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Antiangiogenic Therapy Combined with Chemotherapy Including Platinum Agents as a Therapeutic Option for Triple Negative Breast Cancer

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Abstract

Triple negative breast cancer (TNBC) is an aggressive histological subtype with limited treatment options. While rationally-derived regimens are emerging from the results of recent gene profiling studies, TNBC is an angiogenesis-dependent malignancy, and antiangiogenic therapies have been examined energetically in this field. Antiangiogenic agents in combination with chemotherapeutic platinum compounds have shown some benefit in recent randomized control studies for the treatment of TNBC. These combinations could be more safe and efficacious in patients, when pharmacotherapy schedule is modified taking into account its tolerability.

Keywords: Triple negative breast cancer; Antiangiogenic therapy; BRCA

Brief Report

TNBC defined by the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expressions, is a highly aggressive malignancy [1-3]. Recently, gene expression (GE) profiling has identified that the distinct molecular subtypes of TNBC—including basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), luminal androgen receptor (LAR) and unclassified (U)—have different biological features, driver mutations for cell growth, natural history, and clinical behaviors [4]. Revelation of this heterogeneity has led to the identification and elucidation of 'druggable' targets for TNBC. For example, the BL 1 subtypes demonstrate higher expression of cell cycle and DNA damage response genes, suggesting that they may respond well polyADP ribose polymerase inhibitors (PARPi) [5] and DNA damaging agents including platinum agents. M and MSL subtypes highly express epithelial-mesenchymal transition and growth factor pathways genes, and were shown to respond to NVP-BEZ235 (a PI3K/mTOR inhibitor) using *in vitro* models. Similarly, LAR cell lines were shown to be sensitive to bicalutamide (an androgen receptor {AR} antagonist) [4]. Thus as rationally-derived regimens are important candidates that should replace nonspecific standard therapies for TNBC, many phase 1–3 clinical studies are being conducted based on recent molecular findings.

Apart from being classified with distinct gene expression profiles, evidence such as higher expression of vascular endothelial growth factor (VEGF) [6,7], increased microvessel density (MVD) in BL1 than in non-BL TNBCs [8], and a significant inverse relationship between VEGF levels and survival rates [3] have demonstrated that TNBC is also an angiogenesis-dependent malignancy. Treatment with anti-VEGF monoclonal antibody bevacizumab has shown some benefit in breast cancer treatment where its addition to the standard chemotherapy improved the pathological complete response (pCR) rate in neoadjuvant settings [9-12], as well as the progression free survival and response rates of metastatic TNBC patients [13]; Nevertheless these results were not consistent in regards to the overall survival (OS), predictive biomarkers, and appropriate chemotherapy backbone.

BRCA maintain genomic stability and are critical regulators of DNA repair, mainly double–stranded breaks [14,15]; thus DNA repair defects that are characteristic of BRCA mutations in cancers such as the BL subtype [16,17] confer sensitivity to DNA damaging agents like platinum compounds [18,19]. BRCA1 has also been reported to be involved in neovascularization *via* the regulation of some angiogenic transcription factors [20]. VEGF and Angiopoietin 1 in particular are negatively regulated by BRCA1 [21]. Thus, compared to the sporadic cancer group, elevated levels of angiopoietins and VEGF mRNA [22], as well as the higher expressions of VEGF, hypoxia inducible factor-1 alpha (HIF-1a)—which is a major activator of VEGF—and MVD in BRCA1-2 carriers could be attractive angiogenic therapeutic targets [23].

Recently, a higher proportion of patients achieving pCR in adjuvant trials was reported when bevacizumab was administered simultaneously with cytotoxic agents such as carboplatin (Cb), despite the conflicting data from long-term outcomes [24,25]. In the phase II GeparSixto trial, 294 TNBC patients were concomitantly treated for 18 weeks with a weekly dose of 80 mg/m^2 paclitaxel and 20 mg/m^2 non-pegylated-liposomal doxorubicin, and a 15 mg/kg bevacizumab administered every 3 weeks. Additionally, all patients were randomized 1:1 to concurrently receive Cb AUC 2 once every week for 18 weeks. Results showed that the TNBC patients receiving additional Cb had a higher pCR rate (53.2% *vs.* 36.9%, P=0.005) and improved survival rates with a median follow-up duration of 35 months (85.8% *vs.* 76.1%; HR 0.56, 95% CI 0.33-0.96, P=0.0350) when compared to the control group [24]. In the other phase II CALGB 40603 trial, 443 TNBC patients receiving backbone chemotherapy of weekly paclitaxel (80 mg/m^2) for 12 weeks, followed by 60 mg/m^2 doxorubicin plus 600 mg/m^2 cyclophosphamide every 2 weeks (ddAC) for four cycles, were randomly assigned to concurrent Cb AUC 6 every 3 weeks for four

cycles with or without 10 mg/kg q^2 w bevacizumab for nine cycles. Although the addition of either Cb (60% *vs.* 44%; P=0.0018) or bevacizumab (59% *vs.* 48%; P=0.0089) significantly increased pCR rate [25], this rate was not linked to the improved survival of the treatment group [26]. Currently, it is premature to conclusively interpret the long-term survival affects because both studies were under powered in regard to the long-term outcome endpoints. Notably, observed frequent skipped doses and dose modifications by markedly higher toxicity in these trials could raise a concern over feasibility of these regimens. Decreased anticancer effect by early treatment discontinuations could not reflect constant association of pCR with improved OS in TNBC. Although anthracycline based dose-dense adjuvant therapy is an evidence-based strategy for TNBC [27], the concomitant use of DNA damage agents such as Cb and anthracyclin, did not have a synergic effect in BRCA carriers [28] and over dosage could result in higher toxicity.

Sufficient clinical safety and efficacy of the concurrent use of bevacizumab, paclitaxel, and platinum agents have already been demonstrated among patients with recurrent or advanced non-small cell lung cancers (200 mg/m^2 paclitaxel, Cb AUC 6, and 15 mg/kg bevacizumab every 3 weeks for 6 cycles) [29], metastatic ovarian cancer (175 mg/m^2 paclitaxel, Cb AUC 6 and 15 mg/kg bevacizumab every 3 weeks for 5 cycles) [30], and cervical cancer (135 or 175 mg/m^2 paclitaxel, 50 mg/m^2 cisplatin, and 15 mg/kg bevacizumab every 3 weeks) [31].

Earlier small-scale studies of concurrent use of bevacizumab, paclitaxel, and platinum agents for unselected TNBC also report superior efficacy and safety. In a phase II clinical trial of preoperative chemotherapy for TNBC patients comprising six cycles of 75 mg/m^2 docetaxel, Cb AUC 5, and 15 mg/kg bevacizumab every 21 days, a pCR rate of 42% (n=19) and a clinical response rate of 96% (n=43) were achieved, with only one patient withdrawing from the study [32]. Similarly, another phase II clinical trial on TNBC patients receiving 80 mg/ m^2 paclitaxel plus Cb AUC 2 on days 1, 8, and 15, combined with 10 mg/kg bevacizumab on days 1 and 15 each 28 days, for 5 cycles, followed by a single dose of 5 mg/kg bevacizumab (on day 6), reported the achievement of pCR in breast and axillary lymph nodes in 50% (n=22) without causing any major toxicities [33]. Another study reported a median PFS of 9.2 months, a clinical benefit rate of 94%, and a response rate of 85% in TNBC patients who first received 75 mg/m^2 nab-paclitaxel and Cb AUC 2 on days 1, 8, 15, and 10 mg/kg bevacizumab on days 1 and 15 of a 28-day cycle [33].

Thus, the combination therapy of bevacizumab, taxane, and platinum agents is suggested as a possible therapeutic option for TNBC that confers better tolerability and improved safety. Further studies for this combination therapy should be conducted, as feasible pharmacotherapy schedule taking into account its tolerability and safety, to validate the long-term effects and define predictive biomarkers.

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