5BA Best Abstracts

Clinical validation of in vitro drug sensitivity microarray data: regimen-specific signatures predict pathological complete response to neo-adjuvant chemotherapy for breast cancer in a randomized trial (EORTC 10994/BIG 00-01)

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Background: We recently described gene expression signatures that predict sensitivity to common chemotherapeutic agents (Nature Med 2006). The goal of this study was to confirm their validity in a large series of breast cancer patients with estrogen-receptor negative (ER negative) since these tumours are more sensitive to chemotherapy. We used pathological complete response (pCR) as a surrogate for chemosensitivity. We analyzed samples from a subset of patients included in a recently completed large neoadjuvant phase III trial. The trial compares a non-taxane regimen (fluorouracil + epirubicin + cyclophosphamide $\times$ 6; FEC arm) with a taxane regimen (docetaxel $\times$ 3 then epirubicin + docetaxel $\times$ 3; T $\rightarrow$ ET arm).

Methods: RNA prepared from frozen samples obtained at diagnosis were hybridized to Affymetrix arrays. In vitro single agent signatures generated were combined to obtain a FEC and a T $\rightarrow$ ET regimen-specific signature. Predictions were blinded to patient outcome. With both signatures we calculated the receiver operating curve, its AUC, accuracy, positive predictive value (PPV), sensitivity (Sens), negative predictive value (NPV) and specificity (Spec).

Results: Samples from 125 patients (55 pCR) with ER negative tumours underwent a successful gene-expression array: 66 patients were treated in FEC arm and 59 patients in T $\rightarrow$ ET arm. The results are summarized in the table. Analysis of tumor size, grade, nodal status, age and the regimen-specific signatures showed that the genomic signatures were the only independent variables predicting response.

Specific signature to:	AUC	CI	P	Accuracy (%)	PPV (%)	Sens (%)	NPV (%)	Spec (%)
FEC	0.86	0.76–0.94	<0.001	79	68	96	96	66
T $\rightarrow$ ET	0.85	0.74–0.94	<0.001	80	71	93	92	69

Conclusions: We have validated the use of regimen-specific drug sensitivity signatures in the context of a multicenter randomized trial. Selection of patients with these signatures would increase the pCR rate from 44% to around 70% in the patient sample tested here. The high NPV of both signatures indicates the potential to select patients who should be considered for trials with new agents.