Int J Clin Exp Med 2016;9(10):18808-18815
www.ijcem.com /ISSN:1940-5901/IJCEM0031155

Review Article

Meta-analysis of capecitabine-based chemotherapy versus capecitabine-free chemotherapy in patients with metastatic breast cancer

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Received April 25, 2016; Accepted May 20, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: Objective: Discordant efficacy and safety of capecitabine-based chemotherapy versus capecitabine-free chemotherapy were reported by previous trials. Our meta-analysis aimed to determine the efficacy and safety of capecitabine-based chemotherapy verse capecitabine-free chemotherapy in patients with metastatic breast cancer. Methods: Literatures were searched in Pubmed, Medline and Embase from January 1990 to January 2015 in this study. Studies of parallel group design comparing capecitabine-based chemotherapy and capecitabine-free chemotherapy for metastatic breast cancer were screened. After independent review of 732 citations by 2 authors, ten studies were identified as meeting the inclusion criteria. Results: Our study showed that capecitabine-based chemotherapy had a similar clinical response, partial response, overall response and progression free survival with capecitabine-free chemotherapy. However, patients treated with capecitabine-based chemotherapy had a better overall survival than patients treated with capecitabine-free chemotherapy (OR=0.8, 95% CI: 0.68 to 0.95). Neutropenia (OR=1.22, 95% CI: 1.05-1.41) and leukocytopenia (OR=1.36, 95% CI: 1.13-1.63) occurred less in capecitabine-based chemotherapy group. Significantly more diarrhea (OR=0.46, 95% CI: 0.32-0.65), nausea (OR=0.47, 95% CI: 0.24-0.89) and hand-foot syndrome (OR=0.07, 95% CI: 0.04-0.17) occurred in capecitabine-based chemotherapy group than in capecitabine-free chemotherapy group. Conclusion: Our study indicated that capecitabine-based chemotherapy is as effective as capecitabine-free chemotherapy in patients with metastatic breast cancer with better overall survival and acceptable toxicity profiles.

Keywords: Capecitabine, chemotherapy, drug safety, efficacy, meta-analysis

Introduction

Breast cancer is a common malignant disease in woman and nearly half of these patients develop into metastatic breast cancer [1]. Prognosis and treatment for metastatic breast cancer is still a challenge [2]. Hormone therapy, chemotherapy and radiotherapy are main treatments to control the disease progression.

Chemotherapy is used as first-line treatment for metastatic breast cancer. Previous clinical studies have showed that chemotherapy could improve the response rate and progression free survival. Doxorubicin is widely used in USA and epirubicin is preferred in Europe [3, 4]. The choice of first-line anthracycline/taxane therapy for metastatic breast cancer depends on geographic region, patient characteristics and safety profile.

Capecitabine is an oral fluoropyrimidine which is converted to 5-fluorouracil in tumor tissue [5]. It is an approved treatment for metastatic breast cancer in both monotherapy and combination with other chemotherapy. Pretreated patients treated with capecitabine alone achieve a response rate of 20% [6], while those treated with the combination of capecitabine and other agents achieve a response rate of 30% [7].

The efficacy of capecitabine alone or combination with other agents reported in previous tri-

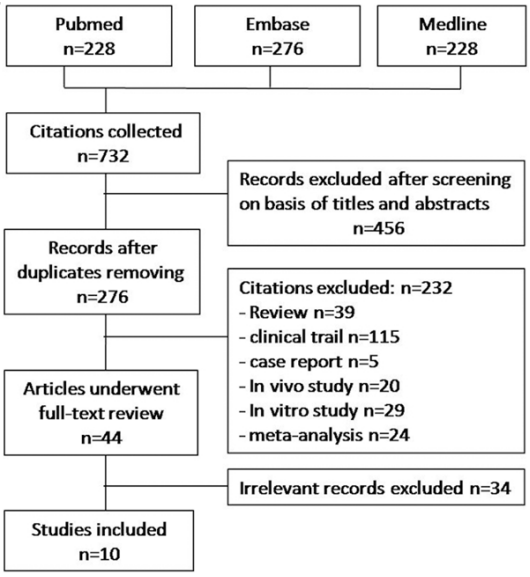

Figure 1. Flow chart of the study selection.

als was not the same. Some studies reported that the efficacy of capecitabine and other chemotherapy was comparable [8]. However, recent trials suggested that capecitabine improved overall survival [9].

To determine the efficacy and safety of capecitabine-based chemotherapy versus capecitabine-free chemotherapy in patients with metastatic breast cancer, we performed this meta-analysis including all published studies.

Methods

Search strategy and inclusion criteria

Databases (Embase, Medline, and Pubmed) were searched for randomized controlled trials (RCTs) from January 1990 to January 2015. The key words "metastatic breast cancer" and "capecitabine" were used in screening relevant citations. The inclusion criteria were: (1) the studies were RCTs; (2) the studies provided the data at least with one of main outcomes, including complete response, partial response, overall response, progression free survival and overall survival.

Data extraction and quality assessment

Two authors extracted the data from included studies independently. The following information was extracted from each study: first author name; year of publication; number of patients; complete response, partial response, overall response, progression free survival and overall survival. The Jadad score was used to assess the quality of included studies [10]. The studies with score no less than 3 were regarded as high quality RCTs, while studies with score less than 3 were defined as low quality RCTs.

Assessment of efficacy and statistical analysis

Complete response, partial response, overall response, progression free survival and overall survival were used to evaluate the efficacy in metastatic breast cancer. Data analysis was performed by using the Stata12 software for each individual study, dichotomous data were reported as odds ratio (OR) with 95% confidence interval (CI). Heterogeneity between studies was assessed by Cochrane Q statistics and I-square test. A significant level of above 50% for I^2 test was considered as evidence of heterogeneity. Fix-effect model was used when there was no evidence of heterogeneity, otherwise random-effect model was chosen.

Results

Search results and characteristics

A total of 228 citations were obtained via database searches, among which ten met the inclusion criteria for this study (**Figure 1**). A total of 1910 patients have been involved, in which 973 subjects were treated with capecitabine-based chemotherapy, and 937 subjects with capecitabine-free chemotherapy. The information in these citations is summarized in **Table 1**. All ten studies have been assessed by Jadad score system with score no less than 3 (**Table 1**).

Complete response

Complete response was reported in eight studies. According to the results of meta-analysis, there was no significant difference in complete response rates between patients allocated chemotherapy with capecitabine versus those treated by chemotherapy without capecitabine. The OR for complete response was 0.74 (95% CI: 0.5 to 1.09). There was no heterogeneity with I^2=0% (**Figure 2**).

Partial response

Partial response was reported in eight studies. There was no significant difference in partial

Table 1. Main charac teristic of the included studies

Study	Year	Age	Location	Ethnicity	Follow up (m)	Regimens	No. of patients	Status	Jadad score
Janni [11]	2014	>18	Europe	Caucasian	28	Lapatinib	75	HER2+MBC	3
						Lapatinib+Cap	37		
Smorenburg [12]	2014	>65	Nederland	Caucasian	30	PLD	40	HER-/HER2+MBC	3
						Cap	38		
Lück [13]	2013	18-75	German	Caucasian	48	EPI+paclitaxel	170	MBC	3
						Cap+paclitaxel	170		
Glück [9]	2013	27-79	USA	Caucasian	42	docetaxel	178	MBC	3
						Cap+docetaxel	178		
Hatschek [14]	2012	NR	Sweden	Caucasian	54	EPI+paclitaxel	143	HER-/HER2+MBC	3
						TEX	144		
Bachelot [15]	2011	>18	France	Caucasian	54	DDP+docetaxel	35	HER2-MBC	3
						Cap+docetaxel	33		
Stemmler [16]	2011	18-70	German	Caucasian	47	GEM+DDP	45	HER-/HER2+MBC	3
						GEM+Cap	50		
Wardley [17]	2010	>18	UK	Caucasian	50	HT	110	HER2+MBC	3
						HT+Cap	112		
Chan [7]	2009	>18	Europe	Caucasian	50	GEM	153	MBC	3
						Cap	152		
Pajk [8]	2008	31-71	Europe	Caucasian	NR	vinorelbine	24	MBC	3
						Cap	23		

Cap, capecitabine; PLD, pegylated liposomal doxorubicin; EPI, epirubicin; DDP, cisplatin; TEX, epirubicin, paclitaxeland capecitabine; GEM, gemcitabine; HT, trastuzumab and docetaxel; HER2, human epidermal growth factor receptor-2; MBC, metastatic breast cancer.

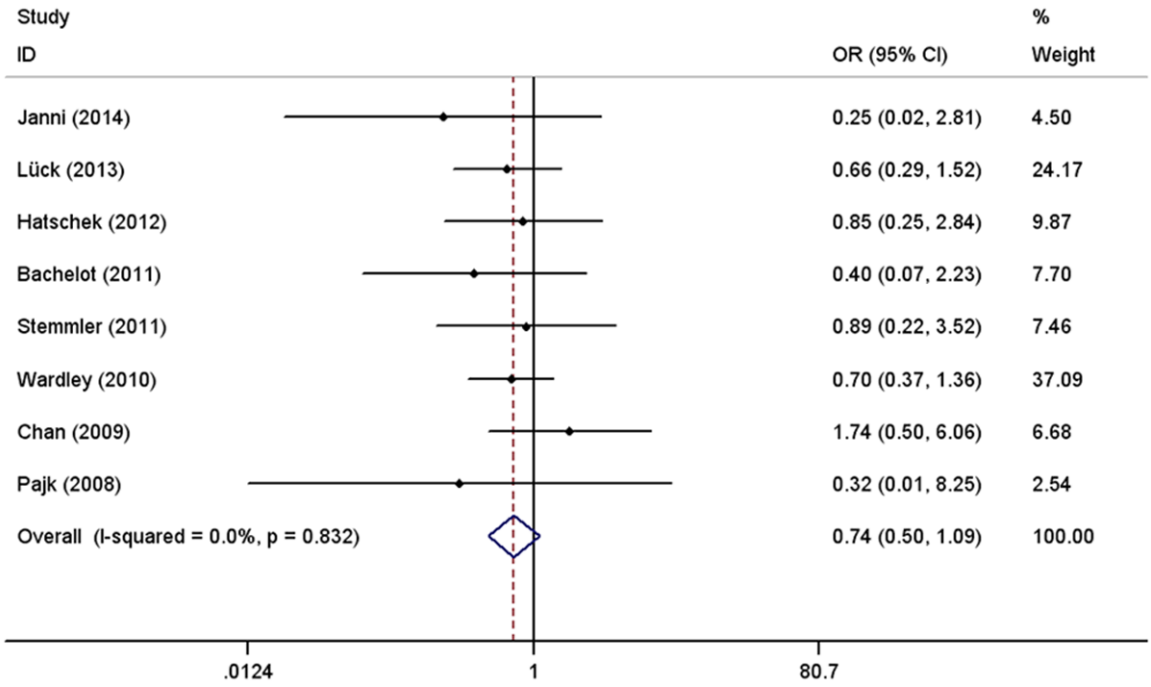

Figure 2. Forest plots of complete response of patients treated with capecitabine-based chemotherapy in comparison to capecitabine-free Chemotherapy.

response rates between patients allocated chemotherapy with capecitabine versus those treated by chemotherapy without capecitabine. The OR for partial response was 1.11 (95% CI:

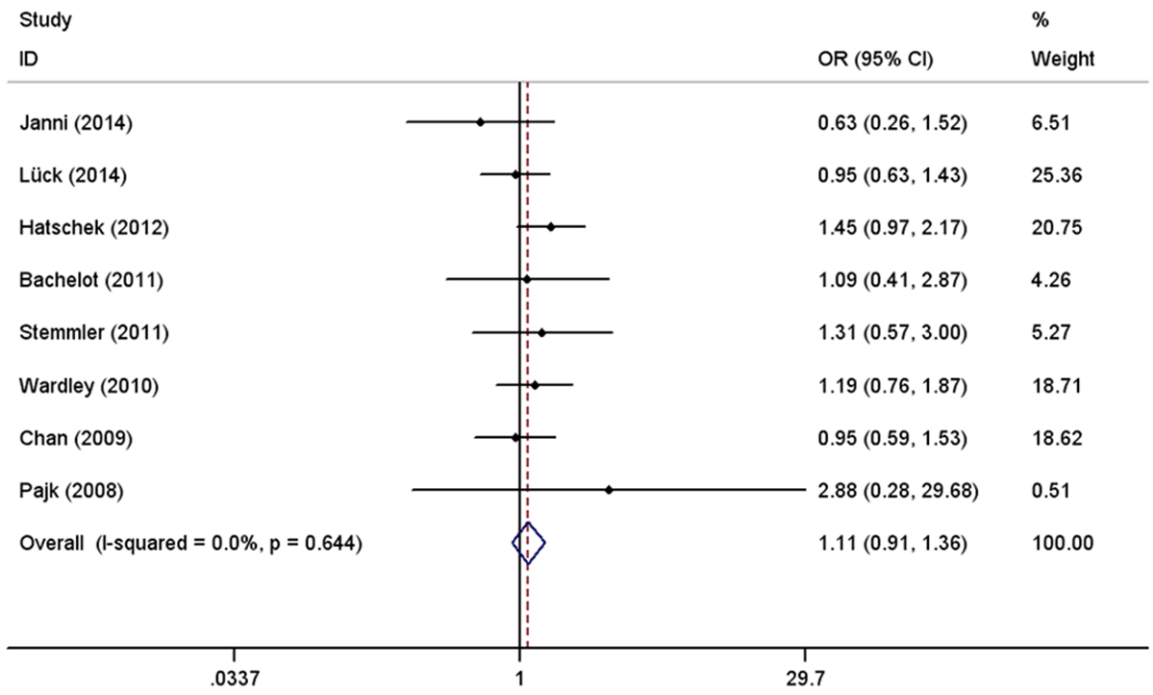

Figure 3. Forest plots of partial response of patients treated with capecitabine-based chemotherapy in comparison to capecitabine-free Chemotherapy.

0.91 to 1.36). There was no heterogeneity with I^2=0% (**Figure 3**).

Overall response

Overall response was reported in nine studies. There was no significant difference in overall response rates between patients allocated chemotherapy with capecitabine versus those treated by chemotherapy without capecitabine. The OR for overall response was 0.93 (95% CI: 0.77 to 1.12). There was no heterogeneity with I^2=0% (**Figure 4**).

Progression free survival

Progression free survival was reported in five studies. According to the results of meta-analysis, there was no significant difference in progression free survival between patients allocated chemotherapy with capecitabine versus those treated by chemotherapy without capecitabine. The OR for progression free survival was 0.87 (95% CI: 0.69 to 1.09). There was heterogeneity with I^2=58.9% (**Figure 5**).

Overall survival

Overall survival was reported in eight studies. According to the results of meta-analysis, capecitabine-based chemotherapy could increase the overall survival compared with capecitabine-free chemotherapy for metastatic breast cancer. The OR for overall survival was 0.8 (95% CI: 0.68 to 0.95). There was no heterogeneity with I^2=0% (**Figure 6**).

Grade 3-4 toxicities of capecitabine-based chemotherapy versus capecitabine-free chemotherapy

Our meta-analysis compared grade 3-4 adverse effects of capecitabine-based chemotherapy and capecitabine-free chemotherapy. Neutropenia (OR=1.22, 95% CI: 1.05-1.41) and leukocytopenia (OR=1.36, 95% CI: 1.13-1.63) occurred less in capecitabine-based chemotherapy group. Significantly more diarrhea (OR=0.46, 95% CI: 0.32-0.65), nausea (OR=0.47, 95% CI: 0.24-0.89) and hand-foot syndrome (OR=0.07, 95% CI: 0.04-0.17) occurred in capecitabine-based chemotherapy group than in capecitabine-free chemotherapy (**Table 2**).

Discussion

Our meta-analysis gave a precise estimation of the efficacy of capecitabine-based chemotherapy in metastatic breast cancer patients

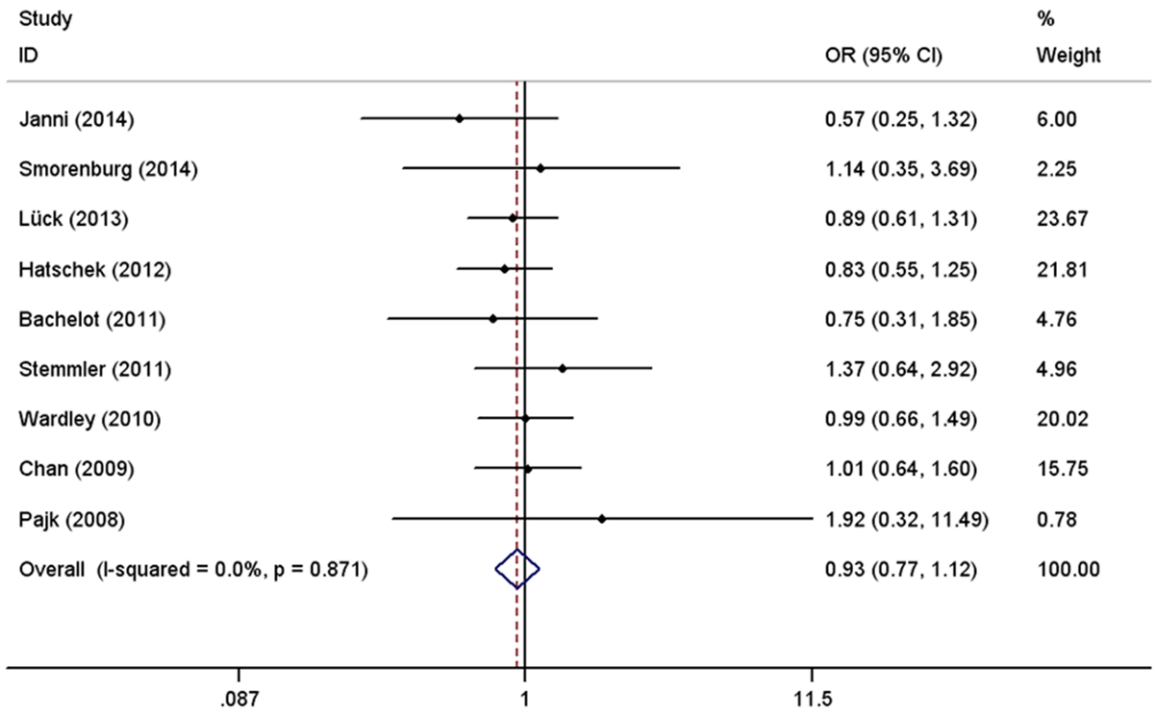

Figure 4. Forest plots of overall response of patients treated with capecitabine-based chemotherapy in comparison to capecitabine-free Chemotherapy.

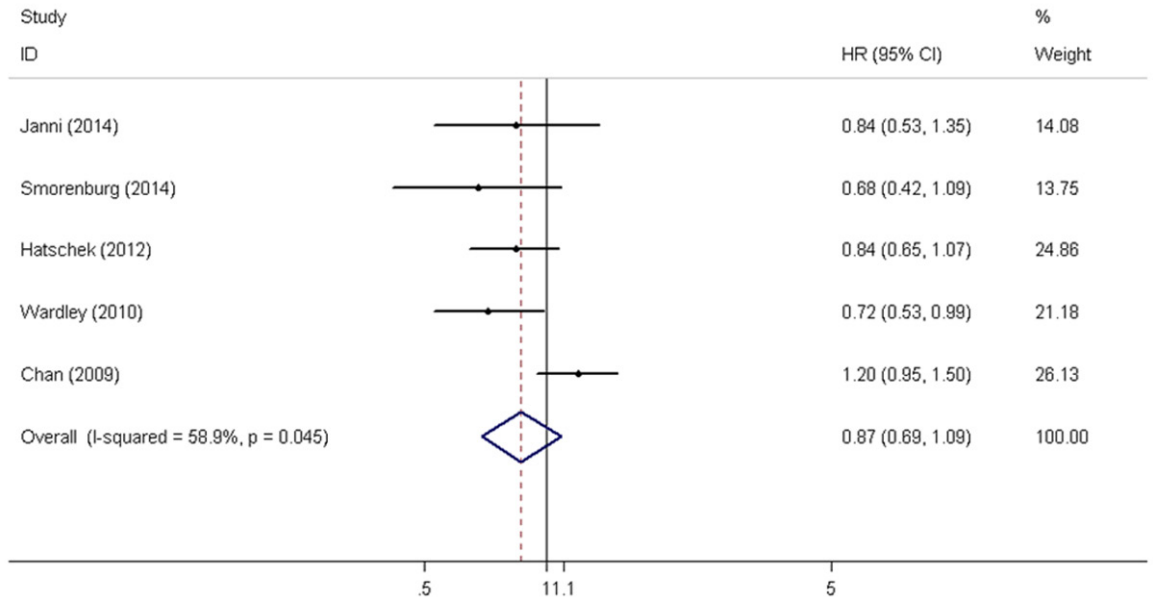

Figure 5. Forest plots of progression free survival of patients treated with capecitabine-based chemotherapy in comparison to capecitabine-free Chemotherapy.

compared with capecitabine-free chemotherapy. The results of our study showed that capecitabine-based chemotherapy had a similar complete response, partial response, overall response and progression free survival with capecitabine-free chemotherapy. However, patients treated with capecitabine-based chemotherapy had a better overall survival than

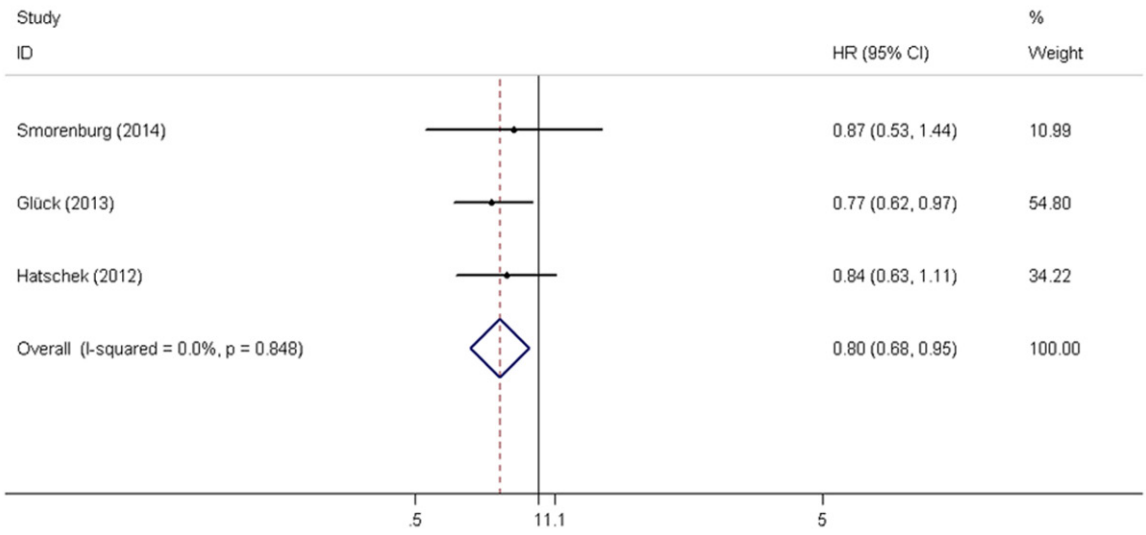

Figure 6. Forest plots of overall survival of patients treated with capecitabine-based chemotherapy in comparison to capecitabine-free Chemotherapy.

Table 2. Summary of grade 3-4 side effects of capecitabine-based chemotherapy versus capecitabine-free chemotherapy

Variables	OR	95% CI	Heterogeneity (%)	No. of studies
Hematological toxicity				
Neutropenia	1.22	1.05-1.41	71.7	7
Neutropenic fever	1.12	0.85-1.47	35	6
Anemia	1.72	0.83-3.59	38	5
Thrombocytopenia	1.69	0.88-3.26	0	4
Leukocytopenia	1.36	1.13-1.63	74.8	4
Gastrointestinal toxicity				
Diarrhea	0.46	0.32-0.65	0	9
Nausea	0.47	0.24-0.89	0	7
Vomiting	0.52	0.24-1.11	9.3	6
Others				
Asthenia	1.02	0.65-1.6	62.1	5
Hand-foot syndrome	0.07	0.04-0.14	49.5	9

patients treated with capecitabine-free chemotherapy. In addition, neutropenia and leukocytopenia occurred less in capecitabine-based chemotherapy, while diarrhea, nausea and hand-foot syndrome occurred less in capecitabine-free chemotherapy group.

Efficacy and adverse effects should be well balanced in patients with metastatic breast cancer. Our study suggested that the effectiveness of capecitabine-based chemotherapy was comparable with capecitabine-free chemotherapy. There was no significant difference in partial response and complete response. The partial response was about 35% in the two groups, and the complete response was about 7%. Capecitabine monotherapy and combination with other agents may contribute to a better overall survival.

Less hematological toxicity was observed in capecitabine-based chemotherapy. However, more Grade 3-4 gastrointestinal toxicity was observed in the capecitabine group, which was mainly caused by capecitabine [1]. Hand-foot syndrome occurred more in the capecitabine group, but this adverse event could be managed by treatment interruption or dose reduction. Therefore, we think the safety of capecitabine-based chemotherapy was acceptable.

In addition, there were some limitations in our study. First, the basic characteristics of the included studies were slightly different. Second, the sample size of some trials was small. Third, subgroup analysis for human epidermal growth factor receptor-2 (HER2) status of the tumors was not performed, because not all of the studies offered the data according to the HER2 status. Fourth, there was significant heterogeneity in adverse events. We thought the potential

source of this heterogeneity was the variant baseline in these included studies, thus the results should be taken cautiously. Regardless of these limitations, we believe that our analysis could contribute to the evaluation of capecitabine in metastatic breast cancer.

Conclusion

In conclusion, our study indicated that capecitabine-based chemotherapy is as effective as capecitabine-free chemotherapy in patients with metastatic breast cancer with acceptable toxicity profiles. In addition, large-sample RCTs are needed to confirm our findings.

Disclosure of conflict of interest

None.

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