Breast Cancer Neoadjuvant Therapy Referrals

A Guidance Document for Optimal Multidisciplinary and Appropriate Care of Patients with High-Risk Breast Cancer Type Who May Benefit from Neoadjuvant Chemotherapy

Purpose

This document is a clinical summary of expectations for the care of breast cancer patients in the province of Manitoba across various disciplines of medicine, so that women may be given the optimal treatment and best chance of cure. It is specifically designed to aid clinicians in deciding who to send to for consideration of neoadjuvant therapy, and the updated processes needed to get them to the best treatment expediently.

The Background

Neoadjuvant therapy in breast cancers has been well established for unresectable or borderline resectable disease for many decades. For resectable disease, large historic studies have not shown a survival advantage to a broad adoption of this approach, though specific issues such as downsizing to allow for smaller surgery are a consideration [1.2].

Two recent studies have shown possible improved outcomes with neoadjuvant chemotherapy in high-risk subtypes of breast cancer, namely triple-negative and HER2 positive disease if there is residual disease after such approach [3, 4]. Both studies (CreateX and the Katherine trial) had a similar schema, whereby patients got routine neoadjuvant chemotherapy; those that did not have a complete pathologic response were given alternatives systemic therapies post-operatively. It is identifying these non-complete responders and personalizing additional post-operative treatment that is the crux of what is new for these high-risk subtypes.

On the other end of the spectrum, preliminary results from the RxPonder study (node-positive, ER-positive, HER2 negative breast cancer) suggest that some node-positive patients do not require chemotherapy at all [5]. In this study, patients with 1-3 nodes positives were subjected to an OncotypeDx test and those with scores under 26 did not benefit from the addition of chemotherapy to endocrine therapy. This study is in abstract form alone at this time but gives indirect evidence that many ER-positive, HER2 negative easily resectable patients may never need chemotherapy, even if they have N1 disease. Thus, many with this biomarker profile should have surgery first, even if node-positive - with decisions on chemotherapy delayed to post-operative pathology with Oncotype testing.

Put together, these studies show that women with palpable and/or node-positive disease but have resectable tumours must have a treatment plan that is decided based largely on their biomarker profile and overall health status.

Work up

Since treatment decision is based on biomarker profile, most cases will require this information expediently to decide on care. To provide the best management to patients, various pathways in our healthcare system need updating.

We propose that all invasive breast cancers over 2cm or node-positive, in women 75 years or less have ER, PR, and HER2 testing is done urgently on the biopsy specimen. Turn around time target should be 7 days.

Practice change – Radiology:

- All radiologists in Manitoba use core biopsy to diagnose breast cancers whenever feasible (greater than 95 percent of all cancers in each facility should be diagnosed on core).

- All radiologists in Manitoba to use the standardized pathology requisition for breast biopsies (insert form#), including inserting all relevant image information – especially tumour size.

- All radiologists in Manitoba should ultrasound the axilla of patients 75 years or younger, if the primary tumour is 2 cm or more, or there is clinical or mammographic suspicion of nodal involvement. Core biopsy of abnormal nodes is required for confirmation.

- Liberal use of clips to the primary tumour should be employed at the time of diagnosis, as this will be required before the start of neoadjuvant chemotherapy for those that qualify.

Practice Change – Pathology:

- Reflex test for HER2 on any specimen where the requisition notes tumour 2cm or greater, or lymph node involvement, and the patient is 75 years old or younger (if the biopsy shows invasive disease and there is adequate tissue for immunohistochemistry).

- Turn around time to confirm invasive cancer and all applicable biomarkers to be 5-7 working days, 7 -10 calendar days (goal).

Practice Change – Surgery:

- In patients under 75 years old, with tumour 2cm or greater or lymph node involvement, book first consultation for 7-10 working days after the biopsy, so that biomarkers are available for consultation.

- If a patient is seen without all necessary pathologic information, an attempt to ascertain that information before OR should generally occur. Patients should be informed that their treatment plan could change as more information becomes available.

Referral Criteria

CancerCare Manitoba will accept referrals for neoadjuvant therapy for patients where neoadjuvant therapy may be indicated. (Note some of these criteria are pre-existing and others are a practice change for medical oncology)

A referral is strongly advised for the following:

- Inflammatory breast cancers
- Breast cancers that are deemed surgically unresectable at presentation
- Palpable triple-negative or HER2 positive cancers that are 2 cm or greater, or biopsy has proven lymph node-positive (see footnote 1)

A referral is an option and will be considered for the following:

- Patients who refuse mastectomy with a reasonable chance that it can be converted into lumpectomy (Strongly ER/PR positive tumours and low-grade tumours are often poor candidates for this approach)
- Resectable ER-positive, HER2 negative tumours that are greater than 5 cm, or N2 (4 or more abnormal nodes, or fixed nodes) AND grade 2 or 3 (tumours with mucinous and tubular histology are excluded)

Referral Process

Referral to CancerCare Manitoba is through standard existing processes.

All patients with tumours >5cm or palpable axillary nodes require a CT scan of the chest, abdomen, pelvis, bone scan, and MUGA before being seen. Patients not meeting these criteria should have staging ordered, but in general, do not need to wait for results for booking.

Practice change – Surgery (occasionally primary care, acute care):

- Staging will be ordered, as above
- Ensure that patient has a clip in their primary tumour. Order if they don't have one already.
- Book the patient back for surgical discussion and re-assessment of tumour size midway through their chemotherapy. If the patient wishes mastectomy and reconstruction and is medically appropriate, then early referral to CCMB plastic surgery is encouraged so that they can be seen midway through chemotherapy in that clinic.

Practice change – medical oncology:

- Goal to see the patient within two weeks of receipt of consult, knowing this is dependant on referral volumes.

- Patients with T1-2, N0-1 tumours may be booked scans booked but not completed, with results to follow in the window between consultation and first chemotherapy dose. (Note the rate of synchronous metastatic disease in this group is <5 percent). In cases where a patient is at high-risk to have a cardiac impairment, then waiting for the MUGA result for consultation is reasonable.

- In the event that a patient is seen and not appropriate for neoadjuvant therapy, then a reasonable attempt should be made by the medical oncologist to reach the surgeon of record via phone/text/email so that alternate arrangements can be made expediently.

Footnotes: Final Notes to Consider

1. The above algorithm is for patients who are in generally good health for cytotoxic chemotherapy regimens. Those with significant comorbidities are often inappropriate for a neoadjuvant approach unless frankly unresectable. Phone consultation in medical oncology (via the CCMB central referral office) is always an option for clinicians who may be uncertain. In the same vein, neoadjuvant chemotherapy is generally not done in those over 75 years old. Proceeding first to surgery, if resectable, is a reasonable clinical approach in this age group.

2. Neoadjuvant referrals should have a disease that can be followed clinically (i.e., palpable/measurable mass).

3. Remember that supportive services are available for patients throughout their cancer journey. Shared Health Breast Health Centre, the Breast and Gyne Cancer Centre of Hope and nurse navigators/CCMB referral office are excellent places to get patient support, particularly as they make their way through diagnosis and establishing the best treatment plan.

4. Neoadjuvant endocrine therapy is generally not encouraged in otherwise healthy patients. Endocrine therapy alone may be considered for unresectable patients, either due to tumour extent or general unfitness for surgery. Endocrine therapy can be prescribed by various providers depending on knowledge and comfort level (eg. Medical oncology, radiation oncology, surgery/surgical oncology). If the patient is being referred for endocrine therapy due to unfitness for surgery, please ensure that is clear in the consultation result.

This document has been jointly developed by CancerCare Manitoba's Department of Surgical Oncology, Shared Health Breast Health Centre, and CancerCare Manitoba Breast Cancer Disease Site Group.

REFERENCES

1. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B -18 and B – 27. J Clin Oncol 2008. Feb 10; 26(5):778-85.

2. Early Breast Cancer Trialists Collaborative Group (EBCTCG). Long-term oucomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomized control trials. Lancet Oncol 2018. Jan;19(1):27-39.

3. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017. Jun 1;376(22):2147-59.

4. Von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasice HER2-positive breast cancer. N Engl J Med 2019. Feb 14;380(7):617-628.

5. Kalinsky K, Barlow WE, Meric-Bernstam F. et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) <= 25: SWOG S1007 (RxPonder). San Antonio Breast Cancer Symposium, San Antontio, Texas/Virtual. December 10, 2020. Abstract available at: https://www.abstractsonline.com/pp8/#!/9223/presentation/2794. Accessed: March 23, 2021.