BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Which Patients With Early-Stage Triple-Negative Breast Cancer Should Receive a Platinum?

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H&O What forms of cancer are typically treated with platinum agents?

WS Platinum analogues are used to treat a wide range of solid tumors, including ovarian cancer, head and neck cancers, lung cancers, gastrointestinal cancers, and bladder cancer. The most commonly used platinum analogues are carboplatin and cisplatin, although oxaliplatin is the agent of choice in patients with colorectal and other gastrointestinal cancers.

H&O How do platinum agents work?

WS Platinum analogues are atypical alkylating agents. Although they do not have the structure of classic alkylating agents, they act by binding to DNA, thereby interfering with both replication and transcription. The excision of sites where the platinum analogue is bound results in single-strand and sometimes double-strand breaks that the cell must repair before the DNA can be replicated. The cell's most accurate option to repair these breaks involves homologous recombination (HR), which requires intact BRCA proteins; we believe that this explains the enhanced cytotoxic sensitivity of cancers to platinum analogues and other DNA-damaging agents in individuals who carry a *BRCA* mutation. When the cell cannot repair damage—especially double-strand DNA breaks—by HR, it is forced to use other, less reliable DNA repair pathways, which can lead to replication errors that may be lethal. Cancers arising in individuals who do not carry a *BRCA* mutation sometimes exhibit downregulation of BRCA or other genetic modifications that impair HR, leading to a condition referred to as HR deficiency.

Most ovarian cancers are, at least initially, very sensitive to the platinum analogues; the development of platinum resistance is a poor prognostic sign in these patients. The gene expression pattern for most triple-negative breast cancers (TNBCs)—the subtype referred to as *basal-like*, which accounts for 70% to 90% of TNBCs—is very similar to what we find in ovarian cancer. This is consistent with the observed clinical activity of platinum agents in TNBC.

H&O In what respects do the platinum agents differ?

WS The major differences in the platinum analogues show up in their toxicities. Cisplatin is much more likely to cause severe nausea and vomiting, neurologic toxicity, ototoxicity, and nephrotoxicity, whereas carboplatin is much more likely to cause hematologic toxicity. The toxicities associated with oxaliplatin fall between these two. Although a few small phase 2 studies have looked at the activity of oxaliplatin in advanced-stage breast cancer, most studies in TNBC, especially those conducted in patients with stage II or III disease, have looked at cisplatin or carboplatin. Moreover, the vast majority of the studies looking at platinum analogues in the neoadjuvant or adjuvant setting for breast cancer, especially TNBC, have used carboplatin because its side effects tend to be more manageable than those of cisplatin.

Several studies have looked at cisplatin, however. A seminal study by Silver and colleagues from the Dana-Farber Cancer Institute demonstrated that in a small percentage of patients with TNBC, a pathologic complete response (pCR) can be achieved with neoadjuvant single-agent cisplatin. A larger study, by Byrski and colleagues in Poland, enrolled only patients with a *BRCA1* mutation and demonstrated a 61% pCR rate with just 4 cycles of single-agent cisplatin. Finally, an ongoing study, INFORM (Cisplatin vs. Doxorubicin/Cyclophosphamide in BRCA; NCT01670500), is comparing neoadjuvant therapy with single-agent cisplatin vs the combination of doxorubicin and cyclophosphamide (AC) in patients with a *BRCA* mutation.

H&O In which patients with early-stage breast cancer are platinum agents considered standard?

WS The only setting in which the use of a platinum agent in early-stage breast cancer has been accepted as the standard of care is human epidermal growth factor 2 (HER2)–positive breast cancer. Preclinical data demonstrated synergy when a platinum agent was added to a taxane and trastuzumab (Herceptin, Genentech). This finding led to a study conducted by the Breast Cancer International Research Group, BCIRG-006 (Combination Chemotherapy With or Without Trastuzumab in Treating Women With Breast Cancer). This study, of more than 3000 women with HER2-positive, largely node-positive, early-stage breast cancer, was published in the *New England Journal of Medicine* in 2011. Women were randomly assigned to 1 of 3 adjuvant regimens: doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 1 year of trastuzumab (AC-TH), or docetaxel and carboplatin plus 1 year of trastuzumab (TCH). Both regimens that contained trastuzumab produced rates of disease-free survival and overall survival significantly better than those achieved with the non–trastuzumab-containing regimen. Although the study was not powered to compare the 2 trastuzumab-containing arms, long-term follow-up (presented by Dr Dennis Slamon at the 2015 San Antonio Breast Cancer Symposium [SABCS]) demonstrated equivalent results in terms of cancer outcomes. The study clearly showed the anthracycline-containing regimen (AC-TH) to be associated with greater short-term and long-term toxicity, including higher rates of cardiac dysfunction and treatment-related leukemias. As a result, many medical oncologists in the United States and other countries in the developed world use combinations such as docetaxel and carboplatin plus trastuzumab—and now pertuzumab (Perjeta, Genentech)—as neoadjuvant or adjuvant therapy in patients with early-stage HER2-positive breast cancer.

H&O What are some of the studies that have looked at the addition of carboplatin to standard neoadjuvant chemotherapy in TNBC?

WS With the presentation of the BrighTNess study (A Study Evaluating Safety and Efficacy of the Addition of ABT-888 Plus Carboplatin Versus the Addition of Carboplatin to Standard Chemotherapy Versus Standard Chemotherapy in Subjects With Early Stage Triple Negative Breast Cancer) at this year's American Society of Clinical Oncology (ASCO) annual meeting, we now have results from 3 large, randomized trials that address the effect of adding carboplatin to a control neoadjuvant chemotherapy regimen on pCR rates in patients with localized TNBC. The first is CALGB 40603 (Paclitaxel With or Without Carboplatin and/or Bevacizumab Followed by Doxorubicin and Cyclophosphamide in Treating Patients With Breast Cancer That Can Be Removed by Surgery), which I presented at the 2013 SABCS and was subsequently published in the *Journal of Clinical Oncology*. In this study, patients with stage II or III TNBC all received a standard neoadjuvant regimen of weekly paclitaxel for 12 weeks followed by 4 cycles of dose-dense doxorubicin and cyclophosphamide. Patients were randomly assigned to receive carboplatin, at an area-under-the-curve (AUC) dose of 6 every 3 weeks for 4 cycles, concurrently with the paclitaxel or not, and were separately randomized to receive bevacizumab concurrently with paclitaxel (with or without carboplatin) and AC.

We found that the addition of carboplatin to the standard regimen increased the pCR rate in the breast and axillary lymph nodes from 41% to 54%, a highly statistically significant result (P=.0029). At the 2015 SABCS, I presented outcomes with a median follow-up of slightly longer than 3 years. As expected, the patients who achieved a pCR or had minimal residual disease at surgery had event-free survival (hazard ratio, 0.29) and overall survival (hazard ratio, 0.21) rates far superior to those of patients who had more extensive residual disease. The study was not powered to detect differences in long-term outcomes between patients who had received carboplatin and those who did not, but there was a nonsignificant trend favoring better event-free survival with carboplatin.

By testing tumor samples and correlating the results with patient responses, we found that the presence of tumor-infiltrating lymphocytes and markers associated with more aggressive tumor biology was predictive of higher pCR rates overall, but not specifically for the addition of carboplatin.

The second study is the GeparSixto trial (Addition of Carboplatin to Neoadjuvant Therapy for Triple-Negative and HER2-Positive Early Breast Cancer) from the German Breast Group, which Dr Gunter von

Minckwitz presented at the 2013 SABCS. This study used a novel control chemotherapy regimen of weekly paclitaxel and nonpegylated liposomal doxorubicin, plus bevacizumab (Avastin, Genentech) every 3 weeks, for 18 weeks in patients with early-stage TNBC. Patients were then randomly assigned to receive weekly carboplatin at an AUC dose of 2 (subsequently reduced to 1.5 owing to frequent hematologic toxicities at the original dose) or no carboplatin. In this study, as in CALGB 40603, the addition of carboplatin increased the pCR rate in the breast and lymph nodes from 43% to 57%, a difference that was statistically significant (P=.005). As Dr von Minckwitz explained at the 2015 SABCS, this study also showed that the addition of carboplatin significantly improved disease-free survival at 3 years from 76.1% to 85.8% (hazard ratio, 0.56; P=.035).

Regarding the effect of the presence of a *BRCA* mutation, the GeparSixto trial found that patients who had a germline *BRCA* mutation had a higher pCR rate with their control chemotherapy regimen (50% for mutated *BRCA* vs 33% for wild-type *BRCA*). Despite the higher pCR rate with the control regimen in *BRCA*-mutated patients, the addition of carboplatin raised it further (to 62%, although the increase was not statistically significant in this relatively small cohort). As in CALGB 40603, achievement of a pCR was associated with marked improvement in disease-free survival in both *BRCA*-mutated and *BRCA*–wild type patients.

The GeparSixto investigators also assessed the effect of HR deficiency on pCR rates. They found that 70% of their patients overall, and 58% of their patients with wild-type *BRCA*, met their criteria for HR deficiency. Although the HR-deficient patients had a higher overall pCR rate (49% vs 30%), both the HR-deficient and the non–HR-deficient patients exhibited an increase in pCR rates after the addition of carboplatin, although there was no statistically significant interaction between HR status and carboplatin benefit.

The third study, called BrighTNess, was just presented by Dr Charles Geyer at the 2017 ASCO annual meeting. Based on promising results from I-SPY 2 (Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer), this trial was designed to determine whether the addition of carboplatin and the poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor veliparib would increase the pCR rate compared with the standard chemotherapy sequence of weekly paclitaxel followed by doxorubicin and cyclophosphamide. To determine how much veliparib contributed to any observed increase in the pCR, the study included a third arm, in which patients received standard chemotherapy plus carboplatin with a matching placebo in place of veliparib.

The overall results were impressively positive, with the addition of carboplatin and veliparib increasing the pCR rate from 31% in the control arm to 53%, a difference that was highly statistically significant (P<.001). However, the pCR rate in patients who received carboplatin without veliparib was even higher (58%), suggesting that veliparib—at the dose and schedule administered in this study—does not enhance the efficacy of carboplatin at increasing the pCR rate in TNBC. The magnitude of the difference in pCR rates between the control and carboplatin arms in BrighTNess (27%), nearly double that reported from CALGB 40603 and GeparSixto, suggests that those studies may have underestimated the benefit of this agent in TNBC. Although few recurrences or deaths have been reported thus far, early data suggest the possibility of improved event-free survival in patients assigned to the 2 carboplatin-containing arms.

In the BrighTNess trial, the pCR rate was higher in the patients with a *BRCA* mutation (about 15% of the study population) than in those with wild-type *BRCA*, but even their pCR rate increased with the addition of carboplatin.

H&O What is your approach to carboplatin use based on these studies?

WS Patients with stage I and even early stage IIA (T<3 cm N0) TNBC tend to have a very good prognosis with standard chemotherapy with a taxane and an anthracycline, a finding suggesting that they are unlikely to gain significant benefit from the addition of other agents, including carboplatin. However, the results of these studies suggest that in patients who have larger tumors or axillary node involvement (those with larger stage IIA, stage IIB, or stage III disease)—the patients for whom we are most likely to recommend neoadjuvant chemotherapy, to make them better candidates for breast conservation or to limit the extent of their axillary nodal sampling—a pCR or minimal residual disease is more likely to be achieved with the addition of carboplatin to the standard chemotherapy regimen. As a result, I typically add carboplatin to the neoadjuvant regimen in patients with larger stage IIA, IIB, or III disease.

H&O What is the best dosing schedule for carboplatin?

WS We do not yet know whether the every-3-week regimen or a weekly regimen is best. It would be helpful to have a study addressing that specific question in terms of efficacy and toxicity.

In both CALGB 40603 and BrighTNess, carboplatin was administered at an AUC dose of 6 every 3 weeks for

4 cycles. Although that dosing schedule is efficacious at enhancing the local regional response rate, it also increases the risk for neutropenia, including febrile neutropenia (most often during the subsequent AC phase of treatment), the risk for thrombocytopenia, and associated treatment delays. That is why, outside a clinical trial, I prefer to administer carboplatin weekly at an AUC dose of 2 with weekly paclitaxel. We know from the GeparSixto trial that the weekly regimen can be as effective as carboplatin every 3 weeks at enhancing the pCR rate. And I know from personal experience in treating breast cancer and other malignancies that carboplatin is much better tolerated and much less likely to cause cytopenias resulting in treatment delays when it is given weekly at a low dose than when it is given every 3 weeks at a higher dose.

H&O Are there any disadvantages to using a weekly regimen?

WS One concern with weekly carboplatin is the possibility of inducing hypersensitivity reactions after multiple exposures to the drug. However, hypersensitivity reactions to carboplatin are most often seen in patients who are treated with carboplatin, have a treatment-free interval during which the immune system recovers, and are exposed to the drug again, as occurs frequently in patients with ovarian cancer. In my experience, the risk of inducing a hypersensitivity reaction is very low in patients receiving a single 12-week course of treatment consisting of weekly carboplatin plus paclitaxel. In my opinion, this very low risk is outweighed by the benefits of reduced hematologic and other toxicities. All the same, I would be comfortable enrolling patients in a trial that randomly assigned them to a weekly vs an every-3-weeks carboplatin schedule.

H&O Can carboplatin be used in place of an anthracycline, or only in addition to an anthracycline?

WS A number of smaller studies have looked at carboplatin/taxane regimens without an anthracycline in early stage TNBC. For example, studies of carboplatin/paclitaxel and carboplatin/docetaxel—including one that Dr Priyanka Sharma presented at the 2014 ASCO annual meeting—have demonstrated pCR rates in the 50% to 65% range, and patients in these studies were spared the short- and long-term toxicities of an anthracycline.

In certain cases, such as a patient with TNBC who is not a candidate for an anthracycline owing to cardiac dysfunction, I will use the carboplatin/paclitaxel combination and not administer an anthracycline. That approach often produces excellent responses, and those who respond can have very good long-term outcomes.

I think that an interesting approach might be to start by administering carboplatin/paclitaxel, then assess the response after approximately 12 weeks. If the regimen is producing a very good response, the physician may wish to continue it for a total of up to 18 weeks, assuming that a limiting toxicity does not develop, then refer the patient for surgery. In contrast, a patient whose disease has a suboptimal response to carboplatin/paclitaxel—preferably with biopsy confirmation of residual viable cancer to make sure the physician is not fooled by a fibrotic reaction to chemotherapy-induced tumor necrosis—might benefit from a switch to an anthracycline-based regimen. This also might allow us to determine if we can identify a subset of patients who do just as well without being exposed to the toxicities associated with an anthracycline. This is important because in 2017, essentially all patients with TNBC are exposed to both a taxane and an anthracycline in the neoadjuvant or adjuvant setting.

H&O Would you consider adding a platinum to neoadjuvant chemotherapy based on response?

WS If you administer 4 cycles of AC to a patient with stage II or III TNBC and the clinical response is excellent, it is hard to argue that carboplatin will add a great deal of benefit. For that patient, the best approach might be to administer weekly or dose-dense paclitaxel and then send the patient to surgery.

On the other hand, it is plausible that a patient who has a suboptimal response after 4 cycles of AC might benefit from the addition of a platinum when she is switched to the taxane. We do not have any data on that approach, however.

The ongoing EA1131 study (Platinum Based Chemotherapy or Capecitabine in Treating Patients With Residual Triple-Negative Basal-Like Breast Cancer Following Neoadjuvant Chemotherapy; NCT02445391) from the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN) is enrolling patients who have received an anthracycline and a taxane but not a platinum in the neoadjuvant setting, and who have residual disease at the time of surgery. Originally, patients were to be randomly assigned to no further treatment vs carboplatin or cisplatin every 3 weeks for 4 cycles. However, based on the CREATE-X (A Phase III Trial of Adjuvant Capecitabine in Breast Cancer Patients With HER2-Negative Pathologic Residual Invasive Disease After Neoadjuvant Chemotherapy) data that Dr Masakazu Toi presented at the SABCS in 2015, the control arm is now a 6-month course of capecitabine. Although this trial addresses an important question, the fact that essentially all my patients with stage II or III

TNBC receive carboplatin in the neoadjuvant setting means that they would not be eligible for this study.

Another ongoing study that is addressing the carboplatin question is NRG-BR003 (Doxorubicin Hydrochloride and Cyclophosphamide Followed by Paclitaxel With or Without Carboplatin in Treating Patients With Triple-Negative Breast Cancer; NCT02488967). This is a purely adjuvant trial in which patients receive AC followed by weekly paclitaxel, with or without 4 cycles of carboplatin at an AUC dose of 5.

H&O What other ongoing studies are looking at carboplatin?

WS In addition to the large EA1131 and NRG-BR003 trials, a pilot study (Safety and Efficacy of Pembrolizumab in Combination With Chemotherapy as Neoadjuvant Treatment for Participants with Triple Negative Breast Cancer; NCT02622074) is evaluating the efficacy and safety of adding pembrolizumab (Keytruda, Merck) to nab-paclitaxel (Abraxane, Celgene) either alone or in combination with carboplatin followed by AC as neoadjuvant chemotherapy in TNBC. Also, a randomized phase 2 trial is being conducted at the University of Kansas Medical Center that is looking at a regimen of weekly carboplatin plus paclitaxel and AC vs docetaxel and carboplatin alone in early stage TNBC. This is the first randomized study to assess whether similar pCR rates can be achieved without an anthracycline (Neoadjuvant Study of Two Platinum Regimens in Triple Negative Breast Cancer; NCT02413320).

H&O Would you like to add anything else?

WS I hope that the potential value of adding carboplatin to neoadjuvant chemotherapy in patients with stage II or III TNBC will not be overshadowed by the fact that the studies that have demonstrated significantly higher pCR rates with this agent are nowhere nearly large enough to assess its effect on event-free survival or overall survival. Although it is difficult to demonstrate that even a substantial increase in the pCR rate leads to significant improvements in long-term outcomes at the trial level, we know that the achievement of a pCR or minimal residual disease is associated with much lower rates of disease recurrence and death for our individual patients. Ongoing correlative studies hold the promise of identifying subgroups of patients in whom different treatment approaches can be considered, but for now, response to neoadjuvant therapy has greater prognostic value than the clinical factors we usually rely on for prognosis.

Suggested Readings

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Denkert C, Loibl S, Salat C, et al. Increased tumor-associated lymphocytes predict benefit from addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer in the GeparSixto trial (GBG 66). Presented at: 38th Annual San Antonio Breast Cancer Symposium; December 10-14, 2015; San Antonio, TX. Abstract S1-06.

Geyer CE, O'Shaughnessy J, Untch M, et al. Phase 3 study evaluating efficacy and safety of veliparib (V) plus carboplatin (Cb) or Cb in combination with standard neoadjuvant chemotherapy (NAC) in patients (pts) with early stage triple-negative breast cancer (TNBC) [ASCO abstract 520]. *J Clin Oncol.* 2017;35(15)(suppl).

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Toi M, Lee S-J, Lee ES, et al. A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X, JBCRG-04). Presented at: 38th Annual San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract S1-07.

von Minckwitz G, Loibl S, Schneeweiss A, et al. Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto). Presented at: 38th Annual San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract S2-04.

von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol.* 2014;15(7):747-756.