

Effect of antitumor treatments on triple-negative breast cancer patients

A PRISMA-compliant network meta-analysis of randomized controlled trials

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Abstract

Background: Triple-negative breast cancer (TNBC) lacks the expression of the estrogen receptor, progesterone receptor, and receptor tyrosine-protein kinase erbB-2 (HER2/neu), which renders hormone-related endocrine and targeted therapy essentially futile.

Objective: We performed a meta-analysis to assess the effects of antitumor regimens in the treatment of TNBC patients.

Methods: We searched electronic databases, including PubMed, Embase, and the Cochrane Library, through January 2017 using the following keywords: “triple negative breast cancer,” “TNBC,” and “random*” without language restrictions. The major outcome in the present analysis was the overall response rate (ORR), and the secondary outcomes were progression-free survival (PFS) and overall survival (OS). A network meta-analysis and multilevel mixed-effects logistic regression were used to compare antitumor regimens.

Results: We included 35 articles assessing a total of 8476 TNBC patients in our systematic review. The regimen of Bevacizumab, Carboplatin, and Paclitaxel (78.2%) was the most likely to improve the ORR in TNBC patients, followed by EndoTAG-1 and Paclitaxel (69.7%), Carboplatin and Paclitaxel (65.0%), and Bevacizumab and Paclitaxel (61.8%). In the patients without metastasis, the regimen of Bevacizumab, Carboplatin, and Paclitaxel (74.9%) remained the most likely to improve the ORR. We could not analyze the results for patients with metastasis or outcomes of PFS and OS because no >4 regimens formed a network. In the regression analysis, Bevacizumab (odds ratio [OR], 1.71; 95% confidence interval [CI], 1.43–2.05; $P < .001$) and Carboplatin (OR, 2.07; 95% CI, 1.62–2.64; $P < .001$) correlated with superior ORR outcome, and Iniparib (OR, 1.51; 95% CI, 1.11–2.07; $P = .009$) correlated with superior OS outcome.

Conclusion: The regimen including Bevacizumab, Carboplatin, and Paclitaxel was the most likely to improve the ORR in TNBC patients and in advanced metastatic TNBC patients. The administration of Bevacizumab and Carboplatin provided greater benefit toward improved patient ORR.

Abbreviations: CI = confidence interval, OR = odds ratio, ORR = overall response rate, OS = overall survival, pCR = pathological complete response, PFS = progression-free survival, PRISMA = Preferred Reporting Items for Systematic Reviews, RCT = randomized controlled trial, RECIST = response evaluation criteria in solid tumors, SUCRA = surface under the cumulative ranking, TNBC = triple-negative breast cancer.

Keywords: chemotherapy, endocrine therapy, meta-analysis, targeted therapy, triple-negative breast cancer

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1. Introduction

Breast cancer is one of the most common malignant tumors in women. The World Health Organization International Cancer Research Center data from 2012 showed that there are approximately 1.2 million patients with breast cancer every year worldwide, including 540,000 new cases, and 500,000 patients die annually.^[1] Currently, breast cancer treatment includes surgery, radiotherapy, chemotherapy, endocrine therapy, and targeted therapy. Breast cancer is a type of immunogenic tumor that may express a variety of tumor-associated antigens. Targeted therapy and endocrine therapy are effective treatments, particularly for hormone receptor-positive patients.

Triple-negative breast cancer (TNBC) refers to breast cancer that does not express the genes for the estrogen receptor, progesterone receptor, or receptor tyrosine-protein kinase erbB-2 (HER2/neu). TNBC accounts for approximately 10% to 20% of breast cancer patients.^[2,3] The manifestation of TNBC is aggressive; it recurs and metastasizes readily and carries a worse

prognosis than other types of breast cancer. Owing to the negative expression of the estrogen and progesterone receptors, hormone-related endocrine and targeted therapies are essentially futile. Furthermore, the differing therapeutic effects of neoadjuvant chemotherapy between TNBC and non-TNBC in a previous study showed that TNBC patients had a higher pathological complete response (pCR) rate but a lower survival rate.^[4] Therefore, TNBC remains one of the most debated subtypes of breast cancer. Treatment guidelines for TNBC are rare, and the therapeutic strategy is also controversial.

Several meta-analyses have examined the treatment of TNBC. When associated with conventional chemotherapy, targeted therapy including Bevacizumab, Sorafenib, and Iniparib promoted gains in the progression-free survival (PFS) of TNBC patients.^[5] One study indicated that these novel neoadjuvant regimens achieved significant pCR improvement in TNBC patients, particularly a Carboplatin-containing or Bevacizumab-containing regimen.^[6] Platinum-based chemotherapy has been thoroughly researched and was shown to be more advantageous in TNBC patients than in non-TNBC patients.^[7] Platinum-based chemotherapy yielded a higher pCR than did nonplatinum-based therapy in TNBC patients.^[8,9]

All the aforementioned studies focused on the one type of chemotherapeutic drug combination that was analyzed for a TNBC treatment effect and disregarded the effect of other anti-tumor drug combinations. For example, studies of platinum-containing regimens versus nonplatinum-containing regimens disregarded the effects of other chemotherapeutic drug combinations as therapeutic regimens for TNBC treatment.^[7] Therefore, the treatment strategy for TNBC requires further elucidation. In this study, a comprehensive analysis of antitumor regimens for TNBC patients was performed to guide clinical treatment.

2. Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. Because our study was performed on the basis of previous studies, the ethical approval and informed consent were not required.

2.1. Data search strategy and selection criteria

A literature search was independently performed by 2 investigators using electronic databases including PubMed, Embase, and the Cochrane Library to identify articles published before January 2017, using the following search keywords: “triple negative breast cancer,” “TNBC,” and “random.*” The bibliographies of the obtained publications and the references of pertinent reviews were assessed to ensure that no relevant studies were unintentionally omitted. Studies were included in this meta-analysis when the following criteria were met: the study used a prospective randomized controlled trial (RCT) design; the study included TNBC patients; the study researched antitumor agents, including chemotherapy, endocrine therapy, and targeted therapy; the study clearly described the types of drugs used before and after patient randomization but not the investigators’ choice of drugs; the study groups used different types of antitumor agents; and one of the following outcomes was reported: overall response rate (ORR), PFS, and overall survival (OS). The exclusion criteria included the following: the study researched controversial antitumor drugs for suppressing tumor growth,

such as ubenimex, dendritic cells, AE37 polypeptide, and zoledronic acid; the study researched different applied strategies using the same types of agents; the study included radiotherapy or radiotherapy-related trials; and the study assessed undesired outcomes. Reviews, conference abstracts, case reports, and basic research studies were also excluded.

2.2. Data extraction and quality assessment

Two investigators independently extracted the following information from each eligible study: name of the first author, publication year, register ID, sample size, patient age, clinical stage, intervention treatment, control treatment, ratio of allocation, and follow-up. We assessed the methodological quality of the included trials using the Cochrane Collaboration tool. Studies were graded as having a “low risk,” “high risk,” or “unclear risk” of bias across the 7 specified domains.^[10]

We analyzed all the intervention-related antitumor agents applied before and after randomization, including combined agents that might affect patient outcomes. The 3 main outcomes were ORR, PFS, and OS. The major indicator of ORR was an objective response rate for patients with metastasis and a pCR for patients without metastasis (nonmetastatic patients). The objective response rate followed the Response Evaluation Criteria In Solid Tumors (RECIST) standard, which includes a complete response and partial response. A pCR was defined as the absence of invasive tumor in the final surgical breast tissue sample (stage yT0/ypTis) as recorded by the primary pathologist, irrespective of the nodal status (ypN0), according to the included study. Additionally, because of the different follow-up periods, we mainly analyzed the 5-year or median PFS or OS as reference indicators.

2.3. Statistical analysis

We performed a traditional paired meta-analysis using a random-effects model. All the outcome measures were dichotomous, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine the effect sizes. ORs are suitable for all designs with control groups with superior mathematical properties for complex statistical analysis. We also performed subgroup analyses according to the patients’ pathological stage. For research on treatment strategies, we used a random-effects network meta-analysis for mixed multiple antitumor treatment comparisons, which adopted a frequentist framework, and a contrast-based model to evaluate multiarm trials.^[11] The random-effects model fully preserves the within-trial randomized treatment comparison of each trial. The random-effects model allows the existence of other sources of variation in addition to sampling errors with greater robustness. Inconsistency between direct and indirect sources of evidence was assessed globally by comparison of the fit and parsimony of consistency and inconsistency models and locally by calculation of the difference between direct and indirect estimates in all closed loops in the network. To rank the treatment strategy for each outcome, we used the Surface Under the Cumulative Ranking (SUCRA) probabilities. Comparison-adjust funnel plots were used to determine whether small-study effects were present in our analysis. For the antitumor drug research, we attempted to use the multilevel mixed-effects logistic regression model for each antitumor drug^[11]; the components of different therapeutic strategies were evaluated as fixed-effects, whereas different studies were considered using random-effects. We performed the

analysis in STATA (version 14.0) with the “metan” and “meflogit” commands and the “network” command set.

3. Results

3.1. Literature search

In our study, 605 articles were identified after the duplicates were removed. A total of 514 articles were excluded after the titles and abstracts were screened. The full texts of the remaining 91 articles were assessed, and the following types of studies were removed: studies with a nonprospective RCT design (11), studies that did not analyze TNBC patients separately (10), studies that did not report the analyzed outcomes (10), studies in which the types of drugs used were unclear (10), duplicates (5), studies that did not investigate anti-tumor agents (4), studies in which the groups used the same type of drug with different strategies (3), radiotherapy-related studies (2), and basic research (1) (Fig. 1). Ultimately, 35 articles assessing a total of 8476 TNBC patients were included in our systematic review^[12-46] (Table 1).

The included studies were published between the years 2010 and 2016. Few studies were published before 2010 because of a lack of understanding of TNBC. Several studies did not assess TNBC patients independently; they evaluated a subgroup of breast cancer patients and reported the outcome of individual TNBC patients. None of the included studies restricted the age of

the studied populations; however, all patients were older than 18 years. The included studies confirmed the type of disease using pathological examinations. The clinical stage of the patients was grouped into 2 types: metastasis and nonmetastasis. The follow-up period was conducted immediately at the end of the studies and lasted for up to 15 years depending on the purpose of the study. Sixteen trials used a neoadjuvant approach for the nonmetastasis group, and the median follow-up in the neoadjuvant trials was approximately 1 month.

The antitumor agents analyzed in the meta-analysis, in alphabetical order, included Bevacizumab, Capecitabine, Carboplatin, Cetuximab, Cisplatin, Cyclophosphamide, Docetaxel, Doxorubicin, EndoTAG-1, Epirubicin, Eribulin, Everolimus, 5-Fluorouracil, Gefitinib, Gemcitabine, Iniparib, Ixabepilone, Methotrexate, Onartuzumab, Paclitaxel, Ramucirumab, Tamoxifen, Tigatuzumab, Veliparib, Vinorelbine, and YH16. To decrease disputes, controversial antitumor drugs for clearing or suppressing tumor growth, such as ubenimex, dendritic cells, AE37 polypeptide, and zoledronic acid, were not analyzed. However, some of those drugs may be confirmed to have antitumor effects in the future. All included studies had a prospective RCT design, few studies used a blind method, and most randomizations were not rigorous (Figure S1, Supplemental digital content 1, <http://links.lww.com/MD/B938>). However, the assessed outcomes were relatively objective; thus, the overall quality of the included studies was not ideal but was acceptable.

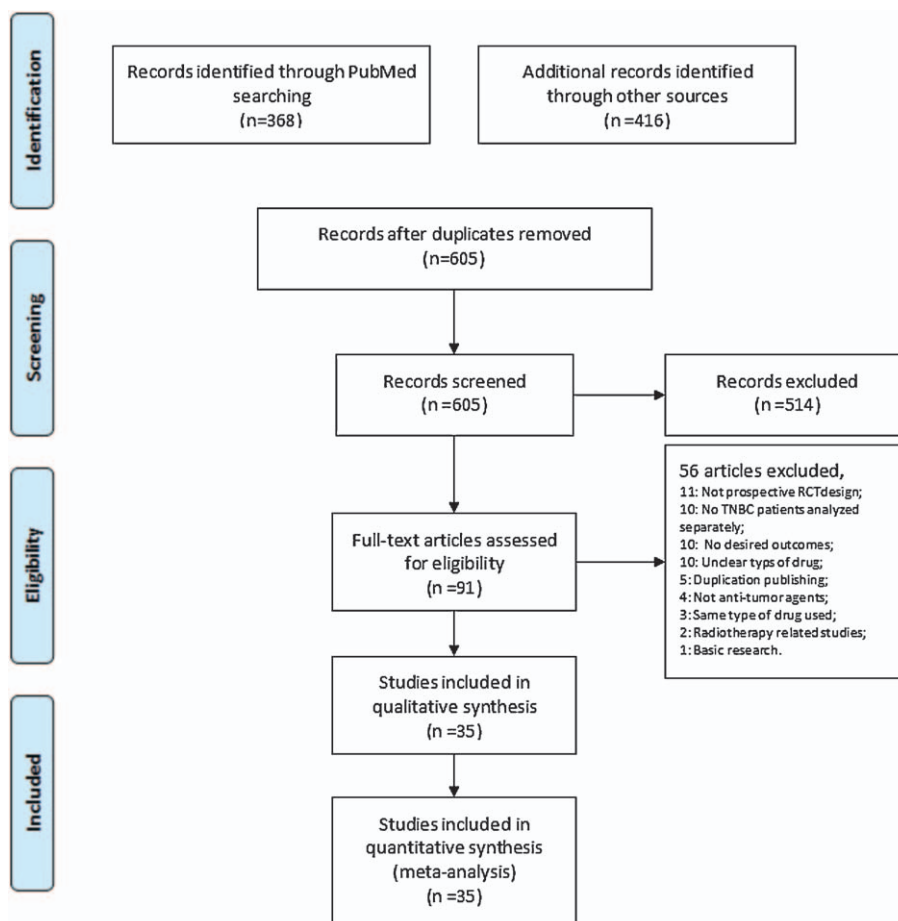


Figure 1. PRISMA flowchart illustrating the selection of studies included in the present analysis. The illustration shows the number of documents obtained from the database, the simple screening process, and the final number of studies included in the analysis.

Table 1

Characteristics of subjects in eligible studies.

Author	Year	Register ID	Sample size	Clinical stage	Therapeutic setting	Type of phase trial	Intervention	Control	Ratio of allocation	Follow-up
Yue et al ^[12]	2014	NA	82	II-III	Neoadjuvant	NA	Epirubicin, Paclitaxel	Carboplatin, Paclitaxel	44; 38	2 wk
Ying and Huang ^[13]	2012	NA	55	IV	Metastatic	NA	Gemcitabine, Cisplatin, YH16	Gemcitabine, Cisplatin	27; 28	15 mo
Yardley et al ^[14]	2016	NCT01427933	43	IV	Metastatic	II	Ramucicromab, Eribulin	Eribulin	21; 22	18 mo
Zhang et al ^[15]	2016	NCT01276769	91	II-III	Neoadjuvant	II	Paclitaxel, Carboplatin	Paclitaxel, Epirubicin	47; 44	55 (4–105) mo
Twelves et al ^[16]	2016	NCT00337103	284	IV	Metastatic	III	Eribulin	Capecitabine	150; 134	6 y
Mahleh et al ^[17]	2016	NCT00856492	67	II-III	Neoadjuvant	II	Bevacizumab, Nabpaclitaxel, Doxorubicin, Cyclophosphamide	Paclitaxel, Doxorubicin, Cyclophosphamide	32; 35	3–6 wk
Kumar et al ^[18]	2016	NCT01306032	45	IV	Metastatic	II	Veliparib, Cyclophosphamide	Cyclophosphamide	21; 18	12 mo
Hilborn et al ^[19]	2016	NCT01204125	87	I-II	Adjuvant	NA	Tamoxifen	Blank	47; 40	15 y
Lombart-Cussac et al ^[20]	2015	NCT01204125	141	II-III	Neoadjuvant	II	Paclitaxel	Paclitaxel, Iriniparib	47; 94	30 days
Dieras et al ^[21]	2015	NCT01186991	185	IV	Metastatic	II	Paclitaxel, Onartuzumab, Bevacizumab	Paclitaxel, Onartuzumab	63; 60; 62	24 mo
Sparano ^[22]	2015	NCT00004125	1025	II-III	Adjuvant	III	Paclitaxel, Bevacizumab	Doxorubicin, Cyclophosphamide, Docetaxel	535; 491	12.1 y
Hu et al ^[23]	2015	NCT01287624	240	IV	Metastatic	III	Cisplatin, Gemcitabine	Paclitaxel, Gemcitabine	118; 118	26.8 mo
Forero-Torres et al ^[24]	2015	NA	64	IV	Metastatic	II	Paclitaxel, Tigatuzumab	Paclitaxel	39; 21	40 mo
O'Shaughnessy et al ^[25]	2014	NCT00938652	519	IV	Metastatic	III	Gemcitabine, Carboplatin, Iriniparib	Gemcitabine, Carboplatin	261; 258	2 y
Brodowicz et al ^[26]	2014	NCT00600340	130	IV	Metastatic	III	Bevacizumab, Paclitaxel	Bevacizumab, Capecitabine	63; 67	3 y
Tredan et al ^[27]	2015	NCT00633464	79	IV	Metastatic	II	Ixabepilone, Cetuximab	Ixabepilone	39; 40	18 mo
Sikov et al ^[28]	2014	NCT00861705	443	II-III	Neoadjuvant	II	Paclitaxel	Paclitaxel, Bevacizumab	108; 110; 113; 112	NA
von Minckwitz et al ^[29]	2014	NCT01426880	315	II-III	Neoadjuvant	II	Paclitaxel, Carboplatin	Paclitaxel, Bevacizumab, Carboplatin	NA	21 days
Ando et al ^[30]	2014	NA	75	II-III	Neoadjuvant	II	Paclitaxel, Doxorubicin, Bevacizumab, Carboplatin	Paclitaxel, Doxorubicin, Bevacizumab	37; 38	12 mo
Gonzalez-Angulo et al ^[31]	2014	NCT00499603	62	II-III	Neoadjuvant	II	Paclitaxel, Everolimus, 5-fluorouracil, Epirubicin, Cyclophosphamide	Paclitaxel, 5-fluorouracil, Epirubicin, Cyclophosphamide	23; 27	24 wk
Awada et al ^[32]	2014	NCT00448305	140	IV	Metastatic	II	EndoTAG-1, Paclitaxel	EndoTAG-1	55; 57; 28	41 wk
Rocca et al ^[33]	2014	NA	156	I-III	Adjuvant	III	Epirubicin, Cyclophosphamide, Methotrexate, 5-fluorouracil	Cyclophosphamide, Methotrexate, 5-fluorouracil	NA	69 mo
Steger et al ^[34]	2014	NCT00309556	127	I-III	Neoadjuvant	III	Epirubicin, Docetaxel, Capecitabine	Epirubicin, Docetaxel	64; 63	Immediately

(continued)

Table 1
(continued).

Author	Year	Register ID	Sample size	Age*	Clinical stage	Therapeutic setting	Type of phase trial	Intervention	Control	Ratio of allocation	Follow-up
Gerber et al ^[35]	2013		678	48 (21–75)	I–III	Neoadjuvant	NA	Epirubicin, Cyclophosphamide, Docetaxel, Bevacizumab	Epirubicin, Cyclophosphamide, Docetaxel	323; 340	28 days
Saura et al ^[36]	2013	NCT00455533	295	48 (25–79)	I–III	Neoadjuvant	II	Doxorubicin, Cyclophosphamide, Ixabepilone	Doxorubicin, Cyclophosphamide, Paclitaxel	73; 71	4–6 wk
Baselga et al ^[37]	2013	NCT00463788	181	53 ± 12.5	IV	Metastatic	II	Cetuximab, Cisplatin	Cisplatin	115; 58	30 mo
Fan et al ^[38]	2013	NA	53	48 (27–71)	IV	Metastatic	II	Docetaxel, Cisplatin	Docetaxel, Capecitabine	27; 26	24 mo
Carey et al ^[39]	2012	NA	102	52 (28–83)	IV	Metastatic	II	Cetuximab	Cetuximab, carboplatin	31; 71	40 mo
von Minckwitz et al ^[40]	2012	NCT00567554	663	48 (21–78)	I–III	Neoadjuvant	III	Epirubicin, Cyclophosphamide, Docetaxel, Bevacizumab	Epirubicin, Cyclophosphamide, Docetaxel	323; 340	28 days
Bonnefoi et al ^[41]	2011	NCT00017095	272	48.8 (22.2–70.9)	III	Neoadjuvant	III	5-fluorouracil, Epirubicin, Cyclophosphamide	Epirubicin, Docetaxel	132; 140	9 y
Martin et al ^[42]	2011	NCT00123929	48	52 (26–79)	II–III	Neoadjuvant	NA	Docetaxel	Doxorubicin	28; 20	5 y
Bernsdorf et al ^[43]	2011	NCT00239343	82	53 (31–74)	I–III	Neoadjuvant	II	Epirubicin, Cyclophosphamide, Gefitinib	Epirubicin, Cyclophosphamide	41; 41	Immediately
O'Shaughnessy et al ^[44]	2011	NCT00540358	123	54 (26–80)	IV	Metastatic	II	Gemcitabine, Carboplatin, Iniparib	Gemcitabine, Carboplatin	61; 62	24 mo
Huober et al ^[45]	2010	NA	1221	NA	III	Neoadjuvant	III	Docetaxel, Doxorubicin, Cyclophosphamide, Vinorelbine, Capecitabine	Docetaxel, Doxorubicin, Cyclophosphamide	384; 837	21 days
Colleoni et al ^[46]	2010	NA	303	52.7 ± 10.1	I–II	Adjuvant	NA	Cyclophosphamide, Methotrexate, 5-fluorouracil, Tamoxifen	Tamoxifen	170; 133	12 y

NA = Not available.

* Mean ± standardization; median (minimum–maximum); minimum–maximum.

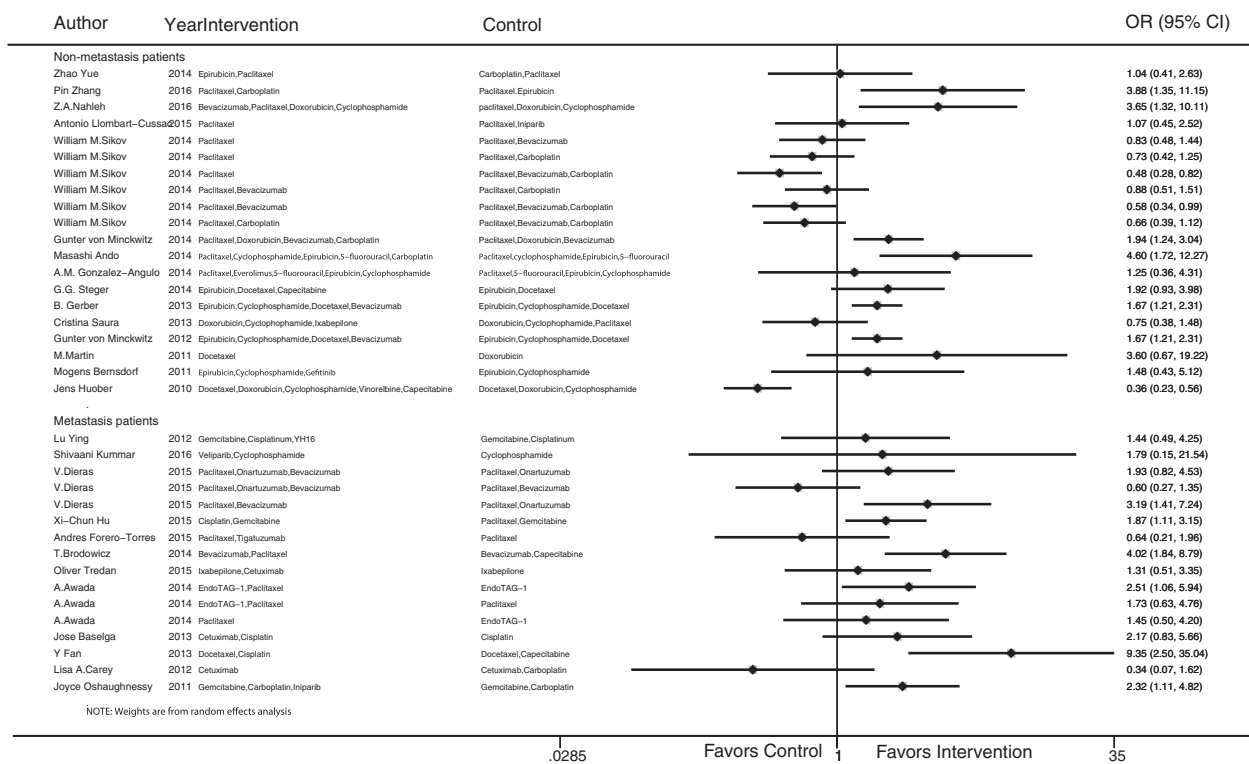


Figure 2. Traditional meta-analysis of overall response rate (ORR) among regimens. The forest plot shows a traditional meta-analysis for ORR results. The results were not pooled because of the various types of intervention and control regimens.

The traditional meta-analysis compared the anti-tumor regimens of each direct comparison in the included studies with ORR outcomes without pooling (Fig. 2). In the patients without metastasis, Paclitaxel combined with Carboplatin had a greater effect than Epirubicin (OR, 3.88; 95% CI, 1.35–11.15; $P = .012$). The regimen that included Paclitaxel, Doxorubicin, and Cyclophosphamide was more effective when combined with Bevacizumab (OR, 3.65; 95% CI, 1.32–10.11; $P = .013$). The regimen of Paclitaxel, Bevacizumab, and Carboplatin was superior to that of Paclitaxel alone (OR, 0.48; 95% CI, 0.28–0.82; $P = .008$) and superior to the combination of Paclitaxel and Bevacizumab (OR, 0.58; 95% CI, 0.34–0.99; $P = .047$). The regimen of Paclitaxel, Doxorubicin, and Bevacizumab was superior when combined with Carboplatin (OR, 1.94; 95% CI, 1.24–3.04; $P = .004$). The regimen of Paclitaxel, Cyclophosphamide, Epirubicin, and 5-Fluorouracil was also superior when combined with Carboplatin (OR, 4.60; 95% CI, 1.72–12.27; $P = .002$). The combination of Epirubicin, Cyclophosphamide, Docetaxel, and Bevacizumab was superior to that without Bevacizumab (OR, 1.67; 95% CI, 1.21–2.31; $P = .002$). However, the regimen including Docetaxel, Doxorubicin, and Cyclophosphamide was inferior when combined with Vinorelbine and Capecitabine (OR, 0.36; 95% CI, 0.23–0.56; $P < .001$). Notably, we only analyzed individuals who did not respond to initial treatment with Docetaxel, Doxorubicin, and Cyclophosphamide. The responders did not undergo changes to their treatment strategy after randomization.^[45] Simultaneously, the ORR results displayed several significant differences between regimens in the patients with metastasis (Figure 2) regarding PFS (Figure S2, Supplemental digital content 1, <http://links.lww.com/MD/B938>) and OS (Figure S3, Supplemental digital content 1, <http://links.lww.com/MD/B938>) outcomes. However, the included regimens were too complex and scattered

to pool, and pairwise comparisons were not possible because of the lack of robustness and reliability.

For the network meta-analysis of ORR outcomes, we analyzed 12 antitumor regimens (Fig. 3A). Other regimens were not included because we could not directly compare the included regimens. No significant differences were observed among regimens in the network pairwise comparisons (Table S1, <http://links.lww.com/MD/B938>). The results of the inconsistency analysis showed no local or global inconsistency. In terms of SUCRA rank, Bevacizumab, Carboplatin, and Paclitaxel (78.2%) were the most likely to improve the ORR in TNBC patients, followed by EndoTAG-1 and Paclitaxel (69.7%), Carboplatin and Paclitaxel (65.0%), and Bevacizumab and Paclitaxel (61.8%). Six regimens were analyzed in the patients without metastasis (Figure 3B). No significant differences were found in the network pairwise comparisons (Table S2, <http://links.lww.com/MD/B938>). In terms of SUCRA rank, the combination of Bevacizumab, Carboplatin, and Paclitaxel (74.9%) remained the most likely to improve the ORR, followed by Carboplatin and Paclitaxel (59.6%), Bevacizumab and Paclitaxel (50.7%), and Iniparib and Paclitaxel (42.7%). The comparison-adjusted funnel plot used to assess publication bias and to determine the presence of small-study effects did not suggest any publication bias. Despite the results of the metastasis and outcomes of PFS and OS, we were unable to draw comprehensive and accurate conclusions because <4 regimens formed the network.

For the multilevel mixed-effects logistic regression analysis, the analysis of ORR outcomes showed that Cisplatin (OR, 5.41; 95% CI, 3.11–9.42; $P < .001$), Paclitaxel (OR, 4.44; 95% CI, 2.83–6.97; $P < .001$), Ixabepilone (OR, 4.32; 95% CI, 2.21–8.44; $P < .001$), Docetaxel (OR, 2.53; 95% CI, 1.47–4.37;

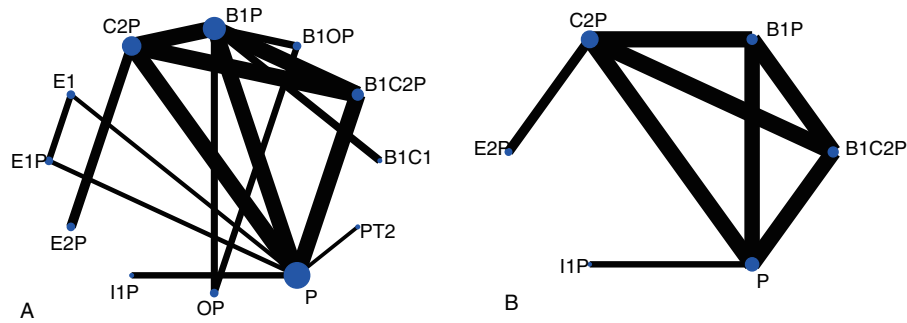


Figure 3. Network of comparisons for overall response rate included in the analyses. (A) All TNBC patients; (B) TNBC patients without metastasis. In the network plot, the connection of two interventions indicates a direct comparison. The nodes are weighted according to the number of studies and the edges according to the precision of the direct estimate for each pairwise comparison. B1 = Bevacizumab, C1 = Capecitabine, C2 = Carboplatin, E1 = EndoTAG-1, E2 = Epirubicin, I1 = Iniparib, O = Onartuzumab, P = Paclitaxel, T2 = Tigatuzumab, TNBC = triple-negative breast cancer.

$P = .001$), Gemcitabine (OR, 2.47; 95% CI, 1.34–4.53; $P = .004$), EndoTAG-1 (OR, 2.36; 95% CI, 1.13–4.93; $P = .022$), Carboplatin (OR, 2.07; 95% CI, 1.62–2.64; $P < .001$), and Bevacizumab (OR, 1.71; 95% CI, 1.43–2.05; $P < .001$) yielded a higher ORR for TNBC patients (Fig. 4). Vinorelbine (OR, 0.24; 95% CI, 0.12–0.46; $P < .001$) reduced patients' ORR (Fig. 4). Additionally, we analyzed patients with and without metastasis separately. Patients without metastasis who received Paclitaxel (OR, 5.48; 95% CI, 1.96–15.33; $P = .001$), Ixabepilone (OR, 4.8; 95% CI, 1.48–15.51; $P = .009$), Capecitabine (OR, 2.22; 95% CI, 1.11–4.44; $P = .024$), Carboplatin (OR, 1.93; 95% CI, 1.49–2.51; $P < .001$), and Bevacizumab (OR, 1.63; 95% CI, 1.36–

1.96; $P < .001$) had a significantly higher ORR. Vinorelbine (OR, 0.15; 95% CI, 0.07–0.34; $P < .001$) reduced the ORR. For patients with metastasis, the application of Ixabepilone (OR, 4.82; 95% CI, 1.99–11.72; $P = .001$), Docetaxel (OR, 4.56; 95% CI, 2.19–9.57; $P < .001$), Gemcitabine (OR, 3.89; 95% CI, 2.49–6.07; $P < .001$), Bevacizumab (OR, 3.4; 95% CI, 2.08–5.53; $P < .001$), Paclitaxel (OR, 2.98; 95% CI, 1.44–6.16; $P = .003$), EndoTAG-1 (OR, 2.9; 95% CI, 1.5–5.61; $P = .002$), and Cisplatin (OR, 2.87; 95% CI, 1.33–6.2; $P = .007$) yielded a significantly higher ORR.

Regarding PFS outcomes, the application of Carboplatin (OR, 4.85; 95% CI, 1.94–12.11; $P = .001$), Epirubicin (OR, 3.1; 95%

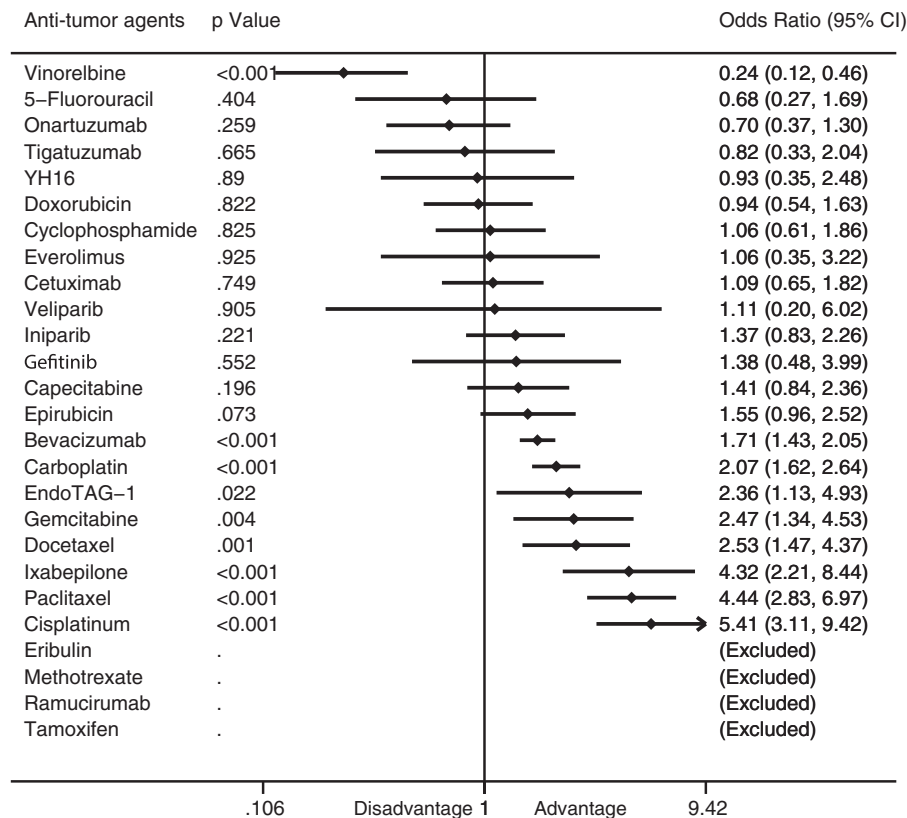


Figure 4. Forest plot of antitumor agents for overall response rate (ORR) by multilevel mixed-effects logistic regression. The components of different therapeutic strategies were analyzed to assess the relationship to the ORR of patients by logistic regression.

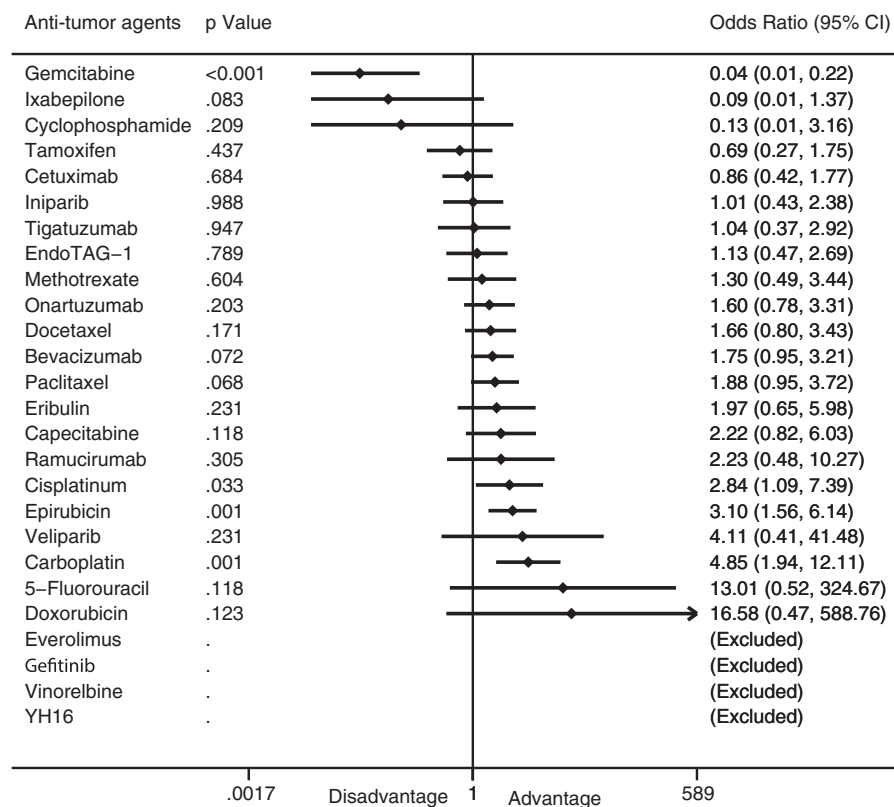


Figure 5. Forest plot of antitumor agents for progression-free survival (PFS) by multilevel mixed-effects logistic regression. The components of different therapeutic strategies were analyzed to assess the relationship to the PFS of patients by logistic regression.

CI, 1.56–6.14; $P=.001$), or Cisplatin (OR, 2.84; 95% CI, 1.09–7.39; $P=.033$) significantly increased the number of patients who experienced PFS during follow-up (Fig. 5). Although Gemcitabine (OR, 0.04; 95% CI, 0.01–0.22; $P<.001$) reduced PFS, it had a large standard error (Fig. 5). In patients without metastasis, Doxorubicin (OR, 8.99; 95% CI, 2.34–34.59; $P=.001$), Carboplatin (OR, 4.3; 95% CI, 1.5–12.28; $P=.007$), and Methotrexate (OR, 4.0; 95% CI, 2.2–7.29; $P<.001$) significantly increased the PFS rate during follow-up. However, Doxorubicin (OR, 8.99; 95% CI, 2.34–34.59; $P=.001$), Carboplatin (OR, 4.3; 95% CI, 1.5–12.28; $P=.007$), and Methotrexate (OR, 4.0; 95% CI, 2.2–7.29; $P<.001$) had opposite effects. For metastatic TNBC patients, Cisplatin (OR, 4.03; 95% CI, 1.49–10.88; $P=.006$), Eribulin (OR, 3.6; 95% CI, 1.01–12.79; $P=.047$), and Paclitaxel (OR, 2.72; 95% CI, 1.28–5.76; $P=.009$) significantly increased the PFS rate, and Gemcitabine (OR, 0.11; 95% CI, 0.02–0.57; $P=.008$) decreased the PFS rate. However, the aforementioned results exhibited large standard errors.

For OS outcomes in metastatic and non-metastatic TNBC patients, the applications of Epirubicin (OR, 2.42; 95% CI, 1.14–5.11; $P=.021$), Cyclophosphamide (OR, 1.93; 95% CI, 1.12–3.32; $P=.018$), and Iniparib (OR, 1.51; 95% CI, 1.11–2.07; $P=.009$) significantly increased the TNBC patients' OS during follow-up (Fig. 6). In patients without metastasis, Carboplatin (OR, 10.48; 95% CI, 2.53–43.48; $P=.001$), Epirubicin (OR, 5.1; 95% CI, 1.95–13.3; $P=.001$), and Cyclophosphamide (OR, 1.81; 95% CI, 1.03–3.17; $P=.037$) significantly increased the OS. In patients with metastasis, only Iniparib (OR, 1.53; 95% CI, 1.12–2.09; $P=.008$) significantly increased the OS. However, to

eliminate collateral influence and minimize the false-positive rate, we calculated the tested level of significance as approximately 0.0023 for each individual drug in accord with the 0.05 general level of significance. Thus, we recommend $P=.002$ as a reference for significant differences in the multilevel mixed-effects logistic regression.

4. Discussion

In the present study, we comprehensively analyzed antitumor treatments for TNBC patients. The assessment index included ORR, PFS, and OS. We considered all antitumor agents applied before and after randomization. A network meta-analysis and multilevel mixed-effects logistic regression were used to analyze the regimens and agents, respectively. In the network analysis, the regimen of Bevacizumab, Carboplatin, and Paclitaxel was the most likely to improve the ORR in TNBC patients and in metastatic TNBC patients. Other antitumor agents could not be analyzed by less direct comparisons. The multilevel logistic regression analysis showed that the application of Cisplatin, Paclitaxel, Ixabepilone, Docetaxel, Carboplatin, and Bevacizumab had advantages in improving patients' ORRs. Carboplatin and Epirubicin were beneficial for patients' PFS. Additionally, we found unexpected results for Paclitaxel, Cyclophosphamide, and Docetaxel in PFS outcomes, which did not significantly reduce patients' PFS. In regimens without Paclitaxel, the application of the more effective agent Epirubicin might bias the results. In regimens without Cyclophosphamide, the application of Epirubicin and Carboplatin might also bias the results.

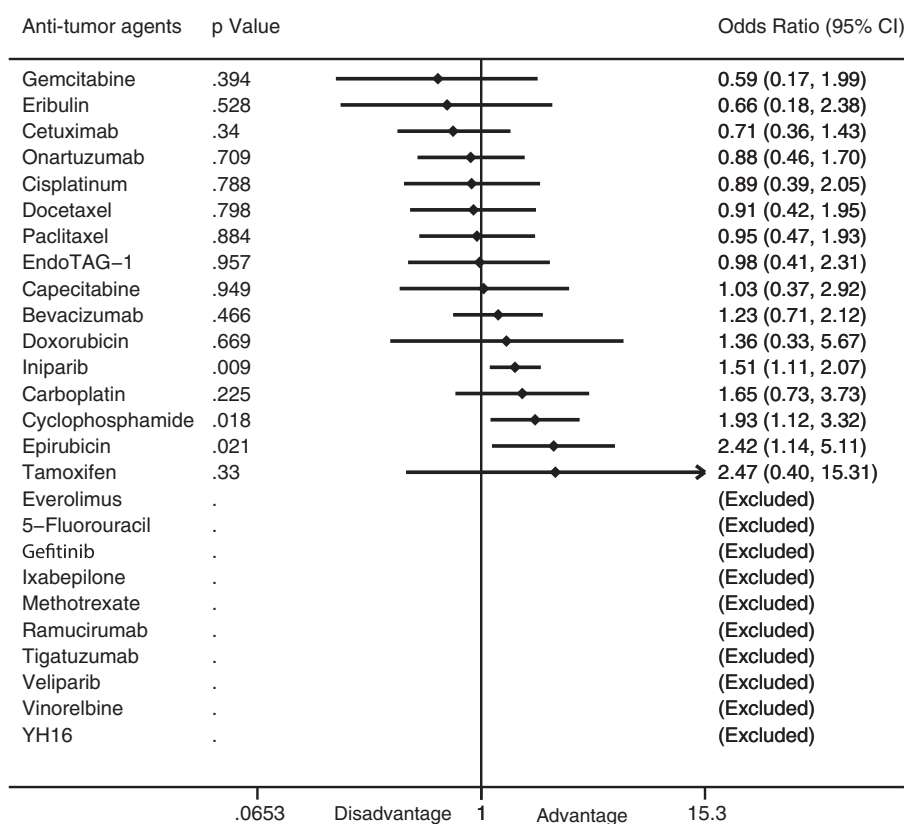


Figure 6. Forest plot of anti-tumor agents for overall survival (OS) by multilevel mixed-effects logistic regression. The components of different therapeutic strategies were analyzed to assess the relationship to the OS of patients by logistic regression.

Several drugs are involved in the chemotherapy strategy used to treat neoplasms. The research protocols for a meta-analysis analyzing this type of treatment included a comparison of combinations of drugs and different types of chemotherapy. These analyses might have ignored the effects from other accompanying treatments and the different strategies in the control group, such as previous analyses of platinum-based chemotherapy versus nonplatinum-based therapy.^[6] With several widely researched strategies, a network meta-analysis could be used for direct and indirect comparisons. However, when strategies are controversial and scattered, a network meta-analysis has low feasibility because of the less direct comparisons among strategies. For example, in our network analysis, many chemotherapy regimens did not connect in the network.

To ensure that all the agents used in the chemotherapy period were included in the analysis, our research first collected all antitumor agents before and after randomization. A multilevel mixed-effects logistic regression was used to analyze the therapeutic effect of each antitumor drug. However, this method had limitations in that it did not consider the combined effect among drugs. For example, if an ineffective drug is combined with an effective drug, the results will show a positive effect associated with that ineffective drug. In that case, this method had relatively higher false positive rates and low accuracy. Similar to other meta-analyses, the small sample size might have produced a larger standard error and reduced the accuracy of the analysis. Additionally, because all the antitumor agents were considered, the probability of a type I error (false-positive error) was increased.

Furthermore, a difference between ORR and PFS persisted in our results. Although the difference might have been caused by

sampling error, we also cannot exclude possible inference because of the lack of a necessary connection between the patients' ORR and OS. Thus, the large standard error in PFS and OS results may also have reduced robustness and induced the difference between ORR and PFS. Therefore, increased sample sizes are necessary to further confirm the effects of antitumor agents.

Design bias and publication bias also affected the results. In most studies, ORR was used as a primary outcome, with PFS and OS as secondary outcomes. Positive ORR results are more easily accepted by institutions or journals, whereas negative results are not. However, negative results for PFS and OS have a greater chance of publication. Notably, only 1 article used PFS as a primary outcome with neoadjuvant treatment. The PFS results reported for the comparison were not significant ($P=.17$).^[41] Other neoadjuvant trials only reported the pCR results. Thus, the conclusion regarding PFS and OS was mainly based on nonneoadjuvant trials. Design bias may be present because most of the included studies did not adopt a blinded approach. Therefore, subjective factors may have affected the results. Thus, we concluded that the reliability of the pCR outcome was inferior to that of PFS and OS. Further studies are necessary in the future, particularly studies on the results of PFS and OS. The details of all patients who withdrew were described in each of the included studies. The main reasons for loss to follow-up were disease progression and adverse events, whereas others included death, other disease onset, and patient/physician decisions. Among the major reasons, the number of patients who withdrew because of disease progression was included in the PFS outcomes. The adverse event-related outcomes were described in each of the

included studies in detail but were outside the scope of our study. Notably, however, the withdrawal of patients due to adverse events may have led to bias in the results of this study.

The results of our study were based on RCT studies. However, the National Comprehensive Cancer Network (NCCN) guideline was based not only on RCTs but also on retrospective and case-control studies with more comprehensive conclusions. Therefore, our study may only serve as a supplement to the NCCN guideline. The recommended regimen for HER-2 negative breast cancer including Doxorubicin, Cyclophosphamide, and Paclitaxel was not included in the network meta-analysis. In traditional meta-analysis, the aforementioned regimen was inferior to that same regimen plus Bevacizumab.^[46] Therefore, we considered that the recommended regimen might be combined with Bevacizumab to increase the therapeutic effect. However, the results are derived from single studies and remain lacking in robustness.

The network meta-analysis lacked critical comparisons to analyze all the included regimens. In the 12 included regimens, Paclitaxel-containing regimens, particularly the combined Paclitaxel, Bevacizumab, and Carboplatin regimen, showed superior ORR improvement. Thus, it may be used clinically when acceptable. Additional critical comparison RCTs, such as Paclitaxel- and Paclitaxel plus Bevacizumab-related comparisons were needed to conduct a more comprehensive network meta-analysis. For single chemotherapeutic drug application, no new evidence emerged to supplement the NCCN guideline.

5. Limitations

Our study had several limitations. First, the present analysis was performed at the study level, not at an individual level. Second, tumor heterogeneity among the TNBC patients affected the outcomes. Thus, the formulation of individualized treatments according to the characteristics of each tumor is crucial. Third, a network meta-analysis cannot include all related regimens. Fourth, factors such as the agents' dosages and the duration of application were not considered in our research.

In conclusion, a regimen including Bevacizumab, Carboplatin, and Paclitaxel was the most likely to improve the ORR in TNBC patients and in advanced metastatic TNBC patients. The application of Bevacizumab and Carboplatin provided greater benefit for improving patients' ORR.

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