The precise chemotherapy guided by the expression of ERCC1, RRM1, TUBB3, TYMS and TOP2A genes versus the classic chemotherapy in the treatment of breast cancer: a comparative effectiveness research

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Abstract

Objective: ERCC1, RRM1, TUBB3, TYMS and TOP2A gene have been shown to be associated with chemotherapeutic drug resistance. And the aim of the present study was to evaluate the guiding significance of the above genes expression in the selection of precise chemotherapy regimen for breast cancer. Methods: 140 well-matched patients with breast cancer, including 70 from the precise chemotherapy group and 70 from the classic chemotherapy group, were retrospectively analyzed. In the precise chemotherapy group, the mRNA expression levels of ERCC1, RRM1, TUBB3, TYMS and TOP2A in breast cancer tissues were measured by the multiplex branched DNA liquidchip (MBL) technology before chemotherapy. And the precise chemotherapy regimen was developed according to the detection results. As a comparison control, patients from the classic chemotherapy group were given TEC(Docetaxel+Epirubicin+Cyclophosphamide) regimen. Survival analysis were performed by the Kaplan–Meier method. The prognostic factors of breast cancer were identified via the Cox proportional hazards model. Adverse reactions were evaluated in the light of the National Cancer Institute Common Toxicity Criteria 4 (NCI-CTC version 4.0). Results: The median follow-up time was 67.5 months (1.0–84.0 months). Compared with the classic chemotherapy group, the DFS and OS of the precise chemotherapy group were significantly longer (DFS:77.4 months vs 67.1 months, $P=0.039$;OS: 81.4 months vs 75.4 months, $P=0.031$), and the incidence of grade 2 or 3 palpitations and chest tightness was lower (12.9% vs 27.1%, $P=0.035$). The chemotherapy strategy guided by genetic detection was an independent protection factor for DFS ($HR=0.389, 95\%CI:0.153, 0.989, P=0.047$), but not an independent protection factor for OS ($HR=0.340, 95\%CI:0.107, 1.078, P=0.067$). Metastasis of axillary lymph nodes was an independent risk factor for DFS($HR=7.049, 95\%CI:1.813, 27.410, P=0.005$). Additionally, the independent risk factor affected DFS($HR=3.378, 95\%CI:1.074, 10.624, P=0.037$) and OS($HR=8.140, 95\%CI: 1.666, 39.759, P=0.010$) was poor endocrine therapy compliance. Conclusions: Combined detection of ERCC1, RRM1, TUBB3, TYMS and TOP2A genes expression for guiding precise chemotherapy can improve treatment efficacy and reduce unnecessary toxicity.

Background

Breast cancer is the most frequently diagnosed tumor and the second leading mortality in female world [1]. As a systemic disease, the comprehensive treatment mode with surgery as the main part, chemotherapy, radiotherapy, endocrine therapy, molecular targeted therapy and other auxiliary parts has become the consensus of breast cancer treatment. There is no doubt that chemotherapy plays crucial roles in controlling and reducing lesions before surgery and preventing recurrence and metastasis after surgery. For advanced breast cancer and triple-negative breast cancer, chemotherapy is still the main means of reducing recurrence and metastasis after surgery [2-3]. However, as a highly heterogeneous tumor, breast cancer with the same pathological type and the same molecular type may have different sensitivity to the same chemotherapy regimen. Not all patients can benefit from the same chemotherapy regimen. It may be the differential expressions of certain genes related chemotherapy. Consequently,

detecting the expressions of these genes and then guiding the selection of chemotherapy drugs are of significance to improve the efficacy of chemotherapy and reduce the toxicity.

Numerous studies have shown that the expression level of excision repair cross complementing 1 (ERCC1) is negatively correlated with the efficacy of platinum drugs ^[4]; the expression level of ribonucleoside reductase subunit M1 (RRM1) is negatively correlated with the efficacy of gemcitabine ^[5-6]; the expression level of class III β -tubulin (TUBB3) is negatively correlated with the efficacy of anti-microtubule drugs ^[7]; the expression level of thymidylate synthase (TYMS) is negatively correlated with the efficacy of anti-metabolism drugs such as capecitabine ^[8]; the expression level of topoisomerase 2 α (TOP2A) is positively correlated with the efficacy of anthracyclines ^[9].

At present, there is no study on combined detection of ERCC1, RRM1, TUBB3, TYMS and TOP2A genes expression for guiding the chemotherapy of breast cancer. Therefore, we carried out this retrospective study to provide new ideas and clinical evidences for precise treatment of breast cancer.

Methods

Clinical data

140 breast cancer patients, who have been treated by the same treatment group from January 1, 2012 to December 31, 2013 at the General Hospital of Western Theater Command of PLA, were enrolled in the retrospective study. All of them had complete medical records and no patient received treatments prior to the surgery. All patients have no distant metastasis.

Detection of mRNA expressions

The expressions of ERCC1, RRM1, TUBB3, TYMS and TOP2A in breast cancer tissues were measured by multiplex branched DNA liquidchip (MBL) technology ^[10-12]. The main points of the steps are as follows: (1) The samples were lysed in buffer at 56°C for 2 hours; (2) The lysed product was added to each well of a 96-well plate which contained blocking reagent, target gene-specific probe sets and capture beads; (3) The plate was sealed, and then incubated for 18 hours at 54°C on a shaker, followed by adding the hybridization mixture; (4) The unbound mRNA and other debris in each well were removed by washing three times with buffer; (5) Signals for bound target mRNA were amplified with streptavidin-hycoerythrin at 50°C for 30 minutes; (6) The fluorescence value of each sample was recognized and analyzed by the Luminex 200 system (Luminex, Austin, TX, USA) to represent the mRNA expression level of each gene. Compared to the cutoff value of each gene, the expression level less than 25% was defined as low expression; the expression level between 25% and 49% was defined as low to medium expression; the expression level being equal to 50% was defined as medium expression; the expression level between 51% and 75% was defined as medium to high expression; the expression level greater than 75% was defined as high expression ^[13].

Selection and implementation of chemotherapy regimens

The regimen of the precise chemotherapy group was based on the genetic report. There are the principles of selection as follows: (1)Patients with low expression of ERCC1 were recommended to use platinum drugs such as cisplatin and oxaliplatin; those with low to medium expression could use it; those with medium to high expression and high expression should avoid it. (2)Patients with low expression of RRM1 were recommended to use gemcitabine; those with low to medium expression could use it; those with medium to high expression and high expression should avoid it. (3)Patients with low expression of TUBB3 were recommended to use anti-microtubule drugs such as docetaxel and paclitaxel; those with low to medium expression could use it; those with medium to high expression and high expression should avoid it. (4)Patients with low expression of TYMS were recommended to use capecitabine; those with low to medium expression could use it; those with medium to high expression and high expression should avoid it. (5)Patients with high expression of TOP2A were recommended to use anthracycline chemotherapeutic drugs such as epirubicin and doxorubicin; those with medium to high expression could use it; those with low to medium expression and low expression should avoid it. As for the other group, the chemotherapy regimen was TEC(Docetaxel +Epirubicin+Cyclophosphamide). The implementation of chemotherapy regimen is shown in Table 1.

Prognosis and safety evaluation

Disease-free survival (DFS) time was calculated as the duration from the end of surgery to tumor recurrence or metastasis. Overall survival (OS) time was calculated as the duration from the end of surgery to death from any cause. Breast ultrasound, abdominal ultrasound focused on the liver, axillary and neck lymph nodes ultrasound, chest CT, skull enhanced MRI/CT, bone ECT, serum tumor markers and pathological examination were performed appropriately to identify whether tumor was local recurrence or distant metastasis. Follow-ups with all patients were implemented through telephone contact to obtain the survival data. The deadline was January 1, 2019. Adverse events related chemotherapy were evaluated in the light of the National Cancer Institute Common Toxicity Criteria 4 (NCI-CTC version 4.0).

Statistical Analysis

The categorical variables were analyzed using the chi-square test and the continuous variables were analyzed by t-test. The survival analysis was performed using the Kaplan–Meier method and the log-rank test. Multivariate factors associated with survival were conducted using the Cox proportional hazards model. P value of < 0.05 was considered statistically significant. All statistic analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

The comparison of baseline characteristics

A total of 140 well-matched female patients with breast cancer were retrospectively analyzed. None of the patients were treated with targeted therapy or traditional Chinese medicine. There were no significant differences in baseline characteristics including age, body mass index(BMI), menstrual status,

histological grade, tumor size, axillary lymph node status, TNM stage, hormone receptor and human epidermal growth factor receptor 2 status, Ki67 expression, molecular classification, type of surgery, hormonal and radioactive therapies status between the two groups. The baseline characteristics of two groups are summarized in Table 2[1].

Expression of the genes

The mRNA expressions of ERCC1, RRM1, TUBB3, TYMS and TOP2A in precise chemotherapy group were detected. High expressions of ERCC1 and RRM1 were observed in 4.3% and 5.7% of the group respectively, while high expressions of TUBB3 and TYMS were observed in 27.1% and 22.9% of the group respectively. Low expressions of TOP2A were observed in 38.6% of the group (Table 3).

Prognosis comparison

The median follow-up time was 67.5 months (1.0–84.0 months). At the deadline, the tumor had progressed in 24(17.1%) patients, including 17 patients in the classic chemotherapy group and 7 patients in the precise chemotherapy group. Moreover, 17(12.1%) patients had died, including 13 patients in the classic chemotherapy group and 4 patients in the precise chemotherapy group. Compared with the classic chemotherapy group, the DFS and OS of the precise chemotherapy group were significantly prolonged. Meanwhile, the 5-year DFS and OS of the patients in the precise chemotherapy group were higher than those in the classic chemotherapy group (87.3% VS 73.8%; 94.3% VS 84.2%)(Table 4, Table 5). The Kaplan-Meier survival curves of the two groups are shown in Fig. A[2] and Fig. B[3].

Prognostic factors

Multivariate regression analyses identified prognostic factors for DFS and OS (Table 6). The results demonstrated that the independent factor increased the risk of tumor progression was the metastasis of axillary lymph node ($HR=7.049$ [95%CI 1.813, 27.410] $P=0.005$). Additionally, the independent risk factor affected DFS ($HR=3.378$ [95%CI 1.074, 10.624] $P=0.037$) and OS ($HR=8.140$ [95%CI 1.666, 39.759] $P=0.010$) was poor endocrine therapy compliance (treatment time less than 5 years). Finally, the precise chemotherapy strategy guided by genetic detection was an independent protection factor of DFS ($HR=0.389$ [95%CI 0.153, 0.989] $P=0.047$). However, that was not the independent protection factor for OS ($HR=0.340$ [95%CI 0.107, 1.078] $P=0.067$).

The comparison of adverse reactions

The incidence rate of dose reduction or the number reduction of chemotherapy (less than 6 cycles) due to adverse reactions was 21.4% in the precise group and 25.7% in the classic group. And this difference between the two groups was not statistically significant ($P=0.550$). Besides, there was no death related to adverse events in both treatment groups. In terms of grade 2 or 3 palpitations and chest tightness, the incidence rate of the precise group was lower than that of the classic group (12.9% vs 27.1% $P=0.035$).

However, there was no statistically significant difference in the incidence of other adverse events between the two groups (Table 7).

[1] Table 2 was placed at the end of the manuscript.

[2] Kaplan-Meier analysis on the association of chemotherapy strategy with disease-free survival of breast cancer patients.

[3] Kaplan-Meier analysis on the association of chemotherapy strategy with overall survival of breast cancer patients.

Discussion

Precise therapy is a recently intensively pursued approach at the molecular level and the role of genetic test in guiding chemotherapy and evaluating prognosis is increasingly significant. The genes ERCC1, RRM1, TUBB3, TYMS, and TOP2A have been widely concerned for their relevance to the efficacy of chemotherapeutic drugs. Nucleotide excision repair (NER) plays a major role in DNA damage repair caused by platinum drugs^[14]. The expression product of ERCC1 gene can limit or regulate NER^[15] and its level reflects the level of overall NER^[16]. Therefore, the high expression of ERCC1 means that the NER is strengthened and the efficacy of platinum drugs is weakened. In these studies^[4,17-19], it was confirmed that patients with high expression of ERCC1 were resistant to platinum drugs and their prognosis was poor. Ribonucleotide reductase consisting of two subunits, RRM1 and RRM2, is the rate-limiting enzyme in the DNA synthesis pathway^[20], which has a significant influence in DNA damage repair. The RRM1 subunit encoded by the RRM1 gene is the main target of gemcitabine. Related studies have shown that^[5,6] high expression of RRM1 is associated with gemcitabine resistance. Microtubules are involved in many key cellular processes including cell division. Paclitaxel drugs can stabilize microtubules, prevent mitotic and further prompt tumor cell death. However, β -III tubulin encoded by TUBB3 gene can decline the stabilizing effect of anti-microtubule drugs on microtubules, induce drug resistance and reduce the efficacy^[21]. This view was confirmed in studies of Kamath et al.^[7] and Scambia G et al.^[22]. Thymidylate synthase (TS) encoded by the TYMS gene is a key enzyme in the synthesis of pyrimidine nucleotides. TS is a major target enzyme of fluorouracils. It exerts anticancer effects by inhibiting the synthesis of deoxythymidylate (dTMP) and further affecting DNA synthesis and repair^[23]. In clinical studies of breast cancer^[24], colorectal cancer^[25], lung cancer^[26] and other tumors, patients with low expression of TYMS have better chemotherapeutic response to fluorochemical drugs and a longer median survival time. The topoisomerase 2A encoded by the TOP2A gene is not only a key enzyme that accelerate transient breaks in the DNA but also a target for anthracyclines. Anthracycline specifically binds to TOP2A and reduces its degradation. So the damaging effect of TOP2A on DNA is enhanced and tumor cells eventually died^[27].

The studies ^[9,28] of anthracycline chemotherapy for breast cancer showed that patients with low expression of TOP2A gene had poor efficacy and poor prognosis.

The mRNA expressions of above genes in 70 patients of precise group were detected by MBL technology. High expressions of ERCC1 and RRM1 were observed in 4.3% and 5.7% of the group respectively, while high expressions of TUBB3 and TYMS were observed in 27.1% and 22.9% of the group respectively. Low expressions of TOP2A were observed in 38.6% of the group. The results indicate that some patients may have primary drug resistance of some chemotherapy drugs.

To the best of our knowledge, there is no study on combined detection of above genes for guiding the chemotherapy of breast cancer. We retrospectively analyzed the survival data of 140 breast cancer patients. The results showed that DFS in the precise group was 10.3 months longer than that of the classic group ($P=0.039$), and the 5-year disease-free survival rate was higher than that of the classic group (87.3% vs 73.8%). In our OS analysis, we found that the OS of the precise group was 6 months longer than that of the classic group ($P=0.031$), and the 5-year overall survival rate was higher than that of the classic group (94.3% vs 84.2%). Moreover, the Kaplan-Meier survival curves of DFS and OS showed that the overall prognosis of the precise group was better than that of the classic group (Log-Rank test: $P=0.039$, 0.031). To explore whether the precise chemotherapy strategy under the guidance of genetic testing is an independent prognostic factor for breast cancer, the relationship between all baseline variables and survival data initially was investigated via univariate analysis. Those variables of $P<0.1$ were incorporated into the Cox hazards regression model for multivariate analysis. The Cox regression analysis revealed that precise chemotherapy strategy can reduce the risk of recurrence or metastasis ($HR=0.389$, 95% CI: 0.153, 0.989, $P=0.047$). Furthermore, metastasis of axillary lymph nodes was an independent risk factor for DFS and poor endocrine therapy compliance was an independent risk factor for DFS and OS.

In terms of drug safety, patients generally tolerated and successfully completed 6-8 cycles of chemotherapy. Although various adverse reactions did occur during chemotherapy, they could be controlled by symptomatic treatment, reduction of drug dosage, intermittent or termination of chemotherapy. There was no grade 5 adverse event in this study. The incidence of grade 2 or 3 palpitations and chest tightness in precise group was significantly lower than that in classic group (12.9% vs 27.1% $P=0.035$). This may be related to that the classic regimen contained anthracyclines and the precise group selectively used it according to the TOP2A gene expression. In addition, there was no statistically significant difference in the incidence of other adverse events (nausea, vomiting, diarrhea, constipation, mucositis, myelosuppression, liver toxicity, fatigue and hand-foot syndrome) between the two groups.

The method selected chemotherapy regimens according to each patient's genetic characteristics can reduce the occurrence of drug resistance, show positive effects and provide new ideas and clinical evidences for individualized treatment of breast cancer. However, our study also has some limitations. Firstly, the study is a single-center study with an inherent selection bias and sample size is not enough

large, which may draw different conclusions with previous studies. Secondly, the gene expression was detected using the MBL technology, but not confirmed by immunohistochemistry with normal breast tissues or para-carcinoma tissues as control. However, the results of this study are reliable, because MBL technology is currently a mature gene detection technology which has been widely applied in the prognosis prediction and individualized treatment of some tumors^[10,29-33]. Additionally, above genes are not only a single biological function. Further research is essential to explore whether they are closely related to other chemotherapeutic drugs. Finally, the application of testing technology may result in an increase of treatment costs. And whether the benefit-cost ratio is maximized should be treated individually. In summary, it is still necessary to further investigate the guiding significance of ERCC1, RRM1, TUBB3, TYMS, TOP2A and other genes in precise therapy through clinical studies of multi-center, large sample, addition of control samples, immunohistochemistry confirmation.

Conclusions

Our findings indicate that combined detection of ERCC1, RRM1, TUBB3, TYMS and TOP2A gene expression for guiding chemotherapy can prolong DFS time and OS time, improve prognosis, reduce cardiovascular adverse reactions such as palpitations and chest tightness, enhance the quality of life and benefit patients.

Abbreviations

ERCC1: Excision repair cross complementing 1; RRM1: Ribonucleoside reductase subunit M1; TUBB3: Class III β -tubulin; TYMS: Thymidylate synthase; TOP2A: Topoisomerase 2 α ; MBL: Multiplex branched DNA liquidchip; T: Docetaxel; E: Epirubicin; C: Cyclophosphamide; DFS: Disease-free survival; OS: Overall survival; P: Cisplatin; G: Gemcitabine; X: Capecitabine; BMI: body mass index; ER: estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor receptor 2; BCS: breast conserving surgery; SLNB: sentinel lymph node biopsy; T-ALND: total axillary lymphadenectomy; NER: Nucleotide excision repair; TS: Thymidylate synthase; dTMP: deoxythymidylate

Declarations

Ethics approval and consent to participate

This single-institution retrospective study was approved by the General Hospital of Western Theater Command of PLA. All patients gave written informed consents for sample retention and analysis for research purposes.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

GX and JCL made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. PS, TH, SDH and LFL were involved in drafting the manuscript or revising it critically for important intellectual content. GX provided final approval of the version to be published. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content, and GX agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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Tables

Table 1 Implementation of chemotherapy regimens

Chemotherapy regimens	Cycles					n
	Four	Five	Six	Seven	Eight	
The precise group						
E _{90mg/m2} P _{80mg/m2}	1	1	2			4
E _{90mg/m2} G _{1000mg/m2}			1			1
E _{90mg/m2} X _{950mg/m2}			1			1
T _{75mg/m2} P _{80mg/m2}		1	4			5
T _{75mg/m2} C _{500mg/m2}			1			1
T _{75mg/m2} G _{1000mg/m2}	1	2	14	3	4	24
T _{75mg/m2} X _{950mg/m2}	1		8	1		10
T _{75mg/m2} E _{90mg/m2} C _{500mg/m2}	1	2	17	1	3	24
The classic group						
T _{75mg/m2} E _{90mg/m2} C _{500mg/m2}	4	6	60			70

E: Epirubicin P: Cisplatin G: Gemcitabine X: Capecitabine

T: Docetaxel C: Cyclophosphamide

Table2c Baseline Characteristics of the Patients n(%)

Characteristic	Group		t / c2 Value	P Value
	Precise	Classic		
Age(years)	51.1±8.1	48.5±7.6	1.939	0.055
BMI(kg/m ²)	23.8±2.9	23.8±3.1	0.011	0.991
Menstrual status				
Premenopausal	37(52.9)	40(57.1)	0.260	0.610
Postmenopausal	33(47.1)	30(42.9)		
Histological grade				
I	9(12.9)	13(18.6)	1.098	0.578
II	47(67.1)	46(65.7)		
III	14(20.0)	11(15.7)		
Tumor size(cm)				
≤2	22(31.4)	29(41.4)	3.161	0.182
2-5	45(64.3)	35(50.0)		
≥5	3(4.3)	6(8.6)		
Nodal status				
Negative	38(54.3)	33(47.1)	0.714	0.398
Positive	32(45.7)	37(52.9)		
TNM staging				
I	14(20.0)	14(20.0)	2.703	0.259
II	43(61.4)	35(50.0)		
III	13(18.6)	21(30.0)		
ER status				
Positive	47(67.1)	45(64.3)	0.127	0.722
Negative	23(32.9)	25(35.7)		
PR status				
Positive	34(48.6)	42(60.0)	1.842	0.157
Negative	36(51.4)	28(40.0)		
HER-2 status				
Positive	32(45.7)	27(38.6)	0.732	0.392
Negative	38(54.3)	43(61.4)		
Ki-67 expression				
≤14%	15(21.4)	9(12.9)	1.810	0.178
>14%	55(78.6)	61(87.1)		
Molecular type				
Luminal A	6(8.6)	4(5.7)	0.541	0.910
Luminal B	41(58.6)	43(61.4)		
HER-2- enriched	9(12.9)	8(11.4)		
Triple-negative	14(20.0)	15(21.4)		
Type of surgery				
Modified radical mastectomy	64(91.4)	67(95.7)	1.844	0.438
BCS+SLNB/T-ALND	4(5.7)	1(1.4)		
Mastectomy+SLNB	2(2.9)	2(2.9)		
Radiotherapy				
Yes	48(68.6)	41(58.6)	1.511	0.219
No	22(31.4)	29(41.4)		
Endocrine therapy				
Yes	42(60.0)	35(50.0)	1.414	0.234
No	28(40.0)	35(50.0)		

BMI: body mass index; ER: estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor receptor 2; BCS: breast conserving surgery; SLNB: sentinel lymph node biopsy; T-ALND: total axillary lymphadenectomy

Table 3 Expression of the genes in the precise group n(%)

Gene	Low	Low to medium	Medium	Medium to high	High
ERCC1	32(45.7)	20 (28.6)	0(0.0)	15(21.4)	3(4.3)
RRM1	45 (64.3)	14(20.0)	0(0.0)	7(10.0)	4(5.7)
TUBB3	17 (24.3)	19(27.1)	0(0.0)	15(21.5)	19(27.1)
TYMS	15(21.4)	21(30.0)	0(0.0)	18(25.7)	16(22.9)
TOP2A	27(38.6)	20(28.6)	0(0.0)	11(15.7)	12(17.1)

Table 4 The comparison of DFS

Group	n	Recurrence/Metastasis (%)	Average DFS (95%CI) (months)	DFS at 5 years(%)
Precise	70	7(10.0)	77.4(72.7,82.1)	87.3
Classic	70	17(24.3)	67.1(60.2,74.1)	73.8

Table 5 The comparison of OS

Group	n	Death (%)	Average OS (95%CI) (months)	OS at 5 years(%)
Precise	70	4(5.7)	81.4(78.6,84.1)	94.3
Classic	70	13(18.6)	75.4(71.1,79.8)	84.2

Table 6a Cox regression model of multivariable analysis for DFS and OS

Factor	DFS		OS	
	HR(95%CI)	P Value	HR(95%CI)	P Value
Tumor size(cm)				
≤2	1.00			
2-5	2.700(0.910,8.008)	0.073		
≥5	1.783(0.377,8.443)	0.466		
Nodal status				
Negative	1.00		1.00	
Positive	7.049(1.813,27.410)	0.005	3.360(0.836,13.504)	0.088
TNM stage				
I	1.00		1.00	
II	0.351(0.053,2.330)	0.279	0.704(0.115,4.313)	0.704
III	0.420(0.051,3.458)	0.420	0.912(0.119,6.990)	0.930
ER status				
Positive	1.00		1.00	
Negative	1.258(0.225,7.037)	0.794	1.452(0.071,29.565)	0.808
PR status				
Positive	1.00		1.00	
Negative	1.727(0.321,9.281)	0.524	1.042(0.050,21.844)	0.979
Chemotherapy strategy				
Classic	1.00		1.00	
Precise	0.389(0.153,0.989)	0.047	0.340(0.107,1.078)	0.067
Endocrine therapy compliance				
Good	1.00		1.00	
Poor	3.378(1.074,10.624)	0.037	8.140(1.666,39.759)	0.010

ER: estrogen receptor; PR: progesterone receptor

Table 7b The comparison of adverse events

Grade	Group		c ² Value	P Value
	Precise	Classic		
Nausea and vomiting				
1	28(40.0)	29(41.4)	0.478	0.788
2	37(52.9)	34(48.6)		
3	5(7.1)	7(10.0)		
Diarrhea				
1	62(88.6)	64(91.4)	0.317	0.573
2	8(11.4)	6(8.6)		
Constipation				
1	63(90.0)	61(87.1)	0.282	0.595
2	7(10.0)	9(12.9)		
Mucositis				
1	51(72.9)	56(80.0)	0.991	0.319
2	19(27.1)	14(20.0)		
Leukopenia/Neutropenia				
1	23(32.9)	26(37.1)	0.319	0.853
2	29(41.4)	28(40.0)		
3,4	18(25.7)	16(22.9)		
Thrombocytopenia				
1	58(82.9)	59(84.3)	0.052	0.820
2	12(17.1)	11(15.7)		
Anemia				
1	66(94.3)	59(84.3)	3.659	0.056
2	4(5.7)	11(15.7)		
Liver toxicity				
1	46(65.7)	58(82.9)	5.351	0.059
2	19(27.1)	10(14.3)		
3	5(7.1)	2(2.9)		
Fatigue				
1	26(37.1)	20(28.6)	1.166	0.280
2	44(62.9)	50(71.4)		
Palpitations and chest tightness				
1	61(87.1)	51(72.9)	4.464	0.035
2,3	9(12.9)	19(27.1)		
Hand-foot syndrome				
1	52(74.3)	58(82.9)	1.527	0.271
2	18(25.7)	12(17.1)		

Figures

Figure 1

The Kaplan-Meier survival curves