

乳腺疾病病理学及基础研究专题 • 临床研究 •

Potential of a COX-2 inhibitor in lowering chemotherapy-induced neutropenia

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【Abstract】 Objective This study was initially designed to evaluate the effect of celecoxib on the regimen of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) combination, followed by docetaxel (T) in neoadjuvant setting. An unplanned preliminary review on safety was conducted after a halt of the study due to the concerned potential cardiovascular risk of using COX-2 inhibitors. **Methods** We studied 23 consecutive cases of operable breast cancer having received four cycles of FEC(500 mg/m², 100 mg/m², 500 mg/m²) followed by four cycles of T(100 mg/m²) with concurrent celecoxib (400 mg twice daily) (group A) or same chemotherapy regimen but without concurrent celecoxib (group B). These combined chemotherapies were administered every 3 weeks. The Chi-square test or Fisher's exact test were used to assess the difference in incidence of limiting hematological toxicities between groups. **Results** 23 patients (group A: $n=12$; group B, $n=11$) received a total of 183 out of 184 planned treatment cycles; one (4%, 1/23) of them omitted the fourth cycle of FEC owing to repeated incidences of febrile neutropenia. Received dose intensity (RDI) for FEC in group A ($90\% \pm 11\%$) was higher than that in group B ($80\% \pm 8\%$) while RDI for T was similar between group A ($93\% \pm 8\%$) and group B ($96\% \pm 9\%$). Of the first 91 treatment cycles of FEC, limiting hematological toxicity, severe neutropenia including febrile neutropenia, was significantly different between group A and B [$(10.4\%, 5/48)$ vs. $(32.6\%, 14/43)$, $P=0.009$]. Other toxicities commonly observed in chemotherapy receiving patients were manageable. **Conclusions** Neoadjuvant use of FEC followed by T with concurrent celecoxib appeared to be safe for treatment of operable invasive breast cancer. The observed lower incidence of chemotherapy-induced neutropenia is possibly contributed by the administration of COX-inhibitor. We believe that further investigation might provide more evidence on the use of COX-2 inhibitors in breast cancer.

【Key words】 Breast neoplasms; Chemotherapy; Cyclooxygenase-2; Neutropenia

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Breast cancer is one of the most common malignancies in women around the world. It consists of 23% of all cancer with an estimated 1.15 million new cases among women in 2002^[1]. In Hong Kong, breast cancer incidence occupies the first place among other cancers in women and it shows an obvious increasing trend from 1995 to 2006^[2]. The demand for active treatment is therefore evident in view of current situation.

Preoperative (neoadjuvant) chemotherapy is a recently adopted therapeutic strategy rendering inoperable tumor operable, making breast conservation surgery possible and allowing objective assessment of response to chemotherapeutic agents. The use of anthracycline in the neoadjuvant setting has been evaluated for patients with breast cancer^[3-7]. Though it did not conclusively show superiority of neoadjuvant anthracycline over adjuvant chemotherapy, addition of taxane in neoadjuvant setting showed better pathologic complete response (pCR)^[8-10] which is one of the key primary goals of neoadjuvant treatment to provide survival advantage^[11-13].

Celecoxib (CXB) is a selective cyclo-oxygenase-2 (COX-2) inhibitor belonging to non-steroidal anti-inflammatory drug (NSAID) which is related to show effects on reducing the incidence of breast cancer^[14-16]. A slight reduction in relative risk (RR) for breast cancer incidence was associated with the use of NSAID (RR 0.82, 95% CI 0.75—0.89)^[17]. It also possesses chemopreventive effect and chemotherapeutic properties in rodent models of breast cancer^[15]. A proof-of-concept study showed an additive effect of celecoxib in patients receiving neoadjuvant anthracycline therapy for breast cancers^[18]. Higher pathologic response rate was observed in the group receiving FEC with concurrent celecoxib 400 mg twice daily (BID). Addition of COX-2 inhibitor to taxane therapy is also recommended as another potential cancer treatment as evident in pre-clinical and clinical settings^[19-20]. The study also found that COX-2 over-expression might be a promising predictive marker of response to the regimen. COX-2 inhibitors might be of use in treatment of breast tumours which over-express the COX-2 enzyme.

Chemotherapy-induced toxicity is still one of the major concerns for treatment of cancers. Neutropenia is commonly observed dose limiting toxicity in patients receiving anthracyclines and taxane^[21-23]. Dose reduction

due to the dose limiting toxicity may diminish the drug efficacy. Maintaining sufficient therapeutic dose chemotherapy is, therefore, crucial to successful treatment. For this reason, we compared the safety profile of chemotherapy between those who was administered with the celecoxib to those without celecoxib.

1 Patients and Methods

1.1 Patient selection

Twenty three female patients with histologically confirmed invasive breast cancer (IBC) were accrued to the phase III randomized controlled study initiated by Organisation for Oncology and Translational Research (OOTR). The study was approved by the local institutional ethics committee. Written informed consents were obtained from all patients. The eligibility criteria included the following: absence of psychiatric or addictive disorders, capability of following prescription instructions, patients aged 20 years or above, histologic proof of IBC, palpable and measurable primary tumor confined to one breast with clinical stage from II_A to III_A on clinical examination, Karnofsky performance status (KPS) $\geq 70\%$, adequate hematologic parameters (WBC $\geq 2.5 \times 10^9 \text{ L}^{-1}$, neutrophil count $\geq 2.0 \times 10^9 \text{ L}^{-1}$, platelet count $\geq 100 \times 10^9 \text{ L}^{-1}$, and hemoglobin $\geq 100 \text{ g/L}$), and adequate hepatic (total serum bilirubin $\leq 2 \times$ institutional upper limit of normal (ULN), transaminases $\leq 2 \times$ ULN, alkaline phosphatase $\leq 2 \times$ ULN) and renal (serum creatinine $\leq 2 \times$ ULN) functions, absence of distant disease; absence of non-breast malignancies within the last 5 years prior to study except curatively treated non-melanoma skin cancer and carcinoma in situ of the cervix. The exclusion criteria were: postmenopausal patients with positive estrogen and progesterone receptor status and negative lymph node involvement, pregnant women or women with suspected pregnancy or lactating women, prior exposure to anthracycline or docetaxel for any malignancy, presence of active cardiac disease or poorly controlled hypertension, active or chronic documented infection, pre-existing peripheral neuropathy, rheumatic disease, and current COX-2 inhibitor medication, carriers of hepatitis B or hepatitis C, known hypersensitivity or contraindication to any study or pre-medications or products formulated in

polysorbate 80.

1.2 Study design and treatment

Randomization was done centrally at the OOTR Data Center after documentation that the subject met all the inclusion and exclusion criteria. Patients were randomly assigned to receive four cycles of FEC (500 mg/m², 100 mg/m², 500 mg/m²) followed by four cycles of T (100 mg/m²) with concurrent celecoxib (400 mg BID) (group A) or four cycles of FEC (500 mg/m², 100 mg/m², 500 mg/m²) followed by four cycles of T (100 mg/m²) without celecoxib (group B). After completion of chemotherapy, patients underwent surgery. Treatment was given in an outpatient setting. Pre-medication consisted of dexamethasone to prevent peripheral fluid retention and anaphylactic reactions, anti-ulcer agents to prevent stomatitis, ondansetron as prophylactic antiemetic therapy and ciprofloxacin as prophylactic antibiotic therapy to prevent infection during docetaxel treatment. Prophylactic subcutaneous administration of granulocyte colony-stimulating factor (G-CSF) filgrastim was not allowed, but it was used as primary prophylaxis at investigator's discretion if febrile neutropenia occurred at first cycle.

1.3 Patient assessment

Baseline assessments including pathological diagnosis of IBC by core biopsy, hormonal receptor status and *Cerb-B-2* oncogene expression by immunohistochemistry, complete medical and surgical histories, physical examination, KPS, complete blood picture (CBP), blood chemistry (BC), and chest X-ray, abdominal ultrasound, contralateral breast imaging and bone scintigraphy or positron emission tomography to exclude metastasis were performed prior to neoadjuvant treatment. Normal baseline electrocardiogram and echocardiography (left ventricular ejection fraction (LVEF) $\geq 55\%$) were also required prior to chemotherapy.

During the neoadjuvant treatment, tumor size measurements by clinical and ultrasound assessments, CBP, BC, KPS, and vital signs were performed before each cycle for response and safety assessments. After four cycles of FEC and after four cycles of docetaxel, mammography was performed as an additional response assessment, and cardiac monitoring was also conducted by means of electrocardiography and echocardiography for LVEF.

Objective response was assessed according to World Health Organization

criteria^[24] while the pCR was defined as the absence of any residual invasive tumor, both in breast and axilla. Toxicity grading was based on the National Cancer Institute common toxicity criteria, version 3.0^[25]. Dose-limiting hematological toxicity was defined as grade (G) 3/4 febrile neutropenia and other G4 hematological adverse events. If this is observed, dosage of all chemotherapeutic drugs would be reduced by 25% in next and subsequent cycles. Reoccurrence of dose-limiting hematological toxicity lead to does reduction of 50% of the starting dose. For all G3 non-hematological toxicities, all chemotherapeutic drugs were reduced by 25% of original dose in next and subsequent cycles.

1.4 Statistical Analysis

Parameters were compared using the SPSS 13.0. Independent t-test was used to compare means of parameters between groups. Fisher's exact test or chi-square test was used to compare the number of events between groups. All statistical tests were two-sided and *P*-value of less than 0.050 was considered as statistically significant. Neither clinical response nor pathologic response was evaluated due to inadequate power to determine the difference in response rates.

2 Results

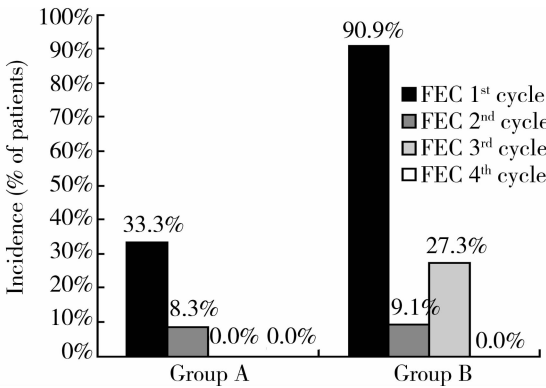
A consecutive 23 patients with operable breast cancer of clinical stage II_A or II_B according to AJCC classification were studied; 12 patients were from group A (with celecoxib); 11 patients were from group B (without celecoxib). Table 1 shows their baseline characteristics. No significant difference in demographics was observed between groups except clinical stages which, however, did not influence the study of the difference in toxicity profile between groups. The 23 patients received a total of 183 treatment cycles out of planned 184 cycles. One patient of group B, accounting for 4% of all cases, omitted the fourth cycle of FEC because of repeated incidences of febrile neutropenia in previous cycles. Received dose intensity (RDI) for FEC in group A ($90\% \pm 11\%$) was higher than that in group B ($80\% \pm 8\%$), whereas RDI for T in group A ($93\% \pm 8\%$) was similar to that in group B ($96\% \pm 9\%$).

Table 1 Patients' characteristics

Group	Age(years)	Menopausal status (n)		Clinical stage (n)			Hormonal Receptor (n)		Cerb-B-2 3(+)(n)	Pathology (n)			Modified Bloom and Richardson's grading (n)			
		Pre-menopause	Post-menopause	II _A	II _B	III _A	ER positive	PR positive		Invasive ductal	Invasive metaplastic	Mixed type ^a	I	II	III	Not graded
A(n=12)	46.5±6.7	9	3	4	8	0	6	4	4	12	0	0	2	3	4	3
B(n=11)	45.9±7.4	9	2	9	2	0	4	3	5	9	1	1	2	4	4	1
P value	0.842	1.000		0.036			0.870	0.961	0.915	0.206			0.956			

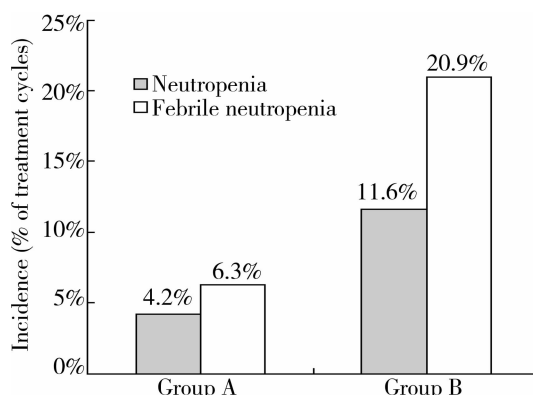
a; invasive ductal and mucinous; ER; estrogen receptor; PR; progesterone receptor

During the first four cycles of FEC, the number of incidence of neutropenia and/or febrile neutropenia was lower in group A than group B [(33.3%, 4/12) *vs.* (90.9%, 10/11), $P=0.005$] at first cycle of FEC as shown in figure 1. In a total of 91 treatment cycles of FEC, lower incidences of neutropenia and/or febrile neutropenia per treatment cycle were also observed in group A (figure 2). Incidence of febrile neutropenia[(6.3%, 3/48) *vs.* (20.9%, 9/43), $P=0.039$] and neutropenia with or without fever [(10.4%, 5/48) *vs.* (32.6%, 14/43), $P=0.009$] showed significant difference between groups. During another four cycles of docetaxel, only one incidence of G4 fistula-in-ano and one incidence of grade 3 febrile neutropenia were observed in two patients from group A. Neither grade 3 nor grade 4 toxicity was observed in other patients. The baseline meant LVEFs between group A and group B patients were similar[(63.2%±4.9%) *vs.* (63.5%±5.3%) , $P=0.877$]. The mean LVEF of patients from group A was slightly lower than that from group B after four cycles of FEC [(63.5%±5.8%) *vs.* (67.7%±5.3%) , $P=0.093$] and another four cycles of T [(66.7%±7.8%) *vs.* (68.0%±8.9%) , $P=0.712$]. Nevertheless, no patient experienced symptomatic cardiac toxicity.



Group A *vs.* group B: 33.3%(4/12) *vs.* 90.9%(10/11) (cycle 1); 8.3%(1/12) *vs.* 9.1%(1/11) (cycle 2); 0.0%(0/12) *vs.* 27.3%(3/11) (cycle 3); 0.0%(0/12) *vs.* 0.0%(0/10) (cycle 4).

Figure 1 Incidence of severe neutropenia and/or febrile neutropenia in each FEC cycle



Neutropenia: group A *vs.* group B, 4.2% (2/48) *vs.* 11.6% (5/43); Febrile neutropenia: group A *vs.* group B, 6.3% (3/48) *vs.* 20.9% (9/43)

Figure 2 Incidence of severe neutropenia and febrile neutropenia in 91 treatment cycles of FEC

One patient from group A and two patients from group B achieved pCR. Higher objective response rates, including clinical complete response and clinical partial response, were observed in patients from group A than from group B after neoadjuvant treatment [(83.3%, 10/12) *vs.* (72.7%, 8/11), $P=0.538$].

3 Discussion

The inducible isoform of cyclooxygenase enzymes, COX-2, is commonly over-expressed in breast cancer and induced by breast cancer chemotherapy^[19]. COX-2-derived metabolites may contribute at multiple points throughout tumorigenesis and promote tumor-specific angiogenesis, inhibits apoptosis and induces proangiogenic factors^[26]. COX-2 inhibition was therefore deemed as one of anti-cancer strategies.

In last two decades, NSAID with COX-2 inhibition has been suggested and widely studied for chemoprevention of several types of malignancy. Harris^[27] has presented the meta-analysis which showed a 25% reduction in relative risk of breast cancer with regular use of NSAID. Notwithstanding a safety concern on the risk of serious arterial thrombotic events using COX-2 inhibitor, the latest meta-analysis of 72 epidemiological studies using celecoxib at 400 mg or less daily showed the composite *RR* of 0.98 (95% *CI*: 0.88–1.10) for celecoxib and thrombotic cardiovascular event. There was lack of evidence on the association between the use of celecoxib ≤ 400 mg daily and the concerned cardiovascular risk from randomized clinical trials

and observational studies. With accumulating evidence of COX-2 overexpression in carcinogenesis, the clinical use of celecoxib in cancer patients remains to be explored.

Prior to the decision to suspend clinical trials using celecoxib recommended by FDA, this randomized study was initially designed to further investigate the additive effect of celecoxib on neoadjuvant use of FEC followed by T regimen in consideration of the promising results from a pilot clinical study^[18]. However, due to the potential cardiovascular risk of prolonged use of NSAID^[28-31], the randomized trial was halted before the scheduled sample size was reached. A preliminary review was therefore conducted to investigate the toxicity profile by comparing groups having received celecoxib to those who did not.

Of the 12 patients from group A, the first five (41.7%, 5/12) patients completed assigned treatment of FEC followed by T with concurrent celecoxib while 11 (91.7%, 11/12) patients have discontinued celecoxib after 4 cycles of FEC as a result of the concerned cardiovascular toxicity. Of the 11 patients from group B, all patients received the 4 cycles of FEC followed by 4 cycles of T without concurrent celecoxib. Due to small sample sizes at time of suspension of the trial, statistical power was inadequate for analysis on efficacy. The superiority of adding celecoxib to chemotherapy versus chemotherapy alone in terms of efficacy from this study is therefore inconclusive.

In this study, neither life-threatening cardiotoxicity nor clinical symptom of cardiac damage was observed. The usual primary hematological dose-limiting toxicities, neutropenia and febrile neutropenia, are commonly observed in patients with anthracycline and taxanes^[21-23]. Prophylactic filgrastim was initially not allowed for the series of cases. Due to inexplicable high incidence of neutropenia or febrile neutropenia in four out of the first five recruited subjects irrespective of treatment assignment, all patients were given prophylactic subcutaneous administration of filgrastim on day 1 and day 8 of 3-weekly chemotherapy cycle. A significantly lower incidence of G3/4 neutropenia and/or febrile neutropenia in group A was still observed during the first 91 treatment cycles of FEC and especially in the first cycle of FEC. A possible reason is that celecoxib is a NSAID which

may possibly reduce fever^[32]. Inhibition of COX-2 enzyme might reduce the conversion of arachidonic acid to prostaglandins which have long known to mediate fever. In principle, COX-2 inhibitor might reduce the incidence of fever in response to inflammatory stimuli associated with chemotherapy. However, precaution should be taken because it might mask the diagnostic signs of infection and, yet, infection was not noticed from patients under study. According to the study result and the underlying physiological mechanism, celecoxib is likely to lower the incidence of severe neutropenia and febrile neutropenia during the chemotherapy FEC.

One recently published clinical trial had similar design of adding celecoxib 400mg BID in neoadjuvant setting^[33]. Nevertheless, excluding patients who were given trastuzumab the study showed different G3/4 neutropenia incidences [(55.4%, 62/112) *vs.* (49.4%, 82/166)] and G3 febrile neutropenia [(10.7%, 12/112) *vs.* (10.2%, 17/166)] in those who received celecoxib and those who did not during four cycles of docetaxel. Despite the higher incidence of severe neutropenia in celecoxib group, statistical analysis was not illustrated and the number of incidence was presented per patients not per treatment cycles. The repeated incidence of hematological toxicity might be omitted. In another similar neoadjuvant trial using FEC followed by T^[34-35], G3/4 neutropenia and febrile neutropenia were observed in 68% of patients, which is obviously less than that observed in our patients from group B (without celecoxib). One of possible reasons for the higher incidences is that our sample size is comparatively smaller than the similar trial, and, therefore, a conclusion can not be drawn. Another possible reason is the use and schedule of prophylactic filgrastim. With prophylactic filgrastim support, the rate of chemotherapy-induced febrile neutropenia should be reduced^[36], however, more than 90% (10/11) of patients from group B experienced G3/4 neutropenia or febrile neutropenia in our study, but the high incidence occurred in the first cycle only. Papaldo et al^[37] suggested that G-CSF should be best administered on day 8 before the expected neutrophil nadir time and on day 12 during neutrophil nadir time. Our day 1 and 8 administration of filgrastim may not fully cope with the neutrophil nadir time till day 12 and, hence, high rates of neutropenia or febrile neutropenia were observed.

This short report on the use of celecoxib with chemotherapy in neoadjuvant setting might not give us a clear picture on its therapeutic capacity against breast cancer. Nevertheless, there is still room for further investigation in clinical setting considering its chemopreventive effects on breast cancer, positive results of a pilot clinical study and the observed potential in lowering chemotherapy-induced hematological toxicities from this study. As the use of celecoxib might not only offer anti-cancer effect, but also better the safety profile for use of chemotherapy such that full dose of chemotherapy can be given to patients in order to maximize the efficacy. Last but not least, more research at molecular levels could help scientists to understand how inhibition of COX-2 enzyme could promote tumor regression and to discover novel predictive or prognostic factors. The translational research will provide clues to clinicians on the application of this biological agent into clinical practice.

4 Conclusion

Analysis of this first phase of patients randomized to receive neoadjuvant FEC followed by T with or without concurrent celecoxib showed that there was no increase in cardiac risk. Neoadjuvant use of FEC followed by T with concurrent celecoxib appeared to be safe for treatment of operable invasive breast cancer. The observed lower incidence of chemotherapy-induced neutropenia is possibly contributed by the administration of COX-inhibitor. There was a substantial reduction of hematological toxicities which would require further confirmatory studies. We believe that further investigation might provide more evidence on the use of COX-2 inhibitors in breast cancer.

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References

- [1] Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin*, 2005, 55:74-108.
- [2] Hong Kong Cancer Registry. Hong Kong Cancer Stat 2006. Hong Kong: Hong Kong Cancer Registry, Hospital Authority, 2008;1-35[2009-12-31]. <http://www.ha.org.hk/cancereg>.

- [3] Eltahir A, Heys SD, Hutcheon AW, et al. Treatment of large and locally advanced breast cancers using neoadjuvant chemotherapy. *Am J Surg*, 1998, 175:127-132.
- [4] Ferriere JP, Assier I, Cure H, et al. Primary chemotherapy in breast cancer: correlation between tumor response and patient outcome. *Am J Clin Oncol*, 1998, 21:117-120.
- [5] Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in woman with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol*, 1997, 15:2483-2493.
- [6] Gianni L, Baselga L, Eiermann W, et al. Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate and fluorouracil and its effects on tumor response as preoperative therapy. *Clin Cancer Res*, 2005, 11:8715-8721.
- [7] Gianni L, Baselga L, Eiermann W, et al. European Cooperative Trial in Operable Breast Cancer (ECTO): improved freedom from progression (FFP) from adding paclitaxel (T) to doxorubicin (A) followed by cyclophosphamide methotrexate and fluorouracil (CMF). *Proc Am Soc Clin Oncol*, 2005:37a.
- [8] Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer. National Surgical Adjuvant Breast and Bowel Project protocol B-27. *J Clin Onco*, 2006, 24:2019-2027.
- [9] Heys SD, Hutcheon AW, Sarkar TK, et al. Neoadjuvant docetaxel in breast cancer: 3-year survival results from the Aberdeen trial. *Clin Breast Cancer*, 2002, 3:S69-S74.
- [10] Hutcheon AW, Heys SD, Sarkar TK, et al. Neoadjuvant docetaxel in locally advanced breast cancer. *Breast Cancer Res Treat*, 2003, 79:S19-S24.
- [11] Bonadonna G, Valagussa P, Brambilla C, et al. Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. *J Clin Oncol*, 1998, 16:93-100.
- [12] Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol*, 1998, 16:2672-2685.
- [13] Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol*, 1999, 17:460-469.
- [14] Masferrer JL, Leahy KM, Koki AT, et al. Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. *Cancer Res*, 2000, 60:1306-1311.
- [15] Lu S, Zhang X, Badawi AF, et al. Cyclooxygenase-2 inhibitor celecoxib inhibits promotion of mammary tumorigenesis in rats fed a high fat diet rich in n-6 polyunsaturated fatty acids. *Cancer Lett*, 2002, 184:7-12.
- [16] Harris RE, Chlebowski RT, Jackson RD, et al. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. *Cancer Res*, 2003, 63:6096-6101.
- [17] Khuder SA, Mutgi AB. Breast cancer and NSAID use: a meta-analysis. *Br J Cancer*, 2001, 84:1188-1192.
- [18] Chow LWC, Toi M. Prospective pilot study of the preoperative use of celecoxib (Celebrex?) and FEC for the treatment of locally advanced breast cancer. Presented at the San Antonio Breast Cancer Symposium, December 11-14, 2002.
- [19] Subbaramaiah K, Marmo TP, Dixon DA, et al. Regulation of cyclooxygenase-2 mRNA stability by taxanes: evidence for involvement of p38, MAPKAPK-2, and HuR. *J Biol Chem*, 2003, 278:37 637-37 647.
- [20] Olsen SR. Taxanes and COX-2 inhibitors: from molecular pathways to clinical practice. *Biomed Pharmacother*, 200, 59:S306-S310.
- [21] Tjuljandin SA, Doig RG, Sobol MM, et al. Pharmacokinetics and toxicity of two schedules of high dose epirubicin. *Cancer Res*, 1990, 50:5095-5101.
- [22] Figgitt DP, Wiseman LR. Docetaxel: an updated of its use in advanced breast cancer. *Drugs*, 2000, 59:621-651.
- [23] Ferraresi V, Milella M, Vaccaro A, et al. Toxicity and activity of docetaxel in anthracycline-pretreated breast cancer patients: a phase II study. *Am J Clin Oncol*, 2000, 23:132-139.

- [24] Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. *Cancer*, 1981, 47: 207-214.
- [25] National Cancer Institute. Common terminology criteria for adverse events v3. 0 (CTCAE). [2006-07-20]. <http://ctep.cancer.gov/forms/CTCAEv3.pdf>.
- [26] Koki AT, Masferrer JL. Celecoxib: a specific COX-2 inhibitor with anticancer properties. *Cancer Control*, 2002, 9: 28-35.
- [27] Harris RE. Cyclooxygenase-2 (cox-2) blockade in the chemoprevention of cancers of the colon, breast, prostate, and lung. *Inflammopharmacology*, 2009, 17: 55-67.
- [28] US Food and Drug Administration. FDA statement on the halting of a clinical trial of the cox-2 inhibitor Celebrex. [2006-07-20]. <http://www.fda.gov/bbs/topics/news/2004/NEW01144.html>.
- [29] US Department of Health and Human Services. Use of non-steroidal anti-inflammatory drugs suspended in large Alzheimer's disease prevention trial. NIH news. [2006-07-20]. <http://www.nih.gov/news/pr/dec2004/od-20.htm>.
- [30] Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*, 2005, 352: 1071 - 1080.
- [31] Caldwell B, Aldington S, Weatherall M, et al. Risk of cardiovascular events and celecoxib: a systemic review and meta-analysis. *J R Soc Med*, 2006, 99: 132-140.
- [32] Crofford LJ, Lipsky PE, Brooks P, et al. Basic biology and clinical application of specific cyclooxygenase-2 inhibitors. *Arthritis Rheum*, 2000, 43: 4-13.
- [33] Pierga JY, Delaloge S, Espié M, et al. A multicenter randomized phase II study of sequential epirubicin/ cyclophosphamide followed by docetaxel with or without celecoxib or trastuzumab according to HER-2 status, as primary chemotherapy for localized invasive breast cancer patients. *Breast Cancer Res Treat*, 2010, 122: 429-437.
- [34] Ohno S, Toi M, Kuroi K, et al. Update results of FEC followed by docetaxel neoadjuvant trials for primary breast cancer. *Biomed Pharmacother*, 2005, 59: S323-S324.
- [35] Iwata H, Nakamura S, Toi M, et al. Interim analysis of a phase II trial of cyclophosphamide, epirubicin and 5-fluorouracil (cef) followed by docetaxel as preoperative chemotherapy for early stage breast carcinoma. *Breast Cancer*, 2005, 12: 99-103.
- [36] Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med*, 1991, 325: 164-170.
- [37] Papaldo P, Lopez M, Marolla P, et al. Impact of five prophylactic filgrastim schedules on hematologic toxicity in early breast cancer patients treated with epirubicin and cyclophosphamide. *J Clin Oncol*, 2005, 23: 6908-6918.

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