Poster # 300P

Mutational patterns across breast cancer subtypes during metastatic disease progression

Hao Liao[1], Jiayang Zhang[1] Tiantian Zheng[2], Xiaoran Liu[1], Xiaoxi Dong[2], Amy Wang[2], Peter Du[2], Shidong Jia[2], Bonnie L. King[2], Jianjun Yu[2], Huiping Li[1]
[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital and Institute, Beijing, China
[2] Huidu Shanghai Medical Sciences Ltd., Shanghai, China

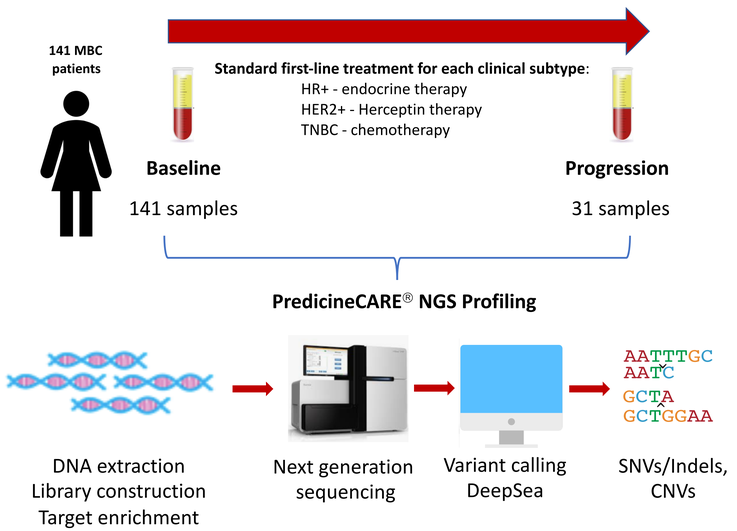
INTRODUCTION

Treatment options for metastatic breast cancer include endocrine therapies for hormone receptor positive (HR+) patients, Herceptin therapy for Her2+ patients and chemotherapy for TNBC (triple negative breast cancer) patients. While temporarily effective, these treatments are all undermined by the eventual emergence of resistance. We have used NGS-based liquid biopsy to profile genomic alterations in HR+, Her2+ and TNBC metastatic breast cancer patients during disease progression following first-line treatment and report the emergence of distinct mutational patterns across clinical subtypes.

METHODS

Blood samples from 141 metastatic breast cancer (MBC) patients were collected at baseline prior to first-line treatment at the Beijing Cancer Hospital. HR+ patients received endocrine therapies (aromatase inhibitors, selective estrogen receptor modulators or selective estrogen receptor degraders), HER2+ patients were treated with HER2-targeted therapies and TNBC patients received chemotherapy. Additional samples were collected from a subset of 31 patients at the time of disease progression. A targeted NGS-based liquid biopsy assay (PredicineCARE®) was used to profile somatic mutations and copy number variations (CNVs) across 152 genes in circulating tumor DNA collected at baseline vs. progression.

Fig. 1: Sample collection and analysis.



RESULTS

Fig. 2: Somatic gene alterations across breast cancer clinical subtypes at baseline and progression. The most frequently altered genes detected across 141 samples collected from patients of all subtypes at baseline were TP53 (44%), PIK3CA (28%) and ERBB2 (25%). The frequencies of the top 20-altered genes in samples collected from a subset of 11 HR+, 8 HER2+ and 12 TNBC patients at baseline and progression are shown below. A higher frequency of alterations was observed at progression vs. baseline in 10/20 genes in HR+ patients (TP53, PIK3CA, ERBB2, CDKN2A, CDH1, FGFR1, PTEN, ESR1, DDR2 and MDM2), in 1/20 genes in HER2+ patients (ARID1A), and in 3/20 genes (CDKN2A, CDH1 and CCNE1) in TNBC patients. The frequency of altered genes in HR+ patients at progression was significantly higher compared to HER2+ and TNBC patients (P = 0.003, Fisher's exact test).

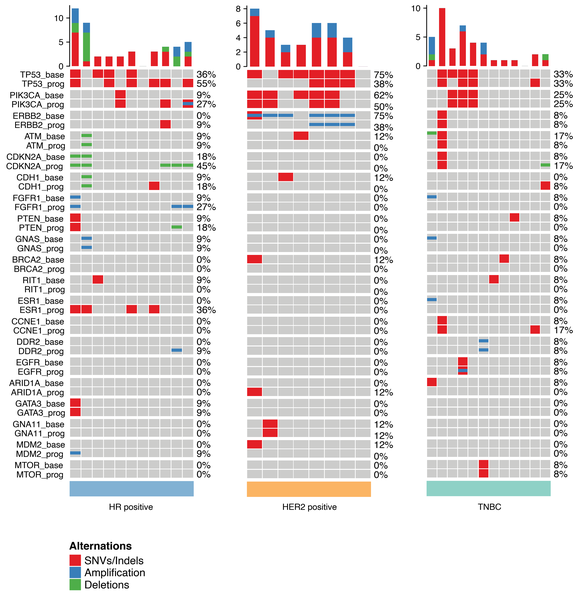
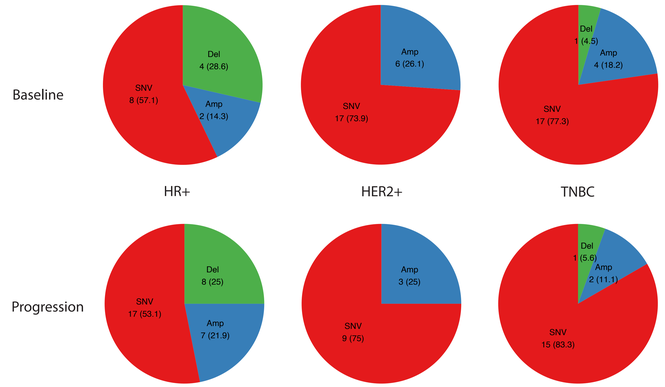


Table 1. The number of variants (SNVs and CNVs) detected per patient at baseline/progression in each subgroup was 1.27/3.54 (HR+), 3.0/1.5 (HER2+) and 2.08/2.375 (TNBC). The total number of variants detected at baseline/progression in each subgroup was 14/39 (HR+), 24/12 (HER2+) and 25/19 (TNBC) (P = 0.0002, Fisher's Exact Test; **HR+ vs HER2+:** 0.0006, **HR+ vs TNBC**: 0.005, Pairwise Fisher's Exact Test, with B-H adjustment).

Number of Variants Detected	HR+	Her2+	TNBC	Total
At Baseline	14	24	25	63
At Progression	39	12	19	70

Fig 3: Proportions of variant types across breast cancer clinical subtypes at baseline and progression. SNVs were the most prevalent type of variant detected in the top 20 altered genes at baseline and progression in all 3 subtypes. CNVS were more prevalent in HR+ patients, who harbored the largest proportion of deletion events. No deletions were detected in the HER2+ subgroup. The proportion of amplification events increased in HR+ patients at progression.



SUMMARY OF KEY FINDINGS

- The most frequently altered genes across all subtypes were TP53, HER2+ and PIK3CA.
- TP53, PIK3CA, ERBB2, CDKN2A, CDH1, FGFR1, PTEN, ESR1, DDR2 and MDM2 variants were enriched in HR+ patients at progression.
- HR+ patients harbored the highest proportion of CNVs and the proportion of amplification events increased at progression.
- Overall, HR+ patients treated with endocrine therapies exhibited a much higher frequency and diversity of variants at the time of disease progression relative to HER2+ and TNBC patients receiving Herceptin and chemotherapy treatments, respectively.

CONCLUSIONS

Our results confirm the capacity of NGS-based liquid biopsy to detect targetable mutations during metastatic breast cancer progression, which can provide options for tailored treatments to extend survival. Moreover, our study has revealed the emergence of distinct mutational patterns across clinical breast cancer subtypes during metastatic progression. As HR+, HER2+ and TNBC patients receive distinct therapies, NGS profiling and characterization of subtype-specific patterns of mutations during progression may reveal unique mechanisms underlying the generation of treatment-related resistance.

Disclosures: Hao Liao , Jiayang Zhang, Xiaoran Liu and Huipng Li have no disclosures. Tiantian Zheng, Xiaoxi Dong, Amy Wang, Peter Du, Shidong Jia, Bonnie King and Jianjun Yu are employees and stockholders at Huidu, Shanghai Medical Sciences, Ltd.