ABSTRACT #: P2-10-06

Identifying Patients Sensitive to Anthracycline-containing Therapy with Quantitative Proteomic and Genomic Profiling

CONTRIBUTING RESEARCHERS

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BACKGROUND

- Selecting chemotherapy based on tumor biology can improve response rates and avert toxicity.
- Studies of the relationship between tumor expression of DNA topoisomerase 2-alpha (TOP2A) protein and response to anthracycline-based chemotherapy have yielded contradictory results.
- p16 is associated with outcomes in breast and gastric cancers. Preclinical studies suggest that low expression of p16 may predict response to CDK4/6 inhibitors in retinoblastoma (Rb)-proficient tumor cells.
- Indoleamine 2,3-dioxygenase (IDO) is an enzyme that catalyzes the rate-limiting first step in tryptophan catabolism and is a negative immune regulator. IDO1 protein expression was suggested as a negative prognostic marker in cancer.
- We used mass spectrometry (MS) to evaluate associations between tumor molecular profiles and pathologic complete response (pCR) in breast cancer patients treated with or without neoadjuvant anthracycline-containing therapy or all comers.

METHODS

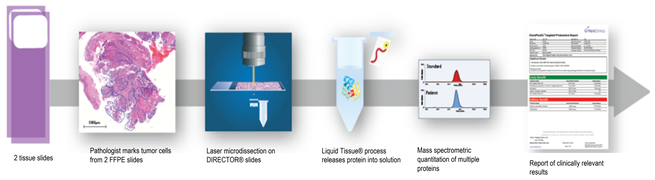

Figure 1.Clinical mass spectrometry. Archived breast cancer samples from the ERNEST-B (Erlangen Neoadjuvant Study Breast) cohort (n=453) were microdissected and solubilized. Multiple protein biomarkers including TOP2A, p16 and IDO1 were quantitated. Differences in pCR (ypT0ypN0) rates were assessed using a z-test for differences in proportion.

HYPOTHESIS

Based on previous exploratory studies, we hypothesized that tumor expression of TOP2A > 515 amol/ug would be predictive of benefit in breast cancer patients treated with anthracycline-based therapy.

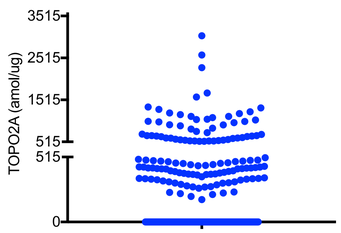

Figure 2. TOP2A Expression in Breast Cancer. TOP2A protein was detected in 131 of 258 tumor samples from anthracycline-treated patients (range: 178 to 3044 amol/ug).

RESULTS

Testing a proteomic cutoff for TOP2A in breast cancer patients who were treated with and without anthracycline

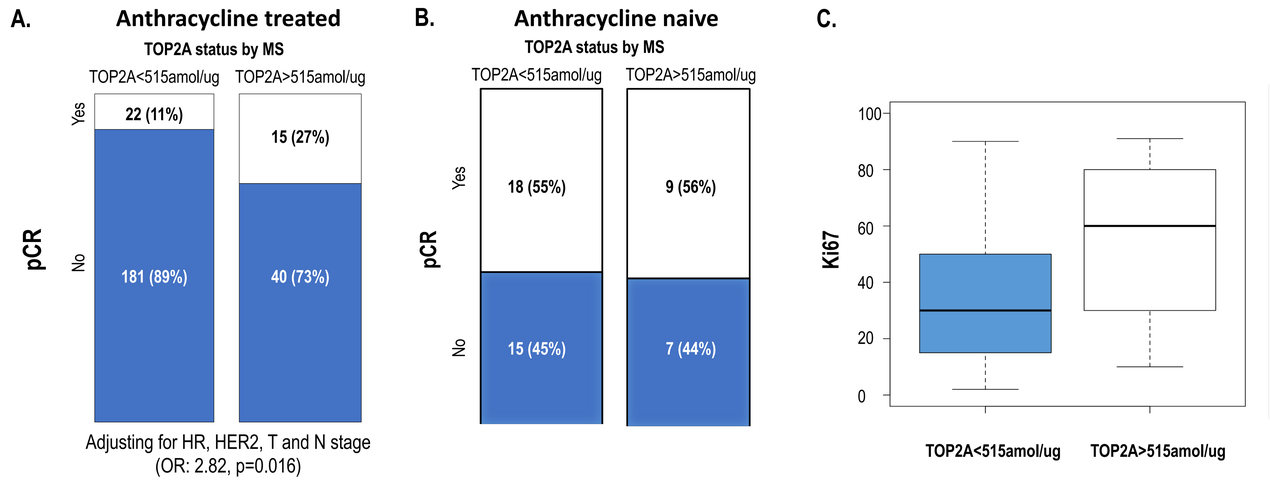

Figure 3. A. Among anthracycline-treated patients (n = 258), those with TOP2A levels > 515 amol/ug had higher pCR rates than patients with lower TOP2A expression (odds ratio (OR): 3.03, Fisher's exact test p = 0.003). The difference retained statistical significance in a logistic regression model adjusting for HR, HER2 status, T and N stage (OR: 2.82, p=0.016). **B.** In 49 breast cancer patients who did not receive anthracycline, there was no association between TOP2A protein expression level and pCR rate. **C.** Patients with TOP2A >515 amol/ug expressed significantly elevated levels of Ki67 (t-test, p<2.2x10^-16). Ki67 correlated with pCR in the anthracycline-treated patients, but not in the untreated patients (data not shown), suggesting that TOP2A and Ki67 play a similar role.

p16 proteomic expression and response in all comers

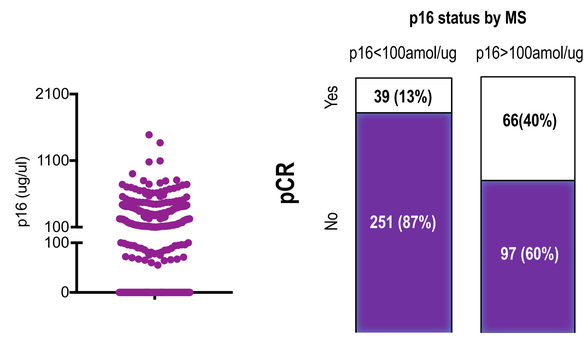

Figure 4. p16 protein expression distribution (**left panel**) in breast cancer patients regardless of treatment (n=453). Patients whose tumor expressed p16 (>100amol/ug) had higher pCR rates than patients with lower p16 expression (OR: 4.51, Fisher's exact test p = 1.51x10^-10). The difference retained statistical significance in a logistic regression model adjusting for HR and HER2 status (OR: 2.65, p-value 0.00022).

IDO1 proteomic expression and response in all comers

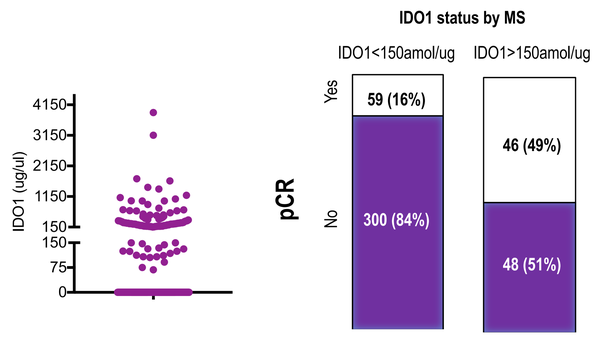

Figure 5. IDO1 protein expression distribution (**left panel**) in breast cancer patients regardless of treatment (n=453). Patients whose tumor expressed IDO1 (>150amol/ug) had higher pCR rates than patients with lower IDO1 expression (OR: 5.11, Fisher's exact test p = 9.94x10^-11). The difference retained statistical significance in a logistic regression model adjusting for HR and HER2 status (OR: 2.59, p-value 0.00076).

CONCLUSIONS

- Quantitative proteomic analysis of TOP2A identified a subset of TOP2A protein-expressing breast cancer patients who benefitted from anthracycline-based treatment. No association was seen in anthracycline-naïve patients. An association was also seen between expression of TOPO2A and Ki67.
- In exploratory studies, targeted proteomics identified p16 expression as a positive prognostic biomarker in breast cancer patients treated with neoadjuvant therapy.
- IDO1 expression was also associated with pCR rate in this study. Since IDO1 is a negative immune regulator, the effect seen here may be immune cell independent, and instead may be related to its tryptophan catabolic activity.
- Our approach combining quantitative proteomic and genomic analysis may accurately identify patients most likely to respond to anthracycline-containing therapy specifically and different types of therapy in general.

FUTURE PLANS

- Larger prospective studies are being planned to assess the utility of proteomic analysis of TOP2A to predict benefit in multiple breast cancer settings.
- Genomic analysis of these samples is in process and will define potential roles of p16 expression in Rb-proficient subpopulation.
- Additional studies are underway to confirm IDO1 results and to assess the role of the immune system in pCR.