

A meta-analysis of the effect and safety of platinum-based neoadjuvant chemotherapy in treatment of resectable triple-negative breast cancer

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Triple-negative breast cancer (TNBC) is the most aggressive and fatal subtype of breast cancer. The effectiveness of platinum-based neoadjuvant chemotherapy in treatment of cancer has many divergent opinions. A search was conducted in the PubMed, EBSCO, Web of Science and Cochrane Library databases for relevant studies published before August 2020. The primary endpoint was pathological complete response (pCR) while the secondary endpoints were objective response rate (ORR), overall survival (OS) and progression-free survival (PFS). Nine randomized controlled trials comprised of 1873 patients were included in this meta-analysis. Platinum-based neoadjuvant chemotherapy showed significant improvements in pCR (RR = 1.51, 95% CI, 1.25–1.82, $P < 0.001$), ORR (RR = 1.20, 95% CI, 1.07–1.34, $P = 0.001$), OS (HR=0.56; 95% CI, 0.15–0.96, $P < 0.001$) and PFS (HR = 0.48, 95% CI, 0.22–0.73, $P < 0.001$) compared to nonplatinum neoadjuvant chemotherapy. Moreover, addition of platinum compounds did not significantly increase the side effects of any grade. However, there was an increase in blood toxicity of grade

3 patients which meant that it was mainly confined to the bone marrow/blood system. Platinum-based neoadjuvant chemotherapy can safely improve short-term and long-term outcomes in resectable TNBC patients. *Anti-Cancer Drugs* 33: e52–e60 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and accounts for 23% of cancer-related deaths in women [1–3]. BC is categorized into three subtypes on the basis of the presence or absence of estrogen receptor, progesterone receptor and human epidermal growth factor 2 (HER-2): hormone receptor-positive (70% of patients), HER-2 positive (15–20%) and triple-negative (10–15%) [4]. Triple-negative breast cancer (TNBC) has the following characteristics: high incidence in younger women, high local recurrence, intense trend of organ metastases and poor prognosis [5–8]. TNBC is more likely to recur than the other two subtypes. Experimental data reveal that the 5-year breast cancer-specific survival

rate for stage I triple-negative tumors are 85% while for hormone receptor-positive and HER-2 positive is 94 and 99%, respectively [4]. Currently, TNBC is universally acknowledged as the most aggressive and fatal subtype of BC despite accounting for only 10–15% of BC cases [9].

Cognizant to this, lots of efforts have been put to study TNBC to improve the therapeutic effect and reduce the mortality rate [10]. Though researchers have proposed a number of treatment strategies such as immunotherapy, radiotherapy, targeted therapy and related breast surgery, their effect is still not satisfactory. TNBC patients have a poor response to related therapy because of lack of drug-targetable receptors, drug resistance and high heterogeneity between different patients which lead to varying sensitivity to the therapy regimen. As such, chemotherapy is the only recommended systemic treatment used to improve TNBC patients' prognosis [11–13].

Researchers have proposed a new scheme 'neoadjuvant chemotherapy' which recommends that systemic chemotherapy is first performed before local treatment (such as surgery or radiotherapy) to improve the effect of

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chemotherapy [14]. In the last decade, numerous studies involving neoadjuvant chemotherapy with immunotherapy [15,16] and targeted drugs [17–19] have been done. This has led to development of innovative, multidrug combination systemic therapies such as platinum-based neoadjuvant chemotherapy that have significantly improved the treatment outcomes [6]. However, there are still many divergent reports on these newly proposed treatments because of varying survival outcomes. For instance, a TNT trial revealed that there were no significant differences between the objective response rate (ORR) of carboplatin and that of docetaxel in the overall population (31.4 vs. 34.0%). On the contrary, a GeparSixto trial reported significant improvements when neoadjuvant carboplatin treatment was used (53.2 vs. 42.7%) compared with noncarboplatin-based neoadjuvant treatment [20,21]. Herein, the effect of platinum-based neoadjuvant chemotherapy on resectable TNBC patients was determined to provide reliable data sets for clinical treatment.

Materials and methods

Literature search

A search was conducted in the PubMed, EBSCO, Web of Science and Cochrane Library databases for relevant studies published before August 2020. The search terms used were ‘triple-negative breast cancer’, ‘platinum’ and ‘neoadjuvant chemotherapy’. In the same line, the complete retrieval formula used were (‘triple-negative breast cancer’ OR ‘TNBC’ OR ‘triple-negative breast cancer’ OR ‘triple-negative breast neoplasms’ OR ‘triple-negative breast carcinoma’), (‘neoadjuvant therapy’ OR ‘neoadjuvant’ OR ‘neoadjuvant chemotherapy’) AND (‘carboplatin’ OR ‘cisplatin’ OR ‘lobaplatin’ OR ‘platinum’ OR ‘oxaliplatin’ OR ‘nedaplatin’). In cases where duplicate literature was involved, the original article was included instead of the abstract if the studies had been published in the form of an abstract and as an original article. In the same line, if a single study had published more than one article, only the latest or the article with the highest quality was included. References of the included studies were also manually reviewed to identify additional relevant articles. This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2009 Checklist [22,23].

Selection criteria

Included studies were those involving randomized controlled trials (RCTs) limited to clinical studies only, studies which only included patients who were diagnosed as resectable TNBC or had categorized them as a subgroup with relevant accessible data, studies whose experimental group in the RCTs were treated with platinum-based neoadjuvant chemotherapy while the control group were treated with other treatments, and studies containing

full-text articles with available data including short- and/or long-term survival outcomes. All included articles were published in English.

Articles involving non-RCT including case reports and observational studies were excluded from the study. Studies including patients with metastatic TNBC or the given treatment was palliative care were also excluded. This was also the case for studies whose relevant outcomes and detailed data were not reported or accessed as well as RCT that did not compare platinum-based neoadjuvant chemotherapy with nonplatinum-based neoadjuvant chemotherapy.

Data extraction and quality assessment

Data extracted from each study included the author’s name, year of publication, clinical tumor stage, trial phase, country where the study was done, median follow-up time, therapeutic regimen, number of inclusions, inclusion time, outcome measures and pathological complete response outcomes in the platinum-based and nonplatinum-based neoadjuvant chemotherapy group.

The methodological quality of each RCT was based on the Cochrane Risk Bias Assessment Tool score. Six domains of the tool were selected to evaluate the risk of bias: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and free of other bias.

Objectives and endpoints

Trials conducted in the included article adopted a variety of objectives and endpoints to record and evaluate their experimental results. Herein, the pathological complete response (pCR) was used as the primary endpoint to standardize the arrangement of the experimental results and relevant data. It was defined as ypT0/is ypN0 which meant absence of invasive and noninvasive residuals in the breast and axilla. Besides pCR, ORR were also used as secondary endpoints to enrich the efficacy and safety analysis regarding addition of platinum compounds in neoadjuvant chemotherapy for resectable TNBC patients. Complete response (CR) and partial response (PR) was defined as the proportion of patients whose tumor had shrunk to a certain amount and maintained for a certain period. Progression-free survival (PFS) was defined as the proportion of cancer patients who lacked disease progression or death because of various reasons within the five years since the beginning of treatment. Overall survival (OS) was defined as the proportion of patients that survived more than 5 years after a series of comprehensive treatments and safety measures.

Data analysis

The RevMan 5.3.5 software for Windows and the Stata 12.0 Software (Stata, College Station) were used

to analyze the data. The Cochrane Q -test and I^2 test were used to quantitatively calculate the heterogeneity between the trials in order to evaluate their differences. On the basis of the Cochrane Manual and experimental characteristics, I^2 values between 0 and 30% indicated mild or insignificant heterogeneity, those between 30 and 70% indicated moderate heterogeneity while those between 70 and 100% indicated high or significant heterogeneity [23].

The confidence interval (CI) of the risk ratio was set at 95% to evaluate the comparison of the pCR outcomes between platinum-based neoadjuvant chemotherapy and nonplatinum-based neoadjuvant chemotherapy. PFS and OS were analyzed on the basis of the hazard ratio of each study. In addition, a random-effects model was employed because there were diverse platinum-based neoadjuvant therapies. This was done to improve the reliability of the meta-analysis. Sensitivity analysis was carried using Begg's test while publication bias was evaluated using Egger's test. P values less than 0.05 ($P < 0.05$) indicate that there were significant differences between groups/treatments.

Results

Study selection and characteristics

The retrieval search identified 615 relevant articles. Among them, 97 articles were eliminated because they were duplicates and another 430 articles excluded after skimming through their titles or abstracts. The remaining 88 articles were thoroughly scrutinized through full-text reading. This led to further elimination of 79 articles. The remaining nine RCTs comprised of 1873 patients were thus included for the meta-analysis [17,21,24–30]. There were no additional records identified through other sources. The search process is described in Fig. 1.

All RCTs were interventional therapies of resectable TNBC patients. Among the nine trials, eight were in phase II and one in phase III on the basis of available trial phase and clinical tumor stage. The experimental groups in all trials were treated with platinum-based neoadjuvant chemotherapy such as carboplatin, cisplatin and lobaplatin while the control groups were treated with other nonplatinum-based neoadjuvant chemotherapy such as epirubicin, gemcitabine, doxorubicin and cyclophosphamide. Detailed characteristics of included clinical trials are outlined in Table 1. In addition, four studies (827 patients) had accessible PFS data and three studies (702 patients) had accessible OS data. Other related characteristics are outlined in Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/ACD/A411>.

Risk of bias assessment

The Cochrane Collaboration's tool was adopted to objectively evaluate the quality of RCTs included in this meta-study. The tool employed six targets and every risk of bias was assessed by either 'low risk', 'high risk'

or 'unclear risk'. Assessment of risk of bias is summarized in Supplementary Table 2, Supplement digital content 1, <http://links.lww.com/ACD/A411>.

Analyses with pCR

All nine studies (1873 patients) used pCR as the primary endpoint of RCTs. Only 926 patients in the experimental group and 936 patients in the control group had available pCR data because side effects, multiple-dose reduction, withdrawal of consent or initial termination of the trial. There were significant improvements in pCR rates among resectable TNBC patients treated with platinum-based neoadjuvant chemotherapy compared to those treated with nonplatinum-based neoadjuvant chemotherapy (RR = 1.51, 95% CI, 1.25–1.82, $P < 0.001$) (Fig. 2). The I^2 test further revealed that the trials had a heterogeneity of 55%.

Analyses with objective response rate

Three studies (310 patients) used ORR (CR and PR) as the secondary endpoints of RCTs; 156 patients in the experimental group and 153 patients in the control group available ORR data. One patient exited the trial because of serious side effects. Adding platinum to neoadjuvant chemotherapy was significantly better than other treatments in improving the pathological response effect of resectable TNBC patients (RR = 1.20, 95% CI, 1.07–1.34, $P = 0.001$) (Fig. 3). The I^2 test further revealed that there was no heterogeneity between these trials ($I^2 = 0$).

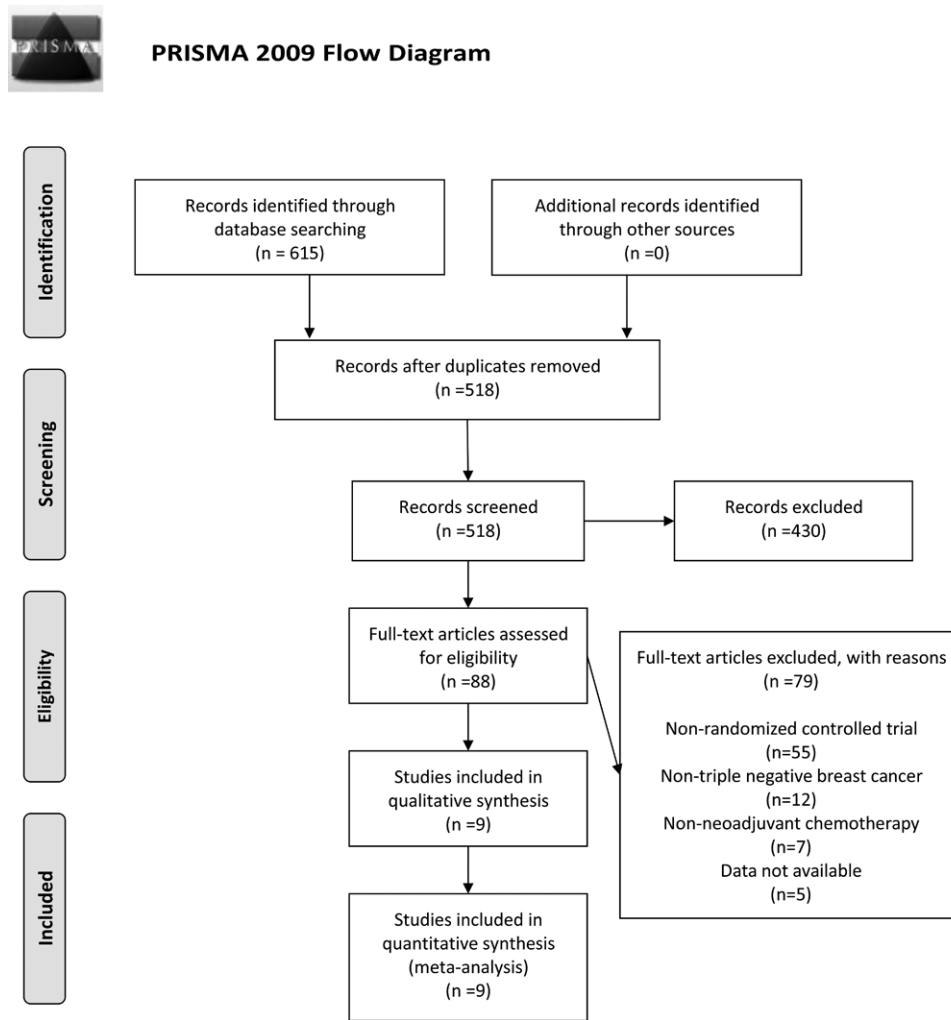
Analyses with overall survival and progression-free survival

Three studies (702 patients) used OS as the long-term outcomes of RCTs while four studies (827 patients) had accessible PFS data. Among the studies, one [21] employed 3-years OS and PFS while the others employed 5-years OS and PFS. Analysis of OS revealed that platinum-based neoadjuvant chemotherapy improved the OS (HR = 0.56, 95% CI, 0.15–0.96, $P < 0.001$) (Fig. 4a). In the same line, analysis of PFS further revealed that the experimental groups had prolonged PFS compared to the control groups (HR = 0.48, 95% CI, 0.22–0.73, $P < 0.001$) (Fig. 4b). Taken altogether, these findings strongly suggested that addition of platinum improved the long-term effect of neoadjuvant chemotherapy in resectable TNBC patients. I^2 test results of OS and PFS were 69.4 and 58.0% which indicated that the trials had moderate heterogeneity.

Toxicity analysis

The side effects of platinum-based neoadjuvant chemotherapy on the basis of the promoted effect in resectable TNBC patients were analyzed to provide data for future clinical applications. There were no significant differences in the adverse events (AEs) for any grade (nausea/vomiting, pain, diarrhea, constipation, myalgia/arthritis, peripheral neuropathy, anemia, leukopenia, neutropenia and

Fig. 1

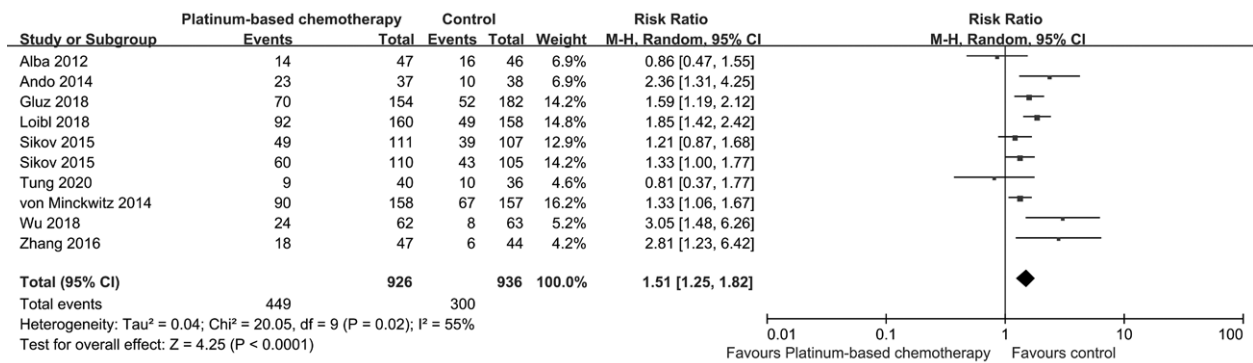


A schematic flow for the selection of articles included in this meta-analysis.

Table 1 Characteristics of included clinical trials in the meta-analysis

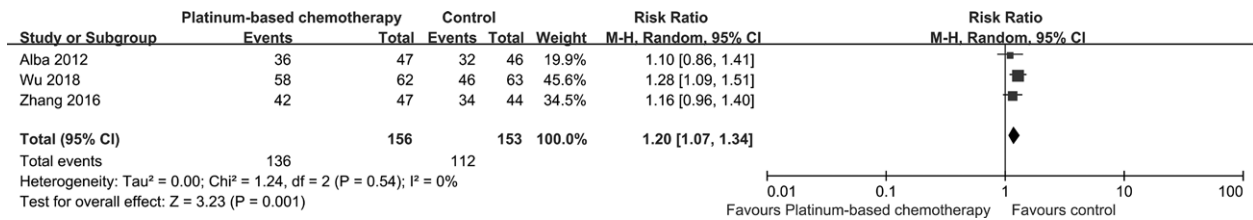
Author, year	Clinical stage	Trial Phase	Country	Median follow-up time	Therapeutic regimen		Number of inclusions	
					Treatment	Control	Treatment	Control
Alba <i>et al.</i> , [24]	I-III	2	Spain	NA	Carboplatin+epirubicin+cyclophosphamide+docetaxel	epirubicin+cyclophosphamide+docetaxel	48	46
Ando <i>et al.</i> , [25]	II-IIIa	2	Japan	6.6 years	Carboplatin+paclitaxel+cyclophosphamide+epirubicin+5-fluorouracil	Paclitaxel+cyclophosphamide+epirubicin+5-fluorouracil	37	38
von Minckwitz <i>et al.</i> , [21]	II-III	2	Germany	47.3 months	Carboplatin+bevacizumab+paclitaxel+non-pegylated liposomal doxorubicin	Bevacizumab+paclitaxel+non-pegylated liposomal doxorubicin	158	157
Sikov <i>et al.</i> , [17]	II-III	2	America	NA	Carboplatin+paclitaxel+doxorubicin+cyclophosphamide	Paclitaxel+doxorubicin+cyclophosphamide	113	108
					Carboplatin+bevacizumab+paclitaxel+doxorubicin+cyclophosphamide	Bevacizumab+paclitaxel+doxorubicin+cyclophosphamide	112	110
Zhang <i>et al.</i> , [30]	IIa-IIIc	2	China	55.0 months	Carboplatin+paclitaxel	Epirubicin+paclitaxel	47	44
Gluz <i>et al.</i> , [26]	II-III	2	Germany	NA	Carboplatin+paclitaxel	Gemcitabine+nab-paclitaxel	154	182
Wu <i>et al.</i> , [29]	I-III	2	China	NA	Lobaplatin+docetaxel+epirubicin	Docetaxel+epirubicin	62	63
Loibl <i>et al.</i> , [27]	II-III	3	Germany	NA	Carboplatin+paclitaxel+doxorubicin+cyclophosphamide	Paclitaxel+doxorubicin+cyclophosphamide	160	158
Tung <i>et al.</i> , [28]	I-III	2	America	NA	Single-agent cisplatin	Doxorubicin+cyclophosphamide	40	36

Fig. 2



Forest plot of the pathological complete response (pCR) of patients with resectable triple-negative breast cancer (TNBC) on platinum-based neoadjuvant chemotherapy.

Fig. 3



Forest plot of the objective response rate (ORR) of patients with resectable triple-negative breast cancer (TNBC) on platinum-based neoadjuvant chemotherapy.

thrombocytopenia) between the experimental and control groups ($P > 0.05$). Similarly, grade 3 or higher AEs, fatigue, nausea/vomiting, pain, diarrhea, peripheral neuropathy and lymphopenia were also not significantly different in both groups ($P > 0.05$). However, occurrence of anemia (RR = 8.22, 95% CI, 1.69–40.04, $P = 0.009$), leukopenia (RR = 1.63, 95% CI = 1.08–2.45, $P = 0.02$), neutropenia (RR = 2.08, 95% CI, 1.08–4.01, $P = 0.03$) and thrombocytopenia (RR = 6.01, 95% CI = 2.77–13.07, $P < 0.001$) was significantly higher in the group treated with platinum-based neoadjuvant chemotherapy compared to the group treated with nonplatinum-based neoadjuvant chemotherapy. Detailed analysis of the AEs is presented in Table 2.

Analysis of publication bias and sensitivity

Herein, publication bias was assessed using Begg’s and Egger’s test. There was no publication bias among included articles ($P > 0.05$). Sensitivity analysis further revealed that the analysis was relatively stable and reliable which meant that individual studies had little impact on the overall results ($P > 0.05$).

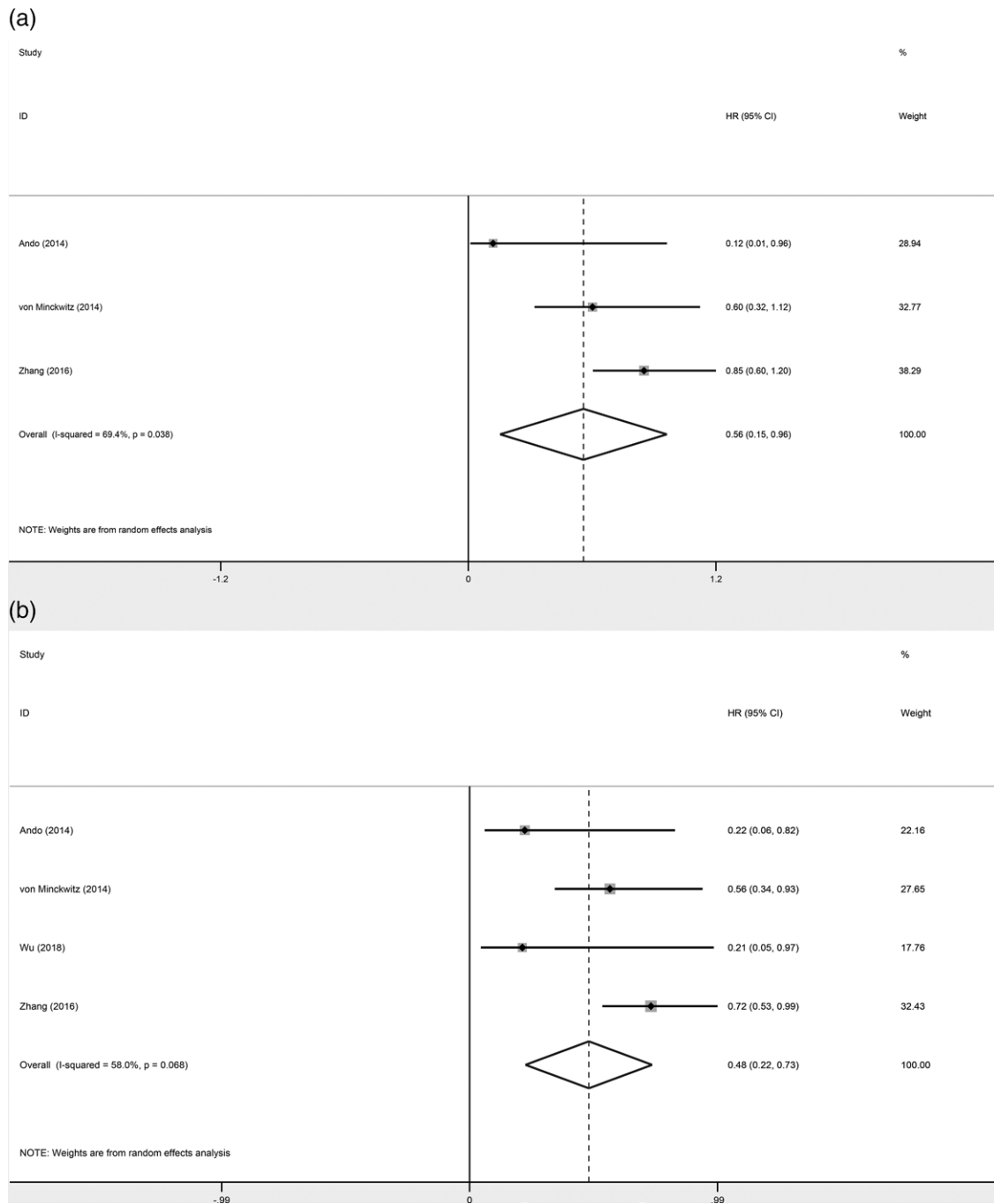
Discussion

TNBC is an aggressive and fatal cancer characterized by poorer prognosis, higher recurrence and more intense

metastasize tendency to other organ sites compared to the other two subtypes of BC (HER-2 positive and hormone receptor-positive) [31]. TNBC patients usually have a poor response to related therapy such as tumor-targeted therapy, radiotherapy or surgery because of deficiencies in drug-targetable receptors, drug resistance and high heterogeneity. As such, chemotherapy is the only recommended systemic treatment that improves TNBC patients’ survival outcomes [12].

Among the different chemotherapy regimens, neoadjuvant chemotherapy shows positive prognosis and less recurrence in TNBC patients. This is particularly the case with addition of platinum anticancer drugs such as carboplatin, cisplatin, lobaplatin, oxaliplatin and nedaplatin [32]. Cognizant to this, this meta-analysis was conducted to compare platinum-based neoadjuvant chemotherapy with nonplatinum-based neoadjuvant chemotherapy in resectable TNBC patients to determine the efficacy of platinum-based neoadjuvant chemotherapy. This was done by analyzing data of short-term outcomes, such as pCR and ORR, and long-term outcomes such as 5-year OS and 5-year PFS. The analyses revealed that resectable TNBC patients who received platinum-based neoadjuvant

Fig. 4



Forest plot for the long-term survival of patients with resectable triple-negative breast cancer (TNBC) on platinum-based neoadjuvant chemotherapy. (a) overall survival, $P < 0.001$; progression-free survival, $P < 0.001$).

chemotherapy had better prognosis than those who did not receive platinum-based neoadjuvant chemotherapy.

Both pCR (RR = 1.51, $P < 0.001$) and ORR (RR = 1.20, $P = 0.001$) of patients who received platinum-based neoadjuvant chemotherapy was significantly better than

that of those who did not receive platinum-based neoadjuvant chemotherapy. Moreover, patients who received platinum-based neoadjuvant chemotherapy had intuitive improvements in short-term survival outcomes compared to those who did not receive platinum-based neoadjuvant chemotherapy. Among the nine RCTs analyzed, seven

Table 2 Subgroup analysis of the adverse events (AEs)

platinum-based chemotherapy vs. control	No. of studies	RR	95% CI	P value	Heterogeneity	
					(I^2)	(%)
Any grade nausea/vomiting	3	1.51	0.78–2.94	0.22	96	
Any grade pain	2	1.23	0.73–2.09	0.44	26	
Any grade diarrhea	2	0.94	0.69–1.26	0.67	0	
Any grade constipation	2	0.98	0.78–1.23	0.84	0	
Any grade myalgia/arthralgia	3	0.98	0.48–2.00	0.95	79	
Any grade peripheral neuropathy	3	1.07	0.87–1.32	0.53	0	
Any grade anemia	2	2.45	0.51–11.65	0.26	96	
Any grade leukopenia	2	2.28	0.78–6.65	0.13	78	
Any grade neutropenia	3	1.61	0.54–4.84	0.39	97	
Any grade thrombocytopenia	3	7.99	0.40–158.47	0.17	92	
Grade 3 or higher fatigue	4	1.24	0.75–2.04	0.40	13	
Grade 3 or higher nausea/vomiting	7	1.38	0.78–2.45	0.27	0	
Grade 3 or higher pain	4	1.66	0.77–3.58	0.19	0	
Grade 3 or higher diarrhea	5	0.90	0.33–2.45	0.83	0	
Grade 3 or higher peripheral neuropathy	6	1.47	0.46–4.64	0.51	33	
Grade 3 or higher anemia	5	8.22	1.69–40.01	0.009	40	
Grade 3 or higher leukopenia	5	1.63	1.08–2.45	0.02	0	
Grade 3 or higher neutropenia	6	2.08	1.08–4.01	0.03	92	
Grade 3 or higher lymphopenia	2	1.07	0.06–19.65	0.96	60	
Grade 3 or higher thrombocytopenia	6	6.01	2.77–13.07	<0.001	12	

studies chose carboplatin with neoadjuvant chemotherapy [17,21,24–27,30], one chose lobaplatin [29] and the remaining one chose cisplatin [28].

To date, there is no specific mechanism of action of platinum compounds agreed by researchers across the world. The homologous recombination deficiency caused by the loss of BRCA function is considered to be the main rationale of platinum efficacy in TNBC [33]. TNBC has a specific biological profile that includes overexpression of vascular epithelial growth factors, high rate of BRCA mutation and deficiency in BRCA function [34]. BRCA-mutation carriers account for 10–20% of TNBC patients [17,35]. BRCA is enriched for proliferation-related genes and expression of genes involved in the DNA damage repair [36]. TNBC is more sensitive to interstrand cross-linking agents, such as platinum agents, which can damage the DNA because it is strongly associated with germline mutations in the BRCA gene which causes them to have a dysfunctional BRCA pathway as a result of deficient DNA repair mechanisms [21,30]. Although there are only 10–20% of patients with TNBC carried germline BRCA mutations, additional mechanisms such as promoter methylation, transcript instability/attenuation or somatic/germline mutations in other homologous recombination pathway genes may compromise the DNA repair machinery thereby increasing TNBC patients' sensitivity to neoadjuvant platinum [37–39].

The mode of platinum action is attributed to its ability to cross-link purine bases on the double-stranded DNA

which can interfere with DNA repair mechanism, cause DNA damage and subsequently induce apoptosis of cancer cells [40]. Although platinum agents have limited efficacy in advanced BC as single agents, they have greater activity in BRCA-mutation carriers. This is consistent with the biological characteristics of TNBC [17]. Decreased BRCA expression may also identify subsets of TNBC which are sensitive to platinum [41]. Telli *et al.* reported that the combination of gemcitabine, carboplatin and iniparib as neoadjuvant chemotherapy in resectable BC resulted in a pCR rate of 33% in wild type BRCA1/2 and 56% in BRCA mutation carriers. This was a strong indication that platinum-based neoadjuvant chemotherapy has better prognosis in patients with BRCA-associated BC [39, 42, 43].

In the same line, patients who received platinum-based neoadjuvant chemotherapy had significantly better PFS (HR = 0.48, $P < 0.001$) and OS (HR = 0.56, $P < 0.001$) than that those who did not receive platinum-based neoadjuvant chemotherapy. These results indicated that addition of platinum improved the long-term effect of neoadjuvant chemotherapy in resectable TNBC patients.

Iwase *et al.* added carboplatin to neoadjuvant chemotherapy in HER-2 negative BC patients and did a long time follow-up with a median follow-up time of 6.6 years (range 0.7–8.0 years). The study recorded and analyzed the DFS (HR = 0.22, $P = 0.015$) and OS (HR = 0.12, $P = 0.046$) in the subset of patients with TNBC. However, there were no significant improvements in the subset of patients with hormone receptor-positive disease and among all patients [44]. Similarly, Wu *et al.* conducted an RCT to test and verify the efficacy of neoadjuvant lobaplatin in TNBC. Data of recurrence and metastasis was then recorded and analyzed after a long follow-up time (HR = 0.21, $P < 0.001$) [29]. These studies confirm that TNBC patients are sensitive to platinum agents and can gain a longer survival time on the basis of the mechanism of action of platinum compounds. Though we have drawn positive survival outcomes about neoadjuvant platinum, researchers held different views.

Andreas Schneeweiss *et al.* carried out a GeparOcto-GBG 84 trial to compare the efficacy and safety of two chemotherapy regimens in high-risk early BC. The study revealed that there were no significant differences in pCR with addition of doxorubicin and carboplatin (48.3 vs. 48.0%) [45]. Nonetheless, the study administered high-dose regimens in high-risk early BC which caused more patients to discontinue treatment in carboplatin arm (34.1 vs. 16.4%) thereby resulting in huge differences in the number of samples between the two groups. Moreover, the trial conducted simultaneous experiments in multiple BC subtypes and thus used the overall effect in BC to replace the specific effect in TNBC.

In the same line, Tutt *et al.* conducted a TNT trial to compare the effect of carboplatin to that of docetaxel in

BRCA-mutated BC. Subsequent analysis revealed that there were no significant differences between the ORR of carboplatin and that of docetaxel in the overall population (31.4 vs. 34.0%). Moreover, there were no significant differences in patient responses between the two drugs [20]. Nonetheless, the study did not collect follow-up data to assess the long-term outcomes of the two drugs. It was also on the basis of BRCA-mutated BC and thus the relevant TNBC data on the efficacy of platinum could not be extracted.

Positive results of neoadjuvant platinum from this meta-analysis necessitated further evaluation of the toxicity of platinum. The AEs of each article were categorized into any grade AEs and grade 3 or higher AEs and analyzed. AEs such as nausea/vomiting, pain, diarrhea and constipation for any grade were not significantly different in the frequency of occurrence ($P > 0.05$). However, grade 3 or higher AEs such as anemia (RR = 8.22), leukopenia (RR = 1.63), neutropenia (RR = 2.08) and thrombocytopenia (RR = 6.01) were significantly higher in neoadjuvant platinum arm. Addition of platinum did not significantly increase the side effects of any grade. However, it increased the side effects of the serious grade. The main increase in grade 3 was blood toxicity. This indicated that the toxicity of platinum was mainly confined to the bone marrow/blood system which manifested as a decrease in red blood cells, white blood cells and platelets. This led to symptoms of anemia, lymphopenia and difficulty in hemostasis. Nonetheless, addition of platinum compounds to neoadjuvant chemotherapy was found to be generally safe.

Though Pandey *et al.* and Wang *et al.* conducted similar meta-analyses of neoadjuvant platinum conducted herein, their studies were limited by several factors. Both studies did not differentiate the stage of tumors and thus regarded both resectable TNBC patients and metastatic TNBC patients as subjects. As such, the studies could not draw convincing conclusions regarding resectable TNBC patients. Moreover, both studies selected carboplatin as the only experimental variable to represent the whole platinum compounds and therefore their findings could not reflect the therapeutic effect of platinum-based compounds on resectable TNBC patients [46,47].

Cognizant to this, this meta-analysis presents relatively high-quality data on treatment of resectable TNBC through comprehensive and systematic analysis. The study further analyzed carboplatin, cisplatin and lobaplatin platinum compounds to evaluate their independent and combined potential in improving the effect of neoadjuvant treatment and prognosis of resectable TNBC patients. The high-quality data presented herein was attributed to inclusion of high-quality articles on the basis of RCTs above phase II.

Nevertheless, this study was limited by several factors. The number of studies and relevant long-term survival

outcomes was relatively small and thus could not provide abundant information especially of long-term survival outcomes. In addition, subgroup analyses were not performed because of data unavailability. The study also included multiple treatment options such as different platinum compounds and doses thus making it difficult to clearly determine the optimal regimen. Cognizant to this, large-scale comprehensive studies should be conducted in the future to verify the findings herein.

Conclusion

This meta-analysis showed that platinum-based neoadjuvant chemotherapy can not only significantly improve the short-term outcomes including pCR, ORR but also improve long-term outcomes including PFS, OS in resectable TNBC patients which manifests as less recurrence and better prognosis comparing those who received non-platinum-based neoadjuvant chemotherapy. Moreover, the AEs of platinum are mainly confined to the bone marrow/blood system, which is generally safe.

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Conflicts of interest

There are no conflicts of interest.

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