Genomic and transcriptomic mediators of resistance to antibody-drug conjugates (ADCs) in metastatic breast cancer (MBC): a comprehensive multi-center study

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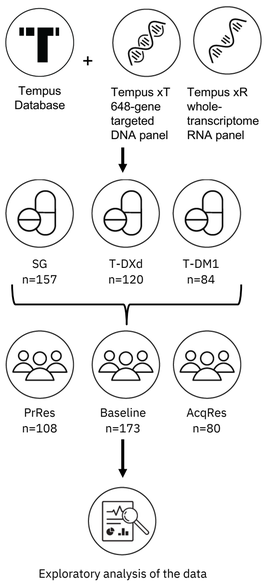
INTRODUCTION

ADCs have revolutionized the therapeutic landscape in oncology. Four ADCs are US FDA-approved in MBC: sacituzumab govitecan (SG), trastuzumab deruxtecan (T-DXd), trastuzumab emtansine (T-DM1), and datopotomab deruxtecan with many others in development. Despite these advances, ADC resistance mechanisms remain unknown. To discern biomarkers of therapeutic resistance, we evaluated genomic and transcriptomic differences in MBC before and after ADC treatment using approximations from unpaired pre- and post-treatment biopsies.

METHODS



De-identified records of MBC patients (32.4% TNBC, 27.1% HR+/HER2-, 20.2% HER2+, 20.2% NOS) treated with the three approved ADCs as of 2024 whose tumors were sequenced as part of routine clinical care were included in this analysis.

The cohort was divided by ADC treatment type and samples were split into pre-treatment (collected within 1 year before or 15 days after the ADC start date) or post-treatment (collected within 3 months after ADC end date) groups.

The cohort was split into three subsets based on resistance evaluation:

Primary resistance (PrRes): pre- and post-treatment samples from patients treated with ADC for 0-3 mo.

Baseline profile: pre-treatment samples from patients that did not exhibit primary resistance (treated with ADC for >3 mo).

Acquired resistance (AcqRes): post-treatment samples from patients treated with ADC for >3 mo.

Potential mediators of resistance were evaluated by investigating differences in DNA alterations and gene expression for genes related to ADC mechanisms of action, including antigen expression, processing mechanism, payload effect, and efflux pumps.

RESULTS

Table 1. AcqRes and baseline cohort overview

Characteristic	SG		T-DXd		T-DM1	
Resistance Status	*Baseline (Pre-treatment, n=64)*	*AcqRes (Post-treatment, n=38)*	*Baseline (Pre-treatment, n=67)*	*AcqRes (Post-treatment, n=27)*	*Baseline (Pre-treatment, n=15)*	*AcqRes (Post-treatment, n=42)*
Age at primary diagnosis, median (IQR) years	51 (45, 63)	52 (40, 60)	51 (43, 61)	47 (39, 53)	53 (43, 61)	46 (41, 53)
Receptor status, n (%)						
HR+/HER2+	1 (1.6%)	0 (0%)	7 (10%)	3 (11%)	19 (45%)	4 (27%)
HR+/HER2-	15 (23%)	9 (24%)	29 (43%)	10 (37%)	4 (9.5%)	4 (27%)
HR-/HER2+	N/A	N/A	9 (13%)	2 (7.4%)	10 (24%)	2 (13%)
TNBC	39 (61%)	18 (47%)	15 (22%)	1 (3.7%)	1 (2.4%)	0 (0%)
NOS	9 (14%)	11 (29%)	7 (10%)	11 (41%)	8 (19%)	5 (33%)
ADC treatment duration, median (IQR) days	189 (130, 287)	214 (163, 266)	203 (134, 273)	255 (209, 292)	227 (148, 368)	219 (169, 308)

RESULTS

ERBB2 status is associated with AcqRes to T-DM1

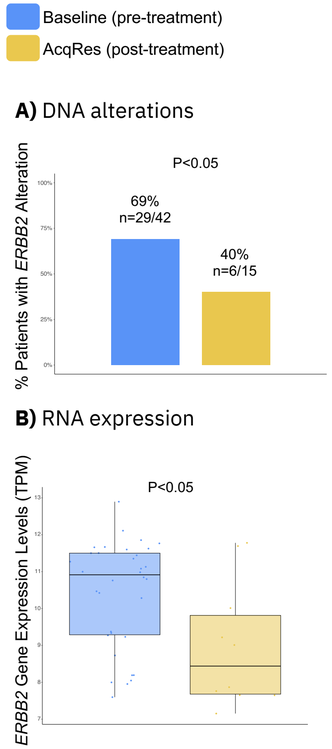


Figure 1. In the acquired resistance cohort, post-treatment samples from patients treated with T-DM1 exhibited A) lower frequency of *ERBB2* alterations (69% vs 40%, p=0.047, Pearson's Chi-squared) and B) lower levels of *ERBB2* expression (10.9 vs. 8.4, p=0.024, Fisher's exact) compared to pre-treatment baseline samples.

Expression of efflux pump genes in the AcqRes and baseline cohorts

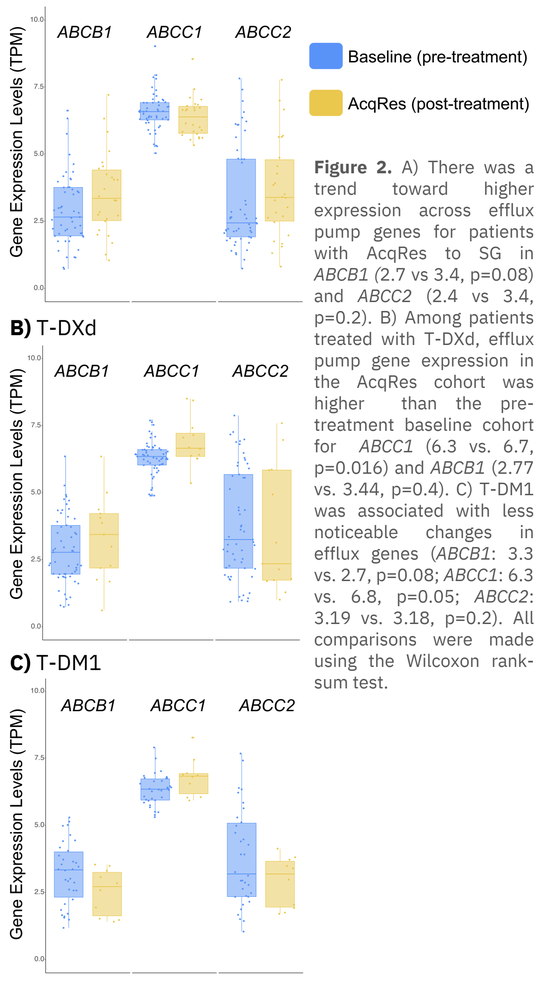


Figure 2. A) There was a trend toward higher expression across efflux pump genes for patients with AcqRes to SG in *ABCB1* (2.7 vs 3.4, p=0.08) and *ABCC2* (2.4 vs 3.4, p=0.2). B) Among patients treated with T-DXd, efflux pump gene expression in the AcqRes cohort was higher than the pre-treatment baseline cohort for *ABCC1* (6.3 vs. 6.7, p=0.016) and *ABCB1* (2.77 vs. 3.44, p=0.4). C) T-DM1 was associated with less noticeable changes in efflux genes (*ABCB1*: 3.3 vs. 2.7, p=0.08; *ABCC1*: 6.3 vs. 6.8, p=0.05; *ABCC2*: 3.19 vs. 3.18, p=0.2). All comparisons were made using the Wilcoxon rank-sum test.

Table 2. PrRes and baseline cohort overview

Characteristic	SG		T-DXd		T-DM1	
Resistance Status	*PrRes (pre- and post-treatment, n=55)*	*Baseline (pre-treatment, n=64)*	*PrRes (pre- and post-treatment, n=26)*	*Baseline (pre-treatment, n=67)*	*PrRes (pre- and post-treatment, n=27)*	*Baseline (pre-treatment, n=42)*
Age at primary diagnosis, median (IQR) years	52 (44, 60)	51 (45, 63)	64 (54, 70)	51 (43, 61)	55 (49, 64)	53 (43, 61)
Receptor status, n (%)						
HR+/HER2+	0 (0%)	1 (1.6%)	0 (0%)	7 (10%)	8 (30%)	19 (45%)
HR+/HER2-	12 (22%)	15 (23%)	13 (50%)	29 (43%)	2 (7.4%)	4 (9.5%)
HR-/HER2+	1 (1.8%)	0 (0%)	2 (7.7%)	9 (13%)	5 (19%)	10 (24%)
TNBC	34 (62%)	39 (61%)	6 (23%)	15 (22%)	3 (11%)	1 (2.4%)
NOS	8 (15%)	9 (14%)	5 (19%)	7 (10%)	9 (33%)	8 (19%)
ADC treatment duration, median (IQR) days	63 (45, 76)	189 (130, 287)	60 (31, 83)	203 (134, 273)	54 (35, 67)	227 (148, 368)

Expression of efflux pump genes in the PrRes vs. baseline cohorts

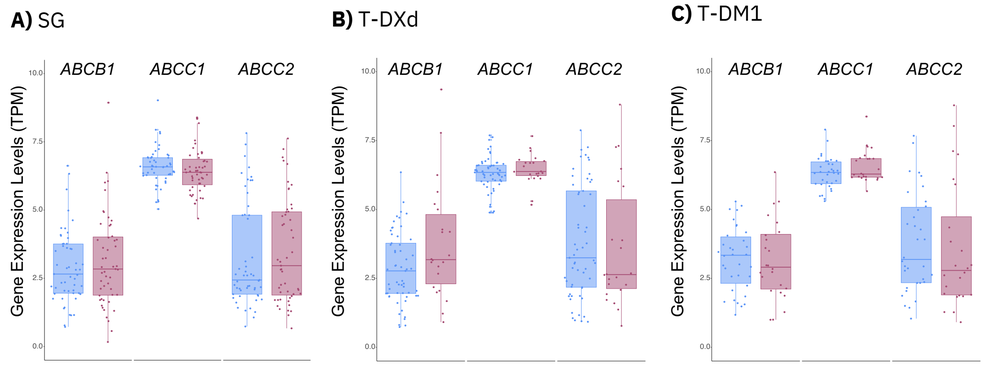


Figure 3. A trend of higher efflux pump gene expression was associated with primary resistance to T-DXd (ABCB1: 3.18 vs. 2.77, p=0.074). All comparisons were made using the Wilcoxon rank-sum test.

SUMMARY

- Genomic and transcriptomic analysis identified potential mechanisms of PrRes and AcqRes to SG and T-DXd, including higher drug efflux pump expression. T-DM1 AcqRes was associated with reduced target expression.
- This might be related to differences in ADC mechanisms of action, particularly the payload release and bystander effect between SG, T-DXd, and T-DM1.
- Additional research is needed to validate these novel findings and the molecular underpinnings mediating resistance to ADCs.

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