terms of histological subtypes there was significant difference only in the number of SC-Ca pts vs non-SC-Ca & high serum CA-125(10/35 vs 36/66, $p<0.05$). Among the stages of the main histological subtypes, there was statistically significant correlation between high serum Cyfra 21.1 in A-Ca pts IIIb+IV (21/40 vs 4/15, $p<0.05$) & NSE in SC-Ca pts IIIb+IV (14/19 vs 4/16, $p<0.01$). All pts received platinum based chemotherapy, 88(88%) completed at least 3 cycles & were reevaluated. Overall response (OR) was documented in 33(37.5%) of them. Increased pretherapeutic vs normal values of CEA & NSE were correlated with poorest OR (10/39 vs 23/49, $p<0.05$ & 10/43 vs 23/45, $p<0.01$ respectively).

Conclusions: In NSCLC pts: 1. NSE, CA-125 & Cyfra 21.1 were the markers with the highest sensitivity, 2. Women had more often high CA-125, 3. A strong correlation between CEA, NSE, CA-125 & Cyfra 21.1 & stages IIIb+IV was observed, 4. About 34% of pts IIIb+IV had at least 4 high markers, 5. Stages IIIb+IV of A-Ca & SC-Ca unlike IIIa, correlated with elevated Cyfra 21.1 & NSE respectively, & 6. CEA & NSE seemed to have predictive usefulness for the outcome.

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Phase I study with topotecan and simultaneous radiation in patients with non small cell lung cancer stage III B

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Background: Topotecan is a specific inhibitor of topoisomerase I which has demonstrated activity against non small cell lung cancer (NSCLC). Preclinical investigations and a phase I clinical trial with topotecan and concurrent radiotherapy suggest a potential radiosensitization effect of topotecan. Patients and Methods: The objective of this phase I trial was to determine the safety profile, dose limiting toxicities, maximum tolerated dose and the recommended dose for subsequent phase II trials of topotecan administered as a 120 h continuous infusion with simultaneous radiotherapy in patients with NSCLC stage III B and limited stage IV. A total of 21 patients with newly diagnosed inoperable NSCLC were enrolled. Cohorts of 3 to 6 patients each were given topotecan i.v. as a 120 h continuous infusion from day 1 to day 5. Topotecan infusion was repeated from day 22 to 26. The dose was subsequently escalated from 0.2 mg/m2/day to 0.4, 0.5, 0.6, 0.7, 0.8 mg/m2/day until the maximum tolerated dose was reached. 3D-planned radiotherapy was administered in daily fraction of 2.0 Gy, 5 days a week up to a total dose of 50 Gy followed by a boost of 10 Gy.

Results: Forty cycles were given at 6 dose levels: 6 at 0.2 mg/m2/day, 6 at 0.4 mg/m2/day, 8 at 0.5 mg/m2/day, 7 at 0.6 mg/m2/day, 11 at 0.7 mg/m2/day, 2 at 0.8 mg/m2/day. The maximum tolerated dose was determined at 0.7 mg/m2/day, based on non-haematological dose limiting toxicities in two out of six patients (tumor bleeding, pneumonia, cardiac failure and sepsis). Since no episodes of dose limiting haematological toxicity were encountered we defined the dose level 0.7 mg/m2/day as maximum tolerated dose. Preliminary response data are available from 15 patients: 8 patients experienced partial response, 2 patients had stable disease, and in 5 cases tumor progression was observed.

Conclusion: The recommended dose for subsequent phase II studies of topotecan given as a 120 h continuous infusion in combination with thoracic radiation therapy is 0.7 mg/m2/day.

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Novel DAF variants in human lung and non-small cell lung cancers

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Background: Decay-accelerating factor (DAF, CD55) is a member of the family of proteins involved in regulation of the complement activation. It was reported that DAF enhanced in the tumors such as colorectal cancer. The physiological meanings of its up-regulation is still unknown, although it is speculated that the increased DAF plays a role in protection of tumor cells from autologous complement attack. Two isoforms of hu man DAF are reported: one is glycosylphosphatidylinositol (GPI)-anchored membrane protein and the other is soluble form produced from the same gene by alternative splicing. In the present study, we isolated novel splicing variants of human DAF to elucidate the physiological and pathological roles of DAF variants in tumors.

Material and methods: The cDNAs of DAF variants were amplified by RT -PCR using human lung cDNA as a template, and the nucleotide sequences of the resulted PCR products were determined. Expression sites of the DAF variants were determined by RT -PCR and Northern blots. The cellular location sites of DAF variant proteins were assessed by transfection of the cDNA constructs into CHO cells. DAF protein in the transformants was detected by Western blots and immunostaning and the soluble form of DAF in culture medium was detected by ELISA. The level of DAF variant mRNA were determined in non-small cell lung cancers (NSCLC) and the normal tissues by RT -PCR.

Results: Novel three isoforms of DAF, termed variants 1, 2 and 3, were isolated, which are produced from the human DAF gene by alternative splicing. The nucleotide sequences revealed that they include three new exons located between exons 9 and 11. Based on hydrophilicity plots of the deduced amino acid sequences, all variants seem to be not membrane-bound form. DAF variant mRNAs were detected in almost tissues tested at different levels. In transfection experiments, Western blots confirmed the production of all variant proteins in CHO cells. The soluble forms of DAF were detected when using the cDNA constructs of variants 1 and 3. Immunostaning revealed that DAF variant proteins were present in the cytosol of CHO cells and not on the cell surface. As compared to normal lung, NSCLC tissues showed distinct expression pattern of DAF variants.

Conclusions: Novel three splicing variants of DAF were isolated from human lung, which include novel three exons. Two of the three encode the soluble forms of DAF. Pathological role of DAF variants in NSCLC is under investigation.

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Multicenter phase II study of gemcitabine-oxaliplatin (GEMOX) chemotherapy in untreated locally advanced or metastatic non-small cell lung cancer (NSCLC) patients

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Background: Platinum-based chemotherapy is considered the standard treatment of advanced NSCLC. Oxaliplatin (OX) is active against NSCLC and the low incidence of severe hematologic toxicity makes it an attractive compound for combination with other anticancer drugs. Gemcitabine (GEM) is considered one of the most active drugs against NSCLC and preclinical studies show a synergistic effect when combined with OX.

Patients and Methods: Chemonaive patients (pts) with locally advanced or metastatic NSCLC were eligible for this phase II multicenter study. GEMOX therapy consisted of GEM on days 1 and 8 at the dose of 1000 mg/m^2 as a 30-min IV infusion, followed by OX at the dose of 130 mg/m^2 on day 1, every 21 days for 2-8 cycles.

Results: From February 2002 to December 2002, 54 pts were enrolled. At the time of this analysis, data from the first 36 pts are available, including the following characteristics: median age of 62 yrs (range, 36-73,); male/female: 24/12; stage IIIB/IV: 6/30; and ECOG PS of 0-1 in all 36 pts. The main histology types were adenocarcinoma in 16 (44%) pts and squamous cell in 10 (28%) pts. Response rate was evaluated on the first 25 pts. So far, a total of 94 cycles (range, 1-6) has been administered. We observed 5 (20%) partial responses and 9 (36%) patients with stable disease. The main WHO toxicities, evaluated on 39 pts and on the first 61 cycles, were hematologic, consisting of grade 3/4 neutropenia in 4/1 cycles and grade 3 thrombocytopenia in only 1 cycle. Grade 3 non-hematologic toxicities consisted of nausea/vomiting in 3 cycles, and neurotoxicity, skin toxicity, and asthenia in 1 cycle each. Because of side effects, 2 pts withdrew consent (1 for grade 3 neurotoxicity and 1 for grade 3 vomiting).

Conclusions: At this time, although analyses are ongoing, the combination of GEMOX appears active with a manageable toxicity profile. Definitive data will be ready for the meeting