Platinum Agents in the Treatment of Early-Stage Triple-Negative Breast Cancer: Is It Time to Change Practice?

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Abstract: Triple-negative breast cancer (TNBC) carries a higher risk of distant recurrence and death in the first 5 years compared with other types of breast cancer. Owing to the largely heterogeneous nature of TNBC, no unifying alteration exists that could benefit from a specific targeted therapy. A subset of TNBC, however, has intrinsic genomic instability caused by deficient DNA repair that could lead to the success of platinum agents (cisplatin or carboplatin) in treatment. Clinically, the addition of platinum agents to neoadjuvant treatment of TNBC is clearly associated with significantly higher rates of pathologic complete response. The utility of platinum agents in addition to standard adjuvant or neoadjuvant chemotherapy remains controversial, however, because data on overall survival and disease-free survival are not available. It remains unclear whether the addition of platinum agents to neoadjuvant chemotherapy improves long-term outcomes of TNBC.

Keywords
Gene expression profiles, platinum agents, targeted therapy, triple-negative breast cancer, TNBC

Introduction

Triple-negative breast cancer (TNBC), which is characterized by the absence of the estrogen receptor (ER) and progesterone receptor (PR) and lack of overexpression or amplification of *HER2,* accounts for at least 15% of all breast cancer subtypes. TNBC tends to be most prevalent in young African-American women[1] and is more aggressive than other types of breast cancer, carrying a higher risk of distant recurrence and death in the first 5 years.[2] The median overall survival (OS) for women with metastatic TNBC is 13 months, and fewer than 30% of women with metastatic TNBC survive longer than 5 years.[3] Although targeted therapies—such as trastuzumab (Herceptin, Genentech), pertuzumab (Perjeta, Genentech), and trastuzumab emtansine (TDM-1; Kadcyla, Genentech) for human epidermal growth factor receptor 2 (HER2)-positive disease, and tamoxifen, aromatase inhibitors, and fulvestrant (Faslodex, AstraZeneca) for ER- or PR-positive disease—have improved OS, the current standard of care for TNBC remains cytotoxic chemotherapy.

Owing to the largely heterogeneous nature of TNBC, no unifying alteration exists that could benefit from a single, more-

specific targeted therapy. However, through the use of gene expression profiling, a large proportion of TNBCs would be classified as basal-like[4] based on the 50-gene prediction analysis of microarray (PAM50) intrinsic subtype classification.[5] These basal-like TNBCs have many similarities to tumors arising in *BRCA1* mutation carriers: an increased likelihood of being high-grade; of being negative for ER, PR, and HER2; of having a high frequency of *TP53* mutations and expression of basal keratins; and of clustering together by gene expression profile.[6] Because *BRCA1*-mutated cancers have extreme genomic instability and sensitivity to DNA cross-linking agents,[7] agents targeted toward DNA repair defects—such as poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors and platinum agents—are clinically effective against these tumors.[8,9] Based on these observations, several studies have examined the use of platinum-based chemotherapy for TNBC, which is the subject of this review.

Platinum Agents in TNBC: Why Would They Work?

The *TP53* tumor suppressor gene is mutated in approximately 30% of breast cancers,[10] but the incidence of a *TP53* mutation is significantly higher in aggressive ER-negative breast cancers[11] and shows a strong association with the basal-like subgroup.[1,11] In a fraction of basal-like tumors, *TP63* is coordinately expressed with *TP73* and may antagonize *TP73* transcriptional activity.[12] Leong and colleagues[12] reported a p63-dependent tumor survival pathway that mediates cisplatin sensitivity, specifically in TNBC cells grown in vitro. Early after the discovery of p73, it was reported that cisplatin was a potent inducer of p73 phosphorylation (tyrosine 99) and transcriptional activity of the protein.[13] In contrast, more-recent studies have shown that cisplatin is a potent inhibitor of p63 expression.[14,15] Thus, cisplatin can regulate p73 activity both directly (through posttranslational modification) and indirectly (through reduction of its binding partner, p63). Extending these observations to the clinical setting, Rocca and associates[16] conducted a retrospective analysis of core biopsies of breast cancer patients treated with neoadjuvant cisplatin-based chemotherapy, and showed that administration of cisplatin without anthracyclines yielded a higher rate of pathologic complete response (pCR) in patients with p63-positive tumors. However, a prospective, single-arm, multicenter phase 2 study evaluating platinum monotherapy with cisplatin or carboplatin in patients receiving first- or second-line treatment of metastatic breast cancer[17] did not show any correlation of *TP53* mutations or p63/p73 status with durable responses or longer progression-free survival (PFS) or OS.

Breast cancer type 1 susceptibility protein (BRCA1) plays a key role in DNA double-strand break repair by mediating homologous recombination and thus maintaining DNA stability.[18] BRCA-deficient tumors rely more heavily on PARP to mediate DNA repair. Platinum salts, including carboplatin and cisplatin, lead to DNA cross-link strand breaks. This may be especially important in cells that are deficient in homologous recombination repair mechanisms, such as *BRCA*-mutated cells[19] and, potentially, basal-like TNBC. The intrinsic genomic instability of certain TNBC cells as a result of deficient DNA repair[20] is responsible for their sensitivity to chemotherapies that induce intra-strand and inter-strand DNA cross-links, stalled replication forks, and DNA double-strand breaks, such as platinum agents.

Using gene expression analyses, Lehmann and associates recently identified distinct TNBC subtypes, each displaying a unique biology.[21] The 6 TNBC subtypes consist of 2 basal-like subtypes (BL1 and BL2), 1 immunomodulatory subtype, 1 mesenchymal subtype, 1 mesenchymal stem–like subtype, and 1 luminal androgen receptor subtype. The luminal androgen receptor subtype is characterized by androgen receptor signaling.[21] Predicted "driver" signaling pathways were pharmacologically targeted in these cell lines; *BRCA1*-mutant and non–*BRCA1*-mutant basal-like cell lines had relatively higher sensitivity to cisplatin treatment compared with all other TNBC subtypes.

Taken together, the above data suggest that the use of platinum agents as a targeted agent, alone or in combination, may benefit patients with the basal-like subtype of TNBC.

Clinical Trials With Platinum Agents in TNBC

The Metastatic Setting

In the metastatic setting, the clinical activity of platinum agents has been modest overall. A retrospective analysis of 143 patients with HER2-negative metastatic breast cancer (of whom 63% had TNBC) who had been treated with platinum-based chemotherapy did not show any difference in median PFS or OS between the TNBC and non-TNBC groups, and only a minor trend toward a higher overall response rate (ORR) in the TNBC group.[22]

A single-arm, multicenter phase 2 study evaluating platinum monotherapy (cisplatin or carboplatin) in 86 patients receiving first- or second-line treatment of metastatic breast cancer[17] reported a 32% and 19% ORR for cisplatin and carboplatin, respectively. Patients who were carriers of *BRCA1/2* (n=11) had a significantly higher ORR (54.5%) than those who were not carriers. The presence of *BRCA1/2* germline mutations, basal-like subtype, *TP53* mutations, *PIK3CA* mutations, or p63/p73 status, and the type of chemotherapy given, had no

correlation with durable responses or longer PFS or OS, however. Interestingly, higher homologous recombination deficiency scores were associated with platinum sensitivity.

In light of the prevalent expression of epidermal growth factor receptor (EGFR) in basal-like TNBC, 2 studies evaluated the combination of a platinum agent with cetuximab, a monoclonal antibody against EGFR. In the phase 2 BALI (Basal-Like) study,[23] patients with TNBC were randomly assigned to cisplatin with or without cetuximab. Both the ORR and PFS were slightly greater in the combination arm (ORR, 20%; PFS, 3.7 months) vs the single-agent cisplatin arm (ORR, 10%; PFS, 1.5 months), but were overall quite low in both arms. No significant difference was seen in OS. TBCRC 001 (Translational Breast Cancer Research Consortium study 001)[24] was a phase 2 study with a slightly different design. This study randomly assigned patients with metastatic TNBC to receive cetuximab alone or cetuximab with carboplatin. About 75% of patients had the basal-like subtype by PAM50 analysis. The response rates were 6% in the cetuximab-alone arm and 17% in the combination arm, both of which were quite low. The time to progression and OS were also lower than predicted (2.1 and 10.4 months, respectively) in the combination arm.

TNT (the Triple Negative Breast Cancer Trial) is an ongoing phase 3 study that is randomly assigning patients with metastatic TNBC to first-line treatment with carboplatin or docetaxel in order to determine the ORR, PFS, and OS in each group. The study investigators are aiming to recruit between 370 and 450 patients (NCT00532727).

Preclinical studies of the use of a DNA-damaging agent (such as a PARP inhibitor) with phosphatidylinositol-4,5-bisphosphonate 3-kinase (PI3K) inhibitors have provided a rationale for using PI3K inhibitors in androgen-receptor–negative TNBC. These studies have demonstrated that in addition to regulating cell growth, metabolism, and survival, PI3K also stabilizes double-strand breaks by interacting with the homologous recombination complex and, in effect, creating a BRCA-deficient state.[25] A phase 2 randomized clinical trial in which patients with androgen receptor–negative metastatic TNBC are randomly assigned to receive chemotherapy with cisplatin with or without a PI3K inhibitor (NCT01918306) is ongoing.

Of note, the study of biomarkers of drug exposure and sensitivity in metastatic tumors, although feasible, is not easy owing to the inherent difficulty of obtaining sequential tumor samples only for research purposes. Testing novel agents for TNBC in the neoadjuvant or post-neoadjuvant setting is so attractive precisely because the tissue collected at the time of definitive surgery would be enriched with a tumor clone that could be studied for mechanisms of therapeutic resistance.

The Neoadjuvant Setting

It is generally established that patients with breast cancer who achieve a pCR—the lack of residual disease in both the breast and the axilla—after neoadjuvant therapy exhibit a good long-term outcome.[26] A high residual disease burden in the posttreatment, surgically excised cancer has been shown to correlate with a high rate of recurrence and death.[27,28] More specifically, at least 40% of patients with TNBC who do not achieve a pCR after anthracycline- and taxane-based neoadjuvant chemotherapy will have a recurrence within 36 months.[29] However, approximately 30% of TNBC patients treated with anthracycline- and taxane-based chemotherapy will achieve a pCR.[29] Consistent with the above data, achieving a pCR to neoadjuvant chemotherapy in this group of patients has been shown to be a strong positive prognostic factor. Nevertheless, it is important to note that achievement of a pCR is still a pathologic endpoint, not a clinical one. A correlation between an increase in pCR rate and event-free survival has not yet been shown.[30] Therefore, it is uncertain whether any of the advances in improvement of pCR rate will ultimately translate into disease-free survival (DFS) or OS benefits.

Several clinical studies have examined the role of platinum agents in the neoadjuvant treatment of TNBC. Byrski and colleagues reported that 9 of 10 patients with stage I to III breast cancer harboring *BRCA1* mutations achieved a pCR after neoadjuvant therapy with cisplatin.[9] In another small study, Silver and associates reported the results of a single-arm trial of 28 women with stage II or III TNBC treated with neoadjuvant cisplatin 75 mg/m^2 every 21 days for 4 cycles followed by surgery. There was a 22% pCR rate (including 2 patients with *BRCA1* germline mutations), a 50% partial response rate, and a 14% complete response rate.[31] Ryan and colleagues reported a pCR of 15% in a trial of 51 patients with TNBC treated with neoadjuvant cisplatin and bevacizumab.[32]

Two large randomized trials have added further evidence of the effect of platinum-based agents in TNBC. The GeparSixto trial was a randomized phase 2 trial including patients with TNBC and those with HER2-positive, stage II or III, previously untreated disease.[33] A total of 315 patients with TNBC were randomly assigned to receive paclitaxel, liposomal doxorubicin, and bevacizumab, with or without carboplatin. The addition of carboplatin resulted in a higher pCR rate of 53.2%, vs 36.9% without carboplatin. Toxicities were greater in the patients receiving carboplatin than in those not receiving carboplatin, including grade 3 or 4 neutropenia (65% vs 27%), grade 3 or 4 anemia (15% vs <1%), grade 3 or 4 thrombocytopenia (14% vs <1%), and diarrhea (17% vs 11%), resulting in a treatment discontinuation rate of 49% among the patients who received carboplatin.[33] CALGB 40603 was a randomized phase 2 trial with a 2 × 2 factorial design

that explored the addition of carboplatin, with or without bevacizumab, to neoadjuvant weekly paclitaxel followed by dose-dense doxorubicin and cyclophosphamide in 443 patients with stage II or III TNBC (NCT00861705).[34] The pCR rate was higher with the use of carboplatin, 54% vs 41% to 54%; bevacizumab added no benefit. Similarly as in GeparSixto, a large proportion of patients did not complete treatment owing to adverse events.

The Post-Neoadjuvant Setting

Patients with TNBC who have a high residual disease burden after completing neoadjuvant therapy, indicating a drug-resistant tumor, have a very high risk of early recurrence. The appropriate treatment for those patients is unknown, and personalized treatment strategies using adjuvant therapies that molecularly target tumor-specific dependencies are sorely needed. The intertumor heterogeneity of TNBCs before and after neoadjuvant chemotherapy underscores the need for powerful and broad molecular approaches to identify actionable molecular alterations and, in turn, better inform personalized therapy of this aggressive disease. Incorporation of these approaches into clinical studies—and eventually, standards of care—will aid in the prioritization of patients with residual disease after neoadjuvant chemotherapy into rational adjuvant studies. The post-neoadjuvant treatment population could be a valuable source for clinical trials initiated to align patients with treatments best suited to target their cancer subtypes.

Dwadasi and colleagues recently reported a randomized phase 2 trial of cisplatin with or without rucaparib, a PARP inhibitor, for patients with TNBC or *BRCA* mutations who had residual tumor burden in the breast (>2 cm) or axilla after being treated with an anthracycline or taxane neoadjuvant chemotherapy.[35] Overall, 73% of the 128 patients enrolled were able to complete treatment. With a median follow-up of 9 months, 1-year DFS was similar (approximately 76%) in both treatment groups, and rucaparib did not add substantial toxicity to the cisplatin treatment. The 1-year DFS in the 22 patients with *BRCA1* or *BRCA2* mutations was approximately 85%, compared with 79% in patients without mutations.

Discussion

The addition of platinum agents (cisplatin or carboplatin) to neoadjuvant treatment of TNBC is clearly associated with significantly higher rates of pCR, suggesting that TNBC could be a potential therapeutic target for these drugs. However, the utility of platinum agents in addition to standard adjuvant or neoadjuvant chemotherapy remains controversial.

Although the GeparSixto and CALGB 40603 phase 2 trials cited above have clearly shown the merit of adding a platinum agent to the systemic treatment of patients with TNBC in the neoadjuvant setting, these trials were underpowered to address DFS and OS advantage. The pooled analysis performed by Cortazar and colleagues[30] could not validate pCR as a surrogate endpoint for improved event-free survival and OS in patients with TNBC. For a given patient, achievement of pCR indeed predicts clinical benefit. However, it is still unknown which magnitude of increase in pCR rate from an intervention will ultimately translate into a DFS or OS benefit for an overall population. Several variables that are independent of pCR rates may influence long-term outcome, such as the possibility of patients being exposed to effective, additional treatment after neoadjuvant chemotherapy; disease biology (akin to ER-positive cancers, not all TNBCs are clinically aggressive and patients may exhibit a good long-term outcome regardless of pCR; conversely, there are TNBCs that, despite achievement of a pCR, will ultimately exhibit a recurrence, because the micrometastatic disease outside the breast area can be drug resistant); and initial disease burden (patients with a larger initial disease burden are less likely to achieve a pCR, but may have an excellent response to treatment in the micrometastatic disease outside the breast area, which will translate into a good outcome regardless of pCR).

Despite the added toxicity, it may be reasonable to consider the addition of a platinum agent in the neoadjuvant setting for patients with high-risk *BRCA*-mutated TNBC, and for patients with TNBC in whom an increase in clinical response to systemic treatment could improve locoregional control (ie, patients with triple-negative inflammatory breast cancer, or inoperable TNBC at the time of diagnosis). However, the extreme TNBC genomic heterogeneity responsible for different pCR rates seen after neoadjuvant chemotherapy, as shown in the retrospective report by Masuda and colleagues,[36] underscores the need for more prospective validation of which subset of TNBC indeed benefits from platinum agents in the early treatment setting.

Our current evidence shows that (1) patients with basal-like TNBC are at the highest risk for recurrence, with a trend toward worse DFS and OS, particularly if they have residual disease after neoadjuvant chemotherapy,[37] and (2) in preclinical models, basal-like TNBC is the most sensitive to cisplatin.[21] To prospectively address these points, a large adjuvant National Cancer Institute–sponsored phase 3 clinical trial is being planned for patients with clinical stage II and III TNBC with residual disease in their surgical specimen after neoadjuvant standard chemotherapy. This trial will compare DFS in patients with basal-like TNBC who are randomly assigned to post-neoadjuvant platinum-based chemotherapy vs DFS in those who are randomly assigned to observation. This study will not only

be adequately powered to detect a DFS or OS advantage with the addition of platinum agents to early treatment of high-risk TNBC, but will also lay the groundwork (ie, the proof of concept) for additional, similarly designed studies as new data and new targeted agents become available.

The reason to treat patients in the adjuvant and neoadjuvant setting is prevention of distant recurrence and death from breast cancer. To this day, OS and DFS data are not yet available to evaluate whether the addition of platinum agents to neoadjuvant chemotherapy improves TNBC outcomes. In summary, larger trials with longer follow-up and better characterization of which patients indeed benefit from the addition of platinum agents to adjuvant and neoadjuvant chemotherapy are necessary.

Disclosures

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