Successful Use of Trastuzumab with Anthracycline-based Chemotherapy Followed by Trastuzumab Maintenance in Patients with Advanced HER2-positive Gastric Cancer

SOFIA PALACIO[1], ARTURO LOAIZA-BONILLA[2], MUAIAD KITTANEH[3], CHRISTOS KYRIAKOPOULOS[4], ROBERTO E. OCHOA[5], MAURICIO ESCOBAR[1], BELISARIO ARANGO[1], MARIA H. RESTREPO[1], JAIME R. MERCHAN[1], CAIO M.S. ROCHA LIMA[1] and PETER J. HOSEIN[1]

[1]*University of Miami Miller School of Medicine Sylvester Comprehensive Cancer Center, Miami, FL, U.S.A.;*
[2]*University of Pennsylvania Abramson Cancer Center, Philadelphia, PA, U.S.A.;*
[3]*Wayne State University Barbara Ann Karmanos Cancer Center, Detroit, MI, U.S.A.;*
[4]*Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, U.S.A.;*
[5]*Chen Medical Centers, Miami, FL, U.S.A.*

Abstract. *Background: There is no standard chemotherapy regimen that is universally accepted for the treatment of advanced gastric cancer. Trastuzumab added to chemotherapy improves survival in patients with metastatic human epidermal growth factor receptor-2 (Her2/neu)-overexpressing gastric cancer. Data are lacking for the combination of trastuzumab with other chemotherapy regimens, apart from the cisplatin/fluorouracil backbone used in the pivotal TOGA trial. Patients and Methods: In this retrospective analysis, we included patients with gastric cancer with HER2 overexpression who received trastuzumab in addition to their first-line chemotherapy, with or without trastuzumab maintenance therapy. The end-points were response and tolerance to treatment. Results: We identified seven patients who met the search criteria; six had metastatic disease and one had locally advanced unresectable disease. Four patients received epirubicin/oxaliplatin/capecitabine/trastuzumab, and the others had non-anthracycline-based chemotherapy with trastuzumab. All patients had radiological responses to treatment – one had a complete response and six had partial responses. Among the four patients who received anthracycline-based chemotherapy with trastuzumab, there was a transient decline in cardiac ejection fraction in three, but all resolved without sequelae. All patients received a period of chemotherapy induction followed by trastuzumab monotherapy for maintenance. The median progression-free survival was 14.6 months and median overall survival was 16.4 months. Conclusion: Trastuzumab is an important agent for the treatment of HER2-overexpressing gastric cancer. We recorded an acceptable safety and efficacy profile in this small cohort treated with anthracycline-based chemotherapy with trastuzumab followed by trastuzumab maintenance.*

Correspondence to: Peter J. Hosein, MD, 1475 NW 12th Avenue. Suite 3400, Miami, 33136, FL, U.S.A. Tel: +1 3052436611, Fax: +1 3052435239 e-mail: phosein@med.miami.edu

Key Words: Gastric cancer, trastuzumab, chemotherapy.

Gastric cancer is one of the most commonly diagnosed types of cancer. It is also one of the most common causes of cancer-related deaths (1). In Europe and the Americas, patients with gastric cancer are usually diagnosed at an advanced stage because routine screening is not conducted, and these patients generally have a poor prognosis despite the use of combination chemotherapy (2). The 5-year survival for advanced metastatic disease ranges between 4 and 20% (2), with the median overall survival being less than a year. There is no universally-accepted standard chemotherapy for advanced gastric cancer. Randomized trials have shown better outcomes with a fluoropyrimidine and a platinum agent, regardless of a third agent (3).

A proportion of gastric carcinomas demonstrate human epidermal growth factor receptor-2 (HER2) overexpression. Trastuzumab is a humanized hybrid monoclonal antibody that selectively binds to the extracellular domain of HER2. Its antitumor action is not fully understood but possible mechanisms include inhibition of PI3K/AKT and mammalian target of rapamycin (mTOR), induction of apoptosis, and antibody-dependent cell-mediated cytotoxicity (4-8). The TOGA trial investigated the clinical efficacy and safety of trastuzumab added to chemotherapy in advanced cancer of the gastric or esophagogastric (EGJ) with HER2 overexpression (9). The trial tested a fluoropyrimidine (capecitabine or 5-fluorouracil) and cisplatin backbone with or without trastuzumab. There was an improvement in overall survival in the trastuzumab-containing regimens without increase in the toxicity profile. This has established trastuzumab with chemotherapy as the standard-of-care for

patients with HER2-overexpressing gastric and EGJ cancer. However, the addition of trastuzumab to other validated chemotherapy regimens for advanced gastric cancer has not been tested prospectively.

Anthracyclines are effective in gastric and EGJ cancer; epirubicin in combination with platinum and fluoropyrimidine demonstrated efficacy in the MAGIC trial (in the adjuvant setting) and the REAL 2 trial in the advanced disease setting (10, 11). Although controversial, HER2 amplification may predict for benefit of anthracyclines in breast cancer (12-15). This is postulated to be due to co-amplification of the topoisomerase II alpha gene that is located in close proximity to the HER2 gene on chromosome 17 (16). Therefore, use of an anthracycline in combination with trastuzumab may be more effective than a non-anthracycline-containing chemotherapy backbone.

Trastuzumab has been used in combination with anthracyclines for breast cancer but the combination has not been reported for gastric cancer. The combination for breast cancer has been associated with an increased risk of cardiac toxicity (17). Traditionally, the anthracycline studied in breast cancer has been doxorubicin, which may be more cardiotoxic than epirubicin (18). There are few studies of cardiotoxicity with epirubicin. The HERCULES trial aimed to study the safety of the combination of epirubicin, cyclophosphamide and trastuzumab for HER2-positive metastatic breast cancer. Dose-limiting cardiotoxicity was more common in the group with high-dose epirubicin (90 mg/m^2 *versus* 60 mg/m^2), but all events were manageable and there were no cardiac-related deaths (17). The rate of cardiotoxicity in the trastuzumab/epirubicin 60-mg/m^2 arm was noted to be less than historical rates with trastuzumab/doxorubicin (17).

Since epirubicin is an established agent for gastric cancer, with a low reported cardiotoxicity rate in combination with trastuzumab, we hypothesized that the epirubicin/oxaliplatin/capecitabine/trastuzumab (EOX-H) combination would be effective and tolerable in patients with advanced gastric cancer. We also hypothesized that continuation of trastuzumab monotherapy in a maintenance fashion after attaining disease control with chemotherapy induction may also be beneficial in patients with gastric cancer. Herein, we report seven cases of advanced gastric cancer that received validated first-line combination regimens with trastuzumab. They all went on to receive trastuzumab monotherapy for maintenance.

Patients and Methods

This was a retrospective analysis at the University of Miami Sylvester Comprehensive Cancer Center and Jackson Memorial Hospital in Miami, Florida, USA. Patients with HER2-positive advanced or metastatic gastric or EGJ adenocarcinoma and patients who had received trastuzumab and combination chemotherapy were identified by a search of the chemotherapy records. The University of Miami Institutional Review Board (IRB) approved the study (approval number 20120953).

Demographic and clinical information were collected, including baseline performance status, age, HER2 expression, tumor location, stage and all chemotherapy treatments administered. Cases were considered to be HER2-positive.

The cases were also reviewed for adverse events, which were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0(19). Data on cardiac ejection fraction (EF) were also collected. All patients had a baseline EF, as well as serial monitoring throughout treatment. The EF was measured through multigated blood pool imaging of the heart (MUGA scanning) and in some instances by transthoracic echocardiography. A change in EF during therapy was expressed as a relative (not absolute) percentage change from the value at baseline. For example if the baseline EF was 60% and the follow-up EF was 48%, this change would be reported as a decline by 20%, *i.e.* (60-48)/60.

Patient survival and follow-up dates were also obtained. Progression-free survival was defined as the time in months from date of initiation of chemotherapy until documented progression, recurrence or death. Overall survival was calculated as the time in months from the date of diagnosis until death. Patients who were alive or progression-free were censored at the date of last follow-up. Median survival times were estimated by the Kaplan-Meier method using the statistical software SPSS (Version 20, IBM, New York, USA).

Results

We identified seven patients that met the search criteria. Patient 1 was a 49-year-old female who presented with a 4-month history of dysphagia and weight loss. Esophago-gastroduodenoscopy (EGD) revealed a circumferential mass at the EGJ. A biopsy confirmed HER2-positive poorly-differentiated adenocarcinoma. Staging computed tomographic (CT) scans revealed metastases to the cervical, mediastinal and celiac lymph nodes, as well as to the bone. She received treatment with EOX-H every three weeks, as well as zoledronic acid every four weeks. A combined positron-emission tomography (PET) CT scan performed after six 3-week cycles of chemotherapy demonstrated a complete radiological response. Repeat endoscopy showed resolution of the previously visualized mass. The patient then continued on trastuzumab monotherapy (maintenance) every three weeks for 11 cycles. Approximately one year after the initial diagnosis, while still receiving trastuzumab maintenance, the patient had progression of disease, characterized by an enlarging left supraclavicular lymph node. Chemotherapy with capecitabine/oxaliplatin (XELOX) was initiated and trastuzumab was continued. Her cardiac ejection fraction remained unchanged throughout the course of her treatment.

Patient 2 was a 59 year-old male who presented with weight loss and dysphagia. His EGD revealed a large friable distal esophageal mass that extended into the lesser curvature of the stomach. Biopsy confirmed HER-2 negative adenocarcinoma.

Staging CT scans did not reveal any evidence of metastases and he received preoperative docetaxel/cisplatin/fluorouracil (DCF) for three cycles. The patient then underwent transhiatal esophagectomy and partial gastrectomy and pathology revealed EGJ adenocarcinoma that was HER2-negative and a separate adenocarcinoma 3 cm from the EGJ that was HER2-positive. The surgical margins were negative and there were 6 positive lymph nodes out of 15. He received postoperative radiation therapy. Nine months later, this patient presented with new hepatic and pulmonary metastases and was started on EOX-H and achieved a partial radiological response after seven cycles. He continued on trastuzumab monotherapy but during this maintenance he was found to have an asymptomatic decrease in EF from 59% to 49% on routine MUGA surveillance. Electrocardiogram revealed asymptomatic bradycardia with occasional premature ventricular contractions. Consequently, trastuzumab was discontinued and he was prescribed carvedilol. Sixteen months later, he had disease progression with new metastasis to the lungs, and was then treated with fluorouracil/leucovorin/oxaliplatin (FOLFOX). The patient developed progressive disease after eight months of FOLFOX and was then treated with fluorouracil/leucovorin/irinotecan (FOLFIRI), which is still ongoing. A repeat MUGA scan while on FOLFIRI showed a return to the baseline EF of 55%.

Patient 3 was a 58-year-old female who presented with abdominal pain, nausea and vomiting. A CT scan revealed multiple hypodense liver lesions consistent with metastases and a percutaneous biopsy revealed a poorly-differentiated adenocarcinoma. A subsequent EGD revealed a gastric mass and biopsy confirmed a HER2-positive adenocarcinoma. She underwent chemotherapy with EOX-H for six cycles with resolution of her abdominal pain. CT scans demonstrated a partial response, with decrease in the size of the primary gastric tumor as well as the liver metastases. She continued trastuzumab maintenance but this was suspended after 13 cycles due to a decreased EF to 43% from a baseline of 51%. At the time, the patient was complaining of mild fatigue and was started on carvedilol but had no deterioration in her performance status, she remained physically active. Six months later, she was found to have progression of her local and metastatic disease. She was restarted on chemotherapy with FOLFOX and then had a complicated course with persistent gastrointestinal bleeding from the tumor, requiring multiple transfusions and radiation therapy. During this time, serial EF monitoring showed improvement to 58% and later 63%, and trastuzumab was resumed. However, after three months, her EF dropped again to 49% and trastuzumab was permanently discontinued.

Patient 4 was a 54-year-old female who presented with abdominal pain and anemia. EGD revealed a polypoid ulcerated mass in the lesser curvature of the stomach, and biopsy confirmed HER2-positive adenocarcinoma. Staging CT scans showed advanced nodal disease and a large primary tumor. She was treated with EOX-H and had a dramatic clinical and partial radiological response. After three cycles her pain disappeared and there was significant regression of the lymph nodes and primary mass on CT scans. She went on to have a subtotal gastrectomy with loop gastrojejunostomy. The resected specimen revealed a small focus of residual malignancy in the stomach and none of 17 lymph nodes resected was involved by malignancy. This patient was treated with postoperative EOX-H for 3 additional cycles and then received trastuzumab maintenance, which is planned for a total of one year of perioperative treatment.

Patient 5 was a 52-year-old female who initially presented with a neck mass, as well as left upper arm pain. CT scanning revealed a mass in the EGJ and extensive lymph node metastases in her neck, mediastinum, and retroperitoneum. EGD with biopsy confirmed the diagnosis of metastatic HER-2-positive adenocarcinoma of the EGJ. She was started on treatment with XELOX-H but had very poor tolerance to this regimen, with grade 3 nausea and vomiting. Despite the poor tolerance to treatment, she had a quick clinical response, with complete disappearance of the neck mass in a few weeks and partial radiological response and resolution of the pain in her left upper arm. She was switched to FOLFOX-H, which she tolerated better and received six cycles of this combination, with a partial radiological response to treatment. As maintenance therapy, she was continued on trastuzumab and remains with stable small-volume residual disease. Her EF has remained stable throughout the course of treatment.

Patient 6 was a 31-year-old male who presented with a 2-week history of diffuse abdominal pain. A CT scan of the abdomen revealed ascites and retroperitoneal lymphadenopathy and an EGD revealed a gastric ulcer that was biopsy-proven to be, HER-2–positive gastric adenocarcinoma. The CT also revealed evidence of metastatic disease in his bones, pleura and mediastinum. He initially received treatment with DCF-H and achieved a partial radiological response, continuing on trastuzumab maintenance therapy for 14 cycles. Eighteen months later, he developed progressive disease with new liver metastases, and was then treated with EOX-H. Trastuzumab was held when a MUGA scan revealed an EF of 49% (baseline EF was 55%). Repeat MUGA scan three months later showed a stable EF at 50%, and six months after initial decrease in EF repeat transthoracic echocardiography revealed the EF had returned to the baseline value of 55%. After nine cycles of therapy, the patient developed progressive dyspnea and was found to have a malignant pleural effusion. His condition rapidly deteriorated and he died shortly thereafter.

Patient 7 was a 62-year-old female who presented with abdominal pain. EGD revealed a large ulcer in the posterior wall of the stomach near the antrum. She subsequently underwent subtotal gastrectomy, which confirmed HER-2-

Table I. *Baseline characteristics of the seven studied patients.*

Age, years	
Median	52
Range	29-61
Gender	
Male	2 (29%)
Female	5 (71%)
ECOG performance status	
0	3 (43%)
1	4 (57%)
Tumor location	
Gastric	4 (57%)
EGJ	3 (43%)
HER2 status*	
2+	1 (14%)
3+	6 (86%)
Disease stage	
III	1 (14%)
IV	6 (86%)

*HER2 was tested by immunohistochemistry and in cases that demonstrated 2+ staining was confirmed by fluorescent "*in situ*" hybridization.

positive poorly-differentiated adenocarcinoma with a surgical stage of pT2pN1. Postoperative CT scans revealed a liver lesion suspicious for metastasis but a biopsy only showed focal fatty steatosis. She was treated with DCF-H and received three cycles with good tolerance. She subsequently declined further therapy and has been followed-up with no evidence of disease progression off therapy for nine months. Her ejection fraction has remained unchanged throughout follow-up.

Table I summarizes the baseline characteristics. Six patients had 3+ staining for HER2 by immunohistochemistry and one had 2+ staining and the HER2 overexpression was confirmed with fluorescent *in situ* hybridization (FISH). Among the seven patients, four received first-line treatment with EOX-H, two received DCF-H and one received XELOX-H, and all seven patients received trastuzumab maintenance. Two patients received trastuzumab beyond progression along with their second-line chemotherapy. Among the seven patients, one had a complete response and six had partial responses. Four of these later had disease progression and were started on second-line chemotherapy. With a median follow-up of 16 months, the median progression-free survival was 14.6 months and the median overall survival was 16.4 months.

The majority of adverse events were hematological and gastrointestinal in nature. All patients experienced adverse events with their first-line chemotherapy regimens – these are summarized in Table II. The most common adverse effects were anemia, neutropenia, elevated liver enzymes, nausea, vomiting and diarrhea. One patient was taken off first-line chemotherapy due to grade 3 nausea and vomiting.

Table II. *Adverse event profile among the 7 treated patients.*

	Grade			
	1	2	3	4
Hematological				
Neutropenia	0	0	1	0
Neutropenic fever	0	0	0	0
Anemia	0	1	4	0
Thrombocytopenia	0	0	0	0
Non-hematological				
Elevated liver transaminases	4	0	0	0
Fatigue	1	0	0	0
Nausea	1	2	1	0
Vomiting	1	1	1	0
Diarrhea	4	1	0	0
Peripheral neuropathy	2	1	0	0
Decreased ejection fraction	0	2	0	0

Two patients required hospitalization for infectious complications: pneumonia and a tunneled catheter infection.

Out of the seven patients reported here, three developed a drop in EF during therapy. In all three cases, the decrease in EF was reversible and improved with administration of carvedilol. One patient had an asymptomatic decline by 16% of the baseline EF – carvedilol was introduced and trastuzumab was withheld; and serial monitoring demonstrated a return to baseline after one year. This patient went on to receive trastuzumab with his second-line chemotherapy without any further issues with the EF. The second patient had a drop in the EF by 15% of baseline and had a concurrent decrease in exercise tolerance. Of note, she had severe anemia requiring a transfusion at that time and the symptoms resolved after transfusion. Trastuzumab was withheld and she was treated with carvedilol. Serial EF monitoring revealed a return to baseline after five months and she was subsequently restarted on trastuzumab with her second-line chemotherapy regimen. The third patient had an asymptomatic drop in his EF by 10% of the baseline value during maintenance trastuzumab. Serial monitoring demonstrated a return to his baseline EF six months later. No patient developed significant clinical signs or symptoms of congestive heart failure.

Discussion

Based on the results of the TOGA trial, trastuzumab is now routinely added to first-line chemotherapy in patients with advanced or metastatic gastric cancer with HER2 overexpression. The chemotherapy backbone in the pivotal trial was cisplatin and capecitabine or fluorouracil. However, the addition of trastuzumab to other combination chemotherapy regimens such as EOX, DCF and FOLFOX that are accepted as alternative standards of care has not been studied in a prospective, randomized fashion. Findings from

the German non-interventional observational study HerMES studied trastuzumab in combination with cisplatin and (5-FU) or capecitabine, as well as other regimens such as oxaliplatin and docetaxel Although most patients did not receive the regimen described in the TOGA trial, the median progression-free survival was comparable at 6.8 months (8). Further studies of trastuzumab in combination with other regimens are required.

The current study describes seven patients with advanced/metastatic gastric cancer with HER2 overexpression that received trastuzumab in addition to combination chemotherapy with regimens that have not been previously described in the medical literature. These few cases achieved impressive clinical and radiological responses, with an overall survival of 16.4 months compared to the median survival of 13.8 months in the trastuzumab-group of the TOGA trial. The decreases in EF were all associated with the anthracycline/trastuzumab combination, but this complication was reversible in all cases. The other common hematological and gastrointestinal toxicities were manageable.

The optimal duration of treatment with trastuzumab is unknown. In the adjuvant treatment of breast cancer, the HERA trial compared observations, with one or two years of trastuzumab maintenance. That study showed an improvement in disease-free survival in the group that received trastuzumab for a year as opposed to observation, with no added benefit with two years of maintenance as compared to one year (20). Maintenance trastuzumab has not been studied in patients with metastatic breast cancer or in gastric cancer. In this case series, all seven patients received trastuzumab maintenance, with an acceptable toxicity profile and median time-to-progression of 14.6 months. One of the potential benefits of trastuzumab maintenance is that patients are spared the toxicity of cytotoxic chemotherapy while still receiving a potentially active anticancer therapy. The 'stop and go' approach has been shown to be effective in colon cancer with the OPTIMOX trials (21). In our series, chemotherapy plus trastuzumab was used as an induction regimen, followed by trastuzumab maintenance, with chemotherapy being re-introduced at the time of progression.

Since our case series is small and retrospective, it is difficult to draw conclusions on the efficacy and safety of combining trastuzumab with other regimens. The group was also heterogeneous with different stages of disease: most patients had stage IV disease, and one had stage III. Furthermore, different chemotherapy backbones were used. Nonetheless, we hypothesize that it might be acceptable to combine alternative regimens with trastuzumab and it might be acceptable to continue patients on trastuzumab as maintenance therapy, given the impressive responses seen in our patients. We demonstrated that an anthracycline/trastuzumab combination is feasible and for patients with a drop in EF, this was reversible. Given the data that suggest increased responsiveness to anthracyclines in patients with HER2 amplification, taken together with our preliminary clinical experience, we believe that the anthracycline/trastuzumab combination should be prospectively tested in advanced gastric cancer with HER2 overexpression.

References

1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer *127*: 2893-917, 2010.

2 Siegel R, Naishadham D and Jemal A: Cancer statistics, 2013. CA Cancer J Clin *63*: 11-30, 2013.

3 Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C *et al*: Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol *24*: 4991-4997, 2006.

4 Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A *et al*: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med *344*: 783-792, 2001.

5 Arteaga CL: Trastuzumab, an appropriate first-line single-agent therapy for HER2-overexpressing metastatic breast cancer. Breast Cancer Res *5*: 96-100, 2003.

6 Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL *et al*: Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer J Clin Oncol *23*: 3676-3685, 2005.

7 Nagata Y, Lan KH, Zhou X, Tan M, Esteva FJ, Sahin AA *et al*: PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. Cancer Cell *6*: 117-127, 2004.

8 Hegewisch-Becker S, Moorahrend E, Kröning H, Petersen V, Hannig C, Pott D *et al*: Trastuzumab (TRA) in combination with different first-line chemotherapies for treatment of HER2-positive metastatic gastric or gastroesophageal junction cancer (MGC): Findings from the German noninterventional observational study HerMES. J Clin Oncol *30(Suppl)*: 4065, 2012.

9 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A *et al*: Trastuzumab in combination with chemotherapy *versus* chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet *28;376*: 687-697, 2010.

10 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M *et al*: Perioperative chemotherapy *versus* surgery alone for resectable gastroesophageal cancer. N Engl J Med *355*: 11-20, 2006.

11 Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F *et al*: Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med *358*: 36-46, 2008.

12 Dhesy-Thind B, Pritchard KI, Messersmith H, O'Malley F, Elavathil L and Trudeau M: HER2/neu in systemic therapy for women with breast cancer: a systematic review. Breast Cancer Res Treat *109*: 209-229, 2008.

13 Gennari A, Sormani MP, Pronzato P, Puntoni M, Colozza M, Pfeffer U *et al*: HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: a pooled analysis of randomized trials. J Natl Cancer Inst *100*: 14-20, 2008.

14 Jarvinen TA, Holli K, Kuukasjarvi T and Isola JJ: Predictive value of topoisomerase IIalpha and other prognostic factors for epirubicin chemotherapy in advanced breast cancer. Br J Cancer *77*: 2267-2273, 1998.

15 Bartlett JM, Munro A, Cameron DA, Thomas J, Prescott R and Twelves CJ: Type 1 receptor tyrosine kinase profiles identify patients with enhanced benefit from anthracyclines in the BR9601 adjuvant breast cancer chemotherapy trial. J Clin Oncol *26*: 5027-5035, 2008.

16 Press MF, Sauter G, Buyse M, Bernstein L, Guzman R, Santiago A *et al*: Alteration of topoisomerase II-alpha gene in human breast cancer: association with responsiveness to anthracycline-based chemotherapy. J Clin Oncol *29*: 859-867, 2011.

17 Untch M, Muscholl M, Tjulandin S, Jonat W, Meerpohl HG, Lichinitser M *et al*: First-line trastuzumab plus epirubicin and cyclophosphamide therapy in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: cardiac safety and efficacy data from the Herceptin, Cyclophosphamide, and Epirubicin (HERCULES) trial. J Clin Oncol *28*: 1473-1480, 2010.

18 Fumoleau P, Roche H, Kerbrat P, Bonneterre J, Romestaing P, Fargeot P *et al*: Long-term cardiac toxicity after adjuvant epirubicin-based chemotherapy in early breast cancer: French Adjuvant Study Group results. Ann Oncol *17*: 85-92, 2006.

19 National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4. National Cancer Institute; 2010 [cited 2013 12/01/2013]; Available from: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

20 Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM *et al*: 2 years *versus* 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet *382*: 1021-1028, 2013.

21 Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M *et al*: OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer – a GERCOR study. J Clin Oncol *24(3)*: 394-400, 2006.

Received November 13, 2013
Revised December 2, 2013
Accepted December 3, 2013