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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.

References

1. Tischkowitz M, Brunet JS, Begin LR, Huntsman DG, Cheang MC, et al. (2007) Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC Cancer 7: 134.
2. Fornier M, Fumoleau P (2012) The paradox of triple negative breast cancer: novel approaches to treatment. Breast J 18: 41-51.
3. Crown J, O'Shaughnessy J, Gullo G (2012) Emerging targeted therapies in triple-negative breast cancer. Ann Oncol 6: 56-65.
4. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, et al. (2012) Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 121: 2750-2767.
5. Robson M, Goessl C, Domchek S (2017) Olaparib for Metastatic Germline BRCA-Mutated Breast Cancer. N Engl J Med 377: 1792-1793.
6. Andre F, Job B, Dessen P, Michiels S, Liedtke C, et al. (2009) Molecular characterization of breast cancer with high-resolution oligonucleotide comparative genomic hybridization array. Clin Cancer Res 15: 441-451.
7. Linderholm BK, Hellborg H, Johansson U, Elmberger G, Skoog L, et al. (2009) Significantly higher levels of vascular endothelial growth factor (VEGF) and shorter survival times for patients with primary operable triple-negative breast cancer. Ann Oncol 20: 1639-1646.
8. Mohammed RA, Ellis IO, Mahmmod AM, Hawkes EC, Green AR, et al. (2011) Lymphatic and blood vessels in basal and triple-negative breast cancers: characteristics and prognostic significance. Mod Pathol 24: 774-785.
9. Bear HD, Tang G, Rastogi P, Geyer CE Jr, Robidoux A, et al. (2012) Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med 366: 310-320.
10. Earl HM, Hiller L, Dunn JA, Blenkinsop C, Grybowicz L, et al. (2015) Efficacy of neoadjuvant bevacizumab added to docetaxel followed by fluorouracil, epirubicin, and cyclophosphamide, for women with HER2-negative early breast cancer (ARTemis): an open-label, randomised, phase 3 trial. Lancet Oncol 16: 656-666.
11. Nahleh ZA, Barlow WE, Hayes DF, Schott AF, Gralow JR, et al. (2016) SWOG S0800 (NCI CDR0000636131): addition of bevacizumab to neoadjuvant nab-paclitaxel with dose-dense doxorubicin and cyclophosphamide improves pathologic complete response (pCR) rates in inflammatory or locally advanced breast cancer. Breast Cancer Res Treat 158: 485-495.
12. von Minckwitz G, Eidtmann H, Rezai M, Fasching PA, Tesch H, et al. (2012) Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 366: 299-309.
13. Miles DW, Dieras V, Cortes J, Duenne AA, Yi J, et al. (2013) First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Ann Oncol 24: 2773-2780.
14. Scully R, Chen J, Ochs RL, Keegan K, Hoekstra M, et al. (1997) Dynamic changes of BRCA1 subnuclear location and phosphorylation state are initiated by DNA damage. Cell 90: 425-435.
15. Shin DS, Chahwan C, Huffman JL, Tainer JA (2004) Structure and function of the double-strand break repair machinery. DNA Repair 3: 863-873.
16. Badve S, Dabbs DJ, Schnitt SJ, Baehner FL, Decker T, et al. (2011) Basal-like and triple-negative breast cancers: a critical review with an emphasis on the implications for pathologists and oncologists. Mod Pathol 24: 157-167.
17. Turner N, Tutt A, Ashworth A (2004) Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 4: 814-819.
18. Kennedy RD, Quinn JE, Mullan PB, Johnston PG, Harkin DP (2004) The role of BRCA1 in the cellular response to chemotherapy. J Natl Cancer Inst 96: 1659-1668.
19. Tomasz B, Pawel B, Malgorzata FK, Foszczynska-Kloda M, Gronwald J, et al. (2012) Results of a phase II open-label, non-randomized trial of cisplatin chemotherapy in patients with BRCA1-positive metastatic breast cancer. Breast Cancer Res 14: R110.
20. Vassilopoulos A, Deng CX, Chavakis T (2010) Crosstalk between the DNA damage response, histone modifications and neovascularisation. Int J Biochem Cell Biol 42: 193-197.
21. Kawai H, Li H, Chun P, Avraham S, Avraham HK. (2002) Direct interaction between BRCA1 and the estrogen receptor regulates vascular endothelial growth factor (VEGF) transcription and secretion in breast cancer cells. Oncogene 21: 7730-7739.

22. Danza K, Pilato B, Lacalamita R, Addati T, Giotta F, et al. (2013) Angiogenetic axis angiopoietins/Tie2 and VEGF in familial breast cancer. Eur J Hum Genet 21: 824-830.
23. Saponaro C, Malfettone A, Ranieri G, Danza K, Simone G, et al. (2013) VEGF, HIF-1alpha expression and MVD as an angiogenic network in familial breast cancer. PLoS ONE 8: e53070.
24. von Minckwitz G, Schneeweiss A, Loibl S, Salat C, Denkert C, et al. (2014) Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 15: 747-756.
25. Sikov WM, Berry DA, Perou CM, Singh B, Cirrincione CT, et al. (2015) Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 33: 13-21.
26. Bonilla L, Ben-Aharon I, Vidal L, Gafter-Gvili A, Leibovici L, et al. (2010) Dose-dense chemotherapy in nonmetastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials. J Natl Cancer Inst 102: 1845-1854.
27. Hahnen E, Lederer B, Hauke J, Loibl S, Kröber S, et al. (2017) Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. JAMA Oncol 3: 1378-1385.
28. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, et al. (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355: 2542-2550.
29. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, et al. (2011) Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 365: 2473-2483.
30. Tewari KS, Sill MW, Long HJ, Penson RT, Huang H, et al. (2014) Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 370: 734-743.
31. Kim HR, Jung KH, Im SA, Im YH, Kang SY, 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: 1485-1490.
32. Guarneri V, Dieci MV, Bisagni G, Boni C, Cagossi K, et al. (2015) Preoperative carboplatin-paclitaxel-bevacizumab in triple-negative breast cancer: final results of the phase II Ca.Pa.Be study. Ann Surg Oncol 22: 2881-2887.
33. Hamilton E, Kimmick G, Hopkins J, Marcom PK, Rocha G, et al. (2013) Nab-paclitaxel/bevacizumab/carboplatin chemotherapy in first-line triple negative metastatic breast cancer. Clin Breast Cancer 13: 41.