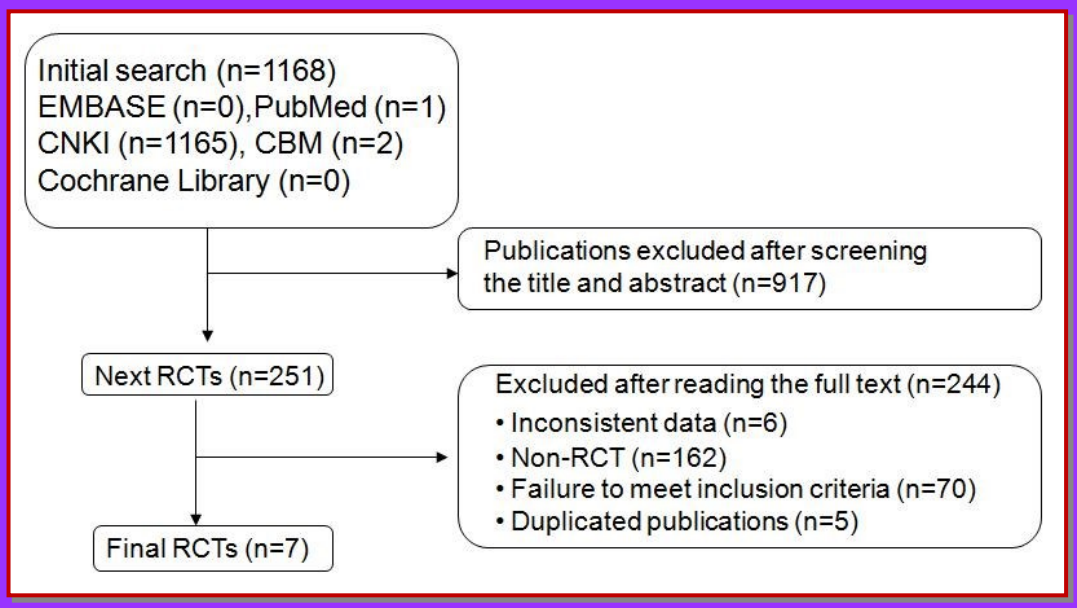

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Meta-analysis

Adjuvant chemotherapy of megestrol acetate in advanced breast cancer: A meta-analysis

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Abstract

To evaluate the effectiveness and safety of adjuvant chemotherapy of megestrol acetate (MA) in advanced breast cancer, we searched CBM, CNKI, VIP, Wangfang Data and PubMed, and collected randomized controlled trials (RCT) of adjuvant chemotherapy of MA in advanced breast cancer. MA significantly increased treatment efficiency (p=0.0010); improve weight (p<0.0001), appetite (p=0.001) and KPS (p=0.06); ameliorate leucopenia (p=0.02), thrombocytopenia (p=0.02) and hemoglobin (p=0.01); reduce gastrointestinal reaction (p=0.0005) of the patients of adjuvant chemotherapy in advanced breast cancer. MA significantly increased treatment efficiency, improve the nutritional situation, reduce bone marrow suppression, and gastrointestinal reaction of the patients of adjuvant chemotherapy in advanced breast cancer. High-quality RCTs are needed to guidance for preliminary studies of the effective treatment of adjuvant chemotherapy of MA in advanced breast cancer.

Introduction

Agency for research on cancer released data show that breast cancer has been the most frequently diagnosed cancer (Jemal et al., 2006). Human epidermal growth factor receptor 2 expression is referred to as triple-negative breast cancer (TNBC), representing about 15% of all breast cancers (Adamo et al., 2012). The leading cause of cancer death among females world wide, accounting for 23% of the total cancer cases and 14% of the cancer deaths in 2008, about 458,400 people, incidence increase rate by 0.2 to 8% annually. Currently, the incidence of breast cancer annual growth rate by 3 to 4%, is higher than the global average growth rate in China (Pu et al., 2014; Zhai et al., 2015).

In recent years, megestrol acetate (MA) is one artificial semi-synthetic progesterone derivative, used to endocrine treatment on breast cancer and other hormone-dependent tumors (Fiorica et al., 2004). MA is applied to the non-hormone-dependent tumor treatment; has inhibitory effect of hormone dependence tumor line, especially breast cancer. At the same time, MA can improve patients' weight and appetite, alleviate gastrointestinal reaction and bone marrow suppression of adjuvant chemotherapy in advanced breast cancer (Demoor-Goldschmidt et al., 2009). MA has some roles of protein assimilation, can promote the patient's protein and fat synthesis; can increase or stabilize patient's weight, improve the quality of breast cancer patient's life in adjuvant chemotherapy period of advanced breast cancer (Partridge et al., 2001; Zhang et al., 2014). However, the results remain controversial. The purpose of our study is to meta-analyze data from randomized clinical trials (RCTs) for evidence on the adjuvant chemotherapy of MA treats patient with advanced breast cancer.

Materials and Methods

Literature search

We searched CBM, CNKI, VIP, WangFang Data and PubMed, and RCT of adjuvant chemotherapy of MA in advanced breast cancer. The quality of included studies was assessed according to the criteria recommended by the Cochrane 4.2.6 Hand-book for systematic reviews of interventions, and meta-analyses were performed using the Cochrane Collaboration's RevMan 5.2 software (Fu et al., 2014). The reference lists of papers authenticated ware scanned for further trials. The under search labels were used conjunctively or individually: 'Breast Caner', 'Advanced Breast Caner', 'Megestrol Acetate', 'Randomized Con-trolled Trial', and 'Clinical Trial'.

Inclusion and exclusion criteria

Inclusion criteria

Type of research: RCT are updated to March 2013; object of observation: Selected patients (more than 18 years of age) is accord with national standard in the diagnosis of advanced breast cancer; intervening measure: MA vs placebo or margin or other therapy; curative effect decision criteria: Clear standard source of curative effect.

Exclusion criteria

Simple descriptive study has no control group or is not rigorous trial design; diagnosis and clinical criteria of RCT are not standardized; selected patient contains male patients; repeat reported; the sample data confessed unclear or incomplete etc.

Quality assessment

Three authors managed the literature searching, studied literature, and extracted data independently. Disagreement was resolved by discussion. The abstracted data included title and authors of study, study size, age, year of publication, details of methodological message, sex of the participants, name, specifics of the control interventions ,treatment process, outcomes and adverse reaction for every research. At the same time, the 'risk of bias' assessment tool were used to assess all studies to address the following six criterion in accordance with the 'Cochrane 4.2.6 Hand-book of Systematic Reviews of Interventions': Randomization, allocation concealment, blinding, loss of imitation and exit cases, intention-to-treat (ITT) analysis, baseline, and Cochrane score. The quality of all the included studies was categorized to (C) low/ (B) unclear/ (A) high-risk of bias. These studies which met all criterions were categorized to (A) high-risk of bias, studies which met none of the criteria were categorized to (C) low-risk of bias, and other studies met some criterion were categorized to (B) unclear-risk of bias if insufficient information acquired to make judgment.

Data extraction

Read the title, summary and full text to extract data. Three researchers independently conducted quality assessment, and discussed the quality of each paper and decision.

Data analysis

We used RevMan 5.2 software to analysis data. Clinical heterogeneity and methodological heterogeneity of the included studies were analyzed. p values of <0.05 were considered significant.. Meta-analysis was utilized if the studies had receivable homogeneity of study design, controls, interventions, participants, and outcome measures. The statistical heterogeneity was tested by examining I^2 square 15 or p value; an I^2>50% or a p value <0.1 indicates the possibility of statistical heterogeneity (Zhang et al., 2013). I^2<25% is low heterogeneity, 25%≤I^2≤50% is moderate heterogeneity and I^2>50% is highly heterogeneous. Data was summarized using risk ratio (RR) with 95% confidence intervals (CI) for binary outcomes or mean difference (MD) with a 95% CI for continuous outcomes. Publication bias was explored by way of a funnel-plot analysis (Ciliberto et al., 2012). Missing or lost to cases count data should be counted as treatment failure cases. So, we have demonstrated sensitivity analysis.

Results

Description of studies

We searched primarily from the five databases, 2240 documents were screened. We eliminated duplicate 1259 documents by electronic and hand searches. We eliminated 368 documents with review of literature/ time too long literature/the no-research object. We eliminated 591 documents with non-randomized controlled trial/interventions and the results have not met the inclusion criteria by reading abstract. We eliminated 14 documents with data in question/ random method is not correct by reading full text. Finally full-text papers of 8 studies (Cao et al., 2012; Feng, 2012; Gong et al., 2012; Goodwin et al., 2008; Lu et al., 2012; Tang et al., 2012; Tang et al., 2012; Zhou et al., 2012) were searched from all the citations. A flowchart described the search method and study chose (Figure 1).

General characteristics of included reviews

These 8 trials literature included the 610 cases including 307 cases of MA group and 303 cases of the control group. These studies were the largest number of 194 cases, at least 28 cases. In the 8 included trials, the treatment efficiency was reported by 4 trials, the gain weight was reported by 3 trials, the increased appetite was reported by 4 trials, the improve KPS was reported

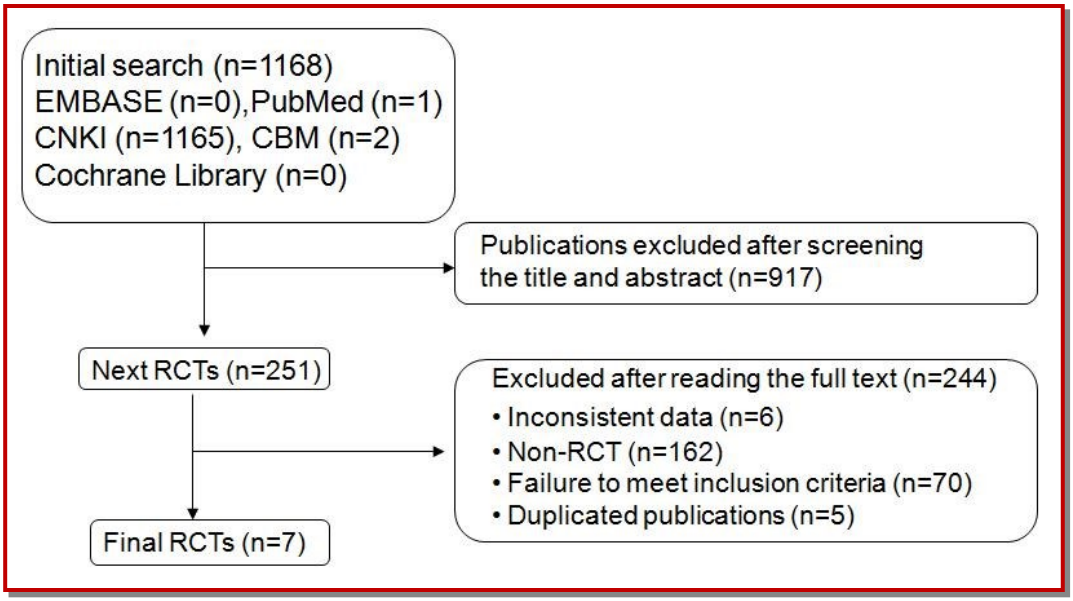

Figure 1: Flowchart of identification of studies included in the review

by 3 trials, the leukopenia was reported by 3 trials, the thrombocytopenia was reported by 3 trials, the hemoglobin was reported by 3 trials and the gastrointestinal tract bad effect was reported by 3 trials of adjuvant chemotherapy of advanced breast cancer patients. The features of included studies were cataloged in Table I.

Methodological quality of included reviews

Eight studies were assessed in accordance with the 'Cochrane 4.2.2 Handbook of Systematic Reviews', including 1 study was categorized to (B) unclear-risk of bias, 7 studies were categorized to (C) low-risk of bias. All studies had no sample estimate and belonged to low quality of research. The basic situation of these studies was shown in Table II.

Effect estimates

All studies alleged active effects useful though many of the studies turned out to be effective, when analyzed by standard statistical skills using mean differences or odds ratios.

Treatment efficiency

The 4 included trials with treatment efficiency of adjuvant chemotherapy of MA in advanced breast cancer were reported, which included 280 patients. Meta-analysis showed, MA group and the control group were 101/135, 60/145. The heterogeneity test results p = 0.005, I^2 = 77%. We had chosen random effects model (REM). Z = 2.58, RR = 1.75, 95% CI [1.14~2.67], p<0.0010. The results show the treatment efficiency of adjuvant chemotherapy of advanced breast cancer in MA group was significantly higher than the control group (Figure 2).

The nutritional situation of the advanced breast cancer patient

The 4 included trials reported patient's nutritional situation of adjuvant chemotherapy of MA in advanced breast cancer was reported. Meta-analysis showed, p = 0.004, I^2 = 63%. We had chosen REM. Z = 4.22, RR = 2.10, 95% CI [1.49~2.97], p<0.0001. The results showed, MA can markedly improve the patient's nutritive condition in adjuvant chemotherapy of advanced breast cancer (Figure 3, Table III).

The bone marrow suppression situation of the patient

The 3 included trials with the bone marrow suppression situation of adjuvant chemotherapy of MA in advanced breast cancer were reported. Meta-analysis showed, p = 0.62, I^2 = 0%. We had chosen FEM. Z = 3.99, RR = 0.45, 95% CI [0.31~0.67], p<0.0001. The results showed, Summary, MA can markedly reduce the adverse reaction of the patient's bone marrow in adjuvant chemotherapy of advanced breast cancer (Figure 4, Table III).

The gastrointestinal reaction of the patient

The 3 included trials with patient's gastro-intestinal *reaction* of adjuvant chemotherapy of MA in advanced breast cancer were reported, which included 338 patients. Meta-analysis showed, MA group and the control group were 39/172, 68/166. The heterogeneity test results p = 0.60, I^2 = 0%. We had chosen FEM. Z = 3.44, RR = 0.57, 95%CI [0.41~0.79], p = 0.0006. The results show that MA can markedly reduce gastro-intestinal tract bad effect in adjuvant chemotherapy of advanced breast cancer (Figure 5).

Heterogeneity analysis

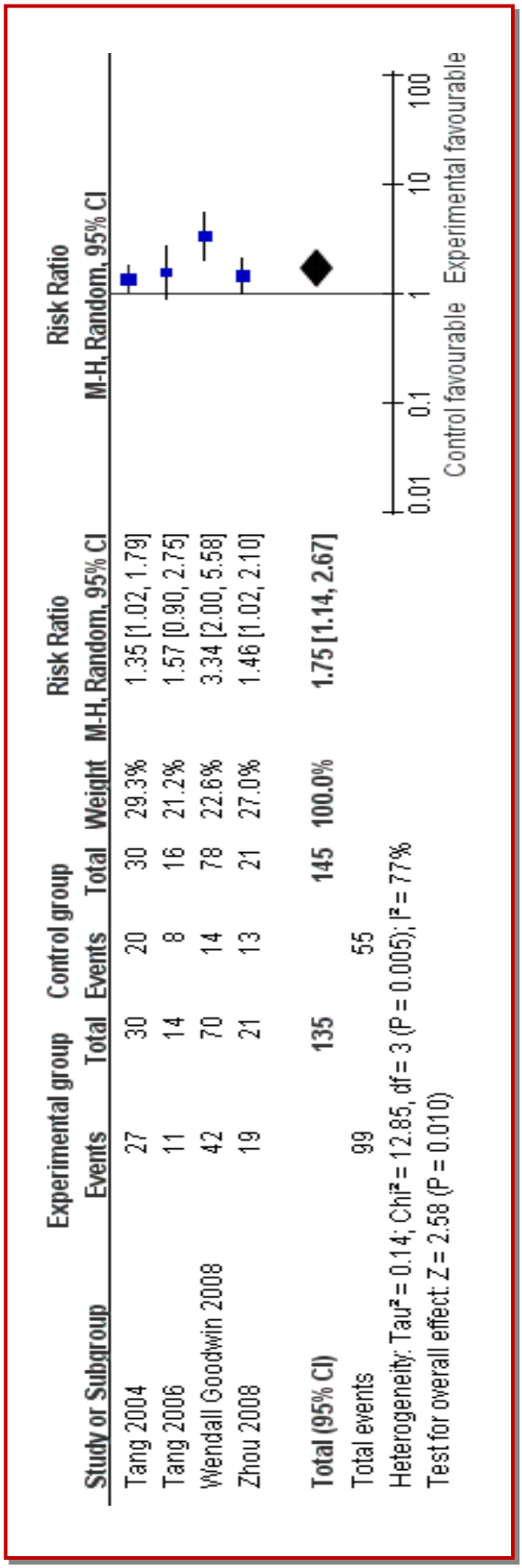

Figure 2: The treatment efficiency of adjuvant chemotherapy of advanced breast cancer

There were 8 indexes in this study. The homogeneity of 5 indexes (I^2 = 0%) was satisfactory, which develop *heterogeneity analysis*. The homogeneity of 1 index was moderate (25%<I^2<50%), which was selected FEM. The homogeneity of 1 index was high (I^2>50%), which was selected REM. The homogeneity of 1 index was too high (I^2>75%), which was descriptive analysis. We have analyzed the reason for the formation of heterogeneity, for example, KPS and gastrointestinal reaction. The measuring methods and technical means were very variable in the different years and different areas. In the meantime, the measuring time of many researches was big variable too. Homogeneity of study results was preferably, because the evaluation criterion of better homogeneity indexes was more objective.

The result of sensitivity analysis

In the 8 included trials, 2 pieces reported 7 loss of patients. The sensitivity analysis showed that with low quality trials precluded, the summary RR and 95% CIs for above effects were still similar to the results before they were eliminating (Table IV), which indicates that the results of our studies were believable and responsible.

Discussion

Comprehensive literature evaluation, clinical effects of adjuvant chemotherapy of MA in breast cancer, including: 1) treatment efficiency, p = 0.0010; 2) gain body weight, p<0.0001; 3) increased appetite, p = 0.001; 4) improve KPS, p = 0.06; 5) leucopenia, p = 0.02; 6) thrombocytopenia, p = 0.02; 7) hemoglobin, p = 0.01; and 8) gastrointestinal reaction of the patient, p = 0.0006. MA significantly increased treatment efficiency, markedly improve the patient's nutritional situation, reduce the adverse reaction of the patient's bone marrow and gastrointestinal tract in adjuvant chemotherapy of advanced breast cancer, p<0.001.

TNBC has an aggressive clinical phenotype with early brain and other distant metastases and a poor prognosis (Lin et al., 2012). MA, a semisynthetic progestin, is among the most commonly used, especially in the United States, while in European countries the drug has not yet gained widespread acceptance. Its efficacy has been documented in several studies which suggested that postmenopausal patients, treatment with this agent can expected to yield about 20-30% objective responses. Clinical studies found that MA can improve appetite, increase food intake, promoted protein and fat synthesis of adjuvant chemotherapy in advanced breast cancer patients (Jang et al., 2011; Lara-Medina et al., 2011). MA has a certain degree of protection function of bone marrow and direct treatment of cancer role. *In vitro* experiments showed that MA can inhibit mitosis and activation of stem cell, these cells hold in the G0

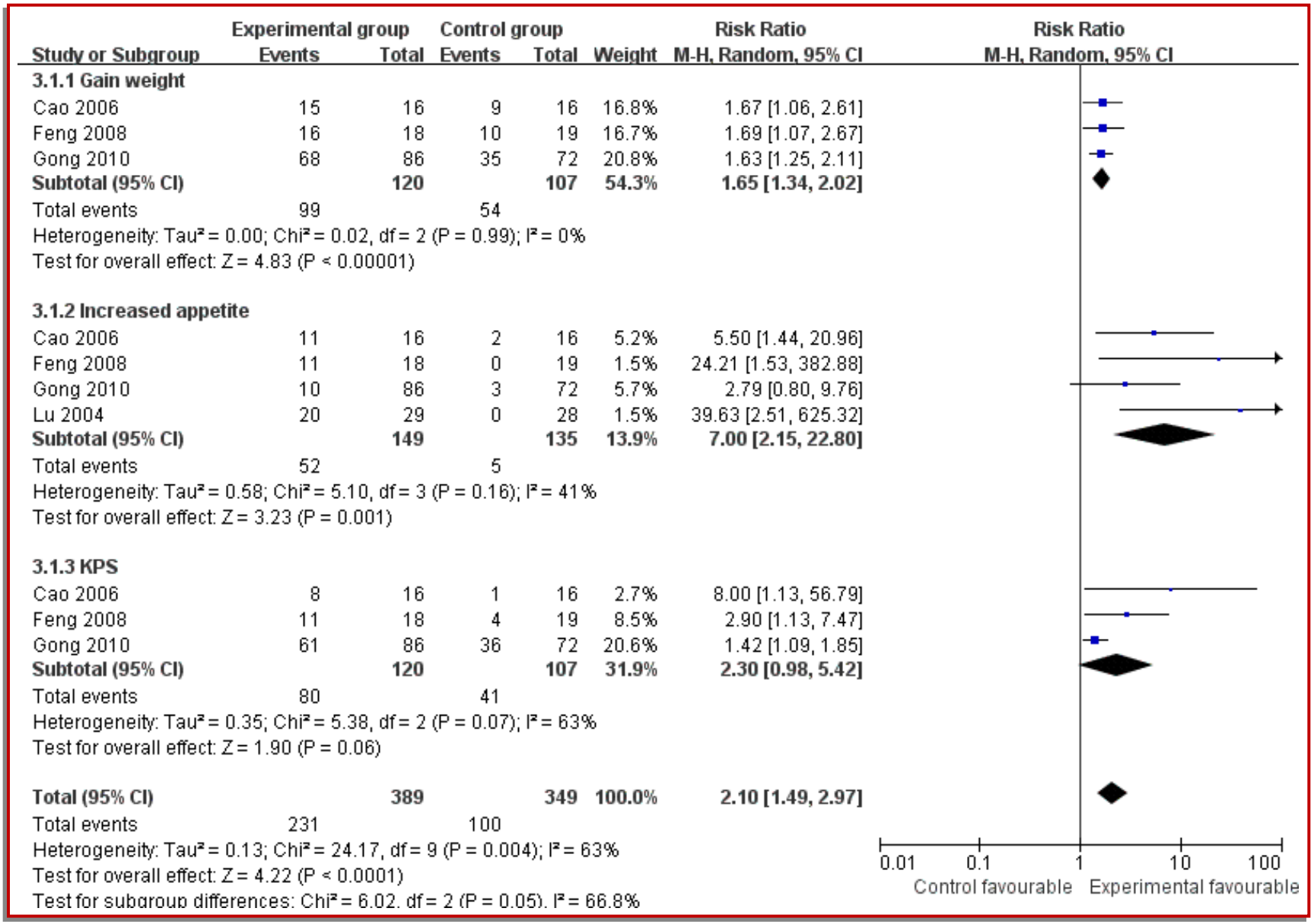

Figure 3: The nutritional situation of the advanced breast cancer patient

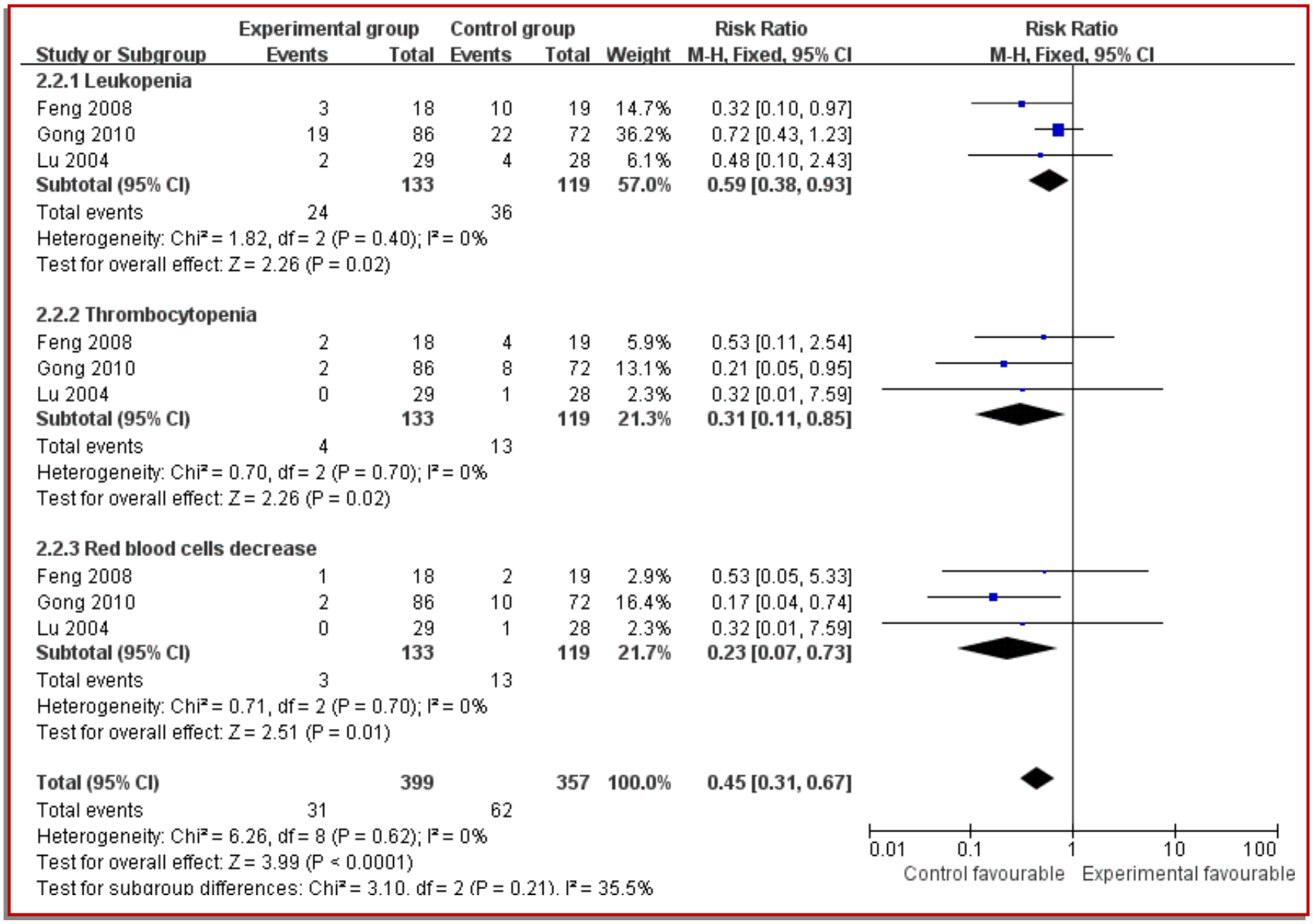

Figure 4: The bone marrow suppression situation of the patient

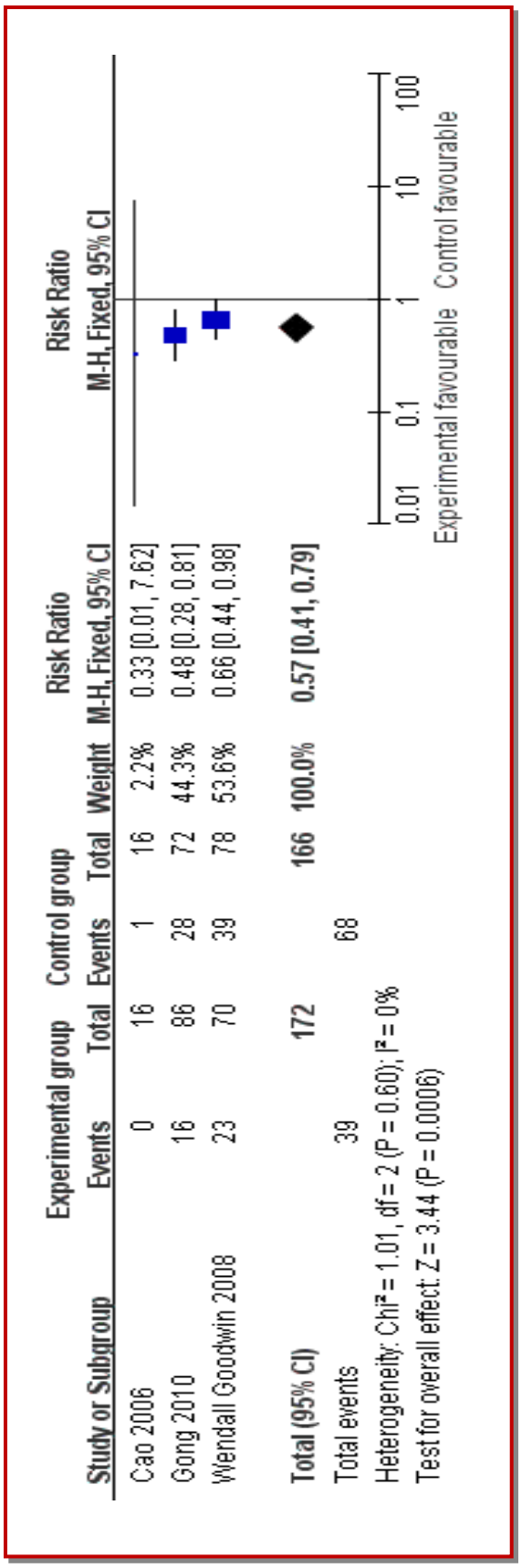

Figure 5: The gastrointestinal reaction of the patient

phase. Thus, MA can maintain a normal number of neutrophile granulocyte in peripheral blood, ensure the normal conduct of chemotherapy, help to maintain the continuity of chemotherapy and improve tolerance to chemotherapy of patients (Licchetta et al., 2010). In summary, MA is a chemotherapy adjuvant drugs, can improve the nutritional status of patients, reduce the complications of chemotherapy and improve chemotherapy in advanced breast cancer. As a result, MA has great clinical application value.

In summary, 2 studies (25%) described the random method and process in 8 RCT, the other experiments mention "Random". None reported distribution, hiding scheme and double-blind method. 2 studies (25%) reported loss of cases and confessed exit reason, the dropout rate from 8.1 to 23.7%. Randomized reported rate of RCT was 48.9% in domestic core journals (Mills et al., 2005) and 48% abroad (Moher et al., 2012). The improper use of random method/pseudo-random caused selective bias and great impact of the test results. This is the inadequacies of the study. At the same time, all literature reported pathological grading and staging of patients, treatment programs etc. The results showed that baseline characteristics between experimental and control groups was basically consistent, $p>0.05$.

These 8 trials literature were included 610 cases including 307 cases of MA group and 303 cases of the control group. These studies were the largest number of 194 cases, at least 28 cases. The average number of 38.4 cases of MA group and the average number of 37.9 cases of the control group. 2 studies (25%) were study population ≥100 cases. Sample size is too small in all trials, which reduced the accuracy of the test results and increased incidence of type II error. This is the inadequacies of the study. At same time, an important factor was the low-quality randomized controlled trials.

The next trials will furnish message about standardization including specific regimen, duration and quality control of treatment. Our study suggested that the future studies will avoid low-level redundant and design experiment of multicenter, large sample randomized controlled double-blind trial. Experimental methodology will use CONSORT 2010 standards to report experiment of fully random, fully implement allocation concealment and loss and exit of patients (Ciliberto et al., 2012). We wished that the more negative results of clinical trials will be report. We hoped that these advancing studies will be report in the future. High-qualified proof will come out afford clinical evidence for adjuvant chemotherapy of MA on advanced breast cancer.

Financial Support

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Table I

Baseline characteristics of the eligible trials

References	Randomization	Allocation concealment	The form of double-blind	Loss of imitation and exit cases	ITT analysis	Base-line	Cochrane Score
Lu and Ding, 2004	Unclear	Unclear	Unclear	Clear	Unclear	Yes	C
Feng, 2008	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	C
Gong et al., 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	C
Tang and Luo, 2004	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	C
Cao and Jiao, 2006	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	C
Tang and Duan, 2006	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	C
Zhou et al., 2008	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	C
Goodwin et al., 2008	Registered	Unclear	Unclear	Clear	Unclear	Yes	B

Table II

Methodological quality scores

References	Sample size (Rx = C)	Age (yr, Rx=C)	Experimental intervention	Control inter-vention	Duration of treatments
Lu and Ding, 2004	29/28	47.6	Megestrol acetate (80 mg/d)	Placebo	6-13W
Feng, 2008	18/19	48/46	Megestrol acetate (160 mg/d) plus conventional chemotherapy	Conventional chemotherapy	1W
Gong et al., 2010	86/72	-	Megestrol acetate (160 mg/d) plus CEF	CEF	21D
Tang and Luo, 2004	30/30	52-62	Megestrol acetate (160 mg/d) plus CEF plus ondansetron (8 mg)	CEF plus on-dansetron (8 mg)	6 × 21 D
Cao and Jiao, 2006	16/16	38-67	Megestrol acetate (2 × 160 mg/d) plus Aspirin (50 mg)	Aspirin (50 mg)	2W
Tang and Duan, 2006	16/14	35-62	Megestrol acetate (160 mg/d) plus pamidronate (60 mg/21 d plus MS Contin tablet (2 × 30 mg)	MS Contin tablet (2 × 30 mg)	>8W
Zhou et al., 2008	21/21	50.2	Megestrol acetate (250 mg) plus Zoledronic acid (4 mg/M)	Zoledronic acid (4 mg/M)	>6W Megestrol plus 3-4M Zoledronic acid
Goodwin et al., 2008	93/101	38-78/35-82	Megestrol acetate (160 mg)	Placebo	3 M

Financial Support

Self-funded

Conflict of Interest

Authors declare no conflict of interest

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Table III

The nutritional situation and bone marrow suppression situation of the patient

Adverse reactions	MA group	Control group	RR [95% CI]	p value
Weight gain	99/120	54/107	1.65 [1.34,2.02]	p<0.00001
Increased appetite	52/149	5/135	7.00 [2.15,22.08]	p=0.001
KPS	80/120	41/107	2.30 [0.98,5.42]	p=0.06
Leucopenia	24/133	36/119	0.59 [0.38,0.93]	p=0.02
Thrombocytopenia	4/133	13/119.	0.31 [0.11,0.85]	p=0.02
Hemoglobin	3/133	13/119	0.23 [0.07,0.73]	p=0.01

Table IV

Sensitivity analysis

References	Item	Excluding ago RR [95% CI]	After Excluding RR [95% CI]	p value	Statistical significance
Lu and Ding, 2004	Increased appetite	7.00 [2.15,22.08]	7.02 [2.14,23.31]	p=0.001	No difference
Lu and Ding, 2004	Leucopenia	0.59 [0.38,0.93]	0.59 [0.38,0.94]	p=0.02	No difference
Lu and Ding, 2004	Thrombocytopenia	0.31 [0.11,0.85]	0.31 [0.11,0.86]	p=0.02	No difference
Lu and Ding, 2004	Hemoglobin	0.23 [0.07,0.73]	0.23 [0.07,0.72]	p=0.01	No difference
Goodwin et al., 2008	Treatment efficiency	1.75 [1.14,2.67]	1.75 [1.14,2.67]	p=0.010	No difference
Goodwin et al., 2008	Gastrointestinal reactions	0.57 [0.41,0.79]	0.57 [0.41,0.79]	p=0.0006	No difference

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