Resource Guide: Preoperative Management of Patients Treated with Neoadjuvant Systemic Therapy

Purpose

This resource guide aims to provide an overview of the optimal timing for surgery and key considerations for the preoperative workup in patients with breast cancer who have recently completed neoadjuvant systemic therapy (NST).

Associated ASBrS Guidelines or Quality Measures

- Performance and Practice Guidelines for the Use of Neoadjuvant Systemic Therapy in the Management of Breast Cancer
- A Surgeon's Resource Guide Endocrine Therapy for the Management and Risk Reduction of Hormone Receptor Positive Breast Cancer

Methods

This is a literature review of current guidelines, recommendations, or extant literature on the preoperative management of patients with breast cancer treated with neoadjuvant systemic therapies. The literature search focused on articles on the preoperative management of immune checkpoint inhibitors, anthracyclines, taxanes, anti-metabolites, alkylating antineoplastic agents, monoclonal antibodies, selective estrogen receptor modulators (SERM), nonsteroidal aromatase inhibitors (AI), steroidal aromatase inhibitors (AI), and CDK 4/6 inhibitors. This is not a systematic review but rather an organized summary of the existing literature, providing practical information for optimal clinical practice.

Approval

Please see the list of authors and disclosures at the end of this resource guide. The ASBrS Committee on Critical Writing, Editing, and Review Committee (CWERC) provided guidance for this resource guide, which the ASBrS Board of Directors reviewed and approved.

Background

Neoadjuvant systemic therapy (NST) has been associated with improving eligibility for breast conservation surgery and providing in vivo evidence of the tumor response to systemic therapies, which is used to guide adjuvant therapies.[1-3] The interval between the last dose of systemic therapy and surgery is critical as studies have demonstrated poorer survival outcomes in patients who experience extended delays following neoadjuvant

systemic therapy (NST).[4-6] Moreover, NST-related adverse events can have significant implications for surgery eligibility and perioperative complications.

The subsequent sections of this resource guide provide an overview of the available data regarding the timing for surgery and considerations for preoperative workup in patients with breast cancer who have recently completed NST.

ASBrS Recommendations on Timing for Surgery and Systemic Therapy Discontinuation Following NST

Immune Checkpoint Inhibitors

- Immune checkpoint inhibitors (e.g., pembrolizumab) can be continued during the perioperative period. However, the potential for immune-related adverse events (irAEs) and treatment related adverse events (TRAEs) require additional preoperative testing and a potential need for medical optimization before surgery.

Chemotherapy

- Patients receiving neoadjuvant chemotherapy should undergo surgery 3-8 weeks after their final dose of chemotherapy.

HER 2 Directed Therapy

- Monoclonal antibodies (e.g., trastuzumab, pertuzumab) can be continued in the perioperative period.

Endocrine Therapy

Neoadjuvant selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) are not currently the standard of care. However, SERMs or AIs may be used in specific clinical scenarios or clinical trials during the perioperative period.

- SERMs should be discontinued 7 days before surgery. For patients at high risk of venous thromboembolism, consider discontinuation 3 weeks before surgery.
- Aromatase inhibitors (e.g., letrozole, anastrozole, exemestane) can be continued in the perioperative period.

CDK 4/6 Inhibitors

The use of CDK4/6 inhibitors in the neoadjuvant setting is not standard of care. However, they may be used in specific clinical scenarios or clinical trials during the perioperative period.

- CDK 4/6 inhibitors should be discontinued 7 days before surgery.

Table 1: Summary of Recommendations for Timing for Surgery and Consideration for Preoperative Testing			
	Timing for Surgery	**Routine Preoperative Testing***	**Preoperative Testing to Consider for Treatment Toxicity****
Immune check point inhibitors Pembrolizumab	Continue in perioperative period	CBC CMP TSH Free T4 Morning (6-9am) cortisol	**Severe Skin Reactions** No additional preoperative testing is warranted. **Hyperthyroidism** Consult with endocrinology
Neoadjuvant Chemotherapy Anthracyclines (doxorubicin, epirubicin) Carboplatin Cyclophosphamide Capecitabine Taxanes (paclitaxel, docetaxel)	3-8 weeks	CBC CMP	**Anthracycline Cardiotoxicity** **ECG** history of cardiac disease or anthracycline induced cardiotoxicity **ECHO** history of heart failure or anthracycline induced cardiotoxicity
Monoclonal antibodies Trastuzumab Pertuzumab Trastuzumab/pertuzumab/hyaluronidase-zzxf	Continue in perioperative period	CBC CMP	**Cardiotoxicity:** **ECG** history of cardiac disease **ECHO** Decision to obtain ECHO should be based on 1) a review of quarterly ECHO obtained for HER-2 directed therapy 2) ongoing evaluation of HER-2 related cardiotoxicity or 3) new onset symptoms for heart failure.
Selective estrogen receptor modulators (SERM) Tamoxifen Toremifene	7 days 3 weeks *(if patient has multiple risk factors for VTE)*	None recommended	**Wound Healing** No additional preoperative testing is warranted. **Venous Thromboembolism**

			No additional preoperative testing is warranted.
Nonsteroidal aromatase inhibitors Letrozole Anastrozole **Steroidal aromatase inhibitors** Exemestane	Continue in perioperative period	None recommended	**Wound Healing** No additional preoperative testing is warranted.
CDK 4/6 Inhibitors Ribociclib Abemaciclib	7 days	CBC CMP	**Ribociclib QT Prolongation** ECG for patients with history of cardiac disease or unresolved QT prolongation secondary to Ribociclib. **Abemaciclib VTE:** No additional preoperative testing is warranted.

*Preoperative testing: Defined as labs and imaging obtained after the last dose of systemic therapy and within 30 days of surgery date for all patients.

** Preoperative testing to consider for patients who have chemotherapy-associated adverse events, immune-related adverse events, or treatment-related adverse events. Imaging or lab tests conducted within 30 days of surgery may not require repetition; decisions to repeat should be guided by multidisciplinary input or the emergence of new symptoms.

Summary of Data Reviewed

Immunotherapy

Pembrolizumab, an immune checkpoint inhibitor (ICI), has emerged as a key drug in neoadjuvant treatment regimens for early-stage triple-negative breast cancer. Existing literature indicates that including pembrolizumab in neoadjuvant systemic therapy is associated with an increased complete pathologic response rate and prolonged event-free survival.[7,8]

Toxicities associated with ICIs, known as immune-related adverse events (irAEs), differ from those caused by chemotherapy or other biologic treatments.[9] Notably, combining pembrolizumab with other agents results in a higher incidence of adverse events compared to pembrolizumab monotherapy.[9] However, these events are not additive but rather reflect the distinct toxicity profiles of each agent. Adverse events arising from the combined use of ICIs and cytotoxic chemotherapy are classified as treatment-related adverse events (TRAEs), which are distinct from irAEs.[9] Although irAEs typically occur within weeks to months of treatment initiation, they can also arise at any time, including after treatment discontinuation.[10]

The management of irAEs are based on their severity: mild toxicities (grade 1) typically require close monitoring, while moderate to severe toxicities (grade 3) necessitate treatment holds and glucocorticoid administration. Permanent discontinuation of therapy is recommended for grade 4 irAEs.[11] Despite these potential toxicities, there is no evidence suggesting the need for pembrolizumab discontinuation during the perioperative period.[9] Furthermore, the administration of steroids for the management of immune-related adverse events (irAEs) is not a contraindication for surgery, as the immunosuppressive effects of steroids are predominantly limited to T-cell activity, with neutrophil and B-cell functions remaining intact.[12]

In the KEYNOTE-522 trial, the most common TRAEs of any grade were nausea, alopecia, anemia, neutropenia, and fatigue.[7] The most frequently reported irAEs of any grade included hypothyroidism (15.1%), severe skin reactions (5.7%), hyperthyroidism (5.2%), adrenal insufficiency (2.6%), pneumonitis (2.2%), thyroiditis (2.0%), and hypophysitis (1.9%).[7] Severe (grade $\geq$ 3) irAEs were less common, with severe skin reactions being the most frequent (4.7%).[7] Grade 3 endocrinopathies, such as adrenal insufficiency (2.6%), hypophysitis (1.3%), hypothyroidism (0.5%), and hyperthyroidism (0.3%, thyroiditis (0.3%) were rare.[7]

Nevertheless, despite their rarity as grade 3 irAEs, endocrinopathies such as hypothyroidism, hyperthyroidism, adrenal insufficiency, and hypophysitis have significant implications for perioperative surgical complications. Moreover, these endocrinopathies are frequently permanent and require lifelong hormone replacement therapy.[10]

Preoperative Workup

Adrenal Insufficiency: Adrenal insufficiency can be primary insufficiency or secondary insufficiency due to hypophysitis. Per manufacturer recommendations, all patients who have received pembrolizumab should have a morning (6 am to 9 am) blood cortisol drawn before surgery.[13,14] However, in patients receiving synthetic corticosteroids, these agents can interfere with serum cortisol assays, and therefore, routine measurement of serum cortisol is not recommended.[15] For patients on corticosteroids, current steroid doses and plans for taper need to be reviewed with the prescribing physician. Additionally, on the day of surgery, the

surgical team should work with the anesthesia team to clarify stress dosing and the continuation of steroids in the perioperative period.[16]

Patients presenting low am cortisol in the preoperative period should be further evaluated with am ACTH, a basic metabolic panel (sodium, potassium, CO2, and glucose), renin, and aldosterone for diagnosis and subsequent referral to endocrinology for corticosteroid management.[15,17]

Hypothyroidism: All patients who have received pembrolizumab should undergo a preoperative workup that includes Thyroid stimulation hormone (TSH) and free T4 (fT4).[18]

Severe skin reaction: No additional testing beyond preoperative CBC and CMP.

Hyperthyroidism: Hyperthyroidism is usually transient and happens before hypothyroidism.[10] However, for patients with confirmed hyperthyroidism, preoperative workup for hyperthyroidism should be coordinated with an endocrinologist.

Summary of ICI preoperative workup: All patients should undergo **CBC, CMP, TSH, Free T4, and am (6-9 am) cortisol**.[18] However, cortisol should not be routinely obtained in patients on corticosteroids.

Chemotherapy

A recent meta-analysis conducted by Cullinane et al. recommends that patients with breast cancer undergo surgery within 4-8 weeks following the completion of neoadjuvant chemotherapy (NAC).[5] Specifically, their analysis demonstrated that patients who underwent surgery within this 4-8 week window experienced significantly improved overall survival (OS) and disease-free survival (DFS) compared to those whose surgery was delayed beyond 8 weeks.[5] Notably, there was no significant difference in OS and DFS between patients who had surgery within 4 weeks and those who underwent surgery between 4 and 8 weeks.[5] Consequently, these guidelines recommend scheduling surgery within 3 to 8 weeks post-chemotherapy, thereby allowing a minimum interval of 3 weeks post-chemotherapy to ensure recovery from the neutropenic window.[19]

Chemotherapy-associated adverse events significantly impact surgical eligibility and postoperative outcomes. For instance, anthracyclines and fluoropyrimidines have been linked to cardiotoxicity.[20-22] As a result, prior to administering cardiotoxic agents, consensus guidelines recommend a cardiac exam, ECG, evaluating baseline left ventricular ejection fraction (echocardiograms) and cardiac biomarkers.[23] In the preoperative setting, patients with pre-existing cardiac conditions or chemotherapy-associated cardiotoxicity need cardiac testing to assess their cardiac status. Specifically, all patients with pre-existing cardiac disease (coronary heart disease, arrhythmias, peripheral artery disease, cerebrovascular disease, or other significant structural heart disease) and/or chemotherapy associated cardiotoxicity should undergo a **12-lead ECG**.[24] In addition, patients with a history of heart failure, those experiencing worsening heart failure, or individuals with anthracycline-induced heart failure need a **pre-operative ECHO**.[24] The timing of the ECHO should be coordinated with the patient's cardiologist based on current symptoms and prior ECHO results. **For patients with no history of cardiac disease or chemotherapy-associated cardiotoxicity, routine cardiac testing with ECG or ECHO is not recommended.**[24]

Other chemotherapy-related adverse events that may influence perioperative and postoperative management include nausea, vomiting, neutropenia, lymphopenia, and anemia, which should be evaluated through routine preoperative laboratory testing (**complete blood count (CBC) and comprehensive metabolic panel (CMP**).

Monoclonal antibodies

The evidence regarding the optimal timing for discontinuing trastuzumab or pertuzumab prior to surgery remains limited. However, available literature suggests that both agents can be safely administered during the preoperative and postoperative periods.[25]

One of the most common treatment-related adverse events associated with trastuzumab is cardiotoxicity. However, its incidence varies depending on the co-administered drug. For example, patients treated with trastuzumab and doxorubicin (13%) or trastuzumab, doxorubicin, and cyclophosphamide (27%) exhibit significantly higher rates of cardiotoxicity compared to those receiving trastuzumab and epirubicin (5%) or trastuzumab and pertuzumab (4%).[26] The current Food and Drug Administration guidelines recommend **an ECHO every three months** during treatment with any HER2-targeting therapy in the early breast cancer setting.[27] In the preoperative setting, cardiac workup (e.g., ECG and ECHO) before surgery should be informed by existing cardiac comorbidities, cardiac surveillance during treatment (ECG, ECHO), cardiotoxicity severity, and the emergence of new cardiac symptoms.[28] For instance, patients with no history of cardiac disease, negative ECGs, and normal quarterly ECHOs do not warrant additional cardiac testing.[24] Conversely, patients with a history of cardiac disease, new cardiac symptoms, an abnormal ECG or ECHO warrant repeat cardiac testing and possibly consultation with cardiology before surgery.

The combined administration of trastuzumab and pertuzumab has been implicated in wound-healing complications. Specifically, one study evaluated patients who underwent breast surgery 4-6 weeks after receiving trastuzumab alone or in combination with pertuzumab. The results showed a higher rate of wound complications among patients who had a lumpectomy and received the combination of trastuzumab and pertuzumab compared to those who received trastuzumab alone.[29] Similarly, another study assessed outcomes in patients undergoing breast reconstruction treated with trastuzumab alone or both trastuzumab and pertuzumab. The findings indicated that patients who received the combination therapy had a higher incidence of wound dehiscence and a greater need for reoperation compared to those who did not receive HER2-directed therapy.[30] Conversely, there was no significant difference in complication rates between patients treated with trastuzumab alone and those not treated with HER2-directed agents.[30] Notably, in the reconstruction study cohort, surgery was performed approximately 6 weeks after the last dose of treatment.[30] Overall, these studies indicate that combination therapy with trastuzumab and pertuzumab may influence wound healing; however, they do not provide conclusive evidence to warrant discontinuing trastuzumab and pertuzumab in the perioperative setting.

Endocrine Therapy

Although not currently the standard of care, the use of neoadjuvant endocrine therapy in patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer is becoming increasingly common, highlighting the need for effective perioperative management strategies.[31-33] Tamoxifen, a selective estrogen receptor modulator (SERM), has been linked to an elevated risk of venous thromboembolism (VTE).[34,35] A recently proposed algorithm by Hussain et al. recommends discontinuing tamoxifen three weeks before surgery for patients with high-risk factors, including a “family history of deep vein thrombosis (DVT), body mass index (BMI) >30 kg/m², relevant comorbidities, increased DVT risk, recent chemotherapy, and procedures lasting longer than 90 minutes”.[36] In contrast, the Society for Perioperative Assessment and Quality Improvement (SPAQI) guidelines suggest stopping Tamoxifen seven days before surgery, even if VTE risk factors are present. They advise continuing Tamoxifen for patients without additional patient- or procedure-related VTE risks during the perioperative period.[37]

Similarly, SPAQI recommends the continuation of aromatase inhibitors during the perioperative period.[37] The discrepancies in the recommended timing for discontinuing SERMs indicate that clinicians must make individualized decisions regarding the cessation of these medications, considering specific patient-related and procedure-related risk factors. It is important to note that both Tamoxifen and aromatase inhibitors have been associated with impaired wound healing.[38 39]

CDK4/6 inhibitors

CDK4/6 inhibitors have traditionally been used in the metastatic setting but are increasingly becoming incorporated into neoadjuvant treatment regimens in nonmetastatic patients.[40-42] Consequently, strategies for their management in the perioperative setting are still evolving. While specific guidelines for managing ribociclib or abemaciclib in the preoperative period are not yet established, current recommendations for palbociclib suggest discontinuing the medication 7 days before surgery and resuming it 3 weeks postoperatively.[43,44]

All patients receiving neoadjuvant CDK 4/6 inhibitors should undergo a **CBC** and **CMP** as part of their preoperative assessment, given that hematologic and gastrointestinal adverse events are the most frequently observed in patients who received ribociclib and abemaciclib, respectively.[44-47] In patients treated with abemaciclib, the most common adverse events included diarrhea, fatigue, and neutropenia.[44,48] Additionally, emerging studies suggest a higher risk of VTE in patients receiving abemaciclib.[49] For patients receiving ribociclib, common adverse events include nausea, diarrhea, fatigue, neutropenia, and infections.[50-52] Notably, in those receiving ribociclib, hypertension and elevated liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) are among the most common grade 3 or 4 adverse events.[50-52] Moreover, approximately 3% of patients receiving ribociclib experienced QT prolongation.[50]

Conclusion

The ongoing management of breast cancer as both a local and systemic disease is essential for improving patient outcomes. Furthermore, the rise in novel systemic therapies necessitates that surgeons remain well-informed about their indications and implications during the perioperative period. Collaboration with a multidisciplinary team (e.g., medical oncology, anesthesia, primary care, etc.) is critical to ensure medications are appropriately discontinued prior to surgery and avoid unnecessary or duplicate testing.

Lead authors: Samilia Obeng-Gyasi MD MPH, Linda Han MD, Margaret Gatti-Mays MD, Tina J Hieken MD

Critical Writing Editing and Research Committee: Jessica E. Maxwell MD, Zahraa Al-Hilli MD MBA, Anna C. Beck MD, Kathie-Ann P. Joseph MD MPH, David W. Lim MDCM MEd PhD FRCSC, Megan Miller MD, Lee Gravatt Wilke MD

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