Chinese Medical Journal®

Assessment of the safety and efficacy of combination chemotherapy and PD-1/PD-L1 inhibitor treatment of breast cancer: A meta-analysis

Da Qian[1], Yuhao Xu[2], Yihao Wu[3], Jie Qiu[2], Weimin Hong[4], Xuli Meng[5]

[1]Department of Burn and Plastic Surgery-Hand Surgery, The Changshu Hospital Affiliated to Soochow University, Changshu, Soochow, Jiangsu 215500, China;
[2]Second Clinical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang 310000, China;
[3]College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou, Zhejiang 310000, China;
[4]Faculty of Basic Medicine, Hangzhou Medical College, Hangzhou, Zhejiang 310000, China;
[5]Department of Breast Surgery, Cancer Center, Zhejiang Provincial People's Hospital, Hangzhou, Zhejiang 310000, China.

Abstract

Background: As the efficacy of programmed cell death-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors combined with chemotherapy in curing breast cancer is still controversial, this meta-analysis compares the efficacy and safety of PD-1/PD-L1 inhibitors combined with chemotherapy and chemotherapy alone in the treatment of breast cancer, which provides guidance for the clinical treatment.

Methods: Relevant studies published as of April 2022 in the various databases including EMBASE, PubMed, and Cochrane Library were selected. Randomized controlled trials (RCTs) in which control patients underwent chemotherapy alone and experimental group patients underwent combination chemotherapy and PD-1/PD-L1 inhibitor treatment were included in this investigation. Investigations without complete information, researches from which information could not be extracted, duplicate articles, animal studies, review articles, and systematic reviews were excluded. STATA 15.1 was employed for all statistical analyses.

Results: In total, eight eligible studies were identified, revealing that combination chemotherapy and PD-1/PD-L1 inhibitor treatment was linked to significant increases in progression-free survival (PFS) relative to chemotherapy alone (hazard ratio [HR] = 0.83, 95% confidence interval [CI]: 0.70–0.99, $P = 0.032$) but not overall survival (HR = 0.92, 95% CI: 0.80–1.06, $P = 0.273$). Pooled adverse event rates were also increased within the group of combination treatment relative to the chemotherapy group (risk ratio [RR] = 1.08, 95% CI: 1.03–1.14, $P = 0.002$). Specifically, nausea rates were lesser within the group of combination treatment relative to the group of chemotherapy (RR = 0.48, 95% CI: 0.25–0.92, $P = 0.026$). Subgroup analyses indicated that the PFS of patients who underwent combination atezolizumab or pembrolizumab and chemotherapy treatment were substantially longer than those of patients who underwent chemotherapy alone (HR = 0.79, 95% CI: 0.69–0.89, $P \leq 0.001$; HR = 0.79, 95% CI: 0.67–0.92, $P = 0.002$).

Conclusions: The pooled results suggest that combination chemotherapy and PD-1/PD-L1 inhibitor treatment approaches help prolong PFS in breast cancer patients, but have no statistically significant effect on overall survival (OS). Additionally, combination therapy can significantly improve complete response rate (CRR) compared with chemotherapy alone. However, combination therapy was associated with greater rates of adverse events.

Keywords: PD-1/PD-L1 inhibitors; Breast cancer; Chemotherapeutics; Meta-analysis

Introduction

Breast cancer is the most prevalent tumor type affecting women globally. The options of treatment for breast cancer cases primarily consist of surgery, radiotherapy, chemotherapy, targeted therapy, and hormone therapy.[1] It is worth noting that chemotherapy is still the main treatment for advanced breast cancer, but high rates of chemoresistance limit the utility of these therapeutic approaches in many patients.[2] The emergence of cancer treatment immunotherapy methods has made people more and more interested in the potential value of chemotherapy combined with immunotherapy in various cancers,[3] with many studies having linked such combination treatment to better therapeutic outcomes in breast cancer and other malignancies.[4–7]

The programmed cell death-1/programmed death-ligand 1 (PD-1/PD-L1) axis is the best studied target of immuno-

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002631

Da Qian, Yuhao Xu, and Yihao Wu contributed equally to this work.

Correspondence to: Dr. Xuli Meng, Department of Breast Surgery, Cancer Center, Zhejiang Provincial People's Hospital, Hangzhou, Zhejiang 310000, China
E-Mail: mxlmail@126.com;
Dr. Da Qian, Department of Burn and Plastic Surgery-Hand Surgery, The Changshu Hospital Affiliated to Soochow University, Changshu, Soochow, Jiangsu 215500, China;
E-Mail: drqianda@hotmail.com

Chinese Medical Journal 2023;136(14)
Received: 13-11-2022; **Online:** 07-06-2023 **Edited by:** Yanjie Yin

therapeutic intervention in the context of cancer treatment.[8] PD-1 is a B7-CD28 superfamily protein that is expressed by B, T, and natural killer (NK) cells and that can modulate immune cell activation and survival through interactions with its ligand PD-L1, which is expressed through certain tumor cells and other cells of the immune system. PD-L1/PD-1 interactions can suppress cell-mediated immunity by promoting the exhaustion or apoptotic death of T cells.[9] As such, PD-L1 overexpression can enable tumors to evade T cell-mediated clearance.[10] Several inhibitors of PD-1/PD-L1 have been employed for treating cancer cases to date including pembrolizumab, durvalumab, atezolizumab, and avelumab, and such therapeutic tools may represent an effective means of enhancing T cell-mediated antitumor immunity in breast cancer patients when applied in combination with chemotherapeutic regimens.[11]

Currently, chemotherapy combined with PD-1/PD-L1 inhibitors has been used in many clinical trials.[12,13] While several trials have reported improved clinical outcomes and satisfactory safety associated with the combined chemotherapeutic and PD-1/PD-L1 inhibitor treatment of breast cancer cases, these results remain controversial. In particular, some researchers have suggested that it remains to be established as to whether these two therapeutic approaches can be safely combined in breast cancer patients in a manner that leads to meaningful enhancements in overall survival (OS) or progression-free survival (PFS).

This meta-analysis compares the efficacy and safety of PD-1/PD-L1 inhibitors combined with chemotherapy and chemotherapy alone in the treatment of breast cancer by summarizing relevant literature, so as to provide guidance for the clinical treatment of breast cancer.

Methods

Study inclusion criteria

Randomized controlled trials (RCTs) in which control patients were treated via chemotherapy alone, and experimental group patients were treated via a combination of chemotherapy and PD-1/PD-L1 inhibitors were eligible for inclusion. Only studies published in English were eligible for inclusion in this analysis.

Studies were excluded from this analysis if they lacked complete information necessary for data extraction, or if they were animal studies, reviews, or systematic analyses.

Search strategy

Various databases including Embase, Pubmed, and Cochrane Library were meticulously explored for all relevant investigations published as of April 2022 with the following search terms: "Breast Neoplasms" AND "Nivolumab" "Pembrolizumab" "Durvalumab" "Tremelimumab" "Avelumab" "Atezolizumab" "PD-1" "PD-L1" AND "Chemotherapy" "Chemotherapeutics."

Research selection and extraction of data

Relevant studies were independently identified by two researchers, with disagreements being resolved through discussion with a third investigator. Information extracted from relevant studies included the authors, research type, year of publication, study region, case number, OS hazard ratio (HR), PFS HR, complete response rate (CRR), and incidence of adverse events.

Assessment of study quality

The RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) risk assessment tool was used by two investigators to independently assess study quality based upon the Cochrane risk assessment scale, which assesses study quality based upon random sequence generation, allocation concealment, blinding method, whether research results were evaluated in a blinded manner, and the completeness of reported data. Studies were also examined for potential selective reporting, sex biases, or other biases. Through discussion with a third researcher, disagreements were resolved. This meta-analysis was executed in compliance with the PRISMA statement.[14]

Statistical studies

All data were analyzed using STATA version 15.1 (StataCorp., College Station, TX, USA). OS and PFS were evaluated based upon HRs with 95% confidence intervals (CIs), while CRR and adverse event incidence were assessed based on risk ratios (RRs) and 95% CIs. Heterogeneity was evaluated implementing the I^2 statistic, with fixed effects models being used to analyze data in the absence of heterogeneity ($P \geq 0.100$ and $I^2 \leq 50\%$), whereas random-effects models or descriptive statistics are used in cases where heterogeneity is significant ($P < 0.100$ and $I^2 > 50\%$) and the sources of such heterogeneity cannot be determined through the analyses of sensitivity. Funnel plots and Egger's assessment were used to examine data for potential publication bias.

Results

Literature search results

In total, an initial literature search identified 1424 potentially relevant studies, of which 795 were retained following the removal of duplicates. Overall, 521 studies were evaluated in detail following abstract and title review, of which 8 were ultimately included in the last meta-analysis [Figure 1].

Study characteristics and quality

Baseline characteristics of included studies

This meta-analysis included eight RCTs enrolling 4781 total patients, including 2076 and 2705 in the control and experimental groups, respectively. These studies included

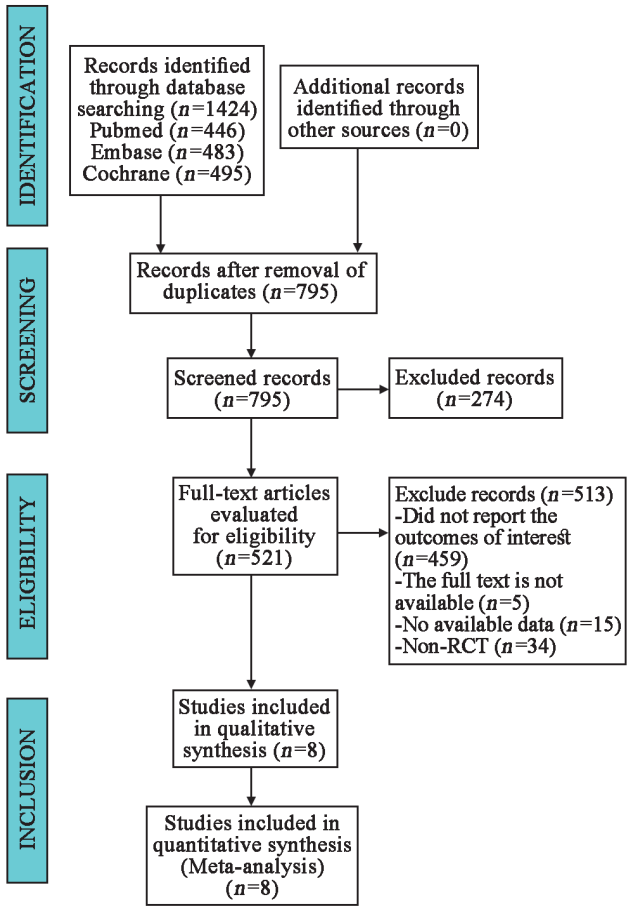

Figure 1: Flow diagram for selection of studies. RCT: Randomized controlled trial.

patients from multiple countries and ethnic groups, with an average age of 50 years consistent with a middle-aged or elderly patient population. PD-1/PD-L1 inhibitors utilized in these various studies included atezolizumab, pembrolizumab, and durvalumab [Table 1].

Included study quality

All of the studies in this meta-analysis described their random sequence generation strategies, while six were double-blinded, one did not use any blinding, and one did not discuss blinding practices [Figures 2A, B]. Additionally, allocation concealment was performed for five of these studies. Overall, this analysis revealed the quality of the included studies to be relatively high.

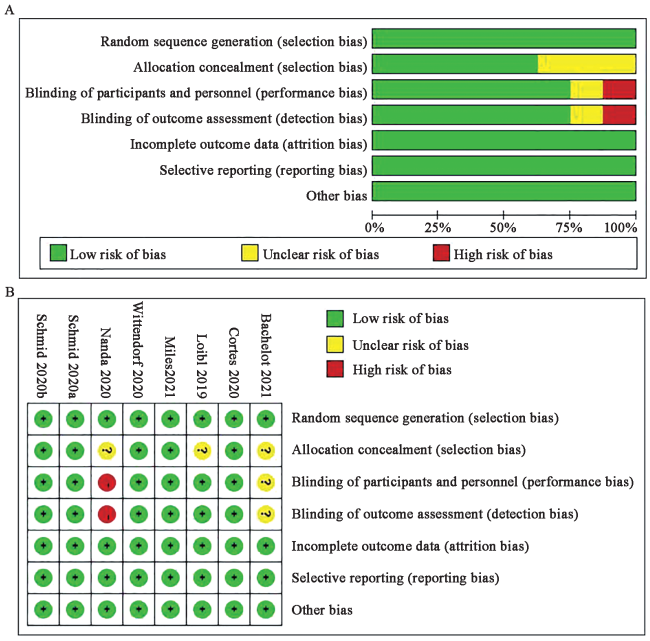

Figure 2: Risk of bias graph (A) and risk of bias summary (B).

Table 1: The baseline characteristics quality assessment of the included studies

Author	Year	Research Type	Study area	Number of cases		Gender (Female/Male)		Age (years)		Intervention	
				Experimental group	Control group	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
Loibl[24]	2019	RCT	Germany	88	86	Women		49.5 (25.0–74.0)	49.5 (23.0–76.0)	Durvalumab plus nab-paclitaxel	Placebo plus nab-paclitaxel
Bachelot[25]	2021	RCT	France	131	68	Women		NA	NA	Durvalumab plus paclitaxel	Paclitaxel
Nanda[26]	2020	RCT	USA	69	181	Women		NA	NA	Pembrolizumab plus paclitaxel	Paclitaxel
Schmid[27]	2020b	RCT	UK	784	390	Women		49 (22–80)	48 (24–79)	Pembrolizumab plus hemotherapy	Placebo plus chemotherapy
Cortes[28]	2020	RCT	29 countries	566	281	Women		53 (44–63)	53 (43–63)	Pembrolizumab plus hemotherapy	Placebo plus chemotherapy
Schmid[33]	2020a	RCT	41 countries	451	451	448/3	450/1	55 (46–64)	56 (47–65)	Atezolizumab plus nab-paclitaxel	Placebo plus nab-paclitaxel
Mittendorf[34]	2020	RCT	13 countries	165	168	Women		51 (22–76)	51 (26–78)	Atezolizumab plus nab-paclitaxel	Placebo plus nab-paclitaxel
Miles[35]	2021	RCT	Multinational	431	220	430/1	220/0	54 (22–85)	53 (25–81)	Atezolizumab plus paclitaxel	Placebo plus paclitaxel

Data are presented as n or median (interquartile range). RCT: Randomized controlled trial; NA: Not applicable.

Meta-analysis results

OS

Overall, four studies reported on the OS of patients who underwent chemotherapeutic treatment alone or in combination with PD-1/PD-L1 inhibitors. These findings were studied with a fixed-effects model owing to a lack of any significant heterogeneity (I^2 = 21.7% and P = 0.280), and the pooled outcomes indicated that the combination treatment group cannot improve the OS than patients who underwent chemotherapeutic treatment alone (HR = 0.92, 95% CI: 0.80–1.06, P = 0.273; Figure 3A).

PFS

In total, six investigations explained on the PFS of cases that underwent chemotherapeutic treatment alone or in combi-

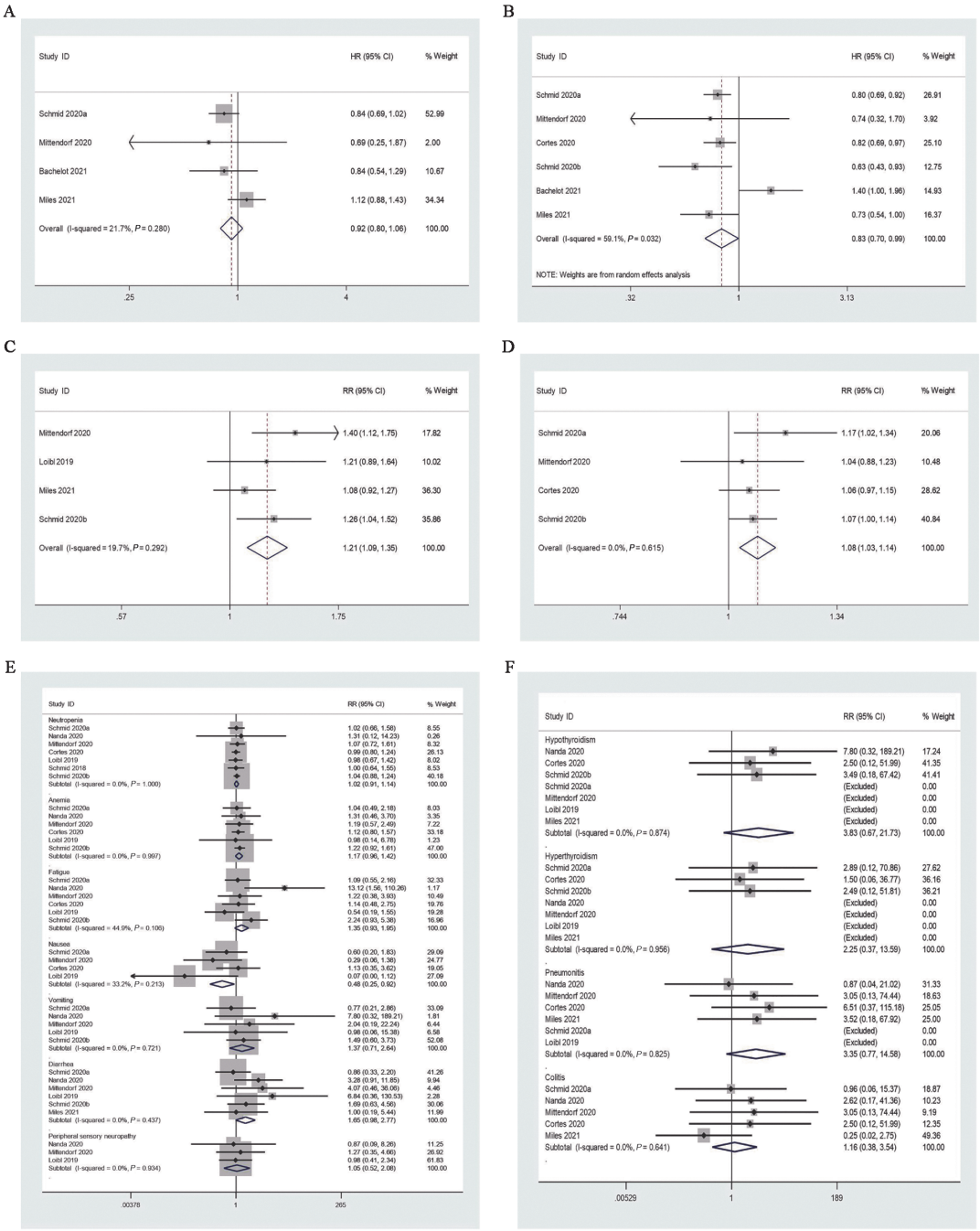

Figure 3: OS of PD-1/PD-L1 inhibitor combined chemotherapy group and chemotherapy alone group (A). PFS of PD-1/PD-L1 inhibitor combined chemotherapy group and chemotherapy alone group (B). CRR of PD-1/PD-L1 inhibitor combined chemotherapy group and chemotherapy alone group (C). Incidence of any adverse events (grade ≥3) of PD-1/PD-L1 inhibitor combined chemotherapy group and chemotherapy alone group (D). Incidence of treatment-related adverse events (grade ≥3) of PD-1/PD-L1 inhibitor combined chemotherapy group and chemotherapy alone group (E). Incidence of immune-related adverse events (grade ≥3) of PD-1/PD-L1 inhibitor combined chemotherapy group and chemotherapy alone group (F). CI: Confidence interval; CRR: Complete response rate; HR: Hazard ratio; OS: Overall survival; PD-1/PD-L1: Programmed cell death-1/programmed death-ligand 1; PFS: Progression-free survival.

nation with PD-1/PD-L1 inhibitors. These data were assessed with a random-effects model as significant heterogeneity was detected (I^2 = 59.1% and P = 0.032). Pooled results indicated that the PFS of patients within the combination treatment group was considerably longer than that of patients who only underwent chemotherapeutic treatment (HR = 0.83, 95% CI: 0.70–0.99, P = 0.032; Figure 3B).

CRR

Four of the included investigations explained the CRR of patients who underwent chemotherapeutic treatment alone or in combination with PD-1/PD-L1 inhibitors. Since there was no significant heterogeneity, a fixed-effect model was used to combine effects (I^2 = 19.7% and P = 0.292). Pooled results indicated that the CRR of patients in the combination treatment group was markedly longer than that of patients who only underwent chemotherapeutic treatment (risk ratio [RR] = 1.21, 95% CI: 1.09–1.35, $P \leq 0.001$; Figure 3C).

Incidence of adverse events

Overall, four studies reported rates of adverse events (grade ≥3) in patients who underwent chemotherapeutic treatment alone or in combination with PD-1/PD-L1 inhibitors. These findings were studied with a fixed-effects model owing to a lack of any significant heterogeneity (I^2 = 0.0% and P = 0.615), with pooled results revealing that the rate of any adverse events was greater in the combination treatment group relative to the chemotherapy group (RR = 1.08, 95% CI: 1.03–1.14, P = 0.002; Figure 3D).

We additionally explored the incidence of treatment-associated adverse events (neutropenia, anemia, fatigue, nausea, vomiting, diarrhea, and peripheral sensory neuropathy) and immune-related adverse events (hypothyroidism, hyperthyroidism, pneumonitis, and colitis) among patients who underwent these different treatment regimens. No significant differences between patients who did and did not undergo combination treatment were observed with respect to the incidence of neutropenia (RR = 1.02, 95% CI: 0.91–1.14, P = 0.707), anemia (RR = 1.17, 95% CI: 0.96–1.42, P = 0.114), fatigue (RR = 1.35, 95% CI: 0.93–1.95, P = 0.117), vomiting (RR = 1.37, 95% CI: 0.71–2.64, P = 0.348), diarrhea (RR = 1.65, 95% CI: 0.98–2.77, P = 0.060), or peripheral sensory neuropathy (RR = 1.05, 95% CI: 0.52–2.08, P = 0.900). However, rates of nausea were remarkably lesser in the combination treatment group relative to the group of cases that underwent chemotherapy only (RR = 0.48, 95% CI: 0.25–0.92, P = 0.026; Figure 3E). Overall, these pooled results additionally suggested that there were no considerable discrepancies in immune-related adverse event rates when comparing these two patient groups (hypothyroidism: RR = 3.83, 95% CI: 0.67–21.73, P = 0.130; hyperthyroidism: RR = 2.25, 95% CI: 0.37–13.59, P = 0.378; pneumonitis: RR = 3.35, 95% CI: 0.77–14.58, P = 0.107; and colitis: RR = 1.16, 95% CI: 0.38–3.54, P = 0.788; Figure 3F).

Subgroup analyses

As there were multiple PD-1/PD-L1 inhibitors applied in the different investigations included in this meta-analysis, we conducted subgroup analyses with the goal of specifically assessing efficacy outcomes associated with particular therapeutic regimens. Three studies described OS outcomes for patients treated with a combination of chemotherapy and atezolizumab, while one study reported the OS of cases treated by taking advantage of a combination of chemotherapy and durvalumab. Pooled results indicated that the OS of patients who received combination treatment with atezolizumab was not significantly better than that of patients who received chemotherapeutic treatment alone (HR = 0.93, 95% CI: 0.80–1.09, P = 0.375; Figure 4A). Similarly, no comparable difference in OS was detected between control and experimental groups was evident for patients who were treated utilizing durvalumab and chemotherapy (HR = 0.84, 95% CI: 0.54–1.30, P = 0.433; Figure 4A).

PFS outcomes for patients who underwent combination treatment with chemotherapy and atezolizumab, pembrolizumab, and durvalumab were reported in three, two, and

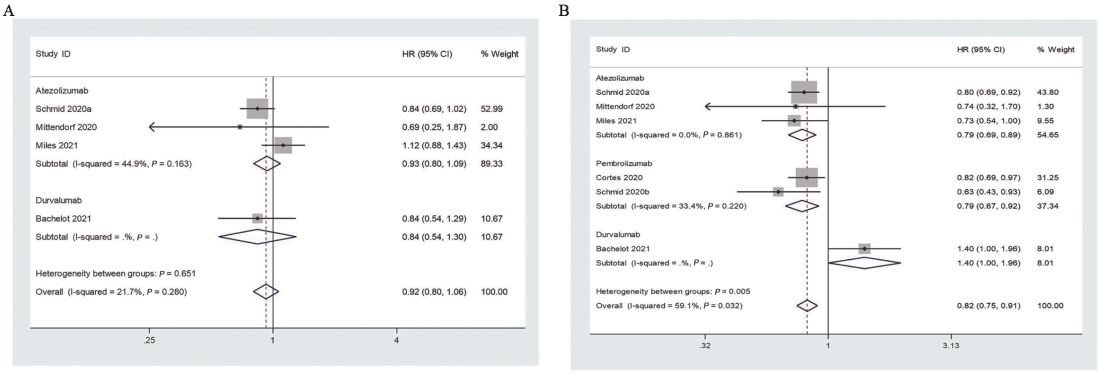

Figure 4: Subgroup analysis of the OS of different PD-1/PD-L1 inhibitors in the treatment of breast cancer (A). Subgroup analysis of the PFS of different PD-1/PD-L1 inhibitors in the treatment of breast cancer (B). CI: Confidence interval; HR: Hazard ratio; OS: Overall survival; PD-1/PD-L1: Programmed cell death-1/programmed death-ligand 1; PFS: Progression-free survival.

one studies, respectively. Pooled results revealed that the combination of atezolizumab or pembrolizumab with chemotherapy was linked to a remarkable increase in PFS relative to chemotherapy alone (HR = 0.79, 95% CI: 0.69–0.89, $P \leq 0.001$; HR = 0.79, 95% CI: 0.67–0.92, $P = 0.002$; Figure 4B), whereas no comparable difference in PFS was realized between control and experimental groups for patients who were treated with durvalumab and chemotherapy (HR = 1.40, 95% CI: 1.00–1.96, $P = 0.05$; Figure 4B).

Sensitivity analysis

To assess whether any individual study included in this meta-analysis had an undue impact on the overall results, we next performed a sensitivity analysis wherein individual studies were sequentially excluded from the summary analysis. This approach indicated that none of the included studies had an excessive impact on the overall results of our meta-analysis, as evidenced by the stability of the summary analysis results, further emphasizing the reliability of these findings (see Supplementary Figures 1–4, http://links.lww.com/CM9/B465, Supplemental Content, which illustrates the stability of the summary analysis results).

Publication bias

Next, a publication bias analysis was performed. Funnel plots corresponding to comparisons of the OS of cases in the combination and chemotherapy groups were essentially symmetrical [Figure 5A], with an Egger's test P value of 0.781, consistent with an absence of any apparent publication bias associated with this endpoint. Similarly, funnel plots corresponding to the PFS [Figure 5B] and CRR [Figure 5C] of patients in the combination and chemotherapy only groups in this study were symmetrical with Egger's test P-values of 0.885 and 0.470, respectively, indicating a lack of publication bias. Likewise, no publication bias was detected when evaluating adverse event rates in these combination and chemotherapy-only patient groups [Figure 5D], with a corresponding Egger's test P-value of 0.645.

Discussion

Breast cancer is among the most prevalent tumor types in females. We already know that breast cancer screening is the key to improving survival rates and controlling cancer outcomes. However, in low- and middle-income countries such as Africa, breast cancer screening is still slow.[15] The majority of patients are diagnosed with stage III–IV disease such that the overall rate of survival for these breast cancer patients is <30%.[15] Overall, just 5–10% of advanced breast cancer patients survive for >5 years, and the median survival duration for these individuals is just 2–3 years after diagnosis.[16] Fortunately, recent studies have found that the combination of internally enhanced Breast Imaging Reporting and Data System (BI-RADS) descriptors and apparent diffusion coefficient (ADC) values is useful for the differential diagnosis of lesions that show non-mass enhancement, which will help to improve the diagnosis rate of breast cancer in the future.[16] Chemotherapy is a primary approach employed to treat individuals with advanced breast cancer, but the prognosis of these patients remains poor owing to high rates of chemoresistance.[17] The emergence of further studies of immunotherapeutic drugs and associated regulatory pathways in recent years have informed efforts to reverse tumor cell therapeutic resistance, with agents such as anti-PD-1/PD-L1 antibodies having exhibited some degree of clinical efficacy in the treatment of specific malignant tumor types when deployed together with chemotherapy.[18–20]

To evaluate the safety and anti-tumor efficacy of combination chemotherapy and PD-1/PD-L1 inhibitor treatment in breast cancer cases, we herein conducted a meta-analysis of eight eligible surveys. These investigations included 4781 total patients, including 2076 that underwent chemotherapy alone, and 2705 that underwent a combination of chemotherapy and PD-1/PD-L1 inhibitor treatment. Therapeutic agents used in these studies included one PD-1 inhibitor (pembrolizumab) and two PD-L1 inhibitors (atezolizumab and durvalumab). Patient OS, PDS, CRR, and adverse event-related data were extracted from included studies for subsequent evaluation, and subgroup analyses were performed to compare patient outcomes as a function of the different PD-1/PD-L1 inhibitors employed in these different investigations.

We found that the PFS of breast cancer patients who underwent combination chemotherapy and PD-1/PD-L1 inhibitor treatment were considerably longer than those of patients who treated with chemotherapy alone (HR = 0.83, 95% CI: 0.70–0.99, $P = 0.032$). Similarly, the CRR of

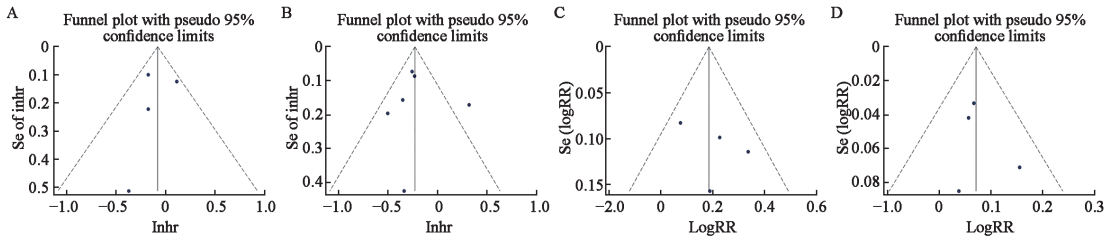

Figure 5: Funnel plot of OS of PD-1/PD-L1 inhibitor combined chemotherapy group and chemotherapy alone group (A). Funnel plot of PFS of PD-1/PD-L1 inhibitor combined chemotherapy group and chemotherapy alone group (B). Funnel plot of CRR of PD-1/PD-L1 inhibitor combined chemotherapy group and chemotherapy alone group (C). Funnel plot of incidence of any adverse events of PD-1/PD-L1 inhibitor combined chemotherapy group and chemotherapy alone group (D). CRR: Complete response rate; Inhr: Inhibitor; OS: Overall survival; PD-1/PD-L1: Programmed cell death-1/programmed death-ligand 1; PFS: Progression-free survival; RR: Risk ratio; Se: Standard error.

patients in the combination treatment group was remarkably greater than that of patients in the chemotherapy group (RR = 1.21, 95% CI: 1.09–1.35, P = 0.000). However, the pooled outcomes indicated that the combination treatment group cannot improve the OS than patients who underwent chemotherapeutic treatment alone. This shows that combined therapy can significantly improve the efficacy of breast cancer treatment compared with chemotherapy alone. In cases with early-stage triple-negative breast cancer (TNBC), combined chemotherapy and atezolizumab treatment has been reported to be superior than chemotherapy treatment alone irrespective of patient PD-L1 status. However, we have previously found that the PFS of advanced breast cancer patients harboring PD-L1-positive immune cells was higher whereas treatment had no impact in the PD-L1 negative patient subgroup.[21] It was postulated that the tumor immune microenvironment associated with early-stage TNBC could be more robust and responsive to immunotherapy as compared to that associated with metastatic TNBC, thus better enabling patients to mount an effective anti-tumor response.[22] Combined chemotherapy and durvalumab treatment has been reportedly linked to greater rates of pathological complete response (PCR) in treated patients, thus predicting a better prognosis.[23] While overall levels of PD-L1 or increases in stromal tumor-infiltrating lymphocytes have been found to be related to increased immune responses in certain contexts, they have not been reported to predict durvalumab response in treated patients.[24,25] The tumor microenvironment also appears to play a role in influencing therapeutic outcomes associated with durvalumab, with certain factors such as CD274 representing potential biomarkers of therapeutic sensitivity.[25] In early-stage breast cancer, pembrolizumab combined with chemotherapy was correlated with better patient OS and PFS and with a higher PCR rate. However, we found that in developed breast cancer patients, pembrolizumab was associated with prolonged PFS but not OS relative to chemotherapy alone.[26–28] These differences may be attributable to patient PD-L1 status, with pembrolizumab treatment efficacy increasing with PD-L1 enrichment.[29]

The results of our adverse events analysis indicated that rates of nausea were significantly lower among patients undergoing combination treatment relative to patients in the chemotherapy group (RR = 0.48, 95% CI: 0.25–0.92, P = 0.026), whereas diarrhea rates were substantially greater among patients in this combination group (RR = 1.73, 95% CI: 1.00–3.00, P = 0.049). This results show that the incidence of adverse events of combination therapy is higher than that of chemotherapy alone, which suggests that clinicians need to pay attention to the occurrence of adverse reactions while adopting combination therapy, and choose the best treatment method by balancing the pros and cons. Immunosuppressive agents may thus alleviate chemotherapy-induced nausea to some degree. Other adverse events such as diarrhea, anemia, and neutropenia observed among these patients may be attributable to the non-specific activation of antigen-presenting cells, the reversal of latent immunosuppression, and enhanced T cell infiltration and activation.[30] Loibl *et al*[24] previously reported that the most common immune-related adverse event associated with durvalumab was thyroid dysfunction of any grade, affecting 47% of analyzed individuals.[31] In subgroup analyses, we found that the PFS of patients who underwent combination chemotherapy and atezolizumab treatment were significantly longer than those of patients who treated with chemotherapy only. Furthermore, the PFS of patients who treated with a combination of chemotherapy and pembrolizumab was significantly longer than that of patients who treated with chemotherapy only. These data may thus suggest that a combination of chemotherapy and atezolizumab or pembrolizumab could be recommended to appropriate breast cancer cases in accordance with their PD-L1 status.

This study is subject to two major limitations. First, the data included herein were based upon research-level evidence rather than analyses of individual patient data, constraining the reliability of these findings. Second, we detected a moderate degree of heterogeneity associated with patient PFS owing to the different PD-1 or PD-L1 inhibitors used in the treatment of different patients.

The pooled results suggest that combination chemotherapy and PD-1/PD-L1 inhibitor treatment approaches help prolong PFS in breast cancer patients, but have no significant effect on OS. Additionally, combination therapy can significantly improve CRR compared with chemotherapy alone. However, combination therapy was associated with greater rates of adverse events. PD-1/PD-L1 inhibitor combined with chemotherapy has a significant effect in the treatment of breast cancer and can be promoted more widely in the clinic, but it is also necessary to pay attention to preventing the occurrence of adverse events in the application. Since the basic characteristics of the patients were not described in more detail in the study, we were unable to carry out more subgroup analyses to rule out the heterogeneity in the study. Therefore, in future studies, we need to include more clinical trials to further verify the reliability of the results of this study.

Acknowledgements

None.

Funding

This work was supported by a grant from the Suzhou Youth Science and Technology Program (No.KJXW2021067).

Conflicts of interest

None.

References

1. Harbeck N, Gnant M. Breast cancer. Lancet 2017; 389: 1134–1150. doi: 10.1016/s0140-6736(16)31891-8.
2. Januskeviciene I, Petrikaite V. Heterogeneity of breast cancer: The importance of interaction between different tumor cell populations. Life Sci 2019;239:117009. doi: 10.1016/j.lfs.2019.117009.
3. Abbott M, Ustoyev Y. Cancer and the immune system: The history and background of immunotherapy. Semin Oncol Nurs 2019;35:150923. doi: 10.1016/j.soncn.2019.08.002.

4. Yu WD, Sun G, Li J, Xu J, Wang X. Mechanisms and therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy. Cancer Lett 2019;452:66–70. doi: 10.1016/j.canlet.2019.02.048.
5. Heinhuis KM, Ros W, Kok M, Steeghs N, Beijnen JH, Schellens JHM. Enhancing antitumor response by combining immune checkpoint inhibitors with chemotherapy in solid tumors. Ann Oncol 2019;30:219–235. doi: 10.1093/annonc/mdy551.
6. Emens LA. Breast cancer immunotherapy: Facts and hopes. Clin Cancer Res 2018;24:511–520. doi: 10.1158/1078-0432.CCR-16-3001.
7. Rocco D, Della Gravara L, Battiloro C, Gridelli C. The role of combination chemo-immunotherapy in advanced non-small cell lung cancer. Expert Rev Anticancer Ther 2019;19:561–568. doi: 10.1080/14737140.2019.1631800.
8. Solinas C, Gombos A, Latifyan S, Piccart-Gebhart M, Kok M, Buisseret L. Targeting immune checkpoints in breast cancer: An update of early results. ESMO Open 2017;2:e000255. doi: 10.1136/esmoopen-2017-000255.
9. Han Y, Liu D, Li L. PD-1/PD-L1 pathway: Current researches in cancer. Am J Cancer Res 2020;10:727–742.
10. Ai L, Xu A, Xu J. Roles of PD-1/PD-L1 pathway: Signaling, cancer, and beyond. Adv Exp Med Biol 2020;1248:33–59. doi: 10.1007/978-981-15-3266-5_3.
11. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and anti-CTLA-4 therapies in cancer: Mechanisms of action, efficacy, and limitations. Front Oncol 2018;8:86. doi: 10.3389/fonc.2018.00086.
12. Zhao J, Huang J. Breast cancer immunology and immunotherapy: targeting the programmed cell death protein-1/programmed cell death protein ligand-1. Chin Med J 2020;133:853–862. doi: 10.1097/CM9.0000000000000710
13. Cheng Y, Li H, Zhang L, Liu JJ, Yang CL, Zhang S. Current and future drug combination strategies based on programmed death-1/programmed death-ligand 1 inhibitors in non-small cell lung cancer. Chin Med J 2021;134:1780–1788. doi: 10.1097/CM9.0000000000001560
14. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097. doi: 10.1371/journal.pmed.1000097.
15. Richman DM, Tirumani SH, Hornick JL, Fuchs CS, Howard S, Krajewski K, *et al*. Beyond gastric adenocarcinoma: Multimodality assessment of common and uncommon gastric neoplasms. Abdom Radiol (NY) 2017;42:124–140. doi: 10.1007/s00261-016-0901-x.
16. Tevaarwerk AJ, Gray RJ, Schneider BP, Smith ML, Wagner LI, Fetting JH, *et al*. Survival in patients with metastatic recurrent breast cancer after adjuvant chemotherapy: Little evidence of improvement over the past 30 years. Cancer 2013;119:1140–1148. doi: 10.1002/cncr.27819.
17. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: An evolving paradigm. Nat Rev Cancer 2013;13:714–726. doi: 10.1038/nrc3599.
18. Zhao S, Ren S, Jiang T, Zhu B, Li X, Zhao C, *et al*. Low-dose apatinib optimizes tumor microenvironment and potentiates antitumor effect of PD-1/PD-L1 blockade in lung cancer. Cancer Immunol Res 2019;7:630–643. doi: 10.1158/2326-6066.CIR-17-0640.
19. Neal JT, Li X, Zhu J, Giangarra V, Grzeskowiak CL, Ju J, *et al*. Organoid modeling of the tumor immune microenvironment. Cell 2018;175:1972–1988.e16. doi: 10.1016/j.cell.2018.11.021.
20. D'Alterio C, Buoncervello M, Ieranò C, Napolitano M, Portella L, Rea G, *et al*. Targeting CXCR4 potentiates anti-PD-1 efficacy modifying the tumor microenvironment and inhibiting neoplastic PD-1. J Exp Clin Cancer Res 2019;38:432. doi: 10.1186/s13046-019-1420-8.
21. Emens LA, Molinero L, Loi S, Rugo HS, Schneeweiss A, Diéras V, *et al*. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer: Biomarker evaluation of the IMpassion130 study. J Natl Cancer Inst 2021;113:1005–1016. doi: 10.1093/jnci/djab004.
22. Hutchinson KE, Yost SE, Chang CW, Johnson RM, Carr AR, McAdam PR, *et al*. Comprehensive profiling of poor-risk paired primary and recurrent triple-negative breast cancers reveals immune phenotype shifts. Clin Cancer Res 2020;26:657–668. doi: 10.1158/1078-0432.CCR-19-1773.
23. Spring LM, Fell G, Arfe A, Sharma C, Greenup R, Reynolds KL, *et al*. Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: A comprehensive meta-analysis. Clin Cancer Res 2020;26:2838–2848. doi: 10.1158/1078-0432.CCR-19-3492.
24. Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, Blohmer JU, *et al*. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: Clinical results and biomarker analysis of GeparNuevo study. Ann Oncol 2019;30:1279–1288. doi: 10.1093/annonc/mdz158.
25. Bachelot T, Filleron T, Bieche I, Arnedos M, Campone M, Dalenc F, *et al*. Durvalumab compared to maintenance chemotherapy in metastatic breast cancer: The randomized phase II SAFIR02-BREAST IMMUNO trial. Nat Med 2021;27:250–255. doi: 10.1038/s41591-020-01189-2.
26. Nanda R, Liu MC, Yau C, Shatsky R, Pusztai L, Wallace A, *et al*. Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: An analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. JAMA Oncol 2020;6:676–684. doi: 10.1001/jamaoncol.2019.6650.
27. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, *et al*. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020;382:810–821. doi: 10.1056/NEJMoa1910549.
28. Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, *et al*. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): A randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020;396:1817–1828. doi: 10.1016/S0140-6736(20)32531-9.
29. Adams S, Schmid P, Rugo HS, Winer EP, Loirat D, Awada A, *et al*. Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: Cohort A of the phase II KEYNOTE-086 study. Ann Oncol 2019;30:397–404. doi: 10.1093/annonc/mdy517.
30. Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH, *et al*. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer 2016;60:12–25. doi: 10.1016/j.ejca.2016.02.010.
31. Hahn AW, Gill DM, Agarwal N, Maughan BL. PD-1 checkpoint inhibition: Toxicities and management. Urol Oncol 2017;35:701–707. doi: 10.1016/j.urolonc.2017.08.005.
32. Miura Y, Mouri A, Kaira K, Yamaguchi O, Shiono A, Hashimoto K, *et al*. Chemoradiotherapy followed by durvalumab in patients with unresectable advanced non-small cell lung cancer: Management of adverse events. Thorac Cancer 2020;11:1280–1287. doi: 10.1111/1759-7714.13394.
33. Schmid P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, Iwata H, *et al*. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): Updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:44–59. doi: 10.1016/S1470-2045(19)30689-8.
34. Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, *et al*. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): A randomised, double-blind, phase 3 trial. Lancet 2020;396:1090–1100. doi: 10.1016/S0140-6736(20)31953-X.
35. Miles D, Gligorov J, André F, Cameron D, Schneeweiss A, Barrios C, *et al*. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. Ann Oncol 2021;32:994–1004. doi: 10.1016/j.annonc.2021.05.801.

How to cite this article: Qian D, Xu YH, Wu YH, Qiu J, Hong WM, Meng XL. Assessment of the safety and efficacy of combination chemotherapy and PD-1/PD-L1 inhibitor treatment of breast cancer: A meta-analysis. Chin Med J 2023;136:1663–1670. doi: 10.1097/CM9.0000000000002631