Curr Oncol, Vol. 22, pp. S29-42; doi: http://dx.doi.org/10.3747/co.22.2360

REVIEW ARTICLE

Systemic treatment approaches in HER2-negative advanced breast cancer—guidance on the guidelines

A.A. Joy MD, M. Ghosh MD,**
R. Fernandes MD,† and M.J. Clemons MD†

ABSTRACT

Despite advancements in the treatment of early-stage breast cancer, many patients still develop disease recurrence; others present with *de novo* metastatic disease. For most patients with advanced breast cancer, the primary treatment intent is noncurative—that is, palliative—in nature. The goals of treatment should therefore focus on maximizing symptom control and extending survival. Treatments should be evaluated on an individualized basis in terms of evidence, but also with full respect for the wishes of the patient in terms of acceptable toxicity. Given the availability of extensive reviews on the roles of endocrine therapy and HER2 (human epidermal growth factor receptor 2)–targeted therapies for advanced disease, we focus here mainly on treatment guidelines for the non-endocrine management of HER2-negative advanced breast cancer in a Canadian health care context.

KEY WORDS

Advanced breast cancer, metastatic breast cancer, treatment guidelines, HER2-negativity, endocrine-resistant breast cancer, chemotherapy, targeted therapy, biologic therapy

1. INTRODUCTION

Despite advancements in the treatment of early-stage breast cancer, some patients will develop distant recurrence, while others will present with *de novo* metastatic disease[1]. Recurrent metastatic or advanced breast cancers (ABCs) are defined as tumours that have spread beyond the original breast and associated lymph nodes to distant sites. Although the situations of some patients can be unique, the treatment intent in ABC patients is primarily noncurative—that is, palliative—in nature. Overall, 5-year survival rates are reported to approximate 24%[2]. However, such statistics do not take into account the various differences between patients (comorbidities and performance status, for instance), previous treatment response or tolerance, or the underlying specific breast cancer biology (for example, intrinsic subtype or cancer genetics)—all of which bear on the ultimate prognosis[3–8].

Although extension of survival can be important in the ABC setting, it should not receive sole focus, to the exclusion of all other matters. Throughout the entire ABC journey, the central role of palliation in easing the severity of symptoms (disease- or treatment-related, or both) cannot be emphasized enough. In addition to any pursuit of life extension, treatment should always include maximizing the patient's quality of life as a co-primary endpoint. The true art in the management of ABC is the maintenance of that balance (Figure 1). And while a patient's willingness to accept potential toxicity

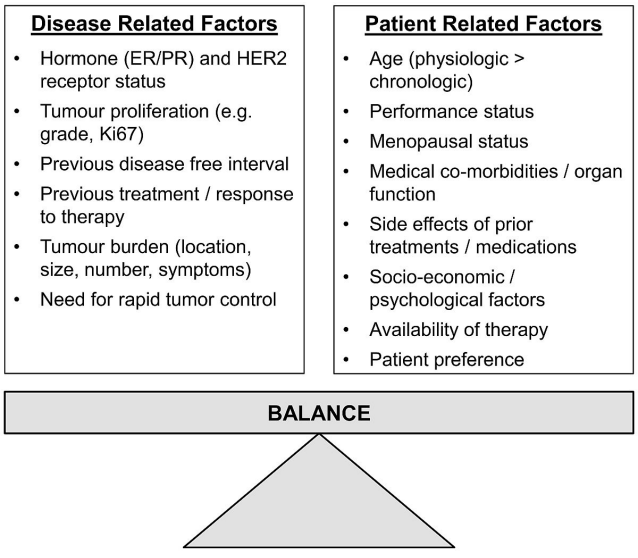

FIGURE 1 Decision factors for advanced breast cancer treatment. When choosing treatment, the clinician must balance the disease-related and patient-related factors to maximize clinical efficacy with toxicity and patient preferences. ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

can be higher in earlier-stage disease presentations, the same might not be the case in the ABC setting[9]. The actual experience (as opposed to the theoretical possibilities) of treatment-related side effects can also modify the expectations and selection of subsequent treatment accordingly. Patient engagement throughout the therapeutic journey is essential to ensure that all factors are being considered.

Here, we discuss and examine the similar, but marginally different, guideline-based approaches to ABC patients. Therapeutic choices and their associated toxicities are examined in depth, and novel therapeutics just over the horizon are addressed.

2. INTERNATIONAL TREATMENT GUIDELINES

International guidelines for the treatment of early-stage breast cancer are relatively consistent[10], but until recently, treatment for ABC has been more difficult to codify, given the heterogeneity of the patients, their disease, and the available treatment options. Canada has no national guideline for ABC management, although disparate provincial treatment guidance—from the BC Cancer Agency[11] and Cancer Care Ontario[12], for example—and various consensus statements[13] are available. The other national[14,15] and international[16,17] guidelines that are available are also not entirely in agreement with respect to treatment strategies. Recognizing this lack of international congruency of practice, the European School of Oncology created an ABC task force, which subsequently led to the establishment of the International Consensus Guidelines on ABC[18–20]. Although these oncology guidelines and consensus statements might have various nuances that are controversial[21], all nonetheless serve as useful foundational tools in clinical practice.

In the present review of the existing guidelines, we focus primarily on ABC 1[18], ABC 2[19,20], and the American Society for Clinical Oncology (ASCO) guidelines[17] pertaining to the non-endocrine management of HER2 (human epidermal growth factor receptor 2)–negative ABC. We highlight that approach to ABC management with a focus on its relevance in a Canadian health care context.

2.1 Patient Factors and a Balanced Approach

Most guidelines agree that patient-related factors are paramount in the decision-making process for the treatment of HER2-negative disease. Patients with ABC should seek to live as normal a life as possible, while maintaining (and hopefully improving) relationships with family and loved ones[22]. Oncologists more easily focus on the disease and the associated physical symptoms in the patient presenting to them[23], but many other psychological symptoms such as anxiety, depression, and insomnia then run the risk of being left unaddressed[24].

If ever a multidisciplinary review in the health care setting was needed, a review related to the management of metastatic cancer would be it. According to one study, the issues most important to patients that were either underrepresented or unmet were in the areas of psychological support and basic information about the disease (that is, prognosis and expected progress)[25]. It is therefore imperative that support services be made available to patients and their families. Even in the absence of imminent death or debilitating metastatic symptomatology, an introduction or earlier referral to palliative care specialist teams has shown outcome benefit in other metastatic cancer settings[26] and should be considered.

Realistic treatment goals and expectations should be thoroughly discussed and reinforced with patients and their families to ensure that everyone has a clear understanding about what can and cannot be reasonably achieved. When reviewing the type, duration, and regimens chosen for treatment, the patient's preferences and the balance of lifestyle and convenience factors also have to be taken into consideration. Each treatment should ideally be tailored to each individual patient. Finally, the potential roles for additional supportive care measures have to be routinely reviewed for each patient. Those measures potentially include evaluation for palliative radiotherapy for localized symptoms, analgesics for pain, antiemetics, oxygen and management of malignant pleural effusion for dyspnea, home support, and bone-targeted agents—all of which have been extensively reviewed elsewhere and are beyond the scope of the present work[27–29].

2.2 Confirmation of Metastatic Disease and Receptor Evaluation

Whenever feasible, a biopsy of the most readily accessible metastatic lesion should be performed to confirm the diagnosis and to re-evaluate the estrogen receptor (ER), progesterone receptor (PR), and HER2 status of the tumour[3,4].

Despite recent recognition of the intrinsic subtypes of breast cancer[30] and further expansion of the molecular characterization and subclassifications of breast cancer[31], there are essentially only 3 subclasses of ABC that have to be considered when making initial systemic treatment decisions in the clinical setting (Figure 2):

- Hormone receptor (HR)–positive ABC (ER- or PR-positive, or both)
- HER2-positive ABC (HER2 amplification or overexpression)
- HER2-negative ABC

The novel targeted therapeutics that have been developed and used in both HR-positive and HER2-positive ABC (Table I) are extensively reviewed

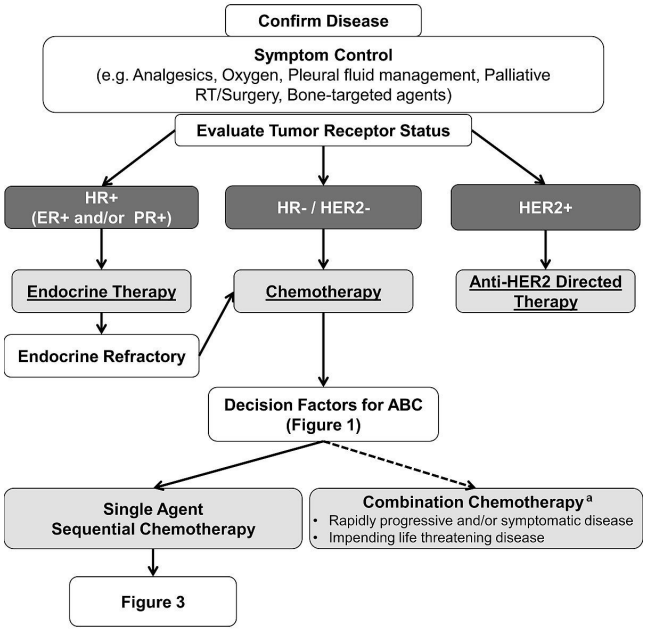

FIGURE 2 Approach to advanced breast cancer (ABC) treatment. RT = radiotherapy; HR = hormone receptor; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2. [a] Compared with single-agent chemotherapy, comes with an increased risk of treatment-related toxicity.

elsewhere[17–20,32]. Disease that is HER2-negative represents the largest and most heterogeneous ABC group because it includes both HR-positive tumours (which can be sensitive or resistant to endocrine therapy) and HR-negative tumours (that is, "basal-like" or triple-negative breast cancers)[33].

2.3 When to Initiate Chemotherapy

Timing the initiation of chemotherapy is a complex decision, with multiple variables at play (Figure 1). In the case of HR-positive HER2-negative metastatic disease, guidelines suggest that endocrine therapy, rather than chemotherapy, should be offered as standard first-line treatment, even in the presence of visceral disease. However, an exception would be the circumstance in which the disease is rapidly life-threatening or there are concerns about upfront endocrine resistance[19,20]. Making the choice requires an evaluation of disease factors, patient-related factors (for example, comorbidities), response to earlier cancer treatments, and patient preferences[34]. Clinicians will also want to make the decision in the context of earlier drug exposures and any residual dysfunction from treatment or coexisting disease. For example, in patients with prior anthracycline exposure or radiotherapy to the mediastinum, the potential risks for cardiotoxicity with subsequent treatment options have to be considered[35,36]. Pre-existing diseases such as poorly controlled diabetes or residual treatment-related toxicities such as neuropathies can significantly alter treatment choices (for example, use of taxanes) so that the patient's current symptoms are not exacerbated. Although other novel tests and assessments of molecular characteristics such as circulating tumour cells[37], circulating free tumour DNA[37], microRNA profiling[38], and *ex vivo* chemosensitivity assays[39] are currently being evaluated in the research setting, no level 1 evidence supports the *a priori* use of any routine clinical test to predict response to palliative chemotherapy. The role of such tests in current practice therefore remains limited.

TABLE I Therapeutic agents for hormone receptor–positive and HER2-positive advanced breast cancer management

Therapy type		
Endocrine	*Anti-HER2–directed*	*Other targeted*
Ovarian suppression	Monoclonal antibody: trastuzumab, pertuzumab	mTOR inhibitor: everolimus
Selective ER modulator: tamoxifen	Antibody–drug conjugate: T-DM1[a]	CK (4/6) inhibitor: palbociclib (phase II)
Aromatase inhibitor: anastrozole, exemestane, letrozole	TKI: lapatinib	
Selective ER downregulator: fulvestrant		

[a] Trastuzumab emtansine.
HER2 = human epidermal growth factor receptor 2; ER = estrogen receptor; TKI = tyrosine kinase inhibitor; mTOR = mammalian target of rapamycin; CK = cyclin-dependent kinase.

2.4 Polychemotherapy Versus Monotherapy

Despite the suggestion in one systematic review that, compared with monotherapy, polychemotherapy is associated with a higher response rate (RR), a longer time to progression (TTP), and a modest improvement in overall survival (OS), considerable controversy still surrounds this topic[40]. The main critique of the findings is that any observed increase in OS could be a result of the lack of availability of the experimental agent in the control arm of the reviewed studies. That critique is further corroborated by the absence of an OS benefit in four other randomized studies in which all treatment arms had access to all drugs[41–44].

A 2013 update examined twelve trials (including 2317 patients who took part in randomized controlled trials) examining combination chemotherapy compared with the same drugs given sequentially in women with metastatic breast cancer in the first-, second-, and third-line settings. A higher RR was noted in the combination arm, but no significant difference in OS was observed[45]. Current guidelines

therefore do not support the use of upfront combination chemotherapy for all ABC patients; instead, they advocate for the use of sequential single-agent therapy until disease progression (Figure 3)[14,15,17,46]. An exception can be made for patients with clinically rapid tumour progression and acute life-threatening or symptomatic visceral metastatic disease[46]. More importantly, all studies and guidelines agree that polychemotherapy comes at greater patient cost in terms of increased toxicity. That increased toxicity always has to be kept in mind given the initial goals and intent of treatment in the ABC setting.

Notably, a systematic review of 189 trials evaluating the concurrent use of chemotherapy and endocrine therapy found that the concurrent approach did not appear to offer any survival advantage and, compared with the sequential use of those treatment modalities, might in fact have reduced treatment efficacy[47].

2.5 Continuous Versus Intermittent Chemotherapy

A meta-analysis of eleven randomized clinical trials evaluating the duration of first-line chemotherapy for ABC demonstrated that longer treatment is associated with a significant benefit in progression-free survival (PFS) and a trend toward improved OS. As a result, it was recommended that each therapy be maintained until maximum disease control or limiting toxicity was observed[48]. Subsequently, a phase III study compared first-line gemcitabine–paclitaxel chemotherapy administered until disease progression with the same regimen administered for 6 cycles[49]. Benefits in PFS, OS, and quality of life were again noted in the group that received treatment until disease progression.

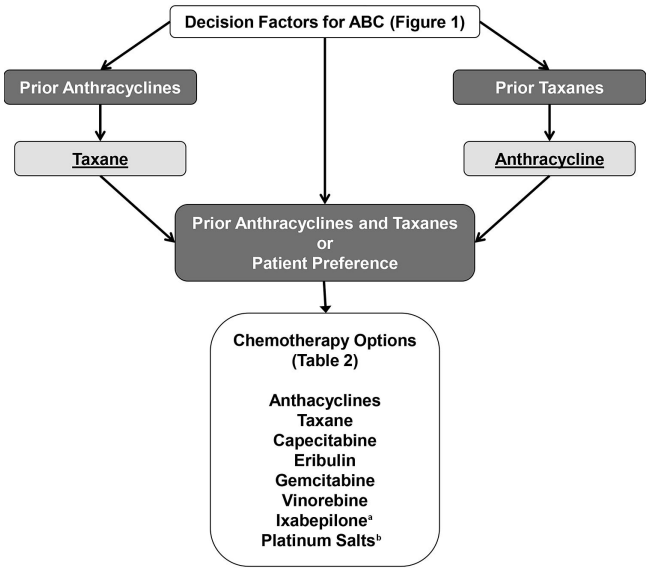

FIGURE 3 Single-agent sequential chemotherapeutic choices in advanced breast cancer (ABC). [a] Not funded in Canada. [b] Potential use in BRCA*-associated or triple-negative breast cancer.*

However, guidelines balance that evidence by noting that the duration of treatment, the number of chemotherapy regimens, and the decision to stop therapy should be tailored to the individual patient.

In the clinical setting, given that quality of life is paramount, "chemotherapy holidays" or treatment breaks are often initiated for increased patient satisfaction. The ASCO guidelines further support that sentiment, recognizing that there is a balance to be achieved between continuing treatment to maintain disease control and coping with progressing adverse effects, and that managing the balance requires continuous dialogue between doctor and patient[17]. When making the decision to take a break, the clinician has to keep in mind—and reassure the patient—that (in the absence of overt disease progression while on treatment) the therapy is merely being put on hold for a set amount of time and is not being discontinued altogether.

3. CHEMOTHERAPY OPTIONS

With respect to chemotherapy treatment options (Table II), most groups support treatment consisting of anthracycline or taxane up front or make no specific recommendation based on the evidence reported[50]. The ABC 1 guideline states that no available data support an optimal sequence of therapies, because very few monotherapy agents have demonstrated an OS benefit in the metastatic setting. The guideline from ASCO also states that no clear evidence suggests the superiority of one drug or regimen from among the various available second-line chemotherapeutic options.

Practically speaking, capecitabine is a common subsequent treatment choice for patients with prior anthracycline and taxane exposure[51,52]. In patients with prior exposure to anthracycline, taxane, and capecitabine, there is evidence for treatment with eribulin[53,54] or ixabepilone[55,56]. In patients who prefer to avoid or reduce the risk of alopecia, capecitabine, vinorelbine, or gemcitabine can be chosen.

All chemotherapies have varying risks of fatigue, emesis, alopecia, gastrointestinal effects (mucositis, diarrhea), and cytopenias (anemia, thrombocytopenia, leucopenia). Although systemic treatment options for ABC were previously reviewed in this journal[57], an update for HER2-negative ABC that addresses additional considerations follows.

3.1 Anthracycline and Anthracenedione

Historically, anthracycline chemotherapy (doxorubicin, epirubicin) was considered to be the first-line treatment in ABC. Response rates in anthracycline-naïve patients are reported to be in the 25%–50% range[58–61]. Prior anthracycline exposure, including evaluation of total cumulative dose and other cardiac risk factors (for example, coronary

artery disease, prior myocardial infarction, prior mediastinal radiotherapy) necessitate a baseline review of cardiac ejection fraction and monitoring thereafter[62]. Although cardiotoxicity (acute and chronic) remains a challenge, strategies such as prolonged infusion, structural drug modifications (for example, mitoxantrone), liposomal encapsulation, and concomitant administration of cardioprotective drugs (dexrazoxane, for instance) have been devised.

3.2 Taxanes

Taxanes are a cornerstone drug in the treatment of HER2-negative ABC, with available evidence for their use either before or after anthracycline-based chemotherapy. A 2005 meta-analysis from the Cochrane Collaboration noted that when all trials are considered, taxane-containing regimens appear to improve OS, TTP, and overall response in women with

TABLE II Common chemotherapeutic agents used in the management of HER2-negative advanced breast cancer

Agent	*Toxicity*	*Special considerations*
Anthracycline Epirubicin Doxorubicin	Cardiotoxicity Venous irritation[a]	Evaluate baseline cardiac risk factors Varying lifetime cumulative dosing Review need for ongoing cardiac monitoring Liposomal doxorubicin is a potentially less cardiotoxic agent
Anthracenedione Mitoxantrone		Evaluate need for a central line[a] Consider for re-use if >1 year of prior adjuvant therapy
Taxane Docetaxel Paclitaxel Nab-paclitaxel	Allergic reactions[b] Neuropathy Taxane acute-pain syndrome Peripheral edema	Hypersensitivity prophylaxis[b] required (except nab-paclitaxel) Consider for re-use if >1 year of prior adjuvant therapy
Capecitabine	Palmar-plantar erythrodysesthesia (hand–foot syndrome) Stomatitis, diarrhea Rare coronary vasospasm	Evidence after anthracycline or taxane exposure Minimal alopecia, minimal nausea Can be used in mild and moderate liver dysfunction
Eribulin	Peripheral neuropathy Liver dysfunction	Minimal alopecia Evidence after anthracycline, taxane, or capecitabine exposure
Gemcitabine	Rare thrombotic microangiopathy	Minimal alopecia, minimal nausea Can be used in renal dysfunction
Vinorelbine	Neuropathy Drug fever Tumour pain	Minimal nausea, minimal alopecia Oral formulation not available in North America
Ixabepilone[c]	Peripheral neuropathy Fatigue Neutropenia	Evidence after anthracycline, taxane, or capecitabine exposure
Platinum salts Cisplatin Carboplatin	Peripheral neuropathy, ototoxicity, nephrotoxicity Arterial thromboembolic disease	Can consider earlier use in triple-negative or known *BRCA* mutation–positive disease

[a] Specific to epirubicin.
[b] Specific to docetaxel and paclitaxel.
[c] Not currently funded for use in Canada.

metastatic breast cancer[63]. Another meta-analysis found that, although there are potential differences in RR and PFS, taxanes are equivalent to anthracyclines (either as single agents or in combination) in terms of OS benefit[64].

The taxanes that are indicated for clinical use mainly in breast cancer are paclitaxel, docetaxel, and nanoparticle albumin-bound paclitaxel ("nab-paclitaxel")[65]. Paclitaxel- and docetaxel-based regimens have comparable efficacy in patients with ABC. However, weekly paclitaxel-based regimens have been associated with less toxicity and better tolerability, which is of particular relevance in vulnerable individuals, including older or frailer patient populations[66]. The common side effects of taxanes include peripheral neuropathy, taxane acute-pain syndrome, fluid retention, stomatitis, alopecia, myalgias, and arthralgias. Clinically relevant hypersensitivity reactions also necessitate the use of antihistamine and steroid premedication (except with the nab-paclitaxel formulation).

3.3 Capecitabine

Capecitabine is an oral prodrug of 5-florouracil and should therefore be avoided in patients who have previously exhibited hypersensitivity to 5-flourouracil or who have a known dihydropyrimidine dehydrogenase deficiency. One of the main advantages of capecitabine is that, being an oral drug, it allows for an additional degree of patient convenience with respect to medication administration.

The efficacy of capecitabine in ABC was first established in a phase II study in patients who had previously received either anthracycline, taxane, or combined therapy[51]. In women with such prior exposures, the RR was 20%, with a median response duration of 8.3 months. Capecitabine has also been studied in the first-line HER2-negative ABC setting and has demonstrated high clinical activity, with an acceptable tolerability profile[67,68]. In a meta-analysis, capecitabine-based chemotherapy was subsequently shown to be at least as effective as other non-capecitabine chemotherapy regimens in the ABC setting and potentially better tolerated overall[69]. In anthracycline-treated, taxane-naïve ABC patients, the combination of capecitabine and docetaxel was shown to be superior to docetaxel alone in a phase III setting[70]. Combination treatment was associated with improvements in TTP and OS, but at the cost of significant additional toxicity (71% vs. 49% grade 3 toxicities). Moreover, the OS benefit has been questioned, given the lack of crossover and comparison of that strategy with sequential single-agent treatment. The combination of capecitabine and docetaxel is therefore not routinely used in clinical practice.

The main toxicities with capecitabine include palmar–plantar erythrodysesthesia ("hand–foot syndrome"), diarrhea, and stomatitis. Compared with other standard chemotherapies, capecitabine is notable for being associated with lower rates of nausea and emesis and a low incidence of significant myelosuppression. Rare (<0.1%) but serious and potentially life-threatening side effects of capecitabine use include coronary vasospasm and cardiac arrhythmias; caution is therefore advised in patients with clinically significant cardiac concerns[71]. Capecitabine is extensively metabolized in the liver and excreted primarily by the kidneys, and so caution is needed in patients who have known renal dysfunction or who are at high risk for renal dysfunction (elderly patients). Capecitabine has also been studied and can be used safely in patients with mild-to-moderate hepatic dysfunction[72].

3.4 Eribulin Mesylate

Eribulin belongs to the halichondrin class of non-taxane inhibitors of microtubule dynamics. Unlike other anti-microtubule agents (taxanes and vinca alkaloids), eribulin inhibits the growth phase of microtubules (without affecting the shortening phase) and also sequesters tubulin into nonfunctional aggregates. It has demonstrated activity even in taxane-resistant cells[73].

The EMBRACE trial, an open-label phase III study in 762 patients, examined eribulin compared with physician's choice of treatment in heavily pretreated ABC (including anthracyclines and a taxane)[74] and found that the eribulin-treated patients experienced a significant increase in OS (13.1 months vs. 10.6 months; hazard ratio: 0.81; $p = 0.041$). A larger phase III open-label study of eribulin compared with capecitabine in 1102 ABC patients previously treated with anthracyclines and taxanes confirmed activity with eribulin, but noted no improvement over capecitabine in terms of RR, TTP, or OS[75]. Eribulin has been approved for use in Canada and the United States, but there are concerns about its cost-effectiveness[76]. The most common adverse effects associated with eribulin include fatigue, neutropenia, peripheral neuropathy, and QT/QTc prolongation[73].

3.5 Gemcitabine

Gemcitabine is a pyrimidine nucleoside analog that interferes with DNA synthesis and induces apoptosis. When used in the ABC setting as a single-agent, its RR ranges from 14% to 37% in the chemotherapy-naïve population and from 12% to 30% in patients with prior anthracycline and taxane exposure[77]. The main clinical benefit of gemcitabine was demonstrated in a phase III setting in which it was given in combination with paclitaxel and, compared with single-agent paclitaxel, was associated with a higher RR (41.4% vs. 26.2%), longer TTP (6.1 months vs. 4 months), and improved OS (18.6 months vs. 15.8 months)[78]. Other drug combinations have also been evaluated with varying degrees of success. Compared with

single-agent vinorelbine, vinorelbine–gemcitabine was associated with improved PFS in ABC, but that improvement did not translate into improved OS[79]. Compared with capecitabine–docetaxel, gemcitabine–docetaxel was noted to be as effective, with less hematologic toxicity[80]. As expected, toxicity was higher with combination chemotherapy than with single-agent treatment.

Gemcitabine as a single agent is relatively well tolerated overall, with asthenia and transient 'flu-like symptoms being the most notable adverse effects. Gemcitabine does not cause a great deal of alopecia or nausea, which can be of particular interest to some patients. In addition to the standard chemotherapy-induced cytopenias, one of the rarer but noteworthy side effects of gemcitabine is that it has been associated with chemotherapy-induced thrombotic microangiopathy (0.25%–0.4%)[81]. The drug is excreted primarily by the kidneys, and it therefore has to be used with caution in patients with renal dysfunction. Gemcitabine can also cause transient transaminitis, but no dose adjustment is typically required with fixed dosing[82,83].

3.6 Vinorelbine

Vinorelbine is a semisynthetic vinca alkaloid that targets microtubules, leading to promotion of cellular apoptosis. It is metabolized primarily in the liver, and transient elevations in liver enzymes can be observed. It is generally well tolerated intravenously, with minimal nausea and alopecia. Oral formulations are not currently available for use in North America. Phase II trials of vinorelbine have demonstrated varied RRs in the ABC setting (25%–47%), depending on the line of therapy[84,85].

The main side effects of vinorelbine are cytopenias. Gastrointestinal toxicity is seen particularly if the drug is taken orally. Vinorelbine has also occasionally been reported to cause pain, primarily abdominal. Rarer still is vinorelbine-induced pain in the tumour-containing tissue, which can be particularly distressful to patients if they are not advised of that possibility before infusion[86].

3.7 Ixabepilone

Ixabepilone is an epothilone B analog that causes microtubule stabilization, mitotic arrest, and apoptosis. Ixabepilone has been evaluated as a single agent[56] and in combination with capecitabine in patients previously treated with anthracycline and taxane therapy[87–89]. A phase III trial noted that, compared with capecitabine alone, ixabepilone–capecitabine was associated with improved RR (43% vs. 29%) and PFS (6.2 months vs. 4.2 months), but no improvement in OS (16.4 months vs. 15.6 months)[88]. Grade 3 or 4 neuropathy occurred in 24% of patients treated with combination therapy, but was reported to be reversible. Myelosuppression, primarily neutropenia, is also a common side effect. Ixabepilone is not currently approved for ABC treatment in the Canadian health care context.

4. NOVEL AGENTS

Many novel agents have been evaluated in the HER2-negative ABC setting, including antibodies (bevacizumab) and tyrosine kinase inhibitors (sunitinib, sorafenib, apatinib, cediranib) against vascular endothelial growth factor (VEGF)[90–94]; antibodies against epidermal growth factor receptor (cetuximab, panitumumab)[95–97]; poly ADP–ribose polymerase inhibitors (iniparib)[98]; and anti-VEGF receptor antibodies (ramucirumab)[99]—all with disappointing results so far.

4.1 Bevacizumab

Bevacizumab is a monoclonal antibody directed against circulating VEGF whose routine role in the management of HER2-negative ABC remains controversial. When added to first-line chemotherapy in ABC patients, it was shown to be associated with an increased RR and prolonged PFS in three randomized phase III trials: Eastern Cooperative Oncology Group 2100, AVADO, and RIBBON-1[100–103]. The ABC 1 and 2 guidelines comment on the absence of known predictive biomarkers for the modest and limited PFS benefit (with no OS improvement) of bevacizumab combined with taxanes. At this time, the ASCO guideline takes a view of bevacizumab that is similar to that for combination chemotherapy: that is, monotherapy is preferable, but in view of improved RR and disease control, single-agent chemotherapy can be combined with bevacizumab in the presence of immediately life-threatening disease or severe symptoms. The potential harms that are uniquely associated with bevacizumab include bleeding, hypertension, proteinuria, gastrointestinal perforation, and thromboembolic disease. Given the totality of the evidence and the drug costs, bevacizumab is not approved for the treatment of ABC in the Canadian health care context. Other strategies to target angiogenesis through the use of so-called metronomic therapies are still being evaluated[104,105].

5. SPECIAL CONSIDERATIONS

5.1 Triple-Negative Breast Cancer

Triple-negative breast cancer (TNBC) is defined by the lack of immunohistochemical expression of ER, PR, and HER2, and represents approximately 16% of all breast cancers. This heterogeneous group of breast cancers exhibits a wide variety of molecular aberrations[106]. Some have basal-like features with high genomic instability and poorer prognosis than for other distinct molecular phenotypes with better prognosis.

Unlike ER- and HER2-positive disease, TNBC has no targeted treatments as yet, and whether treatments that interfere with each of the individual clonal genotypes in these tumours can be developed is questionable. Subset analyses of some trials have shown benefit with bevacizumab[107], eribulin[75], and ixabepilone[108], but the ASCO guideline currently states that chemotherapy regimens should not be specifically tailored to various breast cancer subtypes (including TNBC) because of the absence of evidence proving differential efficacy. Interest in the role of poly ADP–ribose polymerase inhibitors in the management of TNBC is increasing[109,110], but standard treatments still include conventional chemotherapies such as anthracyclines and taxanes[6,111]. However, the ABC 2 guideline makes specific mention of the potential use of platinum salts in the setting of *BRCA*-associated triple-negative or endocrine-resistant ABC previously treated with anthracycline and taxane[8].

5.2 Platinum Salts and Breast Cancer Gene Mutations

Theoretically, the use of platinum salts (cisplatin, carboplatin) causing intra- and inter-strand crosslinks (preventing DNA, RNA, and protein synthesis) should have preferential effects in tumours deficient in DNA repair mechanisms (for example, tumours without active *BRCA1/2*). However, the efficacy of platinum salts in the general triple-negative ABC population has not yet been clearly demonstrated[112], and indeed, the only prospective trial reported to date showed no evidence that carboplatin was superior to docetaxel in the management of unselected metastatic TNBC[113]. However, in an unplanned smaller subgroup of known *BRCA* mutation carriers, higher response rates were observed in the carboplatin treatment arm. As with most platinum agents, specific side effects that must be monitored include cytopenias, nephrotoxicity, peripheral neuropathy, and ototoxicity.

5.3 Therapeutic Strategies to Potentially Delay Palliative Chemotherapy Initiation

5.3.1 Inhibitors of the Mammalian Target of Rapamycin

Although not yet given as a standard combination with chemotherapy in HER2-negative ABC patients, inhibitors of mTOR (the mammalian target of rapamycin) such as everolimus have also been examined and are increasingly used as a bridge to delay the start of palliative chemotherapy.

The BOLERO-2 study examined the addition of everolimus to exemestane in the postmenopausal HR-positive ABC setting[114]. In the interim analysis of that randomized phase III study (724 patients), recipients of everolimus plus exemestane (2:1) experienced an observable improvement in PFS over and above that seen with exemestane alone (6.9 months vs. 2.8 months; hazard ratio for progression or death: 0.43; $p < 0.001$). In central assessment, that finding translated into a median PFS of 10.6 months and 4.1 months respectively (hazard ratio: 0.36; $p < 0.001$). The most common grade 3 or 4 adverse events were stomatitis, anemia, dyspnea, hyperglycemia, and pneumonitis. With longer follow-up, the OS trend continued to favour the combination: median survival in the everolimus and exemestane group was 31 months (a 4.4-month absolute improvement in OS compared with survival in the exemestane-only group); however, the difference did not reach statistical significance[115].

The idea of delaying the onset of chemotherapy in ABC is particularly appealing, and with the safety of the everolimus–exemestane combination being demonstrated in a subset of elderly patients[116], its use should still be weighed against the potential side effects, the cost, and the additional observation required over and above that with standard endocrine therapy alone[117]. However, to obtain more balanced information about the benefits of this combination relative to its toxicity, population studies in the real-world (non-trial) setting are urgently needed[118].

5.3.2 Fulvestrant

Fulvestrant, a serum ER downregulator, acts as a pure estrogen antagonist, enhancing proteasomal degradation of the ER[119]. Although there is evidence that fulvestrant can delay the progression of breast cancer (and subsequent use of palliative chemotherapy) in the ER-positive ABC setting, that evidence is mixed. Fulvestrant's main benefits appear to be linked to combined use with aromatase inhibitors: one study documented significant outcome improvements[120], but another similarly designed study (with a more heavily endocrine pre-treated population) did not[121]. When fulvestrant is used as a single agent, the higher loading dose regimen seems to be the most beneficial in terms of efficacy[122]. The main toxicities of fulvestrant are not unexpected and include hot flashes, arthralgias, gastrointestinal discomfort, and injection site reactions. In the Canadian health care context, the use of fulvestrant is significantly limited because of a lack of universal funding (associated with concerns about cost-effectiveness).

5.3.3 Cyclin-Dependent Kinase Inhibitors

Novel oral cyclin-dependent kinase (CDK4/6) inhibitors are also emerging as potentially viable adjuncts to endocrine therapy in the effort to further delay initiation of palliative chemotherapy. Palbociclib is the agent furthest along in development. In an open-label phase II trial, it demonstrated significant statistical and clinical outcome improvements when added to first-line endocrine therapy with letrozole[123]. Median PFS was reported to be 20.2 months in the combination group compared with 10.2 months in the letrozole-only group (hazard ratio: 0.488;

one-sided $p = 0.0004$). A unique side effect observed with the addition of palbociclib was asymptomatic leucopenia. Given those findings, the U.S. Food and Drug Administration granted breakthrough therapy designation to palbociclib while awaiting the results of the completed phase III TRIO-022 trial.

6. SUMMARY

The care of patients with ABC remains a common clinical challenge. Here, we have tried to bring together the salient features of the key international and national guidelines. The lack of a formal Canadian consensus statement concerning the management of HER2-negative ABC is likely attributable in part to the fact that administration and delivery of health care services is the responsibility of each province or territory, guided by the provisions of the *Canada Health Act*. It also likely reflects the fact that, because of considerable tumour, patient, and treatment heterogeneity, no one "optimal" management strategy can be delineated. Patient preferences and clinical factors continually need to be reconsidered in treatment decisions.

And so the question remains: What will drive the future care of ABC patients in this era of so-called personalized medicine? The answers will be especially important because trial results for many targeted therapies in the HER2-negative setting have, on the whole, been disappointing[9,109,124,125]. While hoping for future novel therapies, use of existing therapies still has to be optimized, and in order for that optimization to happen, major changes are needed in current regulatory processes, which were designed for the development of new agents (see https://clinicaltrials.gov/ct2/show/NCT02173262). Better tools (genomic or otherwise) to predict who will and will not benefit from a particular treatment are a must. And although widespread evidence that the genomics era has improved treatment choices for breast cancer patients has not as yet materialized, laboratory studies remain an essential component of all clinical trials[126]. Better tools are also needed to identify patients at greatest risk of treatment-related toxicities—for example, nausea and vomiting[127–129], sexual dysfunction[130,131], and neuropathy[132]. By optimizing the current therapeutic index in this manner, treatment and outcomes for ABC patients will hopefully be greatly improved.

7. ACKNOWLEDGMENT

We gratefully acknowledge Larissa Vos for manuscript editing assistance.

8. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: AAJ has previously provided advisory board services to Roche, Novartis, Pfizer, Eisai, and AstraZeneca, and has received educational meeting travel support from Novartis and AstraZeneca (all outside of the submitted work). MG and RF have no conflicts to declare. MJC has previously received (non-self-compensated) meeting support from Amgen and Novartis, and has received educational meeting travel support from Novartis (all outside of the submitted work).

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Correspondence to: Mark Clemons, Division of Medical Oncology, The Ottawa Hospital Cancer Centre, Box 912, 501 Smyth Road, Ottawa, Ontario K1H 8L6.
E-mail: mclemons@toh.on.ca

* Department of Oncology, Division of Medical Oncology, University of Alberta, Cross Cancer Institute, Edmonton, AB.
† Division of Medical Oncology, University of Ottawa and The Ottawa Hospital Research Institute, The Ottawa Hospital Cancer Centre, Ottawa, ON.