Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Comparative Analysis of Clinical Efficacy and Safety of Pyrotinib Plus Capecitabine versus Trastuzumab Emtansine (T-DM1) as Second-Line Treatment for HER2-Positive Advanced Breast Cancer: A Retrospective Study

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Background: HER2-positive advanced breast cancer poses significant treatment challenges. In China, T-DM1 and pyrotinib are key second-line therapies. A comprehensive evaluation of the comparative efficacy and safety profiles of these therapies is imperative for optimizing therapeutic strategies and enhancing patient outcomes. This study aims to compare the clinical efficacy and safety of T-DM1 against pyrotinib plus capecitabine.

Methods: Patients are females with HER2-positive, locally advanced, or metastatic breast cancer who at least 18 years old and have received anti-HER2 therapy in the past. This study included 148 patients who satisfied the inclusion criteria. Of these, 74 patients received intravenous T-DM1 (3.6 mg/kg) every 21 days, while the other 74 patients got oral pyrotinib (400 mg, once daily) plus capecitabine (1000 mg/m^2, twice daily on days 1–14 of each 21-day cycle). Progression-free survival (PFS) was the main outcome, while overall survival (OS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs) were the secondary outcomes.

Results: The median PFS was 12.2 months for the pyrotinib group vs 9.1 months for the T-DM1 group. The median follow-up was 12.7 months for pyrotinib and 9.3 months for T-DM1. The pyrotinib group had better DCR (56.8% vs 54.1%) and ORR (40.5% vs 29.7%). While adverse events were manageable, the most common severe AE in the pyrotinib group was diarrhea (24.3%), and in the T-DM1 group, it was thrombocytopenia (16.2%). However, by reducing the drug dosage or providing symptomatic treatment, most adverse events could be controlled at grades 1 to 2, indicating that the adverse events were manageable. Neither group recorded any adverse event-related deaths.

Conclusion: Pyrotinib plus capecitabine significantly improves median PFS compared to T-DM1 in patients with HER2-positive advanced breast cancer, demonstrating a favorable efficacy profile alongside manageable safety concerns.

Keywords: breast cancer, T-DM1, pyrotinib, capecitabine, HER2

Introduction

Breast cancer is one of the most prevalent malignancies in the world, endangering the health of women and being the primary cause of death from cancer in women.[1] Although treatment for breast cancer has been improving, the cure rate and survival rate still face significant challenges. According to estimates, there were 300,590 new events of breast cancer in the United States in 2023, with around 297,790 of them in women. The estimated number of deaths was 43,700, of

Received: 10 January 2025
Accepted: 3 April 2025
Published: 14 April 2025

which around 43,170 were in women.[2] In China, from 1990 to 2019, breast cancer incidence and mortality rates increased significantly and are expected to continue rising until 2034.[3] Breast cancer can be classified into four types based on distinct biological markers and histological characteristics: Luminal A, Luminal B, human epidermal growth factor 2 (HER2) overexpression, and Basal-like.[4] Among these subtypes, HER2-overexpressing breast cancer accounts for approximately 15–20% of all breast cancer cases.[5] The overexpression of HER2 leads to sustained activation of HER2 receptors, even in the absence of external stimuli, resulting in heightened invasiveness and a poor prognosis. However, the survival rate of patients with HER2-positive breast cancer has significantly improved due to the advent of HER2-targeted therapies, such as trastuzumab and pertuzumab.[6] For example, data from the CLEOPATRA clinical trial indicated that the combination of trastuzumab, pertuzumab, and docetaxel significantly improved the median overall survival (mOS) and median progression-free survival (mPFS) for patients with advanced HER2-positive breast cancer, increasing mOS from 40.8 months to 57.1 months and mPFS from 12.4 months to 18.7 months,[7] respectively. Despite the substantial efficacy of these agents, resistance remains a significant challenge in the treatment of HER2-positive breast cancer.[8] Therefore, it is crucial to develop new therapeutic options for patients who have failed previous anti-HER2 therapies.

The first antibody-drug conjugates (ADCs) approved by the Food and Drug Administration (FDA) was Trastuzumab Emtansine (T-DM1).[9] It not only possesses the cytotoxic effects of trastuzumab, such as inducing tumor cells to arrest in the G1 phase and inhibiting tumor proliferation through antibody-dependent cellular cytotoxicity (ADCC), but also demonstrates strong targeting ability, specifically binding to tumor cells that overexpress HER2 and inducing their death.[10,11] Due to the dual advantages of targeted delivery and cytotoxicity, T-DM1 can reduce damage to normal cells and decrease the drug's side effects.[12] As a result, T-DM1 is gradually becoming a new treatment option for patients with HER2-positive metastatic breast cancer and is also a standard second-line recommendation for the treatment of advanced HER2-positive breast cancer abroad. Despite Trastuzumab deruxtecan (DS-8201) demonstrating superior efficacy among ADCs,[13] it has not been included in insurance coverage. Furthermore, its relatively high incidence of serious side effects,[14] such as interstitial pneumonia, can impose a significant financial burden on patients. This situation may lead to treatment discontinuation, ultimately diminishing patients' quality of life.

In addition to ADCs, the pan-HER receptor tyrosine kinase inhibitor (TKI) pyrotinib, which targets HER1, HER2, and HER4, has demonstrated promising efficacy for patients with advanced HER2-positive breast cancer in recent years.[15] Developed independently in China, pyrotinib is now widely used in the treatment of this patient population.[16] The HER family of receptors primarily includes EGFR/HER1, HER2, HER3, and HER4. Pyrotinib primarily exerts its effects by covalently binding to the ATP-binding sites within the intracellular kinase domains of HER1, HER2, and HER4. This binding inhibits the formation of both homodimers and heterodimers within the HER family, prevents autophosphorylation, and blocks the activation of downstream signaling pathways.[17] As a result, pyrotinib causes tumor cells to stagnate in the G1 phase and inhibits their growth. According to the 2024 edition of the Chinese Society of Clinical Oncology (CSCO) breast cancer guidelines,[18] both small molecule TKIs and ADCs are equally recommended for patients who have failed anti-HER2 therapy, based on the findings of the DESTINY-Breast03 study.[19] For patients with HER2-positive metastatic breast cancer, the combination of pyrotinib and capecitabine, as well as T-DM1, is regarded as the preferred second-line treatment in China. Interestingly, international authoritative guidelines, such as those from the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), typically recommend T-DM1 as the preferred option among these therapies.[20] However, there is currently no direct comparison of the efficacy and safety of pyrotinib plus capecitabine versus T-DM1 for HER2-positive metastatic breast cancer.

To address this gap, this retrospective study aims to evaluate the safety and clinical efficacy of pyrotinib plus capecitabine versus T-DM1 in patients with HER2-positive advanced breast cancer who have failed prior anti-HER2 therapies. This research is significant as it provides essential comparative data to optimize treatment strategies in clinical practice. A direct comparison will guide clinicians in selecting the most effective therapy, while an understanding of the safety profiles of each option can help mitigate adverse effects and improve patient management. Ultimately, this analysis may influence treatment guidelines and enhance patient outcomes in this challenging population.

Methods

Participants

This study was carried out in Yantai Yuhuangding Hospital and approved by the Ethics Committee (Grant No. YYYIRB-IIT[2025]001), adhering to the Helsinki Declaration. A total 148 patients who satisfied the inclusion criteria were admitted to this trial between March 2020 and September 2023. All patients meet the following criteria: (1) histologically confirmed HER-2 positive (immunohistochemistry score of 3+ or 2+ with HER-2 amplification detected by FISH) advanced breast cancer, independent of hormone receptor ER, PR status;(2) at least one lesion that can be evaluated using the RECIST 1.1 criteria; (3) for those who have brain metastases, lesions are non-newly developed, show no enlargement, do not require immediate treatment, or have stabilized after treatment; (4) ECOG score of 0–1; (5) prior treatment with anti-HER2 therapy; (6)expected survival time ≥ 6 months; (7) patients with good pulmonary and cardiac function. The following criteria were excluded: (1) male breast cancer patients; (2) patients with severe cardiovascular and cerebrovascular diseases; (3) pregnant or lactating women; (4) patients with other concomitant tumors; (5) patients with psychiatric disorders.

Procedures

This study included 148 patients who met the inclusion criteria. Among them, 74 patients received intravenous T-DM1 at a dosage of 3.6 mg/kg every 21 days, while the remaining 74 patients were administered oral pyrotinib at 400 mg once daily, in combination with capecitabine at 1000 mg/m² taken twice daily from days 1 to 14 of each 21-day cycle. Baseline characteristics and ancillary examination results were obtained from the electronic medical record system at Yantai Yuhuangding Hospital. Progression-free survival (PFS) was designated as the primary outcome, while overall survival (OS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs) were considered secondary outcomes. All patients underwent regular evaluations throughout the treatment period, with imaging studies performed every two cycles to assess treatment efficacy. Follow-up will continue until August 31, 2024, or until disease progression is observed.

Outcomes and Assessments

The efficacy evaluation will be conducted using RECIST version 1.1.[21] Responses will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). (CR + PR) / total number of cases × 100% is the objective response rate (ORR), and (CR + PR + SD) / total number of cases × 100% is the disease control rate (DCR). Progression-free survival (PFS) is the amount of period between randomization and the development of a tumor or death from any reason. Overall survival (OS) is the period between randomization and death from any reason. The National Cancer Institute's CTCAE version 5.0 will be used to evaluate adverse events.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0. Descriptive statistics were employed to analyze patients' adverse events and clinical baseline characteristics. For group comparisons, independent sample *t*-tests and chi-square tests or Fisher's exact test were utilized, with categorical data expressed as [n (%)]. The Kaplan-Meier method was applied to evaluate progression-free survival. A p-value of < 0.05 was established as the threshold for statistical significance.

Results

Patient Characteristics

Initially, the study included 163 patients; however, 15 patients were excluded (2 male patients, 7 patients without follow-up information, 1 patient with a mental illness, 3 patients with severe cardiopulmonary diseases, and 2 patients who had not received prior anti-HER2 therapy) (Figure 1). Consequently, all 148 patients included in the study were female, aged between 35 and 80 years, with an average age of 55.97 years in the T-DM1 group and 56.51 years in the pyrotinib plus capecitabine group. Based on the pathological and immunohistochemical findings at initial diagnosis, the pyrotinib plus

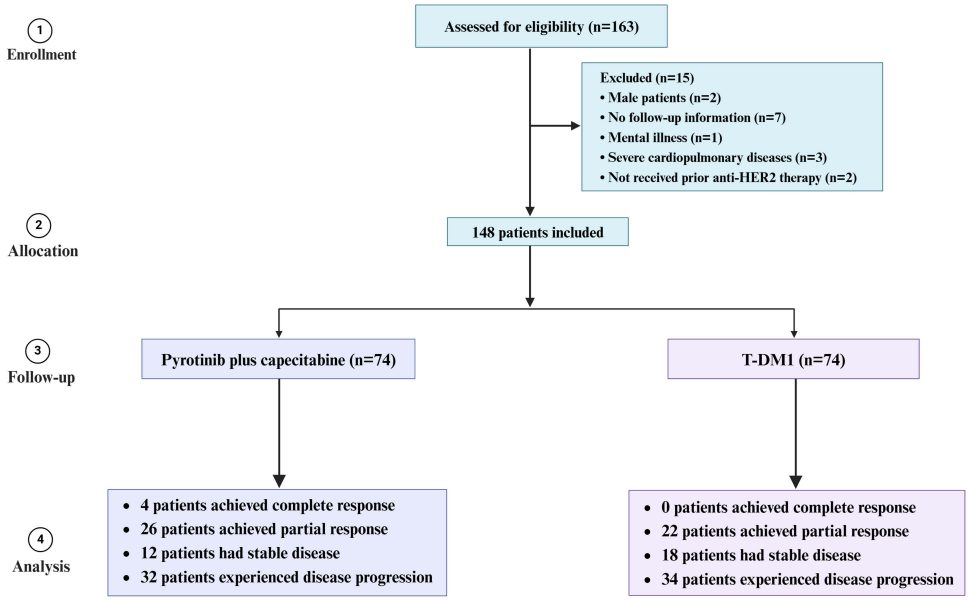

Figure 1 Patient enrollment flow chart.

capecitabine group included 44 patients with negative hormone receptor status, all of whom had invasive carcinoma. Among these patients, 64 had visceral metastasis, and 19 had brain metastasis. A total of 54 patients (72.0%) had previously received single-target therapy (trastuzumab), while 20 (26.7%) had undergone dual-target therapy (pertuzumab plus trastuzumab). In the T-DM1 group, there were 38 patients with negative hormone receptor status, 69 with invasive carcinoma, and 5 with other histological types. This group included 56 patients with visceral metastasis and 14 with brain metastasis, as well as 50 patients (67.6%) who had received single-target therapy (trastuzumab) and 24 (32.4%) who had received dual-target therapy (pertuzumab plus trastuzumab). The baseline characteristics of patients were comparable between both groups. Comprehensive baseline information is detailed in Table 1.

Table 1 Baseline Characteristics of the Enrolled Patients in the Study

Variable	Pyrotinib Plus Capecitabine (n=74)	T-DM1 (n=74)	P value
Age			0.731
Median(range)	56.51(35~72)	55.97(35~80)	
<60	45(60.8%)	42(56.8%)	
≥60	29(39.2%)	32(43.2%)	
ECOG			0.681
0	2(2.7%)	4(5.4%)	
1	72(97.3%)	70(94.6%)	
Hormone-receptor status			0.321
ER and PR negative	44(59.5%)	38(51.4%)	
ER and/or PR positive	30(40.5%)	36(48.6%)	
Histological type			0.058
Invasive carcinoma	74(100%)	69(93.2%)	
Other types	0(0%)	5(6.8%)	
Visceral metastasis			0.093
Yes	64(86.5%)	56(75.7%)	
No	10(13.5%)	18(24.3%)	

(*Continued*)

Table 1 (Continued).

Variable	Pyrotinib Plus Capecitabine (n=74)	T-DM1 (n=74)	P value
Sites of metastasis			
Liver metastasis	26 (35.1%)	16 (21.6%)	0.068
Lung metastasis	38 (51.4%)	34 (45.9%)	0.511
Bone metastasis	24 (32.4%)	20 (27.0%)	0.472
Brain metastases			0.323
Yes	19(25.7%)	14(18.9%)	
No	55(74.3%)	60(81.1%)	
Number of metastatic sites			0.056
0~1	50(67.6%)	56(75.7%)	
2~3	20(27.0%)	16(21.6%)	
≥4	4(5.4%)	2(2.7%)	
Menopause			0.806
Yes	65(87.8%)	64(86.5%)	
No	9(12.2%)	10(13.5%)	
Previous anti-HER2 antibody treatment			0.472
Single target	54(73.0%)	50(67.6%)	
Double target	20(27.0%)	24(32.4%)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, Estrogen receptor; PR, progesterone receptor; HER2, Human Epidermal Growth Factor Receptor 2.

Clinical Curative Efficacy

As of August 31, 2024, the median progression-free survival (mPFS) for the pyrotinib plus capecitabine group was 12.2 months (95% CI: 11.371–13.029), while the T-DM1 group had an mPFS of 9.1 months (95% CI: 5.537–12.663) (Figure 2). The median follow-up duration for the pyrotinib plus capecitabine group was 12.7 months, compared to 9.3 months for the T-DM1 group. The pyrotinib plus capecitabine group demonstrated a lower disease progression rate

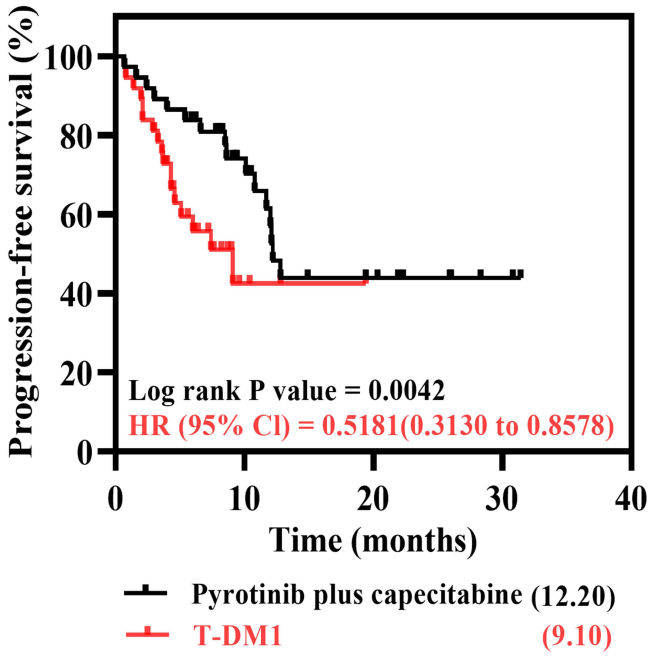

Figure 2 Kaplan-Meier estimates the mPFS in pyrotinib plus capecitabine and TDM1 group.

https://doi.org/10.2147/DDDT.S516394

Table 2 Differential Treatment Outcomes Between Pyrotinib-Capecitabine and T-DM1 Regimens in HER2+ Metastatic Breast Cancer

Group	n	CR (n, %)	PR (n, %)	SD (n, %)	PD (n, %)	ORR (n, %)	DCR (n, %)
Pyrotinib plus capecitabine	74	4 (5.4%)	26 (35.1%)	12 (16.2%)	32 (43.2%)	30 (40.5%)	42 (56.8%)
T-DM1	74	0 (0.0%)	22 (29.7%)	18 (24.3%)	34 (45.9%)	22 (29.7%)	40 (54.1%)

Abbreviations: CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; ORR, objective remission rate; DCR, Disease Control Rate.

than the T-DM1 group (43.2% vs 45.9%) and showed superior outcomes in terms of complete response (CR) (5.4% vs 0%) and partial response (PR) (35.1% vs 29.7%), although stable disease (SD) rates were lower in the pyrotinib plus capecitabine group (16.2% vs 24.3%). In addition, a comprehensive analysis revealed that the pyrotinib plus capecitabine group had a higher overall response rate (ORR) of 40.5% compared to 29.7% for the T-DM1 group, and a greater disease control rate (DCR) of 56.8% versus 54.1%, indicating a more favorable clinical efficacy of pyrotinib plus capecitabine over T-DM1 (Table 2). Furthermore, we also conducted a subgroup analysis based on hormone receptor status, visceral metastasis, and brain metastases. For patients with non-visceral metastases and negative hormone receptor status, there was no significant difference in mPFS between the two groups. However, patients with brain metastases experienced a longer mPFS in the pyrotinib plus capecitabine group compared to the T-DM1 group (11.7 months vs 9.1 months), as did those with visceral metastases (12.2 months vs 7.4 months) and hormone receptor-positive status (12.1 months vs 4.6 months) (Figure 3).

Adverse Events

This study indicates that grades 1 to 2 adverse events were the most commonly reported in both groups. In the pyrotinib plus capecitabine group, the most frequently observed side effects were diarrhea (86.5%), hand-foot syndrome (67.6%), and vomiting (54.1%). Diarrhea was the most prevalent grade 3 or higher adverse event, occurring in 24.3% of patients, with one individual requiring a dose reduction due to its severity. In the T-DM1 group, major side effects included thrombocytopenia (40.5%), fatigue (37.8%), and nausea (35.1%). Thrombocytopenia was also the predominant grade 3 or more severe adverse effect in this group, with an incidence rate of 16.2%, which prompted dose reductions for two patients due to its severity. Importantly, no patients in either group discontinued their medication due to side effects. Furthermore, neither treatment group reported any serious adverse events, such as cardiac or pulmonary toxicity, and no fatalities were recorded. Detailed information regarding the adverse events can be found in Table 3.

Discussion

In 15–20% of breast cancer cases, HER2 overexpression is associated with increased malignancy, a higher likelihood of metastasis, poor prognosis, and resistance to chemotherapy and endocrine therapy.[22] However, the advent of anti-HER2 therapies has improved the quality of life and extended survival for patients with HER2-positive breast cancer, leading to better prognoses.[23,24] Currently, anti-HER2 therapies are classified into three main categories: small-molecule TKIs (such as pyrotinib and lapatinib), ADCs like T-DM1 and DS-8201, and monoclonal antibodies such as trastuzumab and pertuzumab.[25] The CSCO breast cancer guidelines recommend pyrotinib and T-DM1 as second-line treatments for patients with HER2-positive advanced breast cancer. In contrast, the NCCN guidelines tend to prioritize ADCs, such as DS-8201 and T-DM1.[26] This discrepancy may be due to variations in clinical trial data, real-world differences, the guideline development process, and the influence of insurance policies on drug availability and distribution.

Recent clinical trials have shown promising outcomes for pyrotinib and T-DM1 in individuals with HER2-positive metastatic breast cancer. The FDA has approved T-DM1 as the fourth targeted anti-HER2 therapy, following trastuzumab, lapatinib, and pertuzumab. T-DM1 is an ADC composed of trastuzumab linked to DM1 via a novel succinimidyl ester conjugation, combining HER2-targeting properties with the cytotoxic effects of DM1.[27,28] The EMILIA clinical study directly compared the effectiveness of lapatinib plus capecitabine with T-DM1.[29] The final overall survival analysis revealed a mPFS of 9.6 months in the T-DM1 group, compared to 6.4 months in the lapatinib group (HR = 0.650, 95% CI

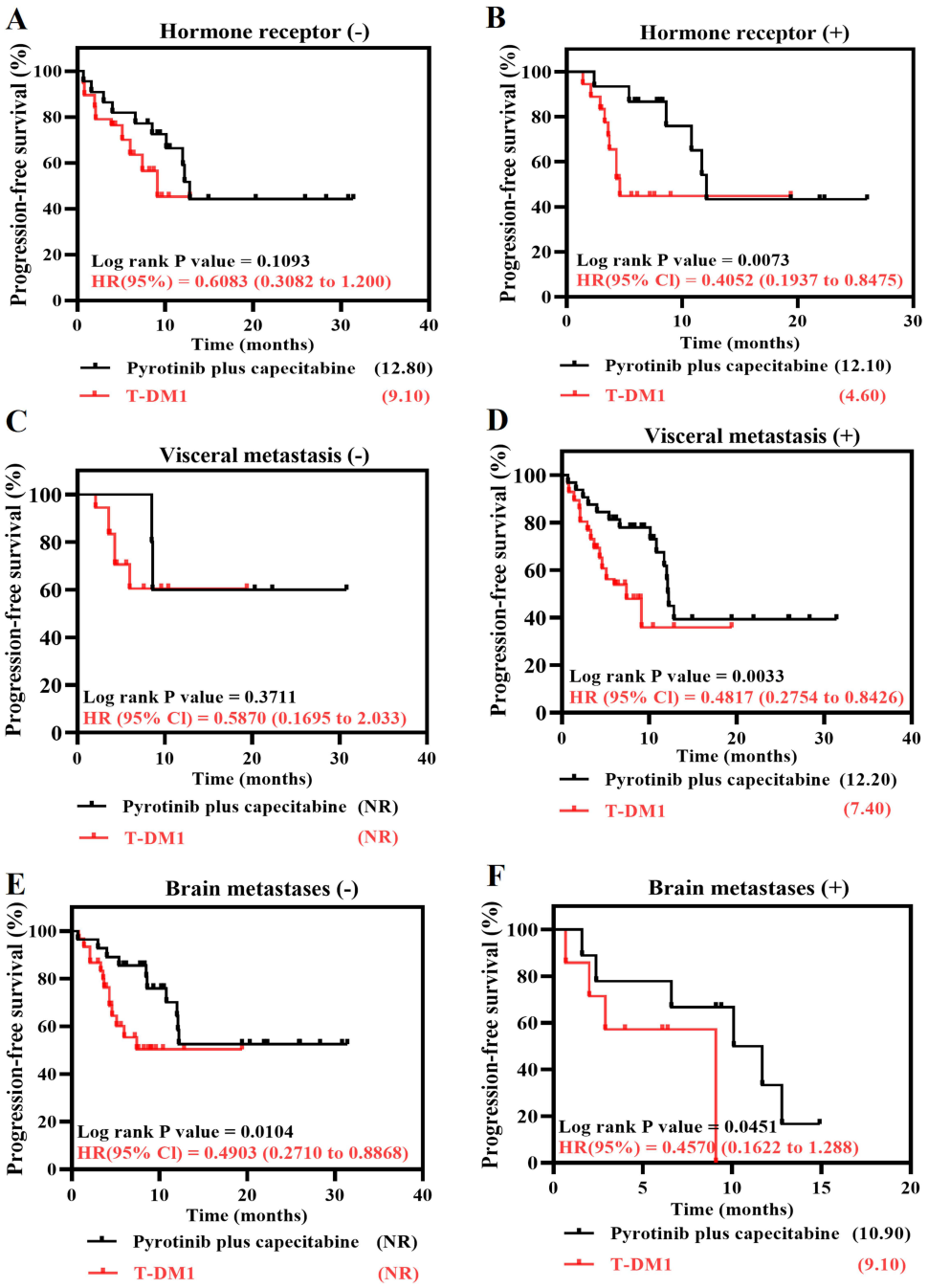

Figure 3 Kaplan-Meier comparison of PFS between the two treatment groups in different subgroups. (**A**) hormone receptor-negative patients; (**B**) hormone receptor-positive patients; (**C**) patients without visceral metastasis; (**D**) patients with visceral metastasis; (**E**) patients without brain metastases; (**F**) patients with brain metastases. Note: NR-Not Reached.

0.55–0.77). Furthermore, the T-DM1 therapy group demonstrated a superior median overall survival (mOS) of 30.9 months, compared to 25.1 months for the lapatinib group (HR = 0.68, 95% CI 0.55–0.85). In our study, the mPFS in the T-DM1 group was slightly lower at 9.1 months, which may be attributed to differences in baseline patient characteristics, disease features, sample size, or prior treatments. The PHOEBE clinical trial indicated that the mPFS for the pyrotinib group was significantly longer than that for the lapatinib group (12.5 months vs 6.8 months, HR = 0.39, 95% CI 0.27–0.56).[29] Additionally, in the PHENIX clinical trial, the pyrotinib group exhibited an extended mPFS of 11.1 months compared to 4.1 months in the control group (HR = 0.18, 95% CI 0.13–0.26). Our study observed an mPFS of 12.2

https://doi.org/10.2147/DDDT.S516394

Table 3 The Incidence and Severity of Treatment-Related Adverse Events in the Two Treatment Groups

Adverse Events	Pyrotinib Plus Capecitabine (n=74, %)		T-DM1 (n=74,%)	
	All Grade	Grade ≥3	All grade	Grade ≥3
Hematologic toxicity				
Anaemia	28 (37.8%)	0	12 (16.2%)	4 (5.4%)
Thrombocytopenia	5 (6.8%)	0	30 (40.5%)	12 (16.2%)
Neutropenia	34 (45.9%)	2 (2.7%)	6 (8.1%)	4 (5.4%)
Gastrointestinal disorders				
Nausea	30 (40.5%)	0	26 (35.1%)	0
Vomiting	40 (54.1%)	6 (8.1%)	15 (20.3%)	0
Diarrhoea	64 (86.5%)	18 (24.3%)	18 (24.3%)	1 (1.4%)
Constipation	0	0	17 (23.0%)	0
Decreased appetite	22 (29.7%)	1 (1.4%)	14 (18.9%)	0
General disorders				
Fatigue	12 (16.2%)	0	28 (37.8%)	0
Headache	2 (2.7%)	0	22 (29.7%)	2 (2.7%)
Others				
Elevated AST	25 (33.8%)	3 (4.1%)	16 (21.6%)	4 (5.4%)
Elevated ALT	24 (32.4%)	2 (2.7%)	11 (14.9%)	2 (2.7%)
Hand-foot syndrome	50 (67.6%)	8 (10.8%)	2 (2.7%)	0
Rash	5 (6.8%)	0	6 (8.1%)	0
Musculoskeletal pain	2 (2.7%)	0	24 (32.4%)	0
Peripheral neuropathy	2 (2.7%)	0	8 (10.8%)	2 (2.7%)
Epistaxis	2 (2.7%)	0	19 (25.7%)	0
Upper respiratory tract infection	12 (16.2%)	0	10 (13.5%)	0
Cough	3 (4.1%)	0	16 (21.6%)	0
Stomatitis	16 (21.6%)	0	2 (2.7%)	0
Hypokalaemia	21 (28.4%)	2 (2.7%)	4 (5.4%)	0

months in the pyrotinib group, which closely aligns with findings from the PHOEBE and PHENIX trials. This suggests that pyrotinib significantly enhances mPFS compared to lapatinib.

Furthermore, our investigation indicates that pyrotinib plus capecitabine demonstrates superior clinical efficacy compared to T-DM1 in HER2-positive metastatic breast cancer. The objective response rate (ORR) was higher in the pyrotinib group (40.5% vs 29.7%), as was the disease control rate (DCR) (56.8% vs 54.1%). Patients receiving pyrotinib plus capecitabine achieved an mPFS of 12.2 months, notably longer than the 9.1 months observed in the T-DM1 group. These findings suggest that pyrotinib plus capecitabine may delay disease progression more effectively. The higher ORR, DCR, and longer PFS indicate that pyrotinib plus capecitabine could be a more effective treatment option, potentially providing patients with an extended treatment duration and improved quality of life. The superior performance of pyrotinib plus capecitabine may be attributed to its mechanism of action, which involves irreversible inhibition of the HER2 tyrosine kinase domain, promoting sustained inhibition of the HER2 signaling pathway compared to T-DM1's ADC mechanism. Our study found that the T-DM1 group did not achieve CR, possibly due to a small sample size or limited follow-up duration. Further investigation is needed to ascertain the long-term efficacy of both therapies.

As a small-molecule drug, pyrotinib demonstrates a greater ability to penetrate the blood-brain barrier compared to macromolecular agents, providing a significant advantage in treating brain metastases. In the PERMEATE clinical trial,[30] the mPFS for patients with brain metastases treated with pyrotinib plus capecitabine was 11.3 months, significantly

surpassing the 5.6 months observed in the control group, underscoring the efficacy and clinical value of pyrotinib. Similarly, our analysis revealed that the mPFS in the pyrotinib group was superior to that in the T-DM1 group for patients with brain metastases (10.9 months vs 9.1 months). These findings suggest that pyrotinib may provide a more effective treatment strategy for patients who have previously failed HER2-targeted therapy and have brain metastases. Additionally, our research showed that the pyrotinib group extended mPFS among patients with visceral metastases (12.2 months vs 7.4 months) and those with hormone receptor-positive status (12.1 months vs 4.6 months). Compared to T-DM1, pyrotinib demonstrated superior efficacy in these subsets, presenting a more advantageous treatment option and offering new insights into the management of visceral metastases and hormone receptor-positive patients. However, the limited follow-up duration and the small number of participants may impose certain limitations on these results. To further confirm the differences in efficacy between pyrotinib and T-DM1 across various patient subgroups, future clinical trials with larger sample sizes, extended follow-up periods, and more rigorous designs are essential.

The adverse event rates observed in this study were consistent with those reported in recent clinical research. In the pyrotinib plus capecitabine group, the most frequent side effects were diarrhea (86.5%) and hand-foot syndrome (67.6%), with 18 patients (24.3%) experiencing diarrhea of grade 3 or higher. Diarrhea typically occurred during the first treatment cycle, particularly within the first 1 to 3 days, and its incidence gradually declined in subsequent cycles. Despite the high incidence, most cases were manageable, primarily classified as grade 1 or 2, through the use of antidiarrheal medications or dose reductions. These episodes were characterized as short-term, frequent, and tolerable. Notably, the prophylactic use of antidiarrheal drugs effectively mitigated both the incidence and severity of diarrhea. In contrast, in the T-DM1 group, the most common adverse effects included thrombocytopenia (40.5%), fatigue (37.8%), and nausea (35.1%). Among these, thrombocytopenia was the most frequently encountered grade 3 or higher adverse event, with an incidence of 16.2%. Thrombocytopenia was notable for its rapid onset and quick recovery, typically reaching its nadir on the 8th day of treatment and returning to baseline before the next cycle. Given the small participant pool in this study, no cardiac or pulmonary toxicities, such as interstitial pneumonia, were reported in either group. Although the pyrotinib plus capecitabine group experienced a higher number of adverse events than the T-DM1 group, the majority of patients tolerated the treatment well, and the side effects were generally manageable. However, for patients with gastrointestinal issues, T-DM1 may be the preferable choice due to its minimal gastrointestinal impact. Conversely, pyrotinib plus capecitabine may be better suited for patients with lung conditions, as it has a lower impact on pulmonary function.

The limitations of this study include its retrospective design, relatively small sample size, and lack of prospective validation, which may affect the generalizability of the findings. Future research should further compare the efficacy of these two treatments from multiple perspectives, including their effectiveness in breast cancer patients with PI3KCA mutations and PTEN loss, which are significantly linked to prognosis and treatment response. Exploring the efficacy differences between these treatments in such patients could inform more personalized therapeutic strategies. Additionally, a deeper investigation into the molecular mechanisms underlying the differential responses in various patient subgroups may provide further insights into personalized treatment approaches for advanced breast cancer.

Conclusion

In conclusion, pyrotinib plus capecitabine has demonstrated superior clinical efficacy compared to T-DM1, with manageable adverse events. However, overall survival data remain immature due to the limited sample size and insufficient follow-up duration. Future multicenter, large-scale clinical studies are needed to further guide clinical practice, benefiting a broader patient population and advancing precision therapy.

Data Sharing Statement

All data included in this study are available upon request by contact with Prof. Jiannan Liu.

Ethics Approval

This study was reviewed and approved by the Ethics Committee of The Affiliated Yantai Yuhuangding Hospital of Qingdao University (Grant No. YYYIRB-IIT[2025]001) in compliance with the ethical principles outlined in the Declaration of Helsinki and China's Ethical Review Regulations for Human Subject Research in Life Sciences and

Medicine (2023). The ethics committee granted a waiver of written informed consent based on three determinations: (1) exclusive use of pre-existing de-identified medical records eliminating re-identification risks; (2) absence of risk of physical or psychological harm; and (3) strict maintenance of patient confidentiality and access limited to authorized researchers.

Acknowledgments

The authors would like to thank patients, nurses and clinicians for their participation in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by grants from National Natural Science Foundation of China (Grant No.82103585), Clinical Research Fund of Shandong Provincial Medical Association (Grant No. YXH2022ZX02107), and Yantai Science and Technology Innovation Development Plan (Grant No. 2024YD039).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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