

## A Brief Review of Treatment Options for Neoadjuvant Chemotherapy in Patients with Triple-negative Breast Cancer

The index patient is a 40-year-old female with a strong family history (breast cancer in mother and ovarian cancer in maternal aunt) who presented with a 3-month history of breast lump. On examination, she had a 4 cm breast lump and fixed axillary nodes. Positron-emission tomography-computed tomography reveals no other site of disease. Core biopsy reveals high-grade invasive ductal cancer with triple-negative phenotype. Germ line testing is positive for the pathogenic BRCA1 mutation. She is well-educated and requests you to offer her the best possible treatment that can maximize her chances of cure and minimize her chances of relapse. At the same time, she would not like to go through unnecessary toxicity unless treatment intensification can improve her disease-free survival (DFS)/overall survival (OS).

After carefully considering her requests, you decide to offer her:

- A. Four cycles of two-weekly (adriamycin + cyclophosphamide) (AC) followed by four cycles of two-weekly paclitaxel
- B. Four cycles of two-weekly AC followed by 12 weeks of weekly paclitaxel
- C. Four cycles of two-weekly AC followed by 12 weeks of weekly nanoparticle albumin-bound -paclitaxel
- D. Four cycles of two-weekly AC followed by four cycles of paclitaxel with carboplatin
- E. Any other.

Triple-negative breast cancer constitutes 15%–20% of all breast cancer cases.<sup>[1]</sup> These tumors are a heterogeneous group, characterized by the lack of human epidermal growth factor receptor-2 (HER2)/neu, estrogen, and progesterone receptors. The absence of these predictive markers makes chemotherapy the primary treatment option for these tumors. Hence, we must choose a chemotherapy regimen that is most likely to benefit our patients in terms of survival.

The current case represents a scenario often faced in clinical practice. A significant proportion of these patients relapse and most of these relapses are within the 1<sup>st</sup> year of treatment. It is because of this problem that multiple treatment options have been studied in this select group. We will gradually dissect these options to conclude the best treatment option for the patient in question.

### Drug Class

A large number of principles and practices of neoadjuvant chemotherapy in breast cancer are based on the evidence generated for the adjuvant treatment. A meta-analysis by the early breast cancer Trialists' Collaborative Group

showed that the addition of four extra cycles of taxanes to the anthracycline-based regimen reduces the risk of recurrence, breast cancer-related mortality, and overall mortality.<sup>[2]</sup> Hence, a sequential therapy of anthracycline and cyclophosphamide followed by taxanes forms the current standard of care neoadjuvant and adjuvant chemotherapy protocol for most patients with breast cancer.

### Chemotherapy Schedule

A dose-dense schedule is preferred over the standard three-weekly schedule. The dose-dense chemotherapy reduces the risk of disease recurrence and improves both OS and DFS.<sup>[3,4]</sup> Therefore, every 2-week anthracycline and cyclophosphamide combination is preferred over every 3-week regimen.

The commonly used dose-dense schedule for the paclitaxel phase is either to give four cycles of paclitaxel at 175 mg/m<sup>2</sup> every 2 weeks or paclitaxel 80 mg/m<sup>2</sup> every week for 12 weeks. These schedules were compared in the SWOG S0221 trial, which failed to show any statistically significant difference between the two arms for survival outcomes. The 2-week paclitaxel arm had greater allergic reactions, musculoskeletal pains, and neuropathy-related side effects.<sup>[5]</sup> Hence, even though in terms of the outcome of the disease there may not be much evidence to guide the choice between these two schedules of administration of dose-dense paclitaxel, lesser musculoskeletal, neuropathic, and allergic side effects give an edge to the weekly regimen over the two-weekly regimens.

These two schedules have not been evaluated specifically in the subgroup of patients carrying BRCA mutation.

### Nanoparticle Albumin-Bound Paclitaxel versus Solvent-Based Paclitaxel

Nanoparticle albumin-bound (Nab)-paclitaxel allows the administration of a higher dose in a short infusion time without the need for steroid-based premedication. The use of weekly Nab-paclitaxel in comparison with solvent-based paclitaxel (paclitaxel) as neoadjuvant therapy in patients with breast cancer has shown an improvement in the pathologic complete response (pCR) rate.<sup>[6]</sup> This increment in pCR is more marked in patients with triple negative breast cancer although, at the cost of higher hematologic (neutropenia and anemia) and nonhematologic (peripheral sensory neuropathy, fatigue, diarrhea, and myalgia) toxicity.<sup>[6]</sup>

Long-term follow-up of patients in the GeparSepto trial showed that the invasive-DFS (iDFS) and event-free survival (EFS) increased in patients with breast cancer who

received nab-paclitaxel in neoadjuvant therapy as compared to s paclitaxel.<sup>[7]</sup> There was no difference in OS between the two groups. It is further noted that the patients who did not achieve pCR drove the benefit in iDFS. Therefore, patients who have large tumors or node-positive disease may draw the maximum benefit with the use of nab-paclitaxel as they are less likely to achieve pCR.

The improvement in pCR rate and long-term outcomes such as DFS or EFS has not been seen consistently in all trials comparing nab-paclitaxel and s paclitaxel. The evaluating treatment with neoadjuvant abraxane trial compared a different regimen of nab-paclitaxel (125 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-day cycle) with s paclitaxel (90 mg/m<sup>2</sup> on day 1, 8, and 15 of a 28-day cycle), followed by anthracycline-based regimen and showed similar pCR in both arms and no difference in long-term outcomes.<sup>[8]</sup>

CREATE-X trial included patients with HER2/neu negative breast cancer who failed to achieve pCR after neoadjuvant chemotherapy. These patients were randomized to receive either additional eight cycles of adjuvant capecitabine with standard treatment or standard treatment alone (control arm). The addition of adjuvant capecitabine led to a statistically significant improvement in both DFS (hazard ratio [HR], 0.58; 95% confidence interval [CI]: 0.39–0.87) and OS (HR, 0.52; 95% CI: 0.30–0.90) in the triple-negative breast cancer subgroup.<sup>[9]</sup>

In the GeparSepto trial, the patients who failed to achieve pCR were not offered adjuvant capecitabine. Hence, the extent of benefit of the addition of Nab-paclitaxel instead of s paclitaxel is not known if adjuvant capecitabine is given to patients who fail to achieve pCR. The role of the addition of Nab-paclitaxel instead of s paclitaxel has not been evaluated in the specific subgroup of patients with triple-negative breast cancer with BRCA mutation.

## Adding Carboplatin

The addition of carboplatin to standard neoadjuvant chemotherapy regimen increases the pCR in patients with triple-negative breast cancer.<sup>[10-12]</sup> Poggio *et al.* in their meta-analysis reported that platinum-based neoadjuvant chemotherapy regimen increases the pCR rate in triple-negative breast cancer from 37% to 52.1% (OR: 1.96, 95% CI: 1.46–2.62).<sup>[13]</sup> This increase in pCR is not noted in the subgroup of patients with BRCA mutation.<sup>[14]</sup>

The long-term outcomes of the addition of carboplatin are available only from the two randomized controlled trials, CALGB 40603 and GeparSixto trial. The CALGB 40603 study showed no improvement in the EFS or OS. On the contrary, the GeparSixto trial showed an improvement in DFS with the addition of carboplatin in the overall cohort of triple-negative breast cancer, but this difference did not reach statistical significance in BRCA-mutated group.<sup>[15-17]</sup> It is also noted that the GeparSixto trial used a nonstandard chemotherapy backbone, and hence, its results are difficult

to extrapolate in the current practice. A meta-analysis evaluating the impact of the addition of platinum in the neoadjuvant setting in patients with triple-negative breast cancer as compared to standard neoadjuvant chemotherapy also found no statistically significant differences in the EFS or OS between the two groups.<sup>[13]</sup>

The addition of carboplatin also comes at the cost of higher Grade 3 and 4 hematologic and nonhematologic toxicity.<sup>[10-12]</sup> It leads to delays and reduction of paclitaxel and carboplatin doses.<sup>[11]</sup>

The absence of evidence to support the survival benefit of platinum-based neoadjuvant regimen and the risk of higher toxicity make it a less desired option.

## Final Take

In the face of the available data, it is preferable to use a dose-dense two-weekly combination of doxorubicin and cyclophosphamide followed by 12 weekly s paclitaxel in most patients with triple-negative breast cancer. In the patients who fail to achieve pCR, an adjuvant six to eight cycles of capecitabine should be added.

Weekly nab-paclitaxel is preferred in situations where an individual either has a hypersensitivity to s paclitaxel or if the use of steroids is contraindicated. Weekly nab-paclitaxel may also find its place in a clinical situation where we are faced with a patient with a large and/or node-positive breast cancer, but an adjuvant use of capecitabine is not being considered even if she fails to achieve a pCR. The use of carboplatin in the neoadjuvant setting should be limited until such time that there is greater clarity on its effect on long-term outcomes.

In the given case, I will use a dose-dense two-weekly combination of doxorubicin and cyclophosphamide followed by 12 doses of weekly s paclitaxel. If the patient fails to achieve a pCR, I will give eight cycles of adjuvant capecitabine.

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## Conflicts of interest

There are no conflicts of interest.

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