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Original Article

Efficacy and safety of capecitabine-containing neoadjuvant chemotherapy for breast cancer: a meta-analysis of randomized controlled trials

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Abstract: Neoadjuvant chemotherapy (NAC) contained capecitabine in breast cancer remains controversial, thus, we conducted a meta-analysis to evaluate the efficacy and safety of this regimen. Methods: We searched the PubMed, Cochrane Library and EMBASE before December 2015. Randomized controlled trials (RCTs) that evaluated anthracycline/taxane-based NAC with or without capecitabine were included. Results: A total of 7 RCTs involving 3979 patients were included. The efficacy outcomes suggested that disease-free survival (DFS), overall survival (OS), pathological complete response (pCR), overall response rate (ORR) and breast-conserving surgery (BCS) rates were not significantly improved in the neoadjuvant chemotherapy contained capecitabine group compared to the control group (DFS: HR = 0.95, 95% CI: 0.80 to 1.12, P = 0.53; OS: HR = 0.95, 95% CI: 0.77 to 1.17, P = 0.61; pCR: HR = 1.06, 95% CI: 0.89 to 1.27, P = 0.49; ORR: HR = 1.00, 95% CI: 0.96 to 1.06, P = 0.86; BCS: HR = 0.99, 95% CI: 0.94 to 1.04, P = 0.60). Pooled OR values suggested that NAC containing capecitabine significantly increased the grade 3 to 4 adverse events (AEs) incidence of febrile neutropenia (OR = 1.49, 95% CI: 1.10 to 2.01, P = 0.010) and hand-foot syndrome (OR = 7.16, 95% CI: 3.09 to 16.60, P<0.00001). Conclusions: Capecitabine-containing NAC regimen for breast cancer did not significantly improve the efficacy in DFS, OS, pCR, ORR and BCS, while increased the incidence of grade 3-4 AEs of febrile neutropenia and hand-foot syndrome. Thus, in short time the addition of capecitabine to NAC anthracycline/taxane-based regimen might not change clinical practice.

Keywords: Capecitabine, Xeloda, breast cancer, preoperative, neoadjuvant chemotherapy

Introduction

Neoadjuvant chemotherapy (NAC), also called preoperative chemotherapy, has become increasingly significant in patients with breast cancer. NAC has the advantage of reducing the size or the extent of tumor, increasing the rate of breast conserving surgery and providing early information on the response to treatment [1]. Currently, NAC with the use of anthracyclines and taxanes, either in combination (eg, docetaxel, doxorubicin and cyclophosphamide [TAC]) or in sequence was recommended [2]. In addition, 5-fluorouracil-epirubicin and cyclophosphamide (FEC) followed by docetaxel was adopted by some trials [3].

Capecitabine (Xeloda) is an oral fluorouracil (FU) prodrug which is converted to 5-FU by a cascade of three enzymes selectively in tumors [4]. It is a promising novel drug for the treatment of breast cancer. Capecitabine has shown convenient, effective and favorable tolerability as single-agent treatment in patients with metastatic breast cancer [5]. Synergistic effect occurs between taxanes and capecitabine through the up-regulation of enzyme thymidine phosphorylase [6]. The combination of capecitabine and taxane docetaxel has shown increased rates of objective response and significant survival benefit in patients with locally advanced or metastatic breast cancer [7]. Recently, capecitabine has been used in NAC and several randomized controlled trials (RCTs) have assessed the efficacy and safety of this chemotherapy [2, 8-18]. In 2013, a meta-analysis, which searched the databases before March 26, 2012, report-

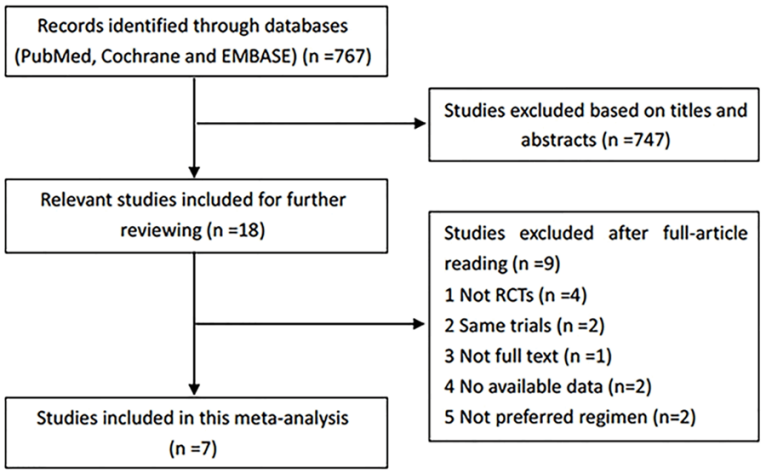

Figure 1. Flow chart of studie selection.

ed that neoadjuvant treatment of breast cancer containing capecitabine did not significantly improve outcomes in preoperative treatment of breast cancer [19]. However, the previous systematic review did not analysis the long-term survivals such as disease-free survival (DFS) and overall survival (OS). Also, after then, the ABCSG-24 reported the final results of a randomized phase III study and it showed the integration of capecitabine into a neoadjuvant regimen increased pCR rate and some other two new associated RCTs were published [11, 12, 14]. Moreover, a meta-regression of 29 randomized prospective studies showed pCR was not an effective surrogate end point for DFS and OS in patients with breast cancer [1].

In order to evaluate and update the efficacy and safety of the capeciatabine-containing NAC regimen in patients with breast cancer, we undertook a meta-analysis of RCTs to provide more detailed and complete evidences.

Materials and methods

Literature search strategy

The meta-analysis was conducted according to the PRISMA guidelines [20]. A systematical search of the publications was performed from the databases included PubMed, EMBASE and Cochrane before December 11, 2015. Medical subject heading terms (Breast neoplasm) and key words (capecitabine OR Xeloda) AND (neoadjuvant OR preoperative OR primary systemic) were used to select eligible studies. After selecting articles, we also searched the references of associated articles. We limited the language to English, but not limit countries of publications.

Inclusion and exclusion criteria

Studies were selected according to the basis of the following inclusion criteria: (1) study design was RCT; (2) the study compared capecitabine contained NAC with wide used anthracycline/taxane-based NAC regimens for breast cancer; (3) full text of the articles published online; (4) original studies written in English; (5) at least 100 patients enrolled in one-arm of RCT; (6) at least one of the efficacy outcomes mentioned below was reported and sufficient data could be extracted. Articles were excluded based on the following data extraction criteria: (1) conference abstracts, comments and articles could not be acquired fell text; (2) patients with metastatic breast cancer; (3) duplicate studies; (4) NAC with endocrine therapy concurrently.

Data extraction and quality assessment

Data extraction and evaluation of each study were undertaken by two independent investigators (Yunan Han and Zhen Qiao). Disagreement was resolved by discussion and a third author. The outcomes of this meta-analysis were focused on efficacy and safety outcomes. Information was extracted from each trial on the followings: the first author's name, the trials' name, the year of publication, the design of study, sample size of participants, treatment regimens, efficacy and safety outcomes. Quality assessment was evaluated according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [21]. The following seven items were assessed the quality of each trial: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); (7) other bias.

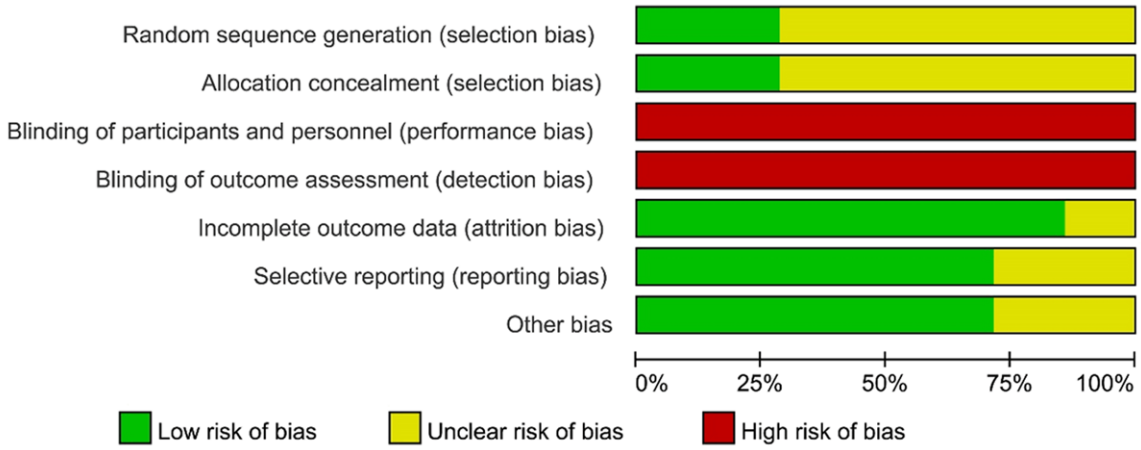

Figure 2. Risk of bias graph showed the percentage of each risk of bias item across all included studies.

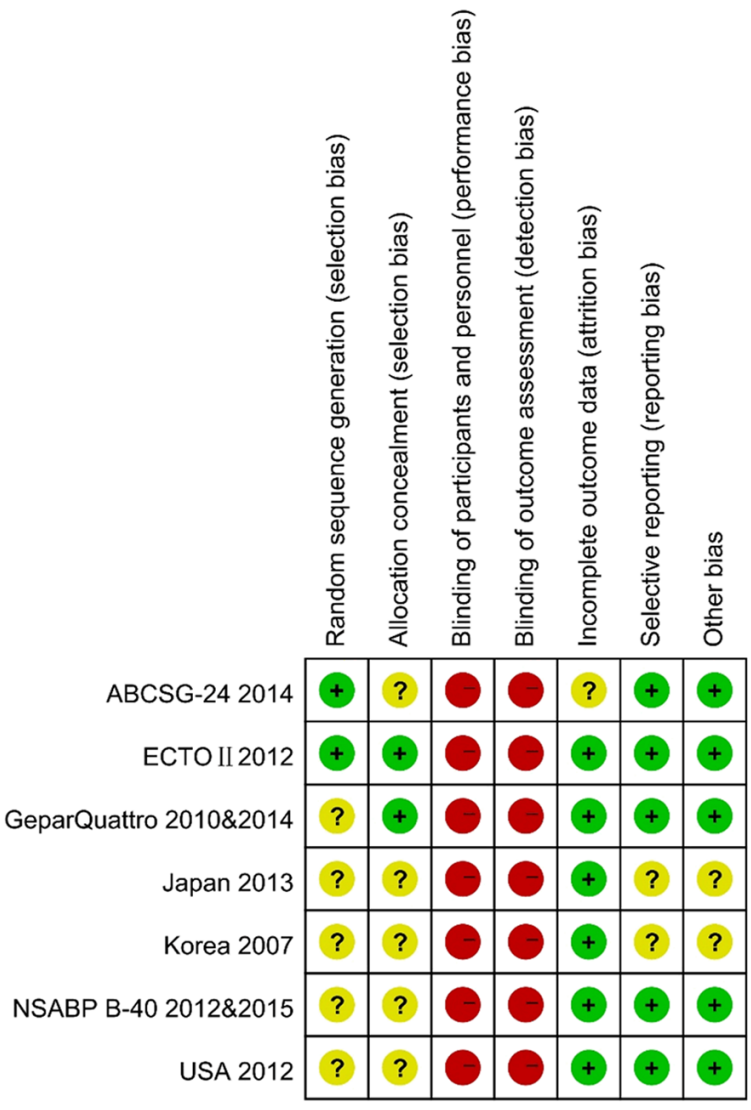

Figure 3. Risk of bias summary showed each risk of bias item for each included study.

Statistical analysis

The meta-analysis was performed using the Cochrane Review Manager (RevMan) version 5.3 software for windows. Hazard ratio (HR) were used to evaluate for DFS and OS, risk ratio (RR) were used to evaluate pCR, ORR and BCS, and odds ratio (OR) were used to evaluate the grade 3 to 4 AEs. We extracted the HR and 95% CI directly from the trials to calculate HR of DFS and OS. If the study did not provide them directly, we used engauge Digitizer 4.1 (available on http://digitizer.sourceforge.net/) to extract the data from the Kaplan-Meier curves for DFS and OS, and the HRs were calculated through the software designed by Tierney et al [22]. All statistical values were combined with a 95% confidence interval (CI) and p-value<0.05 was considered to be statistically significant. Statistical heterogeneities were measured through the Cochran Q-Statistics chi-square test and inconsistency index (I-squared, I^2). P>0.10 and I^2<50% were considered the statistics did not had heterogeneities

Table 1. Characteristics of included 7 RCTs of this meta-analysis

Trials&years	Country	Patients No.		Range of age (year)		Regimen		Outcomes
		Total	Testing/Standard	Testing	Standard	Testing	Control	
1. NSABP B-40 2012&2015 [9, 15]	USA	805	(405/400)	NA	NA	4TX→4AC	4T→4AC	DFS, OS, pCR, ORR, BCS
2. GeparQuattro 2010&2014 [2, 10]	German	1421	(950/471)	23-78	22-75	4EC→4TX or 4T→X	4EC→4T	DFS, OS, pCR, ORR, BCS
3. ABCSG-24 2014 [11]	Austria	536	(270/266)	25-71	27-73	6ETX	6 ET	pCR, BCS
4. Japan 2013 [12]	Japan, China, Hong Kong	477	(239/238)	25-70	25-68	4FEC→TX	4FEC→T	DFS, OS, pCR, ORR, BCS
5. USA 2012 [14]	USA	221	(111/110)	49 (median)	47 (median)	TX→4FEC	P→4FEC	pCR, BCS
6. ECTO II 2012 [13]	Italy, Spain, Austria, Russian Federation	310	(207/103)	24-77	29-71	4AT→4CMF or TX	4AT→4CMF	pCR, ORR
7. Korea 2007 [17]	Korea	209	(106/103)	24-67	21-65	4TX	4AC	DFS, OS, pCR, ORR, BCS

Abbreviations: A: doxorubicin; C: cyclophosphamide; T: docetaxel; E: epirubicin; F: fluorouracil; M: methotrexate; P: paclitaxel; X: capecitabine; NA: not available; pCR: pathological complete responses in breast; ORR: overall response rate; BCS: breast-conserving surgery.

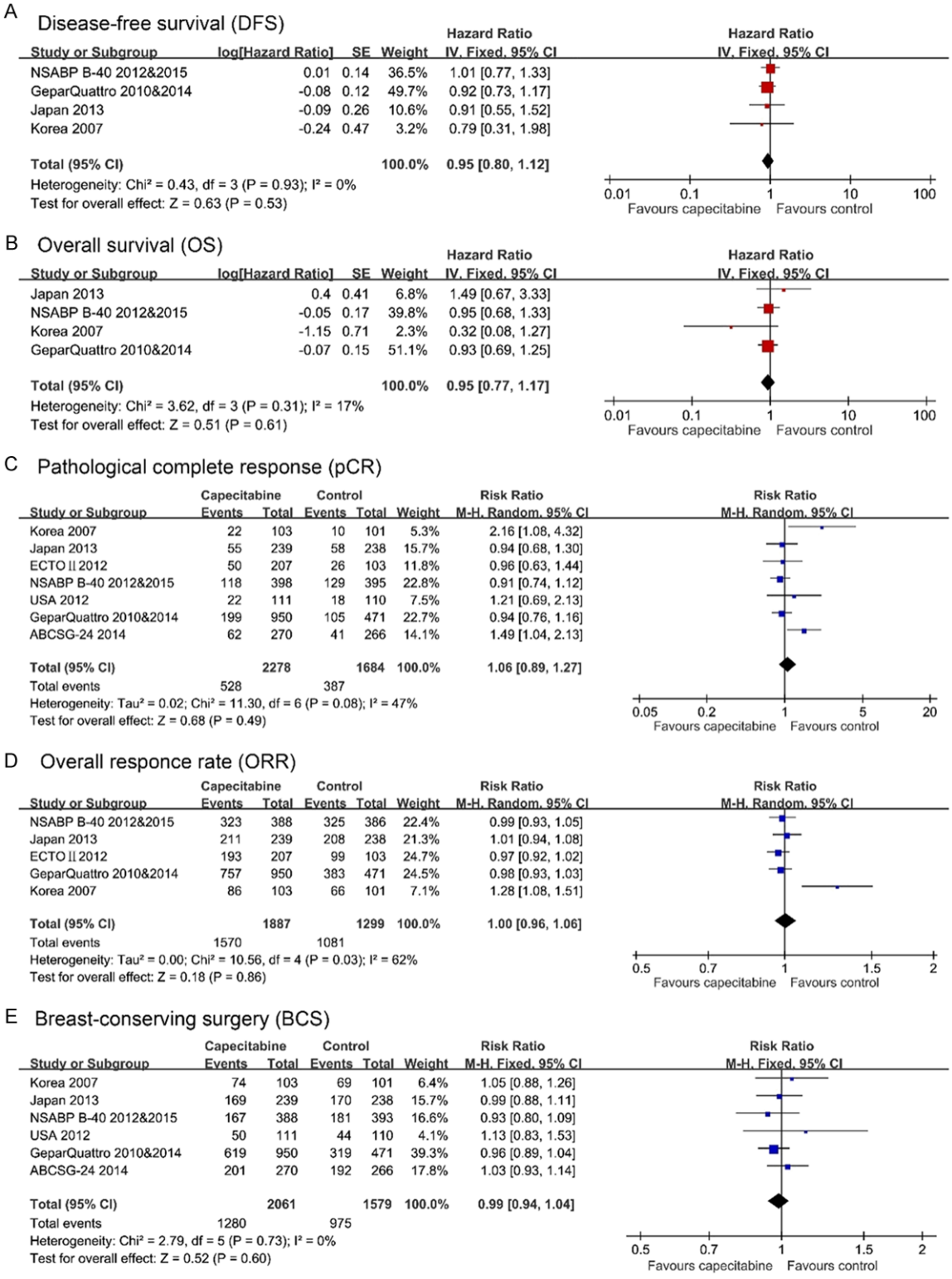

Figure 4. Forest plot showed the efficacy outcomes of meta-analysis. A. Disease-free survival (DFS). B. Overall survival (OS). C. Pathological complete response (pCR). D. Overall response rate (ORR). E. Breast-conserving surgery (BCS).

and a fixed-effects model was used. Otherwise, the random effects meta-analysis was used. Publication bias was evaluated using the funnel plot.

Table 2. Summary of drug-related NCI-CTC grade 3 to 4 adverse events

Adverse events	No. of studies	No. of patients	Heterogeneity		Statistical method	Effect estimate		
			p	I^2 (%)		OR	95% CI	p
1. Febrile neutropenia	5	2708	0.44	0	OR (M-H, Fixed, 95% CI)	1.49	1.10-2.01	0.010
2. Neutropenia	5	3076	<0.0001	86	OR (M-H, Random, 95% CI)	1.36	0.75-2.46	0.31
3. Hand-foot syndrome	4	2902	0.007	75	OR (M-H, Random, 95% CI)	7.16	3.09-16.60	<0.00001
4. Leukopenia	4	3002	0.41	0	OR (M-H, Fixed, 95% CI)	0.84	0.70-1.00	0.08
5. Vomiting	3	2425	0.0005	87	OR (M-H, Random, 95% CI)	0.75	0.21-2.71	0.66

Abbreviations: OR, odds ratio; M-H, Mantel-haenszel.

Results

Study Characterizes and quality

A total of 767 articles (105 from the PubMed, 24 from the Cochrane Library and 638 from EMBASE) were initially identified, from which we excluded those that were not qualified bases on the titles and abstracts. Subsequently, 18 trials were assessed for eligibility. 4 trials were not RCTs, 2 articles were from the same trials, 1 abstract could not get full text, 2 failed to provide data available and 2 were not preferred regimen. Eventually, 7 trials and 9 articles [2, 9-15, 17] were included in this meta-analysis. Among them, two trials (NSABP B-40 2012&2015 and GeparQuattro 2010&2014) reported the primary and secondary outcomes in two respective articles. The flow diagram of study selection was shown in **Figure 1**. Quality assessment was showed in **Figures 2** and **3** in detailed. There were a total of 7 RCTs involving 3979 patients with preoperative NAC treatment, of which 2288 were assigned to the capecitabine group, and 1691 were assigned to the controlled group. The characteristics of included trials of this meta-analysis were summarized in **Table 1**.

Efficacy outcomes

Disease-free survival (DFS): Four studies [9, 10, 12, 17] reported the DFS of patients between the two groups. We chose a fixed-effect model to evaluate the heterogeneity among the four trials (P = 0.93 and I^2 = 0%). Pooled results suggested that there was no significant difference in DFS between two groups (HR = 0.95, 95% CI: 0.80 to 1.12, P = 0.53) (**Figure 4A**).

Overall survival (OS): Four trials [9, 10, 12, 17] reported the OS of patients between the two groups. We chose a fixed-effect model to evaluate the heterogeneity among the five trials (P = 0.31 and I^2 = 17%). Pooled results suggested that there was no significant difference in OS between two groups (HR = 0.95, 95% CI: 0.77 to 1.17, P = 0.61) (**Figure 4B**).

Pathological complete response (pCR): All seven studies reported the pCR of patients between the two groups. We chose a random-effect model to evaluate the heterogeneity among the seven trials (P = 0.08 and I^2 = 47%). Pooled results suggested that there was no significant difference in pCR between two groups (HR = 1.06, 95% CI: 0.89 to 1.27, P = 0.49) (**Figure 4C**).

Overall response rate (ORR): Apart from the study of ABCSG-24 2014 and USA 2012, other five studies reported the ORR of patients between the two groups. We chose a random-effect model to evaluate the heterogeneity among the four trials (P = 0.03 and I^2 = 62%). Pooled results suggested that there was no significant difference in ORR between two groups (HR = 1.00, 95% CI: 0.96 to 1.06, P = 0.86) (**Figure 4D**).

Breast-conserving surgery (BCS): Six studies reported the BCS of patients between the two groups, excluded ECTO II 2012. We chose a fixed-effect model to evaluate the heterogeneity among the four trials (P = 0.73 and I^2 = 0%). Pooled results suggested that there was no significant difference in ORR between two groups (HR = 0.99, 95% CI: 0.94 to 1.04, P = 0.60) (**Figure 4E**).

Safety outcomes

Five of the studies had reported the safety profile and we could extract the available statistics of major adverse events (AEs) according to the NCI Common Terminology Criteria for Adverse Events, version 3.0 [2, 12, 13, 15, 17]. The

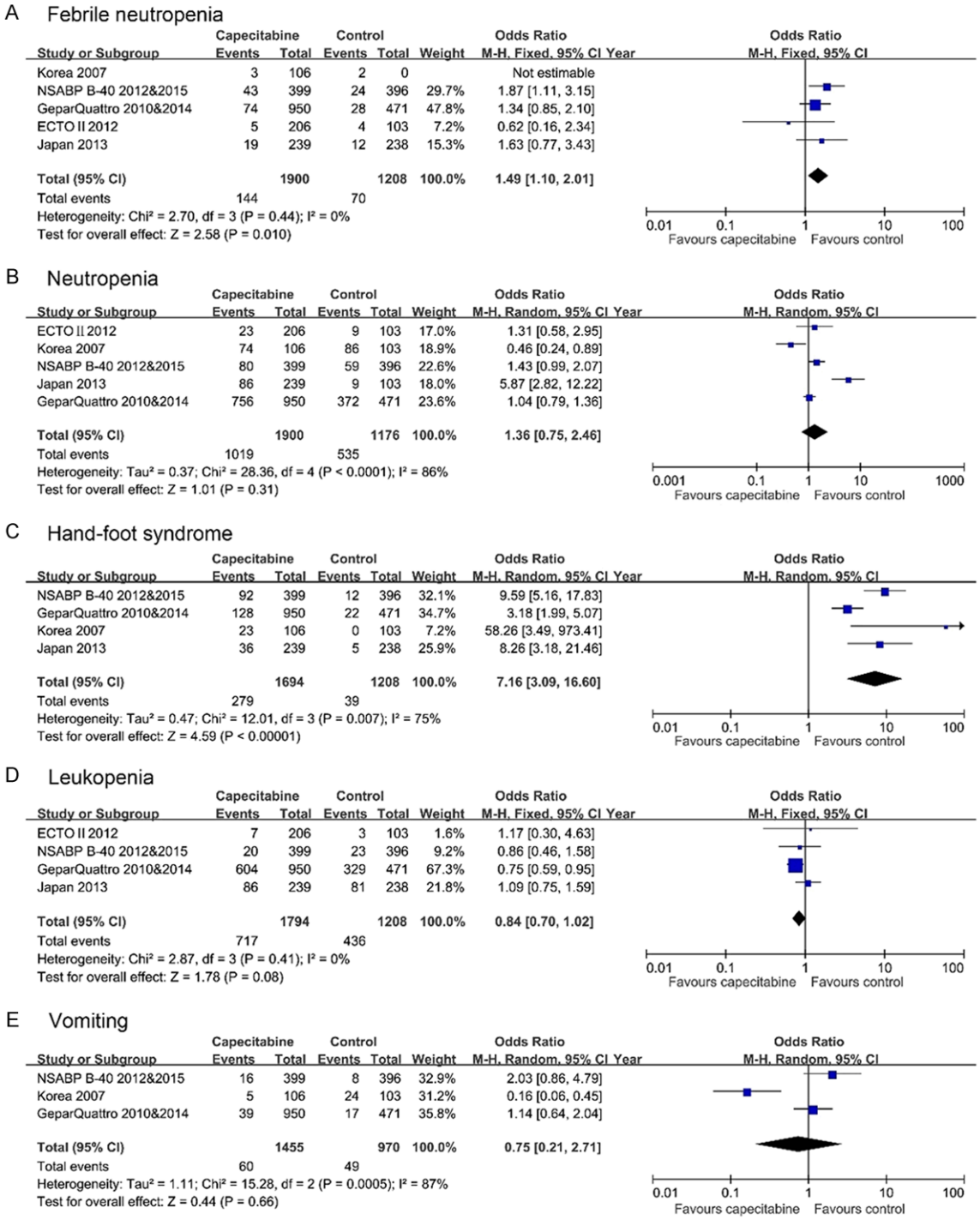

Figure 5. Forest plot showed the NCI-CTC grade 3 to 4 AEs of meta-analysis. A. Febrile neutropenia. B. Neutropenia. C. Hand-foot syndrome. D. Leukopenia. E. Vomiting.

grade 3-4 AEs reported in more than two trials were summarized in **Table 2**, which were febrile neutropenia, neutropenia, hand-foot syndrome, leukopenia, vomiting. Pool OR values suggested that neoadjuvant chemotherapy containing capecitabine significantly increased the incidence of febrile neutropenia (OR = 1.49, 95% CI: 1.10 to 2.01, P = 0.010) (**Figure 5A**), hand-foot syndrome (OR = 7.16, 95% CI: 3.09 to 16.60, P<0.00001) (**Figure 5C**). But it did not

significantly increase the incidence of neutropenia (OR = 1.36, 95% CI: 0.75 to 2.46, P = 0.31) (**Figure 5B**), leukopenia (OR = 0.84, 95% CI: 0.70 to 1.00, P = 0.08) (**Figure 5D**) and vomiting (OR = 0.75, 95% CI: 0.21 to 2.71, P = 0.66) (**Figure 5E**). The heterogeneity might be related to the different dosages or the regimens of the treatments.

Sensitivity analysis

Sensitivity analyses were used to evaluate the influence of individual trials on the overall meta-analysis. No individual study affected the HR for DFS and OS, the RR for pCR, ORR and BCS, and the OR for AEs significantly.

Discussion

According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Breast Cancer, version 1.2016, capecitabine is one of the preferred single agents and combination regimens with docetaxel for recurrent or metastatic breast cancer. The dosing schedule of capecitabine singled chemotherapy was 1000-1250 mg/m^2 PO twice daily days 1-14, cycled every 21 days. In the neoadjuvant setting, capecitabine was considered as an active additional agent and some trials reported controversial results in the efficacy of the additional capecitabine regimen.

The final results of ABCSG-24 randomized phase III study demonstrated that the addition of capecitabine to epirubicin and docetaxel (ETX) increased pCR rate from 15.4% to 23% (P = 0.027) and showed that integreation of capecitabine into anthracycline/taxane-based regimen was an effective NAC option [11]. Another randomized phase III trial from Korea reported that NAC with docetaxel and capecitabine (TX) led to an increased pCR rate from 10% to 21% (P = 0.024) and clinical response rate from 65% to 84% (P = 0.003) compared with doxorubicin and cyclophosphamide (AC) regimen, however these benefit results did not translate into a gain in DFS [17]. These benefit observations with the integration of capecitabine were in accordance with the results of a meta-analysis in metastatic breast cancer, which found that capecitabine-containing arm significantly improve DFS (HR = 0.83, 95% CI: 0.71-0.98, P = 0.027) and OS (HR = 0.71, 95% CI: 0.57-0.88, P = 0.002) [23].

In contrast, the large GeparQuattro phase III study displayed no difference in pCR rate, BCS rate and other secondary efficacy endpoints between the NAC arms with or without capecitabine [2]. In addition, the survival analysis of GeparQuattro study confirmed the findings on pCR rate, which showed no difference in DFS and OS between two arms [10]. The neoadjuvant phase III randomized controlled trial, NSABPB-40 (NGR Oncology) also showed the addition of capecitabine did not significantly increase pCR rate, DFS or OS [9, 15].

The possible explanation for different results might be the lower dose of capecitabine and the preoperative regimen was only administrated for four cycles. In the two positive studies, capecitabine was administrated in front for six cycles, however, in GeparQuattro, four cycles of epirubicin plus cyclophosphamide (EC) was used before four cycles of capecitabine. The doses, optimal timing and duration of capecitabine might affect the effect of NAC treatment [24].

Considering the conflicting findings, we conducted this meta-analysis. To our best knowledge, this is the first meta-analysis of the long-term survival outcomes such as DFS and OS, and it was an update on short-term efficacy outcomes such as pCR, ORR and BCS and the safety outcomes.

The total of 7 RCTs involving 3979 patients with preoperative chemotharapy were included, of whom 2288 were assigned to the capecitabine group, and 1691 were assigned to the controlled group. This meta-analysis aimed to evaluate the efficacy and safety of additional capecitabine to NAC regimens in breast cancer. The current available RCTs indicated that the capecitabine-containing NAC could not improve the clinical efficacy in DFS, OS, pCR, ORR and BCS in patients with breast cancer. In additional, some grade 3-4 adverse events such as febrile neutropenia and hand-foot syndrome could occur in additional capecitabine NAC regimens.

It should be noted that this meta-analysis had several limitations. Firstly, the number of RCTs was limited. Secondly, the sample size of included trials was small. In addition, the trials had varied dosage, regimen and concomitant medication. Finally, the seven RCTs were not double-blinding trials.

In conclusion, the addition of capecitabine to NAC anthracycline/taxane-based regimens did not seem to provide any benefits for patients with breast cancer, and should not change clinical practice in short term. Further refinement studies of capecitabine-containing NAC regimens in conditions, which benefit for patients, are ongoing.

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Disclosure of conflict of interest

None.

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