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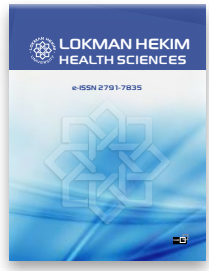

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ORIGINAL ARTICLE

Chemotherapy Effectiveness in Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer after Third-Line or Later Treatment: An Overtreatment Concern in Everyday Clinical Practice

Mustafa Ersoy

Department of Internal Medicine, Kütahya University of Health Sciences Faculty of Medicine, Kütahya, Türkiye

Abstract

Introduction: Despite the availability of numerous novel targeted therapies in our daily clinical practice, chemotherapy remains a predominant treatment modality for patients with human epidermal growth factor receptor 2-negative metastatic breast cancer, often extending beyond the third line. This study aimed to evaluate the efficacy and safety of third-line and subsequent chemotherapies, with the intent of contributing to the existing literature and addressing concerns regarding potential overtreatment in this patient population.

Methods: This retrospective, two-center study analyzed data from 35 chemotherapy protocols administered to 21 patients who received third, fourth, and fifth-line chemotherapy regimens. We evaluated the objective response rates (ORRs), progression-free survival (PFS), and rates of Grade 3–4 toxicities in this patient population.

Results: The ORR in this study was 14.2%. The PFS was 3.7 months, and 45.7% of patients experienced Grade 3 or 4 toxicities.

Discussion and Conclusion: Consistent with existing literature, our small, retrospective, two-center cohort demonstrated a low ORR, short PFS, and a high incidence of severe adverse events. These descriptive findings lack statistical power and cannot be generalized, but highlight the need for careful consideration of the risk–benefit ratio in heavily pre-treated patients. In this context, clinicians should thoughtfully evaluate best supportive care alongside chemotherapy, or consider alternative approaches such as hormonal therapy or novel targeted agents.

Keywords: Breast cancer; Chemotherapy; Overtreatment

Breast cancer is the most common cancer among women, with approximately 85% of patients being human epidermal growth factor receptor 2 (HER2)-negative.[1] Despite the emergence of new treatment approaches, one of the most common challenges encountered in routine clinical practice is the need for multiple lines of chemotherapy in relatively young patients with a relatively long life expectancy.[2–4]

Metastatic chemotherapy regimens, particularly those consisting of three or more lines, continue to be frequently

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Correspondence: Mustafa Ersoy. Kütahya Sağlık Bilimleri Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Kütahya, Türkiye
E-mail: mustafa.ersoy@ksbu.edu.tr **Submitted:** 30.06.2025 **Revised:** 12.01.2026 **Accepted:** 15.01.2026 **Available Online:** 06.08.2026

utilized in everyday clinical practice for HER2-negative breast cancer patients.[5] As chemotherapy regimens progress across successive treatment lines, patients often experience a rising tumor burden and more pronounced cumulative toxicity from prolonged treatment.[6] This leads to a worsening risk–benefit ratio due to the diminishing potential for benefit, resulting in an overtreatment problem that becomes a significant clinical challenge, particularly among patients with good performance status.[7] This challenge arises because clinicians may be inclined to continue therapy in these patients, despite the diminishing therapeutic returns.[8]

Cancer overtreatment is particularly problematic in younger patients with good performance status and slow-growing cancers, where the toxicity of treatment can outweigh the benefits.[9] This clinical dilemma is frequently encountered in routine clinical practice and constitutes a substantial challenge in the palliative management of patients with advanced cancer.[10]

The aim of our study was to share our two-center experience on the efficacy of continued chemotherapy beyond the third line and beyond in HER2-negative patients, who often receive such treatment in routine clinical practice. We also sought to evaluate the rates of significant toxicity and overall efficacy in these patients to draw attention to the efficacy-toxicity profile. By presenting these real-world data, we aim to underscore the risk of overtreatment in incurable stage IV breast cancer and advocate for the consideration of therapeutic alternatives beyond conventional chemotherapy. Ultimately, these findings may facilitate future research initiatives and guide evidence-based decision-making in routine clinical practice.

Materials and Methods

Study Design and Setting

This was a retrospective, two-center study conducted at the Department of Medical Oncology, University of Health Sciences Training and Research Hospital, and City Hospital, both of which are tertiary care institutions affiliated with the University of Health Sciences. Data from patients treated between January 2015 and March 2024 were collected from hospital archives, medical records, and electronic databases.

Ethics Approval

This study was approved by the Non-Interventional Research Ethics Committee of Kütahya University of Health Sciences (Decision No: 2025/05-18, Date: April 7, 2025). The study was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. Because of the retrospective nature of the study, the requirement for informed consent was waived.

Patients and Data Collection

Patients aged ≥18 years with histologically confirmed HER2-negative metastatic breast cancer (MBC) who received at least third-line chemotherapy were included. Data on demographics, hormone receptor status, treatment regimens, line of therapy, treatment response, progression-free survival (PFS), and adverse events were collected.

Inclusion Criteria

- Histologically confirmed HER2-negative MBC,
- Received ≥third-line chemotherapy during the metastatic stage,
- Documented treatment response and progression data available,
- Completed at least one full cycle of chemotherapy protocol.

Exclusion Criteria

- HER2-positive breast cancer,
- Patients who discontinued treatment for reasons other than disease progression,
- Missing data regarding response or toxicity evaluation.

Definitions

- Line of therapy: Each distinct chemotherapy regimen administered for disease progression was considered one line of therapy.
- Response categories: Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), based on imaging 8–16 weeks after treatment initiation.
- PFS: Time from treatment initiation to documented progression or death from any cause.

Clinical and Laboratory Investigations

All patients underwent baseline and follow-up radiological assessments (computed tomography (CT)/magnetic resonance imaging/positron emission tomography-CT)

at 8–16 week intervals. Hematological and biochemical profiles were routinely monitored during treatment. Adverse events were graded according to the common terminology criteria for adverse events (version 5.0).

Statistical Analysis

All statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. As most variables did not follow a normal distribution, non-parametric tests were applied where appropriate. Descriptive statistics were reported as median (interquartile range, [IQR]) for continuous variables and as number (percentage) for categorical variables.

PFS was estimated using the Kaplan–Meier method, with median values and 95% confidence intervals (CIs) reported. Survival curves were compared using the log-rank (Mantel–Cox) test. Cox proportional hazards regression analyses were performed to evaluate prognostic factors for PFS, and hazard ratios (HR) with 95% CI were reported. Due to the limited sample size, multivariable Cox regression analyses were considered exploratory.

All statistical tests were two-sided, and a $p<0.05$ was considered statistically significant.

Results

The study included 21 patients, with a total of 35 third-, fourth-, or fifth-line chemotherapy administrations. The median age was 52 years (IQR: 46–60; range: 32–75), and the cohort comprised 33 women (94.3%) and 2 men (5.7%). Fifteen patients (42.9%) had hormone receptor-positive disease, whereas 20 (57.1%) had triple-negative disease. Eastern Cooperative Oncology Group performance status was 0 in 7 patients (20.0%), 1 in 21 (60.0%), and 2 in 7 (20.0%). The treatment regimens and baseline characteristics are summarized in Table 1.

Table 1. Patient demographics, clinical characteristics, and treatment protocols (n=35)

Variables	n (%) or median (IQR) (range)
Age (years)	52 (46–60) (32–75)
Gender	
Female	33 (94.3)
Male	2 (5.7)
Hormone receptor status	
Positive	15 (42.9)
Negative	20 (57.1)
ECOG performance status	
ECOG 0	7 (20.0)
ECOG 1	21 (60.0)
ECOG 2	7 (20.0)
Line of therapy	Median: 3 (IQR: 3–4)
3rd line	21 (60.0)
4th line	10 (28.6)
5th line	4 (11.4)
Treatment regimens	
Gemcitabine	11 (31.4)
Taxane	1 (2.9)
Platinum combination	4 (11.4)
AC	2 (5.7)
Liposomal doxorubicin	2 (5.7)
Vinorelbine	6 (17.1)
Ixabepilone	2 (5.7)
Eribulin	1 (2.9)
Capecitabine	6 (17.1)

ECOG: Eastern Cooperative Oncology Group; AC: Anthracycline-cyclophosphamide. Values are presented as n (%) or median (IQR) (range). n: Number of patients for demographics and disease characteristics; n: Number of treatment protocols for chemotherapy regimens; IQR: Interquartile range.

Overall, 23 of 35 treatment courses (65.7%) resulted in PD, 7 (20.0%) in SD, and 5 (14.3%) in PR, yielding an objective response rate (ORR) of 14.3%. No CRs were observed. Comparative response distributions by line of therapy, hormone status, and regimen are shown in Table 2. There was a trend toward different response distributions across treatment lines (Pearson χ^2 p=0.060), whereas differences according to hormone status (p=0.292) or regimen (p=0.151) were not statistically significant.

Median PFS for the entire cohort was 3.7 months (95% CI: 2.5–4.9). Kaplan–Meier analyses by subgroups are presented in Table 3 and illustrated in Figure 1. By line of therapy, median PFS was 5.0 months (95% CI: 2.0–7.9) in the third-line, 2.8 months (95% CI: 2.2–3.1) in the fourth-line, and 2.1 months (95% CI: 1.0–3.3) in the fifth-line group, with a statistically significant difference (log-rank χ^2=9.48, df=2, p=0.009). According to hormone receptor status, median PFS was 2.8 months (95% CI: 2.2–3.5) in HR-positive and 3.0 months (95% CI: 2.9–3.1) in HR-negative patients (log-rank χ^2=1.62, df=1, p=0.204). Among regimens, platinum combinations (median PFS 6.0 months) and capecitabine (median PFS 5.3 months; 95% CI: 2.1–8.5) achieved numerically longer PFS compared with other agents, with overall differences reaching statistical significance (log-rank χ^2=18.06, df=8, p=0.021).

Table 2. Comparison of treatment responses by line of therapy, hormone status, and regimen

Group	Progressive disease n (%)	Stable disease n (%)	Partial response n (%)	Complete response n (%)	p
Line of therapy					0.060
3rd line (n=21)	10 (47.6)	6 (28.6)	5 (23.8)	0	
4th line (n=10)	10 (100.0)	0	0	0	
5th line (n=4)	3 (75.0)	1 (25.0)	0	0	
Hormone status					0.292
Positive (n=15)	12 (80.0)	2 (13.3)	1 (6.7)	0	
Negative (n=20)	11 (55.0)	5 (25.0)	4 (20.0)	0	
Regimen					0.151
Gemcitabine (n=11)	9 (81.8)	2 (18.2)	0	0	
Taxane (n=1)	1 (100.0)	0	0	0	
Platinum combo (n=4)	0 (0.0)	2 (50.0)	2 (50.0)	0	
AC (n=2)	1 (50.0)	1 (50.0)	0	0	
Liposomal doxo (n=2)	2 (100.0)	0	0	0	
Vinorelbine (n=6)	6 (100.0)	0	0	0	
Ixabepilone (n=2)	1 (50.0)	0	1 (50.0)	0	
Eribulin (n=1)	1 (100.0)	0	0	0	
Capecitabine (n=6)	2 (33.3)	2 (33.3)	2 (33.3)	0	

p-values were calculated using Pearson chi-square test (two-sided). Fisher's exact test was considered in subgroups with low expected cell counts. AC: Anthracycline-cyclophosphamide; n: Number of treatment protocols.

Table 3. Kaplan–Meier analysis of progression-free survival by line of therapy, hormone status, and regimen

Group	Median PFS (months, 95% CI)	Events (n)	Censored (n)	p
Line of therapy				**0.009**
3rd line (n=21)	5.0 (95% CI: 2.0–7.9)	21	0	
4th line (n=10)	2.8 (95% CI: 2.2–3.1)	10	0	
5th line (n=4)	2.1 (95% CI: 1.0–3.3)	4	0	
Hormone status				0.204
Positive (n=15)	2.8 (95% CI: 2.2–3.5)	15	0	
Negative (n=20)	3.0 (95% CI: 2.9–3.1)	20	0	
Regimen				**0.021**
Gemcitabine (n=11)	3.0 (95% CI: 2.9–3.1)	11	0	
Taxane (n=1)	3.0 (–)	1	0	
Platinum combo (n=4)	6.0 (–)	4	0	
AC (n=2)	3.0 (–)	2	0	
Liposomal doxo (n=2)	2.1 (–)	2	0	
Vinorelbine (n=6)	2.8 (95% CI: 2.6–3.1)	6	0	
Ixabepilone (n=2)	2.1 (–)	2	0	
Eribulin (n=1)	2.0 (–)	1	0	
Capecitabine (n=6)	5.3 (95% CI: 2.1–8.5)	6	0	

PFS: Progression-free survival; CI: Confidence interval; AC: Anthracycline-cyclophosphamide. p-values were calculated using the log-rank (Mantel–Cox) test. n: number of treatment protocols.

Cox proportional hazards regression analyses were performed to evaluate prognostic factors for PFS, and the results are summarized in Table 4. In univariate analysis, patients receiving chemotherapy in the ≥4th line setting had a significantly higher risk of progression compared with those treated in the 3rd line (HR=3.07, 95% CI: 1.33–

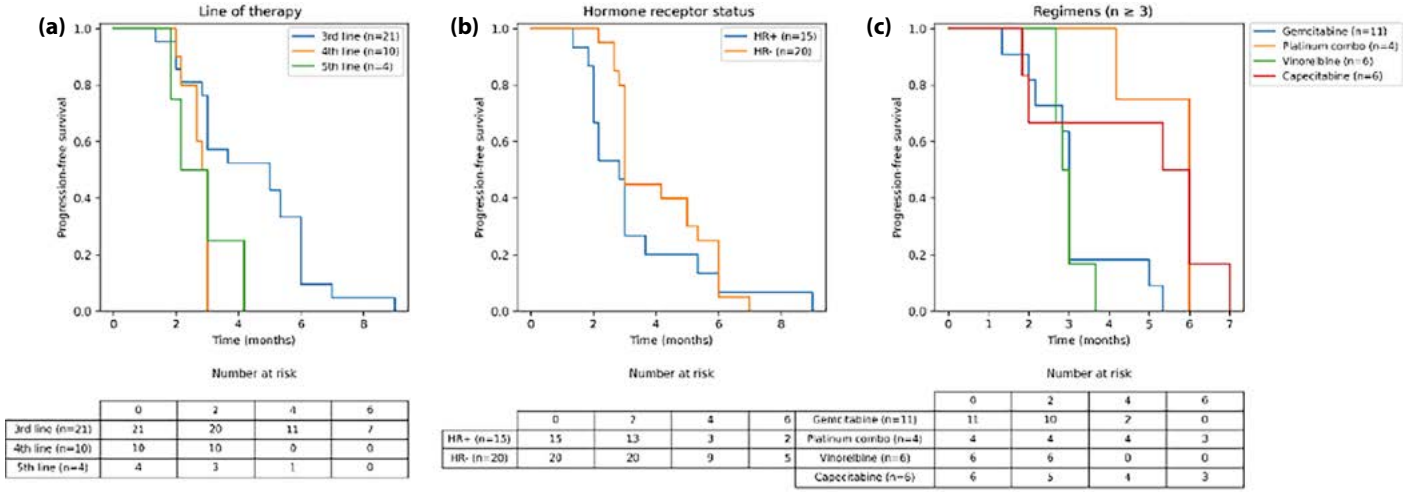

Figure 1. Kaplan–Meier curves for progression-free survival according to **(a)** line of therapy (3rd, 4th, and 5th line), **(b)** hormone receptor status (hazard ratios [H]R+ vs. HR–), and **(c)** treatment regimen. Number-at-risk tables are presented below each panel.

Table 4. Univariate and multivariable cox proportional hazards regression analysis for progression-free survival

Variable	HR	95% CI	p
Univariate analysis			
≥4th line versus 3rd line	3.07	1.33–7.10	**0.009**
Line of therapy (ordinal)	1.90	1.15–3.16	**0.013**
Hormone receptor positive versus negative	1.47	0.74–2.93	0.271
Multivariable analysis			
≥4th line versus 3rd line	3.06	1.32–7.08	**0.009**
Hormone receptor positive versus negative	1.44	0.72–2.87	0.299

*: Multivariable Cox model adjusted for hormone receptor status. Analyses were exploratory due to the limited sample size. HR: Hazard ratio; CI: Confidence interval.

7.10; p=0.009). When the line of therapy was analyzed as an ordinal variable, each subsequent treatment line was associated with a 1.9-fold increase in the risk of progression (HR=1.90, 95% CI: 1.15–3.16; p=0.013). Hormone receptor status was not significantly associated with PFS (HR=1.47, 95% CI: 0.74–2.93; p=0.271).

In an exploratory multivariable Cox model adjusted for hormone receptor status, late-line chemotherapy (≥4th line vs. 3rd line) remained independently associated with shorter PFS (adjusted HR=3.06, 95% CI: 1.32–7.08; p=0.009). Regimen-based variables were not included in the Cox models due to small subgroup sizes and the risk of model instability. Notably, all treatment courses experienced disease progression by the data cutoff date; therefore, no observations were censored, and censor counts are reported as zero across all survival analyses.

Grade 3/4 toxicities occurred in 16 of 35 treatment courses (45.7%), whereas 19 (54.3%) had no severe toxicity. Hematologic toxicities were most common (72.2% of grade 3/4 events), followed by diarrhea (5.6%), neuropathy (5.6%), and mucositis (5.6%). The toxicity profile is summarized in Table 5.

Table 5. Incidence of grade 3/4 toxicities and toxicity profile

Variables	n	%
Grade 3/4 toxicity		
Present	16	45.7
Absent	19	54.3
Toxicity type		
Hematologic (total)	13	72.2
Neutropenia	8	44.4
Anemia	3	16.7
Thrombocytopenia	2	11.1
Diarrhea	1	5.6
Neuropathy	1	5.6
Mucositis	1	5.6

n: Number of treatment protocols; %: Percentage.

Discussion

The low overall response rate and short PFS observed in this cohort are consistent with previously reported data. In a similar patient population of the EMBRACE phase 3 open-label study, eribulin achieved a PFS of 3.7 months, compared to 2.2 months for other chemotherapies. The ORR was 12% for eribulin, whereas it was 5% for the other treatment regimens.[11] Similarly, a pivotal phase II study evaluating ixabepilone monotherapy in 126 patients – most of whom had received at least two prior lines of metastatic therapy – reported an ORR of 11.5% and a median PFS of 3.1 months.[12] These findings align closely with the outcomes observed in our real-world cohort.

While our study looked at treatment responses and PFS, overall survival was not evaluated. However, the literature has established that PFS is an important prognostic indicator of overall survival, particularly in the third-line setting and beyond.[13] Given the importance of overall survival as an endpoint in this patient population, future studies should aim to collect and report this outcome data as well.

In our study, the median PFS for patients receiving third-line therapy was 5 months, whereas those receiving fourth-line treatment had a median PFS of 2.8 months, and patients on fifth-line therapy had a median PFS of 2.1 months. Due to the small sample size and the fact that this was not the primary objective of the study, no statistical analysis was performed. However, while the literature generally suggests that efficacy may decrease as the lines of chemotherapy increase, there is a lack of clear data demonstrating that the decline continues beyond the third-line setting compared to the third-line itself.[13,14]

In this cohort, PFS was numerically longer, at 3.1 months, in the hormone receptor-negative group compared to 2.7 months in the positive group. Although no formal statistical analysis was performed due to the small sample size, this suggests that the hormone receptor-positive patients may derive greater benefit from more intensive attempts to utilize hormonal therapy as part of their treatment regimen. While the existing literature has not demonstrated significant differences in outcomes between these two subgroups, this observation may suggest that, for the hormone receptor-positive patients in particular, a greater emphasis on hormonal therapy rather than cytotoxic chemotherapy may be a more appropriate treatment strategy.[14] This approach could potentially help optimize outcomes and minimize the need for more aggressive chemotherapeutic interventions in this population.

Despite excluding patients who were unable to continue treatment due to toxicity and those with unclear treatment responses and progression timelines due to toxicity, a significant proportion of the remaining patients who received treatment still experienced Grade 3 or 4 adverse events. The most commonly observed toxicities were hematologic in nature. Similarly, the literature has reported a high rate of adverse events, particularly hematologic, in heavily pre-treated patient populations receiving chemotherapy.[11]

In our cohort, platinum-based combinations (median PFS: 6 months) and capecitabine (median PFS: 5.3 months) appeared numerically more effective than other regimens. This observation is consistent with other small retrospective series, which also reported somewhat longer disease control with platinum regimens and oral capecitabine in the late-line setting.[15,16] Nonetheless, these findings should be interpreted with caution due to the small numbers and retrospective design, and they remain descriptive and hypothesis-generating.

Furthermore, the availability of novel agents such as sacituzumab govitecan complicates decisions regarding conventional chemotherapy in the late-line setting.[17] Clinical trials have demonstrated improved response rates and PFS with sacituzumab govitecan compared with standard chemotherapy, albeit with hematologic toxicities.[18] The very limited efficacy and substantial toxicity observed with conventional regimens in our study further support the idea that novel agents may offer a more favorable risk–benefit profile. This also reinforces the concern of overtreatment when less effective cytotoxic drugs are used while more effective targeted therapies are available.

Another important clinical consideration is endocrine resistance in hormone receptor–positive patients. Various strategies, including combinations with CDK4/6 inhibitors, PI3K/AKT/mTOR inhibitors, or new selective estrogen receptor degraders, have been investigated to overcome resistance.[19–21] Our results, although limited, support the prioritization of maximizing endocrine approaches before resorting to cytotoxic chemotherapy, as this may help improve outcomes and avoid unnecessary toxicity.

In patients with advanced-stage disease, particularly younger individuals with preserved performance status who have undergone extensive prior therapy, clinicians should exercise careful judgment when considering additional cytotoxic chemotherapy. As observed in our cohort, such patients often experience high toxicity with limited clinical benefit, underscoring the need for a thoughtful evaluation of the risk–benefit balance. Overtreatment remains a significant concern in heavily

pre-treated populations, and treatment decisions should incorporate not only survival-related endpoints but also quality-of-life considerations.[7] For hormone receptor–positive patients, endocrine therapy should be prioritized whenever feasible,[22] and for all HER2-negative patients, novel targeted agents such as sacituzumab govitecan should be considered when available.[17,23]

Limitations

The retrospective, two-center design and the very small sample size (21 patients, 35 treatment courses) represent major limitations of our study. Therefore, the findings should be considered descriptive and exploratory, lacking statistical power and not generalizable to broader patient populations. To obtain more reliable evidence, larger multicenter prospective studies are needed, ideally comparing chemotherapy with best supportive care and incorporating both PFS and overall survival as well as quality-of-life outcomes. In addition, although next-generation sequencing was not performed in our cohort, its integration into future studies may help identify actionable genomic alterations, personalize treatment strategies, and minimize the risk of overtreatment in heavily pre-treated HER2-negative MBC patients.

Conclusion

In routine clinical practice, patients with HER2-negative MBC who have received two or more lines of chemotherapy constitute a significant proportion of the patient population. However, in our small, retrospective, two-center cohort, the low efficacy and high rate of severe adverse events resulted in an unfavorable risk–benefit ratio, raising concerns about potential overtreatment. These findings are descriptive in nature, lack statistical power, and cannot be generalized, but are consistent with existing literature. Therefore, before deciding on cytotoxic chemotherapy in such heavily pre-treated patients, clinicians should carefully weigh the balance between efficacy and adverse effects, and the option of best supportive care should also be considered. For eligible patients, alternative strategies – including hormonal therapy, novel targeted therapies, and personalized approaches guided by next-generation sequencing – may be evaluated.

Ethics Committee Approval: The Kütahya University of Health Sciences Non-Interventional Research Ethics Committee granted approval for this study (date: 07.04.2025, number: 2025/05-18).

Informed Consent: As this was a retrospective study, no written informed consent was obtained from the patients.

Conflict of Interest: None declared.

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