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REVIEW

Treatment for Triple-Negative Breast Cancer: An Umbrella Review of Meta-Analyses

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Purpose: In recent years, many meta-analyses of triple-negative breast cancer (TNBC) treatment have been published; however, these studies still lack systematic summary. Therefore, the aim of this study is to summarize and evaluate the evidence level and efficacy of treatment for TNBC.

Materials and Methods: Retrospective and prospective studies on treatment of TNBC were searched in the PubMed, Embase, and Cochrane Library databases. The literature search deadline was June 30, 2021. Two investigators independently screened the literature and extracted the data. In addition, the joint World Health Organization–United Nations Food and Agriculture Organization expert consultation was used to evaluate the validity of the evidence.

Results: A total of 28 meta-analyses were included in this study. The treatment interventions for TNBC mainly included surgery, chemotherapy (CT), radiotherapy, molecular targeted therapy, immunotherapy, zoledronic acid, and gonadotropin-releasing hormone (GnRH) analog. Platinum improves the pathological complete response (PCR) rate of patients treated with neoadjuvant chemotherapy (NACT), the objective remission rate (ORR) and overall survival (OS) in patients with metastatic triple-negative breast cancer. Capecitabine improves disease-free survival (DFS) and OS in patients treated with adjuvant CT. Bevacizumab was added to NACT to improve the PCR rate in patients. Immunotherapy improves the PCR rate in patients treated with NACT. The improvement in PCR rate in patients with high Ki67 expression treated with neoadjuvant therapy is highly suggestive. Other interventions had suggestive or weak evidence.

Conclusion: Among the strategies for treating TNBC, platinum, bevacizumab, and immunotherapy can lead to better PCR rates as part of a NACT regimen. Capecitabine as adjuvant CT and platinum in the treatment of metastatic TNBC can benefit patients' survival. However, the effectiveness of other interventions for TNBC is not yet clear. Further research is needed in the future to obtain more reliable clinical evidence.

Keywords: triple-negative breast cancer, treatment, meta-analysis, umbrella review

Introduction

Breast cancer is the most common malignant tumor among female individuals. The incidence of breast cancer has increased year by year in recent years. According to the latest statistics, new cases of breast cancer account for nearly 30% of all new tumors in female individuals.[1] Triple-negative breast cancer (TNBC) is a subtype of breast cancer that is negative on immunohistochemical examination for the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2.[2] TNBC accounts for 15–20% of all breast cancers[3] and more than 50% of metastatic breast cancers. The main clinicopathological manifestations of TNBC are high-grade invasive ductal carcinoma and regional necrosis,[4] as well as myeloid carcinoma. Compared patients with other subtypes of breast cancer, patients with TNBC are younger, have a larger tumor size, and have more frequent lymph node involvement.[5] Moreover, the disease stage in TNBC is typically later,[6] the risk of postoperative recurrence is higher, and metastasis is more likely.

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Because TNBC has special pathological and biological characteristics, its clinical treatment is difficult. In recent years, the treatment of TNBC has become a focus of tumor research. Many meta-analyses of TNBC treatment have also been published; however, these studies still lack systematic evidence summary and evaluation. Therefore, this study aims to further analyze and evaluate meta-analyses of TNBC treatment to provide more reliable evidence for clinical applications and facilitate the formulation of more effective treatment schemes.

Materials and Methods

Retrieval Strategy

We searched for relevant literature in the PubMed, EMBASE, and Cochrane Library databases as of June 30, 2021. The search terms included "TNBC" or "triple negative breast cancer" or "triple negative breast tumors", combined with "systematic review or meta-analysis."

Inclusion Criteria

We included studies that examined patients of any age with TNBC of any disease course; studies that used surgery, chemotherapy (CT), radiotherapy, targeted therapy, immunotherapy, zoledronic acid, GnRH analogs, or their combination as interventions; studies that included overall survival (OS), relapse-free survival (RFS), disease-free survival (DFS), progression-free survival (PFS), event-free survival (EFS), local relapse-free survival (LFS), pathological complete response (PCR), objective response rate (ORR), disease recurrence rate, local recurrence rate, and distant metastasis rate; and studies that were meta-analyses.

Exclusion Criteria

If any of the following conditions were met, the study was excluded from this review: incomplete data, no outcome index literature, only summary text can be obtained, and duplicate publications or those with the same intervention measures.

Literature Screening

Two people independently screened the literature. First, they excluded the studies that obviously did not meet the inclusion criteria after reading the titles and abstracts of all the initially identified studies. The full text of studies passing the initial screening was examined and strictly compared with inclusion and exclusion criteria. Any disagreement about study inclusion was settled by a third evaluator.

Data Extraction

Two people independently extracted data and compared their findings. Extracted data included: title, publication date, author's name, published journal, disease stage, intervention plan, comparison, number of patients, number of studies, OS, RFS, DFS, PFS, LFS, EFS, ORR, PCR, local recurrence rate, distant metastasis rate, etc.

Evidence Evaluation

Evidence evaluation was based on the joint World Health Organization–United Nations Food and Agriculture Organization expert consultation[7] (Table 1). The reliability of evidence was mainly assessed according to the study design (meta-analysis of prospective studies or respective studies), sample number, heterogeneity (I^2), and effect size. The evidence was classified as (a) convincing, (b) highly suggestive, (c) suggestive, or (d) weak.

Results

Search Results and General Characteristics of Included Literature

According to the search strategy, a total of 784 studies were screened out. After reading the full text according to the protocol, 28 studies (10 meta-analyses of observational studies and 20 meta-analyses of interventional studies) including seven treatment methods (surgical treatment, 2 studies; CT, 16 studies; radiotherapy, 1 study; targeted therapy, 6 studies;

Table 1 Criteria Used to Rate the Level of Evidence for the Treatment of Triple-Negative Breast Cancer

Convincing
Level 1a (high): concordance between meta-analyses of RCTs and meta-analyses of observational studies (any)
Level 1b (low): meta-analyses of RCTs with results contrary to those from meta-analyses of observational studies (any)
Probable
Level 2a (high): meta-analyses of prospective studies with no heterogeneity, no potential confounding factors identified, and agreement of results over time and among meta-analyses, including studies with different designs
Level 2b (medium): meta-analyses of prospective studies with no heterogeneity and no potential confounding factors identified
Level 2c (low): meta-analyses of prospective and case-control studies with no heterogeneity and no potential confounding factors identified
Possible
Level 3a (high): meta-analyses of prospective studies lacking information on heterogeneity and potential confounding factors
Level 3b (medium): meta-analyses of prospective and case-control studies lacking information on heterogeneity and potential confounding factors
Level 3c (low): meta-analyses of case-control studies or meta-analyses of any other study design with significant heterogeneity (I^2 > 50%) and potential confounding factors
Limited/contrasting
Level 4: Limited studies included in meta-analyses (n ≤ 3) or evident contrasting results from meta-analyses with the same level of evidence

Note: Table modified from the joint World Health Organization–United Nations Food and Agriculture Organization expert consultation.[7]
Abbreviation: RCT, randomized controlled trial.

immunotherapy, 1 study; zoledronic acid, 1 study; and GnRH analog, 1 study) were included in this study. The literature screening process is shown in Figure 1. The basic characteristics and results of the included studies are shown in Table 2.

Breast-Conserving Surgery Plus Radiotherapy versus Simple Mastectomy

Patients with TNBC with small tumor volume are more likely to choose breast-conserving surgery than simple mastectomy. After breast conserving surgery plus radiotherapy, the local recurrence rate, distant metastasis rate, and all-cause mortality of patients were significantly reduced.[8] The local control rate in patients with TNBC after breast conserving surgery plus radiotherapy was similar to that of patients with non TNBC.[9]

CT versus Non-CT

Adjuvant CT combined with surgery reduced the risk of recurrence in patients (pT1abN0M0),[10,11] and the OS was improved (HR = 0.72, 95% CI: 0.53–0.99);[10] however, further analysis suggested that only T1b patients (rather than T1a) truly benefited from adjuvant CT.[10,11]

Neoadjuvant CT versus Adjuvant CT

Compared with adjuvant CT, neoadjuvant CT (NACT) led to no significant improvement in OS or DFS in patients with TNBC. However, when PCR was achieved after NACT, the OS and DFS were significantly improved. The OS was lower when there were residual lesions after neoadjuvant therapy (HR = 1.18, 95% CI: 1.09–1.28).[12]

Compared with patients with non TNBC, patients with TNBC had higher PCR rates after NACT (OR = 3.10, 95% CI: 2.51–3.82), and DFS and OS were significantly improved in patients with PCR. The PCR rate in patients with TNBC with high Ki-67 expression was higher than that in patients with low Ki-67 expression (OR = 9.87, 95% CI: 3.53–27.62).[13]

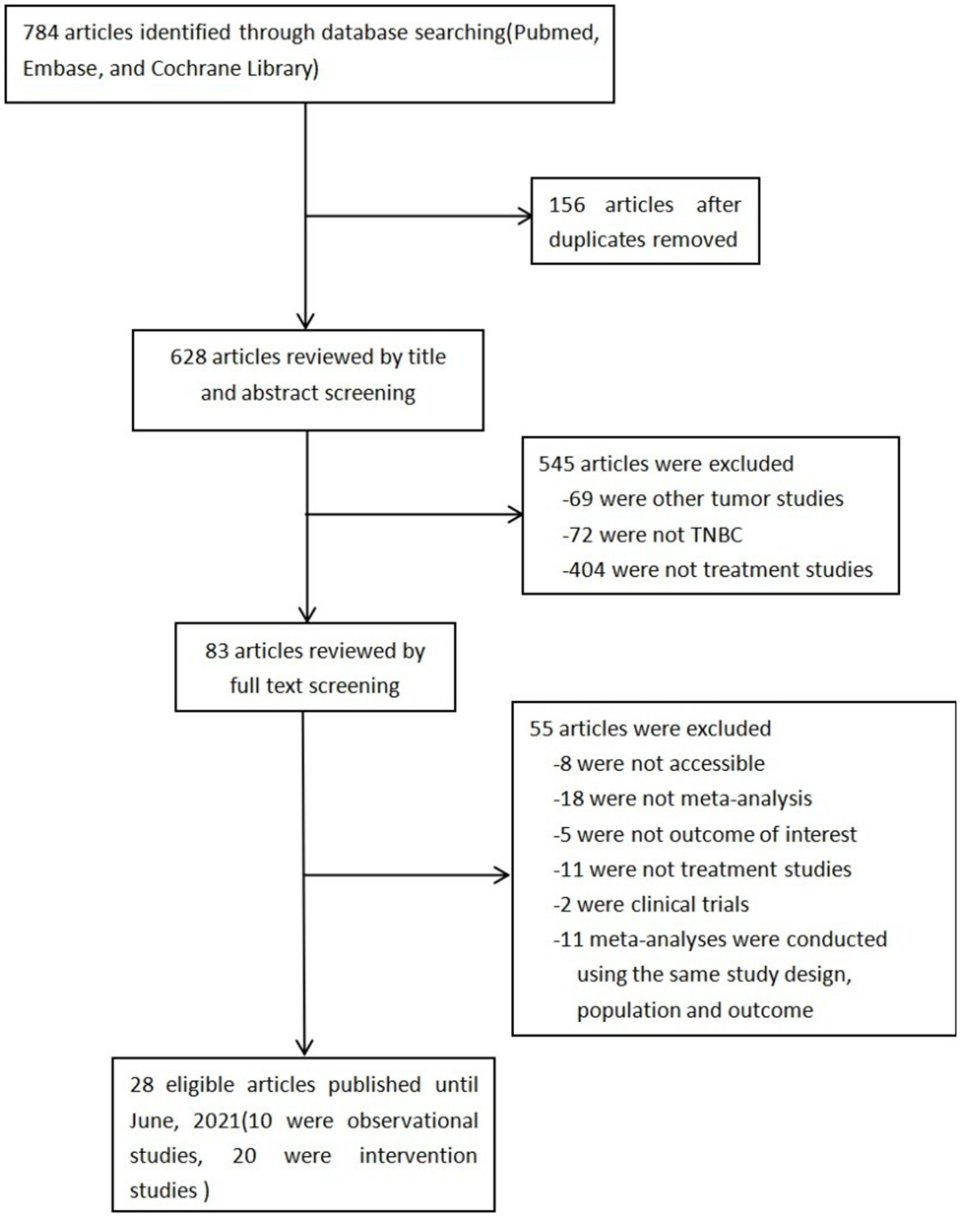

Figure 1 Flow chart of literature screening included in this study.

Platinum Chemotherapy

Platinum-based NACT significantly improved the PCR rate in patients with TNBC patients (OR = 2.12, 95% CI: 1.64–2.73) compared with non-platinum-based NACT[14]. There was no significant difference in ORR between platinum-containing and platinum-free NACT (RR = 1.11, 95% CI: 0.96, 1.29),[15] and there was no significant improvement in long-term survival.[16] Compared with non platinum containing chemotherapy, Platinum-based CT significantly increased ORR (OR = 2.34, 95% CI: 1.66–3.28) in patients with metastatic TNBC[17] and slightly improved OS and PFS in patients with metastatic TNBC.[18] Compared with patients with non TNBC, the PCR rate of patients with TNBC was significantly better after NACT (OR = 2.89, 95% CI: 1.28–6.53). There was no significant difference in PFS between patients with advanced or metastatic TNBC and non TNBC after platinum therapy.[19] For patients with TNBC with *BRCA* mutation, platinum-containing neoadjuvant therapy did not significantly improve the PCR rate.[20,21]

Table 2 Main Characteristics and Results of the Eligible Studies

Author, Year	Participants (n)	Clinical Stage	Comparison	Design (n)	Outcome		Metrics	*P*-value	I^2
Fancellu et al 2021[8]	19,819	NA	BCS plus RT vs Mastectomy	Retrospective study (14)	Locoregional recurrence		OR 0.64 [0.48,0.85]	0.002	40%
					Distant metastasis		OR 0.70 [0.53,0.94]	0.02	40%
					OS		HR 0.78 [0.69,0.89]	0.001	20%
Pan et al 2015[9]	3432	NA	BCS plus RT TNBC vs. non-TNBC	Retrospective cohort design (5)	5-year OS		RR 1.929 [1.329, 2.647]	0.000	0%
					5-year LFS		RR 3.052 [1.629,5.715]	0.000	9.4%
					5-year DFS		RR 2 0.407 [1.910,3.034]	0.000	12.6%
Petrelli et al 2021[10]	15,047	pT1abN0M0	ACT vs Non-ACT	Retrospective study (14)	RFS		HR 0.64 [0.54,0.77]	<0.00001	0%
					OS		HR 0.72 [0.53,0.99]	0.04	74%
An et al 2020[11]	1525	T1a/bN0M0	ACT vs Non-ACT	Retrospective study (7)	Disease recurrence rate		RR 0.60 [0.43,0.83]	0.0004	0%
Xia et al 2020[12]	36,480	I–III stage	NACT vs ACT	Prospective study (2) Retrospective study (7)	OS	Total	HR 1.59 [1.25,2.02]	0.0001	88%
						PCR	HR 0.53 [0.29,0.98]	0.04	52%
						RD	HR 1.18 [1.09,1.28]	<0.0001	40%
					DFS	Total	HR 0.85 [0.54,1.34]	0.49	37%
						PCR	HR 0.52 [0.29,0.94]	0.03	0%
						RD	HR 2.36 [1.42,3.89]	0.0008	0%
Tian et al 2015[13]	6180	I–III stage	NACT TNBC vs non-TNBC	Prospective and Retrospective study (13)	PCR		OR 3.10 [2.51,3.82]	0.00001	7%
			TNBC received NACT high-Ki67 vs Low-Ki67	Prospective study (4)	PCR (high Ki67 expression patient)		OR 9.87 [3.53,27.62]	0.001	0%
Wang et al 2019[14]	2098	II–III stage	NACT Platinum-based vs Non-platinum	RCT (9)	PCR		OR 2.12 [1.64,2.73]	<0.00001	35%

(*Continued*)

Table 2 (Continued).

Author, Year	Participants (n)	Clinical Stage	Comparison	Design (n)	Outcome	Metrics	*P*-value	I^2
Lu et al 2021[17]	590	Metastatic	Platinum-based vs Non-platium	RCT (4)	ORR	OR 2.34 [1.66,3.28]	<0.0001	40%
Egger et al 2020[18]	1349	Metastatic	Platinum-based vs Non-platinum	RCT (6)	OS	HR 0.85 [0.73,1.00]	0.05	1%
				RCT (8)	PFS	HR 0.77 [0.68,0.88]	<0.0001	80%
Wang et al 2020[21]	363	Early or locally advanced stage	NACT Platinum-based vs Non-platinum (BRCA mutant patient)	RCT (3) Retrospective cohort study (2)	PCR	OR1.340 [0.667,2.653]	0	88.1%
Wang et al 2017[15]	184	I–III stage	NACT Platinum-based vs Non-platinum	RCT (2)	ORR	RR 1.11 [0.96,1.29]	0.16	0%
Poggio et al 2018[16]	2109	II–III stage	NACT Platinum-based vs Non-platinum	RCT (2)	EFS	OR 0.72 [0.49,1.06]	0.094	33%
					OS	OR 0.86 [0.46,1.63]	0.651	63.9%
Liu et al 2013[19]	717	All stage	Platinum-based CT TNBC vs non-TNBC	Retrospective cohort study (7)	PCR	OR 2.89 [1.28,6.53]	0.01	0%
					2-year PFS	OR 1.11 [0.35,3.52]	0.85	67.5%
Caramelo et al 2019[20]	808	I–III stage	Platinum-based CT BRCA mutated vs BRCA wild-type	Phase II–III Clinical trial (5) Phase II RCT (2)	PCR	Fixed effects OR 1.36 [0.96,1.92]	0.082	18.54%
						Random effects OR 1.46 [0.95,2.23]		
Huo et al 2021[22]	3842	Early stage	Capecitabine-base vs Non-Capecitabine	RCT (9)	DFS	HR 0.75 [0.65,0.86]	<0.001	28.4%
				RCT (7)	OS	HR 0.63 [0.53,0.77]	<0.001	0%
Li et al 2020[23]	3151	Early stage	Capecitabine-base vs Non-Capecitabine	RCT (7)	DFS America-Europe	HR 0.81 [0.68,0.98]	0.026	30.7%
					DFS Asia	HR 0.67 [0.49,0.90]	0.009	0%
Xu et al 2019[24]	8614	I–III stage	Capecitabine-based combination first-line CT vs Non-capecitabine first-line CT	RCT (5)	DFS	HR 0.77 [0.65,0.92]	0.004	32.3%
	7992			RCT (4)	OS	HR 0.65 [0.51,0.81]	0.000	0%

(*Continued*)

Table 2 (Continued).

Author, Year	Participants (n)	Clinical Stage	Comparison	Design (n)	Outcome	Metrics	*P*-value	I^2
Hoon et al 2021[25]	1577	Metastatic stage	Capecitabine-containing regimen vs non-capecitabine-containing regimen	RCT (5)	OS	HR 1.20 [1.01,1.43]	0.04	69%
					PFS	HR 1.22 [1.04,1.44]	0.02	79%
			Capecitabine monotherapy vs Other chemotherapy	RCT (2)	OS	HR 1.19 [0.98,1.45]	0.08	76%
					PFS	HR 1.16 [0.94,1.41]	0.16	0%
O'Rocker et al 2016[26]	1539	Non-metastatic	BCT vs Mastectomy	Retrospective study (4) Prospective study (1)	Locoregional recurrence	HR 0.61 [0.41,0.90]	0.609	0%
				Retrospective study (5) Prospective study (1)	OS	HR 0.56 [0.36,0.88]	0.073	50.5%
			PRMT vs Mastectomy	Retrospective study (4) Prospective study (1) RCT (1)	Locoregional recurrence	HR 0.62 [0.44,0.86]	0.386	5.40%
				Retrospective study (4) Prospective study (1) RCT (1)	OS	HR 1.12 [0.75,1.69]	0.001	77%
Alnimer et al 2018[28]	7491	Locally advanced	Bevacizumab with CT vs CT	RCT (2)	DFS	OR 0.88 [0.78,0.98]	0.03	0%
Bramati et al 2014[29]	1546	Metastatic stage	Bevacizumab with CT vs CT	RCT (6)	PFS	HR 0.65 [0.57,0.74]	0.00001	54%
Miles et al 2013[30]	621	Metastatic stage	Bevacizumab with CT vs CT	Randomized, open-label, phase III trials (3)	OS	HR 0.96 [0.79,1.16]	0.6732	-
Nahleh et al 2019[27]	4555	I–III stage	Bevacizumab with NACT vs NACT	RCT (5)	PCR	RR 1.30 [1.16,1.45]	0.001	0%
Chen et al 2021[31]	340	Advanced stage	PARPi vs CT	RCT (2)	PFS	OR 0.39 [0.24,0.63]	0.0001	0%

(*Continued*)

Table 2 (Continued).

Author, Year	Participants (n)	Clinical Stage	Comparison	Design (n)	Outcome	Metrics	*P*-value	I^2
Clark et al 2014[32]	197	Metastatic stage	Sorafenib with CT vs CT	Randomized prospective studies (3)	PFS	HR 0.69 [0.49,0.98]	0.04	0%
Tarantino et al 2021[33]	1496	Early stage	PD1/PD-L1 blockade with NACT vs NACT	RCT (5)	PCR	Summary OR:PD-L1 positive 1.65 [1.06,2.57]	-	0%
						Summary OR:PD-L1 negative 1.56 [0.80,3.03]	-	0%
Korep et al 2016[34]	103	II–III	Zoledronic acid with NACT vs NACT	Prospective randomised studies (3)	PCR	OR 1.92 [0.67,5.47]	-	0%
Gorona et al 2017[35]	1192	NA	GnRH analogs vs. CT, placebo or other antineoplastic agents	RCT (4)	OS	HR 0.94 [0.52,1.71]	0.84	74%

Note: A *P* value below 0.05 or I^2 greater than 50% are considered to have substantial heterogeneity.
Abbreviations: BSC, breast-conserving surgery; CT, chemotherapy; NACT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy; BCT, breast conserving therapy; PRMT, post mastectomy Radiotherapy; GnRH, gonadotropin-releasing hormone; RCT, randomized controlled trial; NA, not available; OS, overall survival; RFS, relapse-free survival; DFS, disease-free survival; PFS, progression-free survival; LFS, local relapse-free survival; PCR, pathological complete response; ORR, objective remission rate; EFS, event-free survival; OR, odd ratio; HR, hazard ratio; RR, risk ratio.

Capecitabine Chemotherapy

Adding capecitabine to the CT regimen can significantly improve DFS and OS in patients with early TNBC.[22–24] However, in the subgroup analysis of DFS, patients treated with adjuvant CT containing capecitabine benefited significantly, while patients with NACT did not improve.[22] In patients with metastatic TNBC, there was no significant benefit in OS and PFS in patients treated with capecitabine CT. There was no significant improvement in OS in patients treated with capecitabine alone (HR = 1.19, 95% CI: 0.98–1.45).[25]

Radiotherapy

For patients with TNBC, whether they underwent breast conserving surgery or mastectomy, adjuvant radiotherapy significantly reduced the risk of local recurrence. However, it was not relevant in terms of overall survival. Nevertheless, patients with early-stage disease and young patients may benefit from it.[26]

Targeted Therapy

NACT with bevacizumab improved the PCR rate in patients with TNBC (RR = 1.30, 95% CI: 1.16–1.45).[27] In patients with locally progressive TNBC, DFS was also significantly improved after bevacizumab treatment (HR = 0.88, 95% CI: 0.78–0.98).[28] CT containing bevacizumab can significantly improve PFS.[29] OS was improved in patients with metastatic TNBC, but the result was not statistically significant (HR = 0.96, 95% CI: 0.79–1.16).[30]

Poly (ADP-ribose) polymerase inhibitors (PARPis) can improve PFS in patients with advanced TNBC (OR = 0.39, 95% CI: 0.24–0.63).[31] Moreover, patients with BRCA1/2 mutations and patients who have not received platinum therapy can benefit more from PARPis therapy.[31] Sorafenib plus CT can improve PFS in patients with metastatic TNBC (HR = 0.69, 95% CI: 0.49–0.98).[32]

Immunotherapy

Adding a programmed death ligand 1 (PD-L1) inhibitor to NACT can improve the PCR rate in patients with early PD-L1-positive TNBC (summary OR = 1.65, 95% CI: 1.06–2.57).[33]

Other Therapies

For patients with premenopausal TNBC, treatment with NACT plus zoledronic acid non-significantly increased the PCR rate (OR = 1.92, 95% CI: 0.67–5.47).[34]

Compared with other anti-tumor drugs and placebo, GnRH analog based treatment non-significantly improved OS in patients with TNBC (HR = 0.94, 95% CI: 0.52–1.71). PFS was also not improved.[35]

Evidence Rating

The results of evidence evaluation showed that platinum-containing NACT improved PCR rate, platinum-containing CT improved ORR and OS for patients with metastatic disease, capecitabine-containing adjuvant CT improved DFS and OS; bevacizumab-containing NACT improved PCR rate, and programmed death 1 (PD-1)/PD-L1 blockade-containing NACT improved PCR rate. Probable evidence showed that NACT improved PCR rate for patients with high Ki67 expression. There was suggestive evidence that breast-conserving therapy reduced local recurrence and distant metastasis and improved OS; CT reduced the disease recurrence rate and improved OS for patients with pT1abN0M0 TNBC; NACT improved DFS and OS; platinum-containing CT improved PFS for metastatic disease, platinum-containing NACT improved PCR rate for patients with *BRCA* mutation; capecitabine-containing regimens improved OS and PFS for patients with metastatic disease; radiotherapy reduced local recurrence and improved OS; bevacizumab-containing CT improved PFS for patients with metastatic disease; and GnRH analogs improved OS. However, other evidence is limited (Table 3).

Discussion

TNBC has special pathological and biological characteristics. It is a disease with poor prognosis. At present, surgery combined with conventional CT cannot meet the survival needs of patients. Patients with TNBC have clinical characteristics such as young onset age and large tumor volume. NACT improves the opportunities for surgical resection and breast conserving surgery[36] and reduces the scope of surgery. It is also a frequently selected scheme clinically. The main end point of treatment is to achieve PCR. At present, anthracycline combined with taxane is commonly used clinically; however, long-term use can lead to drug resistance. Studies have shown that adding platinum[37] or capecitabine,[38] to the above CT regimen can benefit patients with TNBC. Other studies have suggested that targeted therapeutic drugs, such as PARPis,[39] bevacizumab,[40] sorafenib[41] and PD-L1 inhibitors[42] also have certain curative effects on patients with TNBC. However, the clinical stages most benefitting from these treatments and the specific benefits of patients need to be further studied.

A comparative analysis of interventional methods for TNBC was summarized in this umbrella evaluation. It was found that platinum, bevacizumab, and immunotherapy improved PCR rate in neoadjuvant therapy; platinum improved ORR and OS in metastatic TNBC; and capecitabine improved DFS and OS as part of adjuvant therapy.

Platinum compounds, as a DNA crosslinking agent, cross connect with DNA after entering tumor cells, interfere with tumor cell DNA replication, lead to tumor cell DNA double strand break, and play an anti-tumor role. Studies have shown that platinum-containing CT can be used as an option for anthracycline and taxus resistant patients.[37] Its advantages in improving the PCR rate of patients with TNBC as part of neoadjuvant therapy and improving long-term survival in patients with metastatic disease have also been confirmed in some other relevant studies.[15–17,43–45]

Capecitabine, as an oral drug for fluorouracil, has often been used in metastatic breast cancer or after anthracycline or taxane treatment.[46] Some studies suggest that capecitabine can benefit patients with TNBC treated with anthracycline combined with taxane.[38] This review showed that it has certain benefits in improving the long-term survival of early-stage patients, especially as an adjuvant treatment. Jiang et al also drew a similar conclusion in their studies.[47]

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor receptor (VEGF). It can bind to VEGF-A, block VEGF, and lose its biological activity. In the studies of Ma et al, it was also found that adding bevacizumab to NACT regimens can improve the PCR rate of patients.[48]

Table 3 Evidence from Studies of Treatment for TNBC

Level of Evidence	Outcome						
	Surgery	**Chemotherapy**	**Radiotherapy**	**Targeted Therapy**	**Immunotherapy**	**Zoledronic Acid**	**GnRH Analogs**
Convincing	-	Platinum-containing NACT improved PCR rate; platinum-containing CT improved ORR, OS for metastatic patients; Capecitabine-containing ACT improved DFS, OS	-	Bevacizumab - containing NACT improved PCR rate	PD1/PD-L1 blockade - containing NACT improved PCR rate	-	-
Probable	-	NACT improved PCR rate for Ki67 high expression patients	-	-	-	-	-
Possible	BCT reduced locoregional recurrence and distant metastasis, improved OS	CT reduced disease recurrence rate and improved OS for pT1abN0M0 patients; NACT improved DFS, OS; platinum-containing CT improved PFS for metastatic patients; Platinum-containing NACT improved PCR rate for BRCA mutant patients; Capecitabine-containing regimen improved OS, PFS for metastatic patients;	Radiotherapy reduced locoregional recurrence, improved OS	Bevacizumab - containing CT improved PFS for metastatic patients	-	-	GnRH analogs improved OS
Limited	-	Platinum-containing NACT improved ORR	-	Bevacizumab - containing CT improved OS for metastatic patients; Bevacizumab - containing CT improved DFS for Locally advanced patient; PARPi improved PFS for advanced patients; Sorafenib improved PFS for metastatic patient	-	Zoledronic acid - containing NACT improved PCR rate	-

Abbreviations: CT, chemotherapy; NACT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy; BCT, breast conserving therapy; OS, overall survival; RFS, relapse-free survival; DFS, disease-free survival; PFS, progression-free survival; PCR, pathological complete response; ORR, objective remission rate; EFS, event-free survival; OR, odd ratio; HR, hazard ratio; RR, risk ratio.

Immunotherapy may play an anticancer role by activating T cell autoimmunity in human body. PD-1 and PD-L1 are co-inhibitory molecules expressed on the surface of a variety of tumor cells. PD-1, as a key cell surface receptor, triggers the activation of inhibitory pathways by binding with its ligand, PD-L1, thereby inhibiting the T-cell response.[49] PD-(L)1 blockade can block the immune escape of tumor cells mediated by PD-1 and PD-L1. Monoclonal antibodies against PD-1/PD-L1 immune checkpoints have become a new tumor treatment strategy. The current analysis results suggest that such an approach has certain advantages in the neoadjuvant treatment of PD-L1-positive TNBC.

Other interventions, such as breast-conserving surgery, radiotherapy, zoledronic acid, GnRH inhibitors, targeted drugs such as sorafenib and PARPis, have also achieved some favorable results. However, due to the retrospective design or small sample size of some studies, the results of some studies have obvious heterogeneity and other problems, the level of evidence in this analysis is low. Therefore, further research is needed.

In recent years, we have a deeper understanding of the typing and molecular biological characteristics of different subtypes of TNBC. Lehmann et al[50] divided TNBC into six subtypes including 2 basal-like (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), and a luminal androgen receptor (LAR) subtype. However, Jiang et al[51] divided TNBC into four transcriptome-based subtypes: luminal androgen receptor (LAR), immunomodulatory (IM), basal-like immune-suppressed (BLIS), and mesenchymal-like (MES). Putative therapeutic targets or biomarkers were identified among each subtype; the comprehensive profile of TNBCs provided here will serve as a reference to further advance the understanding and precision treatment of TNBC. Compared with the European and American patients, premenopausal African American women with breast cancer have higher morbidity and mortality of TNBC.[52] On the one hand, the reason is that their proportion of receiving surgery and chemotherapy is relatively low; on the other hand, factors such as tumor microenvironment or tumor biological characteristics also play an important role.[53] The study found that,[54,55] African American TNBC women are more likely to resist chemotherapy after neoadjuvant chemotherapy than white women, resulting in a lower pathological complete remission rate. Studies have shown that different molecular subtypes, genomic structure and cellular microenvironment may lead to different response and prognosis of TNBC to chemotherapy.[56,57] However, there were not the relevant meta-analysis literatures regarding treatment comparison for different molecular subtypes and races of TNBC.

At present, precision therapy is formulated based on TNBC molecular typing, and better outcomes have been achieved in some studies.[58,59] In the future, more efforts should be devoted to the in-depth exploration of precise treatment based on molecular typing, and more reliable meta-analysis articles are also expected, which is conducive to the individualized treatment of TNBC patients.

Conclusion

TNBC is a heterogeneous disease with poor prognosis. In this study, we comprehensively reviewed the meta-analysis literature of various treatment methods of TNBC and defined the evidence level of each comparison to determine the reliability of the analyses. The results showed that only some analyses of platinum, capecitabine, bevacizumab, and immune checkpoint inhibitors were supported by convincing evidence. Many studies are low-level evidence, because there are various adverse factors in these studies, including retrospective, small sample size, short follow-up time, and other biases. However, we did not find out the relevant meta-analysis literatures regarding different molecular subtypes and races of TNBC treatment. Therefore, more rigorous and detailed researches on the treatment of TNBC are needed in the future to obtain more reliable clinical evidence.

Data Sharing Statement

All data generated or analyzed during this study are included in this article.

Ethical Statement

Ethics statement was not required since the research is an umbrella review of previously published studies.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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