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Pharmacodynamic study of serum EGFR and HER2 in patients with non-small cell lung cancer treated with ZD 1839

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Background: HER2 expression has been correlated with response to ZD183, and the decrease in EGFR expression during ZD1839 treatment has already been documented. However, the possible role of circulating EGFR and HER2 in response to ZD1839 is unknown. The aim of this study was to assess i) serum EGFR and HER2 as pharmacodynamic markers of ZD1839; ii) to evaluate their role as predictors of response to ZD1839 in NSCLC patients (pts).

Patients and methods: Serum samples were collected at following times: within 1 week before the 1st dose of 250 mg ZD1839, as close to day-28 ± 2 (steady-state plasma ZD1839 concentrations achieved) and at every CT-scan evaluation. EGFR and HER2 serum levels were detected by ELISA (Oncogene Science commercial kit). A logistic regression analysis was used to evaluate i) the association between the best response (BR) and the differences of EGFR and HER2 levels obtained at the best CT-scan and at baseline ii) the relationship between BR and basal EGFR and HER2 levels.

Results: 46 pre-treated pts were evaluated from 06/2002 to 02/2003. Pts median age was 65 years (36-90), F/M 11/35, PS 0/1/2 11/31/4, IIIB/IV 11/35, adenocarcinoma/bronchiolar-alveolar/non-adeno NSCLC 26/3/17. At median follow-up time of 6.7 months, 23 pts are alive, 15 are still on treatment. Eleven pts who died within 28 days of treatment were considered as progressive disease (PD) for predictive analysis. In pts treated for >28 days, 5 partial responses (14%), 14 stable disease (40%) and 16 PD (46%) were observed. Median pre-treatment EGFR and HER2 values were: 90 ng/ml (52-170) and 12 ng/ml (1.3-39). The difference between the best CT-scan and basal EGFR values (median 15 ng/ml, range -9 to 70) was predictive for response with 3% increase in the probability of progression for an increase of 1 ng/ml (Odds Ratios (OR) 1.03, 95% 1.01-1.05, p=0.01). No predictive effect on BR was detected for HER2 serum changes. For BR OR the of progression for HER2 were 0.87 (95% CI 0.74-1.03; p=0.11) and 0.96 (95% CI 0.93-0.99; p=0.03) for EGFR.

Conclusion: Modifications of EGFR serum values during treatment seem to reflect ZD1839 activity and appear more predictive than pre-treatment values alone. Mature results of this study will assess the possible role of these parameters in monitoring the disease status.

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Pretreatment clinical prognostic factors influencing survival in patients with stage III non-small cell lung cancer (NSCLC) treated with hyperfractionated radiation therapy (HFX RT) with or without concurrent chemotherapy (CHT)

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Purpose: To investigate influence of various pretreatment clinical factors on survival in patients with stage III NSCLC.

Material and Methods: During a six-year period, three prospective randomised phase III and one prospective phase II study were performed enrolling a total of 536 patients treated with Hfx RT (64.8 or 69.6 Gy; 1.2 Gy b.i.d.) alone or with concurrent CHT consisting of carboplatin and etoposide. Variables examined included gender, age (< 60 years vs. ≥ 60 years), KPS (50-70 vs. 80-100), weight loss (≤ 5% vs. > 5%), and stage (IIIA vs. IIIB).

Results: The median survival time (MST) for all 536 patients is 18 months and 5-year survival is 18%. On Kaplan-Meier survival analysis females did better than males (MST, 27 vs 15 months; 5-year survival, 35% vs 10%; p<0.0001), while age did not influence survival (p=0.3837). Patients having a KPS of 50-70 did significantly worse than those having a KPS of 80-100 (MST, 8 vs 24 months; 5-year survival, 0 vs 24%; p<0.0001), as well as did those with weight loss of > 5% when compared to those having weight loss of ≤ 5% (MST, 12 vs 32 months; 5-year survival, 5% vs 35%; p<0.0001). Finally, stage significantly influenced survival favouring patients having stage IIIA (MST, 26 vs 12 months; 5-year survival, 28% vs 9%; p<0.0001). When Cox univariate model was used only age did not predict survival, confirmed by the full and best multivariate model identifying female gender (p<0.0001), KPS 80-100 (p<0.0001), weight loss ≤ 5% (p<0.0001), and Stage IIIA (p<0.0001) as important predictors of improved survival.

Conclusions: This study showed that only age was not shown to influence survival in patients with locally advanced NSCLC treated with Hfx RT with or without concurrent CHT

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A meta-analysis of efficacy data from two randomised studies on oral topotecan in patients with relapsed SCLC

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Background. Topotecan is established in the treatment of relapsed small cell lung cancer (SCLC). The oral formulation is well characterised and its use offers advantages over the IV formulation; in particular, removing the need for repeated daily dosing over 5 days.

Materials and Methods. Two randomised studies have been conducted in which the tolerability and efficacy associated with oral topotecan have been compared to those associated with IV topotecan [1,2]. Because these studies were conducted on the basis of similar patient selection, treatments, and evaluations, meta-analysis of the data is appropriate.

Results. The primary endpoint of each study was response rate. Response rates were evaluated by independent, blinded radiological review, which were strictly and objectively measurable at baseline. Response rates and median survival for each study individually and pooled are shown in the table below:

Study	CR	PR	Total Response	Median Survival (weeks, 95% CI)
Randomised Phase II [1]				
oral topotecan (n=52)	1	11	23%	32.3 (26.3, 40.9)
IV topotecan (n=54)	2	6	15%	25.1 (21.1, 33.0)
Randomised Phase III [2]				
oral topotecan (n=153)	2	26	18%	33.3 (29.1, 42.4)
IV topotecan (n=151)	0	33	22%	35.0 (31.0, 37.4)
Pooled Data				
oral topotecan (n=205)	3	37	20%	32.7 (29.9, 41.0)
IV topotecan (n=205)	2	39	20%	33.6 (29.7, 35.6)

Outcomes to therapy and tolerability parameters will be presented.

Conclusion. This meta-analysis confirms that oral topotecan is as active as IV topotecan in the treatment of relapsed SCLC.

References

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Evaluation of six serum tumour markers in patients with non-small cell lung cancer

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The aim of the study was to prospectively evaluate the incidence & prognostic impact of serum CEA, NSE, Ca-125, SCC, TPS & Cyfra 21.1 in 101 Non Small Cell Lung Cancer (NSCLC) patients (pts), before & at the end of treatment.

Patients: There were 85(84%) men & 16(16%) women, median age 60y(40-78), consecutively admitted in our Unit, between 6/99-1/03. Stage IIIa had 33(33%) & IIIb+IV 68(67%) pts. Adenocarcinoma (A-Ca) had 55(54%), Squamous Cell (SC-Ca) 35(35%), Large Cell 8(8%) & Undifferentiated Carcinoma 3(3%) pts.

Results: Pretherapeutic high values of CEA, NSE, Ca-125, SCC, TPS & Cyfra 21.1 were observed in 43(43%), 47(47%), 46(46%), 29(29%), 40(40%) & 45(45%) pts respectively. Four or more high serum tumour markers were found in 26(26%) pts. In terms of gender, women had more frequently (12/16 vs 34/85, p<0.05) higher serum CA-125. There was significant correlation between pts of stages IIIb+IV in comparison with stage IIIa & high CEA (36/68 vs 7/33, p<0.01), NSE(38/68 vs 9/33, p<0.01), CA-125(37/68 vs 9/33, p<0.01) & Cyfra 21.1(35/68 vs 10/33, p<0.05). There was a strong association between the number of pts with more than 3, high markers & stages IIIb+IV (23/68 vs 3/33, p<0.01). In

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