 50% stage IV patients in each group. In group A we observed a response rate of 81.8% (CR 19.3%) and in group B a response rate of 76.3% (CR 16.6%). There was no statistical significant difference between the groups. Up to now survival data are not available but they will be presented at the meeting. Hematologic toxities (CTC-grade 3 + 4, % of courses) were as follows: TEC: Neutropenia 45.8%, febrile Neutropenia 2.9%, Anemia 1.8%; CEV: Neutropenia 47.9%, febrile Neutropenia 4.0%, Anemia 5.8%. Following non-hematologic toxicities (CTC-grade 3 + 4, % of courses occurred: TEC: PNP 0.7%, pain 0.7%, nausea 0.9%; CEV: PNP2.2%, pain 1.4%, Nausea 0.7%.

Conclusion: Both regimens showed high activity in treatment of SCLC with a comparable low toxicity profile. Further efficacy data will be presented at the meeting.

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Cancer-associated molecular alterations in bronchial epithelium of former Chernobyl cleanup workers in comparison with smokers and nonsmokers without ionizing radiation exposure

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Purpose: Earlier it has been shown a considerable link between chronic respiratory problems in former Chernobyl cleanup workers (FChCW) and persistence of the inhaled radioactive particles in their lungs (Chuchalin et al, 1997). Since ionizing radiation is suspected to be a potent lung carcinogen, we questioned whether cancer-related molecular abnormalities could be detected in their bronchial epithelium.

Methods: k-ras mutations, p16INK4a promoter hypermethylation, and LOH and MI involving 14 microsatellite markers were investigated in multiple successive biopsies obtained from 43 FChCW (36 smokers and 7 nonsmokers) with evidence of inhaled radioactive dust in their lungs. Control group included 21 smokers and 23 nonsmokers who have never had radiation exposure.

Results: 1) LOH and MA at any chromosomal locus, p16INK4a promoter hypermethylation, and k-ras mutations were detected in 60.9%, 23.4%, 15.6%, and 7.8% of the subjects with a history of any carcinogen exposure, respectively. No molecular alterations were detected in nonsmokers who have never had radiation exposure. 2) FChCW exhibited more frequent allelic loss than the control group of smokers in five out of 7 loci investigated and the difference between these two groups was significant for LOH at 3p14.2 (FHIT), ($p<0.05$). 3) Frequency of molecular alterations corresponded to the severity of histopathologic changes with significant rise occurred at dysplasia stage. In all groups of subjects LOH at 3p12, 3p21, 3p22-24 (hMLH1), 9p21 (p16INK4a) and MI at any locus were early events frequently detected in histologically normal or mildly abnormal (hyperlasia or metaplasia) epithelium. Allelic loss at 3p14.2 (FHIT), 3p25 and 17p13 (TP53), p16INK4a promoter hypermethylation, and k-ras mutations that were strongly associated with dysplasia lesions. 4) Frequency of molecular abnormalities was significantly higher in normal or mildly abnormal epithelial foci that would subsequently progressed to dysplasia than in those without evidence of such progression. 5) Comparative RT-PCR showed significant concordance between decreased mRNA expression and molecular alterations for FHIT, hMLH1 and p16INK4a genes. 6) Occurrence of MI at any locus correlated with both hMHL1 reduced expression and 3p22-24 allelic loss (both $p<0.05$).

Conclusion: FChCW have distinct spectrum of molecular alterations in their bronchial epithelium. Similar to smokers they are at high risk of lung cancer.

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Single-agent versus combination chemotherapy in advanced non-small cell lung cancer (NSCLC): A CALGB randomized trial of efficacy, quality of life, and cost-effectiveness

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Combination chemotherapy is considered the standard of care for patients with advanced NSCLC and good performance status. However, data from selected randomized trials and meta-analyses do not conclusively demonstrate that, despite higher response rates, combination regimens produce superior survival compared to optimal single-agent therapy. For example, phase II studies of paclitaxel (P) in advanced NSCLC showed 1-year survival rates of approximately 40%, clearly comparable to the newer platinum-based combination regimens. Furthermore, data on the impact of combination versus single-agent therapy on quality of life (QoL) and economic resources are conspicuously lacking. Therefore, CALGB performed a phase III randomized trial of carboplatin (C) and P (CP) vs. P alone in patients (pts) with stage IIIB (malignant pleural effusion) and IV NSCLC to compare survival, QoL, and cost-effectiveness. Eligible pts were required to have measurable of evaluable disease, PS 0–2, no brain metastases, and adequate organ function. Pts were stratified by stage (IIIB vs. IV vs. recurrent), PS (0–1 vs. 2), and age (<70 vs. ≥70). Treatment arms consisted of P