Original Study

Effects of Second and Subsequent Lines of Chemotherapy for Metastatic Breast Cancer☆

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Abstract

Continuing cytotoxic chemotherapy is justified in metastatic breast cancer. However, the clinical effects of successive treatment have not been evaluated. In the present study, we assessed 240 patients with metastatic breast cancer who received multiple lines of cytotoxic chemotherapy regimens. We confirmed that the beneficial effects of subsequent chemotherapy for patients with a durable response from previous treatment.

Background: We assessed the effect of chemotherapy regimens beyond first-line agents on the clinical outcomes in patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC). **Patients and Methods:** We included 240 patients who were prospectively enrolled into various clinical trials and were receiving cytotoxic chemotherapy for HER2-negative MBC at the National Cancer Center, Korea, from October 2002 to September 2012. Clinicopathologic data were collected for the analysis. **Results:** A total of 240, 209, and 166 patients received first-, second-, and third-line chemotherapy, respectively. The median age was 49 years (range, 28-77 years), and most had hormone receptor-positive cancer (n = 177; 73.8%). The median progression-free survival (PFS) was 7.6 months for first-line (PFS1) versus 5.1 months for second-line (PFS2) versus 3.6 months for third-line (PFS3) chemotherapy. The PFS from previous chemotherapy significantly affected subsequent PFS: PFS1 for PFS2, PFS1 $\geq$ 7.6 months, hazard ratio (HR) 0.647; 95% confidence interval (CI), 0.0.484-0.864 ($P = .003$); PFS2 for PFS3, PFS2 $\geq$ 5.1 months, HR 0.676; 95% CI, 0.0.484-0.944; $P = .022$). The median overall survival was 31.2 months (95% CI, 26.4-36.0 months). Hormone receptor positivity (HR 0.548; 95% CI, 0.261-0.499; $P < .001$) and PFS1 $\geq$ 7.6 months (HR 0.361; 95% CI, 0.393-0.765; $P < .001$) were significant factors for survival on multivariate analysis. **Conclusion:** The efficacy of previous treatment significantly affected the outcomes of subsequent treatment. We have confirmed that the succession of chemotherapy is justified in patients with MBC who benefited from previous chemotherapy.

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Introduction

The incidence and prevalence of breast cancer are increasing globally. Although a greater proportion of women are diagnosed in early disease stages because of national screening programs and increasing awareness, 3% to 5% of patients still present with metastatic disease at diagnosis.[1,2] In addition, 20% to 85% of patients who undergo complete resection develop distant metastases.[3] Metastatic breast cancer (MBC) is typically incurable, and one of the important aims of treatment is symptom palliation. The median survival of patients with MBC is 18 to 24 months.[4] As understanding about cancer has broadened, several targeted therapies have proved effective against MBC that has shown resistance to previous chemotherapy regimens such as trastuzumab emtansine,[5] lapatinib,[6] and everolimus.[7]

Although randomized trials of some first-line regimens have shown improved survival and quality of life (QoL), few studies have explored the effects of chemotherapy beyond first-line agents. Excluding hormonal therapy, anthracycline- and taxane-containing regimens are considered the first-line chemotherapy agents for $HER2^-$ MBC.[8,9] After tumors progress on these first-line regimens, other chemotherapeutic agents can be used, including capecitabine, gemcitabine, vinorelbine, and cisplatin. Although these drugs have been evaluated as second- or third-line treatment,[10-12] survival gain and preservation of QoL remain debatable. Therefore, a systematic investigation of the benefit of chemotherapy beyond first-line treatment has become necessary, with the introduction of these more effective chemotherapeutic drugs for the treatment of MBC.

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In the present study, we assessed the effect of multiple chemotherapy regimens, specifically beyond the first line, on the survival of patients with HER2$^-$ MBC.

Patients and Methods

Study Population and Treatment

We included 240 patients who had received cytotoxic chemotherapy for MBC at the National Cancer Center, Korea, from October 2002 to December 2012. All the patients had been prospectively enrolled in various phase II and III clinical trials for MBC. A total of 240, 209, and 166 patients received first-, second-, and third-line chemotherapy, respectively. The administered chemotherapeutic regimens are listed in Supplemental Table 1 (available in the online version). A total of 48 patients (20%) participated in > 2 clinical protocols subsequently after 1 regimen had failed. Most patients had received chemotherapy until the documentation of disease progression, unacceptable toxicity, or patient and clinician decision.

Clinical data, such as performance status, age, and the presence of visceral involvement, were collected at the initiation of the first-line chemotherapy for MBC. In addition, data on hormone receptor and HER2 status, Ki-67 expression, and types of adjuvant systemic treatment were collected for all patients from their medical records. Patients with an initial diagnosis of metastatic disease were classified as having de novo stage IV disease. In the present study, we defined hormone receptor–positive disease as > 10% of tumor cells with estrogen receptor or progesterone receptor expression on immunohistochemical analysis.

Statistical Analysis

Five groups of chemotherapy were defined according to the principle agents used: anthracyclines, taxanes, capecitabine, gemcitabine or vinorelbine, and other drugs. The patients who received combination regimens such as a taxane plus capecitabine or a taxane plus anthracycline were arbitrarily assigned to the taxane group. The Response Evaluation Criteria in Solid Tumors, version 1.0, was used to assess the efficacy for measurable or evaluable lesions using the clinical or radiologic findings. The progression-free survival (PFS) of patients receiving each drug was defined as the interval from the date of the first administration of the specific drugs to the date of the first documented tumor progression or death from any cause. Overall survival (OS) was defined as the interval from the date of the first administration of the specific drugs to death from any cause or the last follow-up date. PFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to control for various clinical factors and to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for each factor. Proportions were compared using 2-way tables and χ^2 tests. All *P* values were 2 tailed, with 5% significance levels. All statistical analyses were performed using STATA, version 10.0.

Results

Patient Characteristics and Treatment Efficacies

A total of 240 patients, with a median age of 49 years (range, 28-77 years) were analyzed. Most patients had hormone receptor–positive MBC (n = 177, 73.8%), and 57 patients (23.8%) were initially diagnosed as having de novo stage IV disease. The median distant disease-free interval was 25.4 months (range, 0-246.4 months), and 150 patients (62.5%) had visceral metastasis at diagnosis (Table 1). Of the 240 patients, 122 (50.8%) received anthracycline-based and/or taxane-based adjuvant chemotherapy, and 89 (50.3%) of those with hormone receptor–positive tumors received palliative antihormonal therapy for metastatic disease.

The efficacy stratified by the lines of chemotherapy in terms of response and PFS is presented in Table 2. The most frequently delivered chemotherapeutic regimens differed by the line of chemotherapy. A total of 168 patients (70.0%) received taxane-based chemotherapy as first-line therapy; 85 (40.7%) received capecitabine-containing regimens as second-line therapy; and 90 (54.2%) received gemcitabine- or vinorelbine-containing regimens as third-line chemotherapy. The median PFS decreased with the advancing lines of chemotherapy: 7.6 months for first line (mPFS1) versus 5.1 months for second line (mPFS2) versus 3.6 months for third line (mPFS3). Although the objective response rates to chemotherapy decreased with the increasing number of lines (Table 2), the differences in the rates were statistically significant in the same lines, depending on the chemotherapeutic regimen. As first-line therapy, anthracycline-based chemotherapy

Table 1 Patient Characteristics (n = 240)

Characteristic	Median (Range) or Patients (%)
Age (years)	49 (28-77)
DFI (mo)	25.4 (0-246.4)
Patients with DFI	
<2 years	118 (47.2)
≥2 years	132 (52.8)
De novo stage IV	57 (23.8)
ER/PgR$^+$/HER2$^-$	177 (73.8)
ER/PgR2/HER2$^-$	63 (26.3)
PS	
0-1	199 (82.9)
2	19 (7.9)
Missing	22 (9.2)
Adjuvant chemotherapy	
No	71 (29.6)
CMF	46 (19.2)
AC or FAC/FEC	54 (22.5)
AC-T	68 (28.3)
Other	1 (0.4)
Previous hormonal therapy	
Adjuvant	165 (68.7)
Palliative	77 (32.1)
Visceral involvement	
Yes	150 (62.5)
No	90 (37.5)

Abbreviations: AC = doxorubicin, cyclophosphamide; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; DFI = disease-free interval; ER = estrogen receptor; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; HER2 = human epidermal growth factor receptor 2; PgR = progesterone receptor; PS = performance status; T = docetaxel or paclitaxel.