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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