Clinical practice guidelines for the care and treatment of breast cancer: adjuvant systemic therapy for node-positive breast cancer (summary of the 2001 update)

Mark Levine, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer

This article provides a summary of changes made by Health Canada's Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer to the article "Clinical practice guidelines for the care and treatment of breast cancer: 8. Adjuvant systemic therapy for women with node-positive breast cancer," originally published in 1998[1] (the 2001 update can be found online at www.cma.ca/cmaj/vol-164/issue-5/breastcpg/guideline8rev.htm). There have been some significant changes to this guideline based on data from the recent meta-analysis of the Early Breast Cancer Trialists' Collaborative Group[2,3] and from individual randomized trials. The updated guideline contains revised recommendations regarding the types of chemotherapy regimens to use in premenopausal women, the use of tamoxifen in premenopausal women who refuse chemotherapy and the use of tamoxifen in women over 70 years of age (Table 1).

The Steering Committee's original guideline had recommended either doxorubicin (Adriamycin) plus cyclophosphamide (AC) chemotherapy or cyclophosphamide,

Table 1: Updated recommendations from the clinical practice guideline for the care and treatment of breast cancer: adjuvant systemic therapy for women with node-positive breast cancer

Premenopausal women

- Chemotherapy should be offered to all premenopausal women with stage II breast cancer.
- Acceptable treatment regimens are those using cyclophosphamide, methotrexate and 5-fluorouracil (CMF) or doxorubicin (Adriamycin) and cyclophosphamide (AC) or cyclophosphamide, epirubicin and 5-fluorouracil (CEF). In terms of breast cancer outcomes, CMF and AC are equivalent, and CEF is superior to CMF. CEF is associated with more side effects than CMF. Personal preference and quality of life influence the choice of chemotherapy regimen. The addition of taxanes to anthracycline-containing regimens remains under active investigation. Currently available data concerning the addition of taxanes to anthracycline-containing regimens are inconclusive, although highly informed and motivated patients may choose this treatment. Participation in approved clinical trials should be strongly encouraged.
- Potential toxic effects of chemotherapy should be fully discussed with patients.
- Systemic adjuvant chemotherapy should begin as soon as possible after the surgical incision has healed.
- The recommended duration of therapy is at least 6 cycles (6 months) for CMF or CEF, and at least 4 cycles (2 to 3 months) for AC.
- The recommended CMF regimen consists of 14 days of oral cyclophosphamide with intravenous methotrexate and 5-fluorouracil on days 1 and 8. This is repeated every 28 days for 6 cycles.
- When possible, patients should receive the full standard dosage. High-dose chemotherapy plus stem-cell support is not recommended.
- Ovarian ablation is effective in premenopausal women with estrogen receptor (ER)-positive tumours. However, chemotherapy has been better studied and is considered the intervention of choice. Ovarian ablation should be recommended to women who decline chemotherapy and have ER-positive tumours.
- In the future, a small benefit may be shown for the combination of ovarian ablation plus chemotherapy in women with node-positive, ER-positive tumours. At present, there is insufficient evidence for this to be recommended.
- Tamoxifen can be recommended in premenopausal women with ER-positive tumours who refuse chemotherapy or ovarian ablation.
- Whether tamoxifen should routinely be recommended after chemotherapy in premenopausal women is unclear.
- Before recommending hormonal therapy in premenopausal women, both the long-term side effects and its effects on recurrence must be considered.

Postmenopausal women

- Postmenopausal women with stage II, ER-positive cancer should be offered adjuvant tamoxifen.
- The recommended duration of tamoxifen therapy is 5 years.
- No other hormonal intervention apart from tamoxifen can be recommended for postmenopausal patients.
- Women with ER-negative tumours who are fit to receive chemotherapy (generally younger than 70 years) should be offered CMF or AC. Personal preference and quality of life influence the choice of chemotherapy regimen.
- Women with ER-positive tumours gain an additional benefit from taking chemotherapy in addition to tamoxifen. This is an option for a motivated, well-informed patient.

All ages

- The routine use of bisphosphonates as adjuvant therapy is not recommended.
- Patients should be offered the opportunity to participate in clinical trials whenever possible.

methotrexate and 5-fluorouracil (CMF) chemotherapy in premenopausal women with node-positive breast cancer. It also made a preliminary recommendation for a more aggressive regimen with cyclophosphamide, epirubicin and 5-fluorouracil (CEF) on the basis of results from a trial conducted by the National Cancer Institute of Canada Clinical Trials Group. After an extended follow-up, the updated results of that trial have now been published.[4] Compared with CMF, CEF resulted in improved disease-free survival (63% v. 53%) and overall survival (76% v. 70%) at 5 years.

In addition, a new chemotherapeutic agent, paclitaxel, was evaluated. Paclitaxel is a member of a class of drugs known as taxanes. These drugs act by interfering with microtubules, thereby disrupting the normal mitotic process. Thus they can potentially be used together with anthracycline compounds (doxorubicin, epirubicin), which act by interfering with DNA replication. A number of clinical trials are investigating the incorporation of taxanes with anthracycline-based chemotherapy regimens in the adjuvant setting. A large multicentre trial involving women with node-positive breast cancer showed that adding paclitaxel after AC chemotherapy provided a better result than AC alone.[5] At a median follow-up of 30 months, there was a 22% reduction in the risk of recurrence and a 26% reduction in the risk of death. The benefit was confined to women with estrogen receptor (ER)-negative tumours. For women with ER-positive tumours who were taking tamoxifen, no statistically significant difference was detected in the risk of recurrence or death. A second large multicentre trial, however, failed to detect a statistically significant difference between AC alone and AC followed by paclitaxel.[6] The data are therefore inconclusive at present and require longer follow-up. In the above studies, both the CEF regimen and the AC regimen followed by paclitaxel were associated with an increased incidence of side effects.

The Steering Committee's updated guideline recommends the AC, CMF or CEF regimen for node-positive breast cancer. A firm recommendation for AC followed by paclitaxel is not made. The committee felt that the data were preliminary based on a relatively short follow-up. However, a highly informed and motivated patient may wish to receive this regimen. Participation in clinical trials is encouraged. As before, the choice of chemotherapy regimen depends on the individual woman's preference.

In the original guideline no recommendations could be made concerning high-dose chemotherapy plus stem-cell support. The results of 2 randomized trials published since then do not support this form of treatment. In one trial, conducted in the United States and Canada, women with disease involving 10 or more axillary lymph nodes were randomly assigned to receive either high-dose chemotherapy consisting of cyclophosphamide, cisplatin and BCNU (bis-chloronitrosourea) plus stem-cell support or intermediate doses of these drugs.[7] No difference in breast cancer recurrence and mortality was detected between the 2 groups. In a Scandinavian trial, women with high-risk primary breast cancer were randomly assigned to receive either a dose-intensive regimen consisting of 9 cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) or 3 cycles of FEC followed by high-dose chemotherapy with stem-cell support.[8] No difference in overall survival was detected between the groups.

In the original guideline ovarian ablation was recommended for premenopausal women who refused chemotherapy. In the 1990 meta-analysis by the Early Breast Cancer Trialists' Collaborative Group, data on the use of tamoxifen in premenopausal women were inconclusive. In the group's 1995 analysis, there was a 45% proportional reduction in recurrence among women with ER-positive tumours receiving tamoxifen for 5 years.[3] In the updated guideline, the Steering Committee now recommends the use of tamoxifen in premenopausal women who refuse chemotherapy or ovarian ablation.

The original guideline recommended the use of tamoxifen in postmenopausal women with ER-positive tumours. It was suggested that patients might benefit further by the addition of chemotherapy. In the recent meta-analysis by the Early Breast Cancer Trialists' Collaborative Group, there was a 19% proportional reduction in recurrence and an 11% proportional reduction in mortality among women who received chemotherapy plus tamoxifen compared with those given tamoxifen alone.[2,3] The additional benefit of tamoxifen plus chemotherapy over tamoxifen alone in this group of women is supported by several other recent trials, which are discussed in the updated guideline. Given these findings, the Steering Committee now recommends the addition of chemotherapy to tamoxifen therapy in postmenopausal women with ER-positive tumours. Personal preference and quality of life also influence the choice of chemotherapy.

The Steering Committee's original recommendation for AC or CMF chemotherapy in postmenopausal women with ER-negative tumours who are fit to receive chemotherapy is unchanged.

Previously, it was suggested that tamoxifen could be used in women over 70 years of age with ER-negative tumours. More recent data do not support the use of tamoxifen in any women with ER-negative tumours, regardless of age.[3,9]

The patient version of these guidelines has also been updated and can be found online at www.cma.ca/cmaj/vol-164/issue-5/breastcpg/guideline8revpt.htm.

Dr. Levine is with the Cancer Care Ontario Hamilton Regional Cancer Centre and the Departments of Medicine and of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ont. The Steering Committee is part of Health Canada's Canadian Breast Cancer Initiative.

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Correspondence to: *Dr. Mark Levine, c/o Ms. Humaira Khan, Faculty of Health Sciences, McMaster University Health Sciences Centre, Rm. 2C6, 1200 Main St. W, Hamilton ON L8V 5C2; fax 905 577-0017*