Observational Study

Medicine

OPEN

Rechallenge of trastuzumab-based therapy in HER2-positive breast cancer patients who progressed after lapatinib plus capecitabine

Nijat Khanmammadov, MD[a,*], Izzet Doğan, MD[a], Bayarmaa Khishigsuren, MD[a], Abdulmunir Azizy, MD[a], Pinar Saip, MD[a], Adnan Aydiner, MD[a]

Abstract

Data regarding the use of rechallenge trastuzumab (RTmab)-based therapies in the management of heavily pretreated patients with HER2-positive breast cancer (BC) in the literature are limited. This study aimed to evaluate the efficacy of trastuzumab-based therapy in patients who experienced disease progression after receiving lapatinib plus capecitabine (LC). In this retrospective study, the data of thirty three HER2 positive metastatic BC patients who progressed after LC treatment and subsequently received trastuzumab-based treatment were evaluated. Trastuzumab was administered at an initial loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg every 21 days. The average age of patients is 47 years (range 25–72 years). The predominant histopathological subtype was invasive ductal carcinoma, which was observed in 23 (70%) patients. Estrogen receptor (ER) positivity was also noted in 16 (48%) patients. All patients had received palliative trastuzumab plus chemotherapy (Cht) before the lapatinib. In conjunction with trastuzumab-based therapy, vinorelbine was administered to 14 (42%) patients, paclitaxel to 12 (36%), and other chemotherapeutic agents to 4 (12%). For all patients, the objective response and disease control rates were 27% and 69%, respectively. Furthermore, the median progression-free survival (PFS) was 8.8 months (95% confidence interval [CI]: 6.6–11), and the median overall survival was 20 months (95% CI: 15.1–25.8). There were no statistically significant differences in PFS rates based on several factors, including age, ER status, denovo metastasis, brain metastasis, perioperative Cht, pre-Rtmab hormone therapy, and which Cht was used along with Rtmab ($P > .05$). Mild to moderate adverse events were observed in 17 (52%) patients, whereas only 4 (12%) patients had Grade 3 to 4 toxicity. This study demonstrated that RTmab-based therapy is effective in patients who progressed after LC. These findings contribute to the literature by suggesting that RTmab is a viable treatment option for patients with HER2-positive metastatic BC.

Abbreviations: BC = breast cancer, Cht = chemotherapy, CR = complete response, DCR = disease control rate, ER = estrogen receptor, LC = lapatinib plus capesitabine, ORR = objective response rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, RTmab = rechallenge trastuzumab, SD = stable disease.

Keywords: breast cancer, capecitabine, lapatinib, trastuzumab

1. Introduction

Breast cancer (BC) is considered to be the most prevalent malignancy among women worldwide.[1] Approximately 20% of all BC express the HER2 receptor and are associated with poorer prognosis. HER2 belongs to the HER family of transmembrane receptor tyrosine kinases and plays a pivotal role in cell proliferation, motility, resistance to apoptosis, invasiveness, and angiogenesis.[2] Trastuzumab is the pioneering anti-HER2 agent approved for the treatment of patients with HER2-positive disease. Its introduction dramatically altered the prognosis for women with HER2-positive BC.[3,4] The first-line treatment for HER2-positive advanced BC involves a combination of trastuzumab, pertuzumab, and taxane. However, in cases where patients experience disease progression after the initial treatment, the subsequent therapeutic options include trastuzumab deruxtecan and trastuzumab emtansine.[5] For patients who experience disease progression after trastuzumab-based treatment, lapatinib plus capecitabine (LC) therapy is a viable option, particularly for those favoring an orally administered regimen.[6] This combination therapy is thought to directly target the HER2 receptor, causing structural disruption in existing cancer cells.[7] A phase III trial in which the patients were randomly allocated to receive either LC or capecitabine alone

For this type of research, informed consent is not required.

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The local ethics committee approved this study at the Istanbul University Faculty of Medicine (October 10, 2022).

[a] *Department of Medical Oncology, Istanbul University Institute of Oncology, Istanbul, Turkey.*

** Correspondence: Nijat Khanmammadov, Department of Medical Oncology, Istanbul University Institute of Oncology, Çapa/Fatih, Istanbul 34093, Turkey (e-mail: nicatxanmemmedli@gmail.com).*

How to cite this article: Khanmammadov N, Doğan I, Khishigsuren B, Azizy A, Saip P, Aydiner A. Rechallenge of trastuzumab-based therapy in HER2-positive breast cancer patients who progressed after lapatinib plus capecitabine. Medicine 2025;104:6(e41468).

Received: 1 July 2024 / Received in final form: 11 January 2025 / Accepted: 17 January 2025

http://dx.doi.org/10.1097/MD.0000000000041468

demonstrated the systemic benefit of this treatment. Compared with capecitabine alone, the LC therapy significantly improved the progression-free survival (PFS) and exhibited a trend toward improved overall survival (OS), though the increase in OS was not statistically significant.[8,9]

In oncology practice, once the aforementioned treatment options are exhausted or if current treatments cannot be administered to patients due to side effects or high costs, a combination of rechallenge trastuzumab (RTmab) with various chemotherapeutic agents (e.g., gemcitabine, adriamycin, vinorelbine) is used. Evidence demonstrating the effectiveness of this treatment, particularly after lapatinib, in the literature is scarce. This study aimed to evaluate the efficacy of RTmab-based therapies following LC therapy.

2. Materials and methods

2.1. Patients and data collection

In this cross-sectional retrospective study, data of thirty-three HER2-positive mBC patients treated at a tertiary cancer center between 2010 and 2022 were examined. This study was deemed appropriate to be conducted during the Academic Coordination Committee meeting of the Istanbul Oncology Institute on October 10, 2022. These patients had previously undergone at least 1 course of trastuzumab-based therapy during the metastatic phase and experienced disease progression while receiving LC therapy. After progression under the LC therapy, the patients were administered trastuzumab, which consisted of an initial loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg every 21 days. Patients who received other HER2 treatments (pertuzumab and trastuzumab emtansine) before LC treatment and whose data were insufficient were excluded from the study.

The patients' clinical and demographic characteristics were obtained from hospital records. All the treatments administered to the patients, including surgery, radiotherapy, and systemic cancer therapies, were documented. Estrogen receptor (ER) positivities were evaluated through immunohistochemistry. HER2 receptor positivity was confirmed through either immunohistochemistry score 3+ or score 2+ and FISH-positive.

Response to treatment was assessed radiologically via magnetic resonance imaging or computed tomography every 2 to 3 months. The response to trastuzumab-based treatment was evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1.

Treatment responses were divided into 4 groups: complete response (CR), partial response (PR), stable disease (SD) and progressive disease. The objective response rate (ORR) was calculated by combining CR and PR cases. Meanwhile, the disease control rate (DCR) was determined by including CR, PR and SD cases.

Treatment-related adverse events were recorded in each patient and the severity of these events was graded according to the Common Terminology Criteria for Adverse Events version 5. Records of patient deaths were obtained from the death information system. PFS was defined as the duration from the initiation of RTmab-based therapy to the progression of the disease. OS was calculated as the duration from the initiation of RTmab-based therapy to death from any cause. Univariate and multivariate analysis was executed to examine the impact of clinicopathological factors on PFS.

3. Results

3.1. Patients' characteristics and treatment modality

The study included 33 patients, with a median age of 47 (range: 25–72) years. The numbers of patients with Eastern Cooperative Oncology Group performance scores of 0 to 1 and 2 were 19 (57%) and 14 (42%), respectively. The predominant histopathological subtype was invasive ductal carcinoma, which was observed in 23 (70%) patients. ER positivity was detected in 16 (48%) patients. At initial diagnosis, 12 (36%) patients had denovo metastatic disease. Brain metastases were present in 9 (27%) patients. More than half (55%) of the tumors originated from the right breast. Adjuvant radiotherapy and hormone therapy were administered to 15 (45%) and 14 (42%) patients, respectively. In addition, perioperative chemotherapy (Cht) was administered to 27 patients (81%).

The average number of metastatic sites was 3, ranging from 1 to 5. Mastectomy was performed in 20 patients (61%). All patients received palliative trastuzumab-based Cht prior to LC treatment. Before LC treatment, palliative radiotherapy and hormone therapy were administered to 19 (58%) patients and 15 (45%) patients, respectively. In conjunction with the RTmab treatment, vinorelbine was administered to 14 (42%) patients, paclitaxel to 12 (36%), and other chemotherapeutic agents, such as gemcitabine and docetaxel, to 4 (12%) patients. Three patients received trastuzumab treatment without the addition of Cht. Furthermore, 2 patients (10.8%) underwent palliative

Table 1

Clinical and pathological features of the patients.

Characteristics		n (%)
Age at diagnosis	<50 yr	14 (42)
	≥50 yr	19 (58)
ECOG performance status	0	8 (24)
	1	11 (33)
	2	14 (42)
Gender	Female	32 (97)
	Male	1 (3)
Pathologic subtypes	IDK	23 (70)
	Others	10 (30)
Estrogen receptor	Negative	17 (52)
	Positive	16 (48)
Stage at diagnosis	Stage 1	1 (3)
	Stage 2	3 (9)
	Stage 3	17 (52)
	Stage 4	12 (36)
Primary tumor locations	Right	14 (42)
	Left	18 (55)
	Bilateral	1 (3)
Brain metastasis	No	24 (%73)
	Yes	9 (%27)
Surgery	Mastectomy	20 (61)
	Lumpectomy	4 (12)
	No	9 (27)
Adjuvant Radiotherapy	No	18 (55)
	Yes	15 (45)
Cht before metastatic disease	No	6 (18)
	Neoadjuvant	13 (39)
	Adjuvant	14 (42)
Adjuvant hormone therapy	No	19 (58)
	Yes	14 (42)
Total number of palliative Cht prior to Rtmab treatment	No	0 (0)
	Yes	33 (100)
Total number of palliative HT prior to RTmab treatment	No	18 (55)
	Yes	15 (45)
Total number of palliative RT prior to RTmab treatment	No	14 (42)
	Yes	19 (58)
Metastasectomy	No	31 (94)
	Yes	2 (6)
Chemotherapy with rechallenge trastuzumab treatment	Vinorelbine	14 (42)
	Paclitaxel	12 (36)
	Others (gemcitabine, docetaxel)	4 (12)
After rechallenge trastuzumab treatment	Cht	14 (42)
	Radiotherapy	6 (18)

Cht = chemotherapy, ECOG = Eastern Cooperative Oncology Group, IDK = invasive ductal carcinoma, RTmab = rechallenge trastuzumab, RT = radiotherapy, HT = hormone therapy.

metastasectomy. Bisphosphonate therapy for bone metastases was administered to 24 (73%) patients. The clinicopathological characteristics of the patients are shown in Table 1.

3.2. Survival outcomes and prognosis

The patients were categorized based on treatment response: 8 (26%) achieved PR, 14 (42%) demonstrated SD, and 10 (30%) manifested PD. CR was achieved in only 1 (3%) patient. For all the patients, the ORR and DCR were 27% and 69%, respectively (Table 2). Grade 1 to 2 adverse events related to RTmab-based therapy were reported in 17 patients (52%), whereas grade 3 to 4 hematological adverse events were reported in 4 patients (12%). Hematological toxicities were the most prevalent, affecting 41% of the patients.

After undergoing RTmab treatment, 14 (42%) patients received palliative Cht and 6 (18%) underwent palliative radiotherapy. The median follow-up period after the start of the RTmab-based therapy was 28 (range: 0–142.5) months. Furthermore, the median PFS was 8.8 months (95% confidence interval [CI], 6.6–11 months, Fig. 1) and the median OS was 20 months (95% CI: 15.1–25.8 months, Fig. 2). In multivariate analysis, there was no statistically significant difference in PFS rates depending on various factors such as age, ER status, denovo metastasis, brain metastasis, perioperative Cht, hormone therapy before Rtmab, metastasectomy, and which Cht was used together with Rtmab ($P > .05$) (Table 3).

Table 2

Responses to intrathecal therapy for breast cancer with leptomeningeal metastases.

Response ratios	Total n = 33 n (%)
Complete response	1 (3)
Partial response	8 (24)
Stable disease	14 (42)
Progression	10 (30)
Objective response rate	9 (27)
Disease control rate	23 (69)

4. Discussion

In oncology practice, rechallenge drug therapy is commonly used, particularly with the advent of targeted therapies and immunotherapy.[10] Preclinical evidence suggests that trastuzumab reuse following lapatinib treatment is beneficial. The formation of acquired resistance to trastuzumab could be associated with the degradation and downregulation of the receptor.[11] Lapatinib has the potential to stabilize and accumulate inactive HER2 receptors on the cytoplasmic membrane, potentially leading to renewed responsiveness of HER2-positive tumor cells to the efficacy of trastuzumab.[12] The literature provides scarce data regarding the utilization of RTmab-based therapy after LC therapy in patients with HER2-positive mBC.

Our study demonstrated the effectiveness of reintroducing trastuzumab in patients with HER2-positive mBC who experienced progression while receiving LC therapy. According to our findings, the PFS was 8.8 months, with an OS of 20 months and the ORR was 27%. In a retrospective study conducted by Araki et al, which involved 50 patients diagnosed with mBC, the efficacy of reintroducing trastuzumab-based therapies after progression post-LC therapy was assessed. The study demonstrated that with an average follow-up of 7.9 months, the PFS following LC therapy was 4.6 months whereas the OS was 33.7 months and the clinical benefit rate was detected as 32%.[13] In our study, the rate of patients with Eastern Cooperative Oncology Group performance score > 1, which is a poor prognostic parameter, was higher than in this study (42% vs 4%).

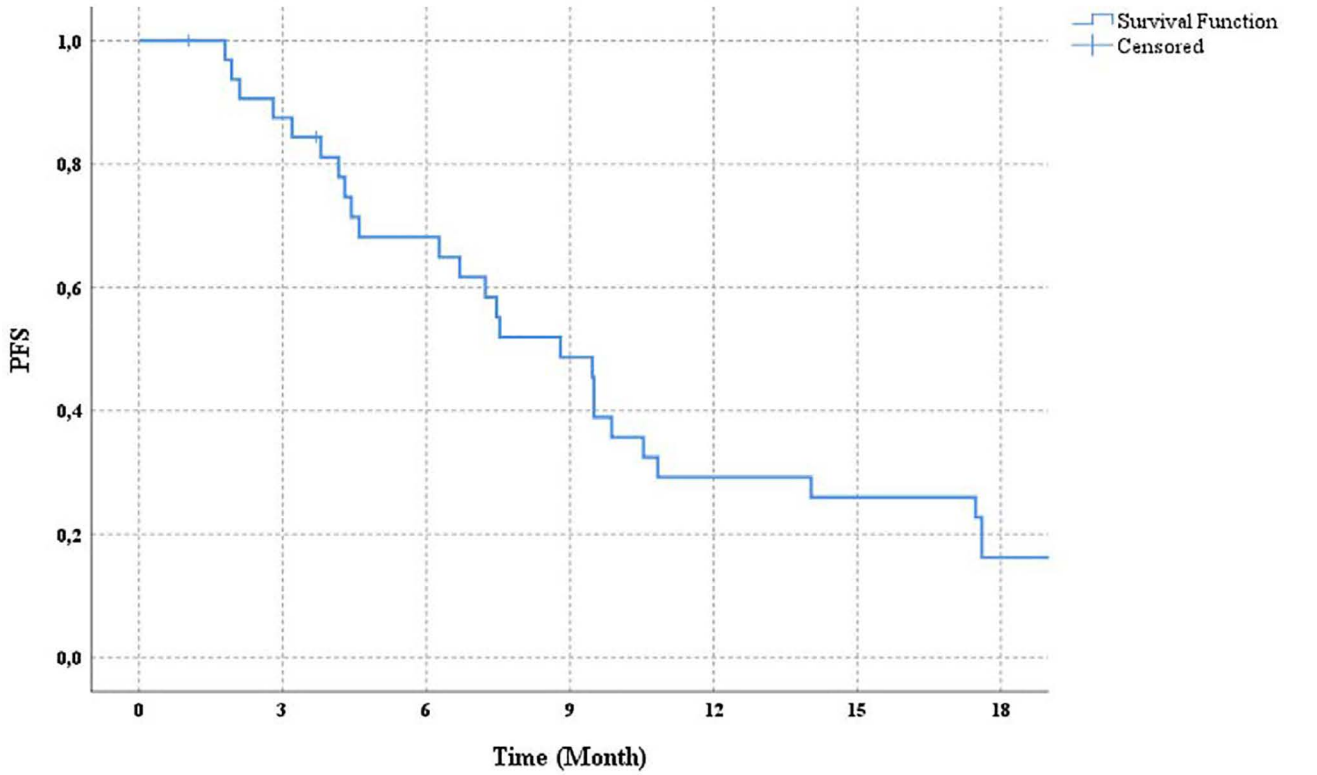

Figure 1. Kaplan–Meier curve of PFS in patients with metastatic breast cancer treated with Rtmab. PFS = progression-free survival, RTmab = rechallenge trastuzumab.

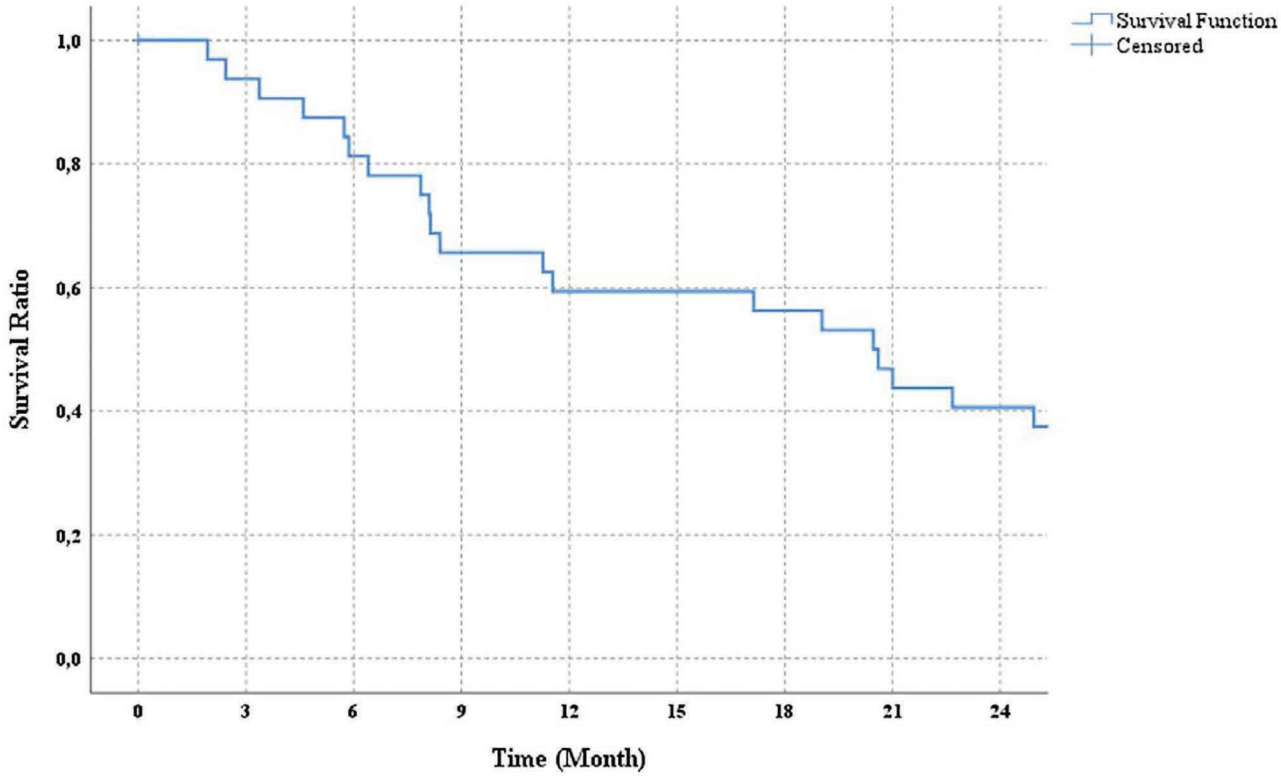

Figure 2. Kaplan–Meier curve of OS in patients with metastatic breast cancer treated with Rtmab. OS = overall survival, RTmab = rechallenge trastuzumab.

Table 3

Univariate and multivariate analysis for PFS in the patients who were treated with Rtmab.

	Univariate analysis	Multivariate analysis	
	P	*P*	Odds ratio (CI 95%)
Age at diagnosis (<50 vs ≥50)	.125	.224	1616 (0.746–3.5)
Er status (negative vs positive)	.027*	.810	1.163 (0.340–3.982)
Denovo metastases (no vs yes)	.164	.839	1.247 (0.148–10.501)
Brain metastases (no vs yes)	.796		
Perioperative chemotherapy (no vs yes)	.169	.939	1.099 (0.099–12.215)
Palliative hormone therapy before Rtmab	.570		
Metastasectomy no vs yes	.631		
Chemotherapy with Rtmab (vinorelbine vs paclitaxel)	.471		

Multivariate analysis model *P*-value.

CI = confidence interval, ER = estrogen receptor, PFS = progression-free survival, RTmab = rechallenge trastuzumab.

*$P < .05$.

Therefore, the median OS in our study may have been shorter compared to the sample study.

In another retrospective study conducted by Gori et al, where data from 69 patients were analyzed, the efficacy and safety of RTmab-based therapies were investigated among patients with HER2-positive mBC who had progressed after LC therapy. The ORR in this study was determined to be 31%. At a median follow-up duration of 13 months, the median response time was 8.1 months and the OS was 19.4 months.[14] Our study results are similar to the results of this study.

Similarly, in a study conducted by Uncu et al, the efficacy of trastuzumab-based therapies was retrospectively explored among patients who experienced progression following LP treatment. In the study where 49 patients were evaluated, ORR was found to be 29%, PFS was 5 months and OS was 10 months.[15] Although the ORR rate in our study was similar to this study, our PFS and OS times were found to be longer than the sample study. The reason for this may be the lower number of patients with brain metastases in our study (27% vs 50%).

The treatment was well tolerated by the patients, with mild to moderate toxicity observed in 17 patients (52%) and severe adverse events, all hematologic in nature, reported in 4 patients (12%). However, due to the retrospective nature of the study, there was variability within the patient population, which led to some data gaps. Furthermore, as the study was conducted at a single center with a limited sample size, selection bias may be introduced.

In the literature, there is limited clinical data regarding the benefits of RTmab in patients with mBC who progressed while receiving lapatinib therapy. The present study showed that RTmab-based therapy is effective in patients who were previously administered trastuzumab-based therapy and then

LP treatment. With these results, our study will contribute to the literature, and RTmab may be an effective option for the treatment of patients with HER2-positive mBC who cannot use new-generation agents (e.g., trastuzumab deruxtecan) due to side effects or high costs.

Author contributions

Conceptualization: Izzet Dogan, Bayarmaa Khishigsuren, Abdulmunir Azizy, Pinar Saip, Adnan Aydiner.
Data curation: Nijat Khanmammadov, Izzet Dogan, Bayarmaa Khishigsuren, Abdulmunir Azizy, Adnan Aydiner.
Formal analysis: Nijat Khanmammadov, Izzet Dogan, Bayarmaa Khishigsuren, Abdulmunir Azizy, Pinar Saip, Adnan Aydiner.
Funding acquisition: Nijat Khanmammadov.
Investigation: Nijat Khanmammadov, Izzet Dogan, Bayarmaa Khishigsuren, Abdulmunir Azizy, Pinar Saip, Adnan Aydiner.
Methodology: Nijat Khanmammadov, Izzet Dogan, Bayarmaa Khishigsuren, Abdulmunir Azizy, Pinar Saip, Adnan Aydiner.
Project administration: Nijat Khanmammadov.
Supervision: Nijat Khanmammadov, Izzet Dogan, Pinar Saip, Adnan Aydiner.
Validation: Pinar Saip, Adnan Aydiner.
Visualization: Nijat Khanmammadov, Izzet Dogan, Bayarmaa Khishigsuren, Pinar Saip, Adnan Aydiner.
Writing – original draft: Nijat Khanmammadov, Izzet Dogan, Bayarmaa Khishigsuren, Abdulmunir Azizy, Pinar Saip.
Writing – review & editing: Nijat Khanmammadov, Izzet Dogan, Abdulmunir Azizy, Pinar Saip, Adnan Aydiner.

References

[1] Deo SVS, Sharma J, Kumar S. GLOBOCAN 2020 report on global cancer burden: challenges and opportunities for surgical oncologists. Ann Surg Oncol. 2022;29:6497–500.
[2] Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist. 2009;14:320–68.
[3] Asif HM, Sultana S, Ahmed S, Akhtar N, Tariq M. HER-2 positive breast cancer: a mini-review. Asian Pac J Cancer Prev. 2016;17:1609–15.
[4] Blondeaux E, Ferreira AR, Poggio F, et al. Clinical outcomes of patients with breast cancer relapsing after (neo) adjuvant trastuzumab and receiving trastuzumab rechallenge or lapatinib-based therapy: a multicentre retrospective cohort study. ESMO Open. 20202020;5:e000719.
[5] Al Sukhun S, Temin S, Barrios CH, et al. Systemic treatment of patients with metastatic breast cancer: ASCO resource-stratified guideline. JCO Glob Oncol. 2024;10:e2300285.
[6] Graff SL, Yan F, Abdou Y. Newly approved and emerging agents in HER2-positive metastatic breast cancer trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. Clin Breast Cancer. 2023;23:e380–93.
[7] Madden R, Kosari S, Peterson GM, Bagheri N, Thomas J. Lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer: a systematic review. Int J Clin Pharmacol Ther. 2018;56:72–80.
[8] Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355:2733–43.
[9] Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat. 2008;112:533–43.
[10] Hanovich E, Asmis T, Ong M, Stewart D. Rechallenge strategy in cancer therapy. Oncology (Huntingt). 2020;98:669–79.
[11] Valabrega G, Montemurro F, Sarotto I, et al. TGFalpha expression impairs trastuzumab-induced HER2 downregulation. Oncogene. 2005;24:3002–10.
[12] Scaltriti M, Verma C, Guzman M, et al. Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicity. Oncogene. 2009;28:803–14.
[13] Araki K, Fukada I, Horii R, et al. Trastuzumab rechallenge after lapatinib- and trastuzumab-resistant disease progression in HER2-positive breast cancer. Clin Breast Cancer. 2015;15:432–9.
[14] Gori S, Montemurro F, Spazzapan S, et al. Retreatment with trastuzumab-based therapy after disease progression following lapatinib in HER2-positive metastatic breast cancer. Ann Oncol. 2012;23:1436–41.
[15] Uncu D, Bayoglu IV, Arslan UY, et al. Trastuzumab-based retreatment after lapatinib in heavily pretreated HER2 positive metastatic breast cancer: an Anatolian Society of Medical Oncology Study. Asian Pac J Cancer Prev. 2015;16:4127–31.