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SURGERY FOLLOWING NEOADJUVANT CHEMOTHERAPY (CISPLATIN, VEPESID) IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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The efficacy of surgery for patients with locally advanced non-small cell lung cancer is limited. From February 1993 to September 1994 32 patients with non-small cell lung cancer (NSCLC) entered a multimodality treatment study with neoadjuvant chemotherapy (Cisplatin+Vepesid) and surgery at Department of Cardiothoracic Surgery in a Medical Academy in Lublin, Poland. Twenty five patients (22 stage IIIa and 3 stage IIIb) have completed the chemotherapy and are available for evaluation of response, toxicity, surgical eligibility and resection rate. The objective response rate to chemotherapy was 56%. The chemotherapy was well-tolerated. Twenty two patients (88%) had a complete resection. No treatment-related mortality was observed. The postoperative complications were observed in 5 of 22 (23%) complete resected cases. After a median follow-up of 16 months (3-32) 15 patients are still alive (60%). The authors conclude that Cisplatin and Vepesid is an effective neoadjuvant regimen for NSCLC in stage III. Applied regimen was not connected with increasing rate of postoperative complications. A longer follow-up is needed to assess the impact of this multimodality approach on long-term survival.

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FREQUENT REPLICATION ERRORS AT MICROSATELLITE LOCI ON CHROMOSOMES 2P AND 3P IN NON-SMALL CELL LUNG CANCER.

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Replication errors (RER) and/or losses of heterozigosity (LOH) on short tandem repeats, have been observed in a variety of tumors including non-small cell lung cancer (NSCLC). We addressed whether alterations on simple (CA)n repeats located on the short arms of chromosomes 2 and 3 occur at early stages of NSCLC, and whether such alterations are related to other genetic aberrations such as K-ras and p53 gene mutations, as well as their prognostic value. Using PCR assay, we analyzed both RER and LOH on 3 dinucleotide repeat markers on chromosome 2p (D2S162, D2S391 and D2S136) and 5 markers on chromosome 3p (D3S1038, D3S1611, D3S1289, D3S1067, and D3S1284) in 64 paired tumor-normal DNA samples from consecutively resected stage I, II, and IIIA NSCLC patients. Samples were also examined for K-ras and p53 gene mutations by PCR-single stranded conformational polymorphism analysis. Forty-two of the 64 (64%) NSCLC patients showed RER at single or multiple loci. RER occurred similarly in all stages and no correlation with clinicopathological characteristics was found. LOH was detected in 23 tumors (36%). The 5-year survival of stage I patients was 80% in those whose tumors were RER negative, and 26% in those with RER (P=0.005). No relationship was established between RER and LOH, K-ras or p53 mutations, nor did these genetic aberrations relate significatly to poorer survival. RER remained a strong predictive factor (hazard ratio, 2.89; 95% confidence interval, 2.23 to 3.79; P=0.002) for all other examined factors such as p53, K-ras, LOH, histology, TNM stage, and tumor differentiation. So, RER are frequent in NSCLC even at early stages and may suppose an important prognostic value.

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LOSS OF HETEROZYGOSITY (LOH) AT 5q21 AND PROGNOSIS IN RESECTED NON-SMALL CELL LUNG CANCER (NSCLC).

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Chromosome 5 appears to be an important target in the pathogenesis of neoplasms including NSCLC. These abnormalities include frequent LOH at 5q21 which contains the APC and MCC genes. We analyzed the frequency and clinical relevance of LOH at the APC/MCC loci in 60 cases of resected NSCLC. Tumor and normal DNA were amplified by PCR at two microsatellite markers: D5S82 (APC gene) and MCC (within MCC gene). Polymorphic PCR products were resolved by electrophoresis through 6% denaturing polyacrylamide gels. Forty-one of the 60 stage I-IIIA NSCLC were informative (heterozygous for LOH analysis at the APC and/or MCC loci). LOH at the APC/MCC loci was found in 20% (8 of 41). No significant differences of LOH were observed among histological types (15% in squamous cell carcinoma and 36% in adenocarcinoma). LOH at 5q was higher in stage IIIA (40%) than in earlier stages (16%) and a trend towards worse survival was detected in stage IIIA patients with LOH at 5q (9 months median survival time) in comparison with patients without LOH (21 months). In addition, LOH was not found to be linked to a higher frequency of mutations affecting K-ras and p53 genes. Our findings underline that LOH at 5q21 plays a role in NSCLC progression and could help to identify resected NSCLC patients with poor prognosis.

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THE ALPI TRIAL: A RANDOMIZED STUDY OF ADJUVANT CHEMOTHERAPY FOR STAGE I-II-IIIA NON-SMALL CELL LUNG CANCER (NSCLC).

G Scagliotti on behalf of the Adjuvant Lung Project Italy (ALPI) trial.

In spite of over 20 studies published so far, the therapeutic role of adjuvant therapy in non-small cell lung cancer is still unsettled. Against this background, in January 1994 a large randomized trial (Alpi trial) was launched in Italy. The primary aims of this trial were to establish the survival gains from adjuvant MVP chemotherapy (Mitomycin C 8 mg/mq on day 1, Vindesine 3 mg/mq on days 1 and 8, Cisplatin 100 mg/mq on day 1 given every 3 weeks for 3 cycles) and to describe the impact of treatment toxicity on patients with NSCLC. Alpi protocol mandates that the referral of patients for postoperative radiotherapy be left to the discretion of the participant centre. Radiotherapy should be timetabled to begin after completing the chemotherapy. Radiotherapy should begin between the 22nd and 35th day since the end of chemotherapy cycles. For patients in the control arm, radiotherapy should begin between the 29th and 42nd day since surgery. Planned total dosage is 50-54 Gy in 5-6 weeks according to the chosen fractioning scheme. The study is planned to detect a 20% relative reduction in mortality for patients undergoing adjuvant MVP with 80% power at the 5% level of significance. Assuming a death rate of 50% at 5 years, it is established that 1500 patients would be necessary. As December 1995, a total of 499 patients have been enrolled into the study by 54 general hospitals across Italy. Patients' characteristics were as follows: median age 62 years; males = 89%; Stage I = 38%, Stage II = 21%, Stage IIIA = 41%; Adenocarcinoma = 44%, Epidermoid = 48%, Large cell = 4%, Bronchioloalveolar = 4%. One hundrend forty five patients randomized to MVP were evaluable for toxicity assessment:: adjuvant chemotherapy was completed in 103 (71%), was interrupted for toxicity in 10 and refused in absence of severe toxicity by 11 patients; two patients discontinued treatment for death. Twenty-eight percent of patients experienced grade 3 toxicity, while grade 4 toxicity accounted for 11% of patients. Radiotherapy was delivered in 210 patients: respectively in 9%, 55% and 67% of stages I, II & IIIa. Among the patients that underwent radiotherapy, mucositis was observed 45% of patients, (WHO III-IV in1.3%).
At a median follow-up of 12 months 54 relapses and 36 deaths occurred. At one year Event Free and Overall Survival are 60% and 74% respectively.

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MITOMYCIN C, VINORELBINE, CARBOPLATIN AND Gm-CSF FOR TREATMENT OF ADVANCED NON SMALL CELL LUNG CARCINOMA (NSCLC)

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Twenty-one patients (13 males, 8 females; median age 56 years, range 20 to 75; median WHO performance status 1, range 0-2) with non resectable NSCLC (stage III B: 6, stage IV: 15) were treated with an intravenous combination chemotherapy regimen consisting of mitomycin C 8 mg/m2 on day 1, vinorelbine 40 mg/m2 on days 1 + 21, carboplatin 250 mg/m2 on days 1 + 21, and GmCSF 5 mcg/kg administered subcutaneously from days 2 to 8 and 22 to 28. Treatment cycles were repeated every 6 weeks. Until today, 17 patients are evaluable in terms of toxicity and response assessment, and 4 cases are too early. A total of 60 courses was administered. Overall objective response was noted in 7 patients (41 %), including 2 complete and 5 partial responses. There was no change in 6 patients, and 4 had progressive disease. Median duration of response, time to progression, and survival have not been reached yet. Myelosuppression was the most frequently encountered adverse reaction, though WHO grade 4 leukopenia/granulocytopenia and/or grade 3 thrombocytopenia necessitating a 25 % dose attenuation occurred in only 4 patients. Non hematologic side effects were generally mild and reversible, and included nausea/emesis in 47%, alopecia in 35%, peripheral neuropathy and constipation both in 17%, and infections in 23%. Preliminary results suggest an encouraging therapeutic index for this combination regimen in advanced NCSLC and encourage the recruitment of a larger number of patients.

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IFOSFAMIDE, CISPLATIN AND ETOPOSIDE (ICE) COMBINATION IN LOCALLY ADVANCED NON SMALL CELL LUNG CANCER (NSCLC): A PHASE II STUDY.

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The present study evaluates both the activity and the toxicity of an ifosfamide-containing regimen (ICE) for the initial treatment of locally advanced inoperable NSCLC.
From March 1993 to today, 33 patients (pts.) with unresectable stage IIIA (6 pts.) or IIIB (27 pts.) histologically confirmed NSCLC (squamous: 20 pts., adenocarcinoma: 11, other: 2), median age of 58 yrs. (range: 38-76), male/female: 27/6, median WHO PS: 0 (range: 0-2) were treated with 3 cycles of the combination of ifosfamide (1.5 gr/m^2 i.v. on days 1-3 and mesna 800 mg/m^2 i.v. three times/day on days 1-3), every 3 wks. with prophylactic rHu-metG-CSF (5 µg/kg/d s.c. on days 6-14). Responder patients underwent surgery if resectable or received two additional courses of chemotherapy and/or curative radiotherapy; cross-over chemo- or radiotherapy was given to non-responders.
Treatment was well tolerated. Grade 3-4 (WHO) neutropenia occurred in 16/65 evaluable cycles (25%) but it was of short duration, leading to Grade 2 neutropenic fever in only 6/65 cycles (9%). Grade 3-4 thrombocytopenia occurred in 8 cycles (12%). Non-hematological toxicity was generally mild. Dose-reductions were required in 7/53 cycles (13%). The overall response rate after three cycles of chemotherapy was 71% in 31 evaluable pts. (21 PRs, 1 CR); 5 pts. (16%) had SD and 4 (13%) had PD. Five pts. (4/5 IIIA, 1/26 IIIB) underwent radical surgery after chemotherapy and 4 remained NED at 24*, 9*, 7* and 5* months.
Preliminary data suggest that ICE is active in locally advanced NSCLC, with acceptable toxicity even in an out-patient setting.