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Role of Carboplatin in Neoadjuvant Chemotherapy for Triple-Negative Breast Cancer

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ABSTRACT

Triple-negative breast cancer is the most aggressive subtype of breast tumors. After a better molecular understanding of breast cancer, the treatment of triple-negative tumors is challenging because there is no known potential therapeutic target. Recently, interesting data about the use of platinum has been published and has generated excitement, especially in patients harboring mutations in BRCA gene. In this paper, the use of platinum agents will be reviewed as a new therapeutic option for mutated BRCA and triple-negative breast cancer. (J CANCEROL. 2015;2:15-20)

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INTRODUCTION

Triple-negative breast cancer (TNBC) is characterized by tumors that do not express estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 (HER2)[1]. Retrospectives studies show that absence of hormonal receptor expression yields a greater response to cytotoxic chemotherapy[2,3].

Neoadjuvant chemotherapy is related to increase of conservative surgery rates, and allows an initial evaluation of systemic therapy efficacy[4]. Historically, TNBC responds well to neoadjuvant chemotherapy, with higher pathologic complete response (pCR) rates when compared to other subtypes of breast cancer[5].

However, more than half of TNBC patients do not achieve pCR, which correlates with a poor prognosis[5]. Therefore, in order to improve pCR rates, several clinical trials have been associating other agents (especially platinum) to anthracycline/taxane as neoadjuvant therapy in TNBC.

Triple-negative breast cancer may be associated to mutations in BRCA 1/2 genes. Those mutations generate a deficiency of DNA repair proteins, thus becoming more susceptible to agents that act directly on DNA. The principal agents are platinum, poly(ADP-ribose) polymerase inhibitors (PARP), tyrosine kinase inhibitors, and microtubule inhibitors.

RELEVANCE OF PATHOLOGIC COMPLETE RESPONSE IN NEOADJUVANT THERAPY

Several studies show that pCR following neoadjuvant chemotherapy correlates with better survival rates. Recently, Cortazar, et al.[5] reported data from a patient-level meta-analysis including 12 randomized trials that evaluated neoadjuvant chemotherapy in 11,955 patients with breast cancer. The study demonstrated that pCR (regardless its definition) yielded greater event-free survival and overall survival than non-pCR (Table 1).

The pCR rate for breast and axillary lymph nodes (ypT0/is ypN0) was low in patients with positive hormone receptor, whereas it was higher in HER2-positive and triple-negative patients (Table 2).

A better correlation between pRC and long-term results was observed in TNBC when compared to other subtypes of breast cancer (HR: 0.24; 95% CI: 0.18-0.33 for event-free survival and HR: 0.16; 95% CI: 0.11-0.25 for overall survival).

Therefore we can conclude from the meta-analysis:

- Eradication of tumor in breast and lymph nodes (tumor *in situ* was allowed) is the definition of pCR better correlated to prognosis.
- Patients who achieve pCR yield higher event-free survival (HR: 0.48) and overall survival (HR: 0.36) when compared to non-pCR patients.
- The pCR rate depends on the tumor phenotype: low for low-grade hormone receptor-positive/HER2-negative tumors; intermediate for high-grade hormone receptor-positive/HER2-negative tumors; relatively high for triple-negative tumors and for hormone receptor-positive/HER2-positive tumors; and pCR may reach up to 50% in hormone receptor-negative/HER2-positive (enriched HER2 tumors) with current therapies.
- Impact of pCR in overall and event-free survival is restricted to patients with more aggressive subtype of tumors (TNBC and HER2-positive).

ACTIVITY OF PLATINUM AGENTS IN NEOADJUVANT CHEMOTHERAPY FOR TRIPLE-NEGATIVE BREAST CANCER

The use of platinum-based therapies has been widely studied for TNBC. The rationale for this strategy

Table 1. Correlation between definitions of pathologic complete response, event-free survival, and overall survival according to meta-analysis[5]

	pCR	EFS	OS
ypT0/is	22%	HR: 0.60; 95% CI: 0.55-0.66	HR: 0.51; 95% CI: 0.45-0.58
ypT0/is ypN0	18%	HR: 0.44; 95% CI: 0.39-0.51	HR: 0.36; 95% CI: 0.31-0.42
ypT0 ypN0	13%	HR: 0.48; 95% CI: 0.43-0.54	HR: 0.36; 95% CI: 0.30-0.44

PCR: pathologic complete response; EFS: event-free survival; OS: overall survival.

Table 2. Correlation between definitions of pathologic complete response, event-free survival and overall survival according to tumor phenotype[5]

Phenotype	EFS (HR)	OS (HR)
Positive hormonal receptor	0.63	0.47
HER2-positive	0.39	0.34
Triple-negative	0.24	0.16

EFS: event-free survival; OS: overall survival.

lies in phenotypic and genotypic similarities between TNBC and mutated BRCA breast cancer[6,7]. Cells with mutation in BRCA genes are deficient in DNA repair mechanism, and thus they are more sensitive to platinum agents[8,9]. Triple-negative tumors, even with no mutation in BRCA, can also present deficiency in DNA repair mechanism[6].

Non-randomized phase II trials

The main non-randomized trials evaluating the role of platinum in a neoadjuvant scenario[10-13] are summarized in table 3. The pCR rates ranged from 15 to 72%. The higher pCR rate was observed in the Gronwald, et al. study[10], which enrolled 25 patients with breast cancer, 80% triple-negative and 100% with mutated BRCA 1. Patients underwent neoadjuvant therapy with cisplatin alone, 75 mg/m^2 every three weeks for four cycles. The pCR rate was 72%, suggesting a strong correlation between mutation in BRCA 1 and sensitivity to cisplatin. Other trials also explored that hypothesis. For example, a study published in 2010 by Silver, et al.[11] showed that 21% of patients diagnosed with TNBC reached pCR after neoadjuvant single-agent cisplatin (75 mg/m^2 every three weeks for four cycles), and all patients with pCR presented mutation in BRCA 1 gene[11] (Table 3).

Randomized phase II trials

A Spanish trial from GEICAM[15], enrolling 94 patients with TNBC, analyzed pCR rates after epirubicin and cyclophosphamide regimen followed by carboplatin and docetaxel versus epirubicin and cyclophosphamide followed by docetaxel. The study obtained similar pCR rates in both groups, about 30%[14], besides a greater toxicity rate in the carboplatin arm, and therefore the trial was negative.

Table 3. Non-randomized phase II trials evaluating platinum in neoadjuvant chemotherapy

Study	(n)	Patient profile	Regimen	pCR (%)
Silver, et al.[11]	28	TN IIA-IIIC (≥ 1.5 cm)	Cis 75 mg/m^2 daily 21 days × 4 cycles	21%
Gronwald, et al.[10]	25	I-III, mutation in BRCA 1 (80% TN)	Cis 75 mg/m^2 daily 21 days × 4 cycles	72%
Ryan, et al.[12]	51	T1-3 TN	Cis 75 mg/m^2 daily 21 days × 4 cycles + Bev 15 mg/kg daily 3 weeks × 3 cycles	15%
Telli, et al.[13]	80	I-IIIA TN or mutation in BRCA 1/2 (T ≥ 1 cm)	Gem 1000 mg/m^2 D 1, 8 + Carbo AUC 2 D 1, 8 + Iniparib 5.6 mg/kg D 1, 4, 8,11 21 days × 6 cycles	36%, BRCA$^{not\ mut}$ = 33%, BRCA^{mut} = 56%

TN: triple-negative; pCR: pathologic complete response; Cis: cisplatin; Bev: bevacizumab; Gem: gemcitabine; Carbo: carboplatin.

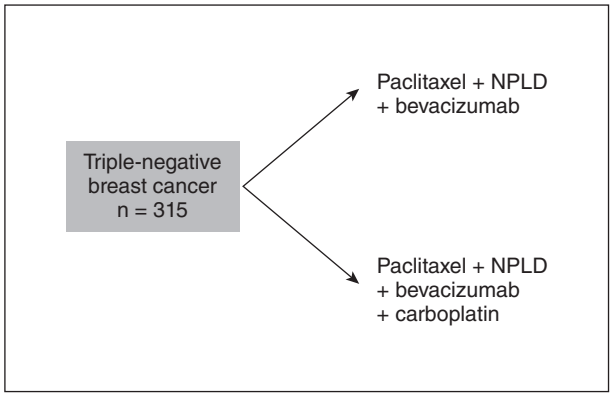

Figure 1. Scheme of GeparSixto trial enrolling triple-negative breast cancer patients.
NPLD: non-pegylated liposomal doxorubicin.

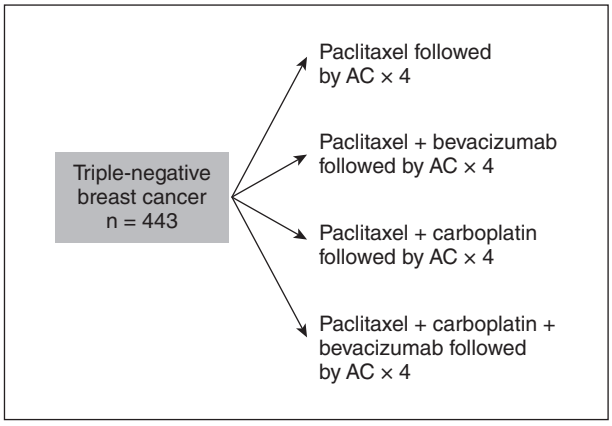

Figure 2. Scheme of CALGB 4063 trial.
AC: doxorubicin + cyclophosphamide.

Two large phase II randomized trials, GeparSixto[15] and CALGB 40603/ALLIANCE[16], studied the role of the addition of carboplatin to neoadjuvant chemotherapy regimens.

GeparSixto[15] is a phase II randomized trial, including 588 patients with stage II/III triple-negative or HER2-positive breast cancer. They were randomized to carboplatin (n = 296) and non-carboplatin (n = 293) groups. All patients were treated with paclitaxel 80 mg/m^2 and non-pegylated liposomal doxorubicin 20 mg/m^2, both weekly for 18 weeks. Additionally, triple-negative patients received bevacizumab 15 mg/kg every three weeks, and HER2-positive patients received dual blockade with trastuzumab plus lapatinib. The primary endpoint was pCR rate (ypT0, ypN0). In the study, 315 triple-negative patients were enrolled, 158 in the carboplatin group and 157 in the non-carboplatin group (Fig. 1). Among the HER2-positive patients, 273 patients were randomized, 137 in the carboplatin group and 136 in the non-carboplatin group. All HER2-positive women received trastuzumab plus lapatinib (Fig. 1)

Among triple-negative patients, the pCR rate was 53.2% for the carboplatin group versus 36.9% for the non-platinum group (p = 0.005). However, in HER2-positive patients, pCR rates were 32.8 vs. 36.8%, respectively (p = 0.581).

The GeparSixto trial suggests that addition of carboplatin in neoadjuvant therapy significantly improves the pCR rate in TNBC, though it did not have favorable impact in HER2-positive disease.

Another important study evaluating the benefit of carboplatin in neoadjuvant therapy is CALGB/ALLIANCE 40603[16], presented at the San Antonio Breast Cancer Symposium in 2013. The randomized phase II trial, 2 × 2 factorial, analyzed the role of addition of carboplatin and bevacizumab in stage II-III TNBC. All patients received paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every two weeks (dose-dense AC) for four cycles. Patients were randomly assigned for carboplatin AUC 6 every three weeks for four cycles, concomitant with first day of paclitaxel, versus non-carboplatin, besides bevacizumab 10 mg/kg every two weeks versus non-bevacizumab (2 × 2 factorial design) (Fig. 2).

Carboplatin significantly improved the pCR rate (54 vs. 41%; p = 0.0029). Addition of bevacizumab also increased pCR; however, it was not statistically significant (52 vs. 44%; p = 0.057). The combination of carboplatin and bevacizumab was also non significant (p = 0.43). In each arm, pCR rates were: 39% in weekly paclitaxel followed by dose-dense AC; 49% in weekly paclitaxel and carboplatin followed by dose-dense AC; 43% in weekly

Table 4. Pathologic complete response rate in most important phase II randomized trials evaluating carboplatin in neoadjuvant chemotherapy in triple-negative breast cancer

Author Trial	(n)	Regimen	pCR (%) with Carbo	pCR (%) without Carbo	Increase (%)	p
Von Minckwitz, et al.[15] GeparSixto	315	P + DLNP + Bev vs. P + DLNP + Bev + Carbo	59%	38%	21%	0.005
Sikov, et al.[16] Alliance	443	P ± Carbo ≥ dose-dense AC	54%	41%	13%	<0.05
Alba, et al.[14] GEICAM	94	EC ≥ D vs. EC ≥ D + Carbo	30%	30%	–	–
Jiayu, et al.[17]	92	P (or D) + Carbo vs. P (or D) + E	37.2%	16.1%	21.1%	0.032
Kenji, et al.[18]	181	P ± Carbo ≥ FEC	61.2%	26.3%	34.9%	0.03

pCR: pathologic complete response; P: paclitaxel; NPLD: non-pegylated liposomal doxorubicin; Bev: bevacizumab; Carbo: carboplatin; AC: doxorubicin + cyclophosphamide; EC: epirubicin + cyclophosphamide; D: docetaxel; FEC: fluorouracil + epirubicin+ cyclophosphamide.

paclitaxel followed by dose-dense AC plus bevacizumab; 60% in weekly paclitaxel and carboplatin followed by dose-dense AC plus bevacizumab. Similarly to GeparSixto, addition of carboplatin or bevacizumab increased adverse event rates.

At the American Society of Clinical Oncology Congress (ASCO) in 2014, two phase II trials were presented. Despite both trials being smaller than GEPARSIXTO and CALGB 4063, they confirm the benefit of carboplatin in a neoadjuvant scenario for TNBC. The first trial was a Chinese study[17], which enrolled 92 patients with locally advanced TNBC and randomized for paclitaxel (or docetaxel) and carboplatin (TC) versus paclitaxel (or docetaxel) and epirubicin (TE) every three weeks for four to six cycles. Primary endpoint was pCR, defined as absence of pathological invasive cancer in breast and axillary region. The TC group had 43 patients and the TE group had 49 patients. The pCR rate was higher in the carboplatin (TC) group (37.2 vs. 16.1%; p = 0.032).

The second trial, performed in Japan[18], randomly assigned 181 patients with locally advanced HER2-negative breast cancer for neoadjuvant chemotherapy with weekly paclitaxel (P) with or without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil (FEC). The pCR rate in the CP-FEC arm was significantly higher than in P-FEC arm (61.2 vs. 26.3%, respectively; p = 0.003). The authors concluded that addition of carboplatin to paclitaxel followed by FEC in a neoadjuvant setting significantly improved the pCR rate with a favorable safety profile.

Table 4 presents a summary of results from the four randomized phase II trials that evaluated the addition of carboplatin to neoadjuvant chemotherapy regimens. Of note, addition of carboplatin improved pCR rates, with a range of 30-61.2% (Table 4).

At ASCO 2014, a German group presented data from GeparSixto related to BRCA mutation and family history of breast or ovarian cancer. Presence of mutation in BRCA 1/2 genes was evaluated in 295 (94%) patients with TNBC from 315 women of the GeparSixto trial. An increase of 26.7% in pCR (OR: 3.04) was observed with addition of carboplatin in patients with a positive family history for breast or ovarian cancer despite absence of BRCA mutation (pCR 49%). In patients harboring BRCA 1/2 mutation, the increase in pCR rate was 23.2% (OR: 2.6; pCR: 55%). On the other hand, patients with no positive family history and no mutation in BRCA 1/2 presented a pCR rate of 46% (Fig. 3). Investigators concluded that mutations in BRCA 1/2 and family

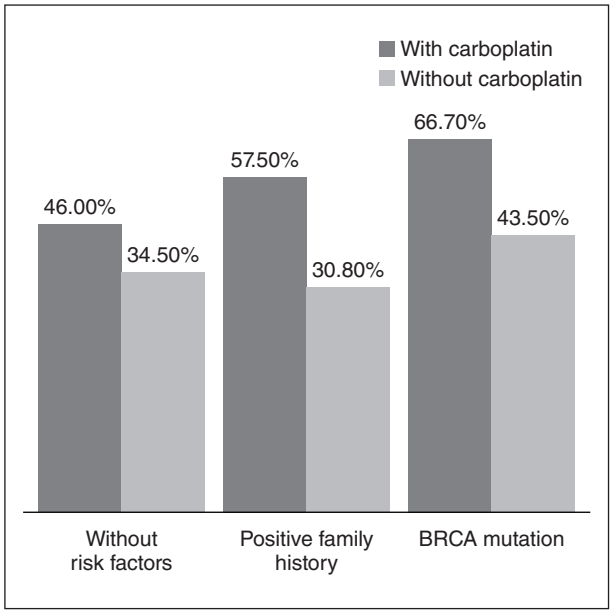

Figure 3. Correlation between pathologic complete response (%) and BRCA mutation or family history of breast/ovarian cancer in GeparSixto study patients[15].

history for breast or ovarian cancer are strong predictors for improvement in pCR rates after carboplatin in TNBC[9,19] (Fig. 3).

CONCLUSION

Given the strong correlation between pCR and prognosis in TNBC, we must use therapies able to achieve the highest possible pCR rate in neoadjuvant therapy for TNBC. Carboplatin is the chemotherapy correlated to better pCR rates so far, and yields consistent improvement in pCR rates in several phase II randomized trials. In our opinion, addition of carboplatin in neoadjuvant chemotherapy regimens must be strongly considered in patients diagnosed with locally advanced TNBC, which does not have a known potential therapeutic target, unlike other subtypes of breast cancer.

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