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ORIGINAL ARTICLE

Predictive factors for efficacy of capecitabine in heavily pretreated patients with metastatic breast cancer

Tomo Osako · Yoshinori Ito · Masaru Ushijima · Shunji Takahashi · Nahomi Tokudome · Tsutomu Sugihara · Takuji Iwase · Masaaki Matsuura · Kiyohiko Hatake

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Abstract
Purpose The purpose of the present study is to evaluate what clinical factors affect the efficacy, time to treatment failure (TTF), and overall survival (OS) of oral capecitabine monotherapy in heavily pretreated patients with metastatic breast cancer (MBC).
Methods A total of 102 consecutive patients with MBC who had been administered capecitabine monotherapy between June 2003 and August 2004 were retrospectively reviewed. Capecitabine (828 mg/m^2) was given twice daily for 3 weeks followed by a 1-week rest period; this was repeated every 4 weeks. We evaluated the potential clinical factors for TTF and OS, using univariate analysis (log-rank test) and the multivariate Cox regression model. Median follow-up was 16.9 months.
Results A total of 100 patients (98%) had been pretreated with either anthracyclines or taxanes, and 81 patients (79%) with both anthracyclines and taxanes. Response rate was 17% and clinical benefit rate was 41%. Median TTF and OS were 4.9 and 24.3 months, respectively. Multivariate analysis demonstrated that no liver metastasis ($P = 0.015$), good performance status ($P = 0.033$), longer disease-free interval ($P = 0.036$), and hormone receptor-positive tumor ($P = 0.038$) were significant for TTF. No liver metastasis ($P = 0.00012$), objective response to capecitabine ($P = 0.00084$), and good performance status ($P = 0.0011$) were significant for OS.
Conclusions Capecitabine monotherapy is effective over the long term for heavily pretreated patients with MBC who have no liver metastasis, good performance status, longer disease-free interval, or hormone receptor-positive tumor. Patients who have no liver metastasis, who respond to capecitabine, or who have good performance status are expected to survive even longer.

Keywords Capecitabine · Metastatic breast cancer · Predictive factors · Time to treatment failure · Overall survival

T. Osako (✉) · Y. Ito · S. Takahashi · N. Tokudome · T. Sugihara · K. Hatake
Department of Medical Oncology,
Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-10-6, Ariake, Koto-ku, Tokyo 135-8550, Japan
e-mail: tomo.osako@jfcr.or.jp

M. Ushijima · M. Matsuura
Bioinformatics group, Genome Center,
Japanese Foundation for Cancer Research, Tokyo, Japan

T. Osako · T. Iwase
Department of Breast Oncology, Cancer Institute Hospital,
Japanese Foundation for Cancer Research, Tokyo, Japan

M. Matsuura
Department of Cancer Genomics, Cancer Institute,
Japanese Foundation for Cancer Research, Tokyo, Japan

Introduction

Metastatic breast cancer (MBC) is an incurable, lethal disease. The aim of systemic therapy against MBC is focused mainly on palliation and improved quality of life.

Capecitabine is an oral fluoropyrimidine carbomate, which is converted to 5-fluorouracil (5-FU) selectively in tumor throughout a cascade of three enzymes. After gastrointestinal absorption, capecitabine is first hydrolyzed in the liver by carboxylesterase to produce 5′-deoxy-5-fluorocytudine. This moiety is then deaminated on its pyrimidine ring to produce 5′-deoxy-5-fluorouridine by cytidine deaminase, an enzyme located principally in hepatic and

neoplastic tissue. The last enzymatic step, activation of 5′-deoxy-5-fluorouridine to 5-FU, is catalyzed by thymidine phosphorylase, highly expressed in tumor tissues, thus minimizing systemic exposure to 5-FU [1].

Capecitabine achieved a high tumor control rate with low toxicity in heavily-pretreated patients with MBC. Our former study [2] and other studies [3, 4] showed the objective response (OR) rate has varied from 17 to 29%, median time to progression (or treatment failure) from 3.6 to 4.9 months, and median overall survival (OS) from 9.4 to 24.3 months.

Patients with incurable cancer have a clear preference for oral chemotherapy over intravenous chemotherapy [5–7]. Moreover, in patients with metastatic colorectal cancer, capecitabine improves their quality of life and medical resource use in terms of avoidance of hospital visits for intravenous drug administration, less expensive drug therapy, and fewer treatment-related hospitalizations for adverse drug reactions, compared to intravenous 5-FU therapy [7]. Therefore, when oral capecitabine monotherapy is effective over time for patients with MBC, patients can improve their quality of life and medical resource use. The purpose of the present study is to evaluate what clinical factors affect the efficacy, time to treatment failure (TTF) and OS of capecitabine monotherapy in patients with MBC.

Patients and methods

Patients

Consecutive patients with MBC who had been administered capecitabine monotherapy between June 2003 and August 2004 at our hospital were retrospectively reviewed. The eligibility criteria were as follows: (1) capecitabine monotherapy for at least one cycle, (2) metastatic lesion(s) measurable according to the Response Evaluation Criteria in Solid Tumors guidelines [9], and (3) performance status of three or less according to the Eastern Cooperative Oncology Group's scale. The patients of the present study were the same as our former study [2].

Treatment plan

Capecitabine was given orally 828 mg/m^2, twice daily for 3 weeks, followed by a 1-week rest period. This was repeated every 4 weeks in an outpatient setting. The dose was calculated on the basis of body surface area at baseline (Table 1).

Patients with an OR or stable disease (SD) could continue to receive the treatment until progressive disease (PD) or unacceptable toxicity developed. Treatment interruption and/or individual dose adjustment of capecitabine was considered when patients experienced any adverse events assessed at grade 2 or more as defined by the National Cancer Institute, Common Toxicity Criteria, version 3.0.

Table 1 Determination of capecitabine dose according to body surface area

Body surface area (m^2)	Dose (mg, twice daily)
<1.31	900
1.31–1.64	1,200
≤1.64	1,500

Evaluation of efficacy

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors guidelines [9] by the investigators and the independent reviewers, with computed tomography scans at baseline and every 2 or 3 months. Complete response (CR) was defined as the disappearance of all known lesions for at least 4 weeks. Partial response (PR) was defined as a reduction by at least 30% of the sum of all measurable lesions. PD was defined as an increase of the sum of all measurable lesions by greater than 20% or as appearance of a new lesion. And SD was defined as neither CR, PR, nor PD. Long SD was defined as SD lasting for more than 24 weeks.

Objective response rate was defined as the sum of CR and PR rates. Clinical benefit (CB) rate was defined as the sum of CR, PR, and long SD rates. TTF was defined as the period from commencement of capecitabine to discontinuation of capecitabine due to PD or unacceptable toxicity. OS was defined as the period from commencement of capecitabine to the patient's death for any reason.

Selection of potential predictive factors for efficacy of capecitabine

We selected the following potential predictive factors for efficacy of capecitabine: age, disease-free interval (DFI), performance status (PS), estrogen receptor (ER), progesterone receptor (PgR), hormone receptor (HR), human epidermal growth factor receptor 2 (HER2), the number of metastatic sites, the site of metastases, and the number and regimens of chemotherapeutic pretreatments.

Disease-free interval was defined as duration from surgery to first recurrence. When metastatic disease was diagnosed at the time of initial presentation, DFI was defined as zero. PS was scored according to the Eastern Cooperative Oncology Group's scale. ER positive or PgR positive were defined the positive cells 10% or more in immunohistochemistry in primary invasive breast cancer. HR positive was defined as ER+ and/or PgR+. HER2 positive were defined HER2 protein scored as 3+ in immunohistochemistry or HER2 gene amplified twofold or greater in fluorescence in situ hybridization in

primary invasive breast cancer. Metastatic sites included lymph node, lung, bone, liver, pleura, and chest wall. The number of chemotherapeutic pretreatments was defined as the sum of prior regimens consisting of at least two courses of anthracyclines (doxorubicin or epirubicin), taxanes (paclitaxel, docetaxel), bolus 5-FU, oral fluoropyrimidines, cyclophosphamide/methotrexate/5-FU (CMF), mitomycin, irinotecan, vinorelbine, and trastuzumab.

In addition, when we analyzed the potential predictive factors for OS, we added OR and CB of capecitabine to the above factors.

Statistical analyses

First we used univariate analysis to screen for potential predictive factors affecting TTF and OS. Next we used multivariate analysis for the significant factors from the univariate analyses. A P value of <0.05 was considered significant. Confidence intervals (CI) were set at the 95% level.

Univariate analysis

The cumulative survival rates were calculated by the Kaplan–Meier method, which was performed to analyze censored data. Univariate exploration of potential predictive factors for TTF and OS employed log-rank tests (Peto–Peto method).

In these analyses, each factor is divided into two groups. Age was grouped using age 40 as the cut point. Two years was used as the cut point for DFI. For PS, patients were grouped as ones with PS = 0–1 and ones with PS = 2–3. For ER, PgR, HR and HER2, we examined two statuses of positive and negative results. For the number of metastatic sites, we defined one group as patients having one and two sites with the other group having three or more sites. For the sites of metastases, we grouped lymph node, lung, bone, liver, pleura, and chest wall into two statuses of involved and not involved. For the number of chemotherapeutic pretreatments, we defined one group as patients who had had 1–2 regimens and the other group as having three or more regimens. And for the regimens of chemotherapeutic pretreatments, we established two groups of anthracycline-pretreated and untreated, taxane-pretreated and untreated, bolus 5-FU-pretreated and untreated, oral fluoropyrimidine-pretreated and untreated, and CMF-pretreated and untreated.

Multivariate analysis

We used multivariate Cox regression model to investigate which factors affect survival time. Initially, all significant factors selected by univariate analysis were entered into the model as binary variables. Next, non-significant variables were removed sequentially using a backward elimination strategy based on the likelihood ratio test. We then selected a model with all factors being significant. These statistical analyses were performed with the open-source software R (http://www.r-project.org/), version 2.6.0.

Results

Patient characteristics

A total of 102 consecutive patients were assessed in the present study. Median follow-up time for patients was 16.9 months, with a range from 0.9 to 46.5 months. All patients were Japanese women. The demographic characteristics of the present study population are presented in Table 2.

The patients in the present study had advanced disease. More than half (57%) had metastasis in three or more organs. Approximately half of the patients had visceral metastasis of the lung (51%) or liver (46%). Moreover, they had been heavily pretreated. A total of 100 patients had been pretreated with either anthracyclines or taxanes (98%), and 81 patients with both anthracyclines and taxanes (79%).

Efficacy

Of the 102 patients, response was assessable in 96. Five patients achieved CR (5%) and 12 achieved PR (12%). Therefore, the OR rate for capecitabine was 17% (95% CI; 9–24%). Moreover, 32 patients achieved SD, and of these, 25 achieved long SD (25%); hence, the CB rate for capecitabine was 41% (95% CI; 32–51%) (Table 3).

Median TTF was 4.9 months, and median OS was 24.3 months (Fig. 1).

Univariate analyses

Log-rank tests showed that the following five and eight factors were statistically significant for TTF and OS, respectively. For TTF, age ($\leq$40 vs. $\leq$41 years; $P = 0.005$), DFI (0–2 (s) vs. $\leq$2 years; $P = 0.024$), PS (0–1 vs. 2–3; $P = 0.018$), HR (+ vs. −; $P = 0.023$), and liver metastasis (− vs. +; $P = 0.001$) were significant. For OS, PS (0–1 vs. 2–3; $P = 0.0005$), number of metastatic sites (1–2 vs. 3 sites $\leq$; $P = 0.004$), bone metastasis (− vs. +; $P = 0.016$), liver metastasis (− vs. +; $P = 0.0002$), number of chemotherapeutic pretreatments (1–2 vs. 3 regimens $\leq$; $P = 0.046$), pretreatment of taxanes (− vs. +; $P = 0.045$), OR (− vs. +; $P = 0.006$), and CB (− vs. +; $P = 0.0002$) were significant (Table 4).

Multivariate analyses

The following four and three factors were statistically significant for TTF and OS, respectively. For TTF, liver

Table 2 Patient characteristics ($n = 102$)

Characteristics	No.	%
Age		
Mean (range)	56.1 (29–85)	
Disease free interval (years)		
Mean (range)	3.5 (0–11.8)	
Performance status		
0–1	82	80
2–3	20	20
Estrogen receptor (ER)		
+	67	66
–	30	29
Unknown	5	5
Progesterone receptor (PgR)		
+	59	58
–	34	33
Unknown	9	9
Hormone receptor (ER and/or PgR)		
+	74	73
–	23	23
Unknown	5	5
HER2 overexpression		
+	6	6
–	87	85
Unknown	9	9
No. of metastatic sites		
Mean (range)	2.8 (1–6)	
1–2	44	43
≤3	58	57
Sites of metastases		
Lymph node	63	62
Lung	52	51
Bone	52	51
Liver	47	46
Pleura	26	25
Chest wall	25	25
No. of chemotherapeutic pretreatments		
Mean (range)	4.0 (1–8)	
1–2	15	15
≤3	87	85
Regimens of chemotherapeutic pretreatments		
Anthracyclines	91	89
Taxanes	90	88
Bolus 5-fluorouracil	86	84
Oral fluoropyrimidines	33	32
CMF	32	31

metastasis (– vs. +; $P = 0.015$), PS (0–1 vs. 2–3; $P = 0.033$), DFI (0–2 vs. ≤2 years; $P = 0.036$), and HR (+ vs. –; $P = 0.038$) were significant (Table 5). For OS, liver metastasis (– vs. +; $P = 0.00012$), OR (– vs. +; $P = 0.00084$), and PS (0–1 vs. 2–3; $P = 0.00113$) were significant (Table 6).

Table 3 Response to capecitabine ($n = 102$)

	No.	%
Response		
Complete response	5	5
Partial response	12	12
Stable disease	31	30
Long stable disease	25	25
Progressive disease	48	47
Not evaluable	6	6
Objective response rate	17	17
Clinical benefit rate	42	41

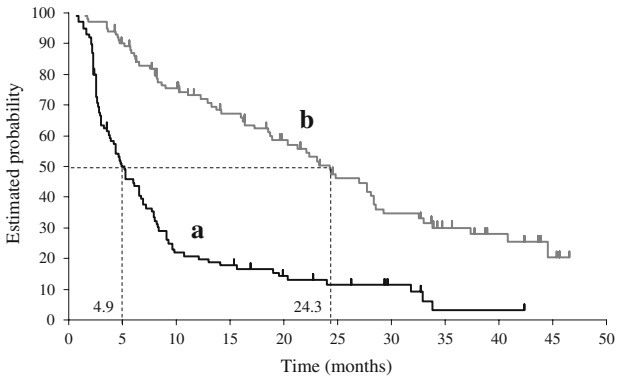

Fig. 1 Time to treatment failure (**a**) and overall survival (**b**)

Discussion

The present study has shown that palliative chemotherapy with oral capecitabine monotherapy can be effective over the long term for heavily pretreated patients who have no liver metastasis, good PS, longer DFI, or HR-positive tumor. The quality of life for heavily pretreated patients having one of these four factors can be expected to improve. Furthermore, in addition to response to capecitabine, two of these four factors —no liver metastasis and good PS—had also a positive influence on longer survival.

These predictive factors resulting from the present study are similar to those from earlier works. Predictive factors for efficacy and survival of cytotoxic chemotherapy have been extensively studied. But unlike the relationship between ER and tamoxifen or HER2 and trastuzumab, no predictive test for a response to cytotoxic chemotherapy has been sufficiently validated to use in a standard clinical setting. Most consistent predictive factors in the metastatic setting are nonspecific clinical features: good PS [10–14], small

Table 4 Univariate analyses of time to treatment failure and overall survival of capecitabine

Category	No.	Time to treatment failure	Overall survival
Age			
≤40 vs. ≤41	9 vs. 93	0.005 (<0.01)	0.06 (NS)
Disease-free interval (years)			
0–2 vs. ≤2	43 vs. 59	0.024 (<0.05)	0.08 (NS)
Performance status			
0–1 vs. 2–3	82 vs. 20	0.018 (<0.05)	0.0005 (<0.001)
Hormone receptor status			
Estrogen receptor + vs. −	67 vs. 30	0.14 (NS)	0.66 (NS)
Progesterone receptor + vs. −	59 vs. 35	0.08 (NS)	0.78 (NS)
Hormone receptor + vs. −	74 vs. 23	0.023 (<0.05)	0.54 (NS)
HER2 overexpression			
+ vs. −	6 vs. 88	0.32 (NS)	0.52 (NS)
No. of metastatic sites			
1–2 vs. ≤3	44 vs. 58	0.10 (NS)	0.004 (<0.01)
Site of metastases			
Lymph node − vs. +	39 vs. 63	0.83 (NS)	0.99 (NS)
Lung − vs. +	50 vs. 52	0.17 (NS)	0.77 (NS)
Bone − vs. +	50 vs. 52	0.66 (NS)	0.016 (<0.05)
Liver − vs. +	56 vs. 46	0.001 (<0.01)	0.0002 (<0.001)
Pleura − vs. +	76 vs. 26	0.82 (NS)	0.75 (NS)
Chest wall − vs. +	77 vs. 25	0.93 (NS)	0.89 (NS)
No. of chemotherapeutic pretreatments			
1–2 vs. ≤3	15 vs. 87	0.20 (NS)	0.046 (<0.05)
Regimen of chemotherapeutic pretreatments			
Anthracyclines − vs. +	11 vs. 91	0.61 (NS)	0.41 (NS)
Taxanes − vs. +	12 vs. 90	0.14 (NS)	0.045 (<0.05)
Bolus 5-fluorouracil − vs. +	16 vs. 86	0.36 (NS)	0.54 (NS)
Oral fluoropyrimidines − vs. +	69 vs. 33	0.28 (NS)	0.53 (NS)
CMF − vs. +	70 vs. 32	0.33 (NS)	0.84 (NS)
Efficacy			
Objective response − vs. +	84 vs. 17	–	0.006 (<0.01)
Clinical benefit − vs. +	60 vs. 42	–	0.0002 (<0.001)

number of metastatic sites [10, 11, 15], no visceral metastasis [12, 13], especially no liver metastasis [12, 14–16], longer DFI [14, 16], ER positive [11, 15], no adjuvant chemotherapy [11, 15, 16], and response to chemotherapy [12, 14].

Some studies have reported the prognostic importance of initial site of metastasis [17, 18]. Patients with breast cancer developing liver metastasis since 1950s have been considered to have a poor prognosis, with median survival rates of less than 6 months [19]. Although survival in MBC patients with liver metastasis can be prolonged by introducing effective modern chemotherapy [19, 20], liver metastasis still contributed most significantly to shorter response and survival in the present study.

Several studies in vitro [21, 22] demonstrated that positive ER was associated with chemoresistance to 5-FU and other antitumor drugs. Some clinical studies showed that positive ER was a predictive factor of resistance to cytotoxic chemotherapy in the neoadjuvant [23] and metastatic setting [24]. On the other hand, the present study and other studies in the metastatic setting [11, 15] demonstrated that positive HR is a predictive factor for longer TTF. HR-positive tumors seem to grow more slowly and less aggressively than HR-negative ones, because survival from first relapse is longer in patients with HR-positive tumors than negative tumors [25, 26]. Therefore, the time to progression with chemotherapy tends to be longer in HR-positive tumors [27].

Previous studies in vitro had shown that introduction of HER2 in breast cancer cells induced resistance to 5-FU [28, 29]. In the clinical setting, patients whose tumors

Table 5 Multivariate analyses: predictive factors for time to treatment failure of capecitabine

	Coefficient	Hazard ratio	95% CI	*P* value
Liver metastasis	0.547	1.728	(1.114, 2.679)	0.015
Performance status	0.611	1.843	(1.049, 3.236)	0.033
Disease-free interval	−0.476	0.621	(0.398, 0.969)	0.036
Hormone receptor	−0.527	0.590	(0.359, 0.971)	0.038

CI confidence interval

Table 6 Multivariate analyses: predictive factors for overall survival of capecitabine

	Coefficient	Hazard ratio	95% CI	*P* value
Liver metastasis	1.058	2.880	(1.678, 4.944)	0.00012
Objective response	−1.243	0.289	(0.123, 0.676)	0.00084
Performance status	1.141	3.131	(1.675, 5.854)	0.00113

CI confidence interval

overexpress HER2 are less likely to benefit from adjuvant nondoxorubicin- and 5-FU-containing regimens, such as CMF [30] or phenylalanine mustard plus 5-FU [31], than patients whose tumors have normal HER2 expression levels. But it is unclear whether patients whose tumors overexpress HER2 are less likely to benefit from capecitabine monotherapy. The present study has a limitation with regard to HER2 status: most patients with HER2-positive breast cancer were excluded because they were administered capecitabine concomitant with trastuzumab. Combination therapy of capecitabine and trastuzumab is effective for patients with HER2-positive MBC [32–34].

The number or content of regimen of chemotherapeutic pretreatments was not important in predicting the efficacy of capecitabine in heavily pretreated patients. Therefore, it seems to be worth giving oral capecitabine to heavily pretreated patients with MBC.

In conclusion, even if patients with MBC are heavily pretreated with chemotherapy, the patients who have no liver metastasis, good PS, longer DFI, or HR-positive tumors can be expected to live longer with capecitabine monotherapy. The heavily pretreated patients who have no liver metastasis, who respond to capecitabine, or show good PS are expected to survive even longer.

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