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Original Article

Clinical Efficacy of Capecitabine and Cyclophosphamide (XC) in Patients with Metastatic Breast Cancer

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Combined low-dose therapy of oral capecitabine (Xeloda) and cyclophosphamide (XC) has been demonstrated to be useful for long-term control of lesions in patients with metastatic breast cancer (MBC) and is aimed at symptomatic alleviation and prolongation of survival. Here, a retrospective review was conducted of MBC patients administered XC at the Okayama University Hospital (OUH), to evaluate responses to XC, adverse events and time to progression (TTP). Twenty patients with MBC received XC between 2006 and 2009. With the exception of 2 elderly patients who were over the age of 70 at the initial examination, all of the patients had received prior treatment with an anthracycline and/or a taxane. No complete response (CR) cases were observed, but partial response (PR) was achieved in 6 patients (30%) and SD in 9 (45%), of whom 5 (20%) sustained SD status for ≥12 months. The median TTP was 6 months (range: 3–27 mo.). Three patients developed Grade 3 adverse events (diarrhea, nausea and stomatitis), but no other patients developed adverse reactions causing interruption of the therapy. XC was safe even in previously treated and elderly MBC patients; moreover, it yielded remarkable clinical responses.

Key words: metastatic breast cancer, metronomic, chemotherapy

With advances in the development of new drugs in recent years, an expanded repertoire of pharmacotherapeutic strategies has become available for breast cancer. As molecular-targeting drugs become more widespread, pharmacotherapy has become increasingly more effective but also more complex. The selection of drugs must be based on results of individual drug sensitivity assessments. In the case of breast cancer treatment, in particular, the most suitable therapeutic regimens should be selected not only based on assessment of the indication for hormone therapy or for the molecular-targeting drug trastuzumab by determining the estrogen receptor (ER) and HER2 expression status, but also by taking into account the tumor characteristics, such as the malignancy grade, extent of lymph node metastasis, and sites of distant metastasis through translational research which has been applied extensively in recent years. Risk factors such as adverse reactions, cost, and the social environment of the patients are also of importance in this determination. In particular, treatment for recurrent carcinoma of the breast is still aimed primarily at prolongation of survival and alleviation of symptoms rather than at cure of the malignancy, so that the weight of each of these factors diverges widely from that during the consideration of adjuvant chemotherapy, which is aimed at cure. It sum, theoretical and clinical evidence-based evaluation

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of the risk *versus* benefit of various therapeutic strategies on a patient-by-patient basis has been increasingly expected in recent years.

Patients with recurrent breast cancer present with diverse symptoms depending on the site(s) of the metastatic lesions and exhibit anxiety about exacerbation of the condition. Many are elderly and inevitably require familial support. Drugs that can be used safely and effectively for prolonged periods of time in such patients are still very few.

This study was undertaken as a retrospective evaluation of the clinical efficacy of and adverse reactions to XC therapy, one of the treatment options employed for recurrent breast cancer, consisting of capecitabine (Xeloda, X) and cyclophosphamide (C), both available in oral formulations.

Patients and Methods

Patients. A retrospective analysis was performed of patients with MBC who received combined capecitabine and cyclophosphamide therapy (XC) between December 2004 and March 2009 at Okayama University Hospital (OUH). The patient population was identified from a database at the Division of Breast and Endocrine surgery. They were followed up until death or, if still alive, until their last visit up to March 2009.

Baseline evaluation included clinical examination, chest X-ray, CT, nuclear bone scan, and biochemical and hematological tests. The complete blood count and biochemical tests were repeated every 21 days. The best response in each patient was assessed according to the WHO criteria. Complete response (CR) was defined as disappearance of all clinical and radiographic evidence of the tumor as assessed on two occasions at least 4 weeks apart. Partial response (PR) was defined as a 30% or greater decrease in the sum of the maximum perpendicular diameters of measurable lesions. Stable disease (SD) was defined as a less than 30% decrease but greater than 25% increase in the sum of the bi-perpendicular diameters of measurable lesions and the absence of the appearance of new lesions; these conditions had to be maintained for at least 12 weeks to be labeled as SD, and SD maintained for over 40 weeks was defined as prolonged SD. Progressive disease (PD) was defined as a greater than 25% increase in the sum of bi-perpendicular diameters of measurable lesions, or the appearance of new lesions. The clinical benefit rate was defined as the proportion of patients in whom a CR, PR or prolonged SD was achieved. The National Cancer Institute common terminology criteria for adverse events (CTCAE) version 2.0 [1] were adopted to determine the toxicity of the treatment.

Evaluation of pathological factors. Surgical specimens were sectioned at 7–10 mm for evaluation of the pathological response by pathologists. Expression levels of ER (1D5, Dako Cytomation, Glostrup, Denmark), PgR (1A6, Novocastra), and HER2 (HercepTest®, Dako Cytomation) were examined by immunohistological staining. The ER and PgR status was labeled as positive when greater than 10% of the cancer cell nuclei exhibited positive staining, regardless of the staining intensity. HER2 expression was scored as follows: (0), no positive cell staining; (1+), slightly positive in more than 10% of the cancer cells; (2+), moderately positive in more than 10% of the cancer cells; and (3+), markedly positive in more than 10% of the cancer cells. Immunohistochemistry (IHC) scores of (2+) or (3+) were defined as HER2-positive.

Treatment. Capecitabine (1,600 or 2,400 mg/day) and cyclophosphamide (100 mg/day) (XC) were administered orally twice daily for 2 weeks, followed by a week of treatment cessation. Treatment was continued until disease progression, appearance of unacceptable adverse events or withdrawal of the patient's consent. In the case of Grade 2 or worse toxicity, XC administration was interrupted and resumed only after the toxicity had resolved entirely or improved to Grade 1.

The time to progression (TTP) was calculated from the day of commencement of XC administration until the day of documented progression. Overall survival (OS) was calculated from the start date of XC therapy to the date of death from any cause. TTP and OS were analyzed according to Kaplan-Meier estimates.

Results

Twenty MBC patients received XC therapy between December 2004 and March 2009 at OUH. Three of these patients were still receiving XC at the last follow-up. Table 1 shows the patient characteristics. The median age was 56 (29–83) years. The

Eastern Cooperative Oncology Group (ECOG) performance status of the patients was <2 in all patients. The site of metastatic disease was the bone and/or soft tissue in 5 patients (25%) and a visceral site(s) (lung, liver, brain and pleura) in 15 patients (75%). Table 2 shows the chemotherapy regimens that the patients had received prior to the XC therapy. The median number of chemotherapy regimens used before the XC regimen was 2 (0–5). All except 2 patients who were older than 70 years old had received an anthracycline and/or a taxane. Three patients (15%) had received vinorelbine and 5 (25%) had received a 5FU derivative prior to the XC therapy. Prior oral formulations received included CMF (2 patients), capecitabine alone (2 patients) and S-1 (1 patient). Eleven (55%) patients were ER-positive and had received hormone therapy prior to the XC treatment. Three patients (15%) with HER2-positive disease had received trastuzumab in combination with a taxane or vinorelbine before the XC treatment, and 2 had received XC with trastuzumab.

The response rate (RR) was 30%, with none of the patients showing clinically complete response (CR) and 30% (6/20) showing PR. Nine patients (45%) showed SD, and prolonged SD with continued XC administration for more than 12 months was observed in 4 (20%) patients (Table 3). The overall clinical benefit rate (CR, PR and prolonged SD) was 50% (10/20). Six out of the 10 patients with clinical benefit had visceral involvement (liver, 4; lung, 2), and 75% (3/4) of the patients who showed prolonged SD had bone metastasis only. Six out of the 10 patients were ER-positive and one was HER2-positive. Four of the patients had triple-negative breast cancer, being negative for ER, PgR and HER2, and the response rate to XC in these patients was relatively high (PR 2, prolonged SD 1 and SD 1). Two of the patients who had received capecitabine alone before the XC treatment showed SD. The median TTP was 6 months (range, 1–27 months; Fig. 1). The median OS from the start of treatment for the metastases was 38 months (range, 9–86 months), and 6 patients (30%) were still alive at the last follow-up.

Overall, the XC regimen was relatively well-tolerated. Table 4 shows the adverse events that were encountered in the patients treated with XC. Grade 3 toxicities were observed in 3 patients (diarrhea, 2; nausea, 1; stomatitis, 1). There was no case of hand-foot syndrome or febrile neutropenia, and none of the XC-related adverse events were fatal. The most frequent reason for treatment discontinuation was disease progression (14 patients, 82%). The XC treatment was discontinued and other chemotherapy started in the 3 patients who showed Grade 3 adverse events. One of the 2 relatively older patients (73 and

Table 1 Patient characteristics

	No. of patients (n = 20)	% of patients
Median age (years; range)	56 (29–83)	
Metastatic site(s) involved		
Bone/soft tissue	5	25
Visceral	15	30
Histology		
Invasive ductal carcinoma	19	95
Invasive lobular carcinoma	1	5
Estrogen receptor status		
Positive	11	55
Negative	9	45
HER2/neu status		
Positive	5	25
Negative	15	75

Table 2 Prior chemotherapy

Prior chemotherapy	No. of patients (n = 20)	% of patients
No. of regimens used		
0/1/2/3/4/5	2/5/7/3/2/1	
Median	2 (0–5)	
Anthracycline	16	80
Taxane	14	70
Vinorelbine	3	15
Capecitabine	2	10
S-1	1	5
Trastuzumab	3	15

Table 3 Response rate

Response	No. of patients (n = 20)	% of patients
CR	0	0
PR	6	30
SD	9	45
Prolonged SD (>12 months)	4	20
PD	5	25

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

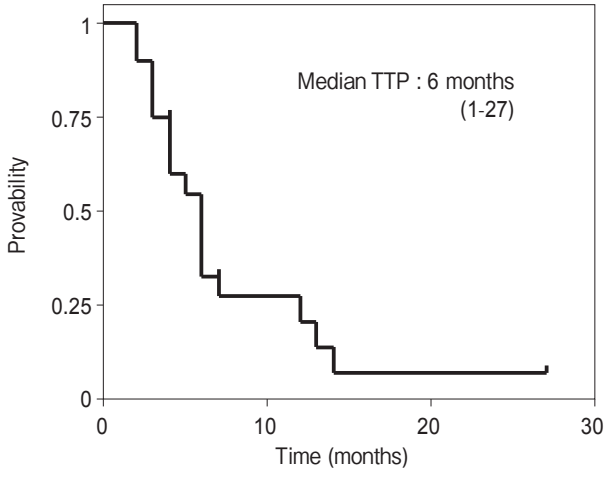

Fig. 1 Time to progression curve of metastatic breast cancer patients treated with Capecitabine and Cyclophosphamide (XC).

Table 4 XC-treatment-related adverse events

event	Grade 1/2 (%)	Grade 3 (%)
Diarrhea	0	1 (5)
Anorexia	1 (5)	0
Nausea/vomiting	0	2 (10)
Stomatitis	0	1 (5)
Generalized fatigue	1 (5)	0
Hand-foot syndrome	0	0

83 y.o.) who were administered XC as first-line chemotherapy showed PR and the other showed prolonged SD without the development of adverse events.

Discussion

Following its administration, capecitabine (X) is converted to its active form 5-FU by thymidine phosphorylase (TP), which occurs at high levels in tumor tissues, to exert its antitumor effect [2]. Disease control with X treatment alone has been reportedly achieved in 57–63% of patients with anthracycline- and taxane-refractory, recurrent breast cancer, with a median survival time of about 1 year [3–5]. The higher the level of TP activity in the tumor tissues, the greater the clinical benefit obtained with X therapy [6]; concomitant use of a drug(s) enhancing the TP activity in the tumor tissues may augment the therapeutic effect of this drug. It has been reported that besides paclitaxel, docetaxel and mitomycin C administration, cyclophosphamide administration is also associated with elevation of the intratumoral TP activity [7–10]. Several clinical trials of combined therapy with capecitabine and paclitaxel or docetaxel have been conducted, with good results, demonstrating the superiority of the combined therapeutic regimens [3, 4, 11–14]. In particular, a study designed to compare the results of treatment with X + docetaxel and docetaxel alone in patients with recurrent breast cancer previously treated with anthracyclines showed that the combined regimen was significantly superior in terms of the response rate and response duration, as well as the survival time [11]. Several clinical studies have been published on the usefulness of combined treatment with molecular-targeting therapeutic agents. Use of these drugs in the treatment of recurrent breast cancer, however, is still controversial, because of the significant adverse reactions and unusually high prices of these drugs, the as-yet insufficient assessment of the therapeutic responses, and the fact that the patient's disease status, social background, *etc.*, must be taken into account when prescribing them.

As for the adverse reactions to X, symptoms related to the gastrointestinal system and myelosuppression are relatively mild, while hand-foot syndrome has been reported to occur at a high frequency. In the present case series, none of the patients developed hand-foot syndrome. Myelosuppression may occur also as an adverse reaction to C but there was no patient in the present case series with febrile neutropenia or bone marrow suppression necessitating treatment discontinuation. In 3 patients (15%), adverse reactions necessitated discontinuation of treatment and a switch to other therapeutic regimens; in all 3 patients, the adverse reaction pertained to the gastrointestinal system. Measures to prevent these gastrointestinal reactions should be taken from the outset. In the present case series, with the patient age reaching up to 83 years, XC therapy proved to be safe, raising no concerns in terms of adverse reactions. Thus, XC therapy is a remarkably well tolerated and safe treatment. Furthermore, it is considered that XC therapy may be safely and effectively employed for the treatment of breast cancer in elderly subjects for whom a definitive treatment policy is yet to be established.

The advantage of orally available medications lies first in their milder adverse reactions and greater

patient compliance, which allow a good QOL to be maintained. As the aims of treatment in patients with recurrent breast cancer are prolongation of survival and alleviation of symptoms, combinations of drugs must be carefully chosen for a therapeutic strategy for maintaining patient QOL. Currently, treatment with capecitabine alone is undertaken in a number of patients with recurrent breast cancer, and this therapy is generally thought to be beneficial for maintenance of a good QOL. The XC therapy in the present series consisted of X in combination with a low dose of C. According to a report by Harvey V *et al.*, XC therapy was superior by 12.6% in terms of the clinical response to treatment with capecitabine alone [15]. In regard to adverse reactions, neutropenia associated with C was noted in the XC therapy group; however, there were no other significant intergroup differences. There has been no large-scale prospective study published to date, so that further investigation is warranted to clarify any differences in survival [7–8, 16]. In the present case series also, partial response were obtained in 30% of all the patients, including patients with a history of prior treatment. Furthermore, for the first time, it has been documented that 20% of the patients showed a prolonged duration of SD that was sustained for ≥1 year. These responses seem to be largely attributable to the metronomic therapeutic effect obtained with the use of the combined XC regimen [2, 7]. XC therapy, when viewed from these viewpoints, may yield responses as satisfactory as those of hormonal therapy, with a long-sustained QOL; therefore, its institution from an early stage of treatment is expected to be of significance especially in patients with breast cancer not showing adequate response to hormonal therapy.

In recent years, the development of an effective therapeutic strategy for dealing with basal-like carcinoma of the breast, which is recognized as a highly malignant type with an unfavorable prognosis, has drawn increasing attention [17]. This type of breast cancer has been shown to involve mutations of BRCA-1, so that genetic instability is likely implicated in its pathogenesis. Further, it has been documented as being refractory to currently available drugs, and no standard treatment has been established yet. There is the possibility, however, that alkylating agents such as C, which directly act upon DNA strands to cause inter-strand linking, may prove effective against it. Therefore, orally available C preparations are currently the focus of attention for the treatment of these breast tumors, and results of relevant studies are eagerly awaited. The present study data suggest the potential usefulness of XC therapy in the treatment of triple-negative breast carcinomas, in that the therapy yielded PR in 50% of the patients with triple-negative breast carcinoma, albeit there were only 4 such patients. However, there is no established therapeutic strategy using these drugs for the treatment of early drug-resistant triple-negative breast carcinomas. These treatment regimens continue to be instituted only after the standard use of anthracyclines and taxanes, as is the case with other types of breast cancer. Further investigations are needed to select the most effective treatment method with prior scrutiny of the tumor susceptibility to drugs. It seems very likely that XC therapy would serve as an important treatment alternative under these circumstances.

The therapeutic concept of inhibition of tumor growth by inhibiting peritumoral neomicrovascularization to produce a resting state of neoplastic growth is referred to as metronomic chemotherapy [18]. Laboratory studies have demonstrated the anti-neoangiogenic and antitumor effects of long-term administration of C at low doses [19]. This concept has been clinically applied, and reports have been appearing in the literature, including one study in which low-dose C was used concomitantly with hormonal therapy [20] and more recently, trials of combined treatment with molecular-targeting drugs that inhibit neovascularization, with the expectation of antiangiogenic effects [21–22]. There has been a growing trend of devising therapeutic strategies based on the same concept for other solid tumors as well as breast cancer [23]. The XC therapy reported herein also represents a regimen for metronomic chemotherapy aimed at long-sustained inhibition of tumor growth via combined use of low-dose C and X, which enhances the effect of the former. These therapeutic regimens may be said to be useful inasmuch as an anti-neoangiogenic effect can be expected from both regimens; in addition, as both drugs are available for oral administration, long-term safe use with well-maintained compliance is more likely. In the present study, the incidence of adverse reactions was remarkably low; as expected, the therapeutic regimen was well-tolerated even in elderly patients over the age of 70 years, with

remarkable drug effects. In particular, the prolonged duration of SD of ≥1 year observed in 20% of the treated patients may be said to exemplify the concept of metronomic chemotherapy. Future incorporation of newer molecular-targeting therapeutic agents, besides expanding the available spectrum of therapeutic options, will undoubtedly allow more effective therapy to be individualized according to the patient's background characteristics, taking into account the biology of the breast cancer. Research to elucidate the biology of breast cancer and the accumulation of pertinent cases and prospective studies are necessary in the future.

References

1. Program NCICTE: Common toxicity Criteria, version 2.0. (April 30, 1999).
2. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I and Ishitsuka H: Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer (1998) 34: 1274–1281.
3. Blum JL, Dees EC, Vukelja SJ, Amare M, Gill DP, McMahon RT, Ilegbodu D, Asmar L and O'Shaughnessy JA: Phase II trial of capecitabine and weekly paclitaxel in patients with metastatic breast cancer previously treated with every-3-week taxane therapy. Clin Breast Cancer (2007) 7: 465–470.
4. Reichardt P, Von Minckwitz G, Thuss-Patience PC, Jonat W, Kolbl H, Janicke F, Kieback DG, Kuhn W, Schindler AE, Mohrmann S, Kaufmann M and Luck HJ: Multicenter phase II study of oral capecitabine (Xeloda(")) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy. Ann Oncol (2003) 14: 1227–1233.
5. Fumoleau P, Largillier R, Clippe C, Dieras V, Orfeuvre H, Lesimple T, Culine S, Audhuy B, Serin D, Cure H, Vuillemin E, Morere JF, Montestruc F, Mouri Z and Namer M: Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer (2004) 40: 536–542.
6. Yamamoto Y, Toi M and Tominaga T: Prediction of the effect of 5' -deoxy-5-fluorouridine by the status of angiogenic enzyme thymidine phosphorylase expression in recurrent breast cancer patients. Oncology Reports (1996) 3: 863–865.
7. Yoshimoto M, Tada K, Tokudome N, Kutomi G, Tanabe M, Goto T, Nishimura S, Makita M and Kasumi F: The potential for oral combination chemotherapy of 5'-deoxy-5-fluorouridine, a 5-FU prodrug, and cyclophosphamide for metastatic breast cancer. Br J Cancer (2003) 89: 1627–1632.
8. Saji S, Toi M, Morita S, Iwata H, Ito Y, Ohno S, Kobayashi T, Hozumi Y and Sakamoto J: Dose-finding phase I and pharmacokinetic study of capecitabine (xeloda) in combination with epirubicin and cyclophosphamide (CEX) in patients with inoperable or metastatic breast cancer. Oncology-Basel (2007) 72: 330–337.
9. Endo M, Shinbori N, Fukase Y, Sawada N, Ishikawa T, Ishitsuka H and Tanaka Y: Induction of thymidine phosphorylase expression and enhancement of efficacy of capecitabine or 5'-deoxy-5-fluorouridine by cyclophosphamide in mammary tumor models. International Journal of Cancer (1999) 83: 127–134.
10. Sawada N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T and Ishitsuka H: Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. Clin Cancer Res (1998) 4: 1013–1019.
11. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, Fumoleau P, Jones S, Lui WY, Mauriac L, Twelves C, Van Hazel G, Verma S and Leonard R: Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. J Clin Oncol (2002) 20: 2812–2823.
12. Chan S, Romieu G, Huober J, Tubiana-Hulin M, Schneeweiss A, Lluch A, Llombart A, du Bois A, Carrasco E, Thareau VA and Fumoleau P: Phase III study of gemcitabine plus docetaxel versus capecitabine plus docetaxel for anthracycline-pretreated metastatic breast cancer patients. J Clin Oncol (2009) 27: 1753–1760.
13. Gradishar WJ, Meza LA, Amin B, Samid D, Hill T, Chen YM, Lower EE and Marcom PK: Capecitabine plus paclitaxel as frontline combination therapy for metastatic breast cancer: A multicenter phase II study. J Clin Oncol (2004) 22: 2321–2327.
14. Batista N, Perez-Manga G, Constenla M, Ruiz A, Carabantes F, Castellanos J, Baron MG, Villman K, Soderberg M, Ahlgren J, Casinello J, Regueiro P and Murias A: Phase II study of capecitabine in combination with paclitaxel in patients with anthracycline-pretreated advanced/metastatic breast cancer. Brit J Cancer (2004) 90: 1740–1746.
15. Harvey VJ, Sharples K, Isaacs R, Jameson MB, Jeffery M, McLaren B, Pollald S, Riley G, Simpson A, Findeay MP: A randomized phase II study comparing capecitabine (C) with C plus oral cyclophosphamide (CCy) in patients (pts) with advanced breast cancer (BC). J Clin Oncol (2008) 26 (Suppl.).
16. Ohno S, Mitsuyama S, Tamura K, Nishimura R, Tanaka M, Hamada Y, Kuroki S and Grp KBCS: Dosage of capecitabine and cyclophosphamide combination therapy in patients with metastatic breast cancer. Anticancer Res (2007) 27: 1009–1013.
17. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lonning PE, Borresen-Dale AL, Brown PO and Botstein D: Molecular portraits of human breast tumours. Nature (2000) 406: 747–752.
18. Cleator S, Heller W and Coombes RC: Triple-negative breast cancer: therapeutic options. Lancet Oncol (2007) 8: 235–244.
19. Munoz R, Shaked Y, Bertolini F, Emmenegger U, Man S and Kerbel RS: Anti-angiogenic treatment of breast cancer using metronomic low-dose chemotherapy. Breast (2005) 14: 466–479.
20. Bottini A, Generali D, Brizzi MP, Fox SB, Bersiga A, Bonardi S, Allevi G, Aguggini S, Bodini G, Milani M, Dionisio R, Bernardi C, Montruccoli A, Bruzzi P, Harris AL, Dogliotti L and Berruti A: Randomized phase II trial of letrozole and letrozole plus low-dose metronomic oral cyclophosphamide as primary systemic treatment in elderly breast cancer patients. J Clin Oncol (2006) 24: 3623–3628.
21. Dellapasqua S, Bertolini F, Bagnardi V, Campagnoli E, Scarano E, Torrisi R, Shaked Y, Mancuso P, Goldhirsch A, Rocca A, Pietri E and Colleoni M: Metronomic Cyclophosphamide and Capecitabine Combined With Bevacizumab in Advanced Breast Cancer. J Clin Oncol (2008) 26: 4899–4905.
22. Orlando L, Cardillo A, Ghisini R, Rocca A, Balduzzi A, Torrisi R, Peruzzotti G, Goldhirsch A, Pietri E and Colleoni M: Trastuzumab in combination with metronomic cyclophosphamide and methotrex-

ate in patients with HER-2 positive metastatic breast cancer. Bmc Cancer (2006) 6: 225.
23. Kamat AA, Kim TJ, Landen CN, Lu CH, Han LY, Lin YG, Merritt WM, Thaker PH, Gershenson DM, Bischoff FZ, Heymach JV, Jaffe RB, Coleman RL and Sood AK: Metronomic chemotherapy enhances the efficacy of antivascular therapy in ovarian cancer. Cancer Res (2007) 67: 281-288.