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REVIEW

The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis

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Abstract Platinum agents such as cisplatin and carboplatin are DNA-damaging agents with activity in breast cancer (BC), particularly in the triple negative (TN) subgroup. The utility of platinum agents, in addition to standard neoadjuvant chemotherapy (NAC), is controversial. To assess the activity of platinum agents in patients with TNBC treated with NAC, we performed a systematic review and meta-analysis of all published studies. A search of PubMed, EMBASE, the Web of Science, SCOPUS, and the Cochrane Central Register of Controlled Trials was performed to identify studies that investigated platinum-based NAC in patients with TNBC. Random effect models were adopted to estimate the summary risk ratio (RR), and the publication bias was evaluated using a funnel plot and Egger's regression asymmetry test. The primary endpoints were the pooled rate of the pathologic complete response (pCR) and the RR to obtain a pCR in patients treated versus not treated with NAC containing platinum agents. 28 studies were included (six randomized controlled trials and 22 retrospective or prospective studies) for a total of 1,598 TNBC patients. Overall, the pooled rate of pCR in patients treated with platinum-based NAC was 45 %. In randomized trials, NAC containing cisplatin or carboplatin significantly increased the rate of pCR compared with nonplatinum agents (RR = 1.45, 95 % CI 1.25–1.68; $P < 0.0001$). Compared with non-TN, TNBCs were associated with a threefold increase in the pCR rate when treated with platinum-based NAC (RR 3.32, 95 % CI 2.39–4.61; $P < 0.0001$). In conclusion, pCR rates increase significantly with the addition of cisplatin or carboplatin in TNBC compared with NAC containing no platinum drugs. TN status is a predictor of benefit from platinum-based NAC.

Keywords Cisplatin · Carboplatin · Neoadjuvant chemotherapy · Triple negative · Breast cancer · Pathologic complete response

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Introduction

Triple-negative breast cancer (TNBC), which lacks expression of estrogen and progesterone receptors (ER and PgR) and human epidermal receptor 2 (HER2), is associated with a dismal prognosis despite responding remarkably well to anthracycline and taxane-based neoadjuvant chemotherapy (NAC). In particular, standard polychemotherapy results in pathologic complete response (pCR) in more than 20 % of patients [1, 2], and this response is considered a surrogate of increased survival compared with patients without a pCR [3]. In a meta-analysis of 12 NAC studies, TNBC was associated with a pooled pCR (the absence of invasive and in situ cancer in the breast and axilla) of 34 % [4], and pCR was associated with significantly improved event-free survival compared with no pCR in TNBC patients (HR = 0.24, $P < 0.001$). In this meta-analysis, the improvement in the pCR odds ratio, however, did not correlate with an improvement in event-free and overall survival (OS).

There is an interest in DNA-damaging agents such as platinum drugs (cisplatin [CDDP] and carboplatin [CBDCA]) in TNBC. This interest derives from the fact that almost all TNBCs belong to the molecular subgroup of

basal-like BCs according to the Perou classification [5]. These tumors exhibit high-proliferation rates and are seldom associated with BRCA1 mutations. A high proportion of TN patients exhibit BRCA1 functional alterations (BRCAness-like status), implying that these tumors are highly sensitive to interstrand cross-linking agents like platinum salts. In a registry of 6,903 patients, 10 out of 12 patients with BRCA1 mutations obtained a pCR when treated with single-agent CDDP [6]. Similarly, among 28 TNBC patients treated with four cycles of neoadjuvant CDDP, 22 % achieved a pCR, including two BRCA-mutated patients [7].

To date, however, no randomized phase III study has evaluated whether the addition of platinum salts to standard NAC including anthracycline and taxanes is capable of improving treatment efficacy in these patients. In 2013, at least two phase II randomized trials instead confirmed the benefit of adding CBDCA to NAC in TNBC. In a CALGB trial, the addition of CBDCA at the AUC of 6 increased the pCR rates from 28 to 42 % in stage II-III BCs [8]. Similarly, in a German study, the introduction of weekly CBDCA (AUC 1.5–2) to non-pegylated liposomal doxorubicin, weekly paclitaxel, and bevacizumab boosted the pCR rate from 37.9 to 58.7 % [9].

Here, we present a meta-analysis evaluating the association of TN histology with pCR after platinum-based NAC for operable or locally advanced BC as well as the benefit of the addition of platinum agents to conventional NAC. Furthermore, the activity of platinum salts in TNBC compared with non-TNBC was calculated.

Methods

Search strategy and selection of studies

PubMed, the Web of Science, EMBASE, SCOPUS, and the Cochrane Register of Controlled Trials (CENTRAL) were searched for studies (including conference abstracts) evaluating the pCR after platinum-based NAC in TNBC from 1990 to December 20th, 2013. We used the medical subject heading terms ("Breast Neoplasms"[Mesh] AND (("cisplatin"[MeSH Terms] OR "cisplatin"[All Fields]) OR ("carboplatin"[MeSH Terms] OR "carboplatin"[All Fields]) OR ("platinum"[MeSH Terms] OR "platinum"[All Fields])) AND (("neoadjuvant therapy"[MeSH Terms] OR ("neoadjuvant"[All Fields] AND "therapy"[All Fields]) OR ("neoadjuvant therapy"[All Fields] OR "neoadjuvant"[All Fields]) OR preoperative[All Fields] OR primary[All Fields])) and limited the results to English language studies. Eligibility criteria included randomized or nonrandomized studies reporting the proportion of pCRs (both in breast and axilla; ypT0N0) in TNBCs (defined as BC with ER and PgR expression in <1 % of cells and HER2-negative status) treated with CDDP or CBDCA-containing NAC, possibly including a taxane and/or an anthracycline. Studies including less than 10 patients as well as studies evaluating high-dose chemotherapy, phase I studies, targeted therapies alone, unconventional combinations (e.g., combinations not approved for advanced or localized disease), or therapies involving platinum as single agent alone were excluded from this analysis. In addition, the reference lists of the retrieved articles were checked to identify additional relevant publications. The "Related Articles" function was also used to improve the search. The study selection, data extraction, and data entry were performed by 2 authors independently (FP and AC), and discrepancies between the two reviewers were resolved by discussion and consensus. The final results were reviewed by the senior investigator (SB).

Data extraction

The following information was extracted from each article: (1) basic information, including the year of publication and the first author's name; (2) study information, including sample size, study design, number of TNBC, and non-TNBC patients; (3) treatment information, including neoadjuvant schedules and number of cycles; (4) outcomes of interest, such as the percentage or number of pCRs in the TNBC population and the percentage (or number) of pCRs in the control arms for randomized studies (NAC without platinum agents); (5) percentage (or number) of pCRs and the ORR in non-TNBC treated with platinum agents; and (6) overall clinical RR (ORR), rate or number of breast-conserving surgery (BCS) in the TNBC population, long-term DFS and OS in TNBC subgroup, and DFS and OS in TNBC patients who obtained a pCR with platinum-based NAC.

Statistical analysis

Both the pooled pCR rates in TNBCs treated with platinum-based NAC and the comparison of the pCR rates of platinum- versus nonplatinum-based NAC in TNBC patients (for randomized studies) were the primary endpoints. Secondary endpoints were the comparison of pCRs in TNBCs and non-TNBCs treated with platinum agents, ORR, rate of BCS, DFS, and OS (for both all treated patients and pCR-only population) in TNBCs treated with platinum-based NAC. The pCR and other comparisons in the TNBC and non-TNBC subgroups were calculated using the method for dichotomous data (assessment of risk ratio [RR]; 95 % CI). Both the fixed-effect model/Mantel–Haenszel method with minimal heterogeneity in the variables among studies and the DerSimonian–Laird method (random effects model) when there was significant heterogeneity were used [10]. The Cochran's Q test, with a

Table 1 Characteristics of included trials

Author/year	Type of study	N° TN/ not TN BCs	Schedule	N cycles	pCR TNBCs with platinum (%)	pCR TNBCs without platinum (%)	pCR not TNBCs with platinum (%)	ORRs TNBCs with vs. without platinum (%)	BCS (%)	DFS/OS (%)	DFS/OS pCR vs. no pCR pts (%)	Median FU (months)
Chen/2010	Phase 2	24/71	wPAC + wCBDCA d1,8,15 q 28	4	33	–	18.3	–	–	–	–	–
Frasci/2009	Prospective series	64/0	wCDDP + wEPI + wPAC	8 weeks	62	–	–	98.3	–	76/89	90/95.6	41
Kim/2013	Phase 2	45/0	CBDCA AUC 5 + 3wDOC + bevacizumab (15 mg/mg) d1 q 21	6	42	–	–	96	78	–	–	–
Torrisi/2008	Prospective series	30/0	EPI d1-2 + CDDP d1 + 5-FU ci d 1–21 × 4 → PAC d 1,8,15 q 28 × 3	7	40	–	–	86	86	–	–	17
Yerushalmi/ 2009	Phase 2	20/54	ADM + PAC d 1 q 21 × 4 → CDDP + PAC d1 q14 × 4 or reverse sequence	8	35	–	16.6	–	–	50/49.5	–	–
Von Minckwitz/ 2013	Phase 2 randomised	315/ 137	wNPLD + wPAC + bevacizumab (15 mg/kg d1 q 14)[a] ± wCBDCA[a]	18 weeks	58.7 vs 37.9		33.1	–	–	–	–	–
Zhang/2013	Phase 2 randomised	91	EPI + PAC d1/2 q21 vs. PAC + CBDCA AUC5 d2/1 q 21	4-6	38.6 vs. 14		–	89.4 vs. 79.6	–	71.1vs. 52.8/ 70.1 vs. 72.5	–	37
Sikov/2013	Phase 2 randomised	186	wPAC × 12 → AC d1 q 14 × 4 ± wCBDCA ± bevacizumab (10 mg/ kg d1 q 14) × 9	16	54 vs. 41[b]		–	–	46 vs. 40	–	–	–
Mayer/2013	Phase 2 randomised	120	wCDDP + wPAC ± EVE 5 mg die × 12 weeks	12	42 vs. 35	–	–	92 vs. 85	–	–	–	–
Kern/2013	Prospective series	30	CBDCA AUC6 + DOC d1 q 21	6	55 (15/27)	–	–	–	–	–	–	–
Rugo/2013	Phase 2 randomised	60	wPAC × 12 → AC d1 q14–21 × 4 ± veliparib/ CBDCA	16	52 vs. 24		–	–	–	–	–	–
Diaz-Correa/ 2011	Prospective series	19	AC d1 q 14 × 4 → wPAC or 3wDOC + CDDP d1 q 21 × 4	8	84	–	–	–	–	–	94 vs. 33/-	24
Alba/2012	Phase 2 randomised	93	EC d1 q 21 × 4 → 3wDOC ± CBDCA AUC5 d1 q21 × 4	8	30 vs. 30		–	76.6 vs. 79.6	72 vs. 67	–	–	–
Hurley/2013	Retrospective series	144	CBDCA AUC5 or wCBDCA or 3wCDDP + 3wDOC or wDOC × 4 ± AC × 4	4/8	31	–	–	–	7.6	55/61	81 vs. 44/78 vs. 51	48
Chang/2010	Prospective series	11/62	CBDCA AUC6 d1 q 21 + 3wDOC d1 q 21 × 4	4	54.6	–	20.9	–	–	–	–	22.8
Sinclair/2012	Prospective series	27/28	w-NAB-PAC + CBDCA AUC6 + bevacizumab (15 mg/kg) d1 q 21 × 12 weeks → ± AC d1 q 14 × 4 + bevacizumab (15 mg/kg) d1 q 21	16	81/27[c]	–	17/0[c]	93 – 91[c]	–	–	–	–
Sikov/2009	Prospective series	12/39	CBDCA AUC6 d1 q 28 + wPAC × 16 weeks	16	67	–	41	–	–	75/75	88 vs. 50/88 vs. 50	28

Table 1 continued

Author/year	Type of study	N° TN/ not TN BCs	Schedule	N cycles	pCR TNBCs with platinum (%)	pCR TNBCs without platinum (%)	pCR not TNBCs with platinum (%)	ORRs TNBCs with vs. without platinum (%)	BCS (%)	DFS/OS (%)	DFS/OS pCR vs. no pCR pts (%)	Median FU (months)
Sirohi/2008	Retrospective series	6/54	EPI d1 q21 + CDDP d1 q21 + 5-FU ci d 1–21 × 6	6	17	–	9	100 – 94[d]	–	–	–	–
Fei/2012	Retrospective series	124	NR	NR	40							
Rahal/2010	Prospective series	18	AC or FEC100 d1 q 21 × 4 + CDDP + 3wDOC d1 q 21 × 4	8	33.3	–	–	85	–	–	–	–
Shinde/2012	Retrospective series	10/29	CBDCA AUC6 + wPAC	NR	60	–	27.5	–	–	–	–	–
Julka/2008	Phase 2	14/22	GEM d1,8 q 21 + ADM d1 or2 q 21 × 4 → GEM d1,8 q 21 + CDDP d1 q 21 × 4	3	50	–	27	82–91[d]	–	–	–	–
Roy/2013	Phase 2	9/48	DOC d1 q 14 + CBDCA AUC6 d2 q 14 × 4	4	44	–	11.9	–	34	–	–	.38
Ithimakin/ 2013	Phase 2	7/33	GEM d1,8 q21 + CBDCA AUC 5 d 1 q21 × 3	3	14.2	–	0	–	–	–	–	–
Snider/2013	Prospective series	42	CBDCA AUC 6 d1 q 28 + w-NAB-PAC d1,8,15 q28 × 4 → AC d1 q 14 × 4 + bevacizumab 10 mg/kg d1 q 14 × 6	8	53	–	–	–	–	–	–	–
Tiley/2012	Phase 2	17/0	wADM + oral CTX × 12 weeks → wPAC + wCBDCA AUC2 × 12 weeks	24	40	–	–	82	–	–	–	–
Telli/2011	Phase 2	49/0	CBDCA AUC2 d1,8 q 21 + GEM d1,8 q 21 + iniparib d1,4,8,11 q 21 × 4	4	34	–	–	–	–	–	–	–
Mrozek/2010	Phase 2	11/19	w-Nab-PAC d1,815 q 28 × 6 + CBDCA AUC 2 d1,8,15 q28 × 6 + bevacizumab 10 mg/kg d1 q15 × 5	6	50 (3/6)	–	0	–	–	–	–	–

N number, *w* weekly, *d* = day, – not available, *TNBC* triple-negative breast cancer, *pCR* pathologic complete response in breast and axilla, *NR* not reported, *BCS* breast-conserving surgery, *ORR* overall response rate, *DFS* disease free survival, *OS* overall survival, *FU* follow up, *CBDCA* carboplatin, *CDDP* cisplatin, *PAC* paclitaxel, *DOC* docetexel, *EPI* epirubicin, *5-FU* 5-fluorouracil, *NPLD* non-pegylated lyposomial doxorubicin, *ADM* adriamycin, *AUC* area under the curve, *AC* adriamycin + cyclophosphamide, *EC* epirubicin + cyclophospamide, *FEC* 5-fluorouracil + epirubicin 100 mg/m^2 + cyclophosphamide, *NAB-PAC* nab-paclitaxel, *GEM* gemcitabine, *CTX* cyclophosphamide

[a] HER2 positive patients received concomitant trastuzumab + lapatinib

[b] Carboplatin versus no carboplatin arms

[c] With and without anthracyclines

[d] Not triple-negative patients

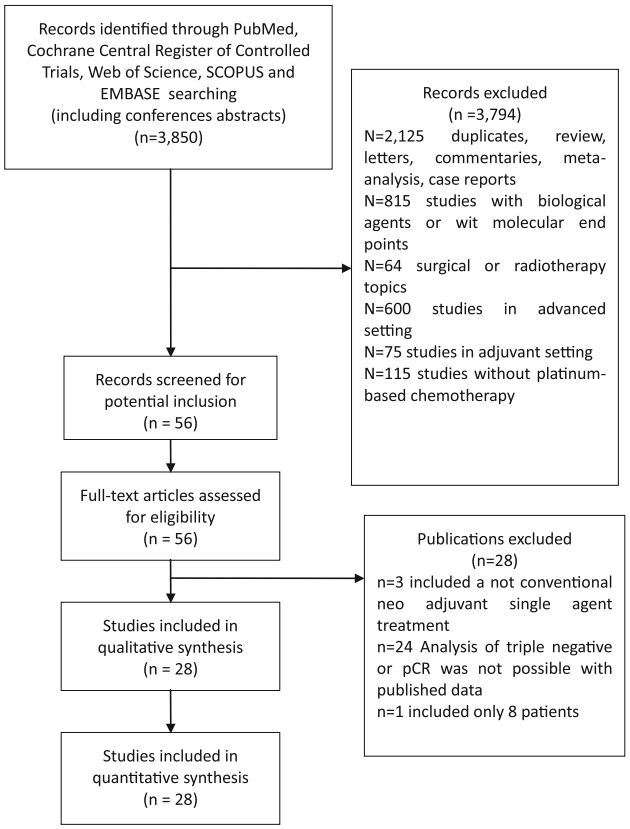

Fig. 1 Selection of publications included in the meta-analysis

predefined significance *P* threshold of 0.1, was used to assess the statistical heterogeneity among the studies. The assumption of homogeneity was considered invalid for *P* values less than 0.1; in this case, summary estimates were reported from the random effect models. Subgroup analysis was performed according to the platinum agent (CDDP vs. CBDCA) and chemotherapy schedule (platinum + taxane vs. platinum + taxane + anthracycline) (Table 1).

Finally, potential publication biases for the primary endpoints were evaluated using funnel plots, which assessed the relative symmetry of the individual study estimates around the overall estimate, followed by the Begg's and Egger's tests. A two-tailed *P* value < 0.05 without adjustment for multiplicity was considered statistically significant. The leave-one-out procedure was also performed for the primary endpoint analysis. The "fail-safe N" was calculated, which is defined as the number of additional "negative" studies (studies in which the intervention effect was zero) required to increase the *P* value for the meta-analysis to above 0.05.

A two-tailed *P* value <0.05 was considered statistically significant, and the results of the meta-analysis were reported as classic forest plots (for the primary endpoints). All statistical analyses were performed using NCSS 2007 software (version 07.1.21 released June 1, 2011) and Comprehensive Meta-Analysis software (version 2.2.064; July 27, 2011).

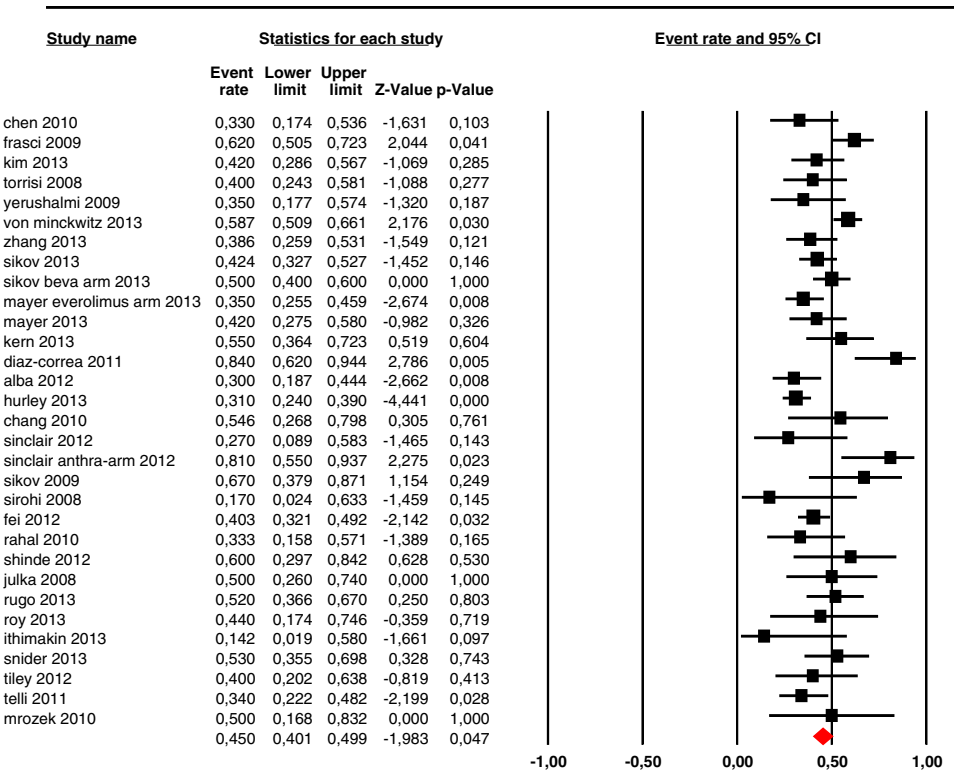

Fig. 2 The pooled ORR for platinum-based neoadjuvant chemotherapy in triple negative breast cancer

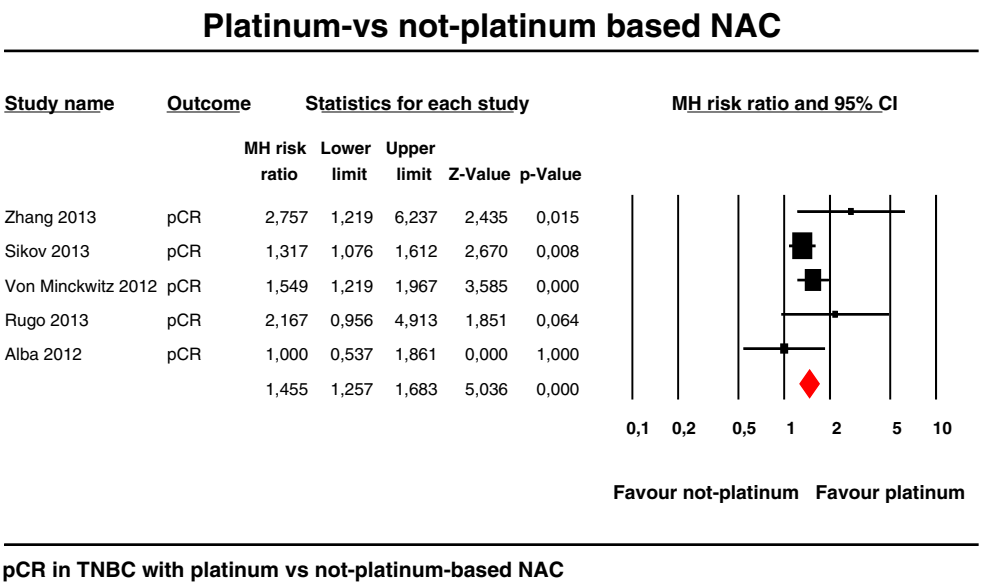

Fig. 3 The forest plots of RR with 95 % CIs for pCR in triple-negative breast cancer treated with versus without platinum-based neoadjuvant chemotherapy

Results

Overall, a total of 3,850 references were identified, and 3,794 studies were excluded by reading the titles and abstracts. The studies were read further to identify case reports, clinical reports that did not provide pCR rates, nonconventional single-agent regimens, and studies where data extraction according to the TN molecular subtype was not possible to exclude a total of 28 studies. Ultimately, 28 studies were selected with a total of 1,598 TNBC and 596 non-TNBC patients [8, 9, 11–36]. Six were randomized phase II trials, and 22 were prospective or retrospective single-arm studies. The number of patients with TN disease treated with platinum drugs ranged from 10 to 315 in each study. The platinum agent was CDDP in eight studies, CBDCA in 18 studies, and both agents in one series (in one study this data was not reported). The reference flow is presented in Fig. 1.

Primary endpoint: pooled pCR and RR for the comparison of platinum- versus nonplatinum-based NAC in TNBC

Overall, the pooled weighted pCR rate in all TNBCs treated with platinum-based NAC ($n = 28$ studies) was 45 % (95 % CI 40–49.9 %; Fig. 2). If we consider the trials that included both a taxane and anthracycline (n = 13 studies), this rate rises to 48.4 % (95 % CI 40–56 %).

Eight trials included CDDP-containing NACs. In one trial, a definition of platinum-based NAC did not permit us to split the CDDP- versus CBDCA-treated patients. The pooled pCR rate was 41.9 % (95 % CI 32–51 %). In 18 trials, CBDCA was the platinum of choice and was associated with a pCR rate of 46.3 % (95 % CI 40.7–52.1 %).

Compared with nonplatinum-based NAC, the addition of a platinum agent in five randomized trials increased the pCR rate by 45 % (RR 1.45, 95 % CI 1.25–1.68, $P < 0.0001$; $I^2 = 31.7$ %, P for heterogeneity 0.2 according to fixed-effect model; Fig. 3). The pCR rate increased from 32 to 48 % (absolute increase 16 %, 95 % CI 10–22 %, $P < 0.0001$).

pCR in TNBC versus non-TNBC with platinum-based NAC

Compared with non-TN histology, TNBCs were associated with a twofold increase in the rate of pCR when treated with platinum-based NAC in 13 studies (from 19.6 to 48.4 %; RR 3.32, 95 % CI 2.39–4.61, $P < 0.0001$, $I^2 < 0.0001$, P for heterogeneity 0.74 according to fixed-effect model).

ORR in TNBC versus non-TNBC, BCS rate, DFS, and OS in all and pCR-only patients

In all TNBC treated with platinum-based NAC, the pooled ORR was 86.7 % (95 % CI 82.7–89 %). This rate was similar to TNBCs treated without CDDP or CBDCA in two studies ($P = 0.164$).

The rate of breast-conserving surgeries ranged from 7.6 to 86 %. Long-term DFS and OS ranged from 50 to 76 % and from 49.5 to 89 %, respectively. In particular, DFS and OS in patients who achieved a pCR were excellent (range 81.8–90 % for DFS and 78–95.6 % for OS) and were

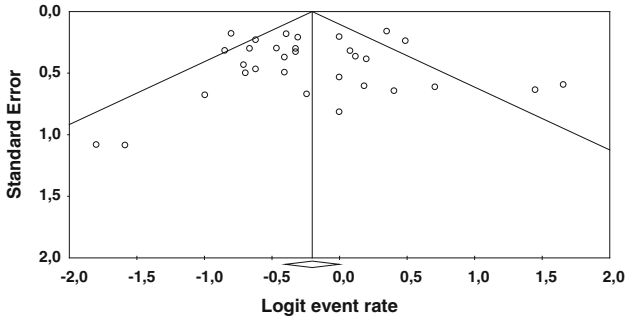

Fig. 4 Funnel plot for publication bias in pooled pCR analysis (triple-negative populations only)

superior to the DFS and OS of TNBC that did not obtain a pCR (range 44-56 % for DFS and 50–51 % for OS). The RRs of progression and death for pCR versus non-pCR patients were 0.29 (95 % CI 0.18–0.49, $P < 0.0001$) and 0.43 (95 % CI 0.24–0.75, $P = 0.004$), respectively.

Publication bias

A funnel plot and both the Begg's and Egger's tests were performed to assess the publication bias of the selected studies for the pooled pCR rate analysis and for comparison of platinum- versus nonplatinum-containing NAC. The shapes of the funnel plots revealed little evidence of asymmetry for pooled pCR analysis in TNBC treated with platinum-based NAC (Fig. 4). However, the Begg's test ($P = 0.7$) and Egger's test ($P = 0.89$) were not significant for pooled pCR analysis. The results remained unchanged after the leave-one-out procedure. Using the trim and fill method to account for asymmetric studies in the funnel plot, there was no effect on the pCR rate. The fail-safe N was 53, indicating that it would be necessary to locate and include 53 "null" studies for the combined 2-tailed P value to exceed 0.05.

Similarly, for the comparison of platinum- versus nonplatinum-based NAC in TNBC, there was no evidence of asymmetry in the funnel plot. Both Begg's ($P = 0.46$) and Egger's tests ($P = 0.44$) were not significant. Using the trim and fill method to account for asymmetric studies in the funnel plot, there was no effect on the RR (RR 1.36, 95 % CI 1.07–1.71). The fail-safe N was 24, indicating that it would be necessary to locate and include 24 "null" studies for the combined 2-tailed P value to exceed 0.05.

Discussion

This systematic review and meta-analysis suggests that TNBC is associated with a high rate of pCR when treated with platinum-based NAC and that the addition of platinum salts increases this rate by 31–45 % in five randomized studies. OS and DFS data are not available to evaluate whether the addition of platinum agents to NAC improves TNBC outcomes, and larger trials with longer follow-ups are necessary. Furthermore, the TN subgroup is associated with a pCR rate nearly double that of non-TNBC when both are treated with platinum-based NAC, suggesting that TN status is a potential therapeutic target for these drugs.

Our review lead to the observation that the treatment of TNBC with platinum salts is associated with a near similar pCR rate as HER2 + BC treated with modern anti-HER2 drugs, such as pertuzumab and lapatinib, added to trastuzumab. The NeoSPHERE and NeoALLTO studies demonstrated infact that the double HER2 blockade similarly increased the pCR rate from 29 to 45 % with pertuzumab plus trastuzumab and from 29 to 51 % with lapatinib plus trastuzumab [37, 38]. In patients who achieved a pCR, there was also an increase in event-free survival and OS compared with non-pCR patients as demonstrated in the NeoALLTO study (HR 0.38 and 0.35). Among trials analyzed in the present review, only three trials provided long-term DFS and OS, and these outcomes were excellent for TNBC treated with platinum-based NAC. Furthermore, in patients who achieved a pCR, there was a significant benefit in relapse and death (70 and 57 % less risk of relapse and death) compared with non-pCR TNBC patients treated with the same platinum agents. In the Cortazar meta-analysis [4], TNBCs (as well as HER2 + and ER + grade 3 BCs) that achieve a pCR in breast and axilla (ypT0N0) were associated with a better event-free survival compared with patients with residual disease. These data and our meta-analysis suggest that adding an active agent to a backbone NAC with demonstrated efficacy could result in a meaningful significant increase of the pCR rate, and a potential cure for some TNBC patients.

Whether all TNBC patients would benefit from platinum agents during preoperative chemotherapy is a matter of debate. It is likely that BRCA-mutated tumors, representing up to 50 % of all TNBC [39, 40], are the most sensitive to DNA-damaging agents. In the Birsky and Silver publications cited above [6, 7], 83 and 100 % of BRCA-mutated patients obtained a pCR with single-agent CDDP. However, BRCAness tumors that shared mixed characteristics of sporadic cancer and inherited BRCA-mutations were more frequent (approximately two-thirds of all TNBCs) and were associated with decreased pCR compared with BRCA-mutated tumors (35 vs. 63 %) [41]. Similarly, BRCA-mutated TNBCs were associated with a better prognosis than nonmutated tumors [41]. In our series, only one trial reported the different responses of TNBC with and without BRCA mutation; these response were 100 and 15 %, respectively, confirming this suggestion. From a

molecular point of view, TNBC is a group of different entities as demonstrated by Masuda et al. [42]. At least 7 subtypes were described, with basal-like-1 that was associated with the highest pCR rate (52 %). This notion is hugely crucial and needs to be validated prospectively; this could permit a better elucidation of responsiveness of TNBC to platinum agents.

Other agents have tested as neoadjuvant therapy in TNBC. The anti-VEGF-A monoclonal antibody bevacizumab was a candidate agent for use in aggressive TNBC subsets. Among more than 600 TNBC patients treated into the GeparQuinto trial and randomized to NAC with four cycles of anthracyclines followed by four cycles of docetaxel with or without bevacizumab added to NAC, the pCR rates (ypT0ypN0 after surgery) were 27.9 % without and 39.3 % with bevacizumab ($P = 0.003$), similar to our results [43]. In our series, trials including bevacizumab as a part of platinum-containing NAC were associated with a pCR rate of 52 %. In the recent CALGB trial lead by Sikov, the addition of bevacizumab to NAC with or without CBDCA increased the pCR by 10 % [9]. Another explored target in TNBC is EGFR. A randomized phase II trial in early BC with ER-negative disease explored the addition of gefitinib to anthracycline NAC. The pCR rate was increased by 5 % with the anti-EGFR agent compared with placebo, but the rate was nonetheless poor (17 vs. 12 %). However, a post-hoc subgroup analysis revealed a significant difference in pCR between TNBC and non-TNBC tumors ($P = 0.03$) [44]. The poly(ADP-ribose) polymerase (PARP) inhibitor veliparib, with chemosensitizing and antitumor activities, confers an added benefit when added to CBDCA and paclitaxel plus standard anthracycline-based NAC. In the randomized phase II study I-SPY 2, the researchers observed a pCR in 52 % of women who were treated with veliparib plus CBDCA and paclitaxel versus a 26 % pCR rate in those who received paclitaxel alone. Both regimens were added to conventional anthracyclines [25].

The best platinum salt to be added to NAC is presently unknown. All randomized trials included in our study used CBDCA-based NAC, suggesting that CBDCA should be applied in clinical practice. In eight studies, CDDP was the agent of choice and resulted in a pCR rate of 41.9 %, similar to the overall pooled analysis and slightly inferior to CBDCA-based NAC studies (46 %). In the Hurley series, however, the use of CDDP, but not CBDCA, was an independent predictor of PFS and OS [30].

Two issues remain unsolved: the prognosis of BC patients with TN histology and residual disease after NAC, and the prediction of patients more likely to obtain a pCR. This and other studies [1, 2] demonstrate that TNBC, which does not get a pCR after NAC, is associated with a dismal prognosis. Early identification and treatment with a non-cross-resistant agent could improve responses and prognoses. In GeparTrio study, however, a different schedule in early nonresponders after 2 cycles of NAC did not permit to obtain a better pCR rate or an improved DFS in $n = 362$ TNBC patients enrolled [45]. Molecular profiling of residual tumor burden in 74 TNBCs treated with NAC identified genetic alterations potentially treatable with targeted therapies in 90 % of cases [46]. Early nuclear medicine tools such as PET could also improve the detection of TNBC NAC non-responders [47, 48]. Other molecular predictors, including grade, young age, BCL-2 expression, p53, high Ki67, LDH, and basal-like status, were associated with better results with NAC in TNBC, but none of these predictors were analyzed in platinum-treated TNBC patients [49–54].

Our systematic review has some limitations. This is a meta-analysis of published trials, and only six studies included a randomized design. The included studies represent a mixed population of operable and locally advanced TNBCs with different prognoses and responses to NAC. Finally, the NAC schemes comprise conventional and nonconventional schedules (e.g., ECF schedule and gemcitabine/adriamycin + gemcitabine/CDDP combination) with slightly different durations. It is likely that polychemotherapy including both anthracyclines and taxanes may obtain the best results as previous publications have confirmed. Nonetheless, our meta-analysis represents about 1,600 TNBCs, all treated with platinum-based NAC. To our knowledge, the present study represents the largest review ever published about this controversial topic. Finally, comparing five randomized phase II trials, we are able to calculate a significant pCR rate in association with platinum salts plus both taxanes and anthracyclines.

This meta-analysis updated a previous Chinese review that included only three out of 28 trials analyzed here [55]. These results are similar to those presented in this review, although the previous authors did not include any randomized studies. The Liu et al. meta-analysis was furthermore extended to metastatic patients, in whom the addition of platinum agents increased ORR but did not improve PFS or OS. Their data confirm an older meta-analysis offered by the Cochrane Collaboration review, which demonstrated an ORR benefit but did not observe any survival or time to progression increase with platinum agents [56]. The different effects of platinum salts in the localized versus metastatic disease suggest that these agents should be introduced early in the course of the disease.

In conclusion, the optimal NAC combination/sequence incorporating platinum salts in the neoadjuvant setting is far from evident given the data available. Nevertheless, the best candidates for platinum-based NAC for BC seem to be those with the TNBC phenotype because these patients respond better compared with non-TN patients and achieve

a significant improvement in pCR rates when CDDP or CBDCA is added.

Conflict of interest All authors disclose any potential conflicts of interest.

References

1. Liedtke C, Mazouni C, Hess KR et al (2008) Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 26(8):1275–1281
2. Carey LA, Dees EC, Sawyer L et al (2007) The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 13(8):2329–2334
3. von Minckwitz G, Untch M, Blohmer JU et al (2012) Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 30(15):1796–1804
4. Cortazar P, Zhang L, Untch M et al (2012) Meta-analysis results from the collaborative trials in neoadjuvant breast cancer (CTNeoBC). Cancer Res 72:93
5. Perou CM (2010) Molecular stratification of triple-negative breast cancer. Oncologist 15(5s):39–48
6. Byrski T, Gronwald J, Huzarski T et al (2010) Pathologic complete response rates in young women with BRCA 1 positive breast cancers after neoadjuvant chemotherapy. J Clin Oncol 28(375–379):18
7. Silver DP, Richardson AL, Eklund AC et al (2010) Efficacy of neoadjuvant cisplatin in triple negative breast cancer. J Clin Oncol 28:1145–1153
8. Sikov WM, Berry DA, Perou CM et al Impact of the addition of carboplatin (Cb) and/or bevacizumab (B) to neoadjuvant weekly paclitaxel (P) followed by dose-dense AC on pathologic complete response (pCR) rates in triple-negative breast cancer (TNBC): CALGB 40603(Alliance). http://www.abstracts2view.com/sabcs13/view.php?nu=SABCS13L_458&terms. Accessed 20 Dec 2013
9. Von Minckwitz G, Schneeweiss A, Salat C et al (2013) A randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto). J Clin Oncol 31(suppl abstr):1004
10. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
11. Alba E, Chacon JI, Lluch A et al (2012) A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study. Breast Cancer Res Treat 136(2):487–493
12. Chang HR, Glaspy J, Allison MA et al (2010) Differential response of triple-negative breast cancer to a docetaxel and carboplatin-based neoadjuvant treatment. Cancer 116(18):4227–4237
13. Chen XS, Nie XQ, Chen CM et al (2010) Weekly paclitaxel plus carboplatin is an effective nonanthracycline-containing regimen as neoadjuvant chemotherapy for breast cancer. Ann Oncol 21(5):961–967
14. Sikov WM, Dizon DS, Strenger R et al (2009) Frequent pathologic complete responses in aggressive stages II to III breast cancers with every-4-week carboplatin and weekly paclitaxel with or without trastuzumab: a Brown University Oncology Group Study. J Clin Oncol 27(28):4693–4700
15. Yerushalmi R, Hayes MM, Gelmon KA et al (2009) A phase II trial of a neoadjuvant platinum regimen for locally advanced breast cancer: pathologic response, long-term follow-up, and correlation with biomarkers. Clin Breast Cancer 9(3):166–172
16. Frasci G, Comella P, Rinaldo M et al (2009) Preoperative weekly cisplatin–epirubicin–paclitaxel with G-CSF support in triple-negative large operable breast cancer. Ann Oncol 20(7):1185–1192
17. Torrisi R, Balduzzi A, Ghisini R et al (2008) Tailored preoperative treatment of locally advanced triple negative (hormone receptor negative and HER2 negative) breast cancer with epirubicin, cisplatin, and infusional fluorouracil followed by weekly paclitaxel. Cancer Chemother Pharmacol 62(4):667–672
18. Julka PK, Chacko RT, Nag S et al (2008) A phase II study of sequential neoadjuvant gemcitabine plus doxorubicin followed by gemcitabine plus cisplatin in patients with operable breast cancer: prediction of response using molecular profiling. Br J Cancer 98(8):1327–1335
19. Sinclair NF, Abu-Khalaf NN, Rizack T et al (2012) Neoadjuvant weekly nab-paclitaxel (wA), carboplatin (Cb) plus bevacizumab (B) with or without dose-dense doxorubicin-cyclophosphamide (ddAC) plus B in ER+/HER2-negative (HR plus) and triple-negative (TN) breast cancer (BrCa): A BrUOG study. J Clin Oncol 30(15):1045
20. Shinde AM, Yim JH, Kruper L et al (2012) Pathologic complete response rates observed in women with locally advanced and inflammatory breast cancer receiving neoadjuvant carboplatin and paclitaxel. J Clin Oncol 30(15):1035
21. Rahal MM, Ramadan H, Hassan E et al (2010) Neoadjuvant platinum containing regimen for locally advanced triple negative breast cancer. Ann Oncol 21(8s):114–115
22. Diaz-Correa E, Singh C, Pereira S (2011) Neoadjuvant chemotherapy (NAC) consisting in dose-dense doxorubicin plus cyclophosphamide followed by cisplatin plus taxane for locoregional advanced triple-negative breast cancer (LATNBC). J Clin Oncol 29(suppl; abstr e11562)
23. Fei F, Du Y, Gu X et al (2012) A retrospective analysis of platinum-based neoadjuvant chemotherapy for local advanced triple negative breast cancer. Ann Oncol 23(9s):130
24. Mayer IA, Jovanovic B, Abramson VG et al A randomized phase II neoadjuvant study of cisplatin, paclitaxel with or without everolimus (an mTOR inhibitor) in patients with stage II/III triple-negative breast cancer (TNBC). http://www.abstracts2view.com/sabcs13/view.php?nu=SABCS13L_397&terms. Accessed 20 Dec 2013
25. Rugo HS, Olopade O, DeMichele A et al Veliparib/carboplatin plus standard neoadjuvant therapy for high-risk breast cancer: First efficacy results from the I-SPY 2 TRIAL. http://www.abstracts2view.com/sabcs13/view.php?nu=SABCS13L_1400&terms
26. Kern P, Kolberg HC, Halisch A et al (2013) Updated results of neoadjuvant chemotherapy with carboplatin AUC 6 and docetaxel 75 mg/m^2 in triple-negative breast cancer (TNBC). J Clin Oncol 31(suppl 26; abstr 149)
27. Zhang P, Yin Y, Xu B et al Carboplatin plus paclitaxel compared with epirubicin plus paclitaxel as neoadjuvant chemotherapy for triple-negative breast cancer: a phase II clinical trial. http://www.abstracts2view.com/sabcs13/view.php?nu=SABCS13L_127&terms
28. Sirohi B, Arnedos M, Popat S et al (2008) Platinum-based chemotherapy in triple-negative breast cancer. Ann Oncol 19(11):1847–1852
29. Kim HR, Jung KH, Im SA et al (2013) Multicentre phase II trial of bevacizumab combined with docetaxel–carboplatin for the neoadjuvant treatment of triple-negative breast cancer (KCSG BR-0905). Ann Oncol 24(6):1485–1490
30. Hurley J, Reis IM, Rodgers SE et al (2013) The use of neoadjuvant platinum-based chemotherapy in locally advanced breast cancer that is triple negative: retrospective analysis of 144 patients. Breast Cancer Res Treat 138(3):783–794
31. Roy V, Pockaj BA, Allred JB et al (2013) A phase II trial of docetaxel and carboplatin administered every 2 weeks as

preoperative therapy for stage II or III breast cancer NCCTG study N0338. Am J Clin Oncol 36(6):540–544
32. Ithimakin S, Ratanawichitrasin A, Veerasarn V et al (2013) A phase II study of the combination of gemcitabine plus carboplatin as the neoadjuvant treatment in locally advanced breast cancer. J Med Assoc Thail 96(suppl 2):S67–S74
33. Snider JN, Sachdev JC, Allen JW et al (2012) Pathologic complete response (pCR) with weekly nanoparticle albumin bound (nab-P) plus carboplatin (C) followed by doxorubicin plus cyclophosphamide (AC) with concurrent bevacizumab (B) for triple-negative breast cancer (TNBC). J Clin Oncol 31(suppl): abstr 1068
34. Tiley S, Raab RE, Bellin LS et al (2012) Results of the East Carolina Breast Center phase II trial of neoadjuvant metronomic chemotherapy in triple-negative breast cancer (NCT00542191). J Clin Oncol 30(15 suppl 1):e11550
35. Telli ML, Kurian AW, Jensen KC et al (2011) A phase II study of gemcitabine and carboplatin (GC) plus iniparib (BSI-201) as neoadjuvant therapy for triple-negative and BRCA1/2 mutation-associated breast cancer. Cancer Res 71(24 suppl 3):abstract P3-14-08
36. Mrozek E, Lustberg MB, Knopp MV et al (2010) Phase II trial of neoadjuvant chemotherapy (NCT) with weekly nanoparticle albumin-bound paclitaxel (Nab-P), carboplatin (CBP), and bevacizumab (BEV) in women with clinical stages II-III breast cancer (BC): Pathologic response prediction by changes in angiogenic volume (AV) by dynamic contrast magnetic resonance imaging (DCE-MRI). J Clin Oncol 28(15 suppl 1):abstr 604
37. Gianni L, Pienkowski T, Im YH et al (2012) Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 13(1):25–32
38. Piccart-Gebhart M, Holmes AP, de Azambuja E et al The association between event-free survival and pathological complete response to neoadjuvant lapatinib, trastuzumab or their combination in HER2-positive breast cancer. Survival follow-up analysis of the NeoALTTO study (BIG 1-06). http://www.abstracts2view.com/sabcs13/view.php?nu=SABCS13L_877&terms. Accessed 20 Dec 2013
39. Greenup R, Buchanan A, Lorizio W et al (2013) Prevalence of BRCA mutations among women with triple-negative breast cancer (TNBC) in a genetic counselling cohort. Ann Surg Oncol 20(10):3254–3258
40. Bayraktar S, Gutierrez-Barrera AM, Liu D et al (2011) Outcome of triple-negative breast cancer in patients with or without deleterious BRCA mutations. Breast Cancer Res Treat 130(1):145–153
41. Lips EH, Mulder L, Oonk A et al (2013) Triple-negative breast cancer: BRCAness and concordance of clinical features with BRCA1-mutation carriers. Br J Cancer 108(10):2172–2177
42. Masuda H, Baggerly KA, Wang Y et al (2013) Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. Clin Cancer Res 19(19):5533–5540
43. Gerber B, Loibl S, Eidtmann H et al (2013) Neoadjuvant bevacizumab and anthracycline–taxane-based chemotherapy in 678 triple-negative primary breast cancers; results from the geparquinto study (GBG 44). Ann Oncol 24(12):2978–2984
44. Bernsdorf M, Ingvar C, Jörgensen L et al (2011) Effect of adding gefitinib to neoadjuvant chemotherapy in estrogen receptor negative early breast cancer in a randomized phase II trial. Breast Cancer Res Treat 126(2):463–470
45. von Minckwitz G, Blohmer JU, Costa SD et al (2013) Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol 31(29):3623–3630
46. Balko JM, Giltnane J, Wang K et al (2013) Molecular profiling of the residual disease of triple-negative breast cancers after neoadjuvant chemotherapy identifies actionable therapeutic targets. Cancer Discov 19(23):6353
47. Koolen BB, Pengel KE, Wesseling J et al (2014) Sequential (18)F-FDG PET/CT for early prediction of complete pathological response in breast and axilla during neoadjuvant chemotherapy. Eur J Nucl Med Mol Imaging 41(1):32–40
48. Groheux D, Hindié E, Giacchetti S et al (2012) Triple-negative breast cancer: early assessment with 18F-FDG PET/CT during neoadjuvant chemotherapy identifies patients who are unlikely to achieve a pathologic complete response and are at a high risk of early relapse. J Nucl Med 53(2):249–254
49. Denkert C, Loibl S, Müller BM et al (2013) Ki67 levels as predictive and prognostic parameters in pretherapeutic breast cancer core biopsies: a translational investigation in the neoadjuvant GeparTrio trial. Ann Oncol 24(11):2786–2793
50. Abdel-Fatah TM, Perry C, Dickinson P et al (2013) Bcl2 is an independent prognostic marker of triple negative breast cancer (TNBC) and predicts response to anthracycline combination (ATC) chemotherapy (CT) in adjuvant and neoadjuvant settings. Ann Oncol 24(11):2801–2807
51. Dennison JB, Molina JR, Mitra S et al (2013) Lactate dehydrogenase B: a metabolic marker of response to neoadjuvant chemotherapy in breast cancer. Clin Cancer Res 19(13):3703–3713
52. Li XR, Liu M, Zhang YJ et al (2011) CK5/6, EGFR, Ki-67, cyclin D1, and nm23-H1 protein expressions as predictors of pathological complete response to neoadjuvant chemotherapy in triple-negative breast cancer patients. Med Oncol 28(Suppl 1):S129–S134
53. Sakuma K, Kurosumi M, Oba H et al (2011) Pathological tumor response to neoadjuvant chemotherapy using anthracycline and taxanes in patients with triple-negative breast cancer. Exp Ther Med 2(2):257–264
54. Huober J, von Minckwitz G, Denkert C et al (2010) Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 124(1):133–140
55. Liu M, Mo QG, Wei CY et al (2013) Platinum-based chemotherapy in triple-negative breast cancer: a meta-analysis. Oncol Lett 5(3):983–991
56. Carrick S, Ghersi D, Wilcken N, Simes J (2004) Platinum containing regimens for metastatic breast cancer. Cochrane Database Syst Rev 3:CD003374