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Editorial

An Evolving Paradigm: Addition of Platinum to Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer

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Triple-Negative Breast Cancer (TNBC) and Neoadjuvant Chemotherapy

Breast cancer is the 2nd leading cause of cancer death in women in the United States. In 2014, more than 232,000 women are projected to be diagnosed with breast cancer, and over 90% of these patients will present with loco-regional disease [1]. Approximately 15% of all breast cancers are triple-negative breast cancer (TNBC) [2]. TNBC is defined by lack of expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Compared with other subtypes of breast cancers, the prognosis of TNBC is worse, characterized by early recurrence and shorter survival, and thus it remains a therapeutic challenge to medical oncologists [2,3].

Traditionally, most patients with loco-regional disease undergo a definitive surgical procedure that also allows for accurate staging followed by systemic therapy and radiation if indicated. Due to lack of specific therapeutic targets (ER, HER2), endocrine therapy and anti-HER2 therapy are not indicated for this population of patients, thus the only beneficial systemic therapy is chemotherapy. Adjuvant chemotherapy is critical to eradicate occult micro metastasis after surgery. After three decades of rigorous clinical studies, anthracycline-taxane combinations are regarded as the most active chemotherapy regimens for TNBC [4]. Other than increasing breast conservation rate, neoadjuvant chemotherapy has also been demonstrated to provide identical disease-free survival (DFS) and overall survival (OS) benefits as adjuvant chemotherapy administered with the same regimens [5,6].

Of note, complete response to neoadjuvant chemotherapy portends a good prognosis. Several recent studies lend support that pathological complete remission (pCR) is associated with improved DFS and OS, and could be used as a surrogate marker for DFS and OS in breast cancer patients [7]. Irrespective of the different definitions of pCR in different clinical trials, the absence of invasive disease in both breast and axilla provides the best overall outcome (This definition will be used for our discussion here). Evaluation of tumor responses to neoadjuvant regimens could thus offer an efficient testing strategy to various regimens or interventions.

While those who achieved pCR have an excellent long-term outcome, the majority of patients with TNBC who do not achieve pCR suffer a dramatically worse outcome compared to those with ER-positive disease. The recurrence rate for those who did not achieve pCR is as high as 40-50% at 5 years for TNBC, explaining the paradox of worse clinical outcome despite the higher likelihood of pCR [8]. Adding capecitabine and gemcitabine to anthracycline-taxane based neoadjuvant chemotherapy does not improve pathological response rate, but rather increases the toxicity [9]. As such, there remains an unmet medical need for more effective chemotherapy for TNBC.

Mounting Evidence of Platinum against TNB in Neoadjuvant Setting

Platinum directly binds to DNA, resulting in formation of DNA-platinum adducts and consequently intra- and interstrand DNA cross links which impede cell division. The platinum compounds have been used to treat breast cancer for over 4 decades, dating back to 1970s. Both cisplatin and carboplatin were assessed in multiple phase II studies against metastatic breast cancer in patients with or without prior chemotherapy exposure. The results are quite consistent for both agents: while they are very active in the first-line setting with overall response rate (ORR) approximately 50%, the efficacy is modest against chemo-refractory metastatic breast cancer with ORR around 10% [10-13]. Platinum compounds have never been considered as the first-line agents perhaps due to their toxicity profile and complexity of administration as well as due to the popularity of anthracycline-based regimens.

In recent years, there has been renewed interest in platinum-based neoadjuvant chemotherapy in triple-negative breast cancer. In a small neoadjuvant study involving 12 BRCA1 mutation carriers, four cycles of chemotherapy with single-agent cisplatin at 75 mg/m^2 every 21 days yielded a pCR rate of 80% [14]. While the same regimen was studied as neoadjuvant chemotherapy in 28 patients with triple-negative breast cancer (including 2 BRCA 1 mutation carriers), a PCR rate of 22% was reported [15]. These two small phase II clinical trials seem to suggest that triple-negative, particularly BRCA 1-mutant tumors, are more susceptible to DNA-damaging agents such as cisplatin.

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The GeparSixto trial, presented at the 2013 American Society of Clinical Oncology (ASCO) annual meeting, is the first large, randomized phase II study involving 315 patients with triple-negative breast cancer, evaluating the impact on pCR rate of the neoadjuvant chemotherapy with weekly paclitaxel (80 mg/m^2) plus weekly non-pegylated-liposomal doxorubicin (20 mg/m^2/week) with or without concurrent weekly carboplatin (AUC 1.5) for 18 weeks (all the patients received bevacizumab) [16]. Addition of carboplatin increased pCR by roughly 20% (58.7% vs 37.9%). Unfortunately, this impressive result was achieved at the price of severe toxicity. As a result, only 50% in carboplatin arm could finish the entire course with 6% neutropenic fever despite growth factor support. In fact, the backbone chemotherapy (weekly paclitaxel, non-pegylated-liposomal doxorubicin and bevacizumab) was unacceptably toxic by itself (only 61% could complete the entire course) and is unlikely to be widely adopted in the United States. However, this randomized, prospective study proved the important concept – addition of carboplatin to neoadjuvant chemotherapy seems to benefit a subset of the triple-negative breast cancer patients.

The Cancer and Leukemia Group B (CALGB)/Alliance 40603 study took a similar approach to assess the potential benefit of adding carboplatin to neoadjuvant chemotherapy in triple-negative breast cancer patients. 443 patients were randomized in this phase II study, and the results were presented at the 2013 San Antonio Breast Cancer Symposium (SABCS). The control arm received standard chemotherapy with weekly paclitaxel (80 mg/m^2) for 12 weeks followed by dose-dense AC (doxorubicin 600 mg/m^2, and cyclophosphamide 600 mg/m^2 every 14 days) for 4 cycles. The study arm also received carboplatin (AUC 6) concurrently with paclitaxel every three 3 weeks for 4 cycles. Addition of carboplatin improved pCR rate from 41% to 54% [17]. Compared with control group, patients who received carboplatin also experienced significantly more toxicities including grade 3 neuropathy (2% vs 7%), Grade 3 neutropenia (22% vs 56%), thrombocytopenia (4% vs 20%), and febrile neutropenia (7% vs 12%). Consequently, 6% of the study patients (vs 0%) discontinued chemotherapy, 62% (vs 88%) completed over 9 doses of paclitaxel, 12% (vs 7%) received less than 6 doses of paclitaxel, and 9% (vs 4%) only received 1 or 2 doses of AC [17]. Indeed, CALGB 40603 study, as a second randomized, prospective phase II trial, confirmed the principal finding of the German study. Of note then, given that weekly paclitaxel and dose-dense AC is a commonly used regimen in the United States, it is reasonable to see this as a potential chemotherapy backbone onto which carboplatin may be added.

Incorporating Platinum in a Response-guided Approach

Although mature survival data from the GeparSixto and CALGB/Alliance trials is unavailable, platinum compounds do show activity against TNBC in the neoadjuvant setting. In view of the overall poor prognosis of TNBC with standard anthracycline-based therapy, it is appropriate to consider the use of carboplatin in the neoadjuvant setting especially given that the achievement of pCR predicts better survival. Nevertheless, many questions remain. Is AC +/- taxane the optimal regimen onto which to add carboplatin? Does BRCA 1 mutation status (not known in either trial above) have an effect? Given the additional toxicity noted above, what is the optimal dose for carboplatin? Would measuring DNA repair enzymes such as ERCC1 be useful in determining which TNBC patients might harbor disease resistant to Carboplatin?

Given the current state of knowledge, TNBC is defined by the absence of ER/PR and HER2. However, there is still significant biological heterogeneity within TNBC. If the ultimate goal in the future lies in potential targeted therapy directed against each molecularly distinct subtype of TNBC, the "one size fits all" approach by adding carboplatin to current standard neoadjuvant chemotherapy for all patients with TNBC may result in needlessly over treating some individuals. As a matter of fact, up to 40% of patients with TNBC are expected to achieve pCR with the current standard chemotherapy, which means they do not require or will not benefit from addition of carboplatin.

Currently, specific targeted therapy for each patient with TNBC is not available. The question then is to identify the high-risk patients and platinum-responders without over treating this heterogeneous group. The substantial toxicity in CALGB 40603 came from the concurrent use of carboplatin and weekly paclitaxel. A sequential approach using Carboplatin has not been explored. The Intergroup C9741/CALGB 9741 study (dose-dense AC followed by dose-dense paclitaxel) convincingly demonstrated that the sequential approach, A X 4, then T X 4, and then C X 4 had equivalent efficacy to concurrent AC X 4 followed by T X 4, with less toxicity, although the duration of therapy was longer [18]. Large clinical trials have also demonstrated that sequential AC for four cycles and docetaxel for 4 cycles is superior to 4 cycles of TAC concurrently and equivalent to 6 cycles of TAC concurrently, but with much less toxicity [19,20].

Given these considerations, before there is an established targeted therapy for every subtype of TNBC, it seems reasonable to consider designing clinical trials using a response-guided approach. That is, patients would receive a current standard chemotherapy – such as dose-dense AC followed by dose-dense paclitaxel or weekly paclitaxel. Imaging studies (as well as biopsy if needed) can be used to assess the clinical response. For patients who have residual disease, single agent carboplatin would then be given as neoadjuvant chemotherapy. For patients who have achieved clinical CR, surgery would proceed without adding sequential carboplatin.

Great advances have been made in personalizing therapy for breast cancer over the past decade. Hopefully, BRCA status and biomarker analysis from these and future neoadjuvant trials will identify subgroups of patients with TNBC who will gain the greatest benefit from the addition of platinum or other agents to the current standard regimens.

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