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PRACTICE GUIDELINE

Adjuvant chemotherapy for early female breast cancer: a systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline

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ABSTRACT

Background

The Program in Evidence-Based Care (PEBC) of Cancer Care Ontario recently created an evidence-based consensus guideline on the systemic treatment of early breast cancer. The evidence for the guideline was compiled using a systematic review to answer the question "What is the optimal systemic therapy for patients with early-stage, operable breast cancer, when patient and disease factors are considered?"

The question was addressed in three parts: cytotoxic chemotherapy, endocrine treatment, and human epidermal growth factor receptor 2 (HER2)–directed therapy.

Methods

For the systematic review, the MEDLINE and EMBASE databases were searched for the period January 2008 to May 2014. The Standards and Guidelines Evidence directory of cancer guidelines and the Web sites of major oncology guideline organizations were also searched. The basic search terms were "breast cancer" and "systemic therapy" (chemotherapy, endocrine therapy, targeted agents, ovarian suppression), and results were limited to randomized controlled trials (RCTs), guidelines, systematic reviews, and meta-analyses.

Results

Several hundred documents that met the inclusion criteria were retrieved. The Early Breast Cancer Trialists' Collaborative Group meta-analyses encompassed many of the RCTs found. Several additional studies that met the inclusion criteria were retained, as were other guidelines and systematic reviews. Chemotherapy was reviewed mainly in three classes: anti-metabolite–based regimens (for example, cyclophosphamide–methotrexate–5-fluorouracil), anthracyclines, and taxane-based regimens. In general, single-agent chemotherapy is not recommended for the adjuvant treatment of breast cancer in any patient population. Anthracycline–taxane-based polychemotherapy regimens are, overall, considered superior to earlier-generation regimens and have the most significant impact on patient survival outcomes. Regimens with varying anthracycline and taxane doses and schedules are options; in general, paclitaxel given every 3 weeks is inferior. Evidence does not support the use of bevacizumab in the adjuvant setting; other systemic therapy agents such as metformin and vaccines remain investigatory. Adjuvant bisphosphonates for menopausal women will be discussed in later work.

Conclusions

The results of this systematic review constitute a comprehensive compilation of the high-level evidence that is the basis for the 2014 PEBC guideline on systemic therapy for early breast cancer. Use of cytotoxic chemotherapy is presented here; the results addressing endocrine therapy and HER2-targeted treatment, and the final clinical practice recommendations, are published separately in this supplement.

KEY WORDS

Early breast cancer, systemic treatment, chemotherapy, adjuvant, cytotoxic, drug therapy

1. INTRODUCTION

The outcomes of patients with early breast cancer have been improved with the use of adjuvant systemic treatments[1], which include chemotherapy, endocrine

The complete version of this guideline will be posted on the Cancer Care Ontario Web site at https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/.

Supplemental material available at http://www.current-oncology.com.

therapy, and targeted agents (trastuzumab) for eligible subgroups of patients. Several clinical practice guidelines make recommendations for the selection of adjuvant systemic therapy based on primary evidence or consensus (or both). Still, practice is variable in the Ontario health care setting[2].

The Program in Evidence Care (PEBC), together with the Breast Cancer Disease Site Group of Cancer Care Ontario (CCO), is charged with developing evidence-based practice guidelines pertaining to breast cancer care. Over many years, the PEBC has created clinical practice guidelines addressing various aspects of adjuvant systemic therapy for early breast cancer. The creation of an updated, comprehensive guideline pertaining to all aspects of systemic therapy for early breast cancer was recently identified as a priority. The resulting guideline is most applicable to the Canadian (and particularly Ontario) setting, but any high-resource health care context might find the guideline to be applicable. A systematic review of the evidence was conducted to inform the guideline recommendations. Thereafter, expert consensus was used to validate compiled recommendations before creation of the final guideline. The recommendations and a summary of the consensus process can be found in this supplement and on the CCO Web site[3].

The present article outlines the evidence base used for the adjuvant chemotherapy recommendations. It can be used as a standalone reference that reviews the extensive data on this important area of breast cancer care. The evidence reviews for endocrine therapy in hormone receptor–positive cancer and for biologic or targeted therapy (trastuzumab) are published elsewhere in this supplement.

Early breast cancer was defined primarily as invasive cancer of stage I–IIA (T1N0–1, T2N0). Studies describing cancers as operable or stages I–IIIA were also included (see the Methods section).

Although several of the systemic therapies discussed here can be considered in the neoadjuvant setting, this review focuses on trials with disease-free (DFS) or overall survival (OS) as endpoints; it thus excludes several neoadjuvant trials that used only pathologic complete response as the primary endpoint.

2. METHODS

One systematic review was conducted for all systemic therapies, and therefore the search strategy and subsequent general results apply to chemotherapy, hormonal therapy, and targeted therapy combined.

2.1 Literature Search Strategy

The literature in the MEDLINE and EMBASE databases was searched for the period January 2008 to March 5, 2012; the search was later updated to May 12, 2014. To be selected, publications had to include terms related both to breast cancer and to systemic therapy (chemotherapy; endocrine therapy, including ovarian suppression; and targeted agents). The search was limited to randomized controlled trials (RCTs), guidelines, systematic reviews, and meta-analyses. Although systemic agents were, in most cases, indexed to terms such as "adjuvant therapy," individual chemotherapy agents or regimens were also included. The full database search strategy is presented in Supplementary Appendix 1. Guidelines were also located in the Standards and Guidelines Evidence directory of cancer guidelines and at the Web sites of organizations known to produce oncology-related guidelines [National Institute for Health and Clinical Excellence (United Kingdom), Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Comprehensive Cancer Network (United States), National Health and Medical Research Council (Australia), New Zealand Guidelines Group]. Evidence was selected and reviewed by one member (GGF) of the PEBC Early Breast Cancer Systemic Therapy Working Group; all authors provided input on the included results once initial screening was complete.

2.2 Study Selection Criteria: RCTs

Clinical trials were included if they evaluated at least 100 female patients with early-stage breast cancer randomized to at least 1 systemic agent and if they used survival (generally OS or DFS) as one of the primary or secondary outcomes. Studies had to describe the patients as having early or operable breast cancer, or allow the population characteristics to be ascertained from the methods or results. Trials evaluating patients with stages IIB and IIIA cancers were included only if stage IIA patients were also part of the population and if at least half the patients had stages I–IIB cancer. When only tumour size and nodal status were reported, stage was estimated according to the *AJCC Cancer Staging Manual,* 6th edition[4,5], to decide whether the study met the inclusion criteria. Studies with mostly stage III or locally advanced tumours were excluded, as were studies that focused on stage IV (metastatic) breast cancer, noninvasive cancers (ductal carcinoma *in situ* or lobular carcinoma *in situ*), or treatment of cancer relapse. Trials primarily evaluating antiemetic drugs, erythropoiesis-stimulating agents, or autologous hematopoietic stem-cell transplantation were excluded. Studies of bisphosphonates to prevent metastasis or cancer recurrence were included; studies evaluating any bone-targeted agents to treat bone metastasis were excluded. Studies were eliminated if they were not relevant to the current practice setting in Ontario (for example, they evaluated older drugs no longer used), reported only exploratory analyses or correlations, or did not report survival endpoints.

2.3 Other Publication Selection

Clinical practice guidelines were considered relevant if the recommendations were based on a systematic review of the literature or were described as evidence-based consensus. Systematic reviews and meta-analyses were also evaluated. Quality of the systematic reviews and meta-analyses was assessed using the AMSTAR tool[6]. For RCTs, study or trial design and quality characteristics were assessed; however, RCTs included in high-quality systematic reviews and meta-analyses were not separately appraised. Relevant RCTs cited in systematic reviews, guidelines, or meta-analyses were compared with those found in the MEDLINE and EMBASE database search results. Any studies that had not been captured in the search were retrieved if deemed important for further evaluation. Studies whose long-term follow-up data were pending and studies referenced in abstract form only were targeted for further literature review to retrieve any updated documents. Referenced trials from before 2008 were also retrieved when deemed appropriate. Abstracts presented at major conferences were initially searched as part of the grey literature; however, most of the relevant studies were found to be included in the updated EMBASE database results, and conference proceedings were therefore not explicitly included.

3. RESULTS AND DISCUSSION

3.1 Overall Literature Search Results

After removal of duplicate citations, the searches in MEDLINE and EMBASE located 14,444 publications (11,435 RCTs and 3009 systematic reviews, guidelines, or meta-analyses). Of the guidelines, systematic reviews, and meta-analysis, 287 were deemed to be of relevance; most were reviewed to locate RCTs not captured in the database search. In addition, those publications helped to inform patient selection criteria for the guideline recommendations. Approximately 50 trials (chemotherapy, hormonal therapy, or targeted therapy) found in MEDLINE or EMBASE had not been cited in the other guidelines and systematic reviews. Ultimately, 516 trial publications (from the database results and targeted searching) were extracted; 221 were pertinent to cytotoxic chemotherapy.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) is an international collaboration that was formed in 1985 to evaluate studies of early (operable) breast cancer. Every 5 years, the group completes an individual patient meta-analysis (considered the highest level of evidence)[7] from all RCTs worldwide on aspects of early breast cancer therapy. Several of the EBCTCG meta-analyses[8–12] are referenced in this series of systematic reviews. Given the rigorous methodology and comprehensiveness of the EBCTCG analyses, many of the individual RCTs were not retrieved for data extraction or quality appraisal; however, some limitations of the EBCTCG data are discussed.

Individual RCTs and the guidelines, reviews, and meta-analyses were sorted into studies of chemotherapy, endocrine therapy for hormone receptor–positive cancers, and targeted therapy for human epidermal growth factor receptor 2 (HER2)–positive cancers. Chemotherapy trials were further subdivided into major cytotoxic classes: anti-metabolites, including CMF [cyclophosphamide–methotrexate–5-fluorouracil)], anthracyclines, taxanes, and other agents. The major endocrine therapies were tamoxifen, aromatase inhibitors (AIs), and ovarian suppression (by luteinizing hormone–releasing hormone agonists) or ovarian ablation (by surgery or radiation). For HER2-positive cancers, trastuzumab was the only biologic or targeted agent that was found to have sufficient evidence to be included in the final guideline recommendations. The results of the chemotherapy studies are discussed in this systematic review; results pertaining to endocrine treatments and trastuzumab are published elsewhere in this supplement.

3.2 Antimetabolites and Anthracyclines

The EBCTCG analysis published in 2005 reported on RCTs of adjuvant chemotherapy or hormonal therapy that began by 1995[9]. Chemotherapy trials during that period primarily compared CMF with no treatment or with anthracycline-based chemotherapy such as FAC (5-fluorouracil–doxorubicin–cyclophosphamide) or FEC (5-fluorouracil–epirubicin–cyclophosphamide). The EBCTCG meta-analyses[8,9] include most of the trials that have been conducted for CMF and anthracyclines. Because most of those RCTs are older trials, most are complete, with mature data. Extended long-term follow-up or exploratory analysis of patient or disease subgroups are pending in a few studies. However, those results are not expected to change the overall conclusions of the meta-analyses.

The EBCTCG review published in 2005[9] concluded that 6 months of FAC or FEC chemotherapy reduced the annual breast cancer death rate by approximately 38% in patients less than 50 years of age and by 20% in patients 50−69 years of age at diagnosis. Those regimens are significantly more effective than classic CMF (with oral cyclophosphamide, which is known to be superior to intravenous cyclophosphamide in this regimen). The most recent EBCTCG analysis[8] concluded that 4 cycles of AC (doxorubicin–cyclophosphamide) and 6 cycles of classic CMF are equivalent, but that anthracycline-based regimens such as cyclophosphamide–doxorubicin–5-fluorouracil or CEF (cyclophosphamide–epirubicin–5-fluorouracil), in which the cumulative dose is higher than that achieved with 4 cycles of AC, are superior to classic CMF. Compared with no chemotherapy, the reduction in mortality was greater with cyclophosphamide–doxorubicin–5-fluorouracil (relative risk 0.64) than

with 4 cycles of AC (relative risk 0.78) or with 6 cycles of classic CMF (relative risk 0.76). The meta-analysis of all regimens based on anthracyclines or taxanes (or both) found that age, nodal status, tumour size or grade, estrogen receptor status, and tamoxifen use had little effect on proportional risk reductions.

Relevant studies found in the literature search are summarized in Supplemental Table 1[13–38] (CMF or other antimetabolites) and Supplemental Table 2[25,36,39–55] (anthracyclines). Supplemental Table 1 presents seventeen RCTs, of which ten were not reported in the EBCTCG meta-analysis. Supplemental Table 2 presents thirteen studies, of which seven were not included in the EBCTCG meta-analysis. The additional studies do not change the conclusions from the EBCTCG meta-analyses, but do address the use of other chemotherapy agents or specific concepts pertaining to certain drugs. Notably, the study by Muss *et al.*[16] found that capecitabine monotherapy was inferior to either CMF or AC in the elderly population; that regimen is therefore not recommended for adjuvant treatment. Trials that examined the anthracycline–taxane regimens or the addition of gemcitabine or capecitabine to them are discussed in the Taxanes subsection (next). Some studies[31,38] examined drugs not commonly used in Canada for the treatment of breast cancer. Several studies[53,54,56–58] used the FEC regimen with or without taxanes and with doses of epirubicin less than 100 mg/m^2; they are thus not relevant to practice in Ontario. A few publications presented trial subgroup analyses or molecular studies. For instance, Cheang *et al.*[43] evaluated outcomes in the MA.5 study according to intrinsic subtype as determined by the PAM50 test. In that retrospective analysis, patients with disease of the HER2-positive subtype appeared to gain the most benefit from anthracycline chemotherapy, but the difference was not statistically significant. It is unclear whether those results are clinically meaningful, because trastuzumab was not part of the treatment. As noted earlier, additional evidence from the systematic review for the treatment of HER2-positive breast cancer is published separately in this supplement.

3.3 Taxanes

Use of taxanes [docetaxel (T) or paclitaxel (P)] for the adjuvant therapy of breast cancer has been a more recent therapeutic advance. In contrast with earlier work, the most recent EBCTCG meta-analysis included comparisons of taxanes with anthracyclines for trials beginning up to 2003; data available up to mid-2010 were included[8].

Many of the RCTs evaluating the use of taxanes compared them with anthracycline-based regimens, because the latter are superior to older CMF-type regimens. In the present evidence review, trials of taxanes represented the largest number of RCTs (fifty-five trials in ninety-three publications) and are summarized in Supplemental Table 3[21,27–30,35,36,49–54,56–136]. Because taxane studies are relatively recent, our database search found most of the published trials cited in other reviews or meta-analyses. Of those latter publications, the EBCTCG review[8] was again the most complete, and only two additional studies comparing taxanes with anthracyclines were found. Notably, the EBCTCG analysis did not cover neoadjuvant therapy, comparisons of taxane with non-anthracycline regimens, and comparisons of the dose or type of taxane—for example, T compared with P. In the latter category, fourteen RCTs were found in MEDLINE or EMBASE, and one study was identified from other reviews.

3.3.1 Anthracycline Plus Taxane Compared with Anthracycline Chemotherapy Alone

Many of the individual RCTs that compared anthracycline–taxane chemotherapy with chemotherapy based on anthracycline alone demonstrated superiority for the taxane arm (Supplemental Table 3). Interestingly, when those studies were pooled in the EBCTCG meta-analysis, outcomes in the taxane and anthracycline arms were equivalent for several comparisons. On further analysis, it was established that the amount of anthracycline chemotherapy administered in each study arm was important.

In the EBCTCG analysis, trials that compared added cycles of taxane chemotherapy with an anthracycline regimen (for example, AC×4 vs. AC×4→P×4 or AC×4→T×4) were considered "unconfounded." In those studies, the taxane arm included more chemotherapy cycles and was associated with superior outcomes.

Other studies were considered "confounded" because, in the comparator taxane arm, the anthracycline (or other non-taxane chemotherapy) was also altered. Examples of such studies include FEC×6 compared with epirubicin–cyclophosphamide × 4 → T×4, and CEF×6 compared with dose-dense epirubicin–cyclophosphamide × 4 → T×4 or P×4. Most of the studies contained more anthracycline (but less than double the amount) in the control arms; nonetheless, the taxane-containing regimens were still found to be superior. Another example is studies that evaluated taxanes given concurrently with anthracyclines in the comparator arm such that the total number of chemotherapy cycles was not increased, and the difference in anthracycline exposure was minimal or nonexistent: for instance, FAC×6 compared with TAC (docetaxel–doxorubicin–cyclophosphamide) × 6. Those trials also favoured the taxane-containing arms.

In the EBCTCG analysis, the only studies that were ultimately found not to show superiority for the taxane regimen were trials that significantly truncated the amount of anthracycline chemotherapy in the taxane arm. In those trials, the control arm contained double (or close to double) the amount of anthracycline—for example, FEC×6 compared with FEC×3→T×3. Notably, several of the studies, such as

PACS 01 (FEC×6 compared with FEC×3→T×3), favoured the taxane arm and influenced practice with their independent results. Another important consideration is that limiting anthracycline exposure can be clinically important to mitigate adverse effects, including cardiotoxicity and leukemia (the risks of which increase with a higher anthracycline dose).

In summary, the addition of taxanes to anthracycline-based chemotherapy is generally preferred over anthracycline-based chemotherapy alone. Strategies for taxane use vary as already described, and preferred regimens for the Ontario context are summarized in Table I and discussed in the guideline recommendations elsewhere in this supplement. The recommendations also consider additional evidence with respect to taxane chemotherapy as discussed next.

3.3.2 Anthracycline Chemotherapy Compared with Taxane Chemotherapy

A few studies have directly compared an anthracycline and a taxane. The U.S. Oncology Research Trial 9735[103] compared AC×4 with docetaxel–cyclophosphamide × 4 and demonstrated superior survival outcomes for the docetaxel–cyclophosphamide regimen. For patients in whom an anthracycline might not be ideal, docetaxel–cyclophosphamide is considered a reasonable alternative.

3.3.3 Comparison of Taxane-Based Regimens

Although the EBCTCG analysis excluded comparisons of various taxanes or doses, such studies were found during the literature search and are included in Supplemental Table 3. Notable trials include the Eastern Cooperative Oncology Group 1199[116] trial that demonstrated the utility of AC×4→P weekly and found improved survival compared with P every 3 weeks. That trial also demonstrated that P every 3 weeks is inferior to T every 3 weeks. There was no direct comparison of AC→P weekly with AC×4→T×4 every 3 weeks. The Cancer and Leukemia Group B 9741 trial[109] found that, compared with AC→P every 3 weeks, AC→P or A→P→C administered every 2 weeks resulted in better survival (but also in more adverse effects). The MA.21 trial[52] found that dose-dense epirubicin–cyclophosphamide → P is equivalent to CEF and that both regimens are superior to AC×4→P×4 every 3 weeks. In BCIRG 5[112], TAC×6 was found to be effective, and in National Surgical Adjuvant Breast and Bowel Project B-38[119,120], it was found to be equivalent to dose-dense AC → dose-dense P, although disparate toxicities were observed. Finally, TAC×4 was found, in National Surgical Adjuvant Breast and Bowel Project B30[111], to be an inferior regimen.

3.3.4 Neoadjuvant Taxanes

Supplemental Table 3 summarizes sixteen publications representing ten studies[36,51,59,101,102,108,126–136] that evaluated the use of taxanes in the neoadjuvant setting. However, the guideline for which this evidence was compiled focused specifically on adjuvant therapy for these reasons:

- The patient population for whom neoadjuvant therapy can be considered shows significant variability, containing both early operable and locally advanced cases, which represent different classes of disease.
- The systematic review of the evidence focused on trials reporting DFS and OS rates as endpoints and thus excluded several trials that used pathologic complete response as a primary endpoint (a common outcome in explicitly neoadjuvant trials).

TABLE I Recommendations for adjuvant chemotherapy

In patients who can tolerate it, use of a regimen containing anthracycline–taxane is considered the optimal strategy for adjuvant chemotherapy, particularly in patients deemed to be at high risk.
For patients in whom a taxane is contraindicated, an optimal-dose anthracycline regimen (doxorubicin ≥240 mg/m^2 or epirubicin ≥360 mg/m^2) is recommended.
The addition of gemcitabine or capecitabine to an anthracycline–taxane regimen is not recommended for adjuvant chemotherapy.
In patients more than 65 years of age, capecitabine is not recommended as an adjuvant chemotherapy option in lieu of adjuvant doxorubicin–cyclophosphamide or cyclophosphamide–methotrexate–5-fluorouracil (with oral cyclophosphamide).
For patients in whom anthracycline–taxane is contraindicated, cyclophosphamide–methotrexate–5-fluorouracil (with oral cyclophosphamide) is an acceptable chemotherapy regimen.
These adjuvant chemotherapy regimens can be used for patients with early-stage breast cancer: • 5-Fluorouracil–epirubicin–cyclophosphamide × 3, followed by docetaxel × 3 (superior to 5-fluorouracil–epirubicin–cyclophosphamide × 6) • Doxorubicin–cyclophosphamide × 4, followed by docetaxel × 4 (superior to doxorubicin–cyclophosphamide × 4) • Docetaxel–doxorubicin–cyclophosphamide × 6 (superior to 5-fluorouracil–doxorubicin–cyclophosphamide × 6) • Doxorubicin–cyclophosphamide × 4, followed by weekly paclitaxel • Dose-dense, dose-intense epirubicin–cyclophosphamide, followed by paclitaxel • Dose-dense doxorubicin–cyclophosphamide, followed by paclitaxel every 2 weeks
Docetaxel–cyclophosphamide is an adjuvant regimen that can be used when anthracycline is not preferred.

The studies included in our review therefore represent only some of the data pertinent to neoadjuvant therapy in early breast cancer.

3.3.5 Taxanes and Other Chemotherapy Drugs

Several studies[53,54,56–58] used the FEC regimen with or without taxanes and with epirubicin doses less than 100 mg/m^2 and thus are not relevant to practice in Ontario. Based on the FINHER study[57], vinorelbine is inferior to docetaxel when followed by FEC. The FINXX study[21] evaluated capecitabine (X) and found an improved breast cancer–specific survival rate and fewer local relapses for TX→CEX compared with T→CEF. However, the difference in the OS rate was not statistically significant. In addition, the doses of the taxane and the anthracycline are both considered nonstandard in the Ontario setting. A trial by Kelly *et al.*[125] also demonstrated no benefit for the addition of capecitabine to an anthracycline–taxane regimen. In National Surgical Adjuvant Breast and Bowel Project B-38[121,122], the addition of gemcitabine to dose-dense AC×4 → dose-dense P×4 was associated with improved outcomes, but increased adverse effects.

3.4 Other Systemic Therapy Agents

3.4.1 Bisphosphonates

A previous PEBC guideline[137] evaluated the use of bisphosphonates in both early and metastatic breast cancer. At that time, many studies were ongoing, and those studies were still largely unreported at the time of the most recent literature search. However, subsequent to the literature search and consensus conference, new data from the EBCTCG meta-analysis were presented in abstract form[138], highlighting the utility of adjuvant bisphosphonates in improving breast cancer survival outcomes in postmenopausal women. The final publication of those data is still pending, and the use of adjuvant bisphosphonates will be specifically addressed in future work.

3.4.2 Bevacizumab

The BEATRICE trial[139] studied the use of bevacizumab, a vascular endothelial growth factor inhibitor, for 1 year in addition to chemotherapy in patients with triple-negative operable breast cancer. Of the chemotherapy regimens studied, 36% were based on anthracycline; 58%, on anthracycline–taxane; and 5%, on taxane. The target number of events had not been reached, and extended follow-up continues. At a median follow-up of 32 months, no significant difference in invasive DFS or in OS had been observed with the addition of bevacizumab to chemotherapy. Patients receiving bevacizumab experienced increased incidences of grade 3 or 4 hypertension (12% vs. 1%), severe cardiac events (1.5% vs. 0.3%), and treatment discontinuation (20% vs. 2%). The ARTemis trial[140,141] gave patients with early-stage HER2-negative breast cancer neoadjuvant docetaxel followed by FEC chemotherapy with or without 4 cycles of bevacizumab; survival outcomes have not yet been reported.

3.4.3 Metformin

In the NCIC trial MA.32, adjuvant metformin for 5 years is being compared with placebo (in addition to other standard adjuvant treatments) in early-stage breast cancer[142]. Follow-up is ongoing.

3.4.4 Goserelin in Hormone Receptor–Negative Patients

The Prevention of Early Menopause Study (SWOG S0230)[143,144] evaluated the use of goserelin in preventing chemotherapy-induced ovarian failure in hormone receptor–negative patients. Compared with patients receiving standard chemotherapy alone, those in the goserelin arm indeed experienced less premature ovarian failure (8% vs. 22%), with improved pregnancy rates. At 4 years, patients in the goserelin arm were experiencing better DFS (hazard ratio: 0.49; $p = 0.04$) and OS (hazard ratio: 0.43; $p = 0.05$). That result is recognized to be exploratory, given early closure of the study, a small sample size, and the fact that survival outcomes were tertiary endpoints.

3.4.5 Vaccines

Our systematic review identified early-phase randomized studies evaluating the HER2 peptide vaccines AE37 and E75 as novel adjuvant systemic therapy agents. In a phase II study, the AE37 vaccine[145] has been associated with promising reductions in recurrence risk, particularly in certain disease phenotypes such as triple-negative; phase III study is recommended. In optimally dosed patients, the E75 vaccine has been associated with improved DFS in early studies[146,147]; a phase III trial (http://www.clinicaltrials.gov/show/NCT01479244) is under way.

4. SUMMARY

A comprehensive systematic review of the literature concerning the use of adjuvant systemic therapy for early breast cancer addressed the question "What is the optimal systemic therapy for early breast cancer when patient and disease characteristics are considered?" The use of adjuvant chemotherapy, outlined here, demonstrates the overall superiority of anthracycline–taxane regimens for eligible patients. That evidence, together with the systematic reviews of endocrine therapy and HER2-targeted treatment in this supplement, forms the basis of the recommendations in the PEBC's systemic therapy guideline for early breast cancer[3].

5. REVIEW AND UPDATE

Practice guidelines and literature reviews developed by the PEBC are reviewed and updated regularly. For the full 1-21 evidence-based series and subsequent

updates, please visit the CCO Web site at https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/.

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7. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SG has received speaking honoraria from Novartis. AE has received a grant from Genomic Health for a pending research study and was a NCIC principal investigator for the olympiA trial. SFD was a principal investigator for the APHINITY trial; has received speaking honoraria from Hoffman–La Roche, Amgen, and Novartis; travel support from Celgene and Roche; and unrestricted educational grants from Roche, Pfizer, GlaxoSmithKline, and Amgen. MET has overseen funds from Roche and Amgen for the Sunnybrook Odette Cancer Centre chemotherapy suite renovation, from Amgen for a drug reimbursement specialist, and from Eisai, Roche, Novartis, and Amgen for fellowship funding. MET has also received grants or research support from Astellas, Medivation, and Novartis. The other working group members declared that they had no conflicts.

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