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SPECIAL FEATURE

Meta-analyses from the Japanese Breast Cancer Society: clinical practice guidelines for breast cancer

Risks and benefits of bevacizumab combined with chemotherapy for advanced or metastatic breast cancer: a meta-analysis of randomized controlled trials

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Abstract

Background The combination of bevacizumab and chemotherapy has greatly improved progression-free survival (PFS) and objective response rate (ORR) in HER2-negative metastatic breast cancer in many pivotal trials. However, risk–benefit balance related to bevacizumab addition could not be confirmed because of a lack of overall survival (OS) improvement. Therefore, we conducted a meta-analysis to evaluate multiple endpoints pertaining to bevacizumab use in metastatic breast cancer (MBC) treatment.

Methods We searched PubMed and Cochrane Library databases and included seven studies in our meta-analysis in which bevacizumab combined with chemotherapy was compared with chemotherapy alone in MBC.

Results Compared to the chemotherapy-alone group, the combination treatment group had significantly improved PFS [hazard ratio (HR): 0.72, 95% CI 0.67–0.77, $P < 0.00001$]. Furthermore, bevacizumab addition did not significantly improve OS (HR: 0.95, 95% CI 0.87–1.03, $P = 0.22$). The ORRs in the combination treatment and chemotherapy-alone groups were 42% and 32%, respectively (HR: 1.47, 95% CI 1.26–1.71, $P < 0.00001$). Bevacizumab addition significantly increased the incidence of therapy discontinuation due to toxicity and toxicity of grade 3 or higher (HR: 1.43, 95% CI 1.06–1.93, $P = 0.02$, HR: 1.43; 95% CI 1.25–1.64, $P < 0.00001$, respectively). A qualitative systematic review of two randomized controlled trials indicated no significant differences in quality of life from baseline between the two groups.

Conclusions Compared to chemotherapy alone, bevacizumab combined with chemotherapy significantly improved PFS in the HER2-negative MBC patients. However, the lack of a significant OS difference remained.

Keywords Metastatic breast cancer · Bevacizumab · Meta-analysis · Systematic review

Introduction

Metastatic breast cancer (MBC) is unlikely to be cured, however, survival improvements have been demonstrated with administrating newer systemic therapies in clinics [1, 2]. Currently, the median overall survival of patients with MBC is approximately 3 years, with the range being a few months to many years [3]. Most patients with MBC receive systemic therapy consisting of chemotherapy, endocrine therapy, molecular targeted therapies, and supportive care [4]. The therapeutic strategy is designed to depend on clinical characteristics, tumor biology, and patients' preferences, with the goal being a tailored approach.

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In e decade, targeting vascular endothelial growth factor (VEGF)-dependent tumor including agents that bind and inhibit VEGF, its ligands and VEGF receptors have been thought to be promising approaches. Bevacizumab is a humanized monoclonal antibody that blocks the binding of all VEGF-A isoforms to VEGF receptors. Data from the preclinical studies provided a strong rationale expected for the clinical development of bevacizumab for the treatment of solid tumors including breast cancer [5]. However, conflicting results have been reported for the use of bevacizumab in the treatment of patients with advanced cancers.

With regard to breast cancer, the results of some pivotal trials have been thought to be disappointing in terms of overall survival (OS) [6–12]. On the other hand, the clinical value of bevacizumab remains because of its promising improvements in terms of progression-free survival (PFS) and objective response rate (ORR) [6–12]. Previously performed systematic reviews that estimated the efficacy of VEGF-targeting therapies for MBC have reported the same results as that of each clinical trial [13]. To explore the magnitude of the efficacy and tolerability of adding bevacizumab to chemotherapy for HER2-negative MBC, we conducted a meta-analysis with carefully selected randomized controlled trials (RCTs).

Materials and methods

Strategy of literature search

Our meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria [14]. We searched PubMed and Cochrane Library databases to identify original articles of RCTs in which bevacizumab plus chemotherapy was compared with chemotherapy alone for breast cancer treatment. The terms breast neoplasms, drug therapy, bevacizumab, metastatic breast cancer, and advanced breast cancer were used as keywords for the search. The latest search was performed on February 2, 2017.

Screening of original articles

We identified 183 abstracts from PubMed and 53 from the Cochrane Library database. To avoid missing relevant studies that might not be properly indexed in electronic databases, we also performed a manual search and screened 245 abstracts. We excluded 232 inappropriate abstracts and reviewed the complete articles for the remaining 13 abstracts. Finally, seven original articles were selected for our meta-analysis (Fig. 1).

Outcomes and significance level

We considered specific outcomes and significance levels to evaluate the efficacy and safety of bevacizumab combined with chemotherapy. OS was considered as the most important outcome. PFS, ORR, quality of life (QOL), toxicity of grade 3 or higher, and the rate of therapy discontinuation were considered as important outcomes. Regarding PFS, ORR, and the rate of therapy discontinuation, a quantitative systematic review was performed for the results of eight RCTs in seven articles. Because of lack of data, OS or toxicity of grade 3 or higher was evaluated in the quantitative systematic review of seven or five RCTs, respectively. QOL was qualitatively evaluated in two original articles.

Statistical analysis

We performed a systematic assessment using RevMan Version 5.3 software (https://community.cochrane.org/help/tools-and-software/revman-5, Cochrane Community). The analyses were performed using a fixed-effects model or a random-effects model depending on the heterogeneity of the results among the eligible trials. We used the I2 statistic to test for heterogeneity and visually inspected forest plots. A funnel plot was generated to evaluate publication bias. All *P* values were two-sided and the type I error rate was set at 0.05.

Results

Evaluation of the risk of bias

The Cochrane risk-of-bias assessment was performed to evaluate the quality of the included studies. We judged the six trials as having an unclear risk of selection bias due to the inadequate procedure of random sequence generation. Because of an open-label trial design, we assessed three trials as having a high risk of performance bias. In summary, six trials were considered to have an unclear risk of bias and two trials as a low risk of bias (Fig. 2).

Characteristics of the studies included

Detailed characteristics of the studies included are shown in Table 1. Seven trials were categorized as phase III and one as phase II. A total of 4526 advanced breast cancer or MBC patients were included, of which 2722 were in the bevacizumab combined with chemotherapy arm and 1804 in the chemotherapy-alone arm. Five trials were available for the comparison of first-line chemotherapy with

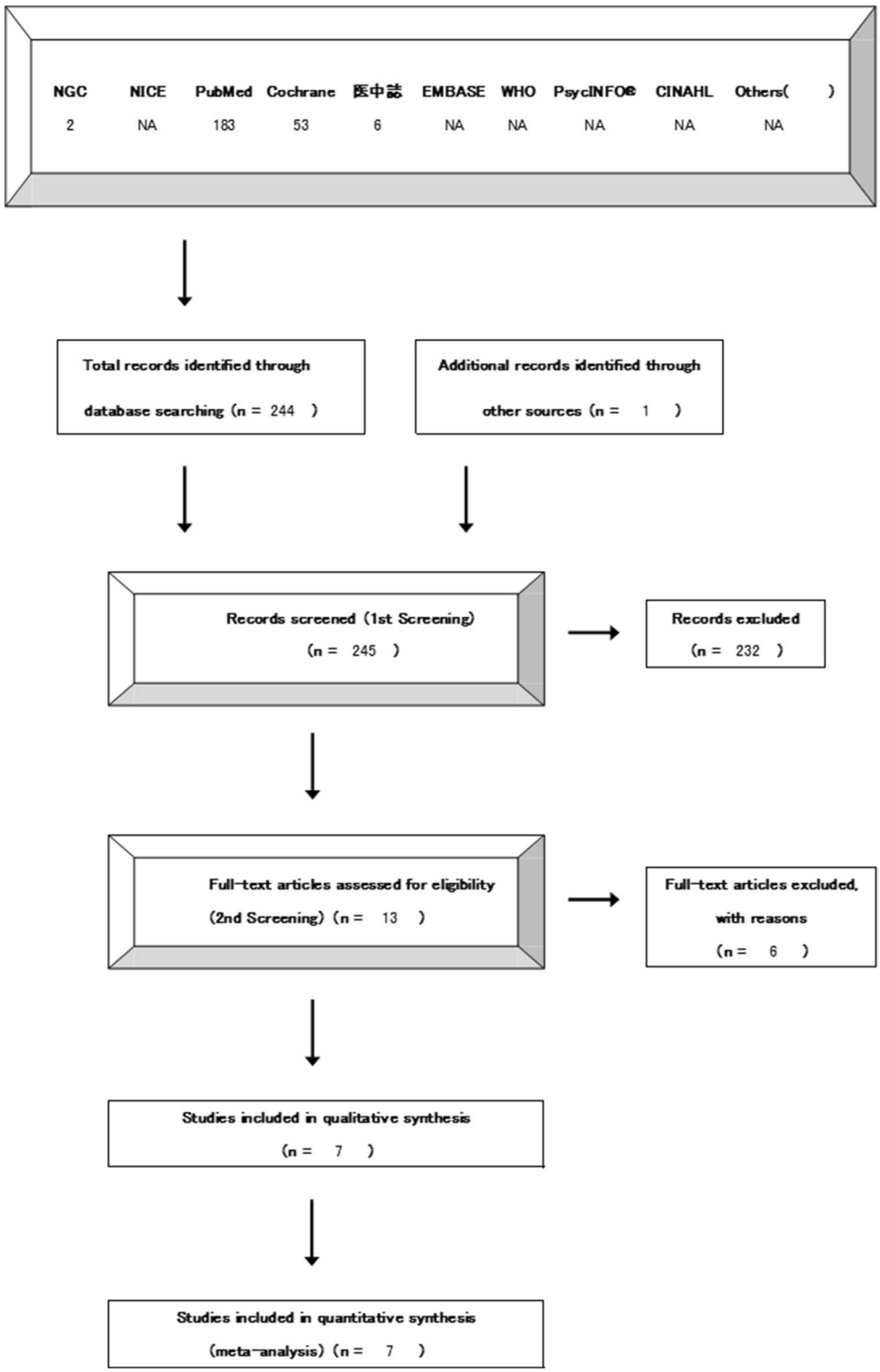

Fig. 1 Article screening diagram (e.g., progression-free survival)

or without bevacizumab, and two trials were available for the comparison of second-line chemotherapy with or without bevacizumab. In the AVF2119g trial, bevacizumab was administered as part of the first- to the sixth-line treatment.

Effects of interventions

The analysis of PFS in all of the eight included trials revealed that PFS significantly improved in the bevacizumab

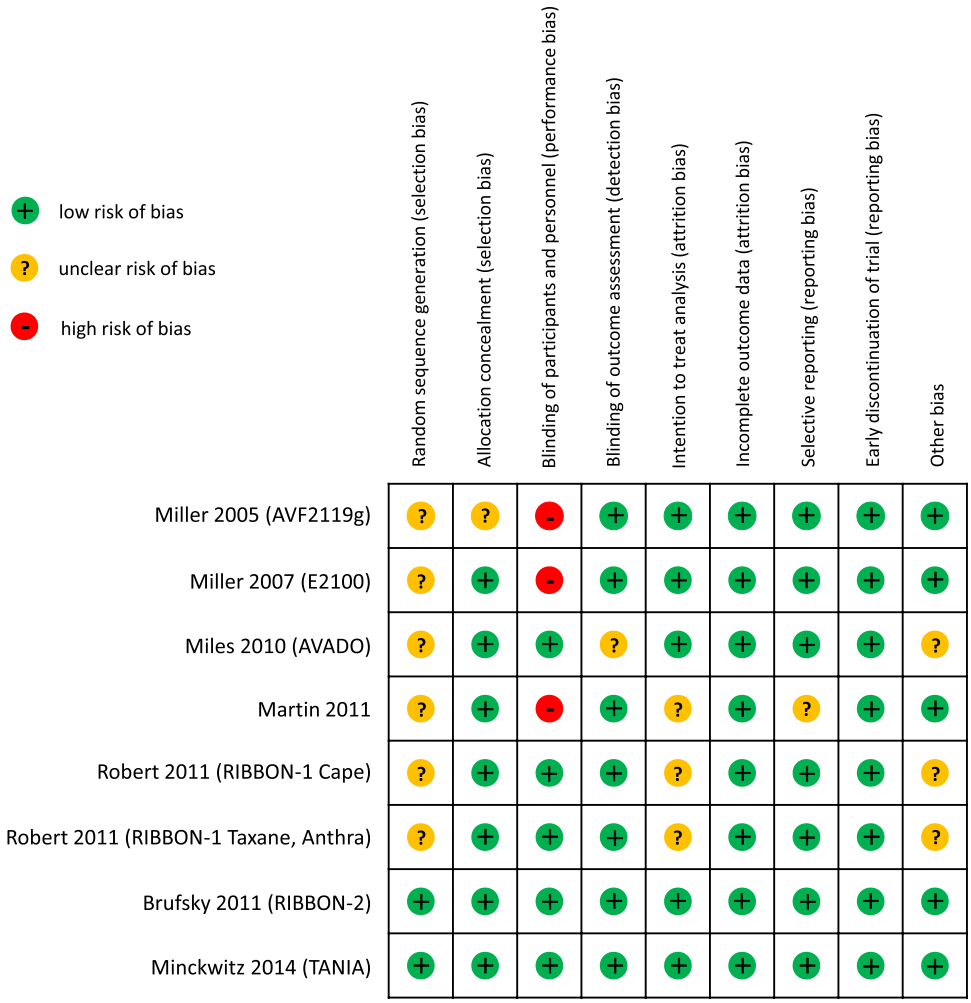

Fig. 2 Risk of bias summary (e.g., progression-free survival)

Table 1 Characteristics of the included studies

Study	Phase	Tx line	Pts population	No. of pts (Exp vs Con)	Treatment (Exp vs Con)	Primary endpoint
Miller et al. [6] (AVF2119g)	III	1st–6th	All subtypes	232 vs 230	Bevacizumab + capecitabine vs capecitabine	PFS
Miller et al. [7] (E2100)	III	1st	HER2 negative	368 vs 354	Bevacizumab + paclitaxel vs paclitaxel	PFS
Miles et al. [8] (AVADO)	III	1st	HER2 negative	495 vs 241	Bevacizumab + docetaxel vs docetaxel	PFS
Martin et al. [10]	II	1st	HER2 negative	97 vs 94	Bevacizumab + paclitaxel vs paclitaxel	ORR
Robert et al. [11] (RIBBON-1 Cape cohort)	III	1st	HER2 negative	409 vs 206	Bevacizumab + capecitabine vs capecitabine	PFS
Robert et al. [11] (RIBBON-1 A/T cohort)	III	1st	HER2 negative	415 vs 207	Bevacizumab + A/T vs A/T	PFS
Brufsky et al. [9] (RIBBON-2)	III	2nd	HER2 negative	459 vs 225	Bevacizumab + chemotherapy vs chemotherapy	PFS
von Minckwitz et al. [12] (TANIA)	III	2nd	HER2 negative	247 vs 247	Bevacizumab + chemotherapy vs chemotherapy	PFS

Tx therapy, *Pts* patients, *Exp* experimental, *Con* control, *HER2* human epidermal growth factor receptor 2, *PFS* progression-free survival, *ORR* objective response rate, *A/T* anthracycline/taxane

combined with chemotherapy group compared to that in the chemotherapy-alone group [hazard ratio (HR): 0.72, 95% CI 0.67–0.77, $P < 0.00001$] (Fig. 3). We found significant heterogeneity between the two groups, with I2 = 61% ($P = 0.01$) in the overall analysis. However, we applied the result to the PFS analysis, because the values of HR in all the eight trials were consistently less than 1.0 as well as because of the findings of the visual inspection of forest plots. In the OS analysis, seven eligible trials were including barring the trial reported by Martin et al. [10]. The overall analysis demonstrated no significant improvement in OS in the bevacizumab combined with chemotherapy group compared to the chemotherapy-alone group (HR = 0.95, 95% CI 0.87–1.03, $P = 0.22$) (Fig. 4). ORR was 42% in the bevacizumab combined with chemotherapy group versus 32% in the chemotherapy-alone group (HR = 1.47, 95% CI 1.26–1.71, $P < 0.00001$) (Fig. 5). The result indicated a significant benefit afforded by bevacizumab addition. There was significant heterogeneity in ORR between the two groups, with I2 = 57% ($P = 0.02$). Nevertheless, a random-effects model was selected. Finally, we applied the result to the ORR analysis, because the values of HR in all the eight trials were consistently greater than 1.0 as well as because of the findings of the visual inspection of forest plots.

Toxicity of interventions

We evaluated the toxicities caused by bevacizumab combined with chemotherapy focusing on the rate of therapy discontinuation due to toxicity or toxicity of grade 3 or higher,

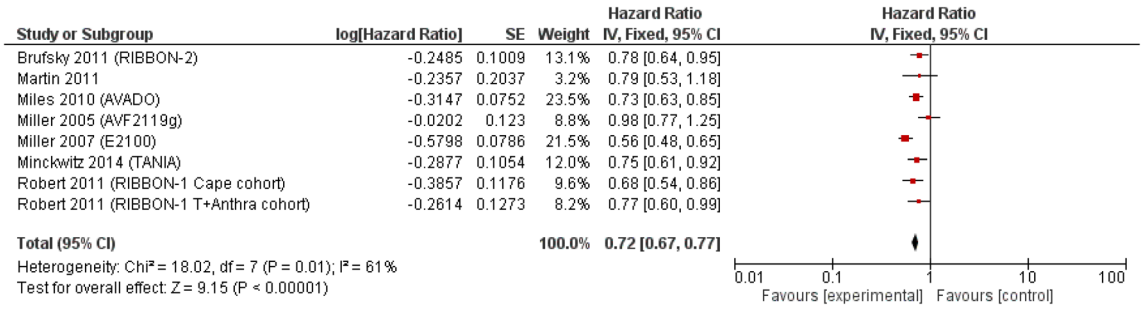

Fig. 3 Forest plot of progression-free survival comparison

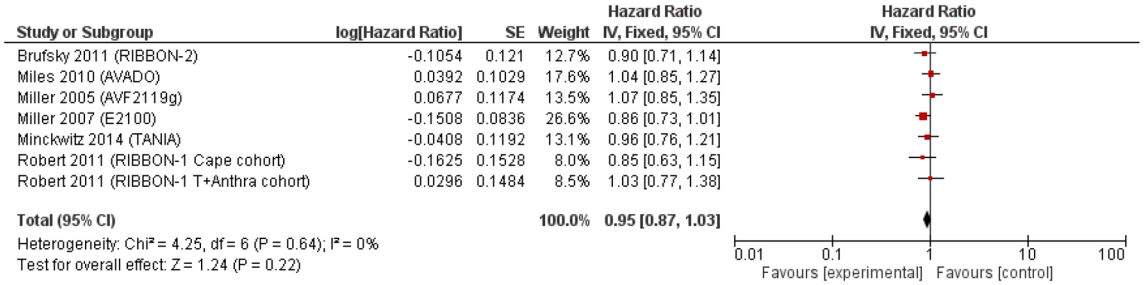

Fig. 4 Forest plot of overall survival comparison

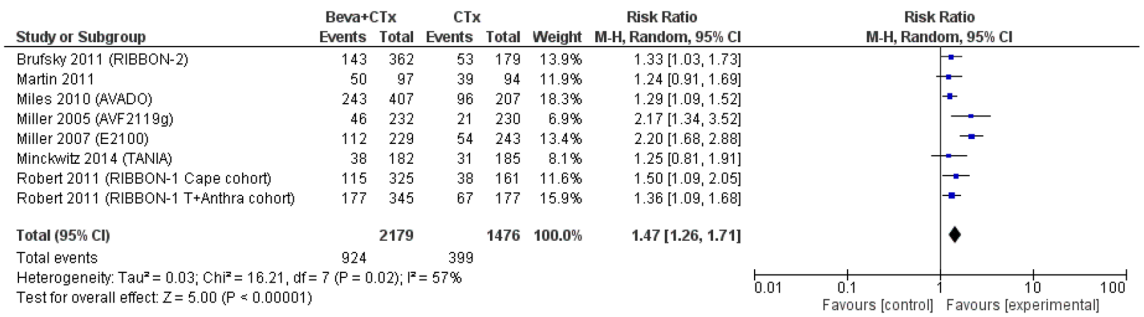

Fig. 5 Forest plot of objective response rate comparison

compared with the chemotherapy-alone group. The incidence of therapy discontinuation due to toxicity significantly increased in the bevacizumab combined with chemotherapy group compared to that in the chemotherapy-alone group (HR = 1.43, 95% CI 1.06–1.93, $P = 0.02$) (Fig. 6). Significant heterogeneity exists in this endpoint between the two groups, with I2 = 70% ($P = 0.002$); nevertheless, a random-effects model was selected. We could obtain detailed data for toxicity grade from five trials. The incidence of toxicity of grade 3 or higher significantly increased in the bevacizumab combined with chemotherapy group compared to that in the chemotherapy-alone group (HR = 1.43, 95% CI 1.25–1.64, $P < 0.00001$) (Fig. 7). There was no significant heterogeneity in the rates of toxicity of grade 3 or higher between the two groups, with I2 = 39% ($P = 0.16$).

QOL assessment

Data of QOL assessment were published in two trials. Miller et al. [6] (AVF2119g) indicated that the time to deterioration in QOL did not differ between the treatment groups (2.86 versus 2.92 months; $P = 0.633$) [6]. In the 2007 trial conducted by Miller (E2100), QOL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire at three points and no significant differences in the mean change in scores from baseline for the FACT-B were observed [7]. In the other trials, QOL was not listed with the study endpoints or the final result has not been published.

Discussion

Our meta-analysis of carefully selected eight randomized clinical trials demonstrated that bevacizumab combined with chemotherapy significantly improved PFS and ORR in patients with MBC or advanced breast cancer, compared to the finding associated with chemotherapy alone. However, improvement of OS due to bevacizumab administration could not be proven as it is the same as the results of previously reported meta-analyses [13]. The US Food and Drug Administration withdrew the approval for the use of bevacizumab in combination with paclitaxel for MBC in 2011, which is the only reason an improvement in OS could not be demonstrated in several clinical trials. In contrast, most therapeutic drugs for breast cancer have been approved despite there being no proven associated OS improvement. Currently, the combination therapy remains approved in several countries including Japan.

Although OS is considered as the most reliable outcome, PFS has been widely used as an alternative endpoint to evaluate the potential benefit of an experimental therapy with an earlier follow-up time [15]. In a situation where survival after progression is relatively longer, such as that in the case of luminal-type breast cancer, the impact of an experimental therapy on OS weakens even if PFS improves [16].

Our meta-analysis demonstrated that the addition of bevacizumab to chemotherapy did not significantly

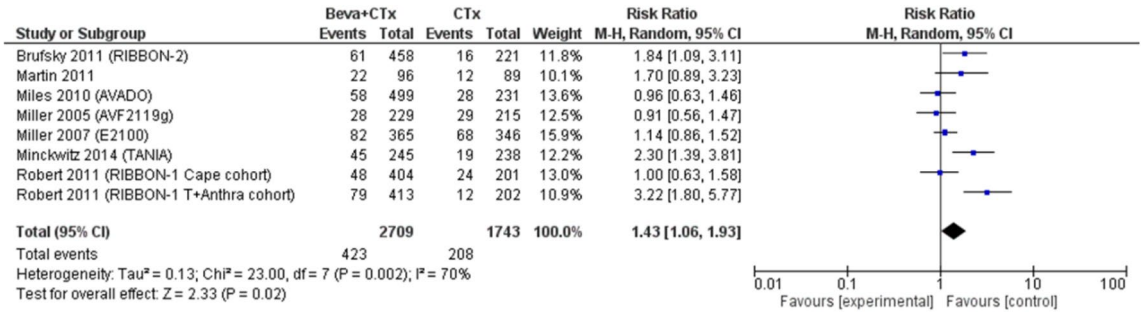

Fig. 6 Forest plot of therapy discontinuation due to toxicity comparison

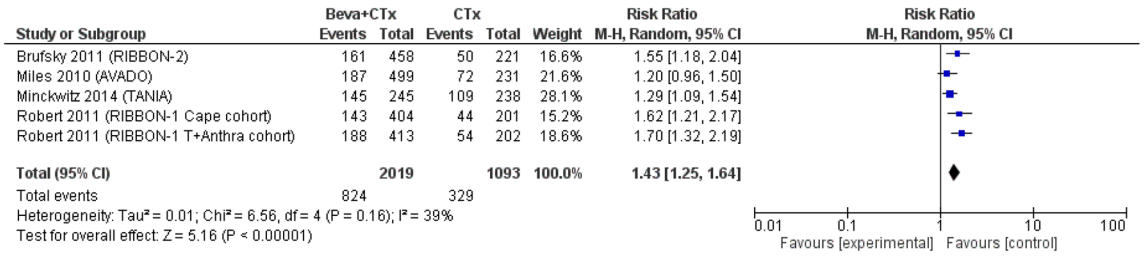

Fig. 7 Forest plot of grade 3 or higher toxicity comparison

prolong OS. The other reasons for this result can be omitted except for the before-mentioned discrepancy between PFS and OS. In almost all trials, the number of patients was statistically calculated for the evaluation of PFS as the primary endpoint. Therefore, these trials were not adequately powered to detect significance of OS in terms of statistical requirements. Many factors affect the final analysis of OS. Breast cancer patients who participated in the RCTs had usually received additional lines of treatment that consisted of endocrine therapy, chemotherapy, and molecular targeted therapy after discontinuing their assigned treatment. Moreover, in some RCTs, patients were allowed to receive crossover treatment with bevacizumab [11].

Some differences in patients' characteristics between real-world settings and clinical trial settings exist in terms of performance status, complications, tumor burden, and percentage of patients with symptomatic diseases such as dyspnea caused by pleuritis carcinomatosa or liver disfunction caused by multiple liver metastases. Real-world evidence is thought to be complementary data for describing the efficacy and safety of investigated drugs and important for bridging the gap between clinical trials and clinical practice. In the French Epidemiological Strategy and Medical Economics database of MBC patients, the efficacy of first-line paclitaxel with or without bevacizumab was examined using prospectively collected patient data. Results from HER2-negative breast cancer patients, 2127 of whom received paclitaxel and bevacizumab and 1299 who received paclitaxel alone showed that adjusted OS, determined by propensity score matching using some prognostic factors, was significantly superior in the paclitaxel and bevacizumab combination group compared with that in the paclitaxel-alone group (HR: 0.67, 95% CI 0.60–0.75; median survival time 27.7 vs 19.8 months) [17]. Adjusted PFS was also longer in the combination group (HR 0.74, 95% CI 0.67–0.81; 8.1 vs 6.4 months) and similar to previously reported results of RCTs [17]. This observational study, with a larger sample size and longer follow-up than those in previous RCTs, could provide evidence to demonstrate treatment value complementary to evidence obtained from strictly designed RCTs with specific inclusion criteria. Indeed, we need to pay attention to both results of RCTs and real-world evidence.

Adding bevacizumab to chemotherapy increased the rate of therapy discontinuation due to toxicity and the rate of toxicity of grade 3 or higher, compared to that associated with chemotherapy alone. However, most toxicities related to the addition of bevacizumab are considered to be manageable. In the setting of MBC, the rate of therapy discontinuation caused by adverse events tends to increase when the treatment period becomes longer by adding effective investigational drugs. In conclusion, our meta-analysis indicates that compared with chemotherapy alone, bevacizumab combined with chemotherapy significantly improved PFS in HER2-negative MBC patients. However, bevacizumab administration was associated with therapy discontinuation due to toxicity of grade 3 or higher.

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Compliance with ethical standards

Conflict of interest Minoru Miyashita reports personal fees from Chugai, personal fees from Lilly, personal fees from Eisai, personal fees from AstraZeneca, personal fees from Pfizer, personal fees from Taiho, personal fees from Daiichi Sankyo, non-financial support from Kyowa Hakko Kirin, outside the submitted work. Masaya Hattori reports personal fees from Chugai Pharmaceutical, personal fees from Eli Lilly Japan, personal fees from Novartis Pharma, personal fees from AstraZeneca, personal fees from Pfizer Japan, personal fees from Eisai, outside the submitted work. Toshimi Takano reports grants and personal fees from Daiichi-Sankyo, grants and personal fees from Kyowa Hakko Kirin, grants and personal fees from Eisai, personal fees from Pfizer, personal fees from Eli Lilly, grants from Ono, grants from MSD, grants from Merck Serono, grants from Taiho, grants from Novartis, grants from Chugai, outside the submitted work. Tatsuya Toyama reports grants and personal fees from Chugai, grants and personal fees from Novartis, grants and personal fees from Esai, grants and personal fees from AstraZeneca, personal fees from Lilly, personal fees from Kyowa Hakko Kirin, personal fees from Taiho, personal fees from Daiichi Sankyo, personal fees from Nippon Kayaku, personal fees from Pfizer, personal fees from Takeda. Hiroji Iwata Dr. Iwata reports grants and personal fees from Chigai, grants and personal fees from Novartis, grants from MSD, grants and personal fees from Lilly, personal fees from AstraZeneca, personal fees from Daiichi Sankyo, from Kyowa Hakko Kirin, from Pfizer, outside the submitted work.

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