# Combination Therapy by Trastuzumab with 5'-deoxy-5-fluorouridine and Cyclophosphamide in Patients with Metastatic Breast Cancer

Yuki SAITO, Yasuhiro SUZUKI and Yutaka TOKUDA

*Department of Surgery, Tokai University School of Medicine*

(Received June 30, 2009; Accepted July 21, 2009)

**Background: Trastuzumab (Herceptin®) was clinically introduced in Japan in 2001 to treat metastatic breast cancer patients who show an over-expression of human epidermal growth factor receptor 2 (HER2). Since that time, this anticancer drug has played an important role in the treatment of cancer. In the present retrospective study, trastuzumab was administered in combination with 5'-deoxy-5-fluorouridine (5'-DFUR) and cyclophosphamide (CPM) as the third- to sixth- line therapy in 25 patients whose HER2-positive metastatic breast cancers did not respond but showed recurrence after treatment with several chemotherapeutic regimens, namely, trastuzumab alone, and trastuzumab combined with taxane or other anticancer drugs.**
**Methods: Trastuzumab was administered at a dose of 2 mg/kg (at a loading dose of 4 mg/kg) once weekly; 5'-DFUR, at an oral daily dose of 800−1200 mg/body; and CPM, at an oral daily dose of 100 mg/body for 2 weeks followed by one week discontinuation of the drug.**
**Results: The response rate to the combination therapy was 32% (95% confidence interval, 17−52%). Grade 3 adverse effects, according to National Cancer Institute-Clinical Therapeutic Conference version 2.0. (NCI-CTC ver. 2.0), included: neutropenia in 7 patients, anemia in one, and elevation of alkaline phosphatase (ALP) in one. Other adverse events of grade 1 or 2 in accordance with NCI-CTC included general fatigue, nausea, vomiting, thrombocytopenia, increased transaminase, and decreased serum albumin. All adverse events were easily controllable and reversible after discontinuation of the drug.**
**Conclusions: Combination therapy with trastuzumab, 5'-DFUR and CPM is effective and well tolerated as the third- to six Ðline treatment option for patients with HER2-overexpressing metastatic breast cancer.**

**Mini-abstract: Combination therapy by trastuzumab with 5'-DFUR and cyclophosphamide can be safely administered on an outpatient basis and is useful to treat patients with HER2-overexpressing metastatic breast cancer.**

**Key words: Metastatic breast cancer, HER2/neu, trastuzumab, 5'-DFUR, Cyclophosphamide**

## INTRODUCTION

Metastatic breast cancer (MBC) cannot be cured by chemotherapy, hormonal therapy, radiotherapy and surgery. Therefore, the therapeutic purpose for MBC is optimal palliation and prolonging the survival of the patients [1]. Anthracyclines are the first-line chemotherapeutics to treat MBC [2, 3] Taxanes show significant effects for MBC patients who previously received anthracyclin regimens [4, 5].

Furthermore, other chemotherapeutic agent, such as vinorelbine, TS-1,capecitabine, may be used following anthracyclines and taxanes.

The clinical introduction of trastuzumab (Herceptin®) to treat HER2-overexpressing breast cancer has changed the treatment options for MBC, and trastuzumab is currently the first-line chemotherapeutic used to treat HER2-positive MBC [6]. The efficacy of the drug was reported in previous studies [7, 8]. Generally, trastuzumab is recommended in combination with taxanes. Trastuzumab combined with paclitaxel showed an additive effect which was proven to be a standard regimen for treating this type of cancer [9]. Seidman and colleagues [10] reported a response rate of 61% by weekly administration of trastuzumab combined with paclitaxel. Estava and coworkers [11] noted a response rate of 63% by weekly administration of docetaxel combined with trastuzumab, although their study was not comparative. Patients, who did not respond to the combination chemotherapy of trastuzumab with taxanes, underwent treatments which are described in the reports noted below [12, 13].

Burstein and associates [12] reported a multicenter Phase II study using trastuzumab combined with vinorelbine in 40 HER2-overexpressing MBC patients who had received two or more chemotherapeutics. This study showed a response rate of 75%. Suzuki *et al.* [13] reported a response rate of 42% with the weekly administration of trastuzumab combined with vinorelbine at a dose of 25 mg/m$^2$ once a week.

However, some patients do not response to the above regimens of trastuzumab combined with other chemotherapeutics, and instead show cancer recurrence. This phenomenon results in critical problems in the clinical setting.

5'-deoxy-5-fluorouridine (5'-DFUR, doxifluridine)

Yutaka TOKUDA, Department of Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193 Japan
Tel: +81-463-93-1121 ext. 2290 Fax: +81-463-95-5941 E-mail: tokuda@is.icc.u-tokai.ac.jp

is an orally administered prodrug of 5-fluorouracil (5-FU). 5'-DFUR exerts anticancer activity after metabolic conversion to 5-FU by pyrimidine nucleoside phosphorylase (PyNPase), thymidine phosphorylase (TP) in humans [14]. Nitani *et al.* [15] reported a Phase II study with oral 5'-DFUR alone showing a response rate of 35.9% in 102 patients with MBC.

Other studies [16, 17] have shown combined oral chemotherapy with 5'-DFUR and CPM to demonstrate a low toxicity and novel, convenient and effective properties for an adjuvant therapy for MBC.

Pegram *et al.* [18] and Jahanzeb *et al.* [19] reported the synergic efficacy of combination therapy with trastuzumab and other cancer chemotherapeutics such as vinorelbin, cisplatin, docetaxel, thiotepa, CPM and etoposide *in vitro*. In addition, an additive effect was found between trastuzumab and doxorubicin, epirubicin, paclitaxel, methotrexate or vinblastine. On the other hand, trastuzumab showed antagonistic activity to 5-FU and gemcitabine *in vitro*. Fujimoto-Ouchi *et al.* [20] reported combination therapy with trastuzumab and 5'-DFUR *in vivo* to be superior to treatment with either of the single drugs alone. Nevertheless, combination with trastuzumab and 5'-DFUR *in vitro* showed antagonistic, but antiproliferative activities. The combined therapy in this study, as described above, thus showed an additive effect.

Based on all of these findings, the current study evaluated combination therapy with trastuzumab, 5' -DFUR and CPM, as the third- to six-line treatment, in 25 patients with HER2-overexpressing MBC. This report presents our results, including the response rate and adverse events of the combination therapy.

## PATIENTS AND METHODS

*Patients*

This study enrolled 25 MBC patients who had not positively responded to treatment, and instead showed recurrence after treatment with trastuzumab alone or in combination with taxane or other anticancer drugs. The Hercep Test@ (DAKO Japan) was used for the immunohistological analysis of the tumor HER2 status. The patients were required, to have a neutrophil count $\geqq 2000/mm^3$, and leukocyte count $\geqq 4000\ mm^3$ 2 weeks before the administration this chemotherapeutic regimen because dose-limiting toxicity of 5'-DFUR as well as CPM is leucopenia. The patients were also required to have normal organ functions, including the cardiac function and a performance status 0−1.

*Treatment*

Trastuzumab was administered weekly at a dose of 2 mg/kg (at a loading dose of 4 mg/kg); oral 5' -DFUR was given daily at a dose of 800−1200 mg/body; and oral CPM was given daily at a dose of 100 mg/body for 2 weeks followed by one week discontinuation of the drugs. The combination regimen with 5'-DFUR and cyclophosphamide was selected based on the findings reported by Tominaga [16] and Yoshimoto *et al.* [17]. All patients in the present study were fully informed of the potential benefits and possible adverse events associated with the treatment before starting the present study. The patients were required to have a neutrophil count of $\geqq 1000/mm^3$ and a leukocyte count of $\geqq 2000/mm^3$ on the day of the drug administration and the study treatments were discontinued for one week if the patients did not meet either of the conditions above, but the regimen was resumed at the same doses when the patients recovered to these established levels in the subsequent weeks.

*Monitoring*

All of the candidate patients underwent evaluations, including a physical examination, complete blood cell count, serum chemistry, serum tumor markers (CEA and CA15−3), chest X-ray, liver ultrasound examination, whole body computed tomography (CT) and bone scintigraphy. The patients also received a physical examination, complete blood cell count, serum chemistry and serum tumor markers on the first days of every treatment cycle with the combination therapy. The presence or absence of cancer recurrence was determined using X-ray, ultrasound, CT and bone scintigraphy.

*Evaluation of the response and toxicity*

A complete response (CR) was defined as the complete disappearance of all clinically and radiologically detectable tumor lesions of patients lasting at least 4 weeks. Partial response (PR) was a reduction of 30% or more in the sum of the longest diameter of all measurable tumors for a duration of at least 4 weeks, with no appearance of new tumor lesions. Progressive disease (PD) was defined as an increase of 20% or more in the sum of the longest diameter of measurable lesions or appearance of new tumor lesion. Stable disease (SD) was neither a sufficient decrease to qualify for partial response nor a sufficient increase to qualify for progressive disease over 8 weeks. SD patients whose cancer remained stable for over 24 weeks were defined as long SD. These response criteria were based on the new guidelines of the response evaluation criteria in solid tumors (RECIST) [21].

*Toxicity*

The severity grades of adverse events were assessed using the NCI-CTC version 2.0. grading system [22].

*Statistical method*

The primary endpoint was the rate of radiologically determined objective response to combination therapy with trastuzumab, 5'DFUR and CPM.

Secondary efficacy endpoints included the time to progression free survival (PFS), and overall survival (OS). A 95% confidence interval was calculated for the objective response rate. Time to tumor progression and overall survival were calculated using the Kaplan-Meier survival analysis methods.

## RESLTS

*Patient and tumor characteristics*

The characteristics of 25 patients with MBC are listed in Table 1. Their median age was 52 years old (range, 27−68 years old). None of the 25 patients responded to the previous treatment, but they showed cancer recurrence after treatments with several chemotherapeutic regimens, including trastuzumab alone, combined therapies with taxanes other anticancer

**Table 1** Patient Characteristics

| Pt. No. | age | HER2 status | ER/PgR status | site of metastasis | response | prior chemotherapy for MBC | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | No. | prior chemotherapy regimens | | | | |
| 1 | 58 | 3+ | -/- | PUL | SD | 3 | H+P | H | H+N | | |
| 2 | 64 | 3+ | -/- | PUL | PD | 2 | H | H+P | | | |
| 3 | 51 | 3+ | -/- | HEP, OSS | CR | 2 | H+P | H+N | | | |
| 4 | 56 | 3+ | +/- | HEP, OSS, LYM | PD | 2 | H+P | H | | | |
| 5 | 45 | 2+ | -/+ | OSS, PUL | PD | 3 | H+D | H | H+N | | |
| 6 | 68 | 3+ | -/- | HEP, OSS, PUL | CR | 5 | EC | P | H+D | H | H+N |
| 7 | 64 | 3+ | -/- | HEP | PD | 3 | P | H+P | H+N | | |
| 8 | 58 | 3+ | ?/? | PUL | PR | 3 | A+D | T+C | H | | |
| 9 | 60 | 3+ | -/- | LYM | PR | 2 | H+P | H+N | | | |
| 10 | 52 | 3+ | -/- | OSS | PD | 3 | H | H+P | H+N | | |
| 11 | 60 | 2+ | -/- | OSS, LYM | SD | 3 | P | H+P | H+N | | |
| 12 | 44 | 3+ | +/+ | HEP, OSS | CR | 4 | CMF | C+E | H+D | H+P | |
| 13 | 55 | 2+ | +/+ | HEP | PR | 3 | H+P | H | H+N | | |
| 14 | 50 | 3+ | -/- | HEP | PD | 3 | D | P | H+P | | |
| 15 | 52 | 3+ | -/+ | HEP, OSS | PR | 2 | H+P | H | | | |
| 16 | 52 | 3+ | -/- | LYM | SD | 4 | H+P+CBDCA | H | H+D | H+N | |
| 17 | 52 | 3+ | +/+ | HEP, OSS, PUL | PD | 5 | A+D | C+D+T | H | H+P | H+N |
| 18 | 29 | 3+ | +/+ | LYM, | SD | 2 | H | H+N | | | |
| 19 | 37 | 3+ | -/+ | HEP, OSS | SD | 3 | H+P | H | H+N | | |
| 20 | 53 | 3+ | -/- | PUL, | PD | 2 | H+P | H+N | | | |
| 21 | 52 | 3+ | -/- | HEP, PUL, OSS, BRI | PD | 4 | H | H+N | H+MMC | H+P | |
| 22 | 27 | 3+ | +/+ | HEP, | SD | 3 | A+D | H+P | H+N | | |
| 23 | 58 | 3+ | -/- | PUL, LYM | PD | 4 | P | H+P | H | H+D | |
| 24 | 31 | 3+ | ?/? | HEP, PUL | PR | 2 | H | H+N | | | |
| 25 | 55 | 3+ | -/- | LYM, SKI | PD | 2 | H+D | H | | | |

ER: estorogen resepter
PgR: progesterone resepter
PUL: lung/pleura, HEP: liver
OSS: bone, LYM: lymph nodes,
SKI: skin, BRI: brain,
A: doxorubicine, E: epirubicin, T: thiotepa, C: cyclophosphamide,
P: paclitaxel, D: docetaxel, N Vinorelbine, MMC: mitomycin C
H: trastuzumab, CBDCA: carboplatin,
CR: complete response, PR: partial response,
SD: stable disease, PD: progressive disease

**Table 2** Tumor response

| Response | Patients | |
|---|---|---|
| | number | (%) |
| overall | 8 | 32%* |
| CR | 3 | 12% |
| PR | 5 | 20% |
| SD (long SD) | 6(3) | 24% |
| PD | 11 | 44% |
| PFS | 6.2 + months (1.1−14) | |

* 95% CI: 17−52%

CR: complete response, PR: partial response
SD: stable disease, PD: progressive disease
PFS: progression free survival

drugs. The level of HER2 over-expression of the patients included; 2+ in 3 patients, and 3+ in 22 patients. The sites of the cancer metastases including plural metastatic sites were; the liver in 13 patients (52%), bone in 11 (44%), lung and pleura in 10 (40%), lymph nodes in 8 (32%), brain in 8 (32%), and skin in one (4%).

*Tumor response*

The median treatment in the present study was 8 cycles (range, 1−27 cycles). The responses of the 25 patients are listed in Table 2. Eight patients showed either CR (n = 3, 12%) or PR (n = 5, 20%). Six patients (24%) showed SD, and 11 patients (44%) had PD. The overall response rate (CR + PR/25 patients) was 32% (95% confidence interval, 17−52%). The median progression free survival (PFS) was 6.2 months (range, 1.1−14 + months; Figure 1). The median overall survival (OS) was 18.1 + months (range, 1.2−44.5 + months; Fig. 2).

*Toxicity*

The most frequently detected adverse events were neutropenia, anemia and elevated alkaline phosphatase. Of these hematologic adverse events, the severity of neutropenia was grade 1 in 2 patients (8%), grade 2 in 5 (20%), and grade 3 in 7 (28%). Reduction of the hemoglobin level was grade 1 in 7 patients (28%), and grade 2 in 6 (24%). Thrombocytopenia was grade 2 in one patent (4%). The patients did not require dose reduction or granulocyte colony-stimulating factor.

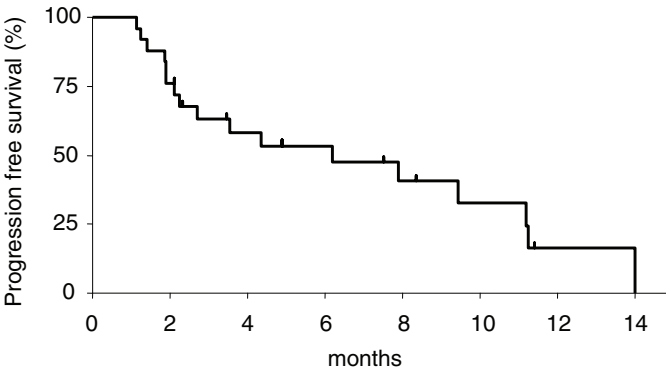


**Fig. 1** Progression free survival curve from the start of the combination chemotherapy

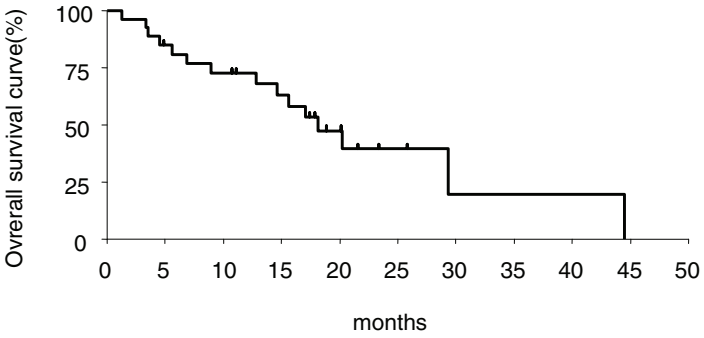


**Fig. 2** Overall survival curve from the start of the combination chemotherapy

**Table 3** Toxicity

| Type | NCI-CTC grade (number) | | | | % (grade 3 + 4) |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| Hematologic | | | | | |
| WBC | 2 | 5 | 7 | 0 | 28 |
| Hb | 7 | 6 | 1 | 0 | 4 |
| Plt | 0 | 1 | 0 | 0 | 0 |
| Non-Hematologic | | | | | |
| GOT | 14 | 2 | 0 | 0 | 0 |
| GPT | 8 | 0 | 0 | 0 | 0 |
| ALP | 4 | 1 | 1 | 0 | 4 |
| T-Bil | 2 | 0 | 0 | 0 | 0 |
| Alb | 0 | 1 | 0 | 0 | 0 |
| Other | | | | | |
| fatigue | 1 | 0 | 0 | 0 | 0 |
| nausea | 9 | 0 | 0 | 0 | 0 |
| vomiting | 3 | 0 | 0 | 0 | 0 |
| diarrhea | 1 | 0 | 0 | 0 | 0 |

These hematologic adverse events were reversible by discontinuation of the drug therapy for 1–2 weeks. Another hematologic adverse event was elevated alkaline phosphatase of grade 3 in one patient (4%). Non-hematologic adverse events were generalized fatigue, nausea, vomiting, and diarrhea all of which were; mild (grade 1), reversible after 1–2 weeks, and controllable on an outpatient basis (Table 3). Neither grade 4 toxicity nor cardiac dysfunction with heart failure was observed in any patient.

## DISCUSSION

Trastuzumab was introduced in Japan in June, 2001 to treat patients with MBC showing over-expression of HER2 protein. Therefore, the treatment of MBC patients is considered to have made a definite progression, and trastuzumab combined with other chemotherapeutics has now become the first-line option to treat MBC patients showing over-expression of HER2. Concretely, trastuzumab is given alone or in combination with other chemotherapeutics in accordance with the performance status (PS) of MBC patients. Generally, trastuzumab is recommended for use in combination with taxanes. Combination therapy with trastuzumab and paclitaxel given weekly reportedly shows an additive effect, which has been established as a standard regimen [9]. Excellent response rates have been reported with combination therapy of trastuzumab and paclitaxel [10] or docetaxel [11]. Pegram *et al.* [18] also reported that trastuzumab

combined with vinorelbine was the most promising candidate regimen next to the combination with trastuzumab and taxanes. Furthermore, Burnstein *et al.* [12] and Suzuki *et al.* [13] showed that the combination regimen with trastuzumab and vinorelbine was the most favorable candidate regimen next to the combination with trastuzumab and taxanes. In spite of these above findings, physicians nevertheless continue to feel it difficult to treat patients with recurrent MBC.

5'-DFUR is a synthetic anticancer drug developed in Japan. 5'-DFUR is converted to 5-FU *in vivo* by PyNPase which exists much more in tumor tissue than in normal tissue. As a result, a higher concentration of 5-FU is provided in tumor tissue than in normal tissue. In addition, TP is an essential enzyme for the activation of the 5'DFUR to 5FU in tumors. Endo *et al.* [23] found that CPM up-regulated human PyNPase and TP levels in the tumor tissue of human mammary tumor xenograft models. Therefore, CPM and 5'DFUR are considered to be good potential partners. Tominaga *et al.* [8] reported that 5'-DFUR combined with CPM was more effective to prevent recurrence of cancers than 5'-DFUR alone. Furthermore, Yoshimoto *et al.* [9] showed that combination therapy with 5'-DFUR and CPM was very effective and tolerable in patients with MBC. Pegram *et al.* [18] and Jahanzeb [19] reported a synergic effect of combined therapy with trastuzumab and cyclophosphamide, although 5-FU shows an antagonistic reaction against trastuzumab *in vitro*. On the other hand, Fujimoto-Ouchi *et al.* [20] showed *in vivo* that combined therapy with trastuzumab and 5-FU resulted in an additive effect. However, the reason for the discrepancy between the *in vitro* and *in vivo* results remains to be elucidated.

Therefore, the present study employed combination therapy with trastuzumab, 5'-DFUR and CPM to treat 25 MBC patients who did not respond or showed the cancer recurrence after treatment by trastuzumab alone or in combination with other chemotherapeutics as the third- to sixth-line regimen. Although the present retrospective study enrolled only a small number of 25 patients, the combination therapy with trastuzumab, 5'-DFUR and CPM resulted in a response rate of 32%, and showed PFS of 6.2 months in spite of the third to sixth treatment option. These results are very satisfactory, and this combination therapy is thus considered to play an important role in the treatment option of MBC patients after the third-line treatment regimen. The regimen was predicted to cause neutropenia, anemia, and elevation of alkaline phosphatase, but all of these adverse events were mild, and no symptomatic cardiac dysfunction was observed. Furthermore, these adverse events were reversible after discontinuing the chemotherapy, and the patients could again receive the chemotherapy. Therefore, this treatment is as safe as treatment with the previous regimens.

In conclusion, the present combination regimen was therefore found to be a safe and effective treatment regimen after third-line therapies. In addition, this combination therapy may improve the quality of life and/or survival of the MBC patients. Furthermore, the toxicity associated with this combination therapy is mild and tolerable and reversible after 1–2 weeks discontinuation of the chemotherapy. The combined regimen of trastuzumab, 5'-DFUR and CPM may therefore be an effective and useful therapeutic option to treat MBC patients as a third-line treatment regimen.

Capecitabine, a novel oral fluoropyrimidine carbamate, is first converted to 5'-deoxy-5-fluorocytidine, then to 5'DFUR and finally to 5-FU by TP preferentially located in tumor tissues. A human mammary tumor xenograft model suggested that the efficacy of capecitabine and CPM combination treatment is more than additive [23].

Furthermore, future studies are now planned to investigate the efficacy and safety of the trastuzumab, capecitabine and CPM combination therapy.

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