

# Treatment recommendations and prioritisation planning for breast cancer patients during COVID-19 pandemic

## Part 2: Triple Negative, HER-2 Positive and Metastatic Breast Cancer - A Caribbean Breast Surgeon's Perspective

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### Abstract

The COVID-19 pandemic has shed significant burden and challenges on the medical systems locally and internationally. This encumbrance has overflowed onto the management of breast cancer throughout the entire world, as well as, our twin island of Trinidad and Tobago. Embracing this precarious period led to the prioritisation model for precise management protocols during this crisis.

This article is a continuum and the finale of the previously discussed COVID-19 guidelines and management protocols for breast cancer by a single Caribbean Breast Surgeon (Part 1). Part 2 of this article entails a thorough discussion of HER-2 positive, triple negative and metastatic breast cancer management. Recommendations are suggested with the surgeon's input into its feasibility and practicality within the existing local systems.

### Introduction

The infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was classified as a pandemic in March 2020. The resulting pandemonium has led to delays and disruptions in current breast cancer management. Several world-recognised organisations focused on breast surgical oncology, have generated prioritization models for breast cancer management during the pandemic. The societies used in this discussion are American Society of Breast Surgeons (ASBrS)<sup>1</sup>, European Society of Medical Oncology (ESMO)<sup>2</sup> and the COVID-19 pandemic breast cancer consortium.<sup>3</sup>

Generally, the recommendations stem from the prioritization of breast cancer into three major categories: A, B and C. This treatment selection criterion permits the redefinition of clinical priorities based on risk-to-benefit ratio and cancer care. Category A involves urgent and life-threatening scenarios. Category B patients are not life threatening but cannot await treatment following the pandemic. Fixed period of delay must be stipulated for this category of patients. Category C patients can be delayed until after the pandemic.

All treatments and the surgical timing are thoroughly and precisely discussed per case within the multidisciplinary team setting. Tumour biology, availability of resources, premorbid conditions and risk/benefit ratios are utilized in

the consensus decision.

## Discussion

### Curative Intent Treatment breast cancer

Newly diagnosed breast cancer cases should be discussed in the multidisciplinary approach. Early breast cancers were previously considered for only surgical resection as the initial modality of treatment and are not offered neoadjuvant therapy. However, this practice of neoadjuvant therapy use in early breast cancer is supported by National Comprehensive Cancer Network (NCCN) guidelines and St. Gallen Early Breast Cancer International Expert Consensus panel consortium<sup>4</sup>. The onset of the COVID pandemic has increased the utilization of this approach. Previously, in the United States, only 20.2% of patients were offered neoadjuvant therapy.<sup>5</sup> However, there was approximately 200% increase in neoadjuvant therapy, in one major North America centre during the first wave of COVID-19 pandemic.<sup>6</sup>

There are several benefits to neoadjuvant therapy in breast cancer patients. The ability to downstage the tumour burden within the breast and axilla to facilitate breast preservation/conservation and the avoidance of axillary lymph node dissection respectively. Additionally, the achievement of a complete pathological response assures a good recurrence-free survival. However, the most important benefit of this approach is appreciated in certain subtypes such as HER-2 positive and Triple Negative Breast Cancer (TNBC).

The adjuvant options of treatment for residual tumour post-surgical resection and Neoadjuvant Chemotherapy (NACT) render another means of 'stepping up' treatment protocol. This group of patients are at high risk for recurrence and the benefit of witnessing the neoadjuvant response fosters the need for an alternative regimen. The availability of effective alternative adjuvant treatment options has demonstrated an improvement in Disease Free Survival (DFS).

### Triple Negative Breast Cancer (TNBC)

A. Breast tumours less than 1 cm with no axillary nodal involvement (T<sub>1a/b</sub>N<sub>0</sub>) and patients who are not candidates for NACT should ideally be offered upfront surgical intervention. This subgroup of patients would not benefit from adjuvant therapy and consequently

would not benefit from neoadjuvant therapy. If operating theatre time proves to still be unavailable, the risk of NACT toxicity needs to be balanced with the possibility of disease progression.

- B. Breast tumours greater than 1 cm but less than and equal to 2 cm (T<sub>1c</sub>) are routinely offered NACT along with clip placement in the breast lesion. The COVID-19 pandemic offers the scenario where this approach should be strongly considered with the unavailability of theatre time and preservation of resources. Adjuvant non-anthracycline containing regimen would be offered; Docetaxel/Cyclophosphamide (TC).
- C. Breast tumours greater than 2 cm with axillary nodal involvement (T<sub>2-4</sub>N<sub>1-3</sub>M<sub>0</sub> / Stage II-III), would routinely be offered NACT dose-dense doxorubicin / cyclophosphamide (AC) followed by weekly paclitaxel (T). Additionally, carboplatin to AC-T regimen normally increases the probability of complete pathological response. However, in the COVID-19 backdrop, the risk of haematological toxicity is increased with no added survival benefit<sup>7</sup>. Following completion of neoadjuvant therapy, surgery should be performed within 4-6 weeks. Therefore, this scenario would be considered B1 because delay beyond the pandemic would affect the patient's outcome since TNBC has a high propensity for Local Recurrence (LR).

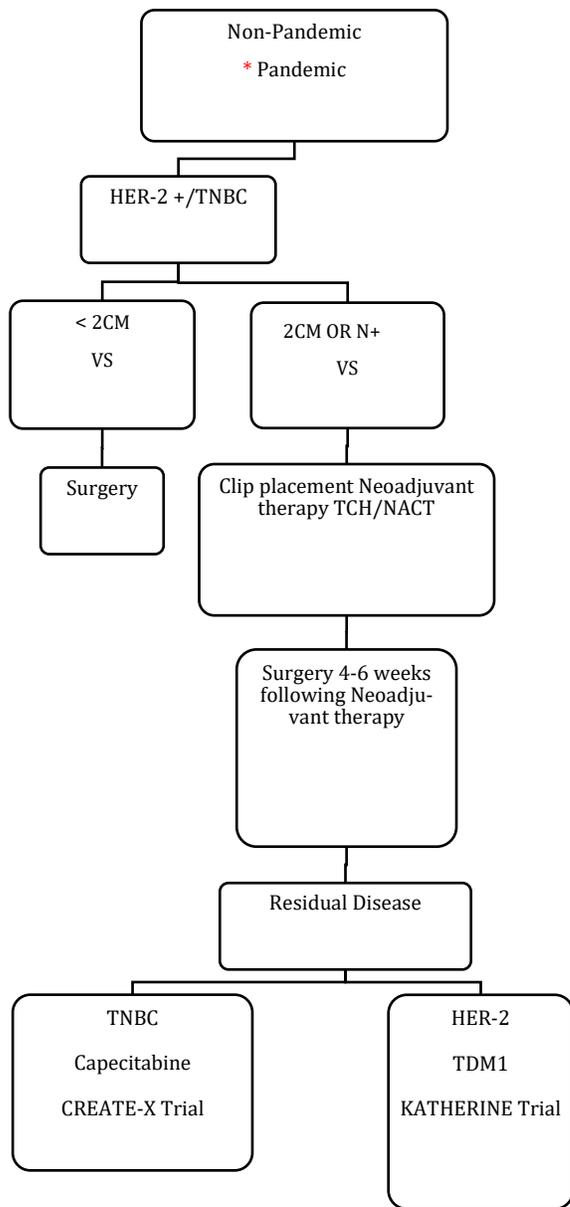
Residual breast cancer disease in the resected specimen would guide the use of oral capecitabine as an alternative regimen. The landmark CREATE-X trial demonstrated the improvement of DFS in this particular scenario.<sup>8</sup> Capecitabine group DFS was 69.8% versus 56.1% in the control group and overall survival rate was 78.8% versus 70.3%, respectively.

Following surgery with or without adjuvant chemotherapy, TNBC patients are referred for adjuvant radiation therapy. A delay in radiation therapy in TNBC is associated with a high risk of local recurrence. Therefore, Radiation therapy should not be delayed in this subset of breast cancer patients.

### HER-2 positive Hormonal Negative

The COVID-19 Breast cancer Consortium recommended up-front surgery only to T<sub>1</sub>N<sub>0</sub> HER-2 positive breast cancers. T<sub>1a/b</sub> generally should be offered up-front

**Figure 1: Management of HER-2/ TNBC during the COVID-19 pandemic (with a comparison during non-pandemic times)**



*\* Reduction in the Indication Size for Neoadjuvant Therapy*

*\*Demonstrates the highlighted changes during the pandemic.*

surgery if the pandemic permits.

T<sub>1c</sub> and greater are generally offered NACT and targeted therapy. However, if surgery can be facilitated, tumours less than 3cm and clinically axillary node negative (cN0), up-front surgical resection is ideal. If these patients are found to be nodal negative, de-escalation of systemic therapy with paclitaxel and trastuzumab could be implemented allowing reduced haematological side effects. The Adjuvant Paclitaxel and Trastuzumab Trial (APT)<sup>9</sup> demonstrated a low-risk group of patients with

less than 3cm in size HER-2 positive BC and node negative disease. The 3-years and 7-years disease free survival were 98.7% and 93%, respectively.

The ATEMPT Trial<sup>10</sup> also provides another alternative to the APT regimen, Ado-Trastuzumab Emtansine (TDM1). TDM1 was associated with significantly fewer Critically Relevant Toxicities (CRT) than those observed in the APT trial. Unfortunately, the pre-planned reduction of 40% toxicity was not achieved. The 3-year DFS is 97.5% for recipients of T-DM1 versus 93.2% for recipients

of paclitaxel plus trastuzumab. Therefore, this monotherapy would offer another alternative regimen to reduce toxicities and hospital visits during this pandemic. Generally, NACT and HER-2 targeted therapy is offered to tumours greater than 3 cm and/or nodal positive. The neoadjuvant regimen consists of docetaxel/carboplatin/trastuzumab (TCH) +/-pertuzumab (P). Surgical excision of the primary tumour should be performed within 4-6 weeks of NACT/HER-2 targeted therapy. If the pandemic restricts surgical intervention, additional doses of trastuzumab may be continued until surgical excision. The presence of residual disease in the surgically resected specimen guides the utilization of TDM1 in these patients. This approach was supported by another landmark trial entitled KATHERINE.<sup>11</sup> Patients with residual disease treated with adjuvant TDM1 were found to have a 50% reduction in the risk of death or recurrence of invasive breast cancer when compared to the trastuzumab only regimen. Alternatively, if there is a complete pathological response (PCR), patients are administered H with or without pertuzumab. Another means of reducing patients' exposure to the contagion and visit to the oncology centre would be to reduce the duration of adjuvant HER-2 targeted therapy to 6 months versus 12 months. The PERSEPHONE trial of early HER-2 positive breast cancer patients has shown that 6-month adjuvant trastuzumab is non-inferior to the 12-month treatment.<sup>12</sup>

Finally, the dosing interval can also be increased to monthly versus three-weekly, which would reduce the number and frequency of patients' visits. Unfortunately, the availability of TDMI, as well as pertuzumab are only in the private sector in Trinidad and Tobago. Therefore, patients may only be offered trastuzumab in combination with the available chemotherapeutic agents previously discussed.

Following surgery with or without adjuvant therapy, patients are referred for radiation therapy within 8-12 weeks. Delay of this adjuvant modality should be avoided because HER-2 positive breast cancer has a high risk of local recurrence.

### ***Author's Opinion***

TNBC should be strongly considered for NACT because capecitabine is readily available for residual disease in the public and private sectors. Therefore, TNBC patients can

undergo neoadjuvant therapy and clip placement during the COVID-19 pandemic. This would permit the overwhelming benefit of delayed surgical intervention as well as the potential of a complete clinical and pathological response. Therefore, full adaptation of NACT for TNBC greater than 1cm can be applicable in our system with comparable outcomes and benefits.

On the other hand, the lack of TDMI availability in the public arena may impact the full implementation of this neoadjuvant approach for HER-2 positive cancers. Lack of TDMI renders the recommended therapy for residual disease unavailable. Alternatively, patients may be offered adjuvant trastuzumab in the public sector. TDMI is available in the private sector and would facilitate the implementation of this neoadjuvant approach for these clientele.

Reduction in the duration and the dose intervals of adjuvant trastuzumab also offers another regimen. This may reduce hospital visits along with the financial burdens in the oncology department without affecting the patients' overall survival. Another important strategically approach during this crisis.

### ***Palliative /Metastatic breast cancer***

Metastatic breast cancer patients are usually on several lines of chemotherapeutic regimens with no particular sequencing. In the pre-pandemic scenario, the management of metastatic breast cancer is crucially governed by the basic principle of maintaining the balance between quality and quantity of life.

Modification of chemotherapy frequency may reduce patients' exposure and hospital visits. Routine restaging imaging may be deferred if the patient has no obvious signs of disease progression. A Multidisciplinary approach assesses the risk-to-benefit ratio of a particular additional palliative option. The benefit may be too minute to outweigh the risk of COVID-19 exposure and subsequent infection.

### ***Triple Negative Breast Cancer***

Immunotherapy for metastatic TNBC such as PD-1 inhibitors should be used with caution because of the pulmonary toxicity association. Treatment for bone metastases with zoledronic acid and denosumab can be delayed until after the pandemic or the dosing intervals increased. Patients with symptomatic hypercalcemia are

at high risk for skeletal-related events and should continue bone modifying agents during the pandemic.

### HER-2

TDMI not available in the public

### HR positive

In HR positive / HER-2 negative metastatic breast cancer, hormonal therapy is the favoured modality of treatment. Ovarian ablation and suppression are of paramount importance in premenopausal patients. The utilization of CK 4/6 inhibitors such as Palbocicib is part of the first-line regimen for HR + HER-2 negative stage four cancers. Unfortunately, the significant immunosuppressive effect of this therapy should be taken into consideration during this pandemic.

Preference for oral agents and dose reduction should be considered in the metastatic group for reduction and avoidance of haematological toxicity. Drugs such as capecitabine and vinorelbine should be considered. The utilization of prophylactic growth factors should be implemented with drugs that are associated with significant immunosuppressive toxicity.

### **Author's Opinion**

First-line therapy for HR positive and HER-2 positive breast cancer are CK 4/6 inhibitors and TDMI, respectively. Unfortunately, both drugs are not available in the public sector. Therefore, avoidance of CK 4/6 immunosuppressive complications would not be applicable in our local treatment planning.

The other mentioned management strategies for metastatic breast cancer therapies could be readily introduced for the COVID-19 pandemic without compromising patient care.

### **Author's General Considerations**

#### Radiological imaging

Radiological mammography-based screening during the pandemic should be temporarily suspended. Follow-up imaging for early breast cancer and metastatic patients may also be abrogated. Tailored radiological planning for disease progression and per symptoms should be implemented during this pandemic.

### Overburdened Medical Oncology Services

The decision and intervention of one specialty would directly impact another specialty as they go hand in hand. Prior to the pandemic, the medical oncology services were already burdened by the various malignancies within our twin islands. The recommendations are heavily tilted towards bridging surgical intervention with neoadjuvant chemotherapy and /or neoadjuvant endocrine therapy. This may result in a substantial increase in medical oncology referrals, further diminishing and incapacitating services offered.

Therefore, the key to the successful management of breast cancer in the low resource environment is a clear methodological definition of the most salient cancer therapies and their appropriate utilization. The multidisciplinary principle would be non-negotiable to prevent this catastrophe of exhausting services. It would analyse and filter the patients requiring immediate surgical intervention versus medical therapy.

### Outpatient clinics

In-person clinic visits are recommended only for specific case scenarios. Suspected oncological emergencies, recurrence of disease, progression, new cancer diagnosis, and unstable or symptomatic metastatic breast cancer. Baseline patient evaluation for neoadjuvant therapy and monitoring of chemotherapy toxicity are other indications for in-person clinics.

Telecommunication is an important technological advancement that may facilitate patient-doctor interaction during this pandemic. Privacy and information safety are some of the intricacies of this technique of clinical follow-up. This modality of communication may provide the bedrock of the patient centred model. Patients' psychological concerns and support during the pandemic may be addressed via web-based platforms or the aforementioned telecommunication methods.

### Multidisciplinary approach

All strategic planning per patient is discussed case by case with an intimate relationship involving the multidisciplinary approach. Prioritisation of cases would ensure the best patient outcomes. Documentation of standard pre-COVID-19 and COVID-19 recommendations should be recorded in the patient's file. Patient's consent for any formulated COVID-19 pandemic medical

intervention should also be clearly recorded.  
All multidisciplinary meetings should be held virtually.

## Conclusion

The primary goals of the aforementioned recommendations are to provide cogent health care planning within the constraints of resources while sustaining the continuum of ideal breast cancer management. The profound impact of this pandemic requires a continuous reassessment of treatment models as COVID-19 pandemic changes. This evolution would require adjustments in the previously discussed prioritisation model. Additionally, the assessment of staff and available resources should be performed monthly during the pandemic to ensure improvement and precise utilisation of our services.

Although COVID-19 presents several limitations to our breast cancer treatment, it fosters a study environment of situations not previously possible. This paradigm shift will ultimately unveil gems that may influence a more efficient and individualised breast cancer management in the future.

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