Original Article

A predictor of pathological complete response to neoadjuvant chemotherapy in triple-negative breast cancer patients with the DNA repair genes

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Background: We conducted this study to investigate the prevalence of potential chemo-response-related gene mutations in triple-negative breast cancer (TNBC) patients and to evaluate the potential relationship between these gene mutations and neoadjuvant chemotherapy response in TNBC patients.

Methods: One hundred sixty-two TNBC patients in Fudan University Shanghai Cancer Center who received NAC with 4 cycles of paclitaxel and carboplatin were enrolled in this study. Fifty-six pathological complete response (pCR) patients and 56 non-pCR patients were enrolled in this retrospective study for the training set. Clinical assessments of postoperative residual tumors were performed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Forty chemo-response-related genes were screened in each tumor specimen by second-generation sequencing analysis. Fifty TNBC patients who received neoadjuvant chemotherapy with paclitaxel and carboplatin were enrolled in the validation group.

Results: Fifty-seven of 112 (50.9%) TNBCs contained at least one detected somatic mutation. As expected, *TP53* mutation was the most common alteration, which was observed in 21.4% of patients. *BRCA1*, *BRCA2*, *RET*, *PI3KCA*, and *PTEN* mutations were each observed in 11.6%, 4.5%, 5.4%, 2.7% and 3.6% of all cases, respectively. No significant differences in any gene mutation frequency between pCR and non-pCR groups were identified. We found that the mutation status of 10 DNA repair genes involved in homologous recombination (HR) pathway successfully discriminated between responding and nonresponding tumors in the training group. Up to 18 patients who were mutation-positive experienced pCR compared to only 6 in the non-pCR group (P=0.006), and 75% the HR related gene mutation patients achieved pCR. In the validation group, TNBC patients with DNA repair gene mutations achieved 77.8% pCR.

Conclusions: A subset of TNBC patients carry deleterious somatic mutations in 10 HR-related genes. The mutation status of this expanded gene panel is likely to effectively predict respond rate to neoadjuvant chemotherapy based on paclitaxel and carboplatin. Our findings need to be validated through follow-up studies in this and additional cohorts.

Keywords: Genes mutation; triple-negative breast cancer (TNBC); neoadjuvant chemotherapy; DNA repair genes

Submitted Jun 21, 2020. Accepted for publication Oct 26, 2020.
doi: 10.21037/atm-20-4852
View this article at: http://dx.doi.org/10.21037/atm-20-4852

Introduction

Triple-negative breast cancer (TNBC) accounts for approximately 15% of all breast cancers worldwide and is characterized by the absence of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) (1,2). Due to the lack of sensitivity to hormone therapy and anti-HER-2 therapy, TNBC has become one of the refractory types of breast cancer in clinical practice, and the risk of disease recurrence and metastasis is high. Currently, no appropriate molecular targets have been identified to treat TNBC due to its heterogeneity (3). There is a close relationship between tumor gene mutation and drug resistance, disease recurrence and metastasis progression. With the development of gene mutation analyses of tumor genomes, a better understanding of response of drug therapy through analysis of tumor markers is an unmet need to elucidate potential new therapeutic targets and treatment options for TNBC.

Anthracycline-/taxane-based chemotherapy remains the standard of care systemic therapy for early-stage TNBC. Although outcomes with chemotherapy are modest overall, it is evident that a subset of TNBC patients have a higher rate of pathological complete response (pCR) to neoadjuvant chemotherapy than those with other disease phenotypes. Many investigators have proposed that hereditary germline breast cancer susceptibility genes 1 (*BRCA1*) mutations occur in approximately 10–20% of women with stage I–III TNBC and play an important role in carcinogenesis and in predicting chemotherapy responsiveness in TNBC with a characteristic pattern of DNA gains and losses (4-8). Thus, *BRCA1*-directed therapeutic approaches, such as platinum agents and poly ADP-ribose polymerase inhibitors, are being explored for the general population of TNBC (3). In the NCT01630226 clinical trial, platinum-based single drug therapy was effective for metastatic TNBC with *BRCA1/2* mutation, and carriers with *BRCA1/2* mutation have a higher therapeutic response rate. However, *BRCA1/2* does not predict improved disease progression free survival (PFS) or overall survival (OS). Researchers found that neoadjuvant chemotherapy regimens containing platinum-based drugs conveyed a pathological complete remission rate (pCR) of more than 60% in *BRCA1* mutated breast cancer (9). As a single drug therapy or in combination with DNA damaging drugs, poly ADP-ribose polymerase (PARP) inhibitors are particularly effective in tumors with defects in DNA damage repair. One study reported that pCR of TNBC patients with *BRCA1* mutation reached 56% in patients who received six courses of carboplatin, gemcitabine and iniparib. In the I-SPY2 clinical trial, pCR of TNBC patients in response to combination therapy of veliparib/carboplatin reached 52%, while that of patients with chemotherapy alone reached only 26% (10).

Neoadjuvant chemotherapy for nonmetastatic TNBC produces a higher overall response rate than other breast cancer types. However, the overall survival (OS) rate in TNBC patients did not reach pCR after receiving neoadjuvant chemotherapy and was lower than in patients with non-TNBC who had residual lesions after neoadjuvant chemotherapy ($P<0.0001$) (11). To improve OS of TNBC patients, these patients should be divided into those with good response and those with poor response according to their gene mutations. Current research is trying to explore the characteristics of TNBC from the perspective of gene phenotypes and molecular medicine with the goal of identifying new potential targeted therapeutic drugs and realizing individualized treatment. We present the following study in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4852).

Methods

Patients and samples

One hundred and twelve TNBC patients for the training set and 50 patients for the validation set in the Fudan University Shanghai Cancer Center were enrolled in this retrospective study from January 2012 to December 2016. Fifty TNBC patients were enrolled in the validation group from January 2017 to July 2019. Eligibility criteria included the following: (I) clinical stage II or III patients collected and evaluated by imaging after hollow needle puncture; (II) ER-negative, PR-negative and HER2-negative; (III) These patients received neoadjuvant chemotherapy treatment with 4 cycles of paclitaxel (80 mg/m^2, d1, d8, d15) and carboplatin (AUC =2 calculated using the Calvert formula, d1, d8, d15); (IV) all enrolled patients had complete clinical and pathological records. Clinical assessments of postoperative residual tumors were performed according to RECIST1.1 criteria. This cohort was subsequently divided into pCR and non-pCR groups. pCR was defined as the absence of invasive carcinoma in the breast and lymph nodes according to the Miller & Payne criteria (12). All patients participating in the study provided written informed consent, and study protocols were approved by the corresponding institutional ethical committees (reference

Table 1 Patient characteristics

Characteristics	Value
Age at diagnosis (years), median [range]	47 [20–75]
Body mass index (kg/m^2)	
≤25	85 (75.9%)
>25	27 (24.1%)
Menopausal status	
Premenopause	76 (67.9%)
Postmenopause	36 (32.1%)
Clinical tumor stage	
cT1	6 (5.4%)
cT2	50 (44.6%)
cT3	48 (42.9%)
cT4	8 (7.1%)
Clinical nodal stage	
cN0	21 (18.8%)
cN1	61 (54.5%)
cN2	13 (11.6%)
cN3	17 (15.1%)
Ki 67 index, median [range]	70% [10–90%]

number: 050432-4-1212B). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Fudan University Shanghai Cancer Center (reference number: 050432-4-1212B) and informed consent was taken from all the patients.

Chemotherapy response related gene sequencing

Forty chemo-response-related genes were screened in each tumor specimen by next-generation sequencing. The Gentra Puregene kit (QIAGEN, Germany) was used for DNA extraction from tumor tissue cells before neoadjuvant chemotherapy. DNA purification and concentration determination were performed using a Nanodrop 2000 (Thermo Fischer Scientific, USA). The a260/280 values of all DNA samples were between 1.8 and 2.0. Next, target genes were simultaneously specifically amplified using oligonucleotide probes designed by Illumina Design Studio (Illumina). Sequencing was performed using a MiSeq NGS system (Illumina). Data were analyzed by MiSeq Reporter software with alignment to a reference genome (grch37/hg19) to determine the type of difference, such as deletion, insertion and single nucleotide polymorphisms. The sequence analysis software was MiSeq.

Statistical analysis

General clinical and pathological characteristics, common pathological molecular indicators, and gene mutations in patients with hollow needle puncture were summarized by descriptive analysis. The relationship between different indicators and pathological remission was evaluated by Chi-square test. Multivariate logistic regression analysis was used to predict factors related to neoadjuvant chemotherapy response. Logistic regression was used to calculate the 95% confidence interval (CI) of the odds ratios (ORs) for each variable. Statistical comparison of gene mutation status between pCR and non-pCR groups was performed using SPSS software. A P value <0.05 was considered statistically significant. Discrimination of the nomogram was graphically shown using a receiver operator characteristic (ROC) curve and quantified using the area under the curve (AUC).

Results

Overview of TNBC patients in the training group

Here, 56 pCR patients and 56 non-pCR patients were enrolled in this retrospective study for the training set (*Table 1*). All patients with breast lump hollow needle puncture were confirmed as having invasive carcinoma. Immunohistochemical pathological reports evidenced the absence of ER, PR, and HER-2, and 16.1% (18/112) of patients with *BRCA1/2* mutation were identified by DNA sequencing of tumor tissues with preoperative hollow needle puncture. After neoadjuvant chemotherapy, the entire cohort was divided into pCR (56 cases) and non-pCR (56 cases) groups. The non-pCR group included 40 PR patients, 8 SD patients and 8 PD patients. Through retrospective analysis of clinical information, 40 patients in this cohort had a family history of malignant tumor, including 10 patients with a family history of breast cancer.

In patients with a family history of malignant tumor, 22.5% exhibited TP53 mutations, while 7.5% presented with *BRCA1/2* mutations. In addition, half of patients with a family history of breast cancer exhibited *TP53* mutations.

Table 2 Odds ratios for pathological complete response according to subgroups

Category	Univariable		Multivariable	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Menopausal status (premenopause *vs.* postmenopause)	0.515 (0.230–1.156)	0.108	0.881 (0.320–2.429)	0.807
Body mass index (<25 *vs.* ≥25 kg/m^2)	0.907 (0.381–2.157)	0.825	0.894 (0.362–2.211)	0.809
Age (<45 *vs.* ≥45 years)	0.593 (0.276–1.270)	0.179	0.798 (0.324–1.967)	0.624
cT (cT1–2 *vs.* cT3–4)	1.000 (0.781–1.280)	1.000	0.944 (0.431–2.071)	0.887
cN (cN0 *vs.* cN+)	1.814 (0.686–4.795)	0.230	1.887 (0.690–5.162)	0.216
Ki67 (≤30% *vs.* >30%)	3.400 (1.132–10.212)	0.029	3.018 (0.884–10.302)	0.078

Table 3 DNA repair gene mutations and neoadjuvant chemotherapy response

HR pathway related genes mutation	pCR patients (n=56)	Non-pCR patients (n=56)	P value
PALB2	4	0	0.118
CHEK2	0	0	NA
BRCA2	4	1	0.364
RAD51D	0	0	NA
BRCA1	8	5	0.376
RAD51C	1	0	1.000
BRIP1	1	0	1.000
ATM	0	0	NA
RAD50	0	0	NA
BARD1	0	0	NA
HR pathway related 10 genes	18	6	0.006

The rate of gene mutation associated with pCR

Here, 40 mutated genes related to DNA repair damage or chemotherapy were detected. We first analyzed *BRCA1/2* and other homologous recombinant repair genes or chemotherapy-related gene mutation rates in both groups of TNBC patients receiving neoadjuvant chemotherapy with pCR and non-pCR. In this cohort, we found that 50.9% (57/112) of 112 TNBC patients presented with at least one somatic mutation. As expected, TP53 mutation was the most common alteration, which was observed in 21.4% of patients (36 of 52). *BRCA1*, *BRCA2*, *RET*, *PI3KCA*, and *PTEN* mutations were present in 11.6%, 4.5%, 5.4%, 2.7% and 3.6% of all cases, respectively. We found no significant differences in gene mutation frequency between the pCR and non-pCR groups (*Table 2*).

Homologous recombination (HR) pathway-related gene mutations and neoadjuvant chemotherapy response

In previous clinical trials, partial TNBC presented with HR deficiency, and platinum drugs may benefit these patients (13,14). Further, we evaluated the potential relationship between gene mutation and neoadjuvant chemotherapy response in TNBC. An independent analysis of the combination of 10 DNA repair genes (*PALB2*, *CHEK2*, *BRCA2*, *RAD51D*, *BRCA1*, *RAD51C*, *BRIP1*, *ATM*, *RAD50* and *BARD1*), which are involved in the HR pathway was performed. We found that the mutation status of these genes, which conveys HR deficiency, successfully discriminated between pCR and non-pCR groups treated with paclitaxel and carboplatin chemotherapy. Up to 18 patients in the pCR group were mutation positive compared to only 6 in the non-pCR group (P=0.006) (*Table 3*). We also found a significant difference in multivariate logistic regression analysis between pCR and non-pCR groups (P=0.013). The DNA repair mutation panel was predictive of pCR rate in TNBC patients who received paclitaxel and platinum. In our research of the mutational subgroup, pCR rate was as high as 75%.

Ten genes whose mutations are related to DNA repair damage were also detected, and 18 of 50 (36%) patients achieved pCR in the validation group. Patients with DNA repair mutations exhibited a higher pCR rate (77.8% *vs.* 12.5%, P<0.001). DNA repair gene mutation testing achieved an AUC of 0.826, with a sensitivity of 77.8% and a specificity of 87.5%.

Discussion

TNBC is a commonly used umbrella term for a histologic group of tumors that are vastly heterogeneous. In fact, TNBC includes a wide range of entities differing in their biology and response to chemotherapy and targeted therapies, leading to different clinical outcomes (15). No matter the stage, local recurrence or distant metastasis occurred earlier, visceral metastasis is more common than bone metastasis, brain metastasis rate is higher, and disease-free survival and overall survival rates are reduced.

With the rapid development of next-generation sequencing (NGS), it is now possible and affordable to sequence individual genomes in a short period to identify somatic genetic alterations (16). In the era of personalized cancer treatment, large-scale genetic analysis of tumors is considered key for a better selection of appropriate anticancer therapy (17). Couch *et al.* assessed the frequency of mutations in 17 predisposition genes, including *BRCA1* and *BRCA2*, in a large cohort of patients with TNBC (n=1,824) not selected for family history of breast or ovarian cancer who were recruited through 12 studies to determine the utility of germline genetic testing in those with TNBC. Results showed that 11.2% had mutations in *BRCA1* (8.5%) and *BRCA2* (2.7%) genes (7). In the Triple-Negative Breast Cancer Consortium (TNBCC), 22 common breast cancer susceptibility variants were investigated in 2,980 Caucasian women with TNBC and 4,978 healthy controls. Six single nucleotide polymorphisms (SNPs) were significantly associated with the risk of TNBC and provided convincing evidence of genetic susceptibility for TNBC (18). It is believed that *BRCA1* plays a critical role in error-free DNA double-strand break repair by HR, and its deficiency can result in genomic instability (19). Due to TNBC patients having relatively high *BRCA1* mutation rates compared to non-TNBC patients, a larger number of studies have demonstrated that a subset of TNBC patients are susceptible to DNA double strand break-inducing therapies, such as platinum agents and poly ADP-ribose polymerase inhibitors. Thus, *BRCA1*-directed therapeutic approaches are being explored for the treatment of TNBC (3). Further, to improve the treatment effects of TNBC, new combination chemotherapy regimens, including platinum drugs and other targeted therapy drugs, such as anti-angiogenesis, poly ADP-ribose polymerase inhibitors and other small molecule inhibitors, are in multiple clinical trials in the field of neoadjuvant therapy. The addition of platinum salts to standard neoadjuvant regimens demonstrated a significant increase in pCR rates in TNBC, reaching more than 50% (20-22).

Despite these advances, no predictive biomarkers are currently available in the clinical setting to identify TNBC patients due to their heterogeneity, although measures of identifying such markers are being aggressively pursued. Previous studies have shown that *BRCA1* and *BRCA2* mutations are important potential biomarkers in TNBC with platinum therapy. *TP53* gene expression and TNBC patient sensitivity to cisplatin are negatively correlated, so p53 may be a potential predictor of the efficacy of platinum-based therapy for TNBC (23). In another study, 15.2% (16/105) of 105 TNBC cases presented changes in *EGFR* copy number, and the mutation frequencies of *KRAS*, *EGFR* and *TP53* genes were 1.9%, 1.0% and 31.4%, respectively. PFS and OS of metastatic TNBC subgroups with *VEGFA* amplification were increased after bevacizumab treatment (24). The prediction of curative effects is often performed on a small sample in a retrospective study, but large sample multicenter prospective studies are urgently needed to confirm these findings further.

Biomarkers predictive of response to neoadjuvant treatment are thus of great importance in TNBC. In addition to *BRCA1/2* mutations, other mutations in DNA repair genes that are likely to be found could also be predictive markers of drug therapy. There were distinct genetic mutations observed between pCR and the no pCR groups of TNBC patients, some of which were useful to predict the efficacy of neoadjuvant treatment. However, until now, the prevalence of somatic mutations in DNA repair genes in TNBC have not been well documented. This knowledge is necessary to guide the application of new targeted therapeutic drugs and to predict the response to drug therapy by fully understanding the genetic variation characteristics of TNBC itself. We conducted this study to investigate the prevalence of potential chemo-response-related genes mutated in TNBC patients and to evaluate potential relationships between these gene mutations and NAC-response in TNBC patients. In pCR and no pCR groups, we used next-generation sequencing technology to analyze 40 gene mutations in TNBC patient tissues after neoadjuvant chemotherapy. A subset of TNBC patients carried a deleterious somatic mutation in 10 HR related genes. Mutation status of this expanded gene panel are likely to effectively predict the respond rate to neoadjuvant chemotherapy based on paclitaxel and carboplatin.

This study has several limitations common to all retrospective analyses and those with a relatively small

number of patients. Our study did not include other regimens commonly used for neoadjuvant therapy, and our findings need to be validated through follow-up of this and additional cohorts.

Acknowledgments

Funding: This research was supported by the National Natural Science Foundation of China (81502289), the Shanghai Natural Science Foundation (19ZR1411100), Shanghai Health Commission Foundation (201940167 and 20194Y0080), Shanghai "Rising Stars of Medical Talent" Youth Development Program (Youth Medical Talents – Specialist Program-Huang Liang) and AstraZeneca. The funders had no role in the study design, data collection or analysis, decision to publish, or preparation of the manuscript.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-4852

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-4852

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4852). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Fudan University Shanghai Cancer Center (reference number: 050432-4-1212B) and informed consent was taken from all the patients.

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Cite this article as: Huang L, Lang GT, Liu Q, Shi JX, Shao ZM, Cao AY. A predictor of pathological complete response to neoadjuvant chemotherapy in triple-negative breast cancer patients with the DNA repair genes. Ann Transl Med 2021;9(4):301. doi: 10.21037/atm-20-4852

