Original Article

The prognostic and predictive significance of cytokeratin 5/6 and epidermal growth factor receptor in metastatic triple-negative breast cancer treated with maintenance capecitabine

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Background: Capecitabine is the most widely used agent for maintenance chemotherapy in patients with metastatic triple-negative breast cancer (mTNBC). However, there are no biomarkers for identifying mTNBC patients who could benefit from capecitabine maintenance.

Methods: The prognostic roles of cytokeratin 5/6 (CK5/6), epidermal growth factor receptor (EGFR), and maintenance therapy were evaluated in mTNBC patients. Both CK5/6 and EGFR were detected using immunohistochemistry. Of 115 patients who achieved disease control, 56 received capecitabine maintenance therapy and 59 underwent observation. The progression-free survival (PFS) and overall survival (OS) of the patients were evaluated.

Results: The median PFS and OS were longer in the maintenance group than that in the observation group (7.3 versus 5.7 months, P=0.0016; 22.4 versus 17.9 months, P=0.0055). Patients with basal-like TNBC had a poorer survival times than in those with non-basal-like TNBC (P=0.0062). Capecitabine maintenance significantly prolonged the OS of non-basal-like TNBC patients (P=0.0257), while in the basal-like TNBC patients, the difference was not significant (P=0.0541). Multivariate analysis revealed that the prolonged OS was related to age >50 years (P=0.005), presence of visceral metastases (P=0.035), response to initial therapy (P=0.017), maintenance therapy (P=0.033), and CK5/6 and EGFR status (P=0.032). Compared with the observation group, toxicities of all grades were more frequently observed in the maintenance group, including neutropenia, 85.71% *vs.* 25.87%, P<0.001; thrombocytopenia, 55.36% *vs.* 11.86%, P<0.001; anemia, 82.14% *vs.* 52.54%, P= 0.001; nausea 83.47% *vs.* 11.86%, P<0.001; vomiting 69.64% *vs.* 8.47%, P<0.001; and hand-foot syndrome (HFS) 32.14% *vs.* 1.69%, P<0.001.

Conclusions: Our study revealed that patients with non-basal-like TNBC had a better clinical outcome than those with basal-like TNBC, and capecitabine maintenance treatment significantly prolonged PFS and OS in patients with TNBC. Patients with non-basal-like TNBC could benefit from maintenance therapy with capecitabine and CK5/6 and EGFR are biomarkers for TNBC prognosis.

Keywords: Maintenance chemotherapy; capecitabine; triple-negative breast cancer (TNBC)

Submitted Apr 03, 2020. Accepted for publication Jan 27, 2021.
doi: 10.21037/tcr-20-1760
View this article at: http://dx.doi.org/10.21037/tcr-20-1760

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Introduction

Breast cancer is the most common female malignancy worldwide. In approximately 5% of cases, the breast cancer has metastasized by the time of initial diagnosis. Despite most operable patients receiving surgery and adjuvant chemotherapy, the rate of recurrence or metastasis reaches 20–35% (1). Metastatic breast cancer (MBC) is an incurable disease, and the major goal of treatment is to relieve and control patients' symptoms, improve their quality of life, and prolong their survival time (2).

Based on gene and immunohistochemistry analyses, breast cancers can be divided into different subtypes. Biological characteristics and clinical outcomes differ among patients with different subtypes, and the treatment strategies also vary. Expert consensus recommends endocrine therapy as the treatment of choice for hormone receptor (HR)-positive tumors. Trastuzumab is also used in combination with chemotherapy and then maintained on its own in HER2-positive patients. Triple-negative breast cancer (TNBC), which is defined as HER2-negative and HR-negative, accounts for nearly 12–17% of all breast cancers (3). TNBC progresses rapidly and is life threatening, and chemotherapy is recommended as treatment (4-6).

Compared with HER2/HR-positive breast cancers, TNBC is more prone to recurrence and metastasis, even with similar treatments, and is associated with shorter progression-free survival (PFS) and overall survival (OS). The median time to recurrence for metastatic triple-negative breast cancer (mTNBC) patients is 1–2 years, and the median OS (mOS) is almost 1 year (7,8). Lehmann et al. compiled the gene expression profiles of 587 TNBC patients from 21 independent studies and identified 6 different TNBC subtypes using cluster analysis (9). These subtypes consist of basal-like 1, basal-like 2, immunomodulatory (IM), mesenchymal (M), mesenchymal stem cell-like (MSL), and lumen androgen receptor (LAR) breast cancer. Different subtypes present with unique gene expression profiles and are associated with different signaling pathways. Of the 6 subtypes, basal-like breast cancer (BLBC) has attracted the most attention. The majority of BLBCs exhibit a triple-negative phenotype and have a poor prognosis (10). Nielsen et al. examined the protein expression patterns in various basal-like breast tumors (11). They reported that the detection of cytokeratin 5/6 (CK5/6) in TNBC could accurately identify BLBC and showed high specificity. Rakha et al. (12) reported that CK5/6-positive and epidermal growth factor receptor (EGFR)-positive patients had more BRCA1 mutations, more distant metastases, and a poor prognosis compared with CK5/6- and EGFR-negative patients.

Capecitabine is widely used in the treatment of breast cancer. The FinXX study (13) and the CSCSG-010 study (14) showed that capecitabine-based adjuvant chemotherapy significantly prolonged the recurrence-free survival and OS of TNBC patients, while the GEICAM/2003-11 (15) study showed that patients with a non-basal-like phenotype could benefit from the addition of extended capecitabine treatment in early TNBC. In mTNBC, capecitabine maintenance therapy has been reported to demonstrate high activity and manageable safety (16,17). Clinical biomarkers to predict the efficacy of capecitabine are extremely important in TNBC, although studies in this area are relatively limited.

This retrospective cohort study focused on the correlations between CK5/6 and EGFR expression, the prognosis of TNBC, and the efficacy of capecitabine maintenance in patients with different TNBC subtypes. We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-1760).

Methods

Patients

Between January 2012 and December 2016, 164 mTNBC patients received first-line combination chemotherapy in the Oncology Department of the First Affiliated Hospital of Wannan Medical College, Anhui, China. *Table 1* shows the baseline characteristics of the patients. All patients were aged 18 years or above, and all had confirmed recurrent or metastatic TNBC. Of 115 patients who achieved disease control after first-line combination chemotherapy, 93 had received an anthracycline-containing regimen, and 85 had received a taxane-containing regimen as adjuvant/neoadjuvant therapy. All patients had a good Eastern Cooperative Oncology Group (ECOG) score and a life expectancy of ≥3 months, along with at least 1 measurable metastatic lesion detected by computed tomography or magnetic resonance imaging examination, and adequate organ function.

Patients with clinically detectable meningeal and/or brain parenchyma metastases, congestive heart failure, or reduced hepatic or renal function were excluded, as were those with HER2- or HR-positive cancers. We also excluded patients

Table 1 Characteristics of 115 mTNBC patients treated with gemcitabine combined with cisplatin

Characteristic	Maintenance (n=56)		Observation (n=59)		P value
	n	%	n	%	
Age (years)					0.896
Median	56		54		
Range	31–74		30–76		
ECOG performance status					0.161
0	32	57.14	26	44.07	
1	24	42.86	33	55.93	
Menopausal status					0.555
Premenopausal	39	69.64	44	74.58	
Postmenopausal	17	30.36	15	25.42	
Lymph nodes number					0.426
0–3	38	67.86	44	74.58	
>3	18	32.14	15	25.42	
Metastatic site					
Liver	20	35.71	18	30.51	0.553
Lung	29	51.79	26	44.07	0.408
Bone	30	53.57	29	49.15	0.636
Brain	4	7.14	5	8.47	0.790
Soft tissue	34	60.71	37	62.71	0.826
Number of metastatic site					0.272
1	19	33.91	18	30.51	
2	16	28.57	25	42.37	
≥3	21	37.50	16	27.12	
Prior chemotherapy					
Taxane	44	78.57	41	69.49	0.268
Anthracycline	47	83.93	46	77.97	0.416
Prior adjuvant/neoadjuvant therapy					0.309
Yes	41	73.21	38	64.41	
No	15	26.79	21	35.59	
Response to initial GP therapy					
Response	25	51.79	30	50.85	0.920
Stable disease	12	21.43	11	18.64	0.709
EGFR and CK5/6 status					0.752
CK5/6 and/or EGFR positive	45	80.36	46	77.97	
CK5/6 and/or EGFR negative	11	19.64	13	22.03	

ECOG PS, Eastern Cooperative Oncology Group performance status; mTNBC, metastatic triple-negative breast cancer; EGFR, epidermal growth factor receptor.

with concurrent tumors and those who had been diagnosed with tumor within the previous 5 years, as well as pregnant or breast-feeding women. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethical Committee of the First Affiliated Hospital of Wannan Medical College (No. 2008-7). Individual consent for this retrospective analysis was waived.

Study design

In this retrospective study, 115 of 164 patients achieved disease control, of whom 56 received capecitabine maintenance chemotherapy and 59 received observation. Patients in the maintenance group received capecitabine (1,000 mg/m^2) orally bid for 2 weeks every 3 weeks along with metoclopramide and dexamethasone to prevent nausea and vomiting, until disease progression, intolerable toxic effects, or withdrawal of consent. In the observation group, patients received observation until disease progression or withdrawal of consent. Laboratory assessments, such as routine blood counts, serum liver function markers, creatinine, and tumor biomarker levels were carried out at the beginning of each cycle. The tumors were measured at baseline and every 2 cycles through computed tomography scanning, magnetic resonance imaging, ultrasound, or physical examinations. Efficacy and toxicity were evaluated every 2 cycles.

Immunohistochemistry

Tumor tissues from TNBC patients were fixed in formalin, embedded in paraffin, and cut to a thickness of 4 μm. The sections were baked and dewaxed, and the endogenous catalase was removed. After blocking, the sections were incubated with primary antibody targeting CK5/6 (1:250, MA5-12429, Thermo Fisher Scientific, France) and EGFR (1:250, MA5-13070, Thermo Fisher Scientific, France) overnight at 4 ℃, then incubated with secondary horseradish peroxidase (HRP)-conjugated antibody (Cell Signaling Technology, Danvers, MA, USA). Sections were then stained with 3,3'-diaminobenzidine. Two independent pathologists scored the results. All sections were observed under fluorescence microscopy. The percentage of positive cells in 5 random high power fields (HPFs) and the intensity of positive staining were evaluated.

Statistical analysis

The primary endpoint of the study was PFS, and clinical efficacy and OS were the secondary endpoints. Response evaluation criteria for solid tumors (RECIST version 1.1) (18) was used to evaluate clinical efficacy. SPSS 19.0 software was used to analyze all data. The Kaplan-Meier estimator and log-rank test were used to analyze median PFS (mPFS) and mOS, and a Cox regression model was used to analyze the effects of age, menopausal status, metastatic sites, prior chemotherapy status, and ECOG. $P<0.05$ in a 2-sided test was considered to represent a statistically significant difference.

Results

Clinicopathological features

After the first 6 cycles of combination chemotherapy, 115 patients (70.12%, 115/164) had achieved disease control. Subsequently, 56 patients received maintenance therapy with capecitabine and 59 patients underwent observation alone. The maintenance group included 39 premenopausal women, and the observation group included 44 premenopausal women. The median ages in the maintenance and observation groups were 56 years and 54 years, respectively. All patients had an ECOG score of 0–1, and most patients in both groups had multiple metastatic sites and visceral metastases. More than 80% of the patients underwent surgical resection and received adjuvant/neoadjuvant chemotherapy. CK5/6 and EGFR were negatively expressed in nearly 20% of cases (*Figure 1*). The clinicopathological features of the patients are shown in *Table 1*.

Efficacy analysis

In the 164 patients investigated, the objective response rate and the disease control rate after the first 6 cycles of combination therapy were 51.83% (85/164) and 70.12% (115/164), respectively. As of the deadline for follow-up (August 31, 2019), 9 patients in the maintenance group were still alive, and 4 were alive in the observation group. In the maintenance group, the median follow-up time was 29.8 months, the mPFS was 7.3 months, and the mOS was 22.4 months. In the observation group, the median follow-up time was 26.1 months, the mPFS was 5.7 months, and the mOS was 17.9 months. Maintenance therapy significantly prolonged the mPFS time by 1.6 months (P=0.0016) (*Figure 2*) and the mOS time by 4.5 months (P=0.0055) (*Figure 3A*). For all 115 patients, those with

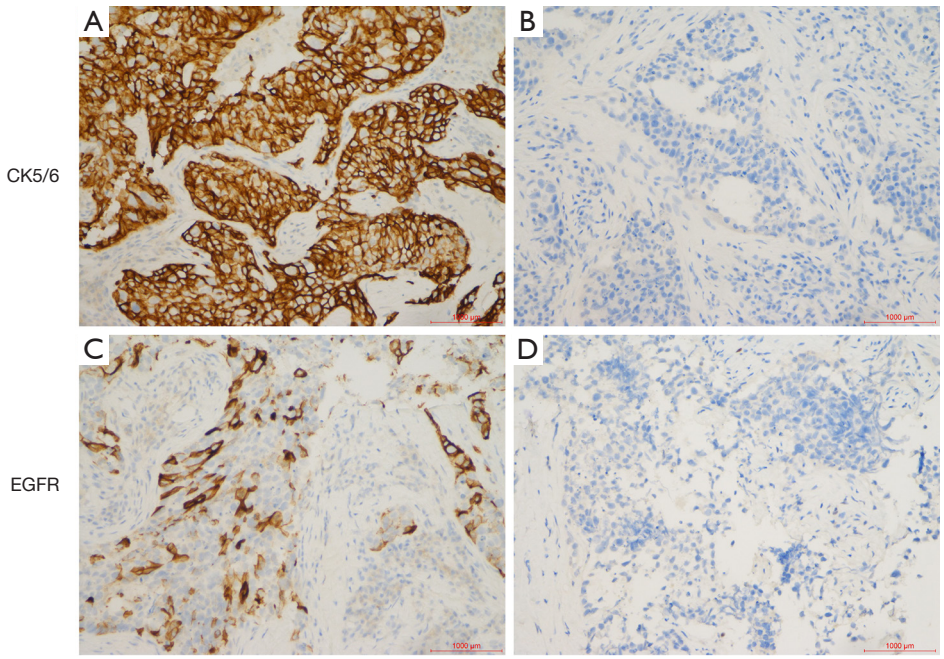

Figure 1 CK5/6 and EGFR expression by immunohistochemistry. (A,B) CK5/6 positive/negative staining; (C,D) EGFR positive/negative staining. EGFR, epidermal growth factor receptor.

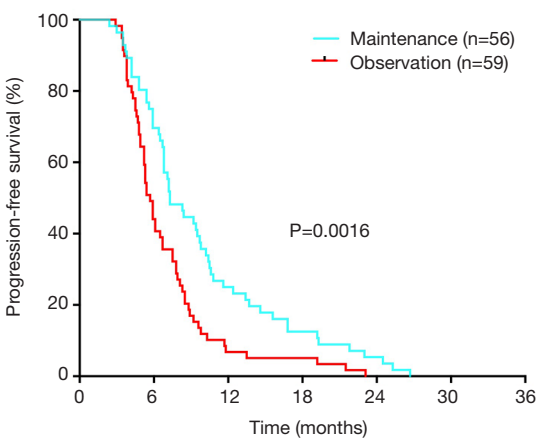

Figure 2 Progression-free survival (PFS) of TNBC patients treated with combination chemotherapy followed by capecitabine maintenance and observation. TNBC, triple-negative breast cancer.

basal-like TNBC had a shorter survival time than those with non-basal-like TNBC (18.6 *vs.* 27.4 months, P=0.0062) (*Figure 3B*). In the maintenance group, the OS of non-basal-like TNBC patients was 9.4 months longer than that of basal-like TNBC patients (30.2 *vs.* 20.8 months, P=0.0285) (*Figure 3C*), whereas in the observation group, the OS of non-basal-like TNBC patients was 5.8 months longer than that of basal-like TNBC patients, although the difference was not significant (22.3 *vs.* 16.5 months, P=0.0658) (*Figure 3D*). Maintenance with capecitabine significantly prolonged the OS of patients with non-basal-like TNBC (30.2 *vs.* 22.3 months, P=0.0257) (*Figure 4A*), but no significant difference was observed in basal-like TNBC patients (20.8 *vs.* 16.5 months, P=0.0541) (*Figure 4B*). In the maintenance group, the OS benefit was found to be present in patients over 50 years of age (P=0.005), in those with visceral metastases (P=0.035), in those with a response to initial therapy (P=0.017), and in those with CK5/6- and/or EGFR-negative cancer (P=0.032) (*Table 2*). Age, visceral metastases, response to initial therapy, maintenance therapy, and CK5/6 and EGFR status were independent prognostic factors.

Toxicity analysis

In the maintenance group, 56 patients received a total of 725 cycles of chemotherapy, including 389 cycles of capecitabine maintenance therapy (median, 8 cycles), and 59 patients in the observation group underwent a total of 354 chemotherapy cycles in the absence of another

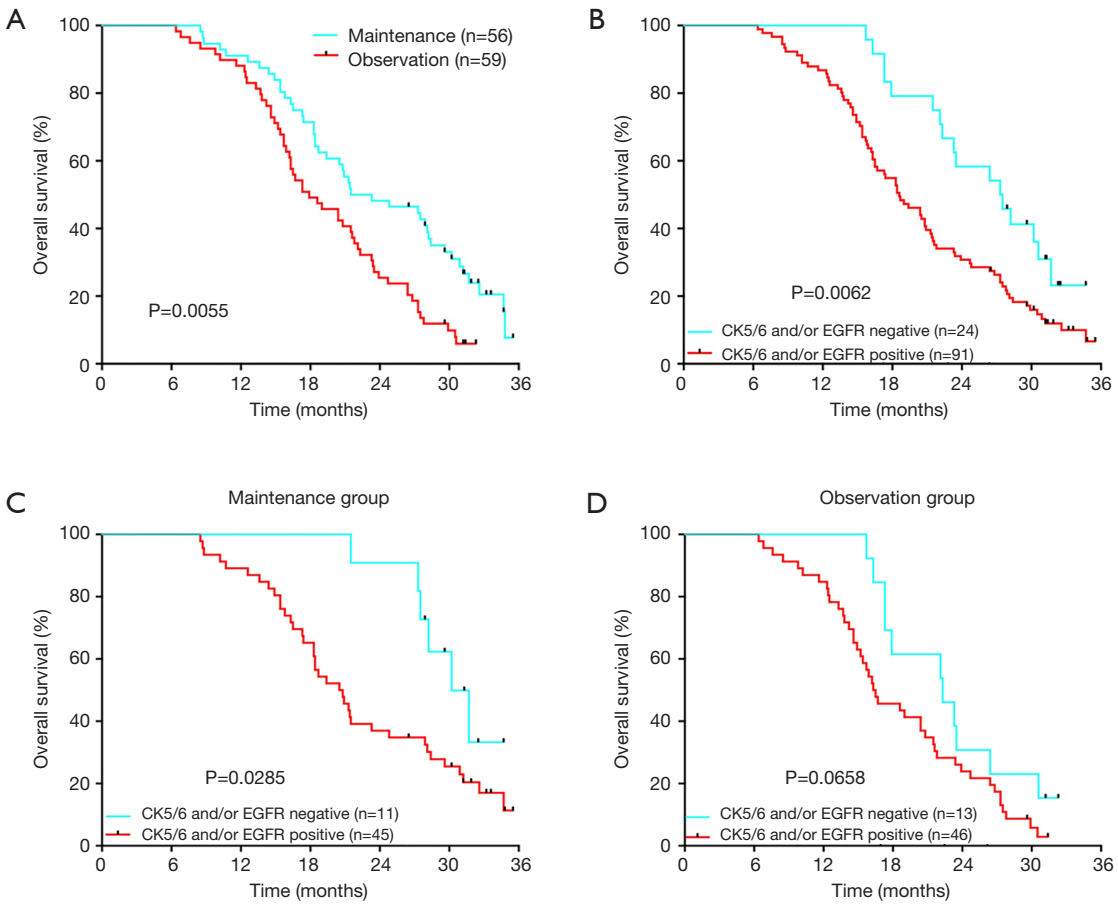

Figure 3 Overall survival (OS) of TNBC patients treated with combination chemotherapy followed by capecitabine maintenance and observation. (A) OS of the maintenance group and observation group. (B) OS of the basal-like TNBC group and non-basal-like TNBC group. (C) OS of basal-like TNBC patients and non-basal-like TNBC patients in the capecitabine maintenance group. (D) OS of basal-like TNBC patients and non-basal-like TNBC patients in the observation group. TNBC, triple-negative breast cancer.

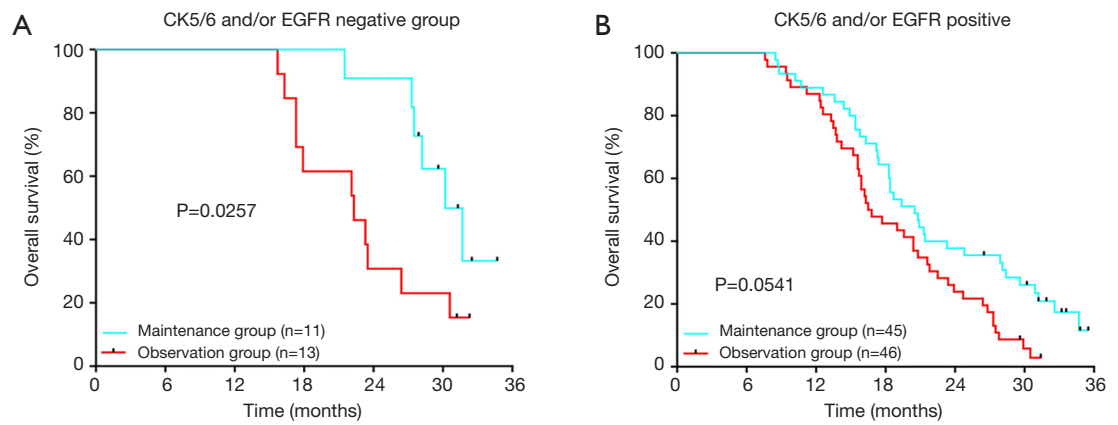

Figure 4 Overall survival (OS) in the capecitabine maintenance group and observation group. (A) OS of CK5/6- and/or EGFR-negative patients in the maintenance group and observation group. (B) OS of CK5/6- and/or EGFR positive patients in the maintenance group and observation group. EGFR, epidermal growth factor receptor.

Table 2 Cox's proportional hazard model analysis of prognostic in patients with mTNBC

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
>50/≤50	0.430	0.255–0.723	0.001	0.388	0.200–0.756	0.005
ECOG performance status						
ECOG 1/ECOG 0	1.143	0.695–1.880	0.598			
Menopausal status						
Premenopausal/postmenopausal	1.519	0.787–2.648	0.141			
Number of metastatic site						
Multiple/single	1.604	1.160–2.219	0.004	1.156	0.751–1.781	0.510
Visceral metastases						
Absent/present	0.285	0.144–0.566	0.000	0.570	0.338–0.961	0.035
Response to initial therapy						
Stable disease/response	1.589	1.048–2.782	0.015	2.076	1.139–3.785	0.017
Prior adjuvant/neoadjuvant therapy						
No/yes	1.376	0.829–2.282	0.217			
Group						
Maintenance/observation	0.337	0.286–0.893	0.047	0.565	0.334–0.954	0.033
CK5/6 and EGFR status						
CK5/6 and/or EGFR negative/CK5/6 and/or EGFR positive	0.490	0.250–0.960	0.038	0.285	0.089–0.917	0.032

mTNBC, metastatic triple-negative breast cancer; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.

treatment until disease progression. According to the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE), we found hematologic and digestive system toxic effects were the most common adverse events (*Table 3*). Toxicities of all grades were significantly more frequent in the maintenance group compared with the observation group (neutropenia, 85.71% *vs.* 25.87%, P<0.001; thrombocytopenia, 55.36% *vs.* 11.86%, P<0.001; anemia, 82.14% *vs.* 52.54%, P=0.001; nausea, 83.47% *vs.* 11.86%, P<0.001; vomiting, 69.64% *vs.* 8.47%, P<0.001), and hand-foot syndrome (HFS), 32.14% *vs.* 8.47%, P=0.002). The incidence rates of grade 3–4 neutropenia and (hand-foot syndrome) were also significantly higher in the maintenance group (55.9% *vs.* 2.6%, P<0.001; 8.93% *vs.* 0%, P=0.019).

Discussion

At present, cytotoxic drugs are still the main treatment for TNBC. However, once chemotherapy is withdrawn, tumors can quickly relapse and metastasize. Several studies have reported mPFS ranging from 3.8–5.1 months after the termination of chemotherapy (19,20). Therefore, maintenance therapy is particularly important, and increased attention is being focused on maintenance therapy in patients with TNBC. However, there is great variation in the mPFS (7.6–9.1 months) and mOS (18.1–19.2 months) reported by different studies (21,22).

The prognosis of TNBC currently depends on the molecular subtype. Among the diverse subtypes of TNBC, basal-like is one of the most malignant. The gold standard for identifying BLBC is still based on gene expression profiling. However, technical problems and high costs limit the detection of gene expression profiles as a routine test in clinical practice. Using immunohistochemistry, numerous studies have shown that BLBC can be identified by ER-, PR-, HER-, CK5/6, and/or EGFR positivity (23-25). In

Table 3 Treatment-related toxicities

Adverse event	All grades					Grade 3–4				
	Maintenance (n=56)		Observation (n=59)		P	Maintenance (n=56)		Observation (n=59)		P
	N	%	N	%		N	%	N	%	
Neutropenia	48	85.71	15	25.87	<0.001	18	32.14	2	3.39	<0.001
Thrombocytopenia	31	55.36	7	11.86	<0.001	3	5.36	0	0.00	0.072
Anemia	46	82.14	31	52.54	0.001	9	16.07	5	8.47	0.213
Nausea	42	83.47	7	11.86	<0.001	3	5.36	0	0.00	0.072
Vomit	39	69.64	5	8.47	<0.001	2	3.57	0	0.00	0.143
Constipation	15	26.79	8	11.86	0.076	0	0.00	0	0.00	NA
Azotemia	3	5.36	0	0.00	0.072	0	0.00	0	0.00	NA
Hypohepatia	9	16.07	4	6.78	0.116	0	0.00	0	0.00	NA
HFS	18	32.14	1	1.69	<0.001	5	8.93	0	0.00	0.019

NA, not assessable; HFS, hand-foot syndrome.

particular, CK5/6 is considered to be an extremely useful marker for identifying TNBC subtypes (26).

CK5/6 expression has been reported in 24–72% of TNBCs (27,28). Patients with CK5/6-positive tumors often show a shorter survival time, and CK5/6 has been put forward as an independent prognostic factor in breast cancer (11,26). The overexpression of EGFR has been observed in more than half (57%) of BLBCs (11), and its expression was reported to be closely related to tumor grade and lymph node metastasis in 60.3–71.4% of patients with TNBC. Another study reported that patients with EGFR-positive TNBC responded poorly to neoadjuvant chemotherapy and showed poor DFS and OS compared with patients with EGFR-negative status. Furthermore, a multivariate analysis showed EGFR to be an independent predictor of PFS and OS in TNBC (29,30). Thus, CK5/6 and EGFR are widely considered as molecular markers for BLBC. Using this surrogate panel, 79.13% of patients with TNBC were classified as BLBC in our study. Among the 115 patients who achieved disease control, we found that the mOS of patients with BLBC was significantly shorter than that of non-BLBC patients (18.6 *vs.* 27.4 months, P=0.0062), and the prognosis of non-BLBC patients was significantly better than that of BLBC patients. Multivariate regression analysis revealed that age, visceral metastases, response to initial therapy, maintenance therapy, and CK5/6 and EGFR status were independent prognostic factors for, which was similar to the results reported by other studies (3,31,32).

Our investigation also confirmed that CK5/6 and EGFR were biomarkers for the prognosis of TNBC patients. Maintenance therapy has been recommended for metastatic TNBC by multiple guidelines, and our study showed that after 6 cycles of initial chemotherapy, capecitabine maintenance therapy achieved improved PFS and OS in TNBC patients. Simultaneously, we also examined CK5/6 and EGFR expression to evaluate the effect of capecitabine maintenance therapy on prognosis in BLBC and non-BLBC patients. We observed that maintenance with capecitabine significantly prolonged the OS of patients with non-basal-like TNBC (30.2 months *vs.* 22.3 months, P=0.0257), but there was no significant difference in the OS of basal-like TNBC patients (20.8 *vs.* 16.5 months, P=0.0541). This suggested that CK5/6 and EGFR might predict the efficacy of capecitabine maintenance therapy in TNBC.

A platinum-based combination chemotherapy regimen has been considered as an alternative or even as the preferred first-line chemotherapy option for treating patients with mTNBC (33-35). Some preliminary clinical trial data (36), a randomized neoadjuvant clinical study (37), and a retrospective case review of adjuvant therapy (21) have provided some level of evidence for platinum activity in TNBC patients. In our study, we observed that the objective response rate and the disease control rate were 51.83% (85/164) and 70.12% (115/164) in patients with TNBC who received 6 cycles of combination chemotherapy as a first-line treatment, which was similar to the results reported by previous studies. Patients in the maintenance group received 6 cycles of combination chemotherapy and another

8 (median) cycles of single capecitabine, while those in the observation group received only 6 cycles of combination chemotherapy. In the maintenance group, the mPFS and mOS were 1.6 and 4.5 months longer, respectively, than those in the observation group (7.3 *vs.* 5.7 months and 22.4 *vs.* 17.9 months, respectively), and the differences were significant. We suspect that these results are attributable to the additional maintenance treatment. More cycles may improve the clinical benefit, but more cycles also encompass more side effects (16,20,38,39). Significantly higher bone marrow toxic effects, especially grade 3–4 neutropenia, were observed in the maintenance treatment group than in the observation group (32.14% *vs.* 3.39%, P<0.001), and the incidence rates of nausea, vomiting, and HFS were also all significantly higher in the maintenance group (83.47% *vs.* 11.86, P<0.001; 69.64.6% *vs.* 8.47%, P<0.001; and 32.14% *vs.* 8.47%, P=0.002, respectively).

In conclusion, our results confirmed that capecitabine maintenance therapy can prolong the mPFS and mOS of patients with mTNBC. This is a widely accepted therapeutic strategy for mTNBC patients. The toxic effects of the maintenance therapy were well tolerated, and the long-term clinical outcomes were encouraging. Moreover, we demonstrated that patients with non-basal-like TNBC had a better prognosis than those with basal-like TNBC and could benefit from maintenance therapy with capecitabine. Our findings suggest that CK5/6 and EGFR may serve as prognostic biomarkers in patients with TNBC and could be used to predict the efficacy of capecitabine maintenance therapy.

Acknowledgments

The authors thank B. Draper and J. Reynolds for English language editing.
Funding: This research was supported by the National Natural Science Foundation of China (No. 81802651) and Foundation of "Peak" Training Program for Scientific Research of Yijishan Hospital, Wannan Medical College (No. GF2019G11).

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-1760

Data Sharing Statement: Available at http://dx.doi.org/10.21037/tcr-20-1760

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-1760). 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 Ethical Committee of the First Affiliated Hospital of Wannan Medical College (No.: 2008-7) and individual consent for this retrospective analysis was waived.

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Cite this article as: Zhu Y, Li K, Zhang J, Wang L, Sheng L, Yan L. The prognostic and predictive significance of cytokeratin 5/6 and epidermal growth factor receptor in metastatic triple-negative breast cancer treated with maintenance capecitabine. Transl Cancer Res 2021;10(3):1193-1203. doi: 10.21037/tcr-20-1760

