



Extending neoadjuvant care through multi-disciplinary collaboration: proceedings from the fourth annual meeting of the Canadian Consortium for Locally Advanced Breast Cancer

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ABSTRACT

The use of systemic therapy before surgery (“neoadjuvant therapy”) is the standard of care for the treatment of locally advanced and nonoperable breast cancer. The advantages of neoadjuvant therapy include improved rates of breast-conserving surgery, the possibility of early measurement of response, and potentially improved outcomes for certain subgroups of high-risk patients. The use of neoadjuvant therapy in operable breast cancer is increasing, although there are no clear guidelines in Canada to help guide patient selection and management.

Multidisciplinary experts in the diagnosis and treatment of locally advanced breast cancer (LABC) converged at the fourth annual meeting of the Canadian Consortium for LABC (COLAB) to further their goals of improved standards for neoadjuvant care and clinical research through education and collaboration. Canadian clinical researchers were joined by Dr. Michael Untch of the Helios Hospital Berlin–Buch—representing the German neoadjuvant treatment groups German Gynecologic Oncology Working Group (Arbeitsgemeinschaft Gynakologische Onkologie) and German Breast Group—to discuss the advancement of research in the neoadjuvant setting and important issues of clinical care and investigator-led research. The group reached a consensus on the importance of multidisciplinary collaboration, the use of clips to mark tumour location, and core biopsy testing for the estrogen and progesterone receptors and the human epidermal growth factor receptor 2 at the time of diagnosis. Other initiatives—including creation of a prospective database, inception of the COLAB Neoadjuvant Network, and development of a clinical survey to evaluate current practice—continue to further the COLAB mandate of transforming the neoadjuvant treatment landscape in Canada.

KEY WORDS

Breast neoplasms, cancer treatment, clinical research, translational research, neoadjuvant therapy, surgery, radiation oncology, pathology

1. INTRODUCTION

Therapy for early breast cancer involves a complex interplay of the three principal treatment modalities: surgery, systemic therapy, and radiation therapy. Traditionally, chemotherapy has been administered to breast cancer patients after surgery, followed by radiation and hormonal therapy. We now acknowledge that breast cancer is a heterogeneous disease that can be classified into molecular subtypes. Systemic therapies are thus often tailored to biologically distinct patient populations, allowing for a more individualized approach to therapy. Molecular and immunohistochemical data—such as human epidermal growth factor receptor 2 (HER2) and hormone receptor status—acquired at the time of diagnosis or surgery provide important information to guide the administration of systemic, targeted, and hormonal therapies, and have resulted in some important breakthroughs in the treatment of breast cancer.

Mounting evidence suggests that, in addition to advances in individualized systemic breast cancer therapy, a shift in the traditional sequencing of treatment modalities may also improve outcomes in early breast cancer patients. Neoadjuvant systemic therapy (NST), typically chemotherapy delivered before surgery, has traditionally been reserved for locally advanced breast cancer (LABC) or inflammatory breast cancer (IBC); now, it is considered to be as effective as adjuvant chemotherapy for earlier-stage disease^{1,2}. Neoadjuvant systemic

therapy increases the rate of breast-conserving surgery² and provides the means to monitor treatment outcomes biologically and clinically. With the potential for correlative tissue studies and an increased understanding of the effects of therapies *in vivo*, this preoperative model provides unique opportunities for the development of individualized treatment strategies and novel therapeutic agents alike. However, there is yet much to learn about the optimal use of NST and other treatment modalities, highlighting the need for increased clinical and scientific collaboration and the development of guidelines for the use of emerging treatment strategies.

The Canadian Consortium for LABC (COLAB) is a multidisciplinary team of oncology professionals dedicated to the advancement of LABC research and treatment. This group offers diverse expertise in basic and translational research, medical oncology, radiation oncology, pathology, surgery, nursing, and pharmacy, among other specialties. Their vision is to drive progress through increased collaboration across disciplines and throughout Canada. Specific goals of the COLAB include the development of clinical care pathways and associated evidence-based treatment guidelines, and the promotion of high-quality basic, translational, and clinical research. The COLAB ultimately endeavours to establish the infrastructure necessary to launch nationwide Canadian research trials by facilitating working relationships, and the group meets regularly to foster those goals.

The fourth annual COLAB meeting, chaired by Dr. Jean-Francois Boileau from the Sunnybrook Regional Cancer Centre, Toronto, Ontario, was held May 1–2, 2011, in Cambridge, Ontario. The keynote speaker, Dr. Michael Untch, head of the German Gynecologic Oncology Working Group [Arbeitsgemeinschaft Gynakologische Onkologie (AGO)] provided a comprehensive review of the AGO/German Breast Group (GBG) guidelines for the diagnosis of LABC and the use of NST in Germany, and the history and organizational structure of these highly influential clinical research groups. Presentations by leading Canadian experts touched on related themes, including the elucidation of clinical care pathways and related treatment guidelines, and organization of inter- and intra-institutional infrastructure to facilitate clinical and correlative research. The interactive meeting sessions fostered unique opportunities for academic debate and nurtured collaboration among the attendees, resulting in a concrete set of initiatives to further COLAB goals.

2. MEETING SESSIONS

2.1 Defining Clinical Care Pathways for Neoadjuvant Therapy

Keynote Speaker: Michael Untch, AGO, Helios Hospital Berlin–Buch, Berlin, Germany

In the German model, NST is commonly used in the treatment of high-risk operable breast cancer. To ensure that patients receive the best treatment options in this complex setting, the AGO designed a set of guidelines to address the use of NST. The guidelines provide valuable insights into patient selection and prediction of response, regimen selection and scheduling, treatment recommendations and clinical care pathways, and the sequencing and timing of surgery and radiation therapy³. Indexed both for the level of corroborative evidence and the clinical consensus supporting each recommendation, the guidelines also demonstrate the powerful results achievable through inter-institutional research collaboration (Table 1).

The AGO and the GBG joined forces in 1998 to improve the quality of care for women with early breast cancer. Through the establishment of an academic research organization comprising an independent data monitoring committee, staff, tumour sub-boards, and more than 565 research sites, the group successfully created a platform from which multiple large-scale investigator-initiated trials have been launched. Since the merger, the group has accrued more than 25,000 patients, and its members published 13 manuscripts in 2010 alone. The consortium also has a strong translational oncology research arm and large databases of core-needle biopsies and tumour specimens (some matched), serum, plasma, and circulating tumour cells to be used for clinical and correlational research. The strong inter- and intra-institutional collaboration of the AGO/GBG has allowed members to develop insights into the selection of targeted regimens and sequencing of treatment modalities, the identification of subgroups that might preferentially benefit from therapy, the use of clips to mark tumour location, and the importance of strong pathology analysis and collection of biologic data at the time of diagnosis. The group is an inspiring example of how collaborative endeavours can reshape a treatment landscape, resulting in improved patient care.

Presenter: Sonal Gandhi, Sunnybrook Odette Cancer Centre, Toronto, Ontario

The nature of neoadjuvant therapy affords unique opportunities for innovative approaches to breast cancer research and treatment. Neoadjuvant systemic therapy is the standard of care for large inoperable

TABLE 1 Arbeitsgemeinschaft Gynakologische Onkologie^a (AGO) guidelines: diagnosis and treatment of patients with primary and metastatic breast cancer, neoadjuvant systemic (primary) therapy³

Guideline subject	Oxford		AGO
	Level of evidence ^b	Grade ^c	grade ^d
<i>Indications</i>			
Inflammatory breast cancer	2b	B	++
Inoperable breast cancer	1c	A	++
Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy, with goal of breast conservation	1b	B	+
If similar postoperative, adjuvant chemotherapy is indicated	1b	A	+ ^f
<i>Response prediction: predicting high chance of pathologic complete response</i>			
Age < 35 years	1a ^e	A	++
Clinical stage T1/T2 tumours	1a ^e	A	++
Negative nodal status	1a ^e	A	++
Grade 3 tumour	1a ^e	A	++
Negative estrogen receptor and progesterone receptor status	1a ^e	A	++
Triple-negative breast cancer	1a ^e	B	++
Positive HER2 status	1a ^e	A	++
Prediction algorithm or score	2b	B	+/-
Gene-expression profiles	2b	C	+/- ^f
Proliferation markers (for example, Ki-67, topoisomerase II α , PARP)	2b	B	+/-
Peritumoural lymphocyte infiltration	1b	B	+
<i>Recommended regimens and schedules</i>			
Planned neoadjuvant treatment should last at least 18 weeks	1a ^e	A	++
AC or EC → D every 3 weeks or P weekly	2b	A	++
dac	2b	B	++
AP → CMF	1b	A	+
Taxane followed by anthracycline sequence	2b	B	+
Dose-dense E → P, followed by CMF postoperatively	1b	B	+
Chemotherapy plus zoledronate	2b	C	+/-
Capecitabine in combination with anthracycline and taxane	2b	B	+/-
Combination of platinum and taxane (including triple-negative breast cancer and known <i>BRCA1</i> mutation)	2b	B	+/- ^f
<i>Recommended methods of monitoring response</i>			
Breast ultrasound	2b ^e	B	++
Palpation	2b	B	++
Mammography	2b	B	++
Magnetic resonance imaging	2b	B	+
Positron-emission tomography (computed tomography)	1b	D	+/-
<i>HER2-positive tumours</i>			
Trastuzumab in combination with chemotherapy	1b	A	++
Lapatinib in combination with chemotherapy	2b ^e	B	- ^f
Lapatinib plus trastuzumab in combination with chemotherapy	2b ^e	B	+/- ^f
Pertuzumab plus trastuzumab in combination with chemotherapy	2b ^e	B	+/- ^f
<i>Procedures in case of early response^g</i>			
Continue and complete all chemotherapy before surgery	1b	A	++
<i>Procedures in case of no early response</i>			

In case of stable disease:			
Completion of neoadjuvant systemic therapy, followed by surgery	2b	C	++
Continuation of neoadjuvant systemic therapy with non-cross-resistant regimen	2b	B	+
AC or EC ×4 → D ×4 OR P weekly ×12	2b	B	+
DAC ×2 → NX ×4	2b	B	+
In case of progressive disease:			
Stop neoadjuvant systemic therapy; immediate surgery or radiotherapy	4	D	++ ^f
Additional adjuvant chemotherapy with non-cross-resistant regimen	4	D	+/-
<i>Surgical procedures</i>			
Precise documentation of tumour location before, during, and at the end of neoadjuvant systemic therapy	5	D	++
Adequate surgery after neoadjuvant systemic therapy	2b	C	++
Microscopically clear margins	5	D	++
Excision within new margins	3b	C	+
Sentinel node biopsy			
Systemic therapy: timing of surgery and radiotherapy			
Surgery:			
After leucocyte nadir (2–4 weeks after last course of chemotherapy)	4	C	++
Radiotherapy after mastectomy:			
2–3 Weeks after surgery; indication according to stage of disease before neoadjuvant systemic therapy (clinically N+, clinically T3/4a–d)	2b	B	++

^a German Gynecologic Oncology Working Group.
^b Oxford levels of evidence ⁴ (for Therapy/Prevention, Aetiology/Harm): 1a—systematic review (with homogeneity) of randomized controlled trials; 1b—individual randomized controlled trials (with narrow confidence interval); 1c—all or none; 2a—systematic review (with homogeneity) of cohort studies; 2b—individual cohort study (including low-quality randomized controlled trials—for example, <80% follow-up); 2c: “outcomes” research; ecological studies; 3a—systematic review (with homogeneity) of case-control studies; 3b—individual case-control study; 4—Case-series (and poor quality cohort and case-control studies); 5—expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles.”
^c Oxford grades of recommendation ⁴: A—consistent level 1 studies; B—consistent level 2 or 3 studies or extrapolations from level 1 studies; C—level 4 studies or extrapolations from level 2 or 3 studies; D—level 5 evidence or troublingly inconsistent or inconclusive studies of any level.
^d AGO grades of recommendation ⁵: ++, this investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed; +, this investigation or therapeutic intervention is of limited benefit for patients and can be performed; +/-, this investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases (according to current knowledge, a general recommendation cannot be given); -, this investigation or therapeutic intervention can be of disadvantage for patients and might not be performed; -/-, this investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case.
^e Conference abstract data used when study results have not yet been published.
^f Study participation recommended.
^g Patients with partial mid-course response may achieve a pathologic complete response with longer treatment duration (at least 18 weeks).
 HER2 = human epidermal growth factor receptor 2; PARP = poly (ADP-ribose) polymerase; AC = doxorubicin, cyclophosphamide; EC = epirubicin, cyclophosphamide; D = docetaxel; P = paclitaxel; DAC = docetaxel, doxorubicin, cyclophosphamide; AP = doxorubicin, paclitaxel; CMF = cyclophosphamide, methotrexate, fluorouracil; E = epirubicin; NX = vinorelbine, capecitabine.

tumours and for patients with IBC. A recent meta-analysis showed that neoadjuvant chemotherapy results in neither better nor worse survival than adjuvant chemotherapy for early disease ¹. However, particular subsets of patients treated with NST can demonstrate differential responses and thus experience varying benefits from NST ^{6–8}. In addition to the biologic features of tumours, clinical patient characteristics may predict individual responses to NST, rates of pathologic complete response, and overall patient outcomes. The identification of patient groups that

preferentially benefit from neoadjuvant therapy may also allow for reductions in surgical intervention; facilitate appropriate follow-up of patients expected to have poor outcomes, such as non-responders and those with triple-negative breast cancer; and help to identify suitable candidates for clinical trials. Most established guidelines for neoadjuvant treatment of LABC and IBC do not generally consider or establish patient selection criteria within treatment recommendations. The creation and improvement of guidelines is therefore an important component in improving the

use of NST. The adoption of patient-specific clinical care pathways to guide NST, such as those currently under development at the Sunnybrook Odette Cancer Centre in Toronto, Ontario, may further facilitate the establishment of such guidelines at a national level.

2.2 Roles of Surgery and Radiation Oncology in Neoadjuvant Therapy

Presenters: Louise Provencher, Centre des maladies du sein Deschênes–Fabia, Laval University, Quebec City, Quebec; and Justin Lee, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario

Surgery has traditionally been the primary treatment modality for patients with early breast cancer. Systemic therapy administered before surgery may reduce the size and cellularity of the tumour, presenting unique challenges for surgeons, including increased difficulty in identifying the tumour bed and ensuring complete macroscopic and microscopic surgical excision. Collaborative interactions between medical oncologists, pathologists, and radiologists are essential to determine the necessity for, and logistics of, surgical intervention. Moreover, simple techniques such as the use of tissue marker clips to indicate tumour location at the time of diagnosis ensures appropriate imaging after NST and can greatly improve surgical outcomes. As the first point of referral, surgeons will continue to play a pivotal role in neoadjuvant treatment selection and clinical trial accrual. Surgeons order molecular analyses of the diagnostic core-needle biopsies [estrogen receptor (ER), progesterone receptor (PR), and HER2 status] to guide subsequent treatment and arrange for the insertion of tissue marker clips to maximize breast-conserving surgery options after neoadjuvant therapy. Surgeons also assess the status of axillary breast tissue, typically by ultrasonography, before NST to guide the surgical approach (sentinel lymph node biopsy or axillary dissection). It is therefore imperative that surgeons continue to cultivate knowledge of NST to ensure optimal patient care.

Radiation therapy is the third element of the neoadjuvant breast cancer treatment strategy. Despite the importance of radiation therapy in the tri-modal approach to breast cancer treatment, evidence to guide its use after neoadjuvant therapy is limited, particularly in instances in which a mastectomy is required. Phase III trials to date have focused primarily on the use of radiation therapy after surgery and adjuvant chemotherapy. Consequently, there are no well-established guidelines for radiation therapy after NST. Studies involving

patients treated with NST demonstrate that clinical stage before NST and pathologic response or extent of residual disease after NST are both independent predictors for locoregional failure^{9,10}. Important steps to achieving consensus for the role of radiation therapy in the context of NST include prospective research initiatives and the establishment of guidelines to achieve consistency in determining optimal radiation therapy treatment strategies.

2.3 Importance of Pathology, Tissue Collection, and Information Management in Neoadjuvant Therapy

Presenters: Judit Zubovits, Sunnybrook Health Sciences Centre, Toronto, Ontario; Christine Simmons, St. Michael's Hospital, Toronto, Ontario; and Mark Basik, Segal Cancer Center, McGill University, Montreal, Quebec

Pathology and molecular assessments play an integral role in the diagnosis, treatment, and monitoring of outcomes at the clinical and biologic levels. Reliable pathology and molecular testing are essential to overall patient management in the neoadjuvant setting, but there is considerable institutional discordance in testing methods and no established guidelines to ensure test quality and consistency. For instance, despite the need for molecular testing to guide systemic therapy, testing for HER2, ER, and PR status is often performed post surgery rather than at the time of diagnosis, so that molecular data to guide NST are lacking. Moreover, the use of tissue marker clips during surgery to mark the tumour bed is not standard practice at many institutions, making later identification of tumour tissue more difficult and significantly reducing the accuracy of subsequent molecular analyses if a complete remission is achieved. Those challenges are further amplified by the lack of established guidelines for pathology assessments of tumour samples after neoadjuvant therapy, and the classification schemes used by institutions can vary, particularly in the evaluation of partial responses. Similarly, procedures across institutions for the collection and analysis of clinical samples for molecular assessments are often discordant, creating barriers to collaborative correlational research efforts, which intend to take advantage of the unique translational research opportunities provided by the neoadjuvant clinical setting. Standardization of techniques is therefore required to achieve reliable pathology and molecular testing and to take the essential first step toward establishing a centralized tissue bank.

The integration of clinical and molecular data is crucial for optimal neoadjuvant care. Accurate

prospective collection of such data can be quite challenging. Dr. Christine Simmons of St. Michael's Hospital therefore designed the LABC E-Path database, which, in addition to being a prospective database, has capabilities that can potentially improve care for LABC patients. E-Path maps the clinical care pathway for LABC patients and provides evidence summaries at key decision points in their care. In addition, it maps individual patient care pathways and captures both qualitative and quantitative treatment outcomes, thereby maintaining quality assurance. Furthermore, it is capable of maintaining stakeholder logs and generating real-time reports. By enabling comprehensive and systematic assessments, communication between medical experts is enhanced, physicians are able to tailor therapy based on outcomes, and the entire multidisciplinary team is able to access the information needed to optimize and expedite care. Indeed, since implementation in May 2010, the LABC E-Path has lowered the time between referral and initiation of chemotherapy at St. Michael's Hospital to a median of 7 days from the pre-implementation 16 days¹¹. A similar database implemented nationally could provide the platform necessary for coordinated research efforts and for informed standards of care across the country.

2.4 Translational Oncology and Translational Clinical Trials

Presenters: Mark Clemons, The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, Ontario; Stephen Chia, BC Cancer Agency, University of British Columbia, Vancouver, British Columbia; and Muriel Brackstone, London Regional Cancer Program, London, Ontario

Molecular profiling of breast cancer has revealed gene expression patterns characteristic of multiple major molecular subtypes (luminal A and B, HER2-positive, and basal-like). Research to date suggests that the selection of the chemotherapy backbone has been largely based on earlier studies conducted in unselected populations. The identification of patient groups that preferentially respond to specific therapies may help to better guide treatment selection. Collaborative initiatives are required to determine the prognostic and predictive value of histologic subtypes and various biomarkers; to identify appropriate treatment populations; and to determine optimal chemotherapeutic, hormonal, or targeted agents, and the sequencing or combination (or both) of therapeutics.

Adjuvant clinical research has been helpful in shaping knowledge about early breast cancer care

to date; however, those endeavours are resource-intensive, requiring the enrolment of large numbers of patients and extensive funding. It is important to consider that targeted therapies often benefit only small, select groups of patients and that biomarker assessments may be impractical when alternative therapy is not available. It is therefore possible that, for most patients, the benefits of chemotherapy have been maximized, and identification of patient populations that do not benefit from either chemotherapy or endocrine therapy will be an important goal of future research. It is imperative that future collaborative research directions be carefully considered to ensure that they serve the greatest number of women.

High-quality, investigator-led collaborative trials are essential for reshaping the early breast cancer treatment setting and for optimizing NST. The Concurrent Neoadjuvant Chemo/Radiation for Locally Advanced Breast Cancer – Translational Clinical Trial to Predict Treatment Resistance is a collaborative trial that will analyze response outcomes by subtype and also assess the value of functional imaging techniques¹². This multifaceted trial exemplifies the power of excellent trial design to answer the important and complex clinical questions involved in neoadjuvant care. For more information on this trial and other similar research initiatives, please visit the Canadian Cancer Trials website at <http://www.ontario.canadiancancertrials.ca>.

3. POINTS OF CONSENSUS

The nature of neoadjuvant therapy affords unique opportunities for innovative approaches to breast cancer research and treatment. Clinical research is increasingly conducted at a global level, providing an ideal opportunity for establishment of Canadian-led trials that will have significant global impact. The discussions and academic debate from this year's COLAB meeting resulted in three overall recommendations to support ongoing research and to improve neoadjuvant care:

- A need for multidisciplinary collaboration
- Use of clips to mark tumours
- Histologic testing of the core biopsy for HER2, ER, and PR status at the time of diagnosis (Table II)

3.1 Multidisciplinary Collaboration

The benefits and challenges of the neoadjuvant treatment model will require new levels of collaboration from Canadian oncology professionals, including surgeons, medical oncologists, radiation oncologists,

TABLE II COLAB fourth annual meeting: key points of consensus

Multidisciplinary collaboration

Intra- and inter-institutional

- Between surgeons, medical and radiation oncologists, and other health care professionals
- Shared diagnosis, treatment, and outcome information through use of a dedicated database
- Establishment of the COLAB Neoadjuvant Network (COLAB-NN)

Use of tumour-marking clips

- Insertion at the time of diagnosis as a standard of care
- Ensure identification of the tumour bed
- Improve the quality and accuracy of surgical excision and pathology assessment

Hormone receptor and HER2 core biopsy testing

- Inter-institutional use of standardized protocols to ensure consistency of timing and analytic methods
- Testing at time of diagnosis
- Repeated analysis of the postoperative specimen if relevant receptor status from the initial core biopsy testing is negative and a different result would affect adjuvant treatment recommendations

radiologists, and pathologists, at both the intra- and inter-institutional levels. It is particularly important that surgeons and medical oncologists develop close working relationships that include diagnosis, treatment, and shared follow-up of patients to ensure optimal administration of neoadjuvant therapy and subsequent surgical management. Multidisciplinary rounds to discuss these complex cases are essential. The COLAB encourages all oncology professionals using neoadjuvant therapy to begin conversations with their colleagues regarding the improvement of neoadjuvant care. To facilitate such initiatives, the COLAB has launched the COLAB Neoadjuvant Network (COLAB-NN), a community of Canadian physicians dedicated to improving the selection and management of breast cancer patients treated with neoadjuvant therapy. (More information about COLAB-NN and about how interested readers can join are given later in this section.)

3.2 Clips

One benefit of NST therapy is clinically observable changes in tumour size, ranging from a minimal response to a pathologic complete response. In addition to a reduction in size, the cellularity of the tumour may change. However those changes make it difficult for surgeons and pathologists to clearly identify the tumour bed and to ensure clear resection margins or the acquisition of appropriate tissue samples for pathology and molecular assessment. The insertion of a clip at the time of diagnosis can ensure the identification of the tumour bed and improve the quality and accuracy of surgical excision and pathology assessment. However, pathologic complete response is very uncommon in patients with LABC, and so insertion

can realistically be restricted to operable patients with HER2-positive or triple-negative disease. The COLAB recommends that insertion of clips at the time of diagnosis become a standard of care.

3.3 Core Biopsy Testing for ER, PR, and HER2 Status

In an era of targeted therapy, pathology data are required to effectively guide treatment selection and to identify optimal populations, particularly in the neoadjuvant setting. The three biomarkers currently most important for guiding therapy are HER2, ER, and PR. At the moment, testing methods show considerable institutional variability. Researchers at some institutions conduct the tests on the core biopsy at the time of diagnosis; others test the surgical specimen after surgery. To ensure that all eligible patients benefit from optimal NST care, the COLAB recommends that institutions establish protocols to ensure consistent and timely testing of the core biopsy for HER2 and hormone receptors at the time of diagnosis. Although receptor testing on core biopsies is generally accurate, repeat marker analysis on the postoperative specimen may be considered if outcomes were negative on the initial core biopsy and if a different result would affect the adjuvant treatment recommendations.

3.4 Ongoing CoLAB Initiatives

The treatment of breast cancer continues to evolve and improve, with advances in research aimed at more effective and individualized therapies. The COLAB has identified a number of exciting initiatives to continue to promote improved patient care and research in the neoadjuvant setting. Those initiatives include launching the COLAB-NN; ongoing development of clinical

care pathways and a prospective database; a tissue bank; and the development of practice statements.

3.4.1 *CoLAB-NN*

The COLAB-NN is a community of oncology professionals that has the goals of producing clinical guidelines, gathering prospective data, participating in research initiatives using the neoadjuvant model, and providing support to physicians and groups who want to develop their neoadjuvant therapy programs. The COLAB-NN is currently seeking site champions who would be willing to provide a list of individuals involved in neoadjuvant care at their institution (surgery or surgical oncology, medical oncology, radiation oncology, radiology, and pathology) from which to create an e-mail list of lead clinicians and investigators, so as to facilitate intra-institutional exchange and sharing of best practice information. Individuals seeking additional information or interested in joining COLAB may contact the COLAB Steering Committee by e-mail at colabnn@gmail.com.

3.4.2 *Neoadjuvant Practice Statements*

To enable experts from across the country to provide their perspectives with regard to optimal management of LABC patients, a modified Delphi technique was used to create a survey of expert opinion. The results of that survey will be used to prepare and publish a consensual practice statement modeled after the AGO guidelines. The practice statement will encompass various aspects of NST, including patient selection, tailoring of treatment to individual patients, and the roles of each treatment modality. The consensual practice statement will serve as a first step in establishing standards of care for NST and will allow the COLAB-NN to identify areas to target with knowledge translation initiatives.

3.4.3 *Prospective Database and Tissue Bank*

The COLAB will continue to work on the development of a prospective database for the collection of data on the clinical care pathway, serving as an educational tool and communication platform for multidisciplinary oncology specialists. The LABC E-Path database has been piloted at St. Michael's Hospital, Toronto, Ontario, and will be further refined and piloted at additional institutions. Utilization of such a database will increase ease of access to information, allowing interdisciplinary teams to follow each patient's treatment pathway. Furthermore, consistent use of standardized methods for gathering treatment and outcomes data across institutions will facilitate inter-institutional clinical research, resulting in improved standards of care and new research opportunities nationally.

4. SUMMARY

The neoadjuvant platform affords many opportunities for improved patient care and innovations in research. Through multidisciplinary collaboration, continued research, and constructive debate, Canadian oncology professionals can significantly contribute to the ongoing dialogue regarding optimal neoadjuvant care. We thank all who attended the 2011 meeting and who helped to make it a success, including our sponsors, Hoffmann–La Roche, Genomic Health, GlaxoSmithKline, AstraZeneca, Pfizer Oncology, and Sunnybrook Health Sciences Centre. We invite you to join in this dynamic conversation by joining the COLAB-NN and participating in the upcoming COLAB meeting, tentatively scheduled for April 29–30, 2012, in Cambridge, Ontario, by contacting the COLAB Steering Committee by e-mail at colabnn@gmail.com.

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7. REFERENCES

- Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst* 2005;97:188–94.
- van Nes JG, Putter H, Julien JP, *et al.* Preoperative chemotherapy is safe in early breast cancer, even after 10 years of follow-up; clinical and translational results from the EORTC trial 10902. *Breast Cancer Res Treat* 2009;115:101–13.
- Lux M, Schütz F. *Neoadjuvant (Primary) Systemic Therapy*. Taufkirchen, Germany: Arbeitsgemeinschaft Gynäkologische Onkologie; 2011. [Available online at: http://www.ago-online.de/_download/unprotected/g_mamma_11_1_0_04_neoadjuvant_primary_systemic_therapy.pdf; cited September 7, 2011]
- University of Oxford, Centre for Evidence-based Medicine (CEBM). *Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009)* [Web resource]. Oxford, U.K.: CEBM; 2011. [Available online at: <http://www.cebm.net/index.aspx?o=1025>; cited October 17, 2011]
- Thomssen C, Harbeck N. Update 2010 of the German AGO recommendations for the diagnosis and treatment of early and metastatic breast cancer – Chapter B: prevention, early detection, lifestyle, premalignant lesions, DCIS, recurrent and metastatic breast cancer. *Breast Care (Basel)* 2010;5:345–51.
- Bear HD, Anderson S, Brown A, *et al.* The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2003;21:4165–74.
- von Minckwitz G, Raab G, Caputo A, *et al.* Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. *J Clin Oncol* 2005;23:2676–85.
- von Minckwitz G, Kümmel S, Vogel P, *et al.* Neoadjuvant vinorelbine–capecitabine versus docetaxel–doxorubicin–cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. *J Natl Cancer Inst* 2008;100:542–51.
- Buchholz TA, Tucker SL, Masullo L, *et al.* Predictors of local–regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. *J Clin Oncol* 2002;20:17–23.
- Mamounas EP, Anderson SJ, Bear HD, *et al.* Predictors of locoregional failure (LRF) in patients receiving neoadjuvant chemotherapy (NC): results from combined analysis of NSABP B-18 and NSABP B-27 [abstract 90]. *Proc ASCO Breast Cancer Symposium 2010*;.. [Available online at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=100&abstractID=60279; cited February 1, 2012]
- Hogeveen S, Han D, George RL, *et al.* Improvement in the quality of care for patients with locally advanced breast cancer through implementation of an integrated electronic care pathway [abstract 207]. *J Clin Oncol* 2011;29:.. [Available online at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=111&abstractID=86061; cited February 1, 2012]
- Ontario Institute for Cancer Research (OICR). Multimodal Evaluation of Individual Response to Neoadjuvant Chemotherapy/Radiation in Locally Advanced Breast Cancer [Web page]. Toronto, ON: OICR; n.d. [Available online at: <http://www.ontario.canadiancancertrials.ca/trial/Default.aspx?TrialId=OCT1202&lang=en>; cited November 10, 2011]

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